Chapter 77: Acute Management of the Brain Injury Patient

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KEY CONCEPTS

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1. Cerebral ischemia is the key pathophysiologic event that triggers secondary neuronal injury following severe traumatic brain injury (TBI). Intracellular calcium accumulation is postulated to be a central pathophysiologic process in amplifying and perpetuating secondary neuronal injury via inhibition of cellular respiration and enzyme activation.

2. *Guidelines for the Management of Severe Brain Injury*, 4th edition, published by the Brain Trauma Foundation (BTF)/American Association of Neurological Surgeons (AANS), serves as the foundation on which clinical decisions in managing adult neurotrauma patients are based; comparable guidelines for infants, children, and adolescents have also been published.

3. Correcting and preventing early hypotension (systolic blood pressure [SBP] less than 100-110 mm Hg depending on age) with an SBP goal of 120 to 140 mm Hg and reversal of hypoxemia are primary goals during the initial resuscitative and intensive care of patients with severe TBI.

4. Nonpharmacologic management of intracranial hypertension includes raising the head of the bed 30°, and ventricular drainage if an extraventricular drain (EVD) is present.

5. The principal monitoring parameter for patients with severe TBI within the intensive care environment is increased intracranial pressure (ICP). Cerebral perfusion pressure (CPP) is also a critical monitoring parameter and should be maintained between 60 and 70 mm Hg (8.0 and 9.3 kPa) (greater than 40 and 50 mm Hg [5.3 and 6.7 kPa] in pediatric patients) through the use of fluids, vasopressors, and/or ICP normalization therapy.

6. Nonspecific pharmacologic management of intracranial hypertension should include analgesics, sedatives, and antipyretics; paralytics may be advantageous under selected circumstances.

7. Specific pharmacologic management of intracranial hypertension includes mannitol, hypertonic saline, furosemide, and high-dose pentobarbital. Neither routine use of corticosteroids nor aggressive hyperventilation (ie, $PaCO_2$ less than 25 mm Hg [3.3 kPa]) should be used in the management of intracranial hypertension.

8. Numerous investigational strategies targeted at limiting injury and/or stimulating axonal repair following severe TBI have been employed; however, no proven therapeutic benefits have been identified.

9. Use of phenytoin (alternatively levetiracetam) for the prophylaxis of posttraumatic seizures generally should be discontinued after 7 days if no seizures are observed.

BEYOND THE BOOK

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Watch the video entitled "Overview of Traumatic Brain Injury (TBI)" (https://www.youtube.com/watch?v=T0WBMM7WKL4) presented by Dr. Christopher Wolf and moderated by Brent Ghan at the University of Missouri School of the Health Professions. This 7.5-minute video provides a general overview of human brain anatomy and physiology and a succinct introduction to the more detailed pathophysiology outlined in the chapter and a context for understanding TBI pharmacologic and nonpharmacologic management. This includes TBI pathophysiology including cerebral contusions, diffuse axonal injury, secondary brain injury, in addition to TBI recovery.

INTRODUCTION

TBI is one of the leading causes of death and disability in the United States.[1] A focus on TBI prevention, improved acute care, and rehabilitation remain national priorities. This chapter summarizes TBI epidemiology and pathophysiology, and highlights the major guidelines and systematic literature reviews pertaining to the severe TBI management.

EPIDEMIOLOGY

Approximately 2.87 million persons sustain a TBI each year in the United States equating to one occurring nearly every 11 seconds.[1] Among these individuals, over 288,000 require hospital admission, and over 56,000 die annually.[1] Importantly, an estimated 5.3 million Americans live with disabilities resulting from their TBI, highlighting the enormous physical and emotional toll of this healthcare problem.[2] The economic effects of acute neurotrauma are also enormous, with estimates of direct and indirect spending on patients requiring hospitalization reaching $76.5 billion in the United States in 2010.[2] Economic costs to society from lost productivity are also massive, especially considering the young age of many patients with TBI.[2] Falls are the leading cause of unintentional TBI (48%), while TBI-related hospitalizations and deaths vary based on age.[1,2] For example, death rates from TBI after a fall are highest in patients aged 65 years or older while motor vehicle crashes are the leading cause of death in persons aged 15 to 34 years and adults over 75 years.[1]

PRIMARY AND SECONDARY BRAIN INJURY PATHOPHYSIOLOGY

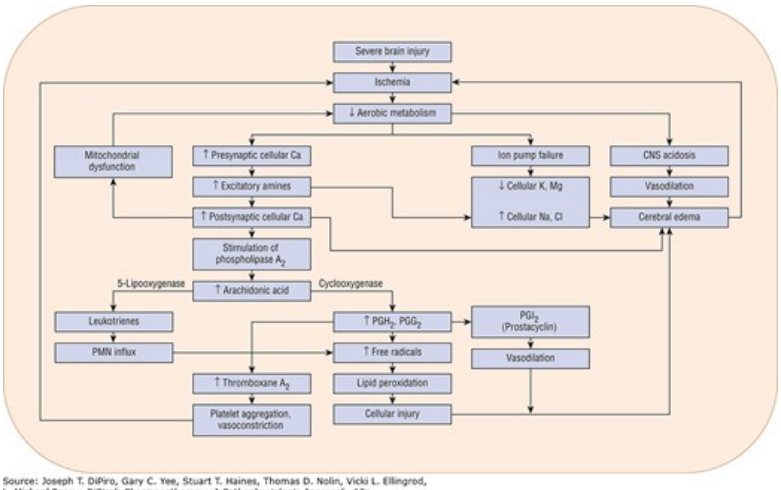
The neurologic sequelae of brain trauma can occur instantaneously as a consequence of the primary injury or can result from secondary injuries that follow within minutes, hours, or days after the initial injury.[3] Primary injury involves the external transfer of kinetic energy to various structural components of the brain (eg, neurons, nerve synapses, glial cells, axons, and cerebral blood vessels). The biomechanical forces responsible for primary brain injury can be classified broadly as contact (eg, blunt-object blow, penetrating-missile injuries) and acceleration/deceleration (eg, instantaneous brain movements following motor vehicle accidents).[3] Contact forces to the head commonly result in skull fractures, brain contusions, and/or hemorrhages. Primary brain injuries are categorized further as focal (eg, contusions, hematomas) or diffuse,[3,4] with the latter usually being associated with shearing or stretch forces, which primarily affect axons within the brain (ie, diffuse axonal injury).[4] The type of primary injury (ie, focal vs diffuse) is a major factor as to which of the secondary injury mechanisms discussed below will predominate following a TBI; however, many patients, especially those involved in high-speed accidents, sustain both types of injury.[3,4]

1 A complex sequence of pathophysiologic events precipitated by primary brain injury may seriously disrupt the normal central nervous system (CNS) balance between oxygen supply and demand resulting in a metabolic crisis.[5,6] Hypotension during the early posttraumatic period is a major contributor to this imbalance and a primary determinant of outcome. The end result of this imbalance is cerebral ischemia, the key pathophysiologic event triggering secondary injury.[5] Figure 77-1 is a simplified schematic of the processes that constitute secondary brain injury and their various interrelationships. The brain is particularly susceptible to ischemia because of its normally high resting energy requirement and its limited capacity to store oxygen, glucose, and adenosine triphosphate (ATP). These phenomena can result in imbalances in cerebral oxygen delivery (CDO_2) and cerebral metabolic rate of oxygen consumption ($CMRO_2$), processes that are closely autoregulated under normal circumstances.[5] Factors that can diminish cerebral oxygen supply following brain injury include cerebral edema, expanding mass lesions (eg, epidural, subdural, and intracerebral hematomas),

cerebral vasospasm, and loss of vasoregulatory control. Vasogenic cerebral edema can develop as a consequence of cerebral capillary endothelial damage and disruption of the blood–brain barrier.[6] Cytotoxic cerebral edema is a consequence of loss of cell wall integrity that accompanies ischemia or hypoxia with accumulation of lactic acid secondary to anaerobic metabolism.[7] With cytotoxic and vasogenic edema comes expansion of the intracellular and extracellular fluid spaces, respectively. Increased intracranial pressure (ICP) is the most detrimental consequence of cerebral edema formation, which occurs as the brain tissue volume increases within the nondistensible skull. A significant ICP increase may further compromise cerebral blood flow (CBF) and extend cytotoxic edema. Hence, increased ICP can be self-perpetuating unless reversed. Hypoxemia can further exacerbate local decreases in cerebral oxygen supply following acute respiratory failure and systemic hypotension. Metabolic demand also can increase following neurotrauma secondary to seizures, agitation, and temperature elevation.

FIGURE 77-1

Schematic illustration of the cascade of biochemical events proposed to occur following severe neurotrauma (secondary brain injury). (Ca, calcium; Cl, chloride; CNS, central nervous system; K, potassium; Mg, magnesium; Na, sodium; PMN, polymorphonucleocyte; PGH_2, prostaglandin H_2; PGG_2, prostaglandin PGG_2; PGI_2, prostaglandin PGI_2.)



