

# MANAGEMENT OF ACUTE TRAUMATIC BRAIN INJURY



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## LEARNING OBJECTIVES

1. Use physical assessment and monitoring data (e.g., intracranial pressure [ICP], hemodynamics) to assess patients with traumatic brain injury (TBI) and develop treatment goals.
2. Develop a treatment plan with primary and secondary options for optimizing ICP and cerebral perfusion pressure in patients with TBI.
3. Develop a treatment plan for supportive care and management of potential and actual complications related to severe TBI (e.g., seizure prophylaxis, infection).
4. Evaluate the utility of selected nonpharmacologic interventions in patients with TBI.
5. Assess the current role of neuroprotective and coma arousal agents in the treatment of patients with TBI.
6. Analyze the role of the pharmacist in quality improvement in the care of patients with TBI.

## INTRODUCTION

Acute traumatic brain injury (TBI) continues to be a public health crisis in the United States. The Centers for Disease Control and Prevention estimates that 1.4 million Americans annually sustain a TBI severe enough to require medical attention. Mortality and morbidity rates caused by TBI are staggering. More than 50,000 people die annually after a severe TBI, and survivors of

severe TBI join more than 5 million Americans (2% of the entire population) living with TBI-related disability. Of note, mortality from TBI is the leading cause of death in children and adults aged 1–44 years. The economic impact of TBI in the United States is also enormous: the 2006 medical and societal costs were about \$60 billion.

Because most deaths occur within the first 2 weeks after injury, it is imperative that optimal care be provided to patients with TBI if morbidity and mortality rates are to be reduced. Traumatic brain injury can be classified as mild, moderate, or severe; this chapter focuses on moderate and severe TBIs, which typically require hospital admission.

Brain damage and death after an acute TBI are consequences of both primary and secondary brain injury. *Primary brain injury* refers to the initial biomechanical events occurring at the moment of impact. *Secondary injury* is the delayed brain insult that occurs in the minutes, hours, and days after the primary injury.

The most common mechanisms of injury in patients with TBI are motor vehicle crashes, followed by sports injuries, assaults, and falls (especially in the elderly). Men are about twice as likely as women to sustain a TBI. Prevention is the most effective strategy for avoiding the enormous emotional, physical, and economic burdens of both primary and secondary brain injuries. However, once a moderate or severe TBI occurs,

## BASELINE REVIEW RESOURCES

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Heegaard W, Biros M. Traumatic brain injury. *Emerg Med Clin North Am* 2007;25:655–78.
- Boucher BA, Timmons SD. Acute management of the brain injury patient. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York: McGraw-Hill, 2011:1019–31.
- Valadka AB, Andrews BT. *Neurotrauma: Evidenced-Based Answers to Common Questions*. New York: Thieme, 2005.

## ABBREVIATIONS IN THIS CHAPTER

BTF	Brain Trauma Foundation
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CT	Computed tomography
GCS	Glasgow Coma Scale
ICP	Intracranial pressure
PaCO <sub>2</sub>	Arterial partial pressure of carbon dioxide
PbrO <sub>2</sub>	Brain tissue oxygen tension
SjO <sub>2</sub>	Jugular venous oxygen saturation
TBI	Traumatic brain injury
VTE	Venous thromboembolism

stabilizing the patient and attenuating secondary injury are the foci of medical interventions. Restoring neuronal function also is a target for pharmacologic and nonpharmacologic measures to improve outcomes in patients with TBI.

Treatment guidelines for severe TBI are published jointly by the Brain Trauma Foundation (BTF), the American Association of Neurological Surgeons, and the Congress of Neurological Surgeons. The most current guidelines (2007) are available free on the BTF Web site ([www.braintrauma.org](http://www.braintrauma.org)). These guidelines (hereafter referred to as the BTF guidelines) rate recommendations as level I (a standard of practice reflecting a high degree of clinical certainty), level II (a moderate degree of certainty), or level III (an unknown level of certainty). The guidelines also give detailed directions for using each therapy.

### Pathophysiology

Primary brain injury results from either contact or inertial forces to the head that exceed the brain's ability to sustain the insult. Contact forces commonly result in skull fractures, brain contusions, and/or hemorrhages. Inertial forces are generally a consequence of acceleration and deceleration and may result in focal or diffuse brain injuries. Because primary injuries are essentially irreversible, the focus of TBI pathophysiology research has largely been on secondary brain injury.

Secondary brain injury is a result of a complex interplay of biochemical mediators that have the potential to extend the injury beyond the primary insult. Mediators implicated in secondary brain injury include oxygen free radicals, excitatory amines (most notably glutamate and aspartate), various cytokines, and other inflammatory substances. It is thought that ischemia after an acute TBI results in the release of these mediators, which disrupt cellular metabolism and function.

Hypoxia from compromised pulmonary ventilation is another important factor contributing to

secondary brain injury. Calcium and sodium influx into the cytosol of damaged neurons is believed to result in mitochondrial dysfunction and cytotoxic edema, respectively. These events can lead to propagation of the primary injury by lipid peroxidation, apoptosis, increased cerebral edema, and disruption of the blood-brain barrier, producing vasogenic edema.

Elevated intracranial pressure (ICP) is a result of increasing brain tissue volume within the nondistensible skull. Increased ICP can result in further decreases in cerebral bloodflow, perpetuating a cycle of events that is life threatening unless interrupted or reversed.

### Diagnosis/Clinical Presentation

The diagnosis of TBI is generally made by combining a history of external forces to the head with the presentation of diminished neurologic function and/or evidence of physical head trauma. The initial neurologic examination consists of assessing the Glasgow Coma Scale (GCS) and pupillary size and reaction to light. The GCS assesses three areas of central neurologic function: speech, eye opening, and motor movement; all are assessed with and without stimulation. Categories of TBI are based on GCS scores (3–8 = severe, 9–12 = moderate, 13–14 = mild, and 15 = normal). Other neurologic signs and symptoms include generalized seizures, posttraumatic amnesia, dizziness, moderate to severe headache, limb weakness, and paresthesia.

Physical examination findings in patients with TBI include skull fractures, scalp lacerations, and cerebrospinal fluid (CSF) otorrhea or rhinorrhea. Instability of vital signs, nausea, and vomiting may also be present. Computed tomography (CT) of the head is an extremely important tool for both confirming TBI and monitoring patients over time.

Initial laboratory tests that are generally performed in suspected TBI include an arterial blood gas, urine drug screen, blood alcohol concentration, and routine serum electrolytes; these aid in excluding other contributing causes of neurologic dysfunction. Recent data challenge the common assumption that blood alcohol concentration, even at concentrations above 200 mg/dL, significantly lowers the GCS score in patients with TBI. As such, clinicians should be wary of attributing an abnormally low GCS score solely to alcohol intoxication without investigating for a potential TBI.

### Prognosis

Predicting the short- and long-term outcomes of TBI is important in acute management of the patient, in counseling family members, and in estimating the use of rehabilitation resources. Initial postresuscitation GCS scores, CT findings, ICP values, pupillary reflexes, hypotension, and age are the most important predictors of outcome in patients with acute severe TBI. In particular, low postresuscitation GCS motor scores are a

significant prognostic indicator of poor outcome. Other predictors of poor outcomes are age older than 56 years and systolic blood pressure less than 90 mm Hg. The presence of subarachnoid hemorrhage, subdural hematoma, midline brain shift, and increasing hematoma sizes also predict poor outcomes.

Serum biomarkers in conjunction with clinical variables continue to garner attention relative to predicting outcomes. Neurotrophic protein S100B, the biomarker most studied in TBI, is a calcium-binding protein primarily produced by brain glial cells and released after an acute TBI. Elevated serum S100B concentrations are positively correlated with the extent of TBI and negatively correlated with outcome. However, the effect of blood-brain barrier disruption on serum S100B concentrations is troublesome because brain and serum concentrations are poorly correlated when the blood-brain barrier is intact. Furthermore, some experimental data show brain S100B may improve long-term cognitive function and may not be a negative determinant of outcome in TBI.

Neuron-specific enolase is another substance that may have potential utility as a biomarker on the basis of the positive association between neuron-specific enolase CSF concentrations and cerebral hypoperfusion. Although no biomarkers are yet routinely used in TBI management, they may be clinically useful in the future.

## TREATMENT PLAN

### System Support

Minimizing secondary brain injury in patients with moderate to severe TBI begins with effective pre-hospital care (i.e., establishing a patent airway and restoring breathing and circulation as quickly as possible). Hypotension in particular must be avoided because it has been associated with a 2-fold increase in mortality in patients having severe TBI. Similarly, hypoxia increases mortality by 14% to 50% and increases morbidity in patients who survive.

Once stable, it is imperative to transport the patient to the nearest level I or II trauma center, where immediate neurosurgical care can be rendered. In the trauma center, patients are typically cared for using the Advanced Trauma Life Support protocol. After stabilization, definitive treatment and monitoring should follow BTF guidelines because adherence to these evidence-based guidelines is associated with a reduction in morbidity and mortality. In addition to improving outcomes, using the BTF guidelines to guide therapy in the medical management of patients with acute TBI is cost-effective.

### Monitoring

#### ICP Monitoring

Intracranial pressure monitoring is indicated in all patients with severe TBI (GCS score 3–8) and CT

showing a brain injury, hematoma, or signs of intracranial hypertension (e.g., compressed ventricles). Monitoring is also indicated in patients with a severe TBI and normal CT if they have several risk factors including age older than 40 years, motor posturing, or hypotension (systolic blood pressure less than 90 mm Hg).

Either a ventriculostomy or an intraparenchymal monitor can be used to monitor ICP. Ventriculostomy is considered the first choice because of its high level of accuracy, ability to recalibrate, and ability to drain CSF to lower ICP, if necessary. Although a ventriculostomy is more invasive, overall complication rates with the two methods are similar. Newer parenchymal monitors are as accurate as a ventriculostomy; however, they cannot be used to lower ICP, and some models cannot be recalibrated. Subarachnoid, subdural, and epidural monitors are available but are not preferred because of their lower accuracy in measuring ICP.

