TRAUMATIC BRAIN INJURY

Chapter 8

Contributing Authors
Scott A. Marshall, MD
Randy Bell, MD
Rocco A. Armonda, MD, LTC, MC, US Army
Eric Savitsky, MD
Geoffrey S.F. Ling, MD, PhD, COL, MC, US Army

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Introduction

Traumatic brain injury (TBI) occurs whenever a physical force that impacts the head leads to neuropathology. This can be as simple as a minor laceration from a small fragment to decapitation. Of all the injuries to the head that are concerning, the most worrisome is TBI.

Traumatic brain injury is a leading cause of death and disability from trauma. In the United States (US), more than 50,000 patients die from TBI each year, accounting for almost one-third of all civilian trauma-related deaths.[1] Most of these injuries are a direct result of falls, motor vehicle accidents, and assaults. The cost for direct TBI medical care is estimated at more than $50 billion per year.[2,3] The majority of victims of both civilian and military TBI are young male adults.[4,5] The societal burden of TBI is staggering. Traumatic brain injury accounts for the greatest number of years lived with trauma-related disability.[5] Many victims of TBI are young and thus require extended rehabilitation and reintegration. Many will likely require medical discharge from the armed forces. The young age of many TBI victims is especially unfortunate as these patients may no longer be productive members of society at a time in their life when their potential contributions are greatest.[4]

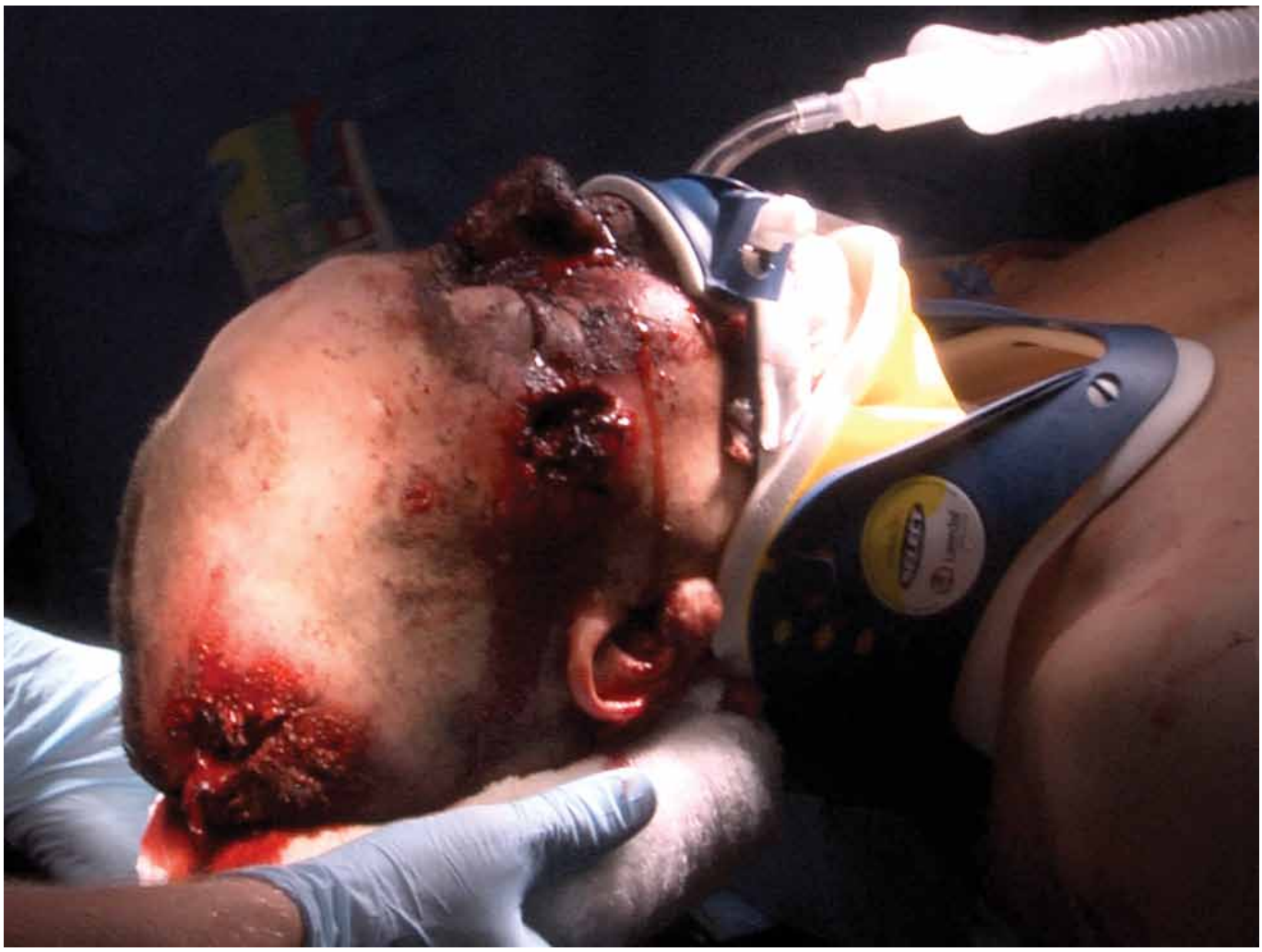


Figure 1. *A US casualty who sustained explosive blast TBI.*

Traumatic brain injury is a common battle-related injury. In the wars of the 20th century, approximately 15 to 20 percent of injuries incurred in combat involved the head.[6] Evidence suggests that this is also the case for casualties sustained in the recent wars, Operation Enduring Freedom (OEF) in Afghanistan and Operation Iraqi Freedom (OIF) (Fig. 1).[7] Some have speculated that a greater percentage of patients from these recent wars have suffered head injury than in prior conflicts.[8] This increase in prevalence is thought to be a paradoxical consequence of the remarkable improvements in medical care and protective body armor.[9] These advances have resulted in the lowest killed-to-wounded ratio in modern warfare.[10] The paradox is that with more wounded warfighters surviving, more are left with severe wounds, especially to less protected anatomical regions such as head and extremities. Thus, TBI, traumatic amputations, and other such injuries are disproportionally represented. Specifically, TBI resulting from explosive blast has become very prominent in the past several years.[11,12,13]

Traumatic brain injury is a common battle-related injury. Treatment goals in the first 72 hours of care for the injured patient with TBI are to provide clinical stability, arrest any element of ongoing injury, preserve neurological function, and prevent medical complications secondary to multisystem trauma.

With advances in battlefield or prehospital clinical management of combat casualties, the outcomes of severe conditions such as TBI have improved. Critical elements include improved training and resources for far-forward medical providers, a highly efficient modern triage and evacuation system, and dramatically shortened length of stay in-theater prior to definitive care in the US.[14] There is evidence that the vast majority of fatal injuries incurred in combat result from injuries that would be nonsurvivable in any setting.[15] Thus, those who can be saved are being saved, even under the austere conditions of war. However, as long as there are survivors left with chronic disabilities, there is opportunity for improvements in medical care.

Treatment goals in the first 72 hours of care for the injured patient with TBI are to provide clinical stability, arrest any element of ongoing injury, preserve neurological function, and prevent medical complications secondary to severe trauma. Initially, brain injury must be suspected, and this must be followed by appropriate field management. Next, TBI patients should be triaged and evacuated to a Level III facility with advanced care capability, such as neurosurgery and neurointensive care. Subsequently, as appropriate, TBI patients are evacuated from theater to the continental US (CONUS) for advanced definitive treatment.

The purpose of this review is to outline the intricacies common to both military and civilian TBI, discuss different forms of closed and penetrating TBI, and expand upon the distinction between primary and secondary brain injuries. A review of the literature outlining various treatment algorithms, both medical and surgical, will also be provided.

Pathophysiology of Traumatic Brain Injury

Primary brain injury is tissue destruction that occurs as a direct result of a physiologic trauma. This leads to near immediate macroscopic and cellular pathological changes. The severity and location of the primary brain injury will dictate the patient's immediate level of consciousness, mental status, and focal neurologic signs. There is no available therapy for primary brain injury at present. The focus of TBI treatment is minimizing secondary brain injury. Secondary brain injury refers to the consequences of pathological

processes that begin immediately after the primary brain injury. Secondary brain injury continues for an indefinite period and can cause further dysfunction and death of neurons and glial supporting structures.

The immediate goal of TBI treatment is minimizing secondary brain injury by optimizing cerebral blood flow. This involves mitigating elevations in ICP and addressing traumatic intracranial hemorrhage, cerebral edema, and metabolic derangements.

Quantifiably, it is widely held that most of the overall brain injury may be ascribable to secondary injury processes. Mechanisms thought to be involved in secondary brain injury include hypoxia, ischemia, free radicals, release of neurotransmitters and intracellular elements (e.g., calcium), temperature dysregulation, intracranial pressure alterations, gene activation, mitochondrial dysfunction, and inflammation.[5,16] Among these, hypoperfusion is the main cause of poor outcomes.[5,17] This is due to the susceptibility of injured neural tissue to ischemia, as it is in a hypermetabolic state following injury. This is exacerbated by dysfunction of cerebral vascular autoregulation so that there is insufficient vascular compensation for compromised cerebral perfusion. Particularly susceptible areas include the hippocampus and border zone or watershed regions such as the high parietal region. It has been hypothesized that delayed neurological dysfunction can often be attributed to the effects of delayed ischemia.[16,18] To this effect, there is evidence that a single episode of hypotension with systolic blood pressures falling below 90 mm Hg is associated with poor outcomes in severe TBI.[16,18,19] Hypoperfusion itself may result in diffuse microvascular damage and loss of blood-brain barrier integrity. This microvascular damage contributes to the prominent pattern of vasogenic edema observed after TBI.[20] Current guidelines likewise caution of the dangers of hypocapnea and hypoxia as markers for poor outcomes following TBI.[16,18,19,21]

Hypotension (systolic blood pressure less than 90 mm Hg) leading to cerebral hypoperfusion has been linked to poor outcomes following severe TBI.

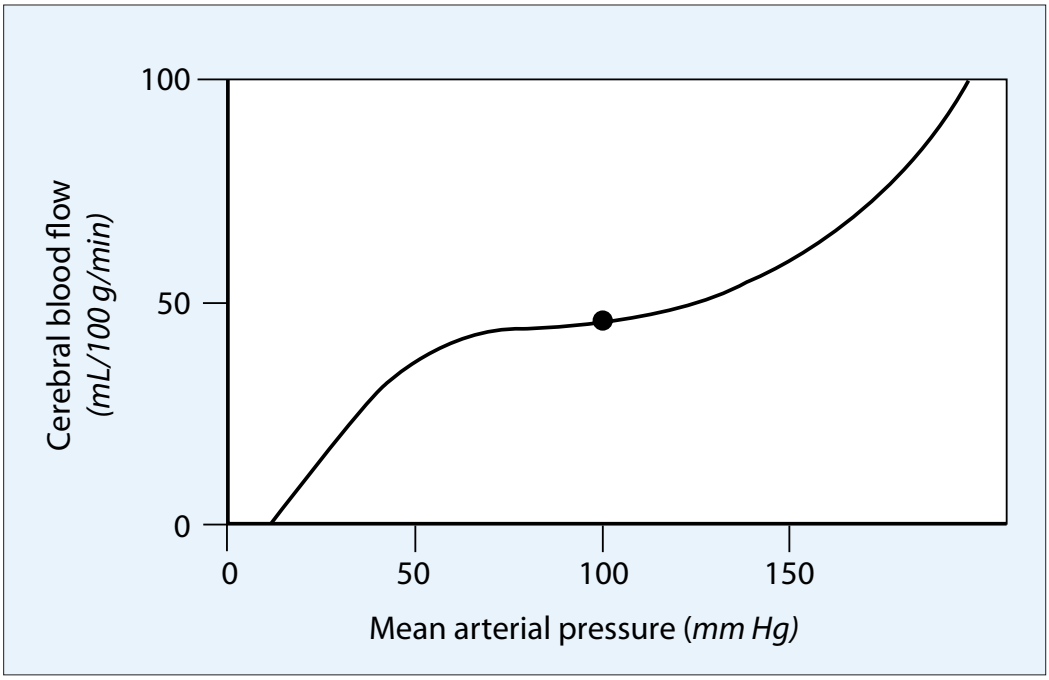


Figure 2. *Cerebral blood flow is well-autoregulated when mean arterial pressures are between 50 to 150 mm Hg.*

Research attempts at developing therapeutic strategies have focused on secondary brain injury processes while public health and technological measures have attempted to prevent primary brain injury. Currently, clinical management centers on supportive measures to mitigate secondary brain injury with particular emphasis on maintaining cerebral perfusion pressure (CPP) and tissue oxygenation, minimizing intracranial pressure (ICP) fluctuations, and treatment of cerebral edema. Various alternative experimental pharmacological therapies (e.g., free radical scavengers) and neuroprotective strategies have been investigated (e.g., therapeutic hypothermia). Unfortunately, none of these experimental therapies or strategies has been proven to effectively mitigate secondary brain injury.[22]

With regard to cerebral autoregulation, cerebral blood flow (normal values 50 to 65 milliliters [ml] per 100 grams of brain tissue per minute) is well-autoregulated when mean arterial pressures (MAPs) are between 50 to 150 mm Hg (Fig. 2). Cerebral blood flow (CBF) is a function of cerebral vascular resistance (CVR) and cerebral perfusion pressure. Since cerebral vascular resistance is proportional to the fourth power of blood vessel radius, even small changes in cerebral vessel caliber translates into significant alterations in CBF. Cerebral perfusion pressure is the pressure gradient driving CBF, and is defined as the difference between mean arterial pressure and ICP (Equation 1).