Two distinctive end points along the spectrum of secondary neuronal injury are: (a) energy-independent cellular necrosis characterized by membrane cell lysis, edema, and inflammation, and (b) energy-independent apoptosis leading to cell shrinkage and cell membrane dissolution.[7] Apoptosis, which is also known as programmed cell death, requires a cascade of intracellular events for cell death completion with ionic homeostasis loss being postulated as a key event in fostering secondary brain injury following cerebral ischemia.[7] In this process, cellular influx of sodium, chloride, magnesium, and water occurs with a corresponding efflux of potassium secondary to cytotoxic edema and Na^+-K^+-ATPase pump dysfunction. Calcium influx into the presynaptic terminal ends of damaged neurons is mediated by N-type voltage-sensitive calcium channels and is postulated to stimulate excessive release of the excitatory amines glutamate and aspartate from the affected neurons. These amines then accumulate in the neuronal synaptic cleft in the presence of cellular energy failure, resulting in ongoing stimulation of postsynaptic cells, which extend neurotoxicity and cell death. The influx of calcium and additional sodium is stimulated by activation of ionophore receptors including the *N*-methyl-D-aspartate (NMDA) receptor.[7] Calcium influx and its intracellular accumulation initiate a number of events that amplify and perpetuate secondary neuronal injury as well as mitochondrial dysfunction, which further inhibits cellular respiration, a process already affected by ischemic and/or hypoxic insults.[5,7] A second major deleterious effect of calcium is activation of autodestructive enzymes, including phospholipases, endonucleases, and proteases, such as the caspase family of enzymes.[7] The effect of phospholipase A_2 stimulation includes formation of several arachidonic acid metabolites derived from membrane lipids (eg, thromboxane A_2, prostaglandins, and leukotrienes) that facilitate lipid peroxidation and reactive oxygen species formation.[5,7] This event occurs early after injury (eg, before hospitalization), which may limit the effectiveness of exogenously administered antioxidants. Cell-mediated injury involving inflammatory mediators (eg, proinflammatory cytokines) and nitric oxide activation is another possible mechanism involved in secondary neuronal injury,[6,7] implicating polymorphonuclear neutrophils, platelets, endothelial cells, and macrophages. However, activation of some inflammatory mediators may actually be beneficial, such that the relative balance of the mediators rather than absolute concentrations may be the

most significant pathophysiologic factor following TBI. Stimulation of platelet aggregation, vasodilation, and vasoconstriction also may occur.[5]

CLINICAL PRESENTATION

CLINICAL PRESENTATION: ACUTE BRAIN INJURY

General

- Level of consciousness on admission ranges from completely unresponsive to awake and alert (ie, Glasgow Coma Scale 3-15 [Table 77-1]).

Symptoms

- Posttraumatic amnesia (eg, greater than 1 hour), increasing dizziness, a moderate-to-severe headache, nausea/vomiting, limb weakness, or paresthesia may indicate more severe injury.

Signs

- Cerebrospinal fluid (CSF) otorrhea or rhinorrhea, seizures, or unequal or unreactive pupils may indicate more severe injury.
- A rapid deterioration in mental status strongly suggests the presence of an expanding lesion within the skull.
- Severe TBI may be accompanied by significant alterations or instability in vital signs, including abnormal breathing patterns (eg, apnea, Cheyne–Stokes respiration, tachypnea), hypertension, or bradycardia.

Laboratory Tests

- Arterial blood gases (ABGs) indicating hypoxia (ie, decreased PaO_2) or hypercapnia (ie, increased $PaCO_2$) may indicate compromised ventilation.
- Blood ethanol concentration and/or urine toxicology results indicates that substance intoxication may be affecting the patient's mental status in addition to the TBI.
- Electrolyte disturbances can cause alterations in mental status, and their effects may interfere with assessment of the patient's neurological status.

Other Diagnostic Tests

- CT scan of the head is an important diagnostic tool for detecting the presence of mass lesions and structural signs of edema (eg, midline shift, compressed ventricles).

The Glasgow Coma Scale (GCS) was designed nearly 50 years ago and is still the most widely used system to grade the arousal and functional capacity of the cerebral cortex,[3] as it defines the level of consciousness according to eye opening, motor response, and verbal response (Table 77-1). A GCS score of 15 corresponds to a normal neurologic examination based on eye, motor, and verbal responses. Scores from 3 to 8 correspond to severe brain injury, while scores from 9 to 12 and 13 to 15 is consistent with moderate, and mild or minor brain injury, respectively.[3] Always consider the impact of ethanol or substance intoxication, hypotension, hypoxia, postictal state, hypoglycemia, electrolyte imbalances, or hypothermia on altering the neurologic examination when administering this scale. Opiates, sedatives, and neuromuscular blockers should not be administered until the initial examination is complete, if at all possible, as they affect the neurologic examination. Simple, rapidly attainable clinical variables that are predictive of poor outcomes include extremes of age, presence of hypotension, hypoxia and/or coagulopathy, increased ICP, decreased GCS score (especially the motor score), and pupillary changes.[8]

TABLE 77-1

Glasgow Coma Scale

Response	Score
Eyes	
• Open spontaneously	4
• To verbal command	3
• To pain	2
• No response	1
Best motor response	
• To verbal command • Obeys	6
• To painful stimulus (pressure to nailbeds)	
• Localizes pain	5
• Flexion, withdrawal	4
• Flexion, abnormal (decorticate rigidity)	3
• Extension (decerebrate rigidity)	2
• No response	1
Best verbal response (Arouse patient with painful stimulus if necessary)	
Oriented and converses	5
Disoriented and converses	4
Inappropriate words	3
Incomprehensible sounds	2

No response	1
Total	3-15

TREATMENT

Desired Outcomes

The overall goal in TBI management is reduction in morbidity and mortality, and optimization of long-term functional outcome for patients. This requires careful attention to the following short-term therapeutic goals: (a) establishment of an adequate airway and maintenance of ventilation and circulation during the initial period of resuscitation and evaluation, (b) maintenance of balance between CDO_2 and $CMRO_2$, (c) prevention or attenuation of secondary neuronal injury, and (d) prevention and/or treatment of associated medical complications.

General Approach to Treatment

The Brain Trauma Foundation (BTF) has developed an extensive document entitled *Guidelines for the Management of Severe Brain Injury* as a joint initiative with the Guidelines Committee of the American Association of Neurological Surgeons (AANS), the Joint Section on Neurotrauma and Critical Care of the AANS, and the Congress of Neurological Surgeons.[9] This document presently constitutes the most widely accepted evidence-based standards, guidelines, and options for the care of patients with severe TBI in the United States.[10] Recommendations are reported as Level I (high quality of evidence), Level II (moderate quality of evidence), or Level III (low quality of evidence). Data show that compliance with the BTF/AANS guidelines results in improved patient outcomes relative to mortality, functional outcome scores, length of hospitalization, and cost. Additionally, guidelines addressing prehospital TBI management[11] and surgical management[12] have also been published, as have TBI management guidelines for infants, children, and adolescents.[13] The recommendations emanating from the published BTF/AANS guidelines on TBI management and various published systematic reviews will be highlighted throughout the remaining portion of this chapter. Recommendations from the BTF/AANS guidelines should serve as the foundation on which all clinical decisions in managing severe TBI are based. Nonetheless, it should be noted that the majority of the guidelines are based on Class II evidence (primarily prospective clinical trials) and Class III evidence (primarily retrospective clinical trials) as few Class I evidence studies (ie, prospective, randomized, controlled trials) are available for treatment of TBI. The pharmacologic management of TBI is summarized in Table 77-2. Recommendations provided in this chapter pertain to adults and children unless specifically noted to the contrary.

TABLE 77-2

Pharmacologic Management of TBI

Hyperosmolar therapy

Mannitol effectiveness in lowering ICP is uncertain (no recommendation level due to insufficient evidence).

Hypertonic saline effectiveness in lowering ICP is uncertain (no recommendation level due to insufficient evidence).

Deep venous thrombosis prophylaxis

LMWH or low-dose unfractionated heparin may be used in combination with mechanical prophylaxis. However, there is an increased risk of expansion of intracranial hemorrhage (Recommendation level III).

Anesthetics, analgesics, and sedatives

Prophylactic administration of barbiturates to reduce burst suppression ECG is not recommended (Recommendation level II B).

High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment in adults. Hemodynamic stability is essential before and after barbiturate therapy (Recommendation level II B).

Propofol is recommended for the control of ICP, but not for improvement in mortality or 6-month outcomes. High-dose propofol can produce significant morbidity (Recommendation level II B).

Antiseizure prophylaxis

Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS (occurring later than 7 days) (Recommendation level II A).

Phenytoin is recommended to decrease the incidence of early PTS (within 7 days of injury) (Recommendation level II A).

Levetiracetam cannot be recommended over phenytoin regarding efficacy in preventing early PTS and toxicity. (No recommendation based on insufficient evidence.)

Corticosteroids

The use of steroids is not recommended for improving outcome or reducing ICP in patients with TBI. In patients with moderate or severe TBI, high-dose methylprednisolone is associated with increased mortality and is contraindicated (Recommendation level I).

ECG, electrocardiogram; LMWH, low-molecular-weight heparin; PTS, posttraumatic seizures; TBI, traumatic brain injury. Level I: Recommendation based on a high-quality body of evidence. Level II A: Recommendation based on a moderate-level quality of evidence. Level II B: Recommendation based on a low-quality body of evidence (direct evidence but overall low quality). Level III: Recommendation based on a low-quality body of evidence.