#### Other Monitoring Modalities

Some centers have adopted the use of specialized oxygen measurements as an adjunct to ICP monitoring. The most common modality used is measurement of the jugular venous oxygen saturation ( $SjO_2$ ), a measure of global cerebral oxygen demand. The goal for  $SjO_2$  is a value greater than 50%. Direct parenchymal monitors that measure brain tissue oxygenation in a small area are also available. The goal for brain tissue oxygen tension ( $PbrO_2$ ) is 15 mm Hg or higher. These monitoring techniques are considered optional (level III) in the BTF guidelines. Low oxygen values with either method are related to poorer outcomes, but it is unclear whether the use of either method provides additional benefit when combined with ICP monitoring.

Noninvasive ICP monitoring is being studied using modalities such as radiologic techniques (e.g., ultrasonography), tympanic membrane displacement, near-infrared spectroscopy, and intraocular pressure measurement. However, none of these modalities is currently considered reliable enough to use clinically. Continuous electroencephalography concomitant with the measurement of somatosensory-evoked potentials has also been studied to monitor changes in brain function. One study suggested that such monitoring added important information in patients with ICP values ranging from 20 mm Hg to 40 mm Hg. It is hoped that continuing research will allow routine use of these techniques for more targeted monitoring and management than is currently achieved with global ICP monitoring.

#### Therapeutic Goals and Outcomes

After admission to the intensive care unit, the overall therapeutic goal is to recover or salvage as much neurologic function as possible. However, the short-term therapeutic targets are treating increased ICP and optimizing cerebral perfusion pressure (CPP). Cerebral

perfusion pressure is the difference between the mean arterial pressure (MAP) and the ICP (i.e.,  $CPP = MAP - ICP$ ). The ICP should be less than 20 mm Hg, and the target range for CPP is 50–70 mm Hg. Normally, cerebral bloodflow is kept fairly constant (i.e., autoregulated) over a wide blood pressure range. However, autoregulation is lost in some patients with TBI, and their cerebral bloodflow is highly correlated with CPP. Thus, these patients are at risk of cerebral ischemia if hypotension occurs.

Patients have poorer outcomes when their ICP is greater than 20 mm Hg or CPP is less than 50 mm Hg. Acutely, patients with frank hypotension and/or CPP less than 50 mm Hg should be treated with intravenous fluids and possibly vasopressors similarly to other critically ill patients with hypovolemia (Figure 1-1). However, after acute resuscitation, the overall fluid goal for patients with TBI is euvolemia. No attempt should be made to artificially increase the CPP to greater than 70 mm Hg with fluids or vasopressors. In one clinical trial, doing so did not improve outcomes and was associated with an increased risk of acute respiratory distress syndrome. Conversely, patients not receiving vasopressors with a CPP greater than 70 mm Hg after resuscitation do not require antihypertensive therapy to lower the CPP into the target range unless the blood pressure is dangerously high or is causing adverse sequelae (e.g., altered neurologic function, increased ICP).

## QUALITY PATIENT CARE

### Pharmacotherapy

#### *Intracranial Hypertension*

Treatment of elevated ICP is easily divided into first- and second-line therapies. In some cases, a second-line therapy may simply be an intensification of a first-line therapy. An algorithm for the management of elevated ICP is presented in Figure 1-2.

#### *Sedation/Analgesia*

Intravenous sedation and analgesia is a first-line therapy for treating intracranial hypertension. Patients with severe TBI are often agitated and require sedation regardless of their ICP. Because of the brain injury, it is not generally possible to determine whether the cause of agitation is pain or another reason. Thus, clinicians often empirically use opioids in addition to sedatives to provide pain control in case the patient is experiencing pain.

In addition to the general dangers of agitation in critically ill patients (e.g., pulling out intravenous lines, self-extubation), agitation in patients with TBI can increase ICP. In the acute phase of care when neurologic examinations must be performed several times throughout the day, propofol is widely regarded as the sedative of choice because of its rapid onset and short duration

of action. Propofol used concomitantly with morphine was shown in a small clinical trial to be superior to morphine alone for ICP control. However, the titratability of propofol must be balanced against many adverse effects, including propofol-related infusion syndrome (at dosages more than 5 mg/kg/hour) and effects related to its lipid vehicle (e.g., hypertriglyceridemia, infection, overfeeding). As with all sedatives, propofol can cause hypotension, which can be detrimental to CPP.

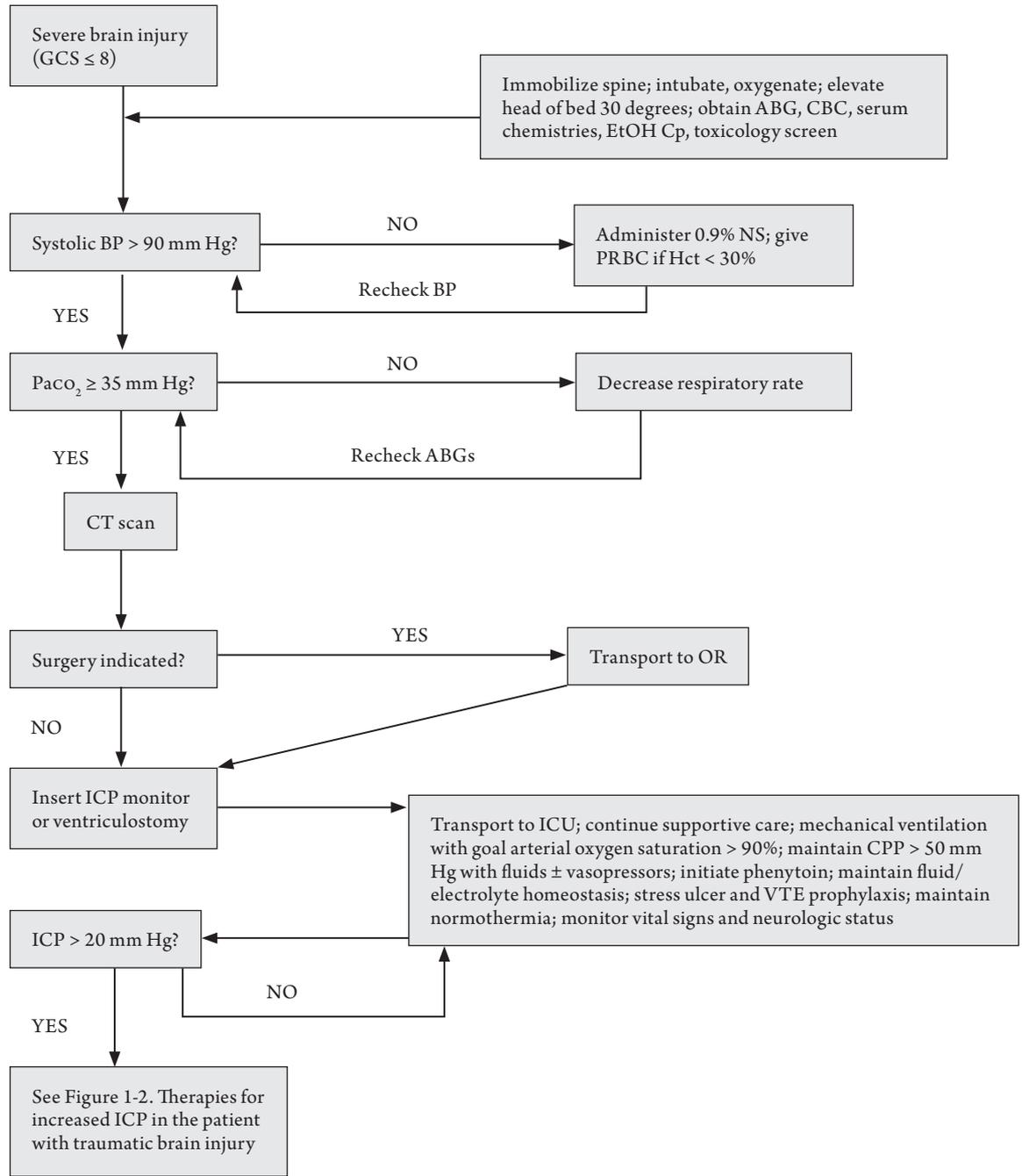
Benzodiazepines are also primary sedative options in patients with TBI. Midazolam is generally preferred to lorazepam early in the course of therapy because its shorter half-life allows easier titration and because it is used in most TBI studies. Despite being an effective sedative, midazolam does not effectively control ICP when used alone or when added to propofol therapy. Nonetheless, midazolam is widely used in patients who cannot receive propofol because of adverse events.

Continuous-infusion or intermittent-bolus morphine is the most widely used opioid for ICP control. Many clinicians prefer agents with a shorter duration of action such as continuous-infusion fentanyl or remifentanyl. Some controversy exists about the effect of opioids on ICP. Some studies suggest that intermittent bolus opioid doses are more likely to cause increased ICP; thus, it is preferable to use continuous infusions rather than bolus dosing when possible.

#### *Hyperosmolar Therapy*

The hyperosmolar agents mannitol and hypertonic saline (3% to 23.4% NaCl) are also first-line agents for treating acute increases in ICP. The primary mechanism of action for both agents is thought to be mobilization of water from the brain into the vasculature and subsequently from the cranial space through an osmotic gradient. However, there is some evidence that mannitol has additional positive rheologic effects, and hypertonic saline may affect a wide range of cellular systems (e.g., microvasculature, immune). Another possibility is plasma expansion that leads to an increase in cerebral bloodflow.