Equation 1: $CPP = MAP - ICP$

Equation 2: $CBF = CPP/CVR$

Primary brain injuries often lead to alterations in the brain's ability to autoregulate CBF even within the normal autoregulatory range.[23] This may further worsen secondary brain injury, in that loss of autoregulatory control may lead to increased CBF with changes in blood pressure and resultant increased intracranial blood volume and disruption of the blood-brain barrier with vasogenic brain edema formation. This may ultimately result in elevated ICP. Alternatively, cerebral ischemia may result if CBF is too low (i.e., less than 20 ml per 100 grams of brain tissue per minute), and the neurovasculature is unable to compensate by autoregulatory vessel dilation to maintain CBF.

It should be emphasized that hypercapnia is a potent vasodilator of cerebral microvasculature, as is hypoxemia. These states may result in cerebral hyperemia and exacerbation of preexisting elevated ICP.[24] Hyperventilation with resultant hypocapnia has a profound effect in causing cerebral microvasculature vasoconstriction.[25] This microvasculature vasoconstrictive response to hypocapnia is often well-preserved, even in the setting of devastating brain injury. Hyperventilation leading to hypocapnia will lead to a progressive decrease in ICP.[25] Loss of ICP responsiveness to hypocapnia is a poor prognostic sign. Hypocapnia will also result in decreases in CBF; every one mm Hg decrease in the partial pressure of carbon dioxide (PCO_2) will result in a proportionate three percent decrease in CBF.[26,27] It is important to understand the relationship between hypocapnia and CBF, as well as how hyperventilation and hypocapnia relate to ICP.

Hyperventilation leading to hypocapnia will cause a progressive decrease in ICP. Loss of ICP responsiveness to hypocapnia is a poor prognostic sign.

Delayed cerebral swelling is the major cause of raised ICP and death. This is often the result of secondary brain injury. Persistent bleeding from damaged brain tissue, contusions, impaired autoregulation, and

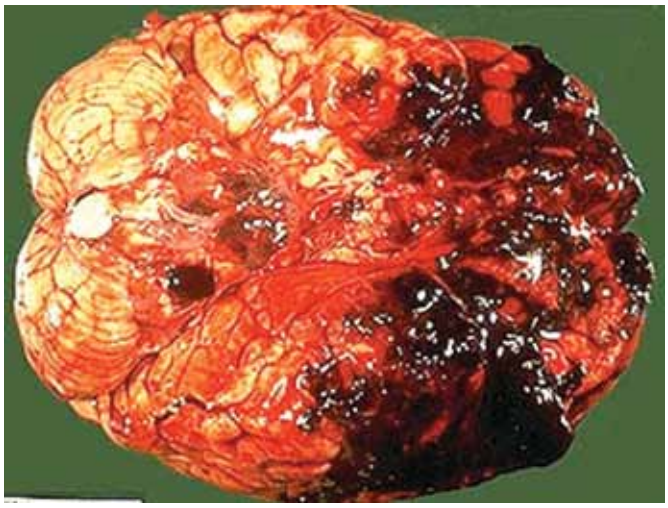


Figure 3. *Persistent bleeding from damaged brain tissue, contusions, impaired autoregulation, and breakdown of the blood-brain barrier may all contribute to brain swelling. Image courtesy of Brian J. Eastridge, MD, FACS, COL, US Army*

breakdown of the blood-brain barrier may all contribute to brain swelling (Fig. 3).[28] This swelling with resultant compression and distortion of brain parenchyma further exacerbates the injury cascade. The Monroe-Kellie doctrine is a convenient method of understanding factors leading to elevated intracranial pressures. It postulates that due to the fixed size of the intracranial compartment, an increase in volume of any of the three intracranial constituents (blood, brain, and cerebrospinal fluid) must be compensated by a decrease in one or more of the other constituents, or ICP will rise.[29,30]

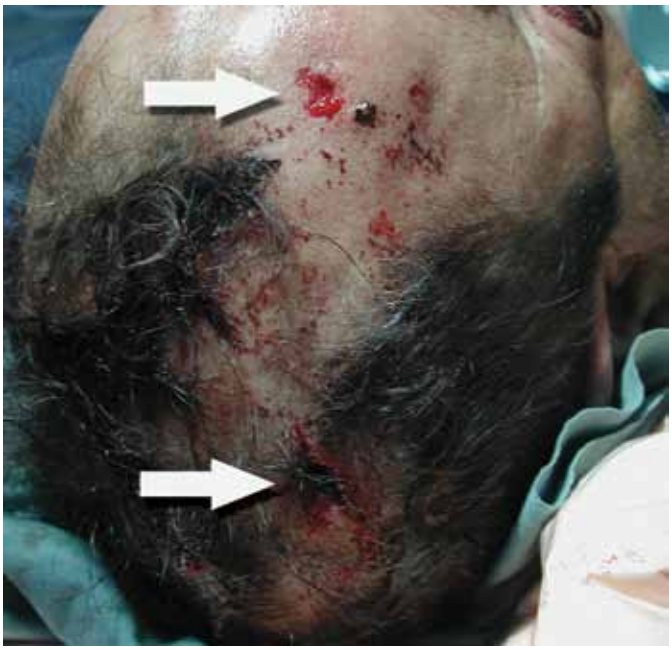
Systemic complications directly related to severe head injuries are not uncommon. Neurogenic pulmonary edema is a well-described phenomenon associated with secondary brain injury.[31,32] Primary myocardial ischemia and dysrhythmias are often seen in the setting of secondary brain injury. Although the exact mechanisms are still unclear, it is theorized that these processes are the result of greatly elevated circulating catecholamine levels.[33] Brain tissue is also rich in thromboplastins, and release of these in secondary brain injury patients may result in the development of a coagulopathy.[34] The syndromes of cerebral salt wasting and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) are also seen in the setting of secondary brain injury.[35,36]

Closed Head Injury

Head injury can be broadly classified into closed versus penetrating head injury (Figs. 4 and 5). With closed head injury, the skull and overlying scalp remain intact. In closed head injury, direct impact of brain against the skull and shearing force upon neurovascular structures from rotational forces result in cell damage at the cell body and axonal level. Among civilians in the US, most closed head injury is due to motor vehicle accidents, but other causes include falls, sporting event injuries, and assault.[37] In studies analyzing US casualties in OIF, some have reported between 5 and 10 percent of all casualties sustained a closed head injury.[38] Neuronal structures strike the skull in both the direct and opposite planes of motion leading to a coup and contrecoup lesion pattern. Contusion or other injury to the brain is seen deep to the site of skull impact, as well as 180 degrees opposite the site of impact (Fig. 6). If there is a rotational component, structures will torque and twist, and thus shearing can occur. This results in diffuse axonal injury seen radiographically as punctuate hemorrhages on computed tomography (CT) or magnetic resonance imaging (MRI) at interfaces of grey and white matter. Patients with diffuse axonal injury are often in a coma after their trauma without elevations in ICP and often have unsatisfactory clinical outcomes.[5]

Mild, Moderate, and Severe Brain Injury

The spectrum of TBI is mild, moderate, or severe. Severity is based largely on the presenting Glasgow Coma



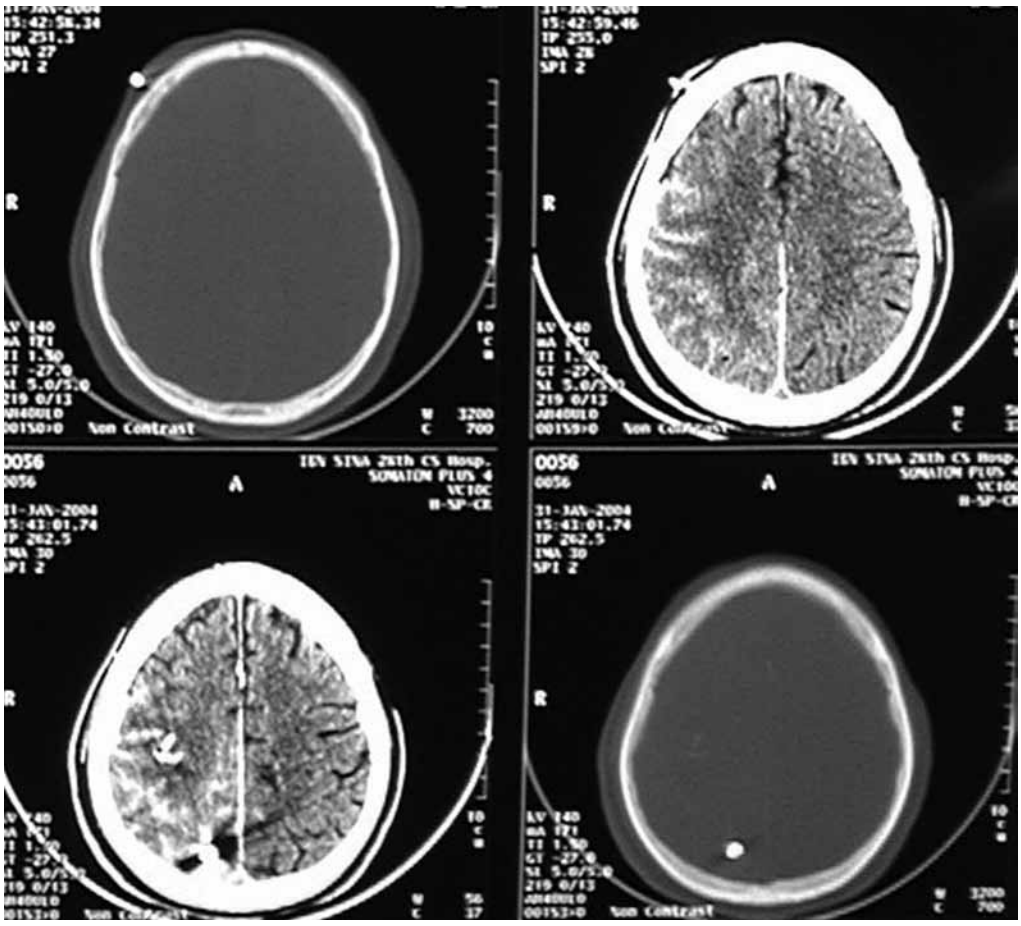


Figure 4. (Top) *The distinction between closed head injury and penetrating head injury may be difficult to make based on neurological findings. Here, one of the scalp wounds denoted by the arrows, was an entry point for a penetrating fragment that caused brain injury. Image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC.*

Figure 5. (Bottom) *Axial CT images demonstrate a right frontal extracranial fragment, traumatic subarachnoid hemorrhage, and an intracranial fragment. Image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC.*

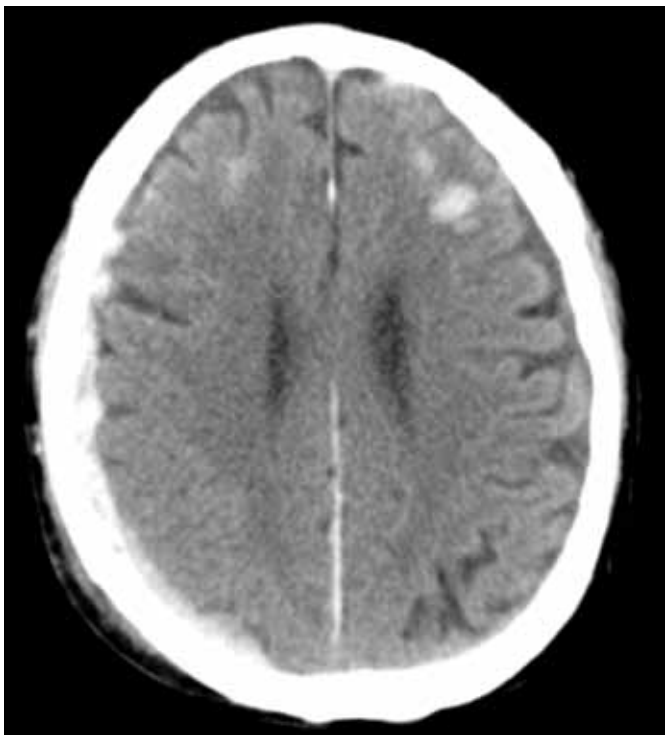


Figure 6. *Coup and contrecoup patterns of brain injury. An impact to the right parietal region has caused a left frontal intraparenchymal contusion.*

Scale (GCS) score (Table 1). These classification categories have prognostic, monitoring, and treatment implications.[39] Patients with mild TBI have an admission GCS score of greater than or equal to 13, with lower scores in this category representing more concerning injury. Mild TBI may often be referred to as concussion. These patients have experienced a brief (less than 30 min), if any, loss of consciousness or alteration in consciousness (less than 24 hrs), and presenting complaints include headache, confusion, and amnesia.[40] The spectrum of presentation and sequelae of mild TBI is broad and usually transient. When symptoms persist for three months or longer, postconcussion syndrome is diagnosed.[41] Moderate TBI is defined by an admission GCS score of 9 to 12 and is usually associated with prolonged loss of consciousness, abnormal neuroimaging, and neurological deficit.[42] Injured service members with moderate TBI will likely require rapid removal from forward areas, subsequent hospitalization, and may need neurosurgical intervention. Patients with GCS scores of 8 or less have significant neurological injury and are classified as having severe TBI. Typically, they have abnormal neuroimaging such as a CT scan demonstrating intracranial hemorrhage, often associated with a skull fracture.[42] These patients require rapid evacuation to a Level III facility and admission to the intensive care unit (ICU) for immediate airway control, breathing support with mechanical ventilation, neurosurgical evaluation, and ICP monitoring.