Data from Reference 9.

Pharmacologic Therapy

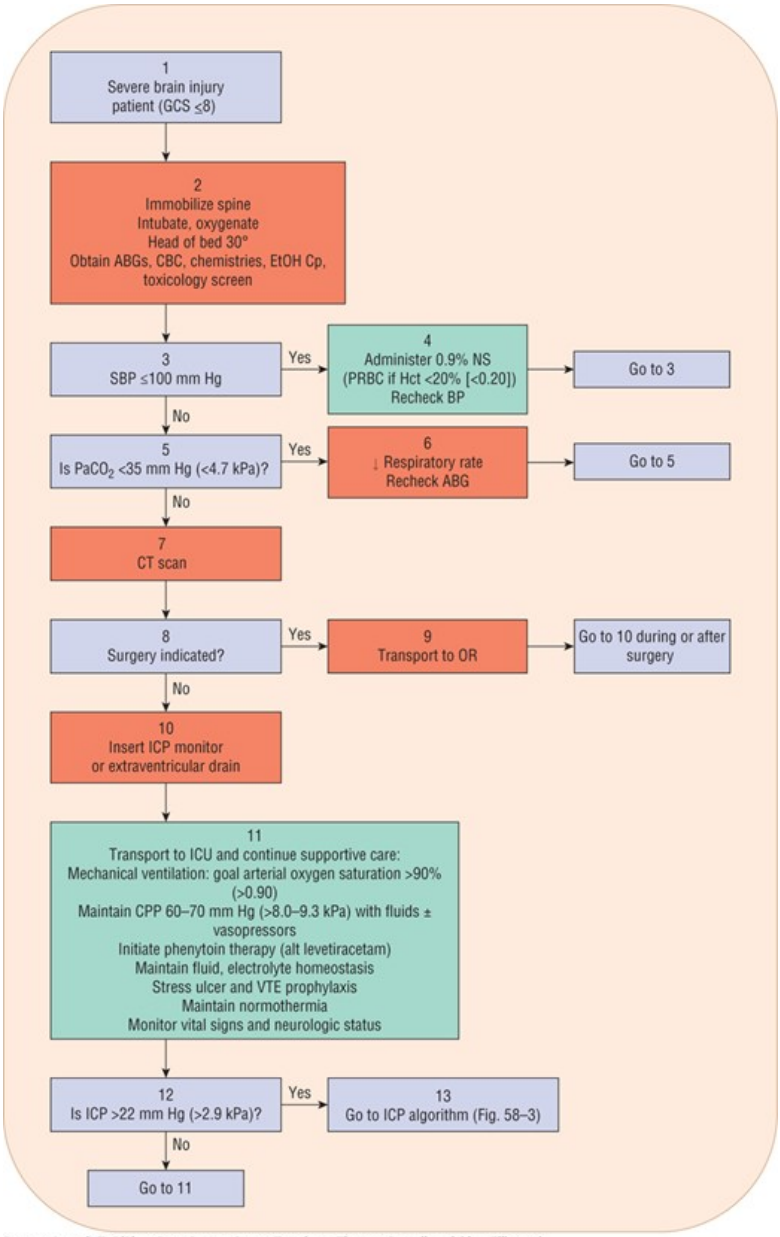
Initial Resuscitation

3 4 The first priority in the unconscious patient is airway establishment that facilitates adequate oxygenation and prevents aspiration.[14] Thereafter, restoration and maintenance of systolic blood pressure (SBP) between 120 and 140 mm Hg is desired since having an admission SBP outside this range is associated with increased mortality.[15] More specifically correcting and preventing early hypotension (goal SBP >100 mm Hg for patients ages 50 to 69 years or >110 mm Hg for patients ages 15 to 49 or over 70 years) is critical as it is among the most powerful predictors of outcome.[9] Isotonic saline (0.9% normal saline) and lactated Ringer's solution have been traditionally used as initial resuscitation fluids of choice in patients with TBI. While some clinicians believe that hypertonic saline (eg, 3% or 7.5% saline) is beneficial in this situation, clinical studies yield equivocal results relative to their superiority over isotonic solutions.[16] Regardless, no clear consensus exists as to the optimal initial resuscitation fluid. Furthermore, the volume of crystalloids administered requires careful monitoring considering there are data associating lower volumes with improved survival.[17] While colloids may be considered an alternative to crystolloid therapy, strong recommendation against their use was made within a consensus statement regarding fluid therapy in neurointensive care patients.[18]

Vasopressors and inotropic agents may be needed to maintain an adequate mean arterial pressure (MAP) if hypotension persists after adequate restoration of intravascular volume. Nonpharmacologic management of intracranial hypertension includes raising the head of the bed 30°, and ventricular drainage if an extraventricular drain (EVD) is present. Figure 77-2 is an algorithm summarizing treatment priorities in the initial management of acute TBI.

FIGURE 77-2

Algorithm for the acute management of the patient with a TBI. (BP, blood pressure; CBC, complete blood count; CPP, cerebral perfusion pressure; CT, computed tomography; EtOH Cp, ethanol plasma concentration; Hct, hematocrit; ICU, intensive care unit; NS, normal saline; OR, operating room; $PaCO_2$, partial pressure of arterial blood carbon dioxide; PRBC, packed red blood cells.) *(Reprinted, with permission, from Management of Acute Traumatic Brain. In: Richardson M, Chant C, Chessman KH, et al., eds.* Pharmacotherapy Self-Assessment Program, *7th ed. Neurology and Psychiatry. Lenexa, KS: American College of Clinical Pharmacy, 2012:143.)*



Postresuscitative Care

Following successful resuscitation, priorities shift toward diagnostic evaluation of intracranial and extracranial injuries, and emergent surgical intervention as needed. In many patients, evacuation of intracranial hematomas (ie, epidural, subdural, and intracerebral hematomas) is essential to control ICP and improve outcome. Elevation of depressed skull fractures and debridement of penetrating wound tracts are other important emergent surgical procedures. Decompressive craniectomies (ie, removal of a variable amount of skull bone) with or without temporal or frontal lobectomy may be considered in patients with increases in ICP refractory to more conservative measures.[5] In the largest randomized study to date, patients with TBI and refractory elevated ICPs undergoing decompressive craniectomy had significantly improved survival but higher rates of vegetative state and disability compared with medical therapy.[19] Thus, decompressive surgery's role in adult patients with TBI and refractory ICP remains controversial in light of these quality of life data outcomes.

Continuous ICP monitoring (eg, EVD and/or intraparenchymal fiberoptic catheter) has been the mainstay of ICP monitoring and treatment for decades in patients with severe TBI. Extraventricular drains have a therapeutic advantage over the alternatives but are associated with higher complication rates and can be difficult to place in the setting of the swollen brain. Specifically, while CSF can be drained using this device as a means to lower ICP, the most recent BTF/AANS guidelines have softened the indications for ICP monitoring based on data suggesting that invasive monitoring may lack superiority over clinical/radiologic monitoring; challenging the traditional paradigm.[9,20] If continuous ICP monitoring is employed, the goal should be to treat any ICP values above 22 mm Hg (2.9 kPa) since values above this level are associated with increased mortality.[9]

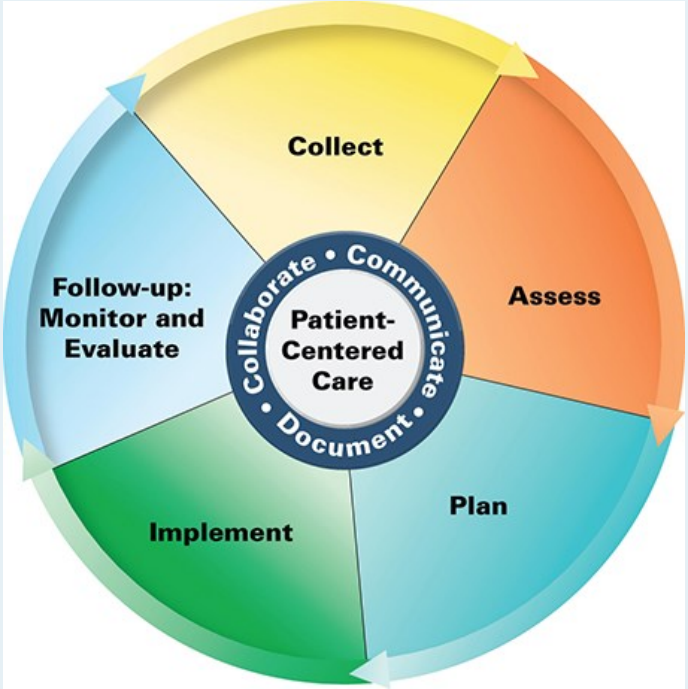
Yet another approach to ICP monitoring or no ICP monitoring is multimodality neuromonitoring (MMM).[21] This practice involves using advanced technologies such as cerebral microdialysis, CBF, brain tissue oxygenation, electroencephalography (EEG), near-infrared spectroscopy, pressure reactivity, and/or transcranial doppler (TCD) monitoring in combination. Although this practice assesses a wide array of cerebral metabolic, oxygen, and cerebrovascular measurements, MMM use is limited to institutions that are equipped to perform such measurements and have individuals capable of utilizing these data to guide expeditious therapy.[22] Furthermore, each of the MMM techniques either alone or in combination with conventional ICP monitoring has limitations and/or potential risks. As such, BTF/AANS guidelines only recommend considering jugular venous oxygen saturation monitoring as a potential advanced monitoring modality to improve outcome in patients with TBI.[9] Biochemical markers (eg, S-100 calcium-binding protein B, neuron-specific enolase, glial fibrillary acid protein, serum substance P[23]) may also have utility in diagnosing and monitoring patients with TBI. However, their role has yet to be defined as each have assorted limitations.[24]