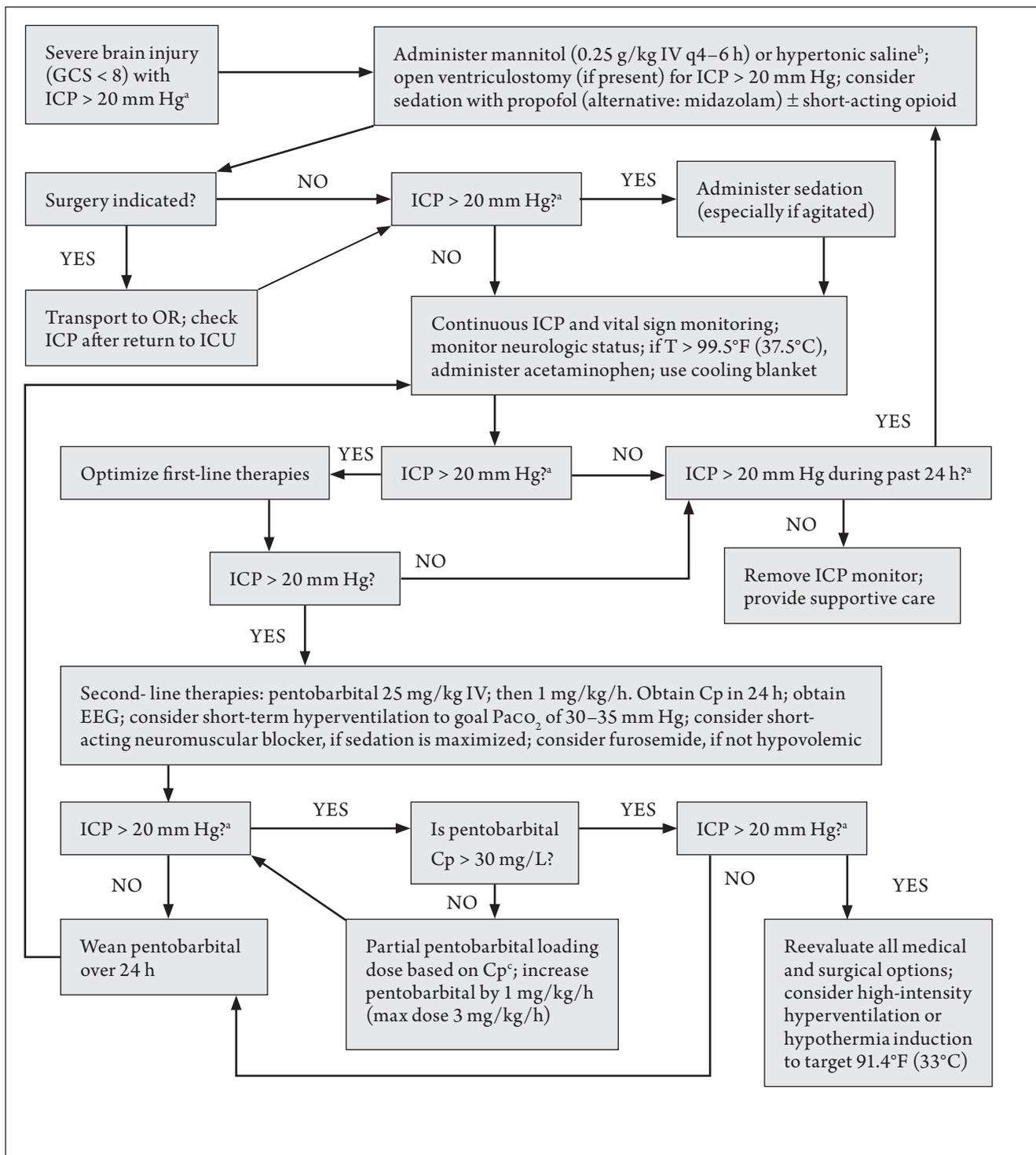
Traditionally, mannitol has been the preferred agent, and it is recommended in the BTF guidelines. Mannitol is given as an intravenous bolus at a dose of 0.25–1 g/kg and repeated as needed. However, a recent study showing that higher mannitol doses (1.4 g/kg) may be more effective than 0.7 g/kg calls into question the current dosing recommendation. Continuous-infusion mannitol therapy is not recommended. Adverse effects of mannitol include diuresis, acute kidney injury, and electrolyte abnormalities. Mannitol can cross the blood-brain barrier, which can negate its beneficial effects by leading to rebound increases in ICP. To avoid nephrotoxicity, mannitol should not be administered if the serum osmolality exceeds 320 mOsm/L.



**Figure 1-1.** Algorithm for the acute management of the patient with traumatic brain injury.

ABG = arterial blood gas; BP = blood pressure; CBC = complete blood cell count; Cp = plasma concentration; CPP = cerebral perfusion pressure; CT = computed tomography; EEG = electroencephalography; EtOH = ethanol; GCS = Glasgow Coma Scale; Hct = hematocrit; Hgb = hemoglobin; ICP = intracranial pressure; ICU = intensive care unit; IV = intravenous; NS = normal saline; OR = operating room; PaCO<sub>2</sub> = arterial pressure of carbon dioxide; PRBC = packed red blood cells; T = temperature; VTE = venous thromboembolism.

Adapted from Boucher BA. Neurotrauma: Pharmacotherapy Self-Assessment Program, 2nd ed. Module 2: Critical Care. Kansas City, MO: American College of Clinical Pharmacy, 1995:220.



**Figure 1-2.** Therapies for increased ICP in the patient with traumatic brain injury.

<sup>a</sup>ICP treatment thresholds: 20–29 mm Hg for longer than 15 minutes; 30–39 mm Hg for longer than 2 minutes; 40 mm Hg or higher for longer than 1 minute. Transient increases may occur after respiratory procedures (e.g., suctioning, chest physiotherapy, bronchoscopy, intubation).

<sup>b</sup>Hold hypertonic if serum osmolality greater than 320 mOsm/kg.

<sup>c</sup>Partial pentobarbital loading dose (mg) = [(30 mg/L – measured Cp) (1 L/kg x wt(kg))]. Patients with burst suppression on EEG may not require higher concentrations.

Cp = plasma concentration; EEG = electroencephalography; EtOH = ethanol; GCS = Glasgow Coma Scale; h = hours, ICP = intracranial pressure; ICU = intensive care unit; IV = intravenous; OR = operating room; PaCO<sub>2</sub> = arterial pressure of carbon dioxide; q = every; T = temperature.

Adapted from Boucher BA. Neurotrauma: Pharmacotherapy Self-Assessment Program, 2nd ed. Module 2: Critical Care. Kansas City, MO: American College of Clinical Pharmacy, 1995:215–38.

Mannitol is generally stored in a warming cabinet to avoid crystallization.

Hypertonic saline was not recommended in the 2007 BTF guidelines because of the lack of sufficient supporting data. However, many clinicians now consider it the first-line option because of the relatively large amount of data supporting its use. A recent meta-analysis concluded that hypertonic saline was more effective than mannitol for controlling ICP. In some studies, the duration of ICP lowering has been longer with hypertonic saline than with mannitol; however, a recent trial showed no difference between the two agents. The duration of action for both agents is about 2–6 hours.

Hypertonic saline has the added benefit of aiding with fluid resuscitation, which could be helpful in hypovolemic patients. This benefit is not seen with mannitol, which acts as an osmotic diuretic. A primary limitation to the use of hypertonic saline has been the variability in the dosing formulations and end points of therapy that preclude firm dosing recommendations. For example, the dosing regimens reported include 3% NaCl given in bolus volumes of 250 mL or 300 mL or by continuous infusion; 7.5% NaCl given in volumes of 100–250 mL or 1.5–2 mL/kg; and 23.4% NaCl given in a volume of 30 mL. In addition, electrolyte abnormalities are common with its use. Some investigators have used sodium lactate or acetate to avoid hyperchloremic acidosis.

Like with all patients, the same precautions regarding hypertonic saline apply to patients with TBI. Serum sodium concentrations should not be allowed to increase by more than 12 mEq/L in a 24-hour period (0.5 mEq/L per hour) to avoid neurologic adverse events. Hypertonic saline is typically not used if the serum sodium concentration exceeds 155 mEq/L.

#### *Barbiturates*

Barbiturates are recommended in the BTF guidelines as a second-line option for ICP control in patients who are refractory or have contraindications to first-line therapies. The guidelines specifically recommend pentobarbital, although thiopental showed equivalent ICP control in one small study. Two early studies showed no benefit to using prophylactic pentobarbital early in therapy; however, a subsequent study of patients with refractory ICP showed improved ICP control.

Of importance, hypotension is common with pentobarbital therapy, which may negate its beneficial effects on ICP if CPP is allowed to fall below the goal range of 50–70 mm Hg. Another limitation of pentobarbital is its very long half-life, which may preclude the performance of accurate neurologic examinations. Pentobarbital is administered as an initial loading dose of 25 mg/kg infused intravenously over 4 hours (an initial 10-mg/kg bolus infused over 30 minutes, followed by a 5-mg/kg/hour infusion for 3 hours). This is followed by a continuous infusion of 1 mg/kg/hour titrated to a serum

concentration of 30–40 mg/dL and/or burst suppression on electroencephalography. The drug can be tapered off during a 24- to 72-hour period after adequate ICP control has been achieved and maintained for 24–48 hours.

#### *Miscellaneous Agents*

Historically, loop diuretics have been used to mobilize water from the brain and decrease ICP. However, there are no clinical trials to support this practice, which is not addressed in the BTF guidelines. If used, loop diuretics should be considered second-line agents and reserved for fluid-overloaded patients. Loop diuretics are inappropriate in patients with TBI with hypovolemia.

Neuromuscular blockers have been used for additional ICP control in patients whose sedation dosages are maximized because of hypotension or dose limitations (e.g., propofol). There are no clinical trials or recommendations from the BTF on the use of neuromuscular blockers. However, in a patient whose ICPs are refractory to all other agents, it may be prudent to administer a neuromuscular blocker to see whether it has a positive effect on the ICP.

Recently, a small study examined the effectiveness of the arginine vasopressin antagonist conivaptan on decreasing ICP in a patient with severe TBI. A single conivaptan dose produced a significant decrease in ICP at 4 hours compared with no therapy. Similarly, a case report showed improved ICP control with one conivaptan dose. More data are needed to determine the role of this agent in the treatment of patients with TBI.

#### *Systemic Hypertension/Hypotension*

In addition to treating elevated ICP, blood pressure needs to be optimized to keep CPP in the desired range. In patients with severe TBI, hypotension (systolic blood pressure less than 90 mm Hg) is associated with worse outcomes, including higher mortality, and should be avoided if possible. Several episodes of hypotension further increase the risk of mortality. The ideal blood pressure in patients with TBI is unknown; however, a systolic blood pressure of 90 mm Hg should be considered the minimum threshold.