Best Eye Opening (E)		Best Verbal Response (V)		Best Motor Response (M)	
				Follows commands	6
		Oriented, alert	5	Localizes to pain	5
Eyes open spontaneously	4	Confused, appropriate	4	Withdrawal to pain	4
Eyes open to speech	3	Disoriented, inappropriate	3	Flexor posturing	3
Eyes open to pain	2	Incomprehensible speech	2	Extensor posturing	2
No response	1	No response	1	No response	1

Table 1. *Severity of TBI is based largely on the presenting GCS score. Glasgow Coma Scale scores carry prognostic, monitoring, and treatment implications.*

Blast Traumatic Brain Injury

Explosive blast TBI refers to TBI resulting from explosive blast exposure, and is presently classified as a subtype of TBI. The improvised explosive device (IED) is commonly implicated in explosive blast TBI in OEF and OIF.[5] Blast TBI may occur in isolation or may also be accompanied by closed head injury and/or penetrating TBI. The mechanism responsible for causing explosive blast TBI is unclear. The

overpressure generated by the explosive device is the leading suspect, but other elements of the violent explosive event, such as toxins or electromagnetic pulses, might also potentially contribute.[43] Once the physical force couples to brain, the TBI itself results from a variety of local pathological effects, including impaired cerebral vascular homeostasis and formation of reactive oxygen species.[44] A recent concern is the probable large number of soldiers who have been exposed to blast and suffered a blast TBI but did not have their injury recognized or treated. This has resulted in concern over the development of psychiatric syndromes that may often be seen with blast TBI, such as post-traumatic stress disorder, anxiety, or depression. This is currently under study and the subject of much scientific and political debate.[38,45,46,47] Blast TBI is a recently recognized condition for which additional preclinical and clinical research is needed.[5]

Psychiatric conditions such as post-traumatic stress disorder, anxiety, or depression may be seen following blast TBI.

Second Impact Syndrome

An important caveat to the management of TBI is minimizing the risk of second impact syndrome. Though relatively uncommon, it can have devastating consequences. Second impact syndrome refers to a subsequent head injury during a recovery period from TBI that may result in significant worsening of the initial neurotrauma.[48] This has been best described among adolescents and younger TBI patients. The mechanism underlying second impact syndrome is not fully understood, and the clinical implications of second impact syndrome continues to be debated.[49,50] It is thought that impaired cerebral autoregulation, diffuse cerebral edema, and intracranial hypertension all play a role. The high mortality of second impact syndrome, up to 50 percent, is the most concerning aspect.[48] The American Academy of Neurology (AAN) guidelines for recommended periods of TBI recovery are often used to determine when soldiers with head injury may return to duty (Table 2).[40] The cited AAN guidelines are currently under review and will be updated and published in late 2011.

Symptom Complex	First Concussion	Second Concussion
Grade I: Transient confusion or cognitive impairment lasting less than 15 minutes without LOC	Remove from source of injury; frequent reevaluation; return to duty if normal cognition in 15 minutes	Return to duty in one week if no residual symptoms with physical stress or exercise
Grade II: Grade I symptoms but lasting greater than 15 minutes without LOC	Remove from source of injury; frequent reevaluation; no duty for one week during which medical observation continues	Return to duty in two weeks if no residual symptoms with physical stress or exercise
Grade III: Any degree of cognitive symptoms with LOC	Remove from source of injury; trained neurologic evaluation; consider imaging; return to duty in two weeks if asymptomatic with physical stress or exercise	Return to duty in one month if no residual symptoms with physical stress or exercise

Table 2. *Return-to-duty guidelines following concussion. LOC, loss of conciousness. Adapted from the American Academy of Neurology Practice Parameter on Management of Concussions.*[40]

Second impact syndrome refers to a subsequent head injury during a recovery period from TBI that may result in significant worsening of the initial neurotrauma.

Focal versus Diffuse TBI

Closed TBI may be further classified as focal or diffuse. Focal injuries occur at the site of impact (coup injury), with neurological damage localized to those areas. This can occur wherever force is transmitted through the skull. The orbitofrontal and anterior temporal lobes are commonly affected in focal contrecoup injury. This is due to the tendency for head trauma to occur in an anterior-to-posterior direction causing the brain to move along those force vectors. As it moves, the brain traverses over the rough surface of the petrous ridge and anterior cranial fossa at the skull base leading to focal injury.

Diffuse injuries occur without the brain impacting a solid structure. This type of injury is caused by brain rotation. Because the brain is tethered by the brainstem, a severe acceleration-deceleration will cause it to rotate about this tethered axis. Axons in cerebral white matter will be disrupted, leading to axonal swelling and subsequent axonal rupture.[51] This condition is known as diffuse axonal injury. It is associated with severe neurological deficits and encephalopathy, including coma. The CT appearance of this type of injury can be delayed by up to 12 hours following initial trauma.[20] Recent evidence also suggests that the incidence of diffuse axonal injury may be higher with forces occurring in a lateral orientation, as opposed to a frontal or oblique impact common in closed head injury.[52]

Epidural and Subdural Hematomas

In both focal and diffuse TBI, one must remain vigilant for intracranial hematomas. Such hemorrhages occur immediately or can be delayed as long as several days after the inciting trauma.[16,18] The highest risk of intracranial hematoma is within the first six to nine hours after injury.[53]

Subdural Hematomas

Subdural hematomas are frequent occurrences in civilian neurosurgical practice (Fig. 7). Subdural hematomas account for over 15 percent of combat-related head injuries.[11] These lesions often require neurosurgical evacuation. The need for surgery is predicated on the clinical status of the patient and radiological appearance of the subdural hematoma. Subdural hematomas that require surgery are greater than 10 millimeters (mm) or cause more than five mm of midline shift with effacement of the basal cisterns. Other indications for surgery are a GCS score of 8 or less with enlarging intracranial lesions or deterioration in clinical exam.[54] This approach must take into consideration circumstances where outcomes are decidedly unfavorable such as advanced age, hematoma volume greater than 90 milliliters, presenting GCS score of 3, and time to surgery more than six hours.[55,56] There is conflicting evidence regarding optimal timing of evacuation, although most favor prompt evacuation once the indication exists.[56,57,58] Smaller subdural hematomas may be managed conservatively utilizing close neurological monitoring and early follow-up neuroimaging.[59] If there is concern that a lesion is enlarging, or that the patient's neurologic exam may decline, then immediate transfer to a facility with neurosurgical and neurointensivist care is justified. In lieu of the ability to transfer, the placement of burr holes for the evacuation of a subdural hematoma by a general surgeon has been described (Fig. 8).[60] Treacy et al. described a number of neurosurgical procedures (including burr holes) performed on patients in remote environments by general surgeons.[60] Three hundred and five procedures were performed over a 12-year

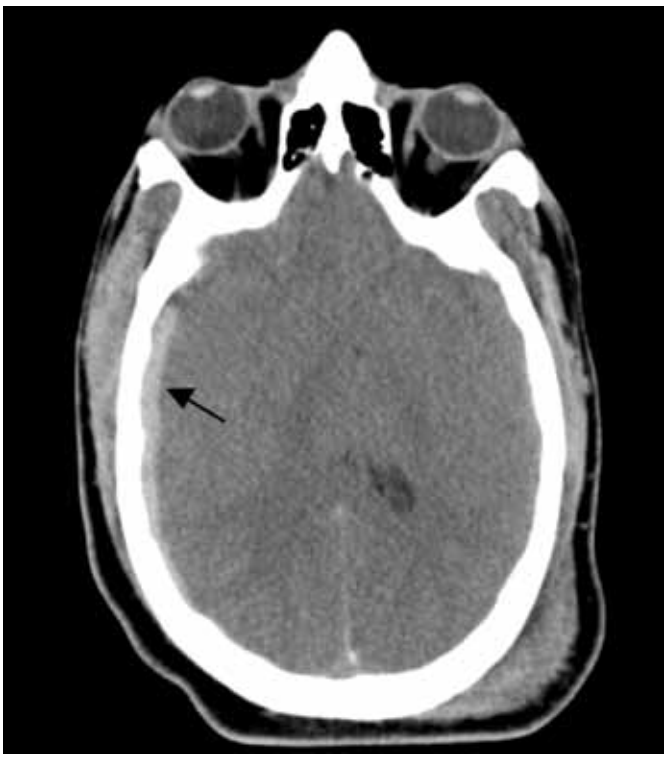


Figure 7. *Acute subdural hematoma.*

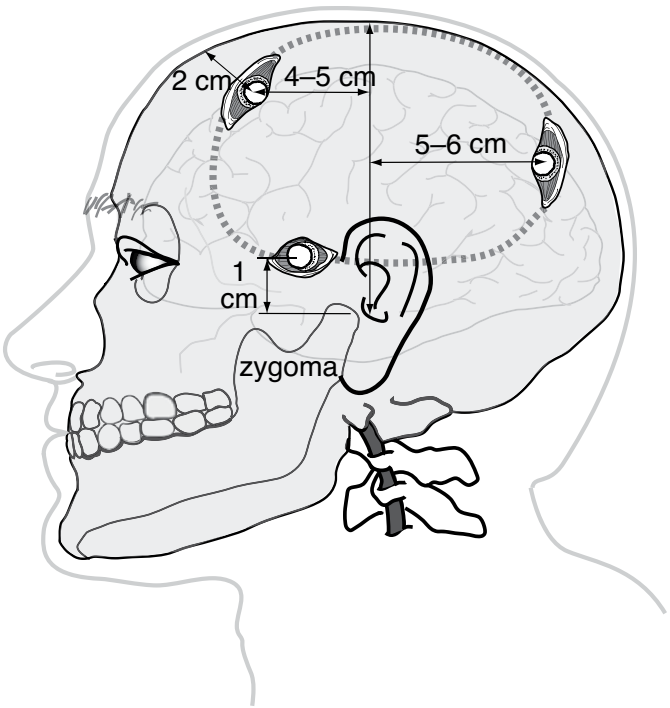


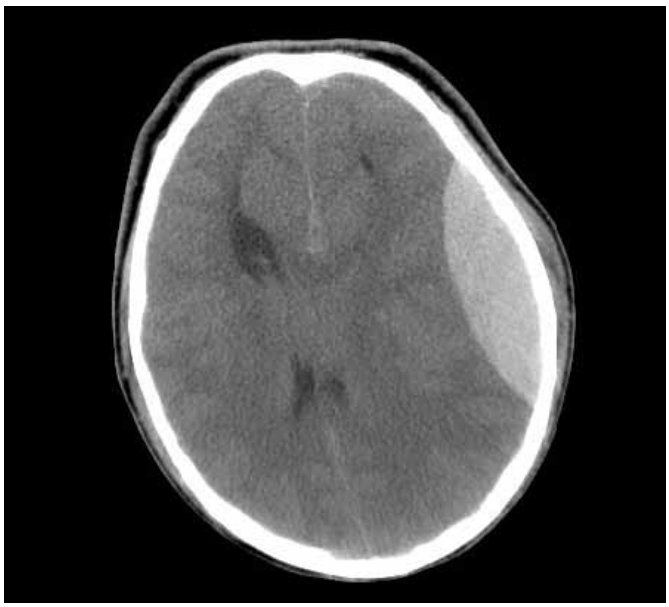
Figure 8. *Cranial landmarks and location for standard burr holes. Image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC. Illustrator: Bruce Maston.*

period (including 130 craniotomies, 88 burr holes, 33 extraventricular drains, 25 elevations of fractures, four decompressive craniectomies, three posterior fossa craniotomies, and two decompressive frontal lobectomies) for an average of over 25 procedures per year.[60] Outcomes for patients with epidural and chronic subdural hematomas were good, while poor outcomes were noted for patients with acute subdural and intracerebral hematomas.[60]

Operative management of subdural hematomas is indicated for bleeds greater than 10 millimeters, those causing more than five millimeters of midline shift with effacement of the basal cisterns, or a GCS score of 8 or less in the context of an enlarging intracranial lesion or deteriorating clinical exam.

