

# Treatment of Elevated Intracranial Pressure

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## LEARNING OBJECTIVES

1. Distinguish the differences between intracranial pressure (ICP) monitoring devices and assess the information they provide.
2. Apply nonpharmacologic therapy interventions to a patient with elevated ICP.
3. Design a dosing plan and monitoring recommendations for the use of osmotherapy in the treatment of elevated ICP.
4. Develop a sedation regimen and monitoring plan for a patient requiring treatment of elevated ICP.

### ABBREVIATIONS IN THIS CHAPTER

BBB	Blood brain barrier
CBF	Cerebral blood flow
CPP	Cerebral perfusion pressure
EVD	External ventricular drain
GCS	Glasgow Coma Scale
HTS	Hypertonic saline
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
MAP	Mean arterial pressure
NPI	Neurological pupil index
IO	Intraosseous
ONSD	Optic nerve sheath diameter
PaCO <sub>2</sub>	Partial pressure of carbon dioxide
PbtO <sub>2</sub>	Brain tissue oxygen tension
TBI	Traumatic brain injury

[Table of other common abbreviations](#)

## INTRODUCTION

The *cranial vault* is a rigid compartment that contains brain, blood, and CSF. *Intracranial pressure* (ICP) is defined as the pressure within this space, and the relationship between volume and pressure within the cranium is nonlinear. A concept developed more than 2 centuries ago, the *Monro-Kellie hypothesis*, is that the sum of brain tissue, CSF, and intracranial blood is constant and an increase in one component should cause a proportional decrease in one or both of the remaining two, or an elevation of ICP will result (Dunn 2002). Intracranial blood (primarily venous blood) and CSF are the two components in which the volume can adapt most easily to accommodate increases in the volume of intracranial contents. When these compensatory mechanisms are exhausted, further volume increases in any of these three components, such as the addition of space-occupying lesions or excess fluid (e.g., tumor, hemorrhage) or the presence of cerebral edema, can lead to large increases in pressure, resulting in an elevated ICP. The pathogenesis of elevated ICP varies depending on the initial insult; however, one of the most common causes is cerebral edema, which is present in most neurologic injuries (Marmarou 2007). As pressure within the skull increases, brain tissue displacement can lead to cerebral herniation, resulting in severe disability or death.

The goals of ICP management are to maintain adequate brain oxygen delivery, to avoid further injury, and ultimately to prevent herniation. Elevated ICP and cerebral herniation should be considered a *brain code*—a life-threatening neurologic emergency. *Intracranial hypertension* is defined as a sustained (more than 5 minutes) elevation of ICP to greater than 22 mm Hg (Carney 2017). *Cerebral perfusion pressure* (CPP) is defined as the pressure gradient across the cerebral

vascular bed, between blood inflow and outflow, and is used as a surrogate for global cerebral blood flow (CBF). Cerebral autoregulation maintains CBF over a wide range of CPPs by innate changes in cerebral vascular resistance. Changes in CPP can occur by altering mean arterial pressure (MAP), such as by vasopressor initiation) or ICP. The following equation approximates the CPP:

$$\text{Cerebral perfusion pressure} = \text{Mean arterial pressure} - \text{Intracranial pressure}$$

A CPP target between 60–70 mm Hg has been shown to reduce 2-week mortality in with traumatic brain injury (TBI) when targeting specific goals for both ICP and CPP (Gerber 2013). The use of CPP targets for other nontraumatic causes of elevated ICP has not been adequately studied.

### BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of hemodynamic pathophysiology particularly the impacts on cerebrovascular blood flow, mean arterial pressure, and intracranial pressure.
- A baseline foundation of neurologic disease states that are associated with or cause cerebral edema and/or intracranial hypertension.
- Understand the pathophysiology of plasma sodium homeostasis and the management of sodium derangements.
- The consequences of sustained intracranial hypertension and complications including death by neurologic criteria.

*Table of common laboratory reference values.*

### ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Neurocritical Care Society. [Guidelines for the acute treatment of cerebral edema in neurocritical care patients](#). Neurocrit Care 2020;32:647-66.
- Brain Trauma Foundation. [Guidelines for the management of severe traumatic brain injury—4th edition](#). Neurosurgery 2017;80:6-15.
- Sterns RA. [Disorders of plasma sodium—causes, consequences, and correction](#). N Engl J Med 2015;375:55-65.
- World Brain Death Project. [Determination of brain death/death by neurologic criteria](#). JAMA 2020;324:1078-97.

### Brain Trauma Foundation Guidelines for Management of Severe TBI

Brain Trauma Foundation guidelines for the management of severe TBI were updated in September 2016. This update is the fourth edition of these guidelines and is considered a *living guideline* (Carney 2017), meaning the Foundation does not intend to produce a fifth edition—rather, it will move to a model of continuous monitoring of the literature, rapidly updating the evidence review, and revising the recommendations as warranted.

The new edition of the guidelines presents 28 evidence-based recommendations. Of those specifically addressing ICP management, 10 recommendations are either new or updated from the previous guidelines. Importantly, the Fourth Edition states that patients with severe TBI should be managed with information from ICP and invasive blood pressure monitoring devices to reduce 2-week post-injury mortality. In addition, the thresholds for blood pressure, ICP, and CPP were updated. The systolic blood pressure goal is 100 mm Hg or greater for patients age 50–69 years and 110 mm Hg or greater for age 15–49 years and older than 70 years. Treatment should be initiated if ICP greater than 22 mm Hg is sustained for more than 5 minutes and the recommended CPP target is between 60–70 mm Hg. The guidelines recommend continuous drainage of CSF from an external ventricular drain (EVD) versus intermittent drainage because use of an EVD may be more effective at lowering the ICP burden. In addition, early use (after the first 12 hours post-injury) of CSF drainage in patients with an initial Glasgow Coma Scale (GCS) score less than 6 may be considered.

With respect to osmotherapy, the recommendation from the prior edition that mannitol is effective for control of raised ICP at doses of 0.25–1 g/kg cannot be maintained in the fourth edition because the studies previously included to support this approach do not meet the standards for literature evaluation set forth in the updated edition. The fourth edition states that, although hyperosmolar therapy may lower ICP, evidence is insufficient regarding clinical outcomes to support a specific recommendation or to support the use of a particular hyperosmolar agent in patients with severe TBI.

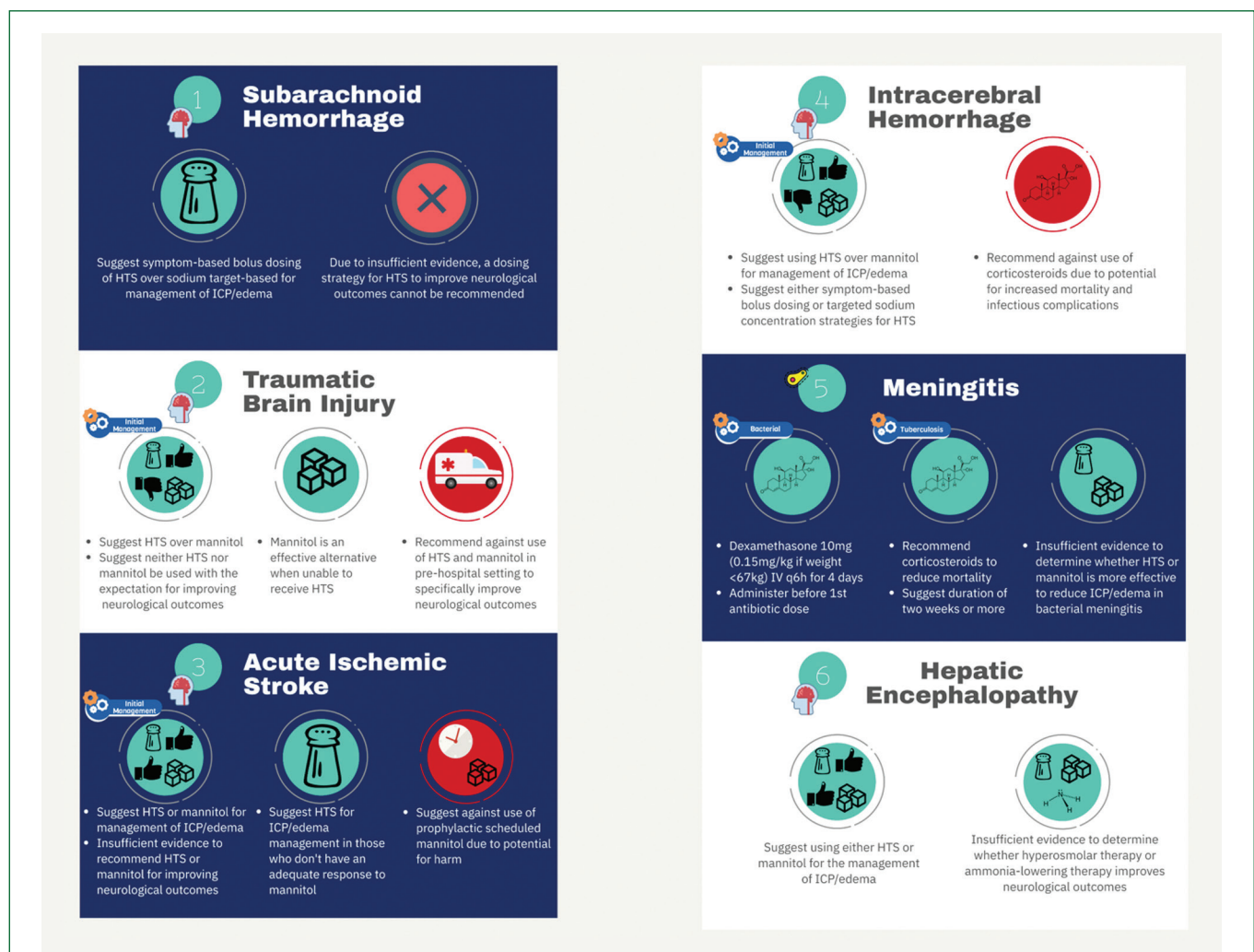
### Neurocritical Care Society Guidelines for Acute Treatment of Cerebral Edema in Neurocritical Care Patients

Cerebral edema is one of the more common contributors to elevated ICP, as noted previously. A Neurocritical Care Society multidisciplinary group of experts was assembled in 2017 to create a guideline that evaluates the role of hyperosmolar agents (mannitol and hypertonic saline [HTS]), corticosteroids, and selected nonpharmacologic therapies in acute treatment of cerebral edema (Cook 2020b). In 2020, the guidelines were published and reported the panel's recommendations regarding the initial management of cerebral edema in different groups of neurocritical care

patients. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to categorize the *quality of evidence* as *high, moderate, low, or very low* to support their official recommendation on the 16 clinical questions generated.

The panel gave detailed responses to the 16 questions they developed; only select recommendations will be summarized here (Figure 1). For patients with subarachnoid hemorrhage, they found with a very low level of evidence that symptom-based bolus dosing of HTS should be used instead of sodium target-based dosing for the management of elevated ICP or cerebral edema. For patients with TBI, they made the following recommendations, with a low level of evidence: 1) HTS should be used over mannitol for initial management of elevated ICP or cerebral edema; 2)

mannitol is an effective alternative to HTS; and 3) neither agent should be used with the expectation of improving neurologic outcomes. They also found that HTS and mannitol should not be used in the pre-hospital setting to improve neurologic outcomes, with a moderate and very low level of evidence, respectively. Cerebral edema in patients with acute ischemic stroke can be managed with either mannitol or HTS (low level of evidence). They also found with a low level of evidence that patients with acute ischemic stroke should not be managed with prophylactic scheduled mannitol because of the potential for harm—two large, retrospective cohort studies reported an increased risk of death at 30 days with prophylactic use of scheduled mannitol (Papagianni 2018; Zuliani 2004). For patients with intracerebral hemorrhage (ICH), they found, with a very low level of evidence, that HTS



**Figure 1.** Guideline recommendations for treatment of cerebral edema.

HTS = hypertonic sodium; ICP = intracranial pressure.

Information from: Cook AM, Jones GM, Hawryluk GWJ, et al. Guidelines for the acute treatment of cerebral edema in neurocritical care patients. *Neurocrit care* 2020;32:647-66.

should be used over mannitol in either a symptom-based or a sodium target-based approach.

This guideline also discussed the use of dexamethasone in various disease states, including bacterial meningitis; however, that information extends beyond the scope of this chapter. Readers are encouraged to refer to this guideline for further details regarding their recommendations on dexamethasone. In addition, this guideline did not address common strategies for refractory cerebral edema or ICP crises, which will be discussed throughout this chapter.