Hypotension should be treated initially with intravenous fluids. Crystalloids are generally preferred to colloids because there is a trend toward improved outcomes in trauma patients, easy availability, and lower cost with crystalloid therapy. The role of hypertonic saline as a resuscitation fluid is unclear: it has been studied more for its ICP-lowering properties than as a resuscitation fluid in patients with TBI. Vasopressors should be used in patients with persistent hypotension despite fluid resuscitation.

Patients with TBI may also develop hypertension. The BTF guidelines do not recommend a threshold

for treating hypertension. However, when therapy is needed, it is preferable to use a short-acting, rapid-onset agent to respond quickly to changes in hemodynamic status. Drug selection also depends on the need to affect the heart rate and, to a lesser extent, on cost. Nicardipine is effective in patients with TBI and hypertension and does not adversely affect brain tissue oxygenation.

### **Neuroprotective Strategies**

In addition to ICP and CPP management, many potentially neuroprotective agents have been studied to block the cascade of secondary brain injury. Hypotheses that supported trials for these drugs were focused on free radical scavenging, antioxidant and anti-inflammatory effects, or inhibition of neuronal calcium influx by various mechanisms. However, virtually all of the large clinical trials in this area have been unsuccessful.

Two recent prospective placebo-controlled trials of the use of progesterone in patients with TBI showed improved outcomes and lower mortality. Larger trials are under way to confirm these results. The exact mechanism of action is unclear, but there are progesterone receptors in the central nervous system, and the drug has neuroprotective properties in preclinical models.

Several novel agents have shown benefit in preclinical TBI models and are in development. These include new antioxidants, free radical scavengers, and calpain protease inhibitors. Of interest, some currently available agents may have beneficial effects in TBI. For example, statins have been effective in reducing functional neurologic deficits in preclinical TBI models. Exposure to  $\beta$ -blockers or erythropoietin has been associated with lower mortality in observational studies; however, the benefit of  $\beta$ -blockers has not yet been studied in a follow-up randomized trial.

### **Coma Arousal and Neurobehavioral Disorders**

There is an emerging body of literature on using drugs for coma arousal or improving neurologic function. Most studies in this area are small and uncontrolled. Methylphenidate has been shown in a few studies to improve cognitive function (e.g., memory, information processing), but it does not help behavioral problems. Preliminary clinical evidence suggests that agitation and aggression after the initial hospital stay could be treated with  $\beta$ -blockers. A limited number of studies suggest that the dopaminergic agents amantadine, bromocriptine, and levodopa/carbidopa promote awakening. A recent randomized trial with amantadine in the rehabilitation phase (i.e., more than 4 weeks after injury) showed promising results in overall recovery. Alternatively, neuroleptic agents can delay cognitive recovery. The BTF guidelines do not address the use of these agents. This area of clinical treatment is extremely important, requiring further research.

## **Nonpharmacologic Interventions**

### **Head Positioning**

Several nonpharmacologic interventions are useful in optimizing ICP and CPP management. It is theorized that raising the head of the bed can facilitate cerebral venous outflow and decrease ICP. Although head positioning is not addressed in the BTF guidelines, evidence suggests that raising the head of the patient's bed 30 degrees can lower ICP and increase CPP compared with supine positioning. Elevations of 15 degrees, 30 degrees, and 60 degrees have been studied, and 30 degrees appears to be optimal. Elevating the head of the bed 30 degrees should be considered a standard therapy for all patients with severe TBI. However, patients must be hemodynamically stable before raising the head of the bed to avoid hypotension and a decreased CPP.

### **Hyperventilation**

Hyperventilation is widely used to treat increased ICP; however, there is little evidence to support its use. Hyperventilation decreases ICP by decreasing arterial partial pressure of carbon dioxide ( $P_{aCO_2}$ ), which causes cerebral vasoconstriction and decreases cerebral blood volume. However, care must be taken to avoid aggressive hyperventilation ( $P_{aCO_2}$  of 25 mm Hg or lower), which can cause cerebral ischemia. Prophylactic hyperventilation is not recommended because worse outcomes resulted from its use in a landmark clinical trial. The BTF guidelines give hyperventilation the lowest-level recommendation (grade III) as an option for treating acute episodes of intracranial hypertension.

Hyperventilation should not be used during the first 24 hours after injury because reduced cerebral bloodflow can occur in patients with TBI during this time. The BTF guidelines also recommend using  $S_jO_2$  or brain tissue oxygen monitoring if hyperventilation is used. A typical goal for the initial use of acute hyperventilation is a  $P_{aCO_2}$  of 30–35 mm Hg. Temporary use of higher-intensity hyperventilation ( $P_{aCO_2}$  of 25–30 mm Hg) may be employed for acute ICP control in patients who are refractory to other therapies. There are no recommendations for the duration of hyperventilation once it has been initiated, but it seems prudent to discontinue it once ICP control is achieved or if it does not provide demonstrable benefit after an adequate trial.

### **CSF Drainage**

For patients with a ventriculostomy, draining CSF fluid from the ventricles appears to be a simple mechanical method of reducing ICP. A small study and two case series showed that CSF drainage was effective at acutely reducing ICP. However, ICP began to increase again within 10 minutes of drainage in all three reports, indicating that CSF drainage needs to be continuous to be effective. Closed-loop ventriculostomy reservoir systems are available that can safely allow continuous

CSF drainage. Although this issue is not specifically addressed in the BTF guidelines, it seems reasonable that CSF drainage could be used as a first-line therapy in patients who have a ventriculostomy. The effect may be lessened in patients with compressed ventricles from increased ICP.

### **Surgery**

Decompressive craniectomy is a surgical procedure in which a portion of the patient's skull is temporarily removed to provide more space for cerebral edema, thereby decreasing ICP. Craniectomy in patients with TBI has been intensely studied for the past decade. Several randomized and nonrandomized studies have shown that craniectomy is effective at lowering ICP postoperatively. However, the effect on long-term outcomes is mixed.

In 2011, a pivotal randomized trial also showed acute effectiveness in ICP control with craniectomy in patients who were refractory to first-line medical therapies. However, long-term outcomes were significantly worse for patients in the surgery group. This study calls into question the routine use of decompressive craniectomy in patients with refractory ICP. A similar trial is under way that will provide important data in this area.

### **Hypothermia/Hyperthermia Control**

Hyperthermia is common in patients with severe TBI and has been associated with poorer ICP control and worse neurologic outcomes in observational studies. However, it is unknown whether normalizing body temperature results in better ICP control or outcomes. Nonetheless, it is currently recommended that fever in patients with TBI should be treated aggressively with traditional pharmacologic and nonpharmacologic methods.

Beyond routine fever control, therapeutic hypothermia has for decades been a strategy for attempting to minimize secondary brain injury after TBI. Early TBI studies suggested promise for this treatment. In addition, other patient populations with brain ischemia (e.g., patients after cardiac arrest) have improved outcomes with hypothermia. Unfortunately, data from recent clinical trials of therapeutic hypothermia in patients with TBI have not shown improved outcomes.

The first of two large randomized clinical trials of therapeutic hypothermia in patients with nonpenetrating TBI used a targeted temperature of 91.4°F (33°C); no improvement was found in outcome compared with a normothermic group. In addition, more hypotension was observed in the group receiving therapeutic hypothermia. The second major multicenter study focused on early cooling (i.e., 2.5 hours or less) to 95.0°F (35°C); then 48 hours at 91.4°F (33°C), followed by gradual rewarming. A control group was treated under normothermia conditions. This study was discontinued

because of futility after enrolling 108 patients. In reality, more poor outcomes, including death, were observed in the hypothermic group. However, selected patients with TBI may have benefited from hypothermia. For instance, patients with TBI with surgically evacuated hematomas benefited more than patients with diffuse brain injury.

The disparities between trials may be related to the inherent heterogeneity of TBIs compared with the focal or global brain ischemia observed in other patient groups (e.g., those with stroke or cardiac arrest). Another limitation may be the inability to effectively evaluate the extent of recovery in patients with TBI using conventional measurement tools such as the Glasgow Outcome Scale and the Disability Rating Scale. Other problems may be related to delays in inducing therapeutic hypothermia in patients with TBI, knowledge of the optimal target temperature in these patients, or identification of the subset(s) of patients with TBI who are most likely to benefit from this therapeutic maneuver (e.g., patients with evacuated hematomas). From the clinical evidence, therapeutic hypothermia is not recommended as a routine neuroprotective strategy in patients with TBI.

Unlike with neuroprotection, studies of therapeutic hypothermia to treat increased ICP have shown favorable results in morbidity and mortality. In addition to common adverse effects, such as coagulopathy, increased infection risk, and shivering, therapeutic hypothermia can affect the pharmacokinetics of drugs. Specifically, for every 1°C (18°F) decrease in core body temperature, cardiac output decreases by 7%. Thus, mild therapeutic hypothermia (defined as 91.4°F ± 1.8°F [33°C ± 1°C]) would be expected to decrease hepatic and renal bloodflow by about 25%, which could significantly affect the elimination of a variety of agents. Moderate hypothermia (defined as a core temperature of 82.4°F–87.8°F [28°C–31°C]) can be expected to have even more profound cardiovascular effects. These pharmacokinetic changes provide an opportunity for the pharmacist to optimize drug dosing and actively evaluate for adverse events related to impaired drug clearance.

### **Supportive Care Measures**

#### **Seizure Prophylaxis**

Patients with TBI have a high risk of seizures. Posttraumatic seizures are described as being either early (in the first 7 days after injury) or late (more than 7 days after injury). The early seizure risk after TBI has been reported to be 4% to 25% and may be higher with penetrating injuries. Risk factors for early seizures include a GCS score less than 10, an intracerebral hematoma, a penetrating injury, a depressed skull fracture, and a seizure in the first 24 hours after injury.

A key randomized trial showed phenytoin to be more effective than placebo for preventing early seizures. However, randomized clinical trials with various agents have failed to show a benefit of seizure prophylaxis on late seizures. Thus, the BTF guidelines recommend seizure prophylaxis for patients with a risk factor only during the first 7 days after TBI.