5 Another important monitoring parameter within the intensive care environment is the cerebral perfusion pressure (CPP), which is the difference between MAP and ICP (ie, CPP = MAP – ICP). Maintenance of an acceptable CPP is postulated to be critical in reducing cerebral ischemia and secondary injury. The BTF/AANS guidelines recommend maintaining a CPP range between 60 and 70 mm Hg (8.0 and 9.3 kPa).[9] It is also recommended that aggressive attempts to maintain CPP greater than 70 mm Hg (9.3 kPa) in adults should be avoided due to the risk of the acute respiratory distress syndrome. In children, the recommended CPP goal is between 40 and 50 mm Hg (5.3 and 6.7 kPa). While using a fixed target range is the most common approach for monitoring CPP, the concept of individualizing the CPP target range to restore cerebral vasoreactivity has been advocated.[23,25]

In order to achieve the goal CPP, the MAP may need to be increased either through the use of fluids and/or vasopressors, and/or by lowering elevated ICP. In general the goal of volume expansion should be euvolemia to avoid a hypoosmolar state and negative fluid balance.[26] If the hemoglobin is below 7 g/dL (70 g/L; 4.34 mmol/L), transfusion of packed red blood cells (PRBCs) is indicated. Liberal transfusions should be avoided since using a target goal of 10 g/dL (100 g/L; 6.21 mmol/L) is associated with a higher incidence of thromboembolic events without neurologic outcome improvement based on a randomized trial.[27] More data are needed before these findings can be applied to all patients with TBI. Furthermore, erythropoietin use was not associated with an improved neurologic outcome in the same trial.[27] Volume status should be targeted to a central venous pressure of 7 to 12 cm H_2O (0.7-1.2 kPa) if invasive monitoring is employed. After euvolemia is achieved, the patient's head should also be elevated by 30° to promote venous drainage and decrease ICP.[9] If intravascular volume restoration is inadequate in elevating MAP to an acceptable level, hypertension should be induced using vasopressors (eg, norepinephrine, phenylephrine, dopamine)[9] and patients should be monitored for renal dysfunction, lactic acidosis, and signs of peripheral ischemia when they are used, especially in large doses.

PATIENT CARE PROCESS

Patient Care Process for Acute Management of the Brain Injury Patient



Collect

- GCS (Table 77-1), vital signs, physical exam and head computed tomography (CT) scan findings, ABGs, ICP and CPP (if available), laboratory data (see "Clinical Presentation" section)
- Prior and current medications, including alcohol and illicit substances

Assess

- Consistency between with the GCS/physical exam and injuries on head CT scan (ie, could there be other reasons for the neurologic deficit such as intoxication)
- ICP (goal less than 22 mm Hg [2.9 kPa]) and CPP (goal 60-70 mm Hg [8.0-9.3 kPa]) (Fig. 77-2)
- Need for general ICU supportive care including: mechanical ventilation/appropriate oxygenation, stress ulcer prophylaxis, and sedation/analgesia
- For VTE prophylaxis, it is important to determine if pharmacologic prophylaxis is contraindicated due to intracranial bleeding
- Need for other supportive care measures more specific to TBI including: spine immobilization, seizure prophylaxis, avoiding fever and excessive hyperglycemia, appropriate fluid therapy with a goal of euvolemia, and starting early enteral nutrition

Plan*

- Unless contraindicated, initiate appropriate supportive care measures for the issues outlined above in the Assess section (Fig. 77-2)
- Nonpharmacologic management of increased ICP with first-line options (eg, raise head of the bed 30°, open extraventricular drain if ICP is greater than 22 mm Hg [2.9 kPa, if present]) (Fig. 77-2)
- Pharmacologic management of increased ICP with first-line agents (eg, short-acting sedation and analgesia, and hyperosmolar agents [hypertonic saline, mannitol]) (Fig. 77-3 and Table 77-2)

- Avoid low CPP with IV fluid therapy, possible administration of blood products, or vasopressors (eg, norepinephrine, phenylephrine, dopamine) if SBP is less than 100 mm Hg
- Treat hyperthermia, if present, using antipyretic agents and/or cooling blankets
- If ICP is uncontrolled after optimizing first-line options for ICP control, move to second-line options (eg, pentobarbital, neuromuscular blocking agents, hyperventilation) (Table 77-3)

Implement*

- Work with the medical team on mutually agreeable and patient-centered implementation of treatments where some differences in opinion and practice may exist (eg, initial choice of sedatives, antiseizure medications, or hyperosmolar agents)
- Work with the medical team and nursing staff to implement an understanding of treatment goals (ie, ICP and CPP), as well as clear priorities in treatment selection and escalation among the many options for treating elevated ICP

Follow-up: Monitor and Evaluate

- Monitor ICP and CPP, especially response to therapies for elevated ICP to determine which modalities work best in each patient (Fig. 77-3)
- Other routine monitoring includes GCS, fluid/electrolyte status, ABGs, and vital signs (Table 77-4)
- Medication-specific monitoring includes issues such as: hypotension from sedatives/opiates, hypertriglyceridemia or PRIS from propofol, risk of bleeding/worsening intracranial hemorrhage from VTE prophylaxis agents, antiseizure medication adverse events such as rash, acute kidney injury from mannitol, or hypernatremia/hyperchloremia from hypertonic saline (Table 77-3)
- Discontinue seizure prophylaxis after 7 days if no seizures occur in the hospital (Table 77-2)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Anesthetics, Analgesics, and Sedatives

6 Analgesics and sedatives have an important primary role in the management of intracranial hypertension (Fig. 77-3 and Table 77-3) that are directly related to the association of pain, agitation, excessive muscle movement, and resisting mechanical ventilation with transient increases in ICP. Paralytics are a secondary option in refractory patients or during stimulatory procedures in patients with elevated ICP.[28] There is no strong evidence that one agent is superior to another in affecting patient outcomes with severe TBI[29] as their effects on ICP, CPP, and MAP are variable.[29] Morphine sulfate is the most commonly used analgesic and sedative in this setting[9,29] and bolus doses of opiates may increase ICP by increasing CBF.[29] While continuous infusions of fentanyl and sufentanil are gaining in popularity, their use also may be associated with mild elevations in ICP.[9,29] Propofol has become the sedative of choice in the treatment of patients with TBI among many clinicians because of its ease of titration, rapidly reversible effects on discontinuation, and possible neuroprotective effects.[9] Although it is used for sedation in infants and children who are mechanically ventilated in the intensive care unit (ICU) setting, the Food and Drug Administration (FDA) requires that the manufacturer labeling contains specific information that it is not approved for sedation of pediatric patients admitted to an ICU. Propofol's biggest safety concerns is the propofol infusion syndrome (PRIS) characterized by hyperkalemia, hepatomegaly, lipemia, metabolic acidosis, myocardial failure, rhabdomyolysis, renal failure, and death in some cases.[30] While initially reported in children, PRIS can also occur in adults; therefore, doses greater than 5 mg/kg/hr and infusions exceeding 48 hours should be used with extreme caution.[30] Triglyceride concentrations also should be monitored in patients receiving prolonged propofol infusions and/or high dosages considering its lipid emulsion formulation and the potential for inducing hypertriglyceridemia under these conditions. Furthermore, evidence of neurotoxicity from animal studies has raised concerns regarding use of this sedative in patients with TBI.[30] Alternative sedatives include short-acting benzodiazepines (eg, midazolam), especially if there is a reasonable suspicion of alcohol withdrawal as the underlying etiology of the agitation,[31] and intermittent low-dose pentobarbital, ketamine,[32] dexmedetomidine,[33,34] or etomidate (particularly useful in rapid-

induction anesthesia). The potential for these agents to decrease MAP and CPP must be monitored closely.[29,30,33] Additionally, the cumulative sedative effects of longer-acting medications, especially benzodiazepines, must be taken into account. The use of any sedative or paralytic agent also must be weighed against its potential to obscure the neurologic examination of the patient.