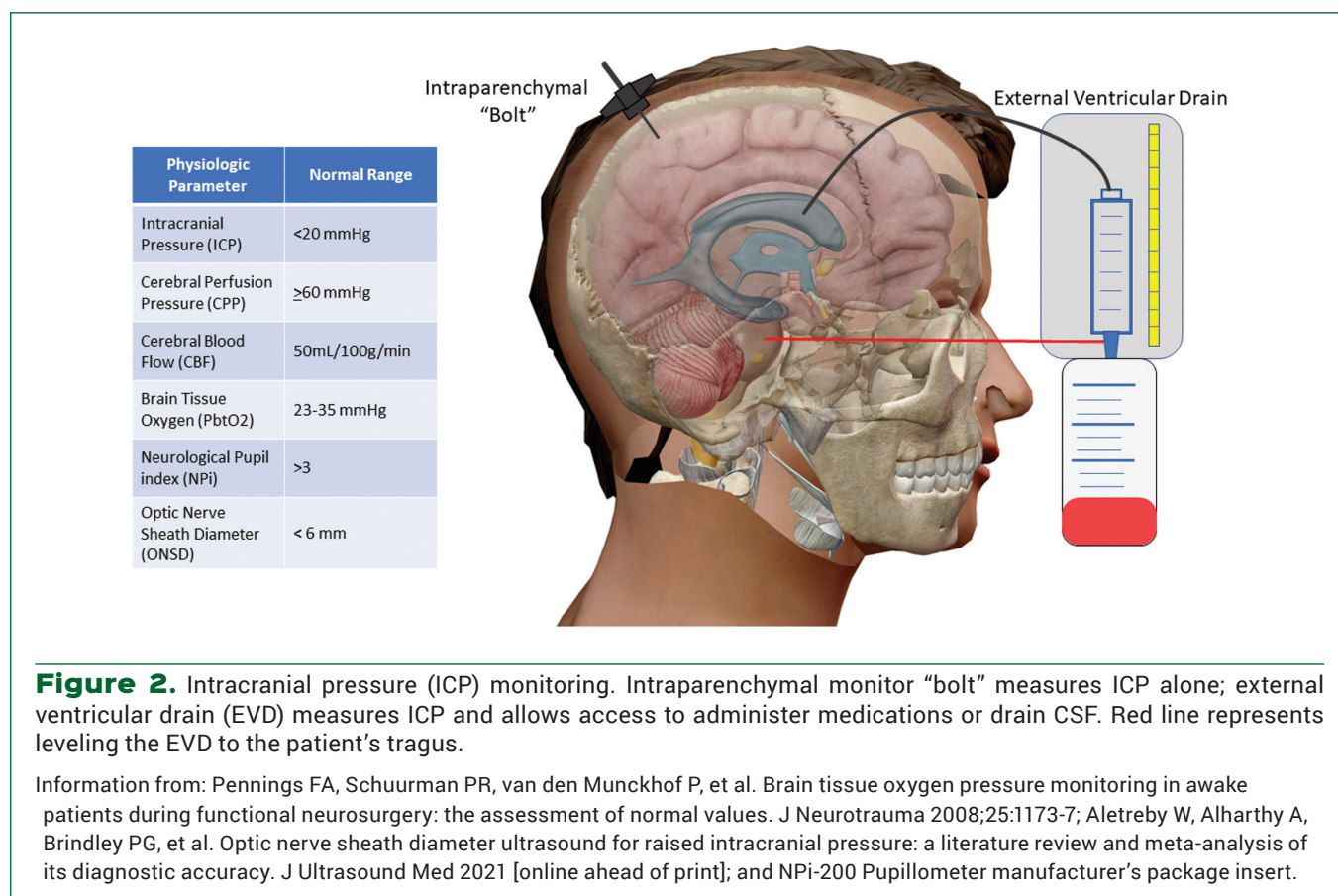
## ICP MONITORING DEVICES

Critical care practitioners are accustomed to using and interpreting advanced and almost continuous monitoring. As for the general ICU, patients admitted to a neuro-ICU use the same basic monitoring and support devices, such as ECG, pulse oximetry, arterial and central venous lines, ventilators, and renal replacement therapy machines. A key difference between general ICU patients and neuro-ICU patients is that specific tools are available for advanced neuromonitoring. These devices are often used in conjunction, termed *multimodality neuromonitoring*. Treatment of ICP is best guided by ICP monitoring, imaging, and clinical evaluation in unison. Management of ICP is assisted by integration of the patient’s examination, imaging, and cerebral physiologic

data derived from a range of neuromonitoring tools and variables, including ICP, brain tissue oxygen tension (PbtO<sub>2</sub>), cerebral microdialysis, and quantitative EEG, among other sources (Le Roux 2014). Rather than depending on the limited information available from a single parameter or device, multimodal neuromonitoring allows for a more comprehensive evaluation of the injured brain.

### External Ventricular Drain

*Ventriculostomy*, or the placement of an EVD, is one of the most common acute neurosurgical procedures. During this procedure, the skull, dura, and brain are penetrated until one of the lateral ventricles is accessed by a small soft catheter. An EVD is the gold standard for ICP measurement, and it can also be used to drain excess CSF, which can be therapeutic and assist with overall ICP management (Figure 2). The primary indication for EVD placement is acute hydrocephalus, secondary to subarachnoid hemorrhage, ICH, intraventricular hemorrhage, infection, brain tumor, or shunt failure (Fried 2016). Brain Trauma Foundation guidelines for the management of severe TBI discuss the use of EVDs for CSF drainage in patients with TBI (Carney 2017), stating that EVDs may be considered to drain CSF to lower ICP after the first 12 hours of injury in patients with a GCS score less than 6.



After placement, EVDs are zeroed. The *zero point* is defined as the center of the head or at the level of the mid-brain, which is anatomically close to the tragus of the outer ear (Freeman 2015). The accuracy of ICP readings depends on patient positioning in relation to the transducer, and the device requires staff to periodically open the transducer to atmospheric pressure and return it to the zero reference point (Schimpf 2012). Once placed, the EVD will be set at a pressure threshold in centimeters of water (cmH<sub>2</sub>O) (Heiferman 2019). The EVD pressure settings generally range from -5 to 20 cmH<sub>2</sub>O or -6.75 to 27 mm Hg. In the open position, EVDs drain CSF into the drainage bag if the pressure threshold is exceeded; however, the patient specific ICP is not be measured, instead the monitor reads the EVD pressure setting. In the closed position, the transducer device produces a waveform and reports ICP in mm Hg; the conversion from cmH<sub>2</sub>O to mm Hg requires division by a factor of 1.35 (Freeman 2015). Similar to other devices, the EVD waveform has a defined configuration, and the accuracy of this waveform should be interpreted by a trained clinician.

Malposition, tract hemorrhage (1%–2% risk), and infection (1%–10% risk) are complications that can occur with EVD placement (Berlin 2015). Although a Neurocritical Care Society evidence-based consensus statement on the insertion and management of EVDs was published, it is not reviewed in detail in this chapter (Fried 2016). It should be mentioned, however, that patients should receive one dose of antimicrobials before EVD insertion, although it is not recommended to continue antimicrobials for the duration of EVD placement.

### Parenchymal ICP Monitor

The parenchymal ICP monitor is a device that sits in the parenchyma, or brain tissue (see Figure 2). These devices are often referred to as a *bolt*. The placement of a parenchymal ICP monitor is less technical than that of an EVD because the accuracy of placement does not depend on the tip of the device being located in one of the lateral ventricles. Before placement, the device must be calibrated and zeroed. The device passes through the skull and dura, and then remains in its final location of the parenchyma. Because of its location, the device does not allow for CSF drainage, and the ICP monitoring accuracy is reliable, second only to an intraventricular monitor (Zhong 2003). However, because of the inability to continuously calibrate the device, the sensor can begin to report imprecise ICP values. The difference between the starting ICP value when the sensor is calibrated (0 mm Hg), and the ICP value that is measured when the sensor is removed is termed *zero drift* (Raboel 2012). Although the incidence of complications is lower with this device compared with an EVD, infection and bleeding (2%) are possible (Berlin 2015).

### Brain Tissue Oxygen Monitoring System

Maintaining adequate systemic oxygenation is a standard goal when managing all critically ill patients. For patients with neurologic disorders, the concern is not only about systemic oxygenation, but also directly monitoring brain tissue oxygenation and using techniques to correct any cerebral oxygen delivery and demand mismatch. Two catheter-based devices are available to continuously monitor the partial pressure of oxygen in extracellular fluid of the brain or PbtO<sub>2</sub>. The Licox (Integra, Plainsboro, New Jersey, USA) and Neurovent (Raumedic, Helmbrechts, Germany) catheters both safely and reliably measure PbtO<sub>2</sub> in an about 1-mm<sup>3</sup> region around the catheter tip, which rests in the brain parenchyma (Leach 2021; Bailey 2019; Okonkwo 2017; Haitsma 2002).

Normal PbtO<sub>2</sub> is 23–35 mm Hg (Pennings 2008). A PbtO<sub>2</sub> of less than 20 mm Hg represents compromised brain oxygen and may be a threshold used to initiate intervention. In single-center, uncontrolled, retrospective studies PbtO<sub>2</sub> values less than 15 mm Hg for more than 30 minutes are an independent predictor of unfavorable outcomes and death (Chang 2009; van den Brink 2000). In contrast, several cohort studies have shown an association between treatment of low PbtO<sub>2</sub> with improved outcomes (Spiotta 2010; Narotam 2009; Stiefel 2005). Monitoring of PbtO<sub>2</sub> is safe and provides accurate data for up to 10 days with measured responses to interventions (Le Roux 2014). Factors that may influence the PbtO<sub>2</sub> include MAP, CPP, partial pressure of oxygen, partial pressure of carbon dioxide (PaCO<sub>2</sub>), and the systemic hemoglobin concentration.

As with general ICP management, a stepwise approach is also used for PbtO<sub>2</sub> augmentation. Currently, the BOOST-II trial remains the only randomized controlled trial investigating the use of PbtO<sub>2</sub> in TBI patients (Okonkwo 2017). This multicenter, phase 2 trial achieved its primary outcome, demonstrating that patients in the intervention arm had improved cerebral oxygenation through both a lower proportion and average amount of time with PbtO<sub>2</sub> less than 20 mm Hg and a trend towards improved clinical outcomes. These findings prompted the phase 3 BOOST-3 trial that is currently enrolling patients as of December 2021 (Brain 2021). The BOOST-3 protocol blinds the treating physician to PbtO<sub>2</sub> data in the control arm; however, in the experimental arm, the treating physician chooses from a tiered system of interventions aimed at reducing ICP and/or augmenting PbtO<sub>2</sub> in the event of an elevated ICP or brain hypoxia.

Theoretically, the use of this advanced monitoring in tandem with ICP adds to the assessment of brain metabolic needs and the effects of the therapies used to treat ICP. Currently, however, no strong evidence suggests that using PbtO<sub>2</sub> should be the standard of care for ICP management (Carney 2017). The results of the BOOST-3 trial will likely change the landscape of how PbtO<sub>2</sub> monitoring is incorporated in the management of ICP.

## Pupillometer

A standard part of the neurologic examination in a patient with known or suspected neurologic injury is the pupillary light reflex (PLR). Pupillary changes are often an indication of elevated ICP (Jahns 2019). The standard pupil examination involves visual assessment of pupil size, shape, symmetry and PLR. Modern pupillometers provide an accurate and reliable evaluation of various aspects of the PLR at precision levels that were previously unobtainable with the naked eye (Olson 2016b). Whereas traditional assessment of PLR depends on clinician assessment skills and the light source used, a pupillometer is a handheld device that uses a high-speed camera and computing technology to provide quantitative, reproducible, and precise measurements regarding the PLR (Olson 2016b). The only device currently available in the United States is the NPi-200 Pupillometer by NeuroOptics (Irvine, California, USA). This device offers clinicians quantitative infrared technology to objectively and accurately measure and trend pupil size and reactivity, and reports a Neurological Pupil Index (NPi), derived by a proprietary formula (Olson 2016a). Based on the device package insert, measured NPi values range from 0.0–4.9, and a value of less than 3.0 is considered an abnormal or sluggish response. More recent research shows that sustained elevations of ICP greater than 20 mm Hg are associated with a concomitant and clinically relevant decrease of quantitative NPi, on average less than 3.0, and treatment of elevated ICP with hyperosmolar agents was associated with NPi normalization (Jahns 2019).