Phenytoin is the drug of choice for preventing early seizures. The loading and maintenance dosages should be aggressive because patients with TBI tend to have a higher phenytoin volume of distribution and clearance than typical patients. The loading dose should be 20 mg/kg, and the starting maintenance dosage should be 6 mg/kg/day divided into two or three doses. These dosages were used in many efficacy and pharmacokinetic studies of patients with TBI. The phenytoin prodrug fosphenytoin has not been studied for this indication; however, it should be an acceptable alternative because it is rapidly converted to phenytoin.

There is no consensus on which agent to use if phenytoin or fosphenytoin cannot be used because of adverse events. The previous version of the BTF guidelines recommended carbamazepine as second-line therapy, but the current version does not. This change was not explained. Carbamazepine was more effective than placebo in a quasi-randomized trial, but its use is limited because an intravenous formulation is not available. Furthermore, there may be "cross-reactivity" (i.e., anticonvulsant hypersensitivity syndrome) between carbamazepine and phenytoin. Valproic acid was as effective as phenytoin in a large randomized trial, but it is not recommended because, in that study, there was a trend toward increased mortality with valproate. Phenobarbital was not effective compared with placebo in a randomized trial and should not be used.

Levetiracetam is a potentially attractive option for seizure prophylaxis in patients with TBI because it can be administered intravenously. However, the drug should be used cautiously because it is not approved as monotherapy for seizures, and effectiveness in patients with TBI has not been studied in a large randomized clinical trial. Indeed, a recent small trial of patients with TBI showed that levetiracetam was inferior to phenytoin at normalizing seizure tendency on electroencephalography. A large randomized trial of patients with spontaneous subarachnoid hemorrhage (not TBI) showed levetiracetam to be inferior to phenytoin for seizure prophylaxis. Overall, it is not clear what is the preferred agent if phenytoin use is not possible.

### **Venous Thromboembolism Prophylaxis**

In general, critically ill trauma patients have extremely high rates of deep venous thrombosis and pulmonary embolism, and patients with TBI are no exception. Thus, venous thromboembolism (VTE) prophylaxis is indicated for all patients with TBI.

The timing and selection of VTE prophylaxis is complex because of the potential for catastrophic intracranial bleeding with anticoagulant use and a lack of randomized clinical trial data specific to patients with TBI. Many patients will have pharmacologic VTE prophylaxis withheld until a follow-up CT scan shows that intracranial bleeding is not worsening. The American College of Chest Physicians (*Chest*) guidelines do not provide recommendations specifically for patients with TBI; thus, many clinicians rely on the recommendations for neurosurgery. The *Chest* guidelines recommend that intermittent pneumatic compression devices be used in all patients until drug therapy can be initiated. Patients at high risk (e.g., with severe TBI) should then have intermittent pneumatic compression devices continued after drug therapy begins.

Regarding drug therapy, either a low-molecular-weight heparin or low-dose unfractionated heparin is recommended. Enoxaparin was shown to be superior to low-dose unfractionated heparin for VTE prophylaxis in a landmark study of adult trauma patients. Unfortunately, that study excluded patients with TBI, so the preference for enoxaparin cannot be easily extrapolated. The most intriguing recent data in this area come from an observational study of patients with TBI that examined the timing of starting drug therapy. Patients with a stable follow-up head CT scan at 24 hours after TBI received enoxaparin with no significant risk of worsening intracranial bleeding. This study provides some insight into the timeline for starting drug therapy.

### **Infection**

Similar to other critically ill patients on mechanical ventilation, patients with severe TBI are at high risk of infections such as ventilator-associated pneumonia and catheter-related bloodstream and urinary tract infections. However, patients with TBI also have a unique risk of meningitis. Risk factors include a ventriculostomy, skull or sinus fracture (particularly basilar skull fracture), cranial surgery, or CSF leak. The overall incidence of meningitis after TBI is 1% to 2% but rises to about 8% in patients with a ventriculostomy. Patients with intraparenchymal monitors have an infection rate similar to those with a ventriculostomy; however, it is more difficult to determine whether the device is the source of infection.

*Staphylococcus aureus* is the most common pathogen isolated, although typical nosocomial Gram-negative bacilli such as *Pseudomonas aeruginosa* are important as well. Anaerobes and fungi are rare. Patients with TBI who have any additional risk factor for meningitis should have an evaluation of the CSF, including culture, as part of any sepsis workup.

Empiric antibiotic therapy should include vancomycin plus an appropriate  $\beta$ -lactam with Gram-negative

activity depending on the patient's risk of *P. aeruginosa* infection. Patients who have had a previous significant interaction with the health care system or who have been in the hospital longer than 5 days require antibiotics with antipseudomonal activity. There is little evidence regarding the use of intrathecal antibiotics administered by a ventriculostomy; however, recent data suggest that they may benefit patients with recurrent infections. Aggressive antibiotic dosing is needed to ensure drug penetration into the central nervous system.

### **Nutrition/Sodium Management**

Early nutrition support is important in patients with severe TBI. A recent study found that an increasing amount of nutrition delivered in the first 5 days after TBI was independently related to lower mortality. Afterward, the Institute of Medicine recommended that military patients with TBI have nutrition support started within 24 hours of injury, if possible.

Patients with severe TBI generally have very high calorie and protein requirements compared with normal adults. Unfortunately, they can also have gastroparesis or other injuries that preclude early enteral feeding. Hyperglycemia is common in patients with TBI and is associated with worse outcomes. The ideal glucose treatment goals for patients with TBI are not known; however, intensive insulin therapy in the ICU is no longer recommended after the negative results of the landmark NICE-SUGAR clinical trial evaluating intensive versus conventional glucose control in critically ill patients.

With or without the use of hypertonic saline for ICP control, patients with TBI can have problems with sodium homeostasis. Both the syndrome of inappropriate antidiuretic hormone and diabetes insipidus are common after TBI. Either condition can result in a mild to life-threatening condition. Diabetes insipidus results in an extremely high urine output and hypernatremia caused by hypovolemia and urinary wasting of water. It is treated acutely with fluid administration to match urine output. In addition, desmopressin may be titrated to decrease urine production and serum sodium until the condition resolves. The syndrome of inappropriate antidiuretic hormone results in hyponatremia; it is treated acutely with fluid restriction, followed by demeclocycline if the patient requires long-term therapy. Cerebral salt wasting also occurs in patients with TBI and results in hyponatremia caused by excess renal sodium excretion. Treatment is with sodium replacement. However, differentiating between these two causes of hyponatremia can be difficult and therefore problematic because the treatments are different.

### **Hemostatics**

The potential benefit of systemic hemostatic agents in patients with TBI with intracranial bleeding seems intuitive. Recombinant factor VIIa has been studied in

more than a dozen recent observational trials but was associated with improved outcomes in only five studies. Most of those studies were in patients with spontaneous intracranial hemorrhage rather than TBI. In two randomized trials of patients with TBI, recombinant factor VIIa was no more effective than placebo in reducing mortality or disability. It also is extremely expensive and may increase the risk of VTE. Tranexamic acid is far less expensive, and its use reduced overall mortality in a recent randomized study of trauma patients. However, no significant benefit was seen in the subgroup of patients with a GCS score of 3–8. More data are needed to determine the role of hemostatic agents in patients with TBI before they can be used routinely.

### **QUALITY IMPROVEMENT**

One area for improvement in the medical management of patients with TBI is using therapeutic drug monitoring to ensure that phenytoin concentrations are therapeutic. Although most patients will receive only 7 days of therapy and will not likely achieve steady-state concentrations, it is desirable to ensure that the serum concentration is therapeutic during therapy. Only 34% of patients in the landmark clinical trial had therapeutic phenytoin concentrations at the end of 1 week. However, clinical pharmacists can significantly improve phenytoin use in patients with TBI, including the percentage of patients achieving therapeutic drug concentrations.

### **ROLE OF THE PHARMACIST**

Pharmacists are well positioned to have a major impact on the acute care of patients with TBI. One example is being involved in the development of patient care pathways that are consistent with BTF guidelines. Pathways should include supportive measures such as VTE and seizure prophylaxis, use of sedatives and analgesics, and appropriate fluid, electrolyte, and nutrition management.

As is true of other critically ill patients, patients with moderate and severe TBI should benefit from ongoing prospective monitoring and management of both therapeutic and prophylactic pharmacotherapy, as well as nutrition support by pharmacists. It is also important to avoid the use of agents in the immediate postinjury period that have been associated with poorer long-term outcomes.

Critical care pharmacy practitioners are optimally used as members of an interdisciplinary team led by a neurosurgeon or trauma specialist. Such a team can increase understanding of the many nuances associated with the care of patients with TBI. A recent before and after study documented cost savings and a statistically significant reduction in the hospital stay associated with adding a clinical pharmacist to a multidisciplinary

neurosurgery team. Nonetheless, pharmacists engaged in more targeted activities (e.g., therapeutic drug monitoring, medication reconciliation, drug interaction screening) can still have a significant effect on the care of this highly vulnerable patient population.

## ANNOTATED BIBLIOGRAPHY

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The BTF guidelines, first developed in 1995, represent the most comprehensive set of clinical practice guidelines for the inpatient management of patients with severe TBI. The 2007 version represents the third edition of this landmark effort to improve uniformity in the care of these patients, mortality rates, and the quality of life of survivors of severe TBI. Each topic addressed in the guidelines represents a comprehensive review of all databases relevant to the neurotrauma literature. Topics most relevant to pharmacotherapy specialists are hyperosmolar therapy; prophylactic hypothermia; infection, seizure, and deep venous thrombosis prophylaxis; anesthetics, analgesics, and sedatives; corticosteroids; and nutrition. The guidelines also address clinical monitoring variables including ICP, CPP, blood pressure, and oxygenation. Recommendations are rated as level I, II, or III on the basis of the quality of the reviewed literature. In addition to the published version, the guidelines are available at the BTF homepage at [www.braintrauma.org/](http://www.braintrauma.org/).

2. Faul M, Wald MM, Rutland-Brown W, Sullivent EE, Sattin RW. Using a cost-benefit analysis to estimate the outcomes of a clinical treatment guideline: testing the Brain Trauma Foundation guidelines for the treatment of severe traumatic brain injury. *J Trauma* 2007;63:1271–8.