FIGURE 77-3

Algorithm for the management of increased ICP. (Cp, plasma concentration; EEG, electroencephalogram; ICU, intensive care unit; OR, operating room; $PaCO_2$, partial pressure of arterial blood carbon dioxide.) (*Reprinted, with permission, from Management of acute trauma. In: Richardson M, Chant C, Chessman KH, et al., eds. Pharmacotherapy Self-Assessment Program, 7th ed. Neurology and Psychiatry. Lenexa, KS: American College of Clinical Pharmacy, 2012:144.*)

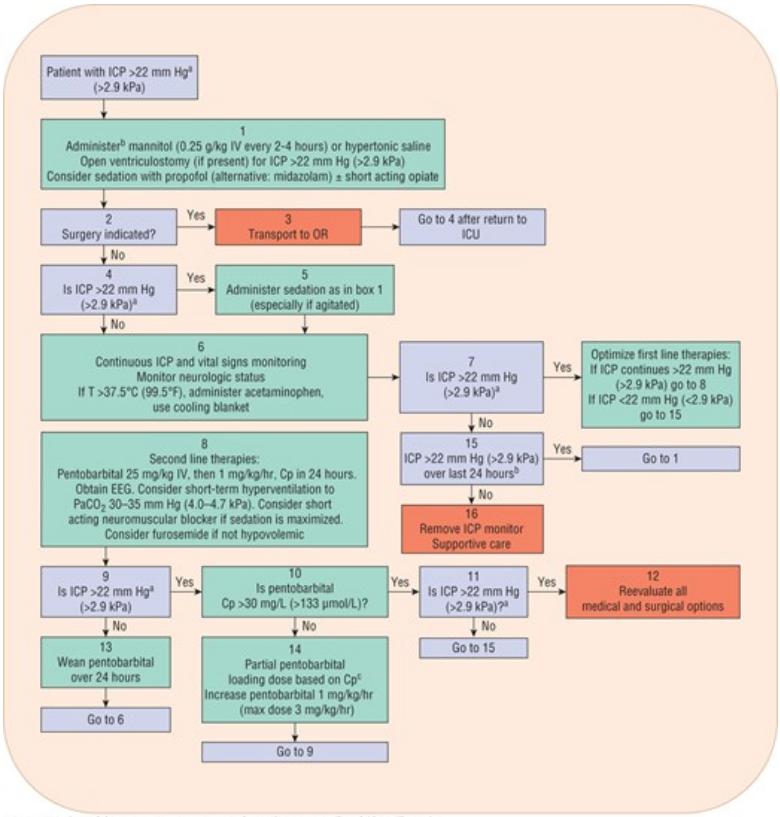


TABLE 77-3

Medication Dosing and Monitoring in Patients with TBI

Medication (Brand Name)	Adverse Medication Reactions	Monitoring Parameters	Dosage	Comments
Levetiracetam (Keppra)	CNS changes	Seizures, SCr	500-1,000 mg IV Q12 hr (during first 14 days)	Caution in patients with renal dysfunction If used for active seizures: increase to 1,000 mg every 12 hours after 14 days, then to 1,500 mg every 12 hours after 28 days
Mannitol (Generic)	Hypotension, renal dysfunction, hyperosmolality	ICP, CPP, BP, serum osmolality, Na, UO, SCr	0.25-1 g/kg IV every 2-4 hours	Avoid in patients with renal failure or CHF
Pentobarbital (Nembutal)	Hypotension, GI hypomotility, induction of hepatic medication metabolism	ICP, CPP, BP, EEG, GI function	10 mg/kg IV over 30 minutes, then 5 mg/kg over 3 hours, then 1 mg/kg/hr	Administer via central line. General dose range for infusion is 1-3 mg/kg/hr
Phenytoin (Dilantin)	Hypotension, dysrhythmias, nystagmus, ataxia, mental status changes, exfoliative dermatitis	Seizures, BP, ECG, phenytoin concentrations, skin	15-20 mg/kg IV over 60 minutes, then 5 mg/kg/day divided every 8 hours or every 12 hours	Administer <50 mg/min; use central line if available Round loading doses up to nearest 250 mg, round maintenance doses up to nearest 25 mg Trauma patients often require higher doses (ie, >6 mg/kg/day) to achieve therapeutic concentrations
Propofol (Diprivan)	Hypotension, hyperkalemia, metabolic, acidosis, rhabdomyolysis, renal failure, hepatomegaly, lipemia	ICP, CPP, BP, SCr, K, arterial pH, triglycerides, lactate	General range: 0.5-3 mg/kg/hr titrated to desired effect	Avoid doses greater than 5 mg/kg/hr or prolonged infusions; not approved for use in children

BP, blood pressure; CHF, congestive heart failure; GI, gastrointestinal; K, potassium; Na, sodium; SCr, serum creatinine; UO, urine output.

7 High-dose barbiturate therapy (ie, barbiturate coma) has been used for decades in the management of increased ICP despite a lack of evidence documenting beneficial effects on patient morbidity and mortality.[34] Nonetheless, BTF/AANS and pediatric guidelines recommend that high-dose barbiturate therapy be considered in hemodynamically stable patients with severe TBI refractory to maximal medical ICP-lowering therapy and decompressive surgery.[9,13] Prophylactic use of barbiturates is not advocated in light of insufficient evidence supporting this practice and the potential for adverse events (eg, hypotension).[9,13,34] The mechanism responsible for the cerebral protective effects of barbiturates is generally attributed to suppression of cerebral metabolism, thereby cerebral metabolic demands and CBV.[34] Prior to inducing a barbiturate coma, the patient with severe TBI must be mechanically ventilated with continuous monitoring of arterial blood pressure, electrocardiogram (ECG), and ICP. Pentobarbital is the most commonly used barbiturate for this indication, although thiopental also has been used. Pentobarbital should be administered as an IV loading infusion totaling 25 mg/kg (ie, 10 mg/kg over 30 minutes and then 5 mg/kg/hr for 3 hours), followed by a maintenance infusion of 1 to 2 mg/kg/hr.[9,34] If the SBP falls during the loading or maintenance infusions, the rate should be slowed temporarily and blood pressure support initiated. The goal of a

barbiturate coma is to maintain ICP and CPP at the previously discussed target thresholds, as well as EEG burst suppression.[9,34] Although there is a poor correlation between serum pentobarbital serum concentrations and outcomes, the goal is to achieve steady-state concentrations between 30 and 40 mg/L (133 and 178 µmol/L).[34] Initiation of barbiturate therapy withdrawal can occur when ICP has been controlled satisfactorily for 24 to 48 hours and should be tapered over 24 to 72 hours to prevent ICP spikes.

Adverse events associated with high-dose barbiturate therapy involve primarily the cardiovascular system. Hypotension caused by peripheral vasodilation may occur in one of every four patients, necessitating decreasing the barbiturate dose or the administration of fluids and vasopressors to maintain blood pressure.[34] Gastrointestinal (GI) effects of barbiturates include decreased GI muscular tone and decreased amplitude of contraction; however, on emergence from coma, there may be a period of GI hypermotility. Care should be taken to avoid extravasation of barbiturate solutions because severe tissue damage may occur. Therefore, barbiturates should be administered by continuous infusion through a central line dedicated for this purpose. The potential for barbiturates to induce the hepatic medication metabolism of concurrent medications should be also considered. Lastly, the potential for prolonged interference with the neurologic examination of patients with TBI must be considered prior to the initiation of high-dose barbiturate therapy.

Corticosteroids

Level 7 Although corticosteroids are effective in preventing or reducing cerebral edema in patients with nontraumatic conditions that produce vasogenic edema, studies in patients with TBI have not demonstrated their ability to lower ICP or improve outcomes.[9,13] Specifically, corticosteroid use following TBI has been associated with increased mortality and complications including GI bleeding, glucose intolerance, electrolyte abnormalities, and infection. The largest investigation to date, known as the Corticosteroid Randomization After Significant Head Injury (CRASH) study, indicated a higher risk of death within 2 weeks of enrollment (relative risk 1.18) in those receiving corticosteroids compared with those receiving placebo.[35] Based on this and several other major randomized trials, the BTF/AANS adult and pediatric guidelines recommend not to use high-dose corticosteroids in patients with moderate-to-severe TBI.[9,13]

Hyperventilation

Level 7 The practice of prolonged aggressive hyperventilation ($PaCO_2$ less than 25 mm Hg [3.3 kPa]) to decrease ICP is no longer recommended[8] as this practice is not associated with improved outcomes. As such, BTF/AANS has removed this intervention as a temporizing measure in managing patients with TBI with elevated ICP from their guidelines.[9]

Hypothermia

Therapeutic hypothermia has been an attractive strategy for attempting to minimize secondary brain injury after TBI for decades. The mechanism underlying its protective effect is likely multifactorial, although a reduction in $CMRO_2$ is most frequently cited as the basis of any therapeutic benefits. Although early studies suggested its benefit for patients with TBI, as well as other patient populations with brain ischemia (eg, cardiac arrest patients), large clinical trials data of prophylactic hypothermia have not demonstrated improved outcomes, but rather may in fact indicate poorer outcomes.[9,36-39] Its potential adverse effects include coagulation disturbances, infectious complications, and cardiac arrhythmias. Thus, prophylactic therapeutic hypothermia is not recommended as a routine neuroprotective strategy,[9] except for perhaps patients with TBI with refractory ICP elevations. However, its use in this case is also unclear at best.[40]

Osmotic Agents

Level 7 Although a number of osmotic diuretics (eg, urea, glycerol) can be used to decrease ICP, mannitol is the most widely employed.[9,41] Despite the common practice of administering mannitol to patients with suspected or actual increases in ICP following brain injury, clinical trials comparing its effects against placebo have not been performed.[42] Based on this lack of evidence, the BTF/AANS guidelines removed the previous recommendation regarding mannitol's effectiveness for control of increased ICP.[9]

Mannitol's beneficial effects likely relate to (a) an immediate plasma-expanding effect that reduces blood viscosity and increases CBF, and (b)

establishment of an osmotic concentration gradient across an intact blood–brain barrier that decreases ICP as water diffuses from the brain into the intravascular compartment.[9] Recommended doses typically range from 0.25 to 1 g/kg IV every 2 to 4 hours with higher doses being used in emergency situations and the lower dose for a maintenance regimen.[43] Increased ICP is reduced within minutes following mannitol administration with a maximum effect within 20 to 60 minutes.[43] To maximize benefit and minimize adverse events, it has been suggested that mannitol be administered as a bolus and not as a continuous infusion in this setting.