Preexisting optic neuropathies, Argyll Robertson pupil, Adie pupil, Horner syndrome, asymmetric glaucoma, and retinal disease may impact both manual and automated pupil examination. Therefore, it is important to document an accurate baseline examination and consider intrinsic eye pathology in the differential for baseline abnormalities (Lussier 2019). In addition, several pharmacologic agents can alter the PLR, and thereby the reported NPi. Patients anesthetized with propofol, barbiturates, or inhaled anesthetics lose sympathetic tone of the pupil, leading to miosis—in fact, after about 10 minutes, pupil size stabilizes close to 2 mm (Larson 2015). This loss of reactivity explains the changes in patients who are initiated on high-dose propofol or undergo a pentobarbital induced coma to help manage ICP. In addition, topical agents, including pilocarpine and atropine, can cause miosis and mydriasis, respectively, which alters the PLR. Interestingly, if a patient has a loss of pupil reactivity and if the status of atropine administration is unknown, dilute pilocarpine (0.1%) will not overcome the antagonism of topical atropine but will readily constrict the pupil of a brain-injured patient (Larson 2015).

## Optic Nerve Sheath Diameter Ultrasound

As the neurocritical care community continues to search for noninvasive methods to estimate ICP, optic nerve sheath diameter (ONSD) ultrasound has become a hypothesized

means of detecting elevated ICP. Ultrasound transmits well through water-like substances, such as the vitreous humor of the eye, making the optic nerve sheath visible at the bedside. The optic nerve sheath is anatomically continuous with the central nervous system and is enclosed by the pia, arachnoid, and dura mater (Aletreby 2021). The CSF is contained within the subarachnoid space surrounding the nerve and directly communicates with the intracranial subarachnoid space. When the ICP increases, in theory, the pressure is transmitted to the space surrounding the optic nerve, causing its diameter to enlarge in real-time (Fernando 2019). Therefore, measurement of the ONSD by ultrasound may be used to detect elevations in ICP.

Enlargement of the ONSD occurs almost concurrently or within minutes of an acute change in ICP (Sekhon 2014; Hansen 1997). The ultrasound measurement of the ONSD is operator dependent and may be inappropriate after simultaneous ocular trauma. In addition, reports are conflicting about the correlation of the ONSD with ICP, the diagnostic accuracy, and the ONSD cutoff value that reflects a clinically significant ICP spike (Robba 2018; Amini 2013). A meta-analysis including 16 prospective studies and 619 patients found a pool sensitivity of 0.9 (95% CI, 0.85–0.94) and specificity of 0.85 (95% CI, 0.8–0.89), suggesting its ability to correctly diagnose patients with elevated ICP is greater than its ability to identify patients with normal ICP (Aletreby 2021). This finding is clinically appropriate given that an undetected elevated ICP could carry significant consequences, whereas a low ICP is less concerning. In addition to the test sensitivity and specificity, the ONSD cutoff value to denote increased ICP is variable. The meta-analysis also found that the highest sensitivity was achieved using an ONSD cutoff of greater than 6mm (Aletreby 2021).

With the most recent report of sensitivity and specificity, if a clinician were to only rely on ONSD, about 10% of patients with increased ICP would be undetected. Given that ICP crises are considered a medical emergency, the risk of missing 10% of patients is unacceptable. One group found that the reason for this lack of reliability may be the location of the lesion in the brain, with unilateral lesions leading to a high degree of inconsistency between ONSD and ICP (Butts 2021). In addition, they found that ONSD may not be a good tool to track dynamic changes in ICP after treatment or further increases in ICP. Although using sonography to detect ONSD enlargement is a convenient noninvasive bedside test to identify elevated ICP, given the current literature, it should not fully replace invasive ICP measurements and should instead be used as a supplementary test, especially for cases in which invasive ICP monitoring is delayed.

## Imaging

To obtain an actual ICP value, invasive monitoring is required. As noted previously, noninvasive techniques such as pupillometry and OSND measurement can be used to obtain

surrogate markers to indicate that ICP may be elevated. In addition to these tools and direct ICP monitoring, imaging is used to monitor for evolving cerebral edema and parenchymal tissue shifts leading to herniation. In general, a CT scan can be adequate to identify parenchymal tissue shifts to identify the following cerebral herniation types: subfalcine, descending transtentorial, cerebellar tonsillar, ascending cerebellar transtentorial, transalar, extracranial (Tadevosyan 2021; Laine 1995). Advantages of CT scans are its wide availability in any ED or hospital, speed (minutes to scan), and production of a high-quality image; however, disadvantages are a radiation dose and poor visualization of soft tissue and diagnosing diffuse axonal injury.

Although invasive ICP monitoring is widely accepted as standard of care in certain types of brain injury, namely TBI, using ICP-directed management of cerebral edema has not led to improved outcomes. In 2012 the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST-TRIP) trial was published. In this study, patients with severe TBI who had ICP monitoring and treatment to maintain ICP less than 20 mm Hg did not have better outcomes compared with those who received interventions based on serial imaging and clinical examination (Chesnut 2012). It is important to note that this study included patients with severe TBI from Bolivia and Ecuador, and it is possible that more severely injured patients may not have survived long enough to reach the hospital because of less developed prehospital resuscitation; thus, the whole study population may have been less severe than populations in higher-income countries. Recently, the International Prospective Observational Study on Intracranial Pressure in Intensive Care (SYNAPSE-ICU) trial of an international and diverse neurologically injured patient population (TBI, subarachnoid hemorrhage, ICH) found considerable variability ICP monitoring indications and use (Robba 2021). These results suggest that ICP monitoring could lead to a more aggressive therapeutic approach aimed at controlling ICP and may be associated with reduced mortality in the most severely ill. The important point is that serial imaging can accurately and quickly identify progressive cerebral edema and intracranial hypertension but must be guided by close neurologic monitoring.

## **STEPWISE APPROACH TO MANAGEMENT: PROPOSED ALGORITHM FOR ELEVATED ICP**

Several neurologic societies have proposed algorithms for the management of elevated ICP that generally follow a tiered approach (Figure 3). Although these algorithms are typically presented in a stepwise approach, it is important to note that interventions may be occurring simultaneously given the emergency nature of the disease. The key to management of intracranial hypertension is to consider the underlying neurologic disorder when choosing the best strategy.

## **NONPHARMACOLOGIC THERAPY**

### **Head Position and Cervical Collars**

In most patients with neurologic injury, head elevation has shown to reduce ICP without significantly impacting CPP (Feldman 1992; Durward 1983). One study found variable changes in ICP but more consistent reductions in CPP with the head elevated at 60 degrees, which the authors postulated to be caused in part by the patients' abdominal girth increasing the intrathoracic pressure and venous backpressure. For every 10-degree increase in head elevation, ICP decreased 1 mm Hg and CPP decreased 2–3 mm Hg (Rosner 1986). Therefore, a semi-recumbent position of up to 30 degrees is recommended in patients with elevated ICP or at risk for intracranial hypertension; however, CPP should be monitored to maintain 60 mm Hg or greater. In addition, for patients who have sustained a TBI, cervical collars should be used until a spinal cord injury is ruled out. Proper fit of the cervical collar is crucial; overtightening may prevent venous outflow and can contribute to ICP perturbations.

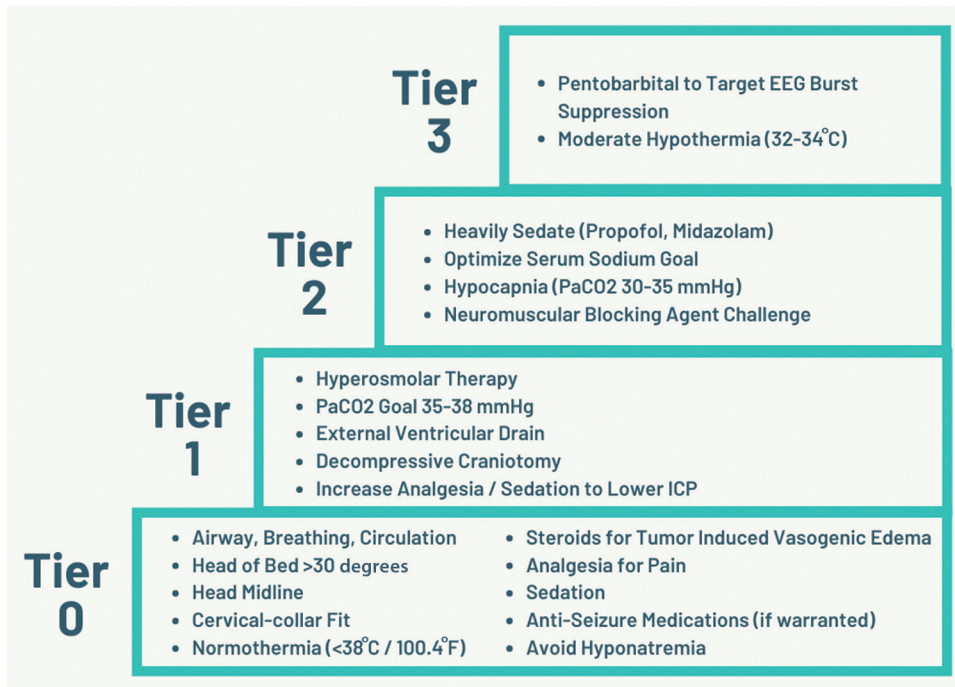
### **Hyperventilation to Induce Hypocapnia**

Hyperventilation to induce hypocapnia can reduce ICP immediately, but the effect may be transient. For each 1-torr reduction in PaCO<sub>2</sub>, a 2% decrease in CBF occurs because of cerebral vasoconstriction (Raichle 1972). Although this relationship provides a beneficial temporizing measure, the risk of worsening ischemia because of reduction in CBF and shifting the oxyhemoglobin dissociation curve to the left must be considered. In the setting of severe TBI, sustained extreme hyperventilation (PaCO<sub>2</sub> less than 30 mm Hg) for 5 days resulted in a significant reduction in favorable outcomes at 3 and 6 months (Muizelaar 1991). If available, brain tissue oxygen monitoring to sustain a near normal range (35–40 mm Hg) may be used to ensure adequate oxygen delivery (Dings 1996).

### **Surgical Considerations**

In the setting of refractory intracranial hypertension caused by mass effect or hydrocephalus, the neurosurgical team considers surgical interventions for EVD placement, mass evacuation, or decompressive hemicraniectomy (DHC). This section will focus on DHC; the section on ICP monitoring devices has more information on EVDs.

The cranial vault is an enclosed space in which brain tissue displacement and downward herniation can be relieved by performing a hemicraniectomy. In the setting of a malignant middle cerebral artery infarction with neurologic decline, early DHC (within 48 hours) is recommended for patients younger than 60 years (Wijdicks 2014). A systematic review reported that this approach improved good functional outcomes (Gupta 2004). In the setting of TBI, DHC is more controversial. Guidelines do not recommend DHC to



**Figure 3.** Stepwise approach to management of intracranial hypertension.

EEG = electroencephalograph; ICP = intracranial pressure; PaCO<sub>2</sub> = partial pressure of carbon dioxide.

Information from: Hawryluk GWJ, Aguilera S, Buki A, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). *Intensive Care Med* 2019;45:1783-94; Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017;80:6-15.

improve outcomes; however, DHC does reduce ICP and days in the ICU (Hawryluk 2020). If performed, a large DHC (greater than 15 cm diameter) is recommended to improve outcomes and reduce complications, such as shear stress along bony ridges, cortical vein compression, and worsening of swelling (Hawryluk 2020).

## Body Temperature

### Normothermia

Maintaining normothermia (less than 99.5°F [37.5°C]) is a widely accepted practice for managing patients with neurologic injury to mitigate further brain injury and intracranial hypertension. Elevated temperatures have been shown to exacerbate ischemic neuronal injury. In reperfusion injury models, hyperthermia has been postulated to be caused by increases in glutamate, which leads to mitochondrial dysfunction, increases in reactive oxygen species, and, ultimately, cellular death (Baena 1997). In addition, it is worth considering that core body temperatures slightly underestimate brain temperature because of local heat production through the high metabolic demand of the tissue (Rossi 2001). First-line treatment of fever should

include scheduled acetaminophen and external cooling blankets, but more invasive measures may also be necessary (Figure 4). For those who require an esophageal cooling device, it is important for the clinician to be cognizant of how hard the machine is working. An increase in the efforts of the cooling device may indicate the presence of an infection; therefore, an infectious workup should be completed. It is common for patients to experience shivering after initiation of first-line therapies, which will not only make it more difficult to attain goal temperatures, but significantly increase the patient's metabolic rate (Jain 2018).