Epidural Hematomas

Epidural hematomas are especially concerning, even in relatively asymptomatic patients.[61] In one case series, epidural hematomas occurred in less than 5 percent of combat-related head injury cases.[11] Classically, an epidural hematoma forms when a skull fracture occurs at the temporoparietal junction causing injury to the middle meningeal artery. Epidural hematomas have a distinctive convex lenticular appearance on CT imaging (Fig. 9). Epidural hematomas usually require neurosurgical intervention. Definitive indications for surgical evacuation include a GCS score less than 8 and a volume greater than 30 milliliters.[62] An epidural hematoma with less than 30 milliliters of volume, less than 15 mm thick, and with no more than five mm of midline shift in a patient who lacks a focal deficit can be managed nonoperatively.[62] However, as this lesion has a very high potential for progression, such patients must be followed closely with frequent neurological examination and serial CT imaging. A study of epidural hematoma patients with GCS score greater than or equal to 12 that did not meet criteria for surgery experienced an eventual surgery rate



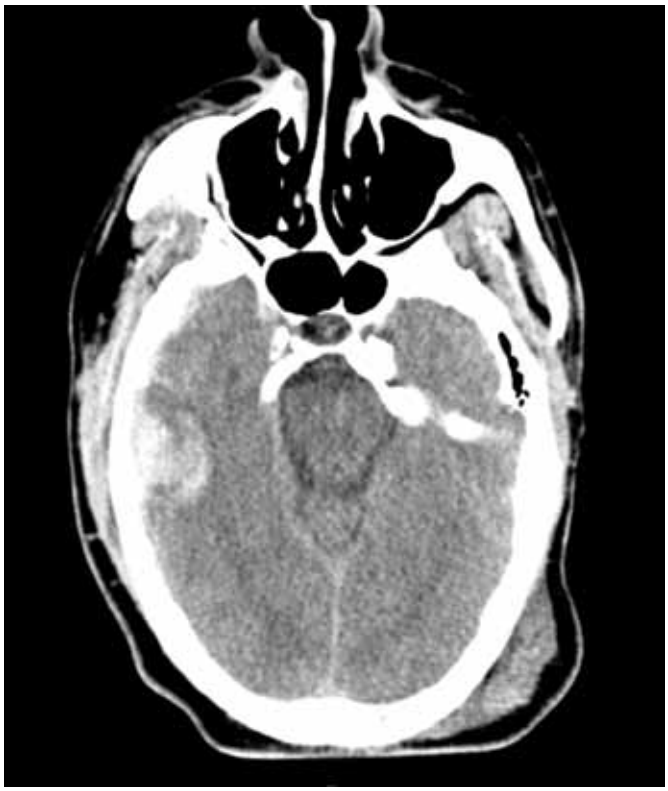


Figure 9. (Above) *Acute epidural hematoma.*

Figure 10. (Right) *Traumatic intracerebral hemorrhage.*

of less than 20 percent with no mortality.[63] The presence of a skull fracture, a six-hour delay from injury to initial CT scan, or heterogeneous density of epidural hematoma did not influence the likelihood of requiring operative management.[63]

Epidural hematomas have a very high potential for progression. If managed nonoperatively, such patients must be followed closely with frequent neurological examination and serial CT imaging.

Traumatic Intracerebral Hemorrhage

Of the many complications of TBI, the development of traumatic intracerebral hemorrhage is one of the most clinically devastating (Fig. 10).[53,64] About 40 percent of traumatic intracerebral hemorrhages progress in size, and risk factors for enlargement include large initial size, presence of subdural hematoma, or associated subarachnoid hemorrhage.[53] One must remain aware of the occurrence of delayed traumatic intracerebral hemorrhage, which can develop up to several days after the inciting trauma. These delayed intracerebral hemorrhages are noted on CT imaging following either focal or diffuse brain injury.[16,18] More recent work has identified that CT progression to intracerebral hemorrhage associated with trauma is most likely to occur within six to nine hours after head injury.[53] Thus, imaging follow-up in conjunction with ongoing neurologic evaluation and bedside clinical monitoring is critical.[53] Indications for surgical evacuation of traumatic intracerebral hemorrhage include the presence of frontal or temporal lobe lesion greater than 50 milliliters, a GCS score of 6 to 8 with frontal or temporal lobe lesion greater than 20 milliliters, effacement of basal cisterns, or midline shift greater than five mm.[65] Traumatic intracerebral hemorrhage patients not meeting surgical criteria may be treated conservatively. This includes minimizing secondary brain injury measures, frequent neurological examinations, and repeated neuroimaging, as indicated. Eventual surgical evacuation is more likely for conservatively managed patients with worsening GCS scores, hematoma expansion greater than five milliliters or effacement of the basal cisterns.[66]

Another area of interest is the use of hemostatic agents to arrest ongoing traumatic intracerebral hemorrhage. If a traumatic intracerebral hemorrhage patient suffers from thrombocytopenia, platelet dysfunction, or coagulopathy, these factors must be corrected rapidly. However, recent trials with the use of recombinant factor VIIa (rFVIIa) for traumatic intracerebral hemorrhage have not shown mortality or outcome benefit with doses up to 200 micrograms per kilogram.[67,68]

Herniation Syndromes

Patients with TBI and intracranial hypertension may progress to a cerebral herniation event. The skull is a fixed and rigid container almost completely filled with blood, brain, and cerebrospinal fluid (CSF). Any increase in volume from hemorrhage or edema is initially compensated by displacement of blood or CSF. When these compensatory mechanisms are exceeded, the brain will herniate out of the cranial vault, resulting in a variety of neurologic signs and symptoms (Fig. 11).

Subfalcine, Central, and Uncal Herniation

Subfalcine herniation is a lateral shift of one frontal lobe into the contralateral side and by default occurs with any degree of midline shift of the cerebral hemispheres. The most common clinical manifestations are increasing lethargy and occasionally neurological deficits related to compromised flow to one or both anterior cerebral arteries. Unilateral anterior cerebral artery compromise classically causes weakness of the contralateral lower extremity, although involvement of the proximal arm and shoulder is reported.[69]

Uncal, or lateral transtentorial herniation, occurs when a supratentorial mass pushes the mesial temporal lobe and uncus anteriorly and downward through the tentorial opening between the ipsilateral aspect of the midbrain and the tentorium. This can result in the Kernohan's notch phenomenon, with hemiparesis ipsilateral to the side of the supratentorial lesion, and is a potentially false localizing sign.[69] Often, a unilaterally large pupil and ensuing third nerve palsy may herald this phenomenon. Radiographic findings of uncal herniation may be seen with resulting midbrain Duret hemorrhages and midbrain ischemia secondary to compromised blood flow to paramedian midbrain perforator vessels (Fig. 12).[69] Duret hemorrhages are small linear hemorrhages along the midline of the brainstem and upper pons caused by traumatic caudal displacement of the brainstem. This is usually an ominous radiographic finding.

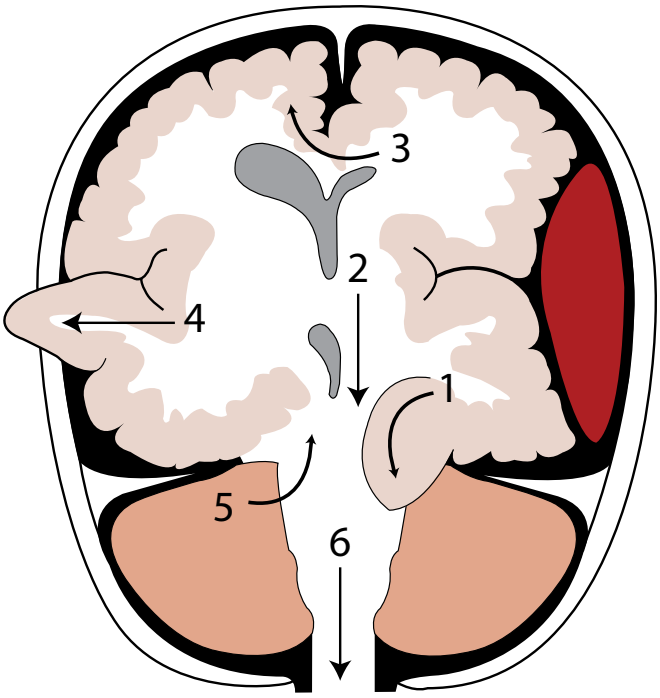


Figure 11. *Six types of brain herniation: (1) Uncal; (2) Central; (3) Subfalcine; (4) Transcranial/extracranial; (5) Upward (upward cerebellar or upward transtentorial); (6) Tonsillar (downward cerebellar).*

Central herniation is downward movement of the brainstem by pressure from the supratentorial brain components. Early findings with central herniation include cranial nerve (CN) VI palsy manifesting

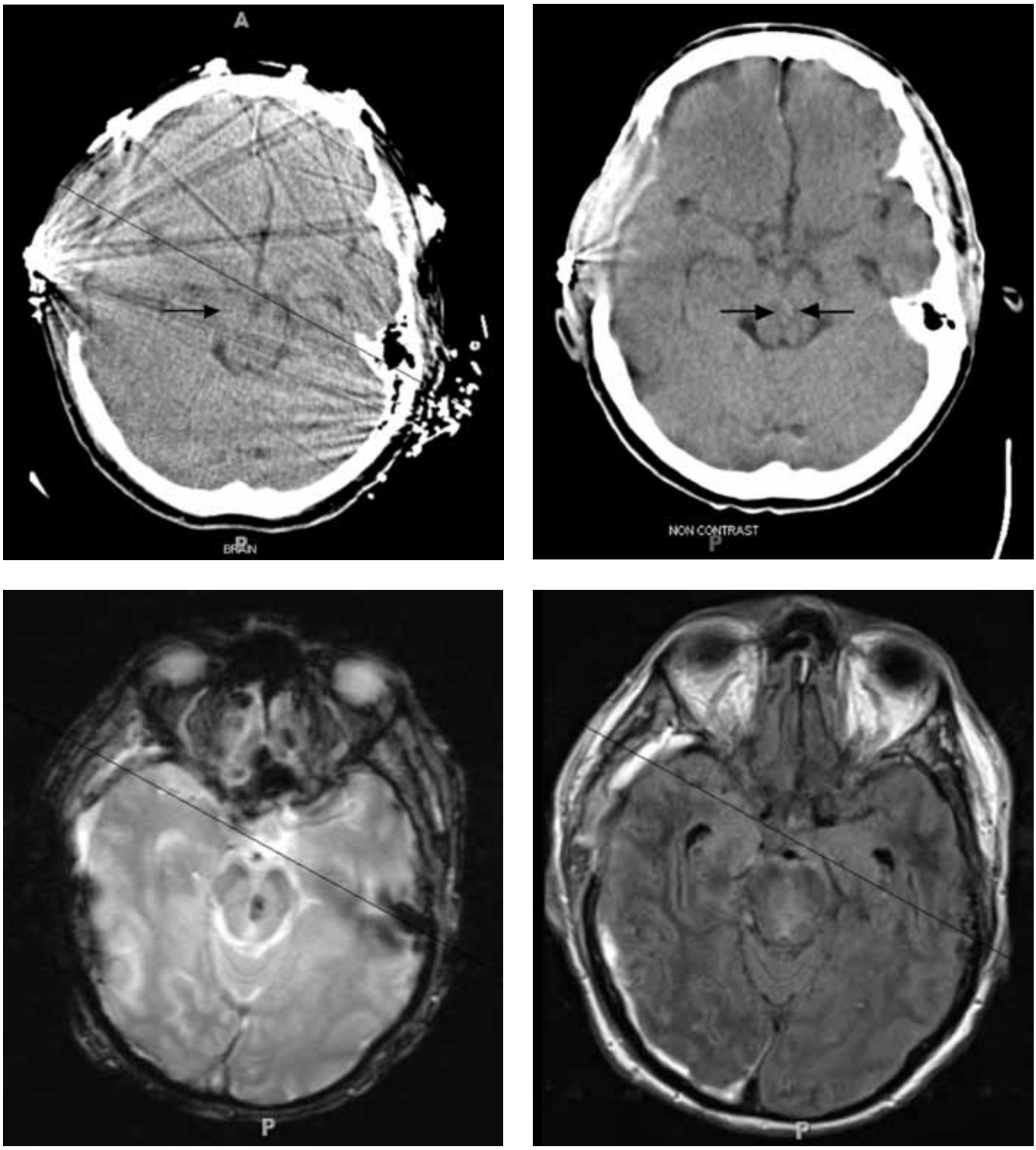


Figure 12. (Top Left) *Uncal herniation on initial head CT image.* (Top Right) *Duret hemorrhages of the midbrain tegmentum on a CT image of the same patient days later.* (Bottom Left) *Duret hemorrhages seen on MRI image.* (Bottom Right) *Duret hemorrhages and ischemic change seen on MRI image of the central midbrain.*

as lateral gaze deficits, which can be unilateral or bilateral. Like uncal herniation, if this progresses, the clinical triad of a CN III palsy (including an ipsilateral nonreactive dilated pupil), coma, and posturing can occur.[70] Occasionally, unilateral or bilateral posterior cerebral artery infarctions can occur with ongoing central or uncal herniation, due to compression of the posterior cerebral artery as it passes upwards over the tentorial notch.[71] Without aggressive management, central herniation is fatal.