Several adverse effects are associated with mannitol.[43] In addition to hypotension resulting from its diuretic effect, a reversible acute renal dysfunction may occur in patients with previously normal renal function after long-term, large-dose administration. Patients particularly susceptible are those with advanced age and preexisting renal dysfunction which is based on data in patients with intracranial hemorrhage.[44] As such, mannitol should be avoided in patients with acute kidney injury or chronic kidney diseases. Acute exacerbation of underlying congestive heart failure and pulmonary edema also may occur following rapid intravascular volume expansion and furosemide is recommended as an alternative diuretic for lowering ICP in these latter patient groups.

While hypertonic saline solutions have been advocated by some as a resuscitative fluid following TBI, solutions ranging from concentrations of 3% to 20% have also been used to acutely lower increased ICP.[43] Doses range from approximately 150 mL of 3% saline solution to 75 mL of 7.5% saline solution to 30 mL of 23.4% saline solution boluses.[43] Saline concentrations greater than 3% should be administered via a central venous catheter.[43] Not only do hypertonic saline solutions create an osmotic gradient in favor of reducing cerebral edema, but they may also have beneficial vasoregulatory, immunologic, and neurochemical effects as well.[45] Plasma expansion may also lead to an increase in CBF. However, the 2016 BTF guidelines do not recommend hypertonic saline due to a lack of supporting evidence[9] consistent with a systematic review which found no mortality benefit or beneficial effect on ICP compared with other ICP-lowering agents.[45] In most of these studies, the goal of therapy was to treat an elevated ICP; however, for some the goal was to increase the serum sodium regardless of ICP. If used in this way, hypertonic saline should target serum sodium concentration less than 160 mEq/L (mmol/L) since additional benefit is unlikely at higher concentrations.[43]

Investigational Therapy

The steady decrease in morbidity and mortality following severe neurotrauma over the past several decades can be attributed largely to the use of conventional treatment strategies to expeditiously and aggressively manage events resulting in secondary injury (ie, ischemia, hypoxia, increased ICP). Numerous neuroprotective agents targeting specific pathophysiologic processes that are theorized to occur following severe TBI have been investigated over the past three decades in an attempt to further enhance the prospects for a meaningful recovery. Prominent among these strategies have been attempts to modulate calcium influx through the administration of calcium antagonists,[46] glutamate antagonists including magnesium, and the use of antioxidants/free radical scavengers.[47,48] Inhibitors of inflammatory mediators have also been considered as potential neuroprotective agents.[48] Unfortunately, none of these agents to date has demonstrated a significant reduction in morbidity or mortality following severe TBI in clinical trials. There was immense enthusiasm for progesterone as a neuroprotective agent based on two moderately sized clinical studies that demonstrated improved outcome following acute TBI.[49] However, two subsequent large randomized, placebo controlled, prospective trials of progesterone in patients with acute TBI were halted early due to lack of functional outcomes improvement.[50,51] In contrast, interest continues to exist for the pleiotropic cytokine, erythropoietin, as a neuroprotective agent independent of its ability to increase hemoglobin concentrations[47] despite data indicating equivocal results relative to improvement in neurologic outcomes and survival benefits.[52] Other agents that may have beneficial effects in TBI based on limited clinical or epidemiologic data include 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and sympatholytics such as β-blockers.[53] While two meta-analysis of β-blockers use in patients with TBI demonstrated mortality benefits,[54,55] their usage was associated with increased infection rates, ICU length of stay, and overall hospitalization days.[55] Thus, evaluation of the benefit to risk ratio for this medication class will require additional prospective, randomized, clinical trials in patients with TBI. Miscellaneous agents and therapies being considered as viable neuroprotective agents based on clinical and/or experimental TBI studies include growth hormone, cyclosporine, nitric oxide synthase inhibitor, minocycline, hyperbaric oxygen, and CNS bone marrow stromal cell transplantation.[53] Others have proposed that stimulation of axonal repair processes versus limiting injury may be the most fruitful neuroprotective pathway for future investigations.[47]

The concept of administering commercially available CNS-active agents for nonapproved indications in patients with TBI should presently be considered investigational. Examples include the use of CNS stimulants in the management and rehabilitation of patients with TBI as data supporting

this approach are equivocal.[47] Another example is the use of Parkinson's disease medications (eg, amantadine, bromocriptine, carbidopa/levodopa) in patients with severe TBI in an attempt to enhance dopamine release and inhibit reuptake within the injured region of the brain.[56] While intuitively appealing, use of psychoactive agents to improve CNS sequalae should be administered cautiously since large, well-controlled studies with a wide array of agents are lacking. Additionally, the timing for administration of these medications is controversial and the potential for cardiovascular adverse effects in the face of uncertain benefit would suggest that these medications should be reserved for the postacute phase of treatment (ie, weeks to months postinjury).

Acknowledging the complexities surrounding acute TBI, a broad-based, multidisciplinary approach is undoubtedly needed before breakthrough therapies are identified for this multifaceted, catastrophic condition. Examples of these types of initiatives include the International Mission on Prognosis and Clinical Trial Design (IMPACT) study group,[58] and the BRAIN Initiative—Brain Research Through Advancing Neurotechnologies, which is a Presidential and National Institutes of Health focused program aimed at revolutionizing understanding of the human brain launched in 2014.[59]

Treatment and Prophylaxis of Complications

In addition to specific management of TBI problems such as intracranial hypertension, the potential for secondary complications must also be considered as a wide variety of complications occur in more than 20% of patients with TBI and are associated with increased mortality and length of stay.[60] Development and implementation of clinical pathways for consistency of care, and clinical investigation of neuroprotective agents are important in advancing TBI treatment in the future.

Posttraumatic Seizures

9 It is generally agreed that adult patients who experience one or more seizures following a moderate-to-severe TBI should receive antiseizure medication therapy to avoid increases in $CMRO_2$ that occur with the onset of subsequent seizures and to prevent the development of (sometimes subclinical) status epilepticus associated with increased mortality.[9] Initial therapy should consist of incremental IV doses of diazepam (5-40 mg adults, 0.1-0.5 mg/kg infants and children) or lorazepam (2-8 mg adults, 0.03-0.1 mg/kg infants and children) to terminate any active seizure activity, followed by IV phenytoin to prevent seizure recurrence. Phenytoin dosing regimens for adults and pediatric patients include an IV loading dose of 15 to 20 mg/kg and 10 to 15 mg/kg, respectively, followed by a maintenance dose of 5 mg/kg/day divided into two or three daily doses. Alternatively, fosphenytoin, a water-soluble phosphate ester of phenytoin, can be administered IV or intramuscularly using the same doses, specified as phenytoin equivalents (PE). The merits of preventive antiseizure medication therapy in patients who have not had a seizure postinjury historically is controversial. Risk factors for early posttraumatic seizures (less than 7 days after injury) include a GCS score of less than 10, a cortical contusion, a depressed skull fracture, a subdural hematoma, an epidural hematoma, an intracerebral hematoma, a penetrating head wound, or a seizure within the first 24 hours of injury.[9] In a landmark randomized, placebo-controlled study, the incidence of early posttraumatic seizures in patients receiving placebo was 14.2% compared with 3.6% in patients receiving phenytoin without a significant increase in medication-related adverse events.[61] Thus, phenytoin should be used to prevent seizures in adult and pediatric patients with TBI for the first 7 days after injury[9,13] despite newer data suggesting that phenytoin may not decrease early posttraumatic seizures and may diminish functional outcome after blunt TBI,[62] which is fueling debate challenging this longstanding practice.[63] Valproate therapy is not recommended for patients with TBI, based on a trend for higher mortality compared to short-term phenytoin therapy.[61] Levetiracetam is a potentially attractive option; however, it should be used cautiously as large randomized clinical trials of its use has not been conducted in patients with TBI. Nevertheless, two meta-analyses found no difference in the rate of early posttraumatic seizures between levetiracetam and phenytoin,[64,65] and levetiracetam may have a superior safety profile based on one of these evaluations.[65] In a survey of nearly 70 neurotrauma centers in Europe, levetiracetam has become the antiseizure medication of choice over phenytoin in patients with TBI.[66] If used in TBI patients, the potential for increased levetiracetam systemic clearance should be considered when dosing this agent.[67] The benefits of prophylactic antiseizure medications beyond 7 days have not been demonstrated, and thus their use for this indication is not recommended.[9,13] Unfortunately, despite reducing the incidence of early seizures following brain injury, no beneficial effects have been documented for antiseizure medications on patient mortality or long-term disability.[9]

Supportive Care

While normalizing ICP and maintaining an adequate CPP are the highest priorities in preventing secondary injury following severe TBI, attention also must be given to preventing and/or treating systemic and extracranial complications. One such complication is systemic hypertension, which can be treated using antihypertensives including IV labetalol, nicardipine, and enaliprilat.