### Hypothermia

In patients with refractory intracranial hypertension who have experienced failure of tier 0, 1, and 2 therapies (see Figure 3), mild-to-moderate hypothermia (89.6–92.3°F [32–34°C]) may be considered. Inducing hypothermia to this degree reduces ICP and increases CPP, but has not shown improved outcomes in patients with primary neurologic injury (Smrcka 2005). Approaches to inducing hypothermia (see Figure 4) and management of shivering (see Figure 5) are similar to maintaining normothermia as



# Monitoring

Record temperature hourly. Once goal temperature attained ( $\leq 37.5^{\circ}\text{C}$  /  $99.5^{\circ}\text{F}$ ) for 2 consecutive hours, monitor every 2 hours if non-invasive monitoring is being used.

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## 1st Line Therapy

Acetaminophen 650 mg every 4 hours (maximum daily dose is 4000 mg or 2000mg in those with hepatic disease); reassess every 48 hours for continuation. Check liver function tests at baseline and weekly.

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## 2nd Line Therapy

Apply external cooling blanket and ice packs to the groin, axilla, and neck if the temperature is  $>37.5^{\circ}\text{C}$  ( $99.5^{\circ}\text{F}$ ) one hour after the first acetaminophen dose.

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## 3rd Line Therapy

Administer cold IV fluids (500 to 1000mL 0.9% NaCl via large bore peripheral IV) if the temperature is  $>37.5^{\circ}\text{C}$  ( $99.5^{\circ}\text{F}$ ) one hour after the external cooling blanket was placed. Move directly to 4th line therapy if patient cannot tolerate volume.

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## 4th Line Therapy

If the patient is intubated, consider esophageal cooling<sup>a</sup>. If the patient is not intubated or needs additional IV access, consider intravascular cooling. When intravascular therapy is initiated remove all surface cooling methods.

**Figure 4.** Management algorithm for targeted temperature in patients with neurologic injury.

<sup>a</sup>Esophageal cooling device contraindications include esophageal varices, recent esophageal or gastric surgery, facial fractures, or basilar skull fracture.

described above. Counter-warming can be used in addition to pharmacologic therapy to reduce shivering (Figure 5). It is important to note that before continuing to brain death examination, patients must have a core body temperature greater than  $96.8^{\circ}\text{F}$  ( $36^{\circ}\text{C}$ ). If hypothermia was induced after cardiac arrest, evaluation of brain death should not be performed until a minimum of 72 hours after rewarming,

unless neuroimaging is suggestive of a devastating and irreversible neurologic injury (Wijdicks 2010). Given that hypothermia can reduce the clearance of medications, the pharmacist plays a critical role in assisting the team on deciding when it is appropriate to perform the brain death examination so that medications do not obfuscate the results.

Step	Medication	Metabolism/Excretion	Common Adverse Reactions	Special Considerations
1	<b>Buspirone 30 mg every 8 hours</b>	Renal	Dizziness, sedation, nausea, headache	CrCl <50 mL/min start a reduced dose of 15mg every 8 hours ----- CrCl ≤ 20 mL/min or ESRD avoid use
	<b>AND</b>			
	<b>Magnesium</b> (goal 3–3.5 mg/dl) If <2 mg/dl initiate maintenance infusion at 0.5 g/hr and titrate by 0.25 g/hr q4hr	Renal	Flushing, Hypotension, heart block, nausea/vomiting, hyporeflexia	CrCl ≤ 30 mL/min start infusion at 0.25 g/hr
2	<b>Dexmedetomidine:</b> Initiate at 0.2 mcg/kg/hr and titrate every 15 minutes to effect (max dose 1.4 mcg/kg/hr)	Hepatic	Bradycardia, hypotension, sedation	Opiate(s) may be preferred over dexmedetomidine in the setting of bradycardia or uncontrolled pain at baseline
	<b>OR</b>			
	<sup>a</sup> <b>Fentanyl:</b> Initiate at 25 mcg/hr and titrate to effect (max dose 250 mcg/hr)	Hepatic	Sedation, respiratory depression	Tachyphylaxis can be seen with prolonged use
	<b>OR</b>			
	<b>Meperidine:</b> 12.5–75 mg IV or IM every 4 hours as needed (0.5 mg/kg/dose)	Hepatic/Renal	Sedation, hypotension, nausea/vomiting, respiratory depression, seizures	Normeperidine, an active metabolite of meperidine, can lower the seizure threshold. If possible avoid scheduled use and do not use in those with severe renal impairment (≤ 20 ml/min)
3	<sup>a</sup> <b>Propofol:</b> Initiate at 20 mcg/kg/min and titrate to effect (max dose 80 mcg/kg/min)	Hepatic	Hypotension, bradycardia, respiratory depression, hypertriglyceridemia	Higher doses may be required (50–75 mcg/kg/min) to achieve shivering control ----- Monitor triglycerides daily if receiving >50 mcg/kg/min ----- EN may need to be adjusted due to caloric content
4	<sup>a</sup> <b>Neuromuscular Blockade</b>	Refer to institutional neuromuscular blockage guideline		

**Figure 5.** Example protocol for shivering management.

CrCl = creatinine clearance; EN = enteral nutrition; ESRD = end stage renal disease; IV = intravenous; max = maximum; q = every.

<sup>a</sup>Patient must be intubated prior to initiating therapy.

Information from: Choi HA, Ko SB, Presciutti M, et al. Prevention of shivering during therapeutic temperature modulation: the Columbia anti-shivering protocol. *Neurocrit Care* 2011;14:389-94.

## OSMOTHERAPY

### Hypertonic Sodium Solutions

The three types of sodium containing solutions used in the treatment of elevated ICP are sodium chloride, sodium acetate, and sodium bicarbonate. Solutions concentrated greater than that of 0.9% sodium chloride, which contains 9 g/L of sodium or 154 mEq/L of both sodium and chloride, can be considered *hypertonic saline* (HTS). Sodium chloride consists of a 1:1 ratio of sodium and chloride ions with a molecular weight of 58.44 g/mol. In solution the pH ranges from 4.5 to 7.0. Physiologically, sodium (135–145 mEq/L) and chloride (100–110 mEq/L) serve as the principal extracellular cation and anion in the blood that contribute to maintaining tonicity. Both molecules distribute highly in plasma and interstitial fluid with minimal intracellular distribution (Yunos 2010). Both are primarily excreted by the kidneys with a majority of both ions being reabsorbed in the proximal tubule. Common preparations are 3%, 5%, 7.5%, 14.6%, and 23.4% HTS. Chloride-sparing solutions that can be used for ICP management are sodium acetate and sodium bicarbonate. Through hepatic metabolism, the former is ultimately converted to bicarbonate, even in the presence of severe hepatic disease; therefore, these agents will be discussed together herein with any specific differences noted.

#### *Mechanism of Action*

##### Osmotic Effect

*Cerebral edema* can be defined as a nonspecific pathologic swelling of the brain caused by excess fluid within either brain cells or extracellular spaces, which contributes to elevated ICP (Cook 2020b). Under normal physiologic conditions, serum and intracellular osmolality are in near equilibrium resulting in a constant cell volume. In the setting of hyponatremia, a volume-regulatory adaptation occurs and initially shunts extracellular cerebral volume into the CSF, which drains into the systemic circulation. Thereafter, potassium and cerebral osmolytes are shifted extracellularly to maintain the osmolar gradient. Once these adaptive processes fail, cerebral edema ensues, which is why avoiding or treating hyponatremia is generally accepted as the rule (Kumar 1998). The practice of attaining supraphysiologic serum sodium levels in part is to create an osmotic gradient between the central and peripheral compartments. However, aiming for hypernatremia is highly debated and may not have a proven physiologic rationale. The transport of solutes across the blood brain barrier (BBB) is a selective process that depends on the osmotic reflection coefficient (RQ). Sodium chloride has a RQ of 1, indicating almost complete exclusion from intact BBB (Favre 1996). After administration of HTS, an osmolar gradient is created resulting in a shift of cerebral water from the interstitial and intracellular spaces of the brain into the vasculature by osmosis (Favre 1996). Wisner et al. assessed brain water content (mL water/g dry

weight) after induction of hemorrhagic shock in mechanically brain injured rats, comparing HTS (6.5%) to lactated Ringer solution. The brain water content was reduced by HTS in the uninjured hemisphere, but not in the injured brain (Wisner 1990). Dehydration of the uninjured cortex is hypothesized to be one of the main driving forces after HTS boluses that results in a reduction of mass effect and ICP (Doyle 2001).

##### Plasma Expansion and Cerebral Microcirculation

Dehydration of uninjured cerebral tissue explains the sustained reductions in ICP after HTS administration, but about 20–30 minutes are required to form an osmolar gradient. Immediate ICP reductions are hypothesized to be caused by the rapid expansion of plasma volume that occurs during HTS administration. These findings are corroborated by earlier studies evaluating HTS resuscitation in the setting of circulatory shock. If diluted solely in the plasma volume of a euvolemic animal (40 mL/kg), the administration of 7.5% HTS (4 mL/kg) would theoretically increase the plasma sodium to 263–268 mEq/L from normonatremia (Rocha-e-Silva 2005). However, these concentrations are not measurable unless a 1 mL/kg bolus of 30% NaCl is administered over 10 seconds, which would result in a rate of infusion far exceeding the standard 5–10 minute administration rate of similar concentrations. At 2 minutes, the sodium concentrations were found to be about 152 mEq/L between 3 doses (1 mL/kg 30% NaCl over 10 seconds, 4 mL/kg 7.5% NaCl over 1 minute, or 4 mL/kg 7.5% NaCl over 2 minutes) (Rocha-e-Silva 2005). The redistribution of the extravascular compartment increases plasma volume in a stepwise fashion; first from red blood cells and endothelium, and subsequently the interstitium and tissue cells (Mazzoni 1988). This increase results in three important physiologic alterations that may result in improved CBF because of reduced vascular resistance, as follows: reduced red blood cell diameter, increased endothelial lumen size, and hemodilution. In addition, HTS acts as an arteriolar vasodilator because of direct relaxant effect on smooth muscle, thereby counteracting vasospasm and increasing CBF (Rocha-e-Silva 2005). If cerebral autoregulation is intact, ICP reduction is immediately observed because of acute plasma expansion, resulting in venoconstriction and reduced venous blood. This compensatory mechanism wanes over 20–30 minutes, allowing time for the osmolar gradient to form and sustain ICP control.

##### Immunologic and Antioxidant Properties

By limiting the inflammatory cascade after brain injury, HTS may aid in attenuation of secondary injury through reduced leukocyte migration and adherence to brain cells (Härtl 1997). In addition to its direct immunologic effects, HTS also aids in the restoration of normal cell polarity through correction of electrolyte imbalances in the damaged brain. The increase in extracellular osmolality results in an intracellular

shift of cerebral osmolytes (i.e., amino acids, polyhydric alcohols, and methyl amines) (Doyle 2001). Lastly, HTS may have inherent antioxidant properties further mitigating the inflammatory process. Mojtahedzadeh et al. compared the oxidative stress response after administration of mannitol 0.25–0.5 g/kg every 6 hours, 125 mL of 5% HTS every 6 hours, or 500 mL of 5% HTS infused continuously for 3 days. Use of HTS resulted in significant reductions in both reactive oxygen species and nitric oxide compared with mannitol. The greatest reduction occurred in the HTS continuous infusion group (Mojtahedzadeh 2014).

### **Efficacy Data**

The idea of reducing ICP by providing hyperosmolar therapies originated more than 100 years when researchers noted that administration of intravenous HTS in cats resulted in the collapse of the lumbar cistern. Thereafter, numerous compounds were investigated (e.g., 50% glucose, 50% sucrose, 50% magnesium sulfate, urea), but ultimately failed because of rebound intracranial hypertension after administration (Otvos 2014). No pharmacologic interventions to date have optimal characteristics – remaining intravascular, not crossing the BBB, and no unwanted toxicities. However, HTS is an attractive agent with a limited adverse effect profile. Guidelines provide the general recommendation that, if using HTS, the upper sodium concentration should be 155–160 mEq/L; however, efficacy may depend on the underlying neurologic injury (see Figure 1). However, no recommendations are provided on the dosing strategy of bolus administration versus continuous infusion because of a lack of evidence and because overall targeting sodium goals may not improve neurologic outcomes (Cook 2020b). The use of HTS in emergency scenarios as a temporizing measure to control ICP is a much less debated practice than that of prophylactically attaining a supraphysiologic serum sodium. The latter can be thought of as a means to preemptively reduce cerebral edema to reduce secondary injury. Prophylactic administration carries the risk of osmolyte accumulation in the injured areas with impaired BBB, resulting in rebound intracranial hypertension or the inability to acutely increase peripheral osmolarity as necessary in an emergency setting. A systematic review of patients with TBI found that the use of continuous intravenous infusions of HTS was associated with higher hospital survival, although no benefit is apparent in long-term outcomes. Although further research is necessary to understand how to best use HTS, this chapter will discuss the current approaches to dosing, common adverse drug effects, and methods to reduce adverse drug effects.