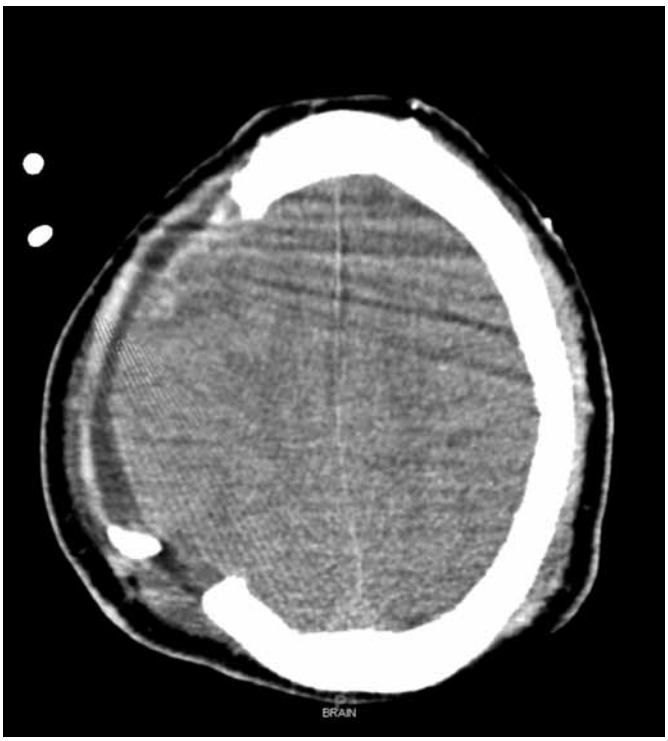


Figure 13. *Extracranial herniation through craniectomy defect.*

Transcranial and Paradoxical Herniation

Transcranial or extracranial herniation occurs when the brain breeches through a skull defect. Most commonly this occurs after craniectomy, as parts of the brain can shift through the surgical site (Fig. 13). This can occur in over 20 percent of postsurgical TBI patients.[72] Essentially, it represents therapeutic decompression of intracranial hypertension. Untoward complications of extracranial herniation do occur, and are related to laceration of cerebral cortex and vascular compromise of venous drainage. Making larger rather than smaller craniectomies may minimize these complications.[72] A less recognized phenomenon is paradoxical herniation, which has been reported during lumbar cistern drainage in the setting of a craniectomy. Paradoxical herniation is when there is downward movement of brain in the setting of an overall lowered intracranial pressure.[73] Only a handful of cases of this type of herniation are reported, although this can also occur in the setting of sodium dysregulation and hypernatremia.[74] Extracranial herniation may also result from primary penetrating injury.

Tonsillar and Upward Herniation

Tonsillar herniation occurs from downward movement of the cerebellar tonsils into the foramen magnum and compression of the lower brainstem. It can result in sudden death from compression of medullary respiratory centers and blood pressure instability.[69,71] Leading causes of this type of herniation are posterior fossa hematomas and obstruction of CSF outflow from the fourth ventricle.[71] A posterior fossa hematoma, or any significant or increasing fourth ventricular dilation, distortion, or obliteration, requires urgent neurosurgical evaluation for possible intervention to include suboccipital craniectomy and placement of an extraventricular drain.

Upward herniation is upward movement of the brain through the tentorium into the cranium. It can cause brainstem compression and can occur with excessive CSF drainage from an extraventricular drain.[75] The clinical presentation of upward herniation is not well-described, although as with all herniation syndromes, a decrease in mental status progressing to obtundation can be expected.

Penetrating Traumatic Brain Injury

In penetrating TBI, the cranial vault is violated by a foreign body. Foreign bodies affecting soldiers in combat include shrapnel fragments and bullets of varying velocities (Fig. 14). Primary brain injury results from the projectile passing through the brain, damaging neural, vascular, and support structures along its tract. In addition to this damage, high-velocity supersonic projectiles can create a vacuum in their trail, giving rise to tissue cavitation. The rapid expansion and retraction of the vacuum cavity compresses and stretches neural and support structures, often tearing them. As the cavity may be many times larger than the projectile's tract, injury is much more severe.[76]

The majority of military penetrating TBI occurs from penetrating fragment injuries and not from fired bullets.[77] Historically, penetrating fragment-related TBI had a significantly lower overall mortality than military gunshot wound TBI.[77] In the past, the clinical management of penetrating TBI involved complete neurosurgical removal and debridement of wounds, to include retrieval of any bone and metal fragments in the brain.[77] This approach was subsequently altered following a detailed analysis of the Israeli-Lebanese conflict. This study confirmed that aggressive surgical debridement was unnecessary and may have worsened outcomes.[78]

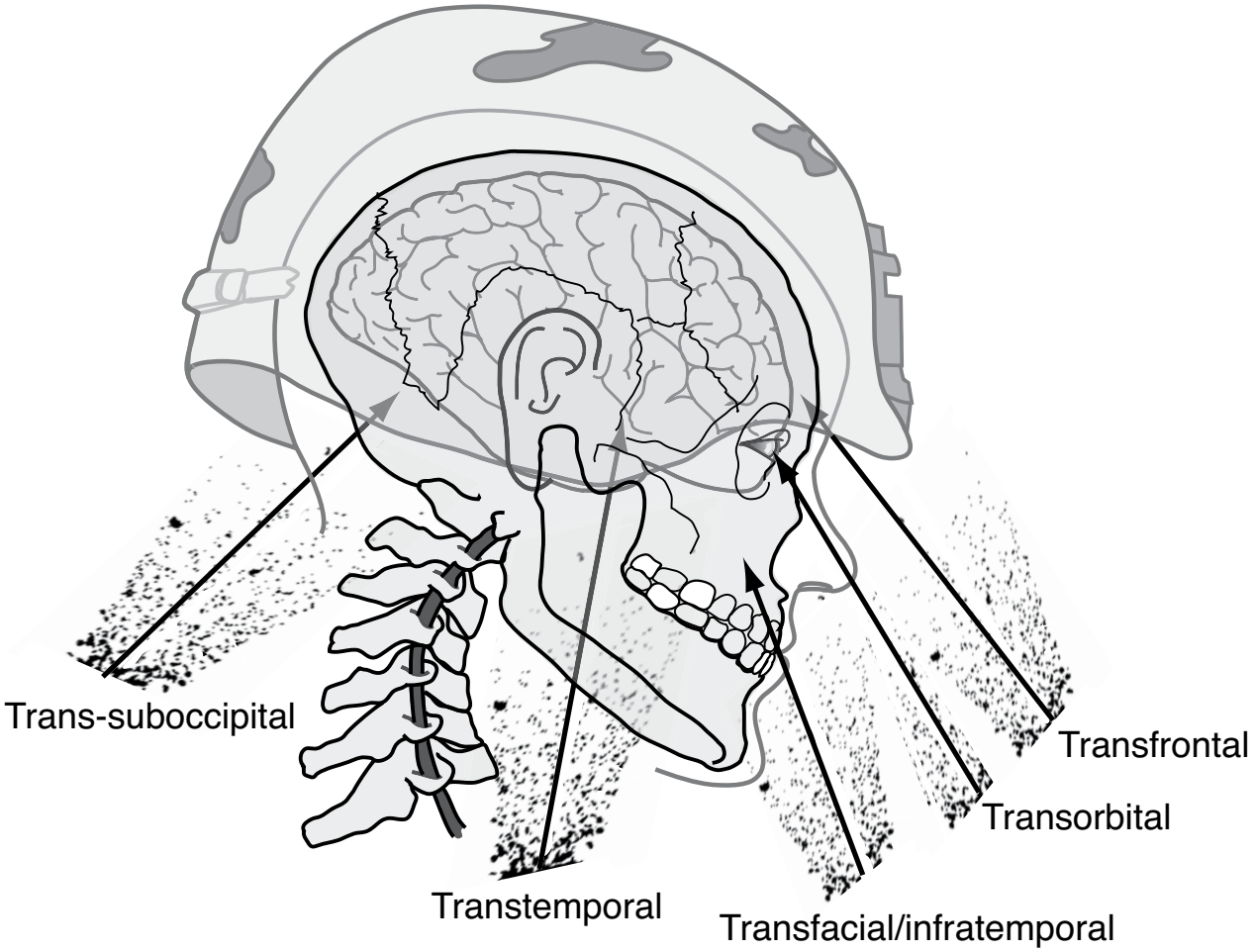


Figure 14. *Common vectors of penetrating TBI. Image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC. Illustrator: Bruce Maston.*

The majority of military penetrating TBI occurs from penetrating fragment injuries and not from fired bullets. Past clinical management of penetrating TBI involved radical wound debridement, surgical removal of fragments from the brain, and minimal decompression. Current strategies favor more conservative debridement and fragment removal coupled with more aggressive brain decompression.

Today, different management strategies are in effect, especially those based on treatment guidelines for penetrating TBI. Evidence suggests that less aggressive neurosurgical management may be warranted.[78,79] Although the level of clinical evidence does not allow for management standards to be issued, current guidelines provide clinical management options. Management options include local wound care and primary wound closure in penetrating TBI patients who have vitalized scalp without significant intracranial pathology, such as midline shift of the falx cerebri, or an intracranial hematoma requiring evacuation. If no significant mass effect is evident on CT imaging, debridement along the path of the projectile is not recommended.[79] If there is tissue devitalization and/or mass effect, then debridement is recommended prior to a primary wound closure.[79]

Infection and Cerebrospinal Fluid Leaks

Infection following penetrating TBI is a concerning complication and can dramatically increase mortality and morbidity from head trauma.[80] The mechanism by which this occurs involves formation of a dural fistula resulting from trauma and subsequent fracture of the skull to which it is adherent. The resulting violation of the dura after penetrating TBI predisposes a patient to infection.[12,81] If temporary CSF diversion (e.g., by lumbar drain) does not lead to spontaneous closure of the CSF leak, surgical correction should be considered.[82]

While the utility of antibiotic prophylaxis following penetrating TBI is unclear, the high likelihood of wound contamination has been used to justify the prophylactic use of antibiotics.

The utility of antibiotic prophylaxis following penetrating TBI is unclear. A common practice is the use of broad-spectrum antibiotics due to the likely contamination of the wound from foreign bodies, skin, hair, and bone fragments.[80] In the authors' opinion, in lieu of standardized guidelines and better evidence-based practice on this subject, it may be worthwhile to continue broad-spectrum antibiotic coverage for these wounds and subsequently narrow antibiotics based on CSF culture data and the clinical picture of the casualty.

Neuroimaging in Penetrating TBI

Advanced neuroimaging is often necessary in penetrating TBI patients. Acutely, CT generally provides sufficient information for appropriate surgical management. Magnetic resonance imaging should not be used in the imaging of acute TBI caused by metallic projectiles.[83] If a vascular injury is suspected, then cerebral angiography is recommended. While conventional angiography is the traditional gold standard imaging modality, computed tomography angiography is widely available and typically utilized in-theater at Level III facilities for this purpose. The sensitivity to diagnose vascular injury such as traumatic dissection of the carotid or vertebral arteries with computed tomography angiography has been reported to be similar or even superior to that of magnetic resonance imaging angiography.[84,85] In terms of other vascular pathology, the incidence of vasospasm in the setting of blast-related penetrating TBI is high, approaching

50 percent.[11] Thus, it is recommended that patients with acute penetrating TBI from explosives undergo regular noninvasive vascular assessment via transcranial Doppler, with follow-up invasive digital subtraction angiography for definitive diagnosis and endovascular intervention.[11]

Patients with acute penetrating TBI from explosives should undergo regular noninvasive vascular assessment via transcranial Doppler studies. Digital subtraction angiography is used for definitive diagnosis and endovascular intervention.

Traumatic Brain Injury Management

An organized team approach is essential to appropriate TBI management. This begins in the field with the medic or corpsman and continues to the CSH and tertiary centers. Proper clinical management in the acute period is essential for optimal outcomes. The Guidelines for Field Management of Combat-Related Head Trauma (available at www.braintrauma.org) and Advanced Trauma Life Support (ATLS) are both useful guides.[86] After evaluation and treatment of airway, breathing, and circulatory (ABC) priorities, the far-forward careprovider must make a rapid initial neurological evaluation (disability assessment), especially determining the patient's GCS score (Table 1).[86] The GCS score is important for triage and is a quantifiable measure of impairment, which can help decide early management sequences. This initial exam helps predict outcomes of moderate and severe TBI and penetrating TBI.[39,87]

Initial Management (Primary Survey)

Optimal clinical outcomes depend on proper battlefield care. It is crucial that first responders recognize the importance of airway, breathing, and circulatory management in order to optimize cerebral oxygenation and perfusion. The brain can tolerate severe hypoxia for a very limited period, and it is well-established that the duration and severity of hypoxia and hypotension in this critical early period have dramatic consequences on ultimate clinical outcome.[21,88] Thus, the goals of early resuscitation are to ensure adequate oxygen saturation (greater than 90 percent) and avoid hypotension (systolic blood pressure less than 90 mm Hg). Ensuring a secure airway and adequate ventilatory support is critical in the management of moderate and severe TBI patients. Circulation management starts with hemorrhage control in concert with damage control resuscitation.