This article describes a cost-benefit analysis of using the BTF guidelines for the inpatient management of adult patients with severe TBI. Two studies were selected from five studies evaluating the effectiveness of adopting the BTF guidelines since their release in 1995. The Glasgow Outcome Scale (GOS) was the principal outcome variable used to compare the before and after periods relative to the adoption of the BTF guidelines. Direct medical, rehabilitative, and societal costs for TBI morbidity and mortality were estimated using published data. A decision analysis tree and probability tree were used to compare the two different treatment periods. Adoption of the BTF guidelines resulted in an increase of more than 3600 patients surviving at least 1 day from the more than 23,000 patients with severe TBI admitted annually to U.S. hospitals. Patients having a good outcome on the basis of their GOS increased from 35% to 66%. Overall, estimated annual cost savings exceeded \$4 billion. This study reveals that adoption of and adherence to the BTF guidelines universally could

have an enormous impact relative to saving the lives of patients with TBI and decreasing overall costs.

3. Hesdorffer DC, Ghajar J. Marked improvement in adherence to traumatic brain injury guidelines in United States trauma centers. *J Trauma* 2007;63:841–8.

Despite endorsement by major medical organizations and the World Health Organization's Neurotrauma Committee and widespread distribution to neurosurgeons, adherence to the BTF guidelines for the inpatient management of patients with acute severe TBI has been inconsistent. Looking primarily at level I- and II-designated trauma centers, the authors compared adherence to selected care maneuvers before the BTF guidelines were developed and 5 years after guideline distribution (2000 and 2006, respectively). From 2000 to 2006, adherence rates for these measures improved dramatically compared with 1999 data. Furthermore, nonadherence to the guidelines fell from 67% to 34.5% between 2000 to 2006. Full adherence to published guidelines rose from 16% to 20.8%. Although improvements in adherence to the BTF guidelines have occurred in the new millennium at designated U.S. trauma centers, substantial opportunity remains for greater use of these life- and cost-saving recommendations.

4. Meyer MJ, Megyesi J, Meythaler J, Murie-Fernandez M, Aubut JA, Foley N, et al. Acute management of acquired brain injury part I: an evidence-based review of non-pharmacological interventions. *Brain Inj* 2010;24:694–705.

This article is the first of a three-part series evaluating the breadth of interventions used in the medical management of patients with acute TBI. Topics in this comprehensive evidence-based review covering 1980–2008 focus on five nonpharmacologic strategies: adjusting head position, body rotation, hyperventilation, hypothermia, and hyperbaric oxygen. The invasive measures of decompressive craniectomy and CSF drainage are also reviewed. Tables summarizing each intervention are provided in the article. The authors conclude that level 1 (strong) supportive evidence was only found for CSF drainage, hyperbaric oxygen, hypothermia, and decompressive craniectomy in the medical management of patients with severe TBI under specific conditions. Of note, this analysis was performed before the publication of a major clinical trial for each of the latter two strategies (i.e., hypothermia and decompressive craniectomy).

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This article represents the second in the three-part series evaluating interventions in the medical management of patients with acute TBI and may be the most relevant for pharmacotherapy specialists. Pharmacologic agents analyzed in this evidence-based review include individual agents such as propofol,

midazolam, mannitol, and dimethyl sulfoxide, as well as drug classes such as barbiturates, opioids, corticosteroids, bradykinin antagonists, and cannabinoids. The effectiveness of hypertonic saline is also methodically reviewed. Of note is the absence of a review on agents blocking the effects of excitatory amines. As in part I, useful tables are provided that list all studies between 1980 and 2008; however, the occasional discordance between the table and text citations and bibliography is disappointing. The authors found some benefit for all but corticosteroids and cannabinoids, although at varying evidence levels (I–IV).

6. Meyer MJ, Megyesi J, Meythaler J, Murie-Fernandez M, Aubut JA, Foley N, et al. Acute management of acquired brain injury Part III: an evidence-based review of interventions used to promote arousal from coma. *Brain Inj* 2010;24:722–9.

This article is the last in the three-part series evaluating interventions in the medical management of patients with acute TBI; it also may be the most specific of the series. Few other comprehensive review articles evaluate the effects of strategies to stimulate neuronal pathways in patients with TBI who cannot be aroused (i.e., comatose patients). Pharmacologic strategies reviewed include agents affecting the dopamine pathways (i.e., amantadine, bromocriptine, and levodopa). Nonpharmacologic approaches include sensory stimulation, music therapy, and peripheral nerve electrical stimulation. Only amantadine research was associated with level 1 (strong) evidence relative to improving arousal in comatose patients. However, this level 1 recommendation is based on only one study of children.

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Progesterone is a promising neuroprotective agent that may benefit patients with acute TBI through a variety of proposed mechanisms. This study, conducted at a single investigative site, represents the first randomized, double-blind, placebo-controlled clinical investigation of progesterone in patients with TBI. Patients with TBI with postresuscitation GCS scores ranging from 4 to 12 received either a progesterone infusion for 3 days or placebo (n=23) within 11 hours of injury. Mortality at 30 days was significantly lower in the progesterone group compared with the placebo group (13.0% vs. 40.0%; relative risk [RR] = 0.33; 95% confidence interval [CI] = 0.13–0.83). Adverse events were similar between the two groups. Favorable recovery from TBI at 30 days was only different for progesterone in patients with moderate TBI. This study is extremely important in suggesting that progesterone treatment appears to be safe in patients with moderate to severe TBI. The study was large enough to adequately assess the effect of progesterone on mortality. It is an important preliminary finding that progesterone treatment is associated with decreased mortality and improved neurologic outcomes.

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This study, conducted by an independent group of clinical investigators, was published shortly after the first randomized, double-blind, placebo-controlled trial of progesterone in patients with TBI. All patients in this study had severe TBI (GCS score 8 or less) and were assigned in a 1:1 ratio to receive either progesterone or placebo by intramuscular injection beginning within 8 hours of injury and continuing for 5 days. Mortality at 6 months was lower in the 82 patients receiving progesterone than in the 77 receiving placebo (18% versus 32%; p=0.039). Good outcomes also favored the progesterone group at 3 and 6 months after injury (p=0.034 and p=0.048, respectively). No differences in adverse events were evident between groups. Despite differences in dosage, administration route, therapy duration, and length of follow-up, results from this study generally corroborated many of the findings reported in the first pilot study of progesterone in TBI studies. Of importance, these two studies collectively served as the impetus for two ongoing large, multicenter, randomized phase III trials evaluating the utility of progesterone in patients with TBI.

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This multicenter study represents a logical follow-up to a landmark 2001 investigation that used therapeutic hypothermia as a neuroprotective strategy in patients with acute TBI. The main differences in this new study were earlier initiation of therapeutic hypothermia and exclusion of older adults. Patients aged 16–45 years with severe acute nonpenetrating TBI were randomized to receive either hypothermia therapy, targeting an initial core temperature of 95°F (35°C) and then 91.4°F (33°C) for 48 hours, or normothermia. Patients were excluded if informed consent could not be obtained within 2.5 hours after injury. Poor outcome was noted in 31 of the 52 patients in the hypothermia group and in 25 of the 56 in the normothermia group (RR = 1.08; 95% CI, 0.58–2.52; p=0.67). However, there was a statistically significant improvement in outcome favoring therapeutic hypothermia versus normothermia management in patients with acute TBI with surgically evacuated hematomas versus diffuse brain injury (p=0.001). Thus, the use of therapeutic hypothermia as a neuroprotective strategy in this more limited subset of patients with acute TBI may be a possibility in the future. Results of this study indicate that therapeutic hypothermia should not be used in patients with acute TBI and diffuse brain injury.

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This is the most recent prospective trial comparing hypertonic saline with mannitol for treating elevated ICP (greater than 20 mm Hg for 5 minutes) in patients with severe TBI (GCS score 3–8). Other management was standardized according to the BTF guidelines. The first dose of either study drug (hypertonic saline or mannitol) was chosen at random, with alternating doses of the two drugs given as needed thereafter. The design of using both agents in each patient has advantages and disadvantages. There were 199 episodes of elevated ICP treated in 29 patients. The mean acute decrease in ICP was about 8 mm Hg with each agent. The mean duration of effectiveness was about 3.5 hours for mannitol and 4.25 hours for hypertonic saline ( $p=0.4$ ). This study suggests that the two agents are equivalent for acute treatment of elevated ICP, contrary to some previous studies that suggested that hypertonic saline was more effective than mannitol.

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This retrospective study sought to better clarify the relationship between early hyperglycemia and mortality in patients with TBI. Hyperglycemia was defined as a serum glucose concentration greater than 160 mg/dL, although various glucose strata were analyzed. A total of 380 patients with TBI were included, 97 of whom had severe TBI (GCS score 3–8). Serum glucose concentrations for the first 5 days of hospitalization were analyzed. Nonsurvivors had significantly higher glucose values on admission and during day 1. Multivariate regression showed admission glucose and maximum glucose on day 1 to be better predictors of mortality than hyperglycemia during days 2–5. Another regression analysis showed that a serum glucose concentration greater than 160 mg/dL was associated with increased mortality; however, the effect was small (odds ratio [OR] = 1.034;  $p<0.001$ ). In addition, increased mortality was associated with glucose concentrations less than 60 mg/dL in this study (OR = 1.130;  $p=0.007$ ). Overall results were similar in the subgroup of patients with severe TBI. This study furthers the understanding of the time course and intensity of hyperglycemia, information that may be important in reducing mortality in patients with TBI.

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Pentobarbital is used as a second-line agent for intracranial hypertension; however, its effects on cerebral oxygenation and autoregulation are unknown. This prospective, observational study included 12 patients with severe TBI. Patients were treated according to the BTF guidelines and had an ICP greater than 20 mm Hg despite intravenous treatment with sedation, mannitol, neuromuscular blockers, and hyperventilation. A pentobarbital

intravenous loading dose (250 mg) was given and followed by a continuous pentobarbital infusion of 4–8 mg/kg/hour until the ICP decreased to less than 20 mm Hg or the therapy was considered ineffective. In the five patients who survived, there was a mean decrease in ICP without a change in CPP and an improvement in brain tissue oxygenation and autoregulation. In the seven nonsurvivors, none of these variables improved. These results provide more insight into the effects of pentobarbital on cerebral oxygenation and hemodynamics. A positive response of these variables to pentobarbital was an indicator of better clinical outcomes.