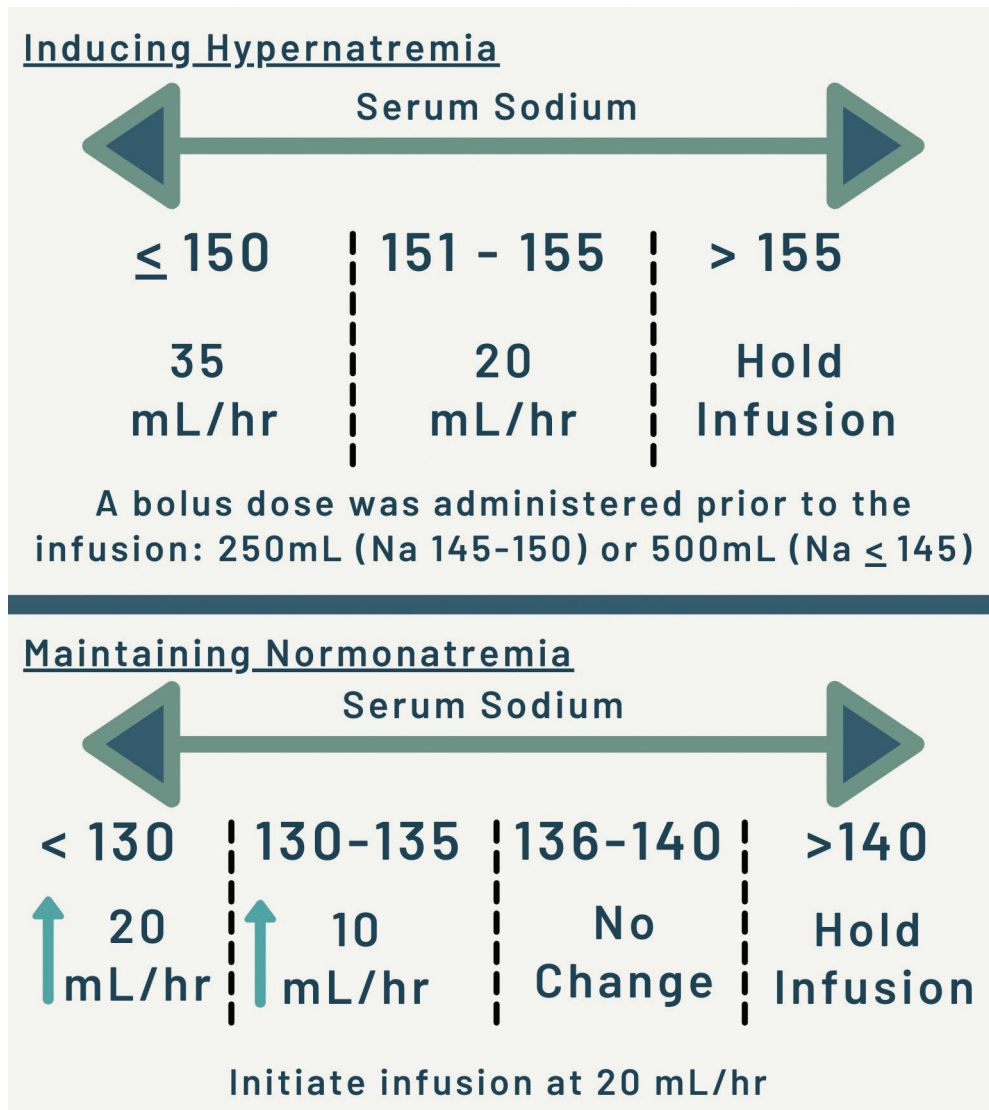
### **Dose and Administration**

Dosing of HTS depends on the clinical scenario. Targeting supraphysiologic serum sodium concentrations (greater than 145 mEq/L) is a topic of much debate and stems from initial research with mannitol. Initially, it was believed that

targeting 310–320 mOsm/L with mannitol would optimize the osmolar gradient while mitigating the risk of renal failure (Bullock 1995). The osmolality theory was extrapolated to target a higher serum sodium (150 mEq/L) to achieve similar osmolality (Qureshi 1998). In general, the presence and severity of symptoms largely determines the pace of correction required. Because of interpatient variability, the dose of HTS needed to attain a specific sodium goal may vary greatly. Depending on the clinician's institution, modifying the HTS continuous infusion may be performed by the provider only, but a few examples of sliding-scale protocols can be considered (Figure 6) (Woo 2009). In patients who are actively herniating or experiencing intracranial hypertension (ICP greater than 20 mm Hg for more than 5 minutes), 30 mL of 23.4% HTS should be administered as an intravenous bolus over 5–10 minutes if central access is available, such as a peripherally inserted central catheter, central venous catheter, femoral catheter, or a tunneled central venous access device (Figure 7) (Faiver 2021; Hirsch 2012).

Usual practice for administration of 23.4% HTS is by central access, but the approach may differ based on local practice. A retrospective study found the administration of 23.4% HTS by peripheral venous access in 57 administrations to be safe, with one case of extravasation and one report of pain (Faiver 2021). Although these data provide some insight on the safety of administering 23.4% HTS peripherally, it is not encouraged, given that alternative options have more robust data and provide similar results. In patients without central access, 2.5 mL/kg of 3% HTS is equiosmolar and can be infused peripherally over 15 minutes at a rate of 999 mL/hour on an intravenous pump (see Figure 7). Administering HTS over shorter durations can result in transient hypotension caused by a decrease in systemic vascular resistance, but this decrease is followed by an increase in MAP and cardiac contractility (Qureshi 2000). Anecdotally, we have observed cardiac arrest with return of spontaneous circulation when 23.4% HTS was inadvertently administered as an intravenous push over 1 minute.

The practice of administering peripheral infusions of 3% HTS varies by institution, and it may be discouraged based on having an osmolarity of 1027 mOsm/L. It is generally accepted that the use of a central line for administration is warranted when the osmolarity of an intravenous solution exceeds 800–900 mOsm/L. This principle is mostly extrapolated from parenteral nutrition administration data because increased local reactions were noted with osmolarity greater than 900 mOsm/L over a period of days to weeks (Isaacs 1977). Osmolarity infusion rates (milliosmoles/hour) was found to correlate well with phlebitis rates ( $r=0.95$ ), and in patients who received 84 mOsm/hour, phlebitis occurred in 4% at 48 hours (Timmer 1991). This osmolarity rate would be comparable to receiving 3% HTS at a rate of 80 mL/hour. Several retrospective studies have found the administration of 3% HTS peripherally to be safe, although duration,



**Figure 6.** Examples of 3% hypertonic saline protocols.

Information from: Woo CH, Rao VA, Sheridan W et al. Performance characteristics of a sliding-scale hypertonic saline infusion protocol for the treatment of acute neurologic hyponatremia. *Neurocrit Care* 2009;11:228–34, Roquilly A, Moyer JD, Huet O, et al. Effect of continuous infusion of hypertonic saline vs. standard care on 6-month neurological outcomes in patients with traumatic brain injury: the COBI randomized clinical trial. *JAMA* 2021;325:2056-66.

dosing, and administration characteristics were heterogeneous among studies (Jannotta 2021; Dillon 2018; Perez 2017; Jones 2016).

Intraosseous (IO) is another route of administration that is used for medications and blood products during emergency situations because access can be obtained within minutes and a first-attempt success rate is as high as 90% (Leidel 2009). The IO access is established by use of a battery-powered handheld drill or a spring-loaded device at the site of a long bone (proximal humerus, proximal or distal tibia) or the sternum. In the setting of controlled hemorrhage

with shock, the Institute of Medicine Committee on Fluid Resuscitation for military combat casualties recommends 250 mL of 7.5% HTS IO with a maximum of 500 mL, but data are conflicting on the safety of IO HTS administration in animal models and in the civilian setting. Whereas one swine model found increased risk of soft tissue or bone necrosis, another observed no alterations in gait, gross tissue necrosis, microscopic ischemia, or necrosis for 5 days after IO administration of 250 mL of 0.9% NaCl, 3% HTS, or 7.5% HTS (Alam 2002). A case series that included two pediatric patients who received 3% HTS IO during critical care

	20% Mannitol	3% HTS	23.4% HTS	8.4% Sodium Bicarb
<b>Equiosmolar Dose</b>	0.5 g/kg	2.5 mL/kg	30 mL	1 mL/kg
<b>Osmolality (mOsm/L)</b>	1098	1027	8008	2000
<b>Infusion Site</b>	Central or PIV	Central or PIV	Central	Central or PIV

### Considerations for PIV Administration

- 2 PIVs should be in place
- Utilize the smallest bore needle (18 or 20 gauge preferred) in the largest vessel at least 2 inches above the wrist and in no areas of flexion
- assess and document site every 2 hours (including blood return)
- if no blood return, infusion site must be changed
- infuse up to a maximum rate of 50mL/hr
- If extravasation occurs the infusion should be stopped, aspirate the IV cannula, immobilize and raise the limb above the heart, and administer hyaluronidase with either a warm or cold compress

**Figure 7.** Comparison of osmotherapy agents and administration considerations.

HTS = hypertonic saline; IV = intravenous; PIV = peripheral intravenous.

Information from: Hawryluk GWJ, Aguilera S, Buki A, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). *Intensive Care Med* 2019;45:1783–94; Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017;80:6–15; Al-Benna S, O'Boyle C, Holley J. Extravasation injuries in adults. *ISRN Dermatol* 2013;2013:856541.

transport demonstrated no adverse site reactions (Luu 2011). A prospective observational case series of five neurologically injured patients who received 3% HTS as an IO continuous infusion (25–100 mL/hour) for up to 24 hours observed no access site adverse events nor reported the experience of severe pain by patients (Lawson 2019).

### Adverse Effect Profile

#### Osmotic Demyelination Syndrome

Acute changes in serum sodium create a concern for an irreversible process known as *osmotic demyelination syndrome* (ODS). Historically, this syndrome was referred to as *central pontine myelinolysis*, given involvement of the pons; however, extra-pontine locations are identified in up to 53% of cases (Gocht 1987). Symptoms often include acute changes in mental status, progressive spastic quadriparesis, and pseudobulbar palsy, which is characterized by dysarthria, dysphagia, facial and tongue weakness, and emotional lability. Ultimately, ODS can result in coma and death (Gocht 1987). In addition to acute changes in serum sodium, another predisposing risk factor to development of ODS may be concomitant hypokalemia. Reduced Na<sup>+</sup>/K<sup>+</sup>ATPase concentrations on the endothelial cell

membrane may predispose cells to injury by osmotic stress associated with rapid rises in serum sodium (Lohr 1994). The risk of ODS is of more concern in those patients are severely hyponatremic, but administering HTS may be acceptable in those who are actively herniating. There are no reports of ODS in patients who are relatively normonatremic and receive HTS for ICP management.

#### Coagulopathies

Coagulopathies are more of a concern with administration of HTS fluids in the setting of uncontrolled hemorrhagic shock because of the potential for hemodilution secondary to plasma volume expansion and impedance of fibrin formation and platelet function (Doyle 2001). These hematologic aberrations are more likely to occur when greater than 10% of the normal plasma is replaced by HTS (Qureshi 2000). One team compared the effects of 15% mannitol and HTS (2.5% or 3.5%) on blood coagulation using thromboelastometry in healthy adults (Luostarinen 2011). Overall, clot formation and strength were less affected in the HTS groups, and the authors concluded that 2.5% HTS may be more favorable than 15% mannitol in the neurocritically ill population.