Ensuring a secure airway and adequate ventilatory support is critical to the management of moderate and severe TBI patients.

Airway and Breathing Management

The decision to secure a reliable airway in the patient with a severe TBI is most often made by the careproviders initially evaluating and treating the patient. Rapid sequence intubation is the method of choice. It involves near simultaneous administration of a sedative agent and a neuromuscular blocking agent to induce a loss of consciousness and motor paralysis. While the benefit of rapid airway intervention in severe TBI patients is without question, the side-effect profiles of the many medications used in rapid sequence intubation warrants discussion. The issues of hemodynamic response and intracranial pressure response to endotracheal intubation become germane when dealing with severe TBI patients. The

ideal agent will decrease or stabilize ICP without inducing systemic hypotension during rapid sequence intubation efforts. The more commonly used medications will be discussed with a special emphasis on any neuroprotective properties they may have.

Preoxygenation should be performed when possible. Delivering 100 percent oxygen through a nonrebreather apparatus will lead to a nitrogen washout from within the lungs. This nitrogen washout may occur over three to four minutes and may allow for several minutes of apnea before hypoxemia develops. This will minimize the chances of any transient hypoxemia during subsequent attempts at endotracheal intubation. Although there are no studies to prove preoxygenation prior to rapid sequence intubation minimizes secondary brain injury, the practice intuitively appears beneficial.[89]

Attempts at endotracheal intubation will elicit gag and cough reflexes, tachycardia, hypertension, and increased ICP. The cardiovascular responses are believed to be primarily sympathetic to the mechanical stimulation of the larynx and trachea by direct laryngoscopy and intubation. There are a variety of premedications touted as being able to blunt these responses. Lidocaine (1.5 milligrams [mg] per kilogram) administered intravenously three minutes prior to direct laryngoscopy has been advocated as an agent that may blunt reflex cardiovascular and ICP responses.[90] The ICP response to endotracheal suctioning in intubated TBI patients has been measured at approximately 22 mm Hg.[91] Studies that measured cardiovascular and ICP responses to endotracheal suctioning or endotracheal intubation using lidocaine as pretreatment to blunt these rises revealed mixed results.[90,92,93,94,95,96,97] Lidocaine has also been delivered topically and in nebulized form, in the hopes of blunting the circulatory response to intubation. The many methodologic flaws and conflicting results of these studies preclude drawing any definitive conclusions. Lidocaine did not appear to pose any short-term adverse side effects in the setting of severe TBI in any of the referenced studies. At best, lidocaine should be regarded as an agent that may have potential benefit in blunting ICP rises associated with endotracheal suctioning or intubation.

Opiates have been advocated as possibly decreasing sympathetic response to endotracheal intubation. Fentanyl has specifically been studied in the setting of severe TBI.[91,98,99,100] Results of several studies suggest it actually causes a paradoxical rise in ICP in this patient subset.[101,102] There is not enough evidence to advocate the use of fentanyl to attenuate ICP rises associated with endotracheal intubation. Some evidence suggests it actually may be harmful. Benzodiazepines are potent sedative hypnotics and have been used as adjunctive medications during RSI (rapid sequence intubation). Midazolam, with its rapid onset and short duration of action, is a popular choice. There are few studies measuring ICP and CBF responses to administration of midazolam in humans. In one of the few studies in the setting of severe TBI, Papazian et al. studied the effect of 0.15 mg per kilogram bolus midazolam intravenous infusion on ICP, MAP, and CPP. Twelve patients with severe TBI in an ICU received midazolam boluses over one minute.[103] In those patients, MAP decreased from 89 mm Hg to 75 mm Hg, CPP decreased from 71 mm Hg to 56 mm Hg, and no statistically significant change in ICP was noted. The minimum acceptable CPP in the setting of severe TBI in many treatment protocols has been set at 70 mm Hg, although current guidelines support slightly lower minimum CPP standards.[104] This study cautions against the indiscriminate use of midazolam in the setting of severe TBI, as it may cause suboptimal CPP in a subset of these patients. At present there is insufficient evidence to make any definitive conclusion regarding the neuroprotective benefit of midazolam in the setting of RSI of the severe TBI patient.

Etomidate is a short-acting, nonbarbiturate, sedative-hypnotic. A dose of 0.3 mg per kilogram

administered intravenously over 30 seconds provides rapid sedation with minimal cardiovascular or respiratory depression.[105,106] It has been shown in some studies to decrease ICP, which makes it an attractive option in severe head injury patients.[107,108] It has several adverse effects; one being it may produce vomiting if not accompanied by a paralytic agent. It has also been reported to temporarily suppress adrenal function with as little as one dose.[109] There is no evidence to suggest this temporary attenuation of adrenal responsiveness is of any clinical significance. There are insufficient studies specifically measuring ICP response in head injury patients to the administration of etomidate to make definitive conclusions. However, available evidence indicates that 0.3 mg per kilogram etomidate administered intravenously over 30 seconds may be an effective adjunct in minimizing secondary brain injury in severe TBI patients.[110] Of note, given etomidate's short duration of action, additional sedatives will need to be administered to patients undergoing mechanical ventilation. Agents such as propofol and thiopental have been reported to have properties that reduce ICP rise associated with endotracheal intubation. Both agents have the propensity to induce systemic hypotension, an undesirable side effect for its relationship to CPP in the severe TBI patient.

Rapid sequence intubation involves the administration of neuromuscular blockade immediately following administration of a potent sedating agent and any pretreatment measures for ICP elevation. Succinylcholine, a rapid-acting, short duration, depolarizing neuromuscular blocking agent used at a dose of 1 to 2 mg per kilogram intravenous bolus, is the traditional first-line agent.[111] Administration of this drug has been reported to increase ICP directly, although the mechanism remains unclear.[112] Estimates of the rise in ICP as a direct result of succinylcholine administration in patients with disorders of intracranial compliance have been between 4.9 mm Hg to 12.0 mm Hg.[113,114] While the exact mechanism is speculative, it is suggested that afferent input from muscle spindle receptors to the central nervous system is responsible. Administering a defasciculating dose of a nondepolarizing neuromuscular blocking agent (pancuronium 0.01 mg per kilogram or vecuronium 0.01 mg per kilogram) intravenously three minutes prior to succinylcholine administration has been reported to blunt any subsequent rise in ICP.[113,114] An alternative to using succinylcholine is the administration of a paralytic dose of vecuronium (0.3 mg per kilogram) in an intravenous bolus fashion. This will provide intubating conditions in 100 seconds; however, this dose has the potential disadvantage of complete motor paralysis for approximately two hours and may complicate further neurologic assessment. Prolonged paralysis is thus discouraged. An alternative nondepolarizing paralytic agent with rapid-onset (one to three minutes) and intermediate duration of action (30 to 45 minutes) is rocuronium (0.6 mg per kilogram dosing). Rocuronium is not contraindicated in the setting of burns, potential hyperkalemia, and myopathies.[115,116]

Administering a defasciculating dose of a nondepolarizing neuromuscular blocking agent intravenously three minutes prior to succinylcholine administration has been reported to blunt any subsequent rise in ICP.

Many of the pharmacological agents used to blunt intubation-related elevations in ICP must be administered several minutes prior to intubation attempts in order to achieve peak efficacy. Combat casualty careproviders must use their judgment in these scenarios. Will several minutes of potential hypercarbia or hypoxemia result by waiting for these premedication drugs with theoretical benefit to take effect? Would the resultant rise in ICP from increased CBF offset any benefit these medications provide? While minimizing transient elevations in ICP with premedication or appropriate muscle blockading agents during RSI is theoretically appealing, no definitive proof linking this to improved neurologic outcomes exists.

Head Position

The traditional practice of elevating the head of TBI patients in order to minimize ICP has been challenged. Advocates of a supine position argued it would allow for higher cerebral perfusion pressures and optimized CBF. Rosner et al. measured the effect of head elevation from zero to 50 degrees on ICP and CPP. They concluded that zero degree head elevation maximized CPP.[117] Durward et al. studied the effect of head elevation at 0, 15, 30, 60 degrees on ICP and CPP. They concluded that 15 to 30 degrees of elevation reduced ICP while maintaining CPP. Further elevations of the head to 60 degrees caused an increase in ICP and a significant decrease in CPP.[118] Feldman et al. measured ICP, CPP, CBF, and mean carotid pressures on head injury patients at zero and 30 degrees head elevation. They found mean ICP values of 14.1 mm Hg at 30 degrees elevation increased to a mean ICP value of 19.7 mm Hg at zero degrees elevation. Mean carotid pressures decreased from 89.5 mm Hg to 84.3 mm Hg when patients went from zero degrees to 30 degrees elevation, and no differences in CPP or CBF were noted.[119] From this data, it appears that elevating the head of severe TBI patients to greater than 30 degrees may be detrimental to CBF. Elevation of the head up to 30 degrees may be of some benefit in selected patients with TBI with respect to decreasing ICP, although it may be at the expense of diminished CPP and CBF. Once ICP monitoring is instituted, a more accurate assessment of the optimal degree of head elevation in the patient with severe TBI patient may be made. Of note, any consideration of head position changes need to take into account the stability of the cervical spine or potential for injury.

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Compromised venous drainage can exacerbate intracranial hypertension. It is prudent to always assume an occult cervical spine injury in any TBI patient with altered mental status or blunt injury above the clavicle until ruled out by radiographic imaging.[86] The cervical spine should be immobilized with a rigid neck collar during the initial survey. The neck collar serves a dual purpose. It protects the cervical spine and keeps the head midline. Spinal injuries concomitant with TBI are not uncommon, as a recent retrospective review of head injury casualties from OEF/OIF included a 16 percent incidence of spinal column trauma of various types.[12] In a recent retrospective review of the epidemiology of spinal trauma in polytrauma patients, 8 percent had associated spinal injuries, and the percentages of cervical, thoracic, lumbar, and sacral injuries were 35, 19, 37, and 27 percent, respectively.[120] It is important to immobilize the spine of a polytrauma patient when spinal instability is suspected, and remain vigilant for exam findings, which may be explained by occult spinal cord injury.

Assume an occult cervical spine injury is present in any TBI patient with altered mental status or blunt injury above the clavicle, until it is ruled out by radiographic imaging and clinical assessment.

Secondary Survey

The secondary survey of a trauma patient follows the primary survey and includes a more detailed yet rapid neurologic examination. Examining the patient and detailing the extent of neurologic impairment is essential. Ideally, this can be accomplished in advance of sedation and/or paralysis for endotracheal intubation and other procedures. The diagnosis of TBI is made on history and physical examination. Neuroimaging provides supportive information. It is important to remember that altered mental status or obtundation may be due to other causes, including impaired ventilation, oxygenation, perfusion, glycemic

derangement, or medication/toxin exposure in addition to occult head injury. These conditions must be considered during the initial trauma evaluation.[86]

TBI Management Guidelines and Options

The overriding concept of management of the moderate and severe TBI patient is the prevention of secondary injury. In the initial hours after the inciting trauma, this involves mitigating elevations in ICP, traumatic intracranial hemorrhage, cerebral edema, and metabolic derangements. Treatment guidelines for the management of severe TBI published by the Brain Trauma Foundation have been instrumental in improving care through guiding therapy with evidenced-based recommendations.[121] Guidelines for the prehospital and field management of brain injury are also published, and all three sets of guidelines can be obtained from the Brain Trauma Foundation free of charge (www.braintrauma.org).

Airway Management and Ventilation

Ensuring adequate oxygenation and appropriate ventilation of the head-injured patient is vital. Oxygenation and ventilation goals should be to maintain adequate oxygenation with partial pressure of oxygen in arterial blood (PaO_2) greater than 60 mm Hg, and avoid either hypocarbia or hypercarbia by maintaining a PCO_2 in the normal range, except for brief periods of hyperventilation discussed below.[21,122]

> Oxygenation and ventilation goals should be to maintain adequate oxygenation with PaO_2 greater than 60 mm Hg, and avoid either hypocarbia or hypercarbia by maintaining a PCO_2 in the normal range.