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This retrospective, matched case-control study evaluated the association between the use of erythropoiesis-stimulating agents (ESAs) and mortality in patients with TBI. The study compared 89 patients treated with ESAs (erythropoietin 100 units/kg/week or darbepoetin 0.45 mcg/kg/week) with 178 randomly chosen patients who did not receive ESAs and who met several criteria matching to the ESA group. Hospital mortality was significantly lower in the ESA group (7.9% vs. 24.2%; OR = 0.27;  $p=0.001$ ). There was a statistical trend toward an increased risk of pulmonary embolism with ESA use (4.5% vs. 2.2%;  $p=0.10$ ). The groups were well matched except that significantly more patients in the ESA group were treated later in the 9-year study period. Thus, changes in care over time may have been a confounder. Moreover, the magnitude of the mortality benefit associated with ESAs was surprisingly high. A prospective trial will be needed to confirm these provocative results.

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This retrospective study evaluated the outcomes of adult patients admitted to a neurosurgical service 2 years before and 2 years after implementation of a dedicated decentralized pharmacist to the service. The pharmacist was responsible for evaluating and monitoring medication therapy for patients both within and outside the neurosurgery intensive care unit in addition to other related duties. Comparison of the costs before and after implementation of pharmacy services revealed a cost savings of about \$1600/patient (2003–2007). Total hospital costs decreased by more than \$146,000 between the two study periods. Overall hospital stay decreased as well (from 8.56 to 7.24,  $p=0.003$ ), although hospital mortality was essentially unchanged (from 8.73% to 8.53%,  $p=0.929$ ). This study provides convincing evidence about the benefits of a dedicated pharmacist in a multidisciplinary neurosurgical setting.

# SELF-ASSESSMENT QUESTIONS

1. As a clinical pharmacy specialist recently assigned to a neurosurgical intensive care unit (ICU), you become aware of inconsistent adherence to the Brain Trauma Foundation (BTF) guidelines for the inpatient management of patients with acute severe traumatic brain injury (TBI). **Which one of the following is the most compelling reason to advocate for greater adherence to the guidelines?**
  - A. Improved family satisfaction with the level of care.
  - B. Reduction in hospital mortality.
  - C. Reduced inpatient hospital costs.
  - D. Reduced ICU length of stay.
2. **Which group of J.W.'s characteristics, radiologic findings, and/or clinical findings is most predictive of a poor neurologic outcome after his acute TBI?**
  - A. Age and medical history of stroke.
  - B. Head CT findings and postresuscitation GCS score.
  - C. Postresuscitation GCS score and age.
  - D. Postresuscitation blood pressure and head CT findings.
3. **On the basis of epidemiologic data, which one of the following drugs that J.W. was receiving before admission will be most likely to have a beneficial effect on his neurologic outcome if continued during this hospitalization?**
  - A. Metoprolol.
  - B. Atorvastatin.
  - C. Aspirin.
  - D. Lisinopril.

## Questions 2–6 pertain to the following case.

J.W. is a 61-year-old man (weight 83 kg, height 152 cm) transported by air ambulance to a level I trauma center after being involved in a motor vehicle crash. His medical history is significant for hypertension and an ischemic stroke 4 years ago with no residual deficits. J.W.'s home drug regimen before admission included aspirin 325 mg/day, atorvastatin 40 mg/day, lisinopril 20 mg/day, hydrochlorothiazide 25 mg/day, and metoprolol 25 mg twice daily. J.W. is intubated, placed on mechanical ventilation (fraction of inspired oxygen [FiO<sub>2</sub>], 1.0), and resuscitated according to the trauma center's Advanced Trauma Life Support protocol. Fluids administered during the resuscitation are primarily 3 L of Ringer's lactate solution and 2 units of packed red blood cells. J.W.'s initial neurologic examination reveals a postresuscitation Glasgow Coma Scale (GCS) score of 8, reactive pupils, and localizing of all extremities upon painful stimulation. Significant findings on physical examination are an obvious left femur fracture and an 8-cm scalp laceration. Computed tomography (CT) reveals a small epidural hematoma, a nondisplaced parietal skull fracture, a left acetabulum fracture, and a displaced left femur fracture. J.W.'s postresuscitative vital signs are blood pressure 155–160 mm Hg/90–96 mm Hg, heart rate 105–110 beats/minute, respiratory rate (ventilator) 14 breaths/minute, spontaneous respirations 20 breaths/minute, and temperature 100.6°F (38.1°C). Laboratory values after resuscitation include the following: sodium 138 mEq/L, potassium 4.4 mEq/L, creatinine 1.2 mg/dL, glucose 165 mg/dL, bicarbonate 22 mEq/L, lactate 2 mmol/L, hematocrit 30%, white blood cell count (WBC)  $10.3 \times 10^3$  cells/mm<sup>3</sup>, platelet count 110,000/mm<sup>3</sup>, international normalized ratio (INR) 1.2, arterial partial pressure of oxygen (Pao<sub>2</sub>) 150 mm Hg (with Fio<sub>2</sub> 0.4), arterial partial pressure of carbon dioxide (Paco<sub>2</sub>) 35 mm Hg, oxygen saturation 99%, and blood alcohol concentration undetectable.

4. J.W.'s neurosurgeon determines that no surgical intervention is warranted at this time, although an intracranial pressure (ICP) monitoring catheter is inserted to allow continuous monitoring in the ICU. J.W. is receiving intravenous propofol at 1 mg/kg/hour and fentanyl at 75 mcg/hour. His initial ICP is 17 mm Hg. During the next 2 hours, his ICP ranges from 20 mm Hg to 26 mm Hg and his mean arterial pressure (MAP) ranges from 100 mm Hg to 110 mm Hg. His sodium concentration is 141 mEq/L. **Which one of the following is the most appropriate for J.W. at this time?**
  - A. No acute therapy for ICP control is needed.
  - B. Administer 35 mL of 15% saline intravenously.
  - C. Administer mannitol 12.5 g intravenously.
  - D. Begin a cisatracurium intravenous infusion at 80 mcg/hour.
5. Fourteen hours after J.W.'s admission, the ICU pharmacist reviewing his drug profile recognizes that no therapy has been initiated for seizure prevention. **Which one of the following is best to recommend for J.W.?**
  - A. Do not administer an anticonvulsant at this time because more than 12 hours have elapsed since his TBI.
  - B. Begin valproate 1500 mg intravenously daily and continue for 1 month as long as there is no seizure activity.

- C. Request immediate electroencephalography to exclude nonconvulsive status epilepticus before initiating anticonvulsant therapy.
  - D. Administer a phenytoin loading dose of 1500 mg intravenously, followed by a dosage of 200 mg every 12 hours for 7 days if there is no seizure activity.
6. Upon reviewing J.W.'s medical records, it is clear that he is at high risk of venous thromboembolism (VTE) because of his pelvic and long bone fracture. **In addition to a sequential compression device (SCD) on his right leg, which one of the following is best to recommend regarding VTE prophylaxis for J.W.?**
- A. No pharmacologic VTE prophylaxis until follow-up head CT documents the absence of a hematoma.
  - B. Begin enoxaparin 30 mg every 12 hours subcutaneously.
  - C. Insert a vena cava filter on hospital day 2.
  - D. Administer 1 unit of fresh frozen plasma; then begin enoxaparin 30 mg every 12 hours subcutaneously.
7. **Which one of the following is most likely to improve mortality in patients with TBI?**
- A. Erythropoiesis-stimulating agents.
  - B. Cyclosporine.
  - C. Statins.
  - D. Progesterone.

**Questions 8–11 pertain to the following case.**

W.S. is a 24-year-old man (weight 110 kg, height 155 cm) transported by ground ambulance from his rural home to the level I trauma center after an accidental gunshot wound that occurred while cleaning his .22 caliber rifle. He has no significant medical history. The paramedics orally intubated W.S. (FIO<sub>2</sub> 1.0) en route to the hospital. The initial neurologic examination reveals a postresuscitation GCS score of 6, nonreactive pupils, flexion withdrawal of his upper extremities upon painful stimulation, and a stable MAP of 70 mm Hg. The only significant findings on physical examination are a penetrating injury to the right frontal region of his skull with a right temporal exit wound. Head CT reveals a depressed skull fracture and a large underlying cerebral contusion in the frontal brain region. W.S. received a 2-g intravenous phenytoin loading dose and cefazolin 1 g intravenously before being rushed to the operating room for a craniectomy, hematoma evacuation, and debridement of the bullet missile tract. An intraparenchymal fiberoptic ICP monitor is placed intraoperatively with an initial reading of 19 mm Hg. Postoperatively, W.S. is transferred to the trauma ICU. Initial intravenous drugs

include fentanyl 100 mcg/hour, propofol 1 mg/kg/hour, esomeprazole 40 mg every 12 hours, phenytoin 250 mg every 12 hours, and cefazolin 1 g every 8 hours for three doses. He is also receiving 0.9% NaCl at 75 mL/hour. The head of his bed is elevated to 30 degrees, and SCDs are placed on both lower extremities. W.S.'s vital signs are blood pressure 120–140 mm Hg/65–80 mm Hg, heart rate 100–115 beats/minute, respiratory rate (ventilator) 16 breaths/minute, no spontaneous respirations, and temperature 100°F (37.8°C). His ICP has ranged from 14 mm Hg to 18 mm Hg since he was transferred to the ICU. J.W.'s laboratory values postoperatively include sodium 141 mEq/L, potassium 3.9 mEq/L, creatinine 1.0 mg/dL, albumin 3.8 g/dL, glucose 135 mg/dL, bicarbonate 23 mEq/L, lactate 1.0 mmol/L, hematocrit 36%, WBC 9.6 x 10<sup>3</sup> cells/mm<sup>3</sup>, platelet count 155,000/mm<sup>3</sup>, INR 1.1, PaO<sub>2</sub> 140 mm Hg (Fio<sub>2</sub> 0.4), PaCO<sub>2</sub> 37 mm Hg, oxygen saturation 100%, and blood alcohol concentration 0.15 mg/dL.