## Electrolyte Abnormalities

Hyperchloremia (chloride greater than 110 mEq/L) and hypobicarbonatemia (bicarbonate less than 20 mEq/L) have been reported to occur at rates of 50% and 10%, respectively, for patients receiving 3% HTS (Jones 2016). Chloride, the body's principal anion, is provided as an equiosmolar concentration with HTS (513 mEq/L in 3% HTS or 856 mEq/L in 5% HTS), which can result in hyperchloremia and has been associated with increased rates of acute kidney injury, length of stay, and in-hospital mortality (Haller 2020). Hypokalemia has also been found to occur at similar rates as hyperchloremia because of exchange of sodium with potassium in the renal distal tubules. To mitigate the risk of developing profound hyperchloremia in neurocritically injured patients, buffered HTS solutions (1:1 mixture of sodium chloride and sodium acetate or bicarbonate) can be used. To ensure tonicity and osmolality of the compounded buffered solution is maintained, it is vital to use

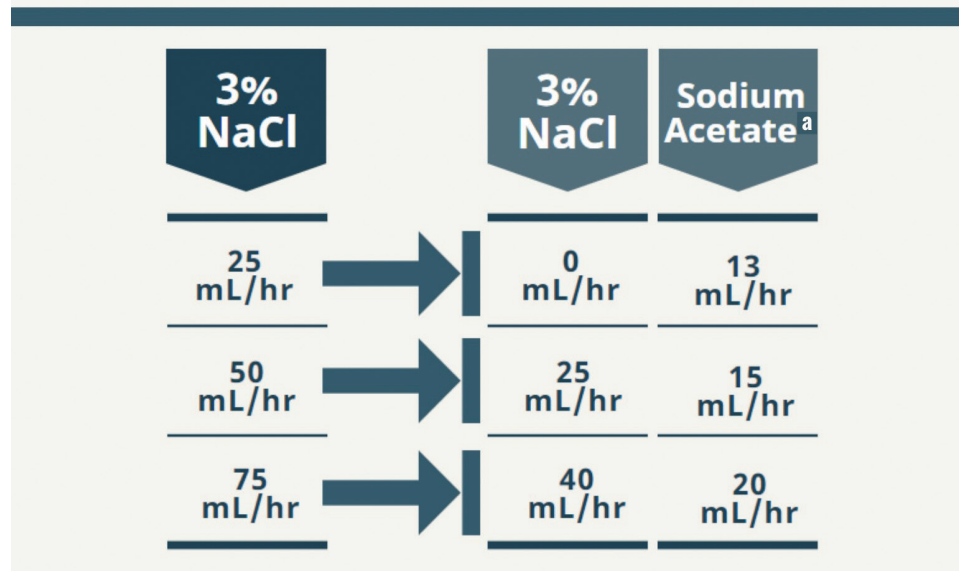
**Table 1.** Formulas for Compounding Balanced Hypertonic Sodium Solutions

Sodium or Water	2% NaCl/ Acetate	3% NaCl/ Acetate
Sodium chloride 4 mEq/ mL	85 mEq (21.25 mL)	128 mEq (32 mL)
Sodium acetate 2 mEq/ mL	85 mEq (42.5 mL)	128 mEq (64 mL)
Sterile water	436.25 mL	404 mL

milliequivalents rather than grams (Table 1) (Cook 2020a). If in-house compounding of a buffered HTS is not feasible, an alternative is to infuse both 3% HTS and a chloride-sparing solution (Figure 8).

Consider modification if chloride  $\geq 115$  mmol/L

**Step 1** | Choose the rate of 3% HTS to infuse  
**Step 2** | Select the correlating sodium chloride / sodium acetate rates



**Figure 8.** 3% Hypertonic saline mixed solution conversion for hyperchloremia.

<sup>a</sup>Sodium acetate 240 mEq in sterile water 250 mL. If serum bicarbonate is greater than 35 mEq/L after transition to mixed solution, reduce sodium acetate by 5 mL/hour and increase 3% NaCl by 10 mL/hour.

HTS = hypertonic saline; NaCl = sodium chloride.

## **Mannitol**

The most common formulation of mannitol for the treatment of elevated ICP is mannitol 20% solution for injection. According to the package insert, mannitol has a molecular weight of 182 kDa and is in solution with a pH range of 4.5–7 with a calculated osmolarity of 1098 mOsmol/L. Primarily excreted by glomerular filtration, mannitol has limited reabsorption in the kidneys. The 20% concentration is the best balance between high osmolarity and solubility at room temperature. When mannitol is exposed to low ambient temperatures, the solution may crystallize. If crystals are visually present in the product at the time of administration, the product should not be used; however, measures can be taken to eliminate the crystals before later administration. According to the package insert, when crystals are present when packaged in a vial, the vial may be gently warmed to redissolve the crystals, either in a warm water bath or with gentle manual rolling. Alternatively, if crystals are present when using mannitol bags, the solution should be heated using a dry-heat cabinet with overwrap intact. Because of the potential for recrystallization with changes in ambient temperature, mannitol concentrations 20% or greater should be infused using a 0.22-micron inline filter.

### ***Mechanism of Action***

#### **Osmotic Effect**

As mentioned, mannitol has an osmolarity of 1098 mOsmol/L and creates a significant osmotic gradient between the brain and the serum. Once the osmotic gradient is established, water moves across the BBB into the vascular compartment; subsequently, ICP decreases by reducing brain water content, which causes a reduction in perilesional edema (Donato 1994). The osmotic effect of mannitol appears to begin within 15 minutes and peak effects occur between 30 and 120 minutes (Sorani 2008). The duration of the osmotic effect has been documented to last 1–6 hours and varies based on the clinical conditions and renal elimination of mannitol (Sorani 2008).

#### **Plasma Expansion and Cerebral Microcirculation**

Plasma volume expansion occurs within minutes of administration of 20% mannitol (Barry 1961). This increased plasma volume has been linked to enhancing cardiac output and MAP after mannitol infusion (Mendelow 1985). In addition, there is an immediate decrease in hematocrit and increase in red blood cell deformability, which leads to an overall reduction in viscosity; this subsequently improves CBF through the cerebral microvasculature (Muizelaar 1983). With intact autoregulation, when CBF is increased, vasoconstriction of the cerebral arteries occurs. This vasoconstriction maintains the already increased CBF; however, it will reduce cerebral blood volume and thus result in a decrease in ICP (Donato 1994). This mechanism is thought to be the more immediate

of the two, reducing ICP within 5 minutes and the effect is thought to last about 2 hours (Muizelaar 1983).

### ***Efficacy Data***

With the similarities in mechanisms of action between mannitol and HTS, traditionally the clinical efficacy has been noted to be similar. Historically, it was difficult to compare HTS to mannitol because comparison studies did not use equiosmolar doses but instead used equal volumes of the two agents. Studies comparing equiosmolar doses of the two osmotherapy options suggest that HTS has greater impact on ICP reduction or ICP burden (Mangat 2015).

More recently, several meta-analyses have been performed to combine all the small clinical studies to evaluate the overall treatment effect. As more evidence is published, the scales continue to tip in favor of using HTS over mannitol; however, as mentioned in the cerebral edema guidelines, no high-quality evidence (using Grading of Recommendations Assessment, Development and Evaluation methodology) is available to support one hyperosmolar agent over the other (Cook 2020b). It is important to note that hyperosmolar therapy is being used to reduce ICP and should not be used with the expectation of improving neurologic outcomes (Cook 2020b; Carney 2017).

### **Dose and Administration**

For osmotherapy in general, clinicians want to administer a high osmolar load over a short period. Historically, mannitol was administered as a continuous infusion with the premise that continuous osmolar withdrawal of brain water may maximize the therapeutic effect. Research now demonstrates that continuous infusion of mannitol is not optimal, and contemporary practice is to infuse mannitol as a rapid intravenous bolus to maximize plasma expansion and potentiate the cerebral venoconstriction response. The safety of rapid infusion mannitol has been established; however, hypotension is a common adverse effect and is more likely to occur if the bolus is administered over a short period of time (less than 5 minutes) (Cruz 2004). To prevent hypotension, slower infusions of 10–20 minutes are recommended and have been shown to successfully reduce ICP (Cruz 2004).

In evaluation of studies that report dose-response data, mannitol doses less than 0.5 g/kg appear to have reduced efficacy and duration of action (Sorani 2008). Studies demonstrate a more significant reduction in ICP and more durable response when using mannitol doses ranging from 0.5–2.5 g/kg (Sorani 2008; Cruz 2004). As mentioned previously, most of the safety data and recommendations on the osmolarity cutoff for peripheral intravenous administration are from parenteral nutrition data. At an osmolarity of 1098 mOsmol/L, administering mannitol through a central line is preferred when available; however, clinicians should not hesitate to infuse mannitol peripherally in



emergency situations because of the short time that the vessel is exposed to this osmolality (see Figure 7).

### **Adverse Effect Profile**

#### **Acute Kidney Injury**

Mannitol-induced acute kidney injury (AKI) is a well described adverse effect. The incidence of mannitol induced AKI varies with the type of neurologic injury and definition of AKI used; however, the incidence is estimated to be between 6% and 12% (Lin 2015; Gondim 2005). Predisposing factors for AKI include advanced age, history of hypertension, sepsis, hypovolemia, hypotension, concomitant nephrotoxic agents, and pre-existing renal disease (Gondim 2005). Potential mechanisms of mannitol-induced AKI include histologic alterations, consisting of proximal and distal tubular cells vacuolization (termed *osmotic nephrosis*), increased sodium delivery to the macula densa which may trigger an intense tubuloglomerular feedback response reducing glomerular filtration and afferent arteriolar renal vasoconstriction.

Mannitol-induced AKI is usually transient and reversible with cessation of administration; the development of AKI appears to be concentration-related, given that the condition appears to be aggravated if mannitol accumulates because of incomplete clearance (Dorman 1990).

Historically, to monitor for the risk of AKI, a measured serum osmolality threshold of 320 mOsm/kg was used. Recently, the Guidelines for Acute Treatment of Cerebral Edema by the Neurocritical Care Society recommends using the osmolar gap (OG) over serum osmolality during mannitol treatment (Cook 2020b). The OG is the difference between the measured serum osmolality (mOsm/kg) and the calculated serum osmolality (mOsm/L) (García-Morales 2004). This measure best correlates with serum mannitol concentration, which is associated with toxicity. An OG less than 20 appears to be the most reliable indicator for mannitol clearance, and thus reduced risk of nephrotoxicity. However, various reports of a mannitol-nephrotoxicity case series suggest that the risk of developing AKI is highest when OG exceeds 60–75 mOsm/kg and that the occurrence of AKI with an OG less than 55 is rare (Visweswaran 1997).

#### **Electrolyte Abnormalities**

Mannitol has variable effects on serum electrolyte concentrations. Hyponatremia can develop after inadequate volume resuscitation in the setting of free water loss caused by mannitol osmotic diuresis (Gipstein 1965). Acute hyponatremia may occur immediately after mannitol administration and begins to return to baseline about 180 minutes after drug administration (Seo 2017). Intracellular potassium may passively move out of the cell in response to cellular dehydration, leading to clinically relevant hyperkalemia (Ropper 2012). Conversely, mannitol may cause hypokalemia secondary to the osmotic diuresis.

#### **Rebound Intracranial Hypertension**

Although debated, a theoretical risk exists for a phenomenon called *rebound intracranial hypertension*, which is associated with mannitol administration. The rebound phenomenon has been hypothesized to be caused by interstitial and intracellular accumulation of mannitol in the brain, producing a reversed osmotic gradient between the blood and interstitial space in the brain, which causes water to be drawn back into the brain. The osmotic reflection coefficient (RQ) for mannitol is 0.9, slightly lower than the RQ of 1 for sodium, which indicates incomplete exclusion from an intact BBB, meaning that a small amount of mannitol may become confined inside the BBB, thereby reversing the osmotic gradient. However, the most likely mechanism of mannitol accumulation is the existence of a disrupted BBB surrounding injured or peri-tumoral brain tissue (Palma 2006). The avoidance of long-term mannitol administration and the use of appropriate osmolar gap monitoring may prevent this theoretical rebound effect. Clinicians should be wary of the potential for rebound effects of mannitol after prolonged consistent mannitol use (more than 2–3 days) or in patients with suspected BBB disruption.

#### **Summary and Place in Therapy**

Given the importance of timing when treating acutely elevated ICP, it is reasonable to advocate that either osmotherapy agents (given at an equiosmolar dose, see Figure 7) should be used and that preference should be given to the agent that can be obtained most quickly. Other considerations for favoring one agent over the other include the serum sodium and osmolar gap. However, if both agents are readily available, HTS appears to have a more sustained effect on ICP.