Fluid and electrolyte management is another important area of focus in the critically ill patient with a TBI, as common electrolyte disturbances, that should be monitored and treated aggressively; it includes hyponatremia, hypomagnesemia, hypokalemia, and hypophosphatemia.

Furthermore, aggressive nutritional support should be initiated, as early feeding of patients with TBI (ie, by 7 days) may be associated with a trend toward better outcomes in terms of survival and disability.[9,68] Early enteral nutrition, in particular, is associated with better survival and outcome compared with matched controls not receiving early enteral nutrition.[69]

Hyperglycemia (glucose greater than or equal to 160 mg/dL [8.9 mmol/L]) is also common in patients with TBI and is associated with worse outcomes.[70] Thus, intensive insulin therapy versus conventional glucose control should not be used since it is associated with adverse effects on brain glucose metabolism with little to no gain in neurological outcome.[70]

Infectious complications commonly encountered in patients with severe TBI include nosocomial pneumonia, sepsis, urinary tract infections, and meningitis. Treatment of these potentially devastating infections should be aggressive, with careful attention being paid to antibiotic blood–brain barrier penetration for intracranial infections.

Hyperthermia should also be avoided in patients with TBI because patients with elevated temperatures have poorer outcomes than normothermic patients.[71] Hence, aggressive maintenance of a core temperature of less than 37.5°C (99.5°F) using acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and cooling blankets is indicated for patients following severe TBI.

Other important therapeutic interventions include acute gastritis prophylaxis, and prevention of decubiti and contractures. Prevention of thromboembolic events is extremely important in the supportive care in TBI patients since they are high risk of developing this complication.[72] This can be accomplished with the use of intermittent pneumatic compression devices (preferred) or graduated compression stockings initially. Thereafter, the decision to start systemic therapy (eg, low-molecular-weight heparin or unfractionated heparin) depends on multiple factors. A noteworthy study revealed better survival and lower thromboembolic complications in patients with TBI receiving LMWH compared with those receiving unfractionated heparin.[73] Generally, patients who had relatively minor bleeding or no bleeding on the initial CT scan and good ICP control can have pharmacological prophylaxis started within 24 to 48 hours postinjury.[74,75] Patients at moderate-to-high risk of intracranial hemorrhage postinjury can safely receive pharmacologic prophylaxis within the first 72 hours postinjury without a corresponding increase in intracranial hemorrhage compared with patients receiving prophylaxis greater than 72 hours after their TBI.[75] Regardless of initiation time, prophylaxis is continued until patients are ambulatory. Systemic anticoagulation must be used with caution in patients with more severe intracerebral hemorrhage, or in patients who may need to undergo craniotomy early in their course.[9] Monitoring for a coagulopathy is important as the incidence is greater than 30%, and coagulopathy is associated with a significantly longer ICU length of stay and an almost 10-fold increase in mortality.[75] A low platelet count was the strongest predictor of intracranial bleeding progression compared with other coagulation tests in patients with TBI based on a retrospective study.[76] Reversal of coagulopathy with recombinant factor VIIa in critically ill trauma patients with TBI was popular among some practitioners despite lacking an approved indication or large clinical trials demonstrating its safety and efficacy in patients with TBI.[77] However, tranexamic acid is a less expensive hemostatic alternative to recombinant factor VIIa. A randomized, placebo-control trial involving over 12,000 TBI patients known as CRASH-3 revealed that patients with a GCS greater than 3, who received tranexamic acid within 3 hours of injury had a significant decrease in overall mortality by 1.5% compared to patients receiving placebo. The reduced mortality occurred without a difference in adverse events (ie, vascular occlusive events or seizures).[78] However, the mortality benefit was not significant in patients with severe TBI suggesting that it may be more effective in mild-to-moderate TBI as outlined in a meta-analysis.[78,79] Based on these findings, it is unclear if tranexamic acid administration will become the standard of care in non-severe TBI patients.

One of the most common general pharmacokinetic challenges seen in patients with TBI is a larger volume of distribution and more rapid hepatic clearance of medications compared to most other patient populations. These pharmacokinetic changes often make phenytoin optimization and, less commonly, pentobarbital optimization difficult. As such, phenytoin and pentobarbital recommended dosing are weight based, and in the case of phenytoin, usually higher than the 300 mg/day dose commonly seen in ambulatory patients. Augmented renal clearance has also been documented in critically ill patients including patients with TBI affecting medications that are renally eliminated.[80] Furthermore, there can be wide interpatient

pharmacodynamic variability in the efficacy of pharmacologic and nonpharmacologic interventions for ICP control. For some patients, there is a high degree of trial and error to find the best combination of interventions that are effective and not contraindicated based on other factors.

CLINICAL PATHWAYS/GUIDELINE IMPLEMENTATION

Use of clinical pathways and formal TBI management guidelines/standardized protocols have been demonstrated to improve TBI patient mortality in studies focused on intracranial hypertension.[81,82] Aggressive ICP monitoring has been associated with improved outcomes in patients with moderate-to-severe TBI as well.[83] Furthermore, a cost–benefit analysis revealed that adoption of the BTF/ASSN guidelines resulted in more than 3,600 lives saved among adult patients with severe TBI admitted annually to US hospitals as the proportion of patients having a good outcome based on their Glasgow Outcome Scale (GOS) was estimated to increase from 35% to 66%. This resulted in an overall estimated annual total cost savings exceeding $4 billion.[84] Unfortunately, improved outcomes are not universally reported as there is a wide guideline compliance variability despite the BTF/AANS guidelines availability for over two decades.[10,85] Regardless, few practitioners would dispute the overall importance of integrating current evidence-based management guidelines into clinical practice as a means to optimize care and improve the functional outcome of patients.[48,86]

EVALUATION OF THERAPEUTIC OUTCOMES

The evaluation of therapeutic outcomes is summarized in Table 77-4. Patients with severe TBI initially require ICU monitoring with the goals of maintaining or reestablishing neurologic and systemic homeostasis, as well as readily detecting any neurologic deterioration. This requires frequent evaluation of the patient's neurologic status (eg, GCS), measurement of vital signs, urine output, and arterial oxygen saturation, and ICP in patients with an ICP monitor in place. Careful attention must be paid to the potential development of various electrolyte, mineral, and acid–base disturbances; coagulopathies; and infections by obtaining appropriate laboratory tests on a daily basis initially. The intensity of monitoring will be a function of the relative degree of patient's neurologic and hemodynamic stability in the hours and days following the neurologic insult. Lastly, radiologic tests (eg, CT scans) are essential not only for the initial diagnostic evaluation, but also as means to evaluate the etiology for any subsequent neurologic deterioration.

TABLE 77-4

Evaluation of Therapeutic Outcomes

General	GCS: Record hourly initially, decrease frequency as neurologic status stabilizes Vital signs (BP, HR, RR, temperature): Record hourly initially, decrease frequency as neurologic status stabilizes UO: Record hourly initially, decrease frequency as neurologic status stabilizes Arterial oxygen saturation: Continuously while in ICU
Risk of increased ICP	ICP: Record hourly, decrease frequency as ICP stabilizes <22 mm Hg (2.9 kPa) (usually not until 48-72 hours postinjury at a minimum) CPP: Record hourly, decrease frequency as CPP stabilizes in the desired range[a]
Laboratory tests	Ethanol concentration and urine toxicology results: On admission ABGs: Daily at a minimum while intubated, repeated as needed based on pulmonary instability requiring ventilator setting changes CBC: Daily while in ICU Serum electrolytes (Na, K, Cl): Daily while in ICU. Serum sodium and osmolality may be monitored as frequently as every 6 hours if osmotherapy (mannitol, furosemide, hypertonic saline) is being used Minerals (Mg, Ca, P): Daily initially until concentrations stable
Radiologic procedures	CT scan: Postresuscitation initially with repeat scan(s) as needed based on degree of neurologic instability (eg, decrease in GCS) or initial CT appearance

BP, blood pressure; Ca, calcium; CBC, complete blood count; Cl, chloride; CT, computed tomography; HR, heart rate; K, potassium; Mg, magnesium; Na, sodium; P, phosphorus; RR, respiratory rate; UO, urine output.

[a]Continuous monitoring mandated initially if technologically feasible.

CONCLUSION

Traumatic brain injuries are exceedingly common and often associated with devastating consequences in both morbidity and mortality. Unraveling the complex pathophysiology of secondary injury following severe TBI has failed to yield major advances to attenuate or reverse these consequences to date. Furthermore, review of several traditional treatment modalities has resulted in recommendations against their use. Adherence to best management practices relative to aggressive treatment of increased ICP, supportive care, and prevention of complications offers victims of severe TBI a promise of improved outcomes. Commitment to this condition at the national level may be the turning point to breakthrough therapies of the future.