8. Six hours after admission to the ICU, W.S. has a sudden increase in his ICP to 30 mm Hg, which is sustained for about 15 minutes. His blood pressure during this period is 115/70 mm Hg. **Which one of the following is the most appropriate initial treatment for W.S.?**
- A. Administer mannitol 50 g intravenously.
  - B. No additional treatment; his cerebral perfusion pressure (CPP) is greater than 50 mm Hg.
  - C. Increase propofol to 2 mg/kg/hour.
  - D. Increase the 0.9% NaCl rate to 125 mL/hour.
9. **Which one of the following sets of physiologic and/or laboratory variables is most important to monitor in W.S. throughout his ICU stay?**
- A. Serum osmolality, ICP, serum triglycerides, PaCO<sub>2</sub>, and urine output.
  - B. Blood pressure, serum sodium, serum phenytoin concentrations, temperature, and serum osmolality.
  - C. Temperature, CPP, PaCO<sub>2</sub>, ICP, and serum sodium.
  - D. Serum triglycerides, blood pressure, urine output, PaCO<sub>2</sub>, and serum sodium.
10. On postoperative day 4, W.S.'s GCS score is 7; his temperature during the past 24 hours has been 101.3°F (38.5°C); and he has developed an erythematous rash across his face, chest, and back. The most likely cause of this new rash is toxic epidermal necrolysis secondary to phenytoin. **In addition to discontinuing phenytoin, which one of the following is the best course of action regarding W.S.'s intravenous anticonvulsant therapy?**

- A. No additional anticonvulsant therapy is warranted.
  - B. Administer a 2-g phenobarbital loading dose; then begin 200 mg twice daily.
  - C. Begin valproate 1500 mg/day.
  - D. Begin levetiracetam 500 mg twice daily.
11. W.S. has not shown dramatic improvement since his admission. The neurosurgical resident asks why therapeutic hypothermia is not being considered. W.S.'s current ICP is 15 mm Hg. **Which one of the following best supports withholding hypothermia therapy in W.S.?**
- A. Therapeutic hypothermia is not effective in patients with TBI.
  - B. The period when he would have most likely benefited from hypothermia has passed.
  - C. No data are available regarding hypothermia in patients with acute penetrating TBI injuries.
  - D. Therapeutic hypothermia's effects on cardiac output would offset any potential benefits.

**Questions 12–16 pertain to the following case.**

P.G. is a 45-year-old Hispanic man (weight 74 kg) who is transported by air ambulance to a level I trauma center after falling two stories from scaffolding. On arrival, he is neurologically unresponsive and intubated, although he had stable vital signs during transport. An initial neurologic examination reveals bilateral unreactive pupils and a GCS score of 5. Emergency CT of the head and pelvis reveals a large parietal subdural hematoma with severely compressed ventricles bilaterally (no midline shift) and a nondisplaced pelvic fracture, respectively. P.G. is taken to the operating room for a craniotomy and emergency subdural hematoma evacuation. An intraparenchymal catheter is placed and reveals an initial ICP of 19 mm Hg with a concurrent blood pressure of 110/65 mm Hg. Single doses of mannitol 50 g and phenytoin 1.5 g are administered intravenously during surgery. Postoperatively, P.G. is admitted to the neurosurgery ICU on mechanical ventilation (FIO<sub>2</sub> 0.5, ventilator rate 16 breaths/minute) with Ringer's lactate running at 50 mL/hour. His GCS score is unchanged. Current vital signs are blood pressure 105/60 mm Hg, heart rate 105 beats/minute, and temperature 99°F (37.2°C). Intravenous midazolam is initiated at 2.5 mg/hour together with fentanyl at 50 mcg/hour. Other orders include phenytoin 200 mg intravenously every 12 hours, ranitidine 50 mg intravenously every 8 hours, and SCDs bilaterally. Laboratory values include sodium 144 mEq/L, potassium 4.5 mEq/L, creatinine 1.2 mg/dL, glucose 145 mg/dL, bicarbonate 21 mEq/L, lactate 0.5 mmol/L, hematocrit 30%, WBC 11.0 x 10<sup>3</sup> cells/mm<sup>3</sup>, platelet count 200,000/mm<sup>3</sup>, INR 1.3, PaO<sub>2</sub> 110 mm Hg (FIO<sub>2</sub> 0.5); PaCO<sub>2</sub> 34 mm Hg, and oxygen saturation 99%. Two hours

after his ICU admission, P.G.'s ICP and blood pressure are 18 mm Hg and 115/62 mm Hg, respectively; at 4 hours, they are 24 mm Hg and 110/55 mm Hg, respectively.

12. **Which one of the following is the best strategy for improving P.G.'s CPP?**
- A. Administer 150 mL of 7.5% NaCl.
  - B. Begin norepinephrine 4 mcg/minute.
  - C. Administer 1 unit of packed red blood cells.
  - D. Increase the midazolam infusion to 5 mg/hour.
13. During the next 20 hours, P.G.'s ICP remains greater than 20 mm Hg despite aggressive sedation and hyperosmolar therapy. **Which one of the following is the most appropriate treatment strategy for P.G.?**
- A. Administer a single dose of a neuromuscular blocker to assess responsiveness of ICP to this agent.
  - B. Administer methylprednisolone 200 mg intravenously, followed by an intravenous infusion of 400 mg/hour for 48 hours.
  - C. Administer pentobarbital 1900 mg intravenously over 4 hours, followed by pentobarbital 75 mg/hour intravenously.
  - D. Increase the ventilator respiratory rate to 20 with a target PaCO<sub>2</sub> of 25–30 mm Hg.
14. **On day 1 of his ICU admission, which one of the following is the most appropriate target glucose range for P.G.?**
- A. 80–199 mg/dL.
  - B. 80–110 mg/dL.
  - C. 60–110 mg/dL.
  - D. 60–159 mg/dL.
15. On day 2 of his ICU admission, the nutrition support team is consulted to provide recommendations. **Which one of the following responses is most appropriate for P.G.?**
- A. He should be initiated on nutrition support within the first 5 days of his ICU admission to reduce his risk of mortality.
  - B. His weight-based caloric and protein requirements are lower than normal because of his comatose state.
  - C. Parenteral nutrition is preferred to enteral nutrition because of the risk of gastroparesis.
  - D. Jejunal feeding has been associated with improved nutritional outcomes compared with gastric or parenteral feeding routes.
16. A new neurosurgical staff member mentions to you that she has rarely observed posttraumatic seizures in patients with severe TBI regardless of whether

they received phenytoin. In the institution where she completed her neurosurgical residency, it was uncommon to give seizure prophylaxis in patients with TBI. You respond that this is not completely surprising because the landmark prospective study comparing phenytoin with placebo in patients with TBI showed a seizure incidence of 3.6% and 14.2%, respectively. **On the basis of these findings, which one of the following is the number of patients with TBI needed to receive phenytoin to prevent one seizure?**

- A. 4.
- B. 9.
- C. 25.
- D. 96.

**Questions 17 and 18 pertain to the following case.**

S.O. is a 43-year-old man who sustained a severe TBI 22 days ago. He has been in the trauma ICU since admission, and has had a ventriculostomy since hospital day 1. S.O.'s current GCS score is 5. Overnight, S.O. develops a high temperature (102.5°F [39.2°C]) and leukocytosis (WBC  $21.4 \times 10^3$  cells/mm<sup>3</sup>). Blood cultures and a CSF culture from the ventriculostomy were collected last night. Today, the blood culture shows gram-negative bacilli in all four bottles, and the CSF culture shows several gram-negative bacilli. S.O. was previously treated for *Pseudomonas aeruginosa* meningitis from hospital days 9 to 20.

**17. Pending final culture and sensitivity reports, which one of the following is the best empiric antibiotic therapy for S.O.?**

- A. Intravenous vancomycin and ceftriaxone.
- B. Intravenous vancomycin and piperacillin/tazobactam.
- C. Intravenous vancomycin and cefepime plus intrathecal tobramycin.
- D. Intravenous meropenem plus intrathecal tobramycin.

**18. It is now day 36 of S.O.'s hospitalization. He has had only a slight improvement in his neurologic examination (current GCS score, 7). The surgical resident asks your opinion regarding pharmacologic agents that might be beneficial for promoting awakening in patients with TBI. You respond that several agents have been used for this indication with limited success. Which one of the following agents has the strongest evidence for efficacy?**

- A. Amantidine.
- B. Methylphenidate.
- C. Donepezil.
- D. Sertraline.

**19. A neurosurgeon approaches you regarding the routine preoperative use of recombinant factor VIIa in patients with TBI with evidence of traumatic intracerebral bleeding on head CT. Which one of the following presents the best reason for not using factor VIIa routinely in such patients?**

- A. It has U.S. Food and Drug Administration-approved labeling only for the treatment of bleeding episodes in hemophilia A or B with inhibitors to factor VIII or IX.
- B. It is a nonformulary drug in your institution with a cost approaching \$10,000 per treatment course.
- C. There is no clear benefit in patients with TBI, and there may be an increased risk of an arterial thromboembolic event.
- D. The drug is clearly effective in patients with spontaneous hemorrhage, but there are no data available in patients with TBI.

**20. Your pharmacy director is presenting a proposal to the hospital's executive staff regarding the expansion of clinical pharmacy services to another ICU. Currently, clinical pharmacists are members of the medical, surgical, and neonatal ICU teams. Which one of the following is the most compelling reason to support the expansion of clinical pharmacy services to the neurosurgery ICU?**

- A. On the basis of the Clinical Pharmacy Task Force Position Paper endorsed by the Society of Critical Care Medicine and the American College of Clinical Pharmacy, optimal pharmaceutical care of patients warrants a critical care pharmacist's presence in all ICUs.
- B. The presence of a critical care pharmacist within a neurosurgery ICU would be an opportunity for the institution to distinguish itself by starting a novel clinical practice.
- C. Critical care pharmacy services within a neurosurgery ICU are associated with improved neurologic outcomes in patients with TBI because of minimization of adverse drug events.
- D. Dedicating critical care pharmacy services to a neurosurgical service including the neurosurgery ICU is cost-effective and decreases hospital length of stay.