## **SEDATION AND ANALGESIA**

Management of agitation through appropriate selections of analgesic and sedative medications is vital in the management of patients with neurologic injuries. If untreated, agitation can exacerbate ICP excursions (e.g., increasing thoracic pressure and systemic blood pressure) and worsen ischemic injury through increasing the cerebral metabolic rate and cortical spreading depolarization. Whereas the former is coupled to CBF, the latter occurs after mass depolarization of neurons propagating from the core injury and places a large energy burden on brain tissue to restore electrochemical equilibrium (Oddo 2016).

The level of sedation required depends on the extent of ICP elevations, and, as noted in Figure 3, ranges along a continuum from initial management to salvage therapies (i.e., pentobarbital). Propofol is a preferred first-line sedative when patients are intubated, given its rapid “on/off” abilities as well as its short context-sensitive half-life. An added benefit is that propofol has a more consistent dose-dependent reduction in CBF, and in turn decline in cerebral metabolic rate, compared with benzodiazepines (Oddo 2016). Given

that propofol may also reduce MAP, it is important to monitor CPP when initiating or aggressively titrating propofol to control ICP. If sedation and/or ICP goals are not being met with propofol, then an alternative agent can be midazolam, which may provide more hemodynamic and CPP stability. Both agents have the disadvantage of tachyphylaxis with prolonged infusions. In addition, prolonged infusions of high-dose midazolam have altered pharmacokinetics with a terminal half-life of 24–48 hours (Bodmer 2008; Naritoku 2000). Ketamine may offer a distinct advantage in patients with spreading depolarization (Hertle 2012). Given that studies have shown ketamine does not increase ICP, it may be an agent that warrants further investigation. Fentanyl is common as a first-line analgesic, and hydromorphone may be considered as an alternative in patients who develop tachyphylaxis. Although remifentanyl has been shown to have significantly faster and more predictable awakening for neurologic assessment, favoring its use in the setting of ICP management would be cost-prohibitive (Karabinis 2004).

## NEUROMUSCULAR BLOCKERS

Inducing paralysis is often reserved as a tier 2 strategy to treat intracranial hypertension that may be caused by posturing, ventilator dyssynchrony, or increases in thoracic or abdominal pressures (see Figure 3). No definitive data support one agent versus another, but pharmacokinetic parameters of the neuromuscular-blocking agents should be considered, including route of elimination, active metabolites, histamine release, and tachycardia associated with vagal inhibition. Agents that should be avoided include succinylcholine and atracurium. Succinylcholine is not recommended for prolonged neuromuscular blockade, and data are mixed regarding whether succinylcholine can increase ICP. Atracurium is known to form the byproduct laudanosine, which can increase the risk of seizures (Smetana 2017). One approach when initiating neuromuscular blockade is to trial a bolus dose of rocuronium and observe if an effect on ICP occurs. If there is a reduction in ICP, cisatracurium can be initiated and titrated to 1 to 2 twitches with train-of-four monitoring.

## PENTOBARBITAL

### Mechanism of Action

Sedation and analgesia are an important aspect of care when managing elevated ICP; however, barbiturates are reserved as a tier 3 therapy for patients with ICPs refractory to conventional therapy (see Figure 3). In addition to the general benefits of sedation (preventing unnecessary movements, coughing and straining), the ICP-lowering effect of barbiturates are believed to be caused by the coupling of CBF to regional metabolic demands. By suppressing cerebral metabolism, barbiturates reduce cerebral metabolic demands, thus reducing cerebral blood volume required to

maintain appropriate oxygenation and reduce ICP (Roberts 2012). In the United States, the barbiturate of choice for refractory ICP treatment is pentobarbital; although thiopental has also been evaluated, it is currently not available in the United States.

### Efficacy Data

One of the first randomized controlled trials in patients with TBI compared the prophylactic use of pentobarbital to standard of care (Ward 1985). This study found no significant differences in mortality or Glasgow Outcome Scale score at 1 year; however, 54% of the patients in the pentobarbital arm developed hypotension (systolic blood pressure less than 80 mm Hg) compared with 7% in the control arm ( $p < 0.001$ ). Given these results, the current recommendation by the Brain Trauma Foundation is that pentobarbital should not be given as prophylaxis against the development of intracranial hypertension (Carney 2017).

After this first trial, a five-center randomized controlled trial was conducted to evaluate the influence of high-dose pentobarbital therapy with elevated ICP refractory to other treatments in patients with a GCS score 4–8 (Eisenberg 1988). Patients were randomized to continue conventional therapy or initiate pentobarbital (10 mg/kg over 30 minutes, 5 mg/kg every 1 hour for 3 doses, or 1 mg/kg/hour continuous infusion adjusted to achieve a level of 30–40 mcg/mL) in conjunction with conventional therapy. Because of trial design, which allowed patients in the control arm to cross over into the pentobarbital arm, the primary outcome was ICP control, but mortality was also assessed. The odds of ICP control were two times greater with pentobarbital treatment and the likelihood of survival for barbiturate responders was 92% at 1 month compared with 17% for nonresponders. The most recent Cochrane Review was completed in 2012 and included seven studies. Conclusions were that barbiturate therapy may reduce ICP, but no evidence supports an association with a reduction in death or disability (Roberts 2012). In addition, they concluded that the hypotension associated with barbiturate therapy may offset any beneficial ICP-lowering effect on CPP. Despite this meta-analysis finding, treating patients with refractory ICP remains challenging. The current recommendation by the Brain Trauma Foundation is that high-dose barbiturate administration is recommended to control elevated ICP refractory to maximal standard medical and surgical treatment after hemodynamic stability is achieved (Carney 2017).

### Adverse Effect Profile and Drug Interactions

See the chapter on refractory status epilepticus for the adverse effect profile and notable drug interactions.

### Limitations

In addition to the adverse effects with pentobarbital administration, the prolonged drug half-life is another significant

## Patient Care Scenario

A 68-year-old woman (89.8 kg [198 lb]) presents after a right middle cerebral artery ischemic stroke. Unfortunately, she presented outside the time window for tissue plasminogen activator, and she does not meet criteria for a mechanical thrombectomy. The patient is hemodynamically stable and on the ventilator with minimal settings.

On hospital day 3, the bedside nurse calls the neurosurgery intern to report a change in neurologic examination. The nurse reports the following:

- GCS score decreased from 12 to 7

### ANSWER

First, you should recognize that this patient has had an acute change in her neurologic examination. The nurse notes that her overall neurologic status has worsened, as noted by changes in her GCS score and her National Institutes of Health Stroke Scale score, indicating that her stroke symptoms have evolved; and she no longer has brainstem reflexes, evidenced by the loss of her gag and cough reflex. In addition, you have objective data to follow with the change in her NPi values from the pupillometer. Based on the device packaging, measured NPi values range from 0.0–4.9 and a value of less than 3.0 is considered an abnormal or sluggish response.

Given that the patient had a previous right middle cerebral artery stroke, two factors may have caused her acute neurologic change: a hemorrhagic conversion or cerebral edema. Given the time over which this acute change has occurred (on hospital day 3), the most likely cause of her neurologic worsening is evolving cerebral edema. These abrupt changes are a concern and should alert you that this patient has developed worsening cerebral edema to the point that her ICP is likely elevated. The neurosurgery intern's order for emergency CT of the head is appropriate;

- National Institutes of Health Stroke Scale score increased from 8 to 18
- Gag and cough reflexes are now absent
- NPi decreased from 4.2 to 2.1 in the right eye and 4.3 to 2 in the left eye

The team wants to send the patient for emergency CT of the head; however, another patient is currently in the CT scanner. What caused this acute change in neurologic examination? What is best to recommend to the neurosurgery intern while the patient is waiting for her CT scan?

however, given these data you should empirically treat this patient for an ICP crisis.

Next, you should remind the intern about all the tier 0 interventions (see Figure 3) that are relevant for this patient, including the following: head of bed elevation to more than 30 degrees, midline head placement, analgesia and sedation as needed for comfort on the ventilator, and ensuring the patient is not hyponatremic and that she is normothermic at less than 100.4°F (<38°C). In addition, as you are waiting for the CT scanner to become available, encourage the team to maintain a PaCO<sub>2</sub> of 35–38 mm Hg and to initiate hyperosmolar therapy.

This patient should receive a bolus dose of mannitol or HTS. According to the cerebral edema guidelines, either agent would be appropriate in a patient who has developed cerebral edema secondary to an acute ischemic stroke. If mannitol is chosen, the patient should receive mannitol 90 g (1 g/kg) intravenously as a single dose given over 15 minutes; if HTS is chosen, the patient could receive 23.4% sodium chloride 30 mL intravenously as a single dose given over 5–10 minutes as an intravenous push or 3% sodium chloride 225 mL (2.5 mL/kg) intravenously as a single dose given over 15 minutes (see Figure 7).

1. NPi-200 Pupillometer [package insert] Irvine, CA: NeuroOptics, 2015.

2. Hawryluk GWJ, Aguilera S, Buki A, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). *Intensive Care Med* 2019;45:1783-94.

3. Cook AM, Morgan Jones G, Hawryluk GWJ, et al. Guidelines for the acute treatment of cerebral edema in neurocritical care patients. *Neurocrit Care* 2020;32:647-66.

limitation to its use. The half-life is estimated to be 15–50 hours, with an average in healthy adults of 22 hours (Ehrnebo 1974). As mentioned, pentobarbital can reduce ICP and lead to patient survival; however, in some cases, the patient's ICP remains refractory to high-dose barbiturate therapy, and herniation will occur. Brain herniation syndrome is usually notable for an extreme increase in ICP, followed by Cushing triad (hypertension, bradycardia, irregular respirations), and, lastly, normalization of the ICP. When a patient has herniated and is considered dead by neurologic criteria, it is imperative to ensure that all severe acid-base, electrolyte, and endocrine abnormalities are corrected before brain death examination. In addition, it is critical to ensure

that pentobarbital is eliminated from the patient's system to the best of the clinical pharmacist's ability to calculate the elimination time. The recent publication by the World Brain Death Project recommends allowing 5 elimination half-lives (assuming normal hepatic and kidney function) to ensure drug elimination before testing for brain death by neurologic criteria (Greer 2020). In the setting of pentobarbital, this duration can be anywhere from 75–250 hours or 3–10 days. Pentobarbital concentrations are no longer recommended to guide dosing; however, if pentobarbital serum testing is readily available, measuring drug concentrations for patients with altered pharmacokinetics may aid to appropriately schedule brain death testing. When obtaining a

pentobarbital concentration, clinicians must ensure that the concentration does not exceed the therapeutic range or, even if in the therapeutic range, it is not thought to confound the clinical examination (Greer 2020). For pentobarbital specifically, the lower limit of the therapeutic range is 10 mcg/mL; however, consensus is lacking on a minimum concentration threshold for pentobarbital to determine brain death (Drake 2017). If drug concentration testing is not readily available or waiting for the concentration to decrease into the therapeutic range is not ideal, ancillary testing or imaging can be performed, including cerebral angiogram, nuclear perfusion scan, CT angiography, magnetic resonance angiography, or transcranial doppler. Ancillary testing should only be completed if all prerequisites for clinical examination have been met and all evaluable components of the clinical examination are consistent with brain death (Drake 2017). These imaging techniques will identify if any blood flow to the brain is present. Ancillary tests to assess blood flow are based on the hypothesis that if blood flow to the brain is absent for a substantial period of time, then there can be no brain function.

### Place in Therapy

The use of high-dose pentobarbital is reserved for patients with refractory ICP who have experienced failure with conventional treatment modalities is discussed throughout this chapter. If initiated, the Eisenberg dosing protocol should be used; however, contemporary practice no longer adjusts the continuous infusion rate to target a serum pentobarbital concentration. Instead of targeting a serum concentration, monitoring the cerebral electrical activity by a continuous EEG and maintaining burst suppression (1–2 burst per screen) is recommended (Pérez-Bárcena 2008). If an ICP crisis occurs, a mini-bolus (1–5 mg/kg) of pentobarbital should be administered and the continuous infusion rate should be subsequently increased by 1 mg/kg/hour. After the ICP is controlled for 48 hours, the pentobarbital continuous infusion should be weaned over 72 hours, reducing the rate by about 50% every 24 hours (Pérez-Bárcena 2008; Eisenberg 1988). If the ICP increases during the weaning process, the patient can be re-loaded, and the continuous infusion rate should be increased to the last effective dose, with plans to repeat the wean when ICP is controlled for another 48 hours.