In the field, oxygen saturation should be greater than or equal to 90 percent. Hypoxic episodes with saturations lower than this are associated with worse outcomes.[123,124] Absolute indications for inserting an artificial airway are a GCS score of 8 or less or suspicion that the patient's ability to ventilate or protect his or her airway is compromised. Oral endotracheal intubation is preferred in Level III facility settings. Nasotracheal intubation is not recommended in the setting of significant head trauma. The possibility exists for increasing ICP due to stimulation of the nares as well as displacing occult skull fractures through nasopharyngeal manipulation.[125,126] Another advantage to intubation is to ensure the maintenance of eucapnea (PCO_2 of 35 to 40 mm Hg), as hypercapnea will induce increased ICP.[127]

Role of Hyperventilation

Acute hyperventilation has traditionally been a first-line intervention in rapidly decreasing ICP. As the ability to monitor CBF, cerebral metabolism, and cerebral ischemia has improved, new information regarding potential pitfalls of hyperventilation has emerged. Recent studies have noted that while hyperventilation acutely decreases ICP, it also decreases CBF, and in many cases may induce cerebral ischemia.[25,27,128,129] Severe TBI patients have been found to have either increased or reduced CBF during the early phases of their injuries. Both states may be associated with elevated ICP. While hyperventilating the TBI patient with increased CBF may be desirable, hyperventilation may induce cerebral ischemia in patients with reduced CBF. In certain patients with increased CBF, hyperventilation has lead to decreased CBF in uninjured areas of the brain, while creating a relative increase in CBF to areas of injured brain. This localized increase in CBF to injured areas of brain is thought to occur due to the diminished responsiveness of the injured brain's microvasculature to hypocapnia.

Optimal titration of hyperventilation therapy requires close monitoring of objective indicators of cerebral ischemia.[130,131] Objective indicators of cerebral ischemia or CBF include measurement of jugular venous saturations, thermal diffusion flowmetry, transcranial Doppler ultrasounds, and xenon-enhanced CT scans. These methods of measuring cerebral ischemia or CBF are not widely available to CCC providers. This has led to the recommendation that hyperventilation only be used in settings of documented elevated ICP and as a temporary and last-line treatment to decrease elevated ICP refractory to other means, such as sedation, paralysis, CSF drainage, lowering of brain metabolism, and osmotic therapy.

Hyperventilation should only be used as a temporary and last-line measure to decrease elevated ICP refractory to other means, such as sedation, paralysis, CSF drainage, lowering of brain metabolism, and osmotic therapy. Physicians should use a PCO_2 level of 30 to 32 mm Hg as their target when they decide to institute hyperventilation therapy in the setting of severe head injury.

Prolonged hyperventilation has been clearly associated with exacerbation of cerebral ischemia.[132] Very brief durations of hyperventilation may be acceptable only as a temporizing measure until other means of managing increased ICP are readied. If hyperventilation is continued for longer than 12 hours, metabolic compensation negates the ameliorative effects of respiratory alkalosis caused by a hypocapnic state, and continued hyperventilation may be harmful.[127] The recommended goal for baseline PCO_2 levels is normocapnia in the 35 to 40 mm Hg range, but during an impending herniation event, hyperventilation will acutely lower PCO_2 and ICP within seconds. Based on available data, physicians should use a PCO_2 level of 30 to 32 mm Hg as their target when they decide to institute hyperventilation therapy in the setting of severe head injury. The current recommended PCO_2 is to strictly avoid levels below 25 mm Hg.[125,127]

Hemodynamic Management

The objective of hemodynamic therapy in TBI is to ensure adequate brain perfusion. The specific treatment goals are systolic blood pressure greater than or equal to 90 mm Hg, CPP greater than or equal to 60 mm Hg, and euvolemia. As discussed above, CPP is MAP minus ICP (Equation 1). Although CPP is neither a direct measure of CBF nor regional cerebral flow, it is indicative of the overall adequacy of brain perfusion, especially in the context of elevated ICP.

Blood pressure management may be challenging in combat-injured patients. Often, the patient is in hemorrhagic shock due to accompanying injuries such as traumatic extremity amputation. As such, hypotension is common and independently associated with TBI, poor outcome, and mortality.[16,133] Systolic blood pressures less than 90 mm Hg has an especially deleterious effect. When compared to hypoxemia, low systolic blood pressure is associated with a worse outcome.[17] With head injury, the ability of the neurovasculature to autoregulate is impaired, and thus regional cerebral blood flow becomes directly dependent on systemic blood pressure.[125] Experimental models show that the injured brain is highly susceptible to even subtle ischemic states.[134] It is therefore imperative to avoid even short episodes of hypotension after TBI. Overall fluid balance of head injured patients is also important. Retrospective data suggests that TBI patients who were volume depleted by about 600 milliliters developed worse outcomes.[135]

Hypotension is common in combat casualties. Hypotension following severe TBI has been associated with poor outcomes and increased mortality.

Hemostasis of the obvious soft-tissue head wound is usually obtained with direct pressure dressing or a field dressing such as HemCon® or QuikClot®. Crystalloid fluids are used for fluid resuscitation in the field phase of the treatment of the brain-injured patient. Later, blood products may be transfused as needed. Analysis of data from OEF and OIF indicates that hemorrhagic shock is best treated with red blood cells and plasma using a 1:1 ratio based on volume.[15] Colloid and hypotonic fluids are relatively contraindicated in TBI. Colloid fluids containing albumin have been shown to increase mortality.[136] Hypotonic fluids, such as half-normal saline and lactated Ringer's, have the potential to exacerbate cerebral edema.[125]

Colloid and hypotonic fluids are relatively contraindicated in TBI. Colloid fluids containing albumin have been shown to increase mortality, while hypotonic fluids, such as half-normal saline and lactated Ringer's, have the potential to exacerbate cerebral edema.

Cerebral perfusion pressure goals are best met with intravenous fluids. If CPP cannot be maintained with intravenous fluids alone, vasoactive pharmacologic agents may be considered. Norepinephrine and phenylephrine are often used, as they are thought to have minimal effect on cerebral vasomotor tone. If vasopressors are used, then continuous hemodynamic monitoring is needed.[76] Aggressive use of vasopressor agents has been associated with increased incidence of acute respiratory distress syndrome; however, this complication potentially could have been the result of exceeding CPP levels of 70 mm Hg.[137]

Goals for ICP Management

The goal for ICP management in brain-injured patients is to maintain a normal ICP which is generally less than 20 cm H_2O or 15 mm Hg. Data suggest that elevations over 25 mm Hg are associated with poor outcomes, and thus interventions should be aimed at reducing ICP to less than this amount.[138] Current guidelines recommend instituting measures to control ICP when pressures of 20 mm Hg are reached and aggressive means employed to prevent ICP elevations over 25 mm Hg.[139] One must keep in mind the achievable CPP based on MAP and ICP during therapy, as many interventions to decrease ICP may also have systemic effects on peripheral hemodynamics. The maintenance of a CPP of at least 60 mm Hg is strongly recommended.[104] This is often accomplished with the use of vasopressor agents, although complications, including higher incidence of adult respiratory distress syndrome, may result from overshooting the goal CPP to greater than 70 mm Hg with vasopressors and intravenous fluids, as previously discussed.[137]

Intracranial Pressure and External Ventricular Drains

The management of ICP is paramount in neurocritical and neurosurgical care. If ICP progresses unchecked, it will culminate in cerebral herniation. Simple therapeutic measures should be instituted in every moderate to severe TBI patient so as to minimize increasing ICP. Such simple interventions include keeping the head midline, avoiding any circumferential neck dressings for wound hemostasis or securing the endotracheal tube, and avoiding placement of internal jugular central venous lines into the dominant internal jugular vein. All of these will optimize venous outflow from the head.[42] The Trendelenburg position should not be used as it will do the opposite.[140]

All TBI patients with suspected elevated ICP should have an ICP monitor placed. Options include an intraventricular catheter, intraparenchymal fiberoptic or solid-state monitor, subdural bolt, and epidural fiber optic catheter. The most invasive is the intraventricular catheter. It provides the most accurate measurement of ICP as it is placed into the third ventricle that is almost at the center of the cranial

vault.[141] It is also the most consistently reliable as it can be zeroed. The other methods are less invasive as they either require only minimal or no penetration of brain parenchyma. As closed systems, they have a lower incidence of infection but, unfortunately, also are subject to measurement drift as they cannot be zeroed. Another benefit of the intraventricular catheter is that it provides a treatment option for ICP management. The intraventricular catheter is also known as an external ventricular drain, as it can be used for CSF removal.[141] If hydrocephalus is seen on CT, an external ventricular drain is the best option (Fig. 15).

There is evidence that with proper training, placement of an external ventricular drain or other ICP monitors can be done safely by non-neurosurgeons.

Indications for placing an ICP monitor include a patient with a GCS score less than or equal to 8 (after resuscitation) and an acute abnormality on CT, such as traumatic intracerebral hemorrhage, compression of the basal cisterns, or evidence of contusion.[142] If a patient has two of the following: systolic blood pressure less than 90 mm Hg, motor posturing on exam, and/or is greater than or equal to 40 years of age, then an ICP monitor should likewise be placed or strongly considered.[142] Typically a neurosurgeon places these devices. However, there is evidence that with proper training, placement of an external intraventricular drain or other ICP monitors can be done safely by neurointensivists and other non-neurosurgeons (Fig. 16).[143,144] It should be stated that this is not yet a mainstream position, and that access to the cranial vault should ideally only occur with neurosurgical oversight.

Hypertonic Saline and Other Medical ICP Management Options

Initial medical intervention for elevated ICP includes avoidance of exacerbating factors such as fever, seizures, venous outflow obstruction, hyperglycemia, or hypercarbia. The next line of therapy involves osmotic therapy. Several agents have been used for this purpose in the past, but currently mannitol and hypertonic saline (HTS) are the mainstays of osmotic or hyperosmolar therapy.

Role of Mannitol

Mannitol is an osmotically active agent that has long been used in the management of elevated ICP.[145] The mechanism of its action involves multifactorial pathways to lower ICP.[146] It has volume expansion and rheologic properties making red blood cell mediated oxygen delivery to brain cells more effective. This in turn may stimulate reflex cerebral microvasculature vasoconstriction.[147,148] Irrespective of the mechanism of action of mannitol, its effectiveness in reducing ICP is well documented.[147] It will consistently decrease ICP by approximately 20 to 35 percent within 10 to 20 minutes of intravenous administration. The ICP reduction effect of mannitol typically lasts at least two hours.[149,150,151] A common fear of inducing acute hypotension in the multiple trauma patient by infusing mannitol precludes its use by many physicians. However, in multiple studies, mannitol infusion resulted in acute increases in central venous pressure and mean arterial pressures.[146,148,150] The osmotic diuresis leading to hypotension was rarely noted. When hypotension did occur, it occurred several hours later and was mild and easily treated with volume replacement. Mannitol appears to be a safe and effective drug in acutely reducing ICP in severe TBI patients.

Mannitol can decrease ICP by approximately 20 to 35 percent within 10 to 20 minutes of intravenous administration, and its effects last for two hours.

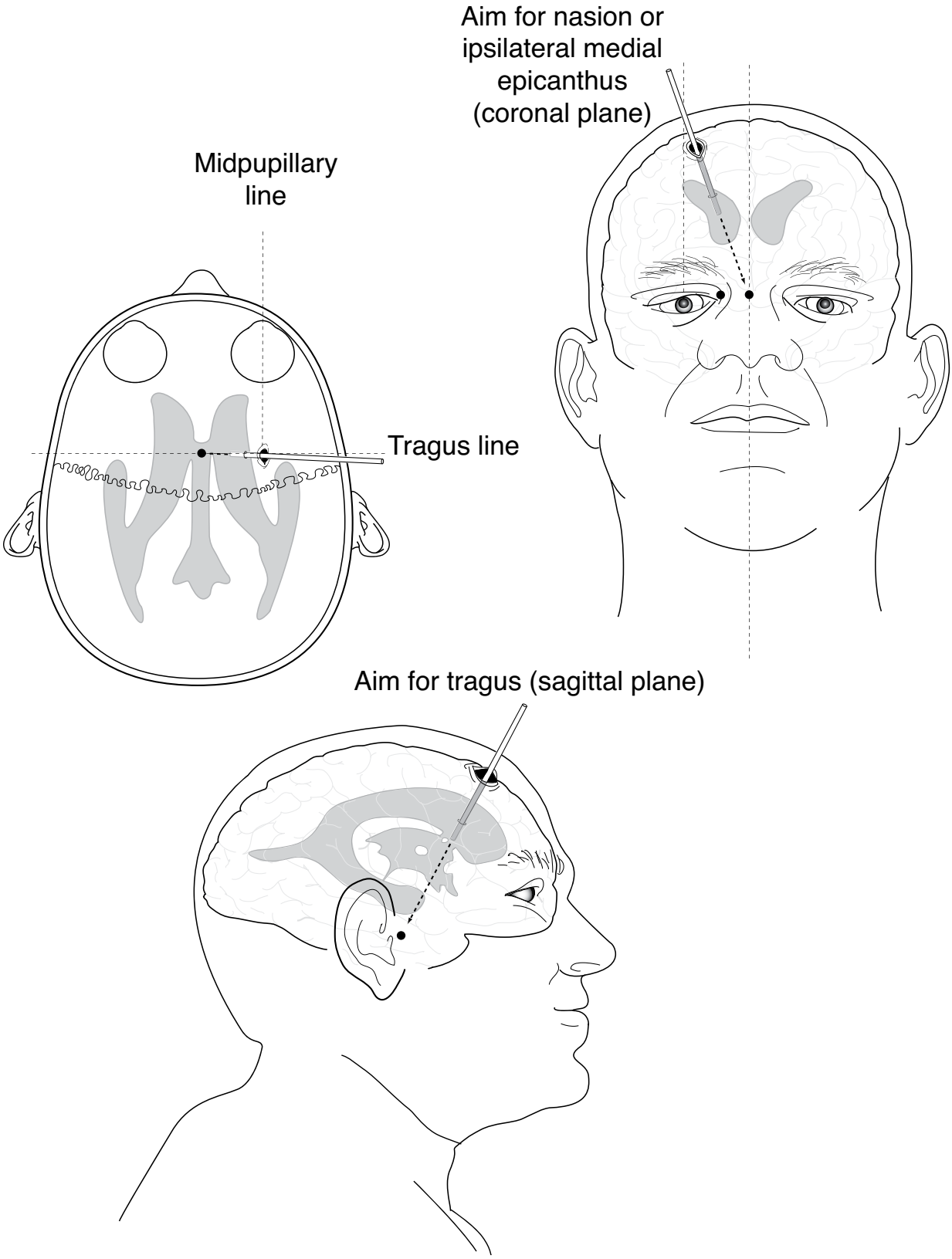

Figure 15. *Landmarks for placement of intraventricular catheter. Adapted image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC. Illustrator: Bruce Maston.*