ABBREVIATIONS

AANS	American Association of Neurological Surgeons
ABG	arterial blood gas
ATP	adenosine triphosphate
BTF	Brain Trauma Foundation
CBF	cerebral blood flow
CBV	cerebral blood volume

CDO_2	cerebral oxygen delivery
$CMRO_2$	cerebral oxygen consumption
CPP	cerebral perfusion pressure
CSF	cerebrospinal fluid
CT	computed tomography
ECG	electrocardiogram
EEG	electroencephalography
EVD	extraventricular drain
FDA	Food and Drug Administration
GCS	Glasgow Coma Scale
GI	gastrointestinal
GOS	Glasgow Outcome Scale
HMG	3-hydroxy-3-methylglutaryl
ICP	intracranial pressure
ICU	intensive care unit
MAP	mean arterial pressure
NMDA	*N*-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
$PbrO_2$	brain tissue oxygen
PRIS	propofol infusion syndrome
PRBCs	packed red blood cells
SBP	systolic blood pressure
$SjvO_2$	jugular venous oxygen saturation
TBI	traumatic brain injury
TCD	transcranial Doppler

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SELF-ASSESSMENT QUESTIONS

1. Which of the following events is the most common cause of TBI?
   A. Gunshot wounds
   B. Sport and recreational accidents
   C. Motor vehicle accidents
   D. Falls
2. Which of the following is thought to be a key component in the pathophysiology of secondary neuronal injury after TBI?
   A. Hyperglycemia
   B. Cellular calcium influx
   C. Inflammatory mediators
   D. Lactic acidosis
3. Which of the following ranges of GCS scores is consistent with a severe TBI?
   A. 1-3
   B. 3-8
   C. 9-12
   D. 13-15
4. During the initial resuscitation period after a severe TBI, which of the following are the minimum goal systolic blood pressure (SBP), and the ideal SBP range that are associated with improved outcomes?
   A. Minimum >60 mm Hg, ideal range 60 to 70 mm Hg
   B. Minimum >100 mm Hg, ideal range 100 to 120 mm Hg
   C. Minimum >100 mm Hg, ideal range 120 to 140 mm Hg
   D. Minimum >120 mm Hg, ideal range >140 mm Hg
5. Which of the following represents the goal ICP and CPP values in an adult patient with a severe TBI?
   A. ICP <20 mm Hg (2.7 kPa), CPP >50 mm Hg (6.7 kPa)
   B. ICP <20 mm Hg (2.7 kPa), CPP 60-70 mm Hg (8.0-9.3 kPa)
   C. ICP <22 mm Hg (2.9 kPa), CPP 60-70 mm Hg (8.0-9.3 kPa)
   D. ICP <22 mm Hg (2.9 kPa), CPP >70 mm Hg (9.3 kPa)

6. Which of the following is the primary advantage of a ventriculostomy over an intraparenchymal ICP monitor?

   A. Cerebrospinal fluid can be drained to lower ICP.

   B. Less difficult and invasive to perform placement.

   C. Lower complication rate.

   D. Superior outcomes in clinical trials.

7. Which of the following is generally the sedative of choice for controlling ICP in patients with TBI?

   A. Midazolam

   B. Pentobarbital

   C. Propofol

   D. Dexmedetomidine

8. Which of the following is the best initial therapy for lowering ICP in a patient with a severe TBI and pulmonary edema from congestive heart failure?

   A. Mannitol

   B. Hypertonic saline

   C. Pentobarbital coma

   D. Furosemide

9. Which of the following is a primary advantage of hypertonic saline over mannitol as an osmotic agent for lowering ICP?

   A. Stronger diuretic effect

   B. Improved mortality in large trials

   C. Lower risk of hyperglycemia

   D. Lower risk of acute renal dysfunction

10. A patient with a severe TBI is having intermittent ICPs in the mid-to-high 20s (mm Hg; or ~3.3-3.9 kPa) despite treatment with a propofol infusion (4 mg/kg/hr) and intermittent doses of mannitol and hypertonic saline. Which of the following should be added for ICP control now?

    A. Fentanyl infusion

    B. Neuromuscular blocker

    C. Pentobarbital coma

    D. Furosemide

11. The neurosurgical team wants to use a neuromuscular blocker as a second-line agent for ICP control in a patient whose ICPs are still elevated. Which of the following is a critical factor in this decision?

    A. Sedation doses must be maximized before use.

    B. A long-acting neuromuscular blocker is preferred.

C. Sedation should be temporarily held to assess efficacy.

D. Monitoring for hypertriglyceridemia before use.

12. Which of the following is the most common dose-limiting adverse event side of pentobarbital coma?

A. Hypotension

B. GI hypomotility

C. Pulmonary edema

D. Hypertriglyceridemia

13. Which of the following describes when the use of therapeutic hyperventilation should be considered in managing patients with TBI?

A. Routine prophylactic use to prevent ICP elevations in all patients with TBI

B. A standard first-line treatment for ICP elevations in all patients with TBI

C. A second-line therapy with a $PaCO_2$ goal of 25-35 mm Hg (3.3-4.7 kPa)

D. A second-line therapy with a $PaCO_2$ goal of less than 25 mm Hg (3.3 kPa)

14. Which of the following best describes drug selection for seizure prophylaxis after a severe TBI?

A. Levetiracetam is preferred because it doesn't require serum monitoring, a better safety profile, and was superior in large randomized trials (RCTs).

B. Valproic acid can be used as a first-line agent because it is available in an IV form and performed similarly to phenytoin in a large RCT.

C. Phenytoin is the drug of choice and can be used for seizure prophylaxis in the early (within the first 7 days) and late (after 7 days) periods.

D. Phenytoin should be used in the early period in patients without seizures and it still has the highest quality of data supporting its use (ie, RCT).

15. Which of the following best describes appropriate use of LMWH products, low-dose unfractionated heparin (LDUH), and intermittent pneumatic compressions devices (IPC) for venous thromboembolism prophylaxis in patients with severe TBI?

A. Only IPCs should be used during the ICU stay due to the increased risk of further intracranial bleeding with LMWH and LDUH.

B. Reviews suggest that LMWH or LDUH can be started within the first 24 hours after injury in all patients with TBI.

C. LMWH or LDUH should be held for 72 hours post injury in patients with a moderate-to-high risk of further intracranial hemorrhage.

D. LMWH or LDUH can be started within 24 to 48 hours post injury in all patients with severe TBI and good ICP control.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Falls are the leading cause of TBI in the United States. See the "Epidemiology" section for more information.

2. **B.** Cellular calcium influx is a key step in the pathophysiology of secondary neuronal injury. See the "Primary and Secondary Brain Injury Pathophysiology" section for more information.

3. **B.** A GCS score of 3-8 indicates a severe TBI. See the "Clinical Presentation" section and Table 77-1 for more information.

4. **C.** During initial resuscitation after TBI, avoiding SBP <100 mm Hg and maintaining SBP 120-140 mm Hg were both associated with improved outcomes. See the "Initial Resuscitation" section and Fig. 77-2 for more information.

5. **C.** In adult patients with TBI, the goal ICP is <22 mm Hg (2.9 kPa) and goal MAP is 60-70 mm Hg (8.0-9.3 kPa). See the "Postresuscitative Care" section and Fig. 77-2 for more information.

6. **A.** The primary advantage of an extraventricular drain is the ability to lower ICP by draining CSF. See the "Postresuscitative Care" section for more information.

7. **C.** Propofol is generally considered the sedative of choice for ICP control because of rapid titratability. See the "Anesthetics, Analgesics, and Sedatives" section, Fig. 77-3, and Table 77-2 and 77-3 for more information.

8. **D.** Furosemide is not normally a first-line agent, but would be preferred in this case because of cardiogenic pulmonary edema. See the "Osmotic Agents" section for more information.

9. **D.** Mannitol can cause acute renal dysfunction. This is not an adverse effect of hypertonic saline. See the "Osmotic Agents" section for more information.

10. **A.** Fentanyl infusion is the only option listed that is a first-line option for ICP control. See the "Anesthetics, Analgesics, and Sedatives" section and Fig. 77-3 for more information.

11. **A.** Sedation should always be maximized prior to using neuromuscular blockers to avoid awareness of paralysis. See the "Anesthetics, Analgesics, and Sedatives" section and Fig. 77-3 for more information.

12. **A.** Hypotension is a common adverse event of pentobarbital. See the "Anesthetics, Analgesics, and Sedatives" section and Table 77-2 and 77-3 for more information.

13. **C.** Hyperventilation to a goal of 25-35 mm Hg (3.3-4.7 kPa) can be considered as a second-line therapy for treating ICP elevations. See the "Hyperventilation" section and Fig. 77-3 for more information.

14. **D.** Even though levetiracetam use is increasing, the authors still recommend phenytoin as the first-line agent for seizure prophylaxis due to it being the only drug to be effective for this indication in a large RCT. See the "Posttraumatic Seizures" section, Fig. 77-2, and Table 77-2 and 77-3 for more information.

15. **C.** An evidence-based review recommends holding pharmacologic prophylaxis for 72 hours in patients with moderate-to-high risk of intracranial hemorrhage. See the "Supportive Care" section for more information.