### CONCLUSION

Elevated ICP is considered a medical emergency in a neuro-ICU because the consequences of sustained elevations are disastrous. It is important to understand the various tools used to identify this intracranial crisis. Although several guidelines are available to address cerebral edema and the management of elevated ICP in patients with TBI, gaps remain in the available evidence for how best to treat elevated ICP and how to ensure safe and efficient access to potentially life-saving therapies for clinicians at the bedside. Despite

### Practice Points

Elevated ICP is a difficult and sometimes elusive condition to treat. The lack of concrete evidence, guidelines, and algorithms to treat elevated ICP is a challenge for the clinical pharmacist when assisting the team in caring for these patients. It is important that the pharmacist understand the urgency of treating elevated ICP, the tools used to identify this condition, and the armamentarium of nonpharmacologic technique and pharmacologic agents available to treat this medical emergency:

- Neurocritical Care Society recently published guidelines on the role of hyperosmolar agents, corticosteroids, and selected nonpharmacologic therapies in the treatment of cerebral edema. This attempt is the first that a multidisciplinary group has made to summarize the available data for the use of these agents and to provide a graded level of recommendation for these interventions.
- Elevated ICP can occur in various types of brain injury. Often, the “Guidelines for the Management of Severe TBI” by The Brain Trauma Foundation is the resource for all patients with elevated ICP. It is important to note that these guidelines have been transitioned to be a living document, which will be updated in real time as more research is conducted in the area of the management of severe TBI.
- Various tools are available to assist with the diagnosis of elevated ICP. It is important to know what devices are available at the clinician’s institution and any local procedures and policies that concern the use of those devices.
- A standardized approach to interpreting data and implementing treatment is key to managing patients with ICP crisis. Although in theory a stepwise approach is ideal, simultaneous intervention is often implemented; however, a broad division of tiered therapy is generally used.
- Given the importance of timing when treating acutely elevated ICP, either sodium chloride or mannitol should be used, with preference given to the agent that can be obtained the most quickly. Other considerations for favoring one agent over the other include the serum sodium concentration and osmolar gap. However, if both agents are readily available, HTS appears to have a more sustained effect on ICP.
- Management of agitation through appropriate selections of analgesic and sedative medications is vital in the management of patients with neurologic injuries because untreated pain and agitation can exacerbate ICP excursions. Propofol is a preferred first-line sedative given its rapid “on/off” characteristic, and it has a dose-dependent reduction in CBF and cerebral metabolic rate. For pain, fentanyl is a commonly used first-line analgesic, and hydromorphone is considered an alternative for patients who develop tachyphylaxis.
- Pentobarbital is considered a tier 3 therapy and should be reserved for patients with refractory ICP for whom conventional treatment modalities have failed. If initiated, the Eisenberg dosing protocol should be used to target burst suppression on the EEG. A significant limitation to the use of this therapy is that one may need to wait several days for the drug to be sufficiently eliminated from the system to complete brain death testing if it is thought a patient has herniated while receiving pentobarbital drip.
- Research in the area of treating elevated ICP continues to evolve. It is important to remain aware of the most up-to-date approaches; however, the information in this chapter is considered the foundation of the pharmacotherapy used.

these efforts, however, it is vital to understand that treating ICP has not been shown to improve neurologic outcomes. As more research is conducted on multi-modal monitoring and individualization of ICP treatment, further advancement in this area is promising.

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# Self-Assessment Questions

1. You have been asked to provide an intracranial pressure (ICP) management update to the neurocritical care faculty at your institution. Which one of the following is most important to include in your update?
  - A. The Neurocritical Care Society Cerebral Edema Guidelines found, with a high level of evidence, that scheduled mannitol should be avoided in patients with acute ischemic stroke because of concern for harm.
  - B. The Fourth Edition of the Brain Trauma Foundation guidelines recommend that mannitol be used over hypertonic saline to control ICP in traumatic brain injury (TBI) patients.
  - C. Neurocritical Care Society Cerebral Edema guidelines found, with a very low level of evidence, that hypertonic saline should be used over mannitol in either a symptom-based or a sodium target-based approach.
  - D. The Fourth Edition of the Brain Trauma Foundation guidelines recommend that ICP should be treated if greater than 20 mm Hg is sustained for more than 5 minutes.
2. A 59-year-old man with no contributory medical history presents to the ED with seizures. After completing a CT scan, it is noticed that the patient has high-pressure hydrocephalus. Neurosurgery is called to the bedside to evaluate for placement of an ICP monitoring device. Which one of the following is best to recommend for this patient?
  - A. A parenchymal monitor, the device is subject to zero drift.
  - B. An external ventricular drain (EVD), the device is dependent on patient positioning.
  - C. A parenchymal monitor, it is easy to place.
  - D. An EVD, it is capable of draining CSF.
3. A 41-year-old woman with a history of methamphetamine use presents after being found unresponsive and is found to have a central pontine hemorrhage. On presentation, the patient is intubated, a cervical collar was placed on scene, with extensor posturing, bilateral fixed pupils, and a Glasgow Coma Scale score of 4. Which one of the following is best to recommend for the management of this patient?
  - A. Ensure she is in Trendelenburg position.
  - B. Administer dexamethasone 10 mg intravenously once.
  - C. Hyperventilation with a goal partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) of 20–25 mm Hg.
  - D. Administer hyperosmolar therapy.

## Questions 4–6 pertain to the following case.

C.S., a 23-year-old man (weight 72 kg [158.7 lb], height 68 inches [172.7 cm]) with a medical history of asthma, presents after being found unresponsive and pulseless with subsequent return of spontaneous circulation (ROSC) after three rounds of cardiopulmonary resuscitation. After arrival, the patient lost a pulse again and achieved ROSC after one round of advanced cardiac life support. A non-contrast head CT found diffuse loss of gray-white differentiation, diffuse edema with sulcal effacement and effacement of the ventricles, and early signs of herniation. Current access is intraosseous (IO) as placed by emergency medical services en route and a 24-gauge peripheral intravenous catheter in C.S.'s wrist.

4. Due to concerns for elevated ICP and herniation, C.S.'s care team is requesting 30 mL of 23.4% sodium chloride (30 mL over 5–10 minutes). Which one of the following alternative agents would provide an equiosmolar dose and is best to recommend for C.S.?
  - A. 3% Sodium chloride 2.5 mL/kg
  - B. 8.4% Sodium bicarbonate 50 mL
  - C. 4.2% Sodium bicarbonate 1 mL/kg
  - D. 3% Sodium chloride 100 mL
5. Despite optimizing analgesia and sedation, C.S. is reported to have uncontrollable shivering and the team is concerned it is contributing to his elevated ICP. Which one of the following is best to recommend to help control C.S.'s shivering?
  - A. Initiate buspirone 5 mg/day.
  - B. Administer succinylcholine to temporarily achieve paralysis.
  - C. No intervention is necessary because shivering cannot increase ICP.
  - D. Provide skin counter-warming.
6. On hospital day 3, C.S. is noted to have an acute change in his left NPi (3.5–1) and is bradycardic and hypertensive. Which one of the following hyperosmolar therapy strategies is best to recommend for C.S.?
  - A. 23.4% Sodium chloride 30 mL by 24-gauge peripheral intravenous catheter in wrist
  - B. 23.4% Sodium chloride 30 mL by central venous catheter
  - C. 23.4% Sodium chloride 30 mL IO
  - D. 23.4% Sodium chloride 60 mL by central venous catheter

## Questions 7–12 pertain to the following case.

T.W., a 49-year-old man (weight 120 kg [264 lb]), is admitted to the neurocritical care unit with TBI after a motor vehicle crash. On arrival, he receives mannitol 50 g intravenously as

a single dose and is started on 3% sodium chloride at 25 mL/hour for a goal sodium of 145–155. Neurosurgery places an intraparenchymal monitor at the bedside when T.W. arrives at the ICU.

7. On day 3 of T.W.'s hospitalization, the nurse reports that his ICP values have been sustained around 30 mm Hg for about 5 minutes. The team calls a brain code and wants to administer 23.4% sodium chloride. On arrival to the bedside, you notice that T.W.'s ICP values are around 30 mm Hg and the resident is actively placing a central line. Due to hospital policy, you cannot allow the team to administer the 23.4% sodium chloride until the central line is placed and verified. You quickly discuss with the team that they can administer 3% sodium chloride or mannitol by the patient's existing peripheral line. They state that they do not care which is given and asks you to assess and place the order. T.W.'s pertinent laboratory values are serum sodium 155 mEq/L, serum chloride 120 mEq/L, and SCr 0.7 mg/dL. Calculated osmolarity is 320 mOsm/kg and measured osmolality is 335 mOsm/kg. Which one of the following best assesses T.W.'s osmolar gap?
- 0
  - 5
  - 10
  - 15
8. Based on T.W.'s osmolar gap and sodium level, you decide to administer mannitol. Which one of the following is the best equiosmolar dose of mannitol to substitute for T.W.'s 30 mL of 23.4% sodium chloride?
- 30 g
  - 60 g
  - 120 g
  - 180 g
9. T.W. receives the mannitol dose. Which one of the following best assesses how this agent will affect T.W.'s ICP?
- Mannitol establishes an osmotic gradient that decreases ICP within 5 minutes.
  - Mannitol increases plasma volume and decreases ICP for about 2 hours.
  - Mannitol is an osmotic diuretic and works to decrease ICP by reducing total body water.
  - Mannitol increases plasma volume and decreases ICP by reducing cerebral blood flow (CBF).
10. After administering mannitol to T.W., you see the ICP decrease immediately. Applying what you know about the mechanism of action of mannitol and the Monro-Kellie hypothesis, which one of the following components adapted initially to lead to the initial reduction in T.W.'s ICP?
- Brain tissue
  - CSF
  - Intracranial blood
  - Anoxic brain tissue
11. After the central line is placed, T.W. receives the 23.4% sodium chloride 30 mL dose as well as the mannitol dose you recommended. The patient's ICP values show no response to conventional therapy, and neurosurgery states the patient is not a decompressive hemicraniectomy candidate. After the team has a long discussion with the family, the decision is made to initiate pentobarbital. The pentobarbital bolus dose arrives to the bedside. Which one of the following is most important to discuss with the nurse on T.W.'s care team?
- It is important for the nurse to draw pentobarbital levels as scheduled to ensure the patient's level is not toxic.
  - The propylene glycol present in the pentobarbital can lead to significant hypotension when the bolus dose is administered.
  - A common adverse effect of pentobarbital is hyperthermia and surface or intravascular cooling devices may be needed.
  - Pentobarbital lowers ICP by increasing cerebral metabolic demands, thus reducing cerebral blood volume.
12. After T.W. receives the total bolus dose the continuous infusion is started at 1 mg/kg/hour. The neurosurgery resident covering the patient overnight asks you, as the clinical pharmacist, how to titrate the drip overnight if the patient has an ICP crisis. Which one of the following is best to recommend for T.W. with each ICP spike?
- Give a mannitol dose of 25 g and increase the pentobarbital rate by 0.25 mg/kg/hour.
  - Give a mini-bolus of pentobarbital (50 mg) and increase the pentobarbital rate by 1 mg/kg/hour.
  - Give a mini-bolus of pentobarbital (300 mg) and increase the pentobarbital rate by 1 mg/kg/hour.
  - Increase the pentobarbital rate by 0.25 mg/kg/hour.
13. A 41-year-old man (weight 80 kg [176 lb]) with no known medical history is hospital day 6 post-TBI. The patient has been receiving midazolam 40 mg/hour for the past 36 hours for ICP control and the care team decides to discontinue the midazolam infusion. At which of the following times would it be most likely that midazolam has cleared from this patient?
- 6 hours
  - 120 hours
  - 12 hours
  - Urine drug screen needed to assess intoxication

**Questions 14 and 15 pertain to the following case.**

L.A., a 48-year-old woman, presents with a large intracerebral hemorrhage with intraventricular extension. On day 2 the patient's ICP values remain elevated despite conventional ICP management therapies.

14. Which one of the following best justifies a recommendation of propofol for L.A.?
- A. Long half-life
  - B. Long context-sensitive half-life
  - C. Reduces CBF and in turn the cerebral metabolic rate
  - D. Provides no calories so no modifications to enteral nutrition are necessary
15. L.A.'s care team decides to administer a neuromuscular blocker to assess if it will reduce her ICP. Which one of the following dosing strategies is best to recommend for L.A.?
- A. Succinylcholine bolus dose
  - B. Rocuronium bolus dose
  - C. Vecuronium continuous infusion
  - D. Cisatracurium continuous infusion