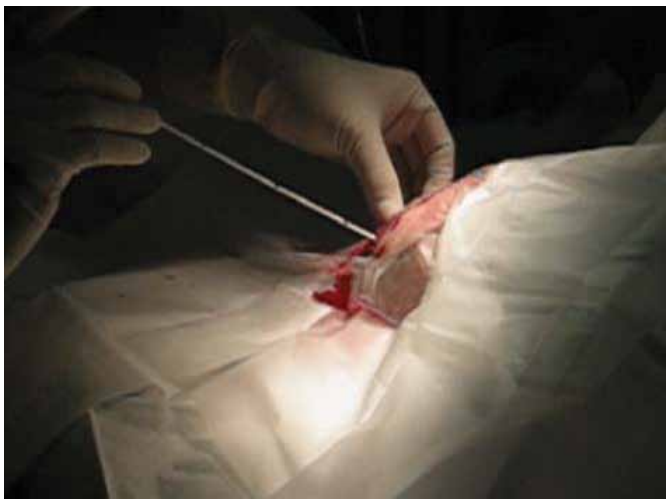

Figure 16. *An intraventricular catheter provides the most accurate measurement of ICP and is a valuable treatment option for ICP management.* (Top Left) *A hole is drilled through the skull.* (Top Right) *The intraventricular catheter is advanced into the third ventricle at the center of the cranial vault.* (Bottom Right) *If needed, CSF can be removed if necessary.*

Mannitol should be given intravenously via a peripheral or central intravenous line at a dose of 0.25 to 1.0 grams per kilogram. Small doses of mannitol (0.25 grams per kilogram) have been shown to effectively reduce ICP in patients with TBI.[152] Earlier data shows that mannitol use in TBI correlates with decreased ICP and improvements in CBF and CPP.[149] Past recommendations for mannitol to be given as bolus infusions rather than continuous are no longer supported. Still, in common clinical practice, a single bolus dose is most widely used.[153] So long as serum osmolality is followed closely, additional doses of mannitol can be given. A serum osmolality of 320 milliosmole (mOsm) per liter is generally accepted as a treatment endpoint, although some investigators advocate that slightly higher levels can be tolerated with caution.[154]

Hypertonic Saline (HTS)

Another option for hyperosmolar therapy is HTS. Studies using 7.5% and 23.4% HTS provide evidence of clinical benefit.[155,156] Recent data support the use of bolus doses of 30 to 60 ml of 23.4% HTS to emergently treat a herniation event.[156] An additional benefit of using 23.4% HTS is that its ameliorative effect on ICP lasts longer than mannitol.[157] When used, 23.4% HTS must be administered via a central venous line over ten to fifteen minutes to prevent hypotension and phlebitis. A commonly used initial treatment goal is to achieve serum sodium levels 145 to 155 milliequivalents (mEq) per liter, which is equivalent to a serum osmolality of 300 to 320 mOsm per liter in most patients.[140] A continuous intravenous infusion of 2% or 3% HTS can be used to maintain high serum osmolality. When doing

so, it is suggested that the fluid be made as a 50%:50% mix of sodium chloride and sodium acetate so as to prevent hyperchloremic metabolic acidosis. At 2% concentration, HTS can be given through a peripheral intravenous catheter, but at 3% or higher, it must be given via a central line due to its potential to cause phlebitis. The infusion rate is set based on a particular patient's intravascular needs. Typically, a maintenance rate of 75 ml per hour is used. However, these solutions can be administered in 250 ml boluses to treat episodes of intracranial hypertension or systemic hypotension.

Studies using 7.5% and 23.4% HTS provide evidence of clinical benefit in reducing ICP in cases of refractory intracranial hypertension.

If continuous infusions of hypertonic solutions are used, serum sodium should be monitored frequently, at least every six hours. Rapid drops in serum sodium are to be avoided so as not to precipitate cerebral edema.[140] Dehydration must also be avoided.[135] Generally, HTS therapy is maintained for the first four to seven days after injury. After the peak edema period elapses, HTS infusion can be switched to normal saline or terminated while observing for the slow return to normonatremia.

Other Pharmacologic Agents to Reduce ICP

If ICP remains poorly controlled after the efforts described above, then induced pharmacologic coma can be considered. The postulated effect of pharmacologic coma on ICP is through reduction of cerebral metabolism with concomitant reductions in CBF and reduced tissue oxygen demand. The most commonly used agent for pharmacological coma is pentobarbital. This drug can be administered intravenously at a loading dose of 5 mg per kilogram, followed by an infusion of 1 to 3 mg per kilogram per hour. There is a high-dose regimen that begins with an intravenous loading dose of 10 mg per kilogram over 30 minutes followed by 5 mg per kilogram per hour infusion for three hours, followed by 1 mg per kilogram per hour titrated to therapeutic goals, which are either burst suppression on continuous electroencephalography (EEG) monitoring or a reduction in ICP.[76] If burst suppression is not obtained with this dose, then a smaller loading dose and increased rate can be given until a satisfactory EEG tracing is seen or ICP is controlled. Other barbiturates may be used including the much shorter acting thiopental, whose half-life of five hours is suited for short-term therapy of elevations in ICP.[140] Thiopental doses of 200 to 500 mg can be given via bolus intravenous push while monitoring for hypotension.

Another option for pharmacological coma is propofol, which is given at an intravenous loading dose of 2 mg per kilogram, followed by a titrated infusion of up to 100 micrograms (mcg) per kilogram per minute. The use of propofol for this clinical indication is controversial. Long-term and high-dose propofol infusions have been associated with the development of hypotension and a newly described metabolic disorder termed propofol infusion syndrome.[158] This consists of renal failure, rhabdomyolysis, hyperkalemia, myocardial failure, metabolic acidosis, lipemia, hepatomegaly, and death. The mechanism for this is not fully understood, but significant caution must be used in any infusion over 5 mg per kilogram per hour or treatment lasting longer than 48 hours.[159] In a study of propofol used for ICP reduction, there was a failure to show a six-month outcome benefit.[160] If propofol is used for induction of a pharmacological coma (and resultant ICP reduction), continuous EEG monitoring will be required to monitor the electrical activity of the brain.

Induced Hypothermia

Induced hypothermia for TBI remains controversial but promising. Recent animal data shows promise for induced hypothermia with improved neurophysiologic metrics in an asphyxial brain injury model.[161] There is also data in brain trauma that induced mild hypothermia (33 to 35 degrees) may improve outcomes as far out as two years following head injury.[162] Current use of prophylactic hypothermia for treatment of ICP in severe TBI is a second-tier therapy but may be helpful in refractory intracranial hypertension. If utilized, modalities of induction of hypothermia include skin-applied gel cooling systems and intravenous methods, as well as traditional air-circulating cooling blankets, iced gastric lavage, and surface ice packing.[140] The goal of maintaining normothermia and avoiding hyperthermia in TBI patients, however, remains strongly recommended.[5]

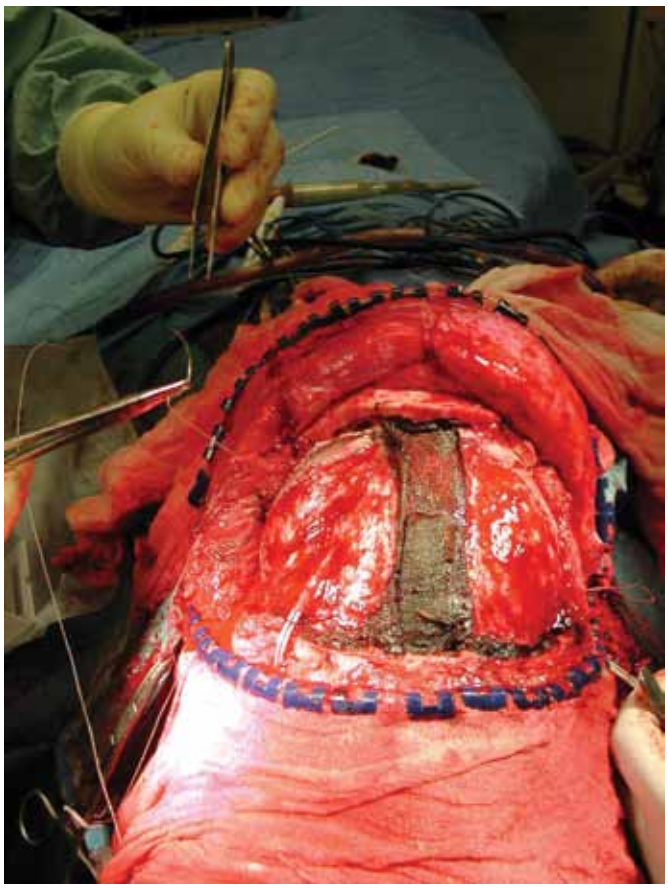

Figure 17. *Early decompressive craniectomy in a patient with blast TBI.*

Decompressive Craniectomy

Decompressive craniectomy is an emerging clinical approach to the early intervention and management of TBI.[163] The reported experience to date is conflicting. In a study of 57 young patients (age less than 50) with severe TBI, early decompressive craniectomy was associated with a good outcome, defined as social rehabilitation, in 58 percent of patients. The authors reported a relatively low mortality of less than 20 percent.[164] A retrospective French study reported a similar outcome in only 25 percent of severe TBI patients.[165] Older data from the Trauma Coma Data Bank has suggested that even though radiographic improvement occurred, there is no significant improvement in patient outcome after craniectomy.[166] One of the difficulties in interpreting the available data is the lack of agreement as to how the procedure is to be performed (e.g., release the dura or not, timing of surgery, cutoff age, and TBI severity on presentation) (Fig. 17).[167]

The authors' OEF and OIF neurosurgical experience supports the practice of early decompressive hemicraniectomy for treatment of severe blast TBI. From a practical military standpoint, this may obviate the need to use more conventional methods to control ICP, such as pharmacologic coma.

Currently, two trials enrolling an estimated combined number of over 800 patients are underway. The Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-Cranial Pressure (RESCUEicp) and the Decompressive Craniectomy (DECRA) trials may better elucidate the role of decompressive craniectomy in severe TBI. The RESCUEicp trial is the larger of the two and is a multicenter trial in Europe comparing decompressive craniectomy to medical management in TBI.[168] The DECRA trial has a smaller planned enrollment and is being conducted in Australia, New Zealand, Canada, and

Saudi Arabia. The authors' OEF and OIF neurosurgical experience supports early hemicraniectomy for treating severe blast TBI.

Current Use of Decompressive Craniectomy with Intractable Intracranial Hypertension

From a practical military standpoint, craniectomy provides an additional measure of safety for ICP control. Early decompressive craniectomy may obviate the need to use more conventional methods to control ICP such as pharmacological coma, which is difficult to execute in a deployed and hostile setting due to the limited number of neurological critical care specialists and lack of EEG support in a war zone. In a recent paper comparing GCS scores of patients at the time of head trauma and at discharge, TBI patients who underwent a craniectomy had lower initial GCS scores than those who underwent craniotomy, but at discharge their GCS scores were not significantly different.[11] This study implies that although these patients were worse initially, they improved after decompressive craniectomy to the point where they appeared indistinguishable from those who initially presented with a better neurologic exam. In the combat setting, decompressive craniectomy may be a practical, though aggressive, approach to ICP management. Future studies on larger cohorts of patients and with more rigorous study design may either support or refute this practice (Fig. 18).

Anticonvulsant Use in TBI

Traumatic brain-injured patients are at risk for both early (less than seven days) and late (more than seven days) post-traumatic seizures. This risk is worsened by traumatic intracranial hemorrhage.[169] A seizure in the acute phase can exacerbate the injury. Phenytoin, a well-established antiepileptic drug, has been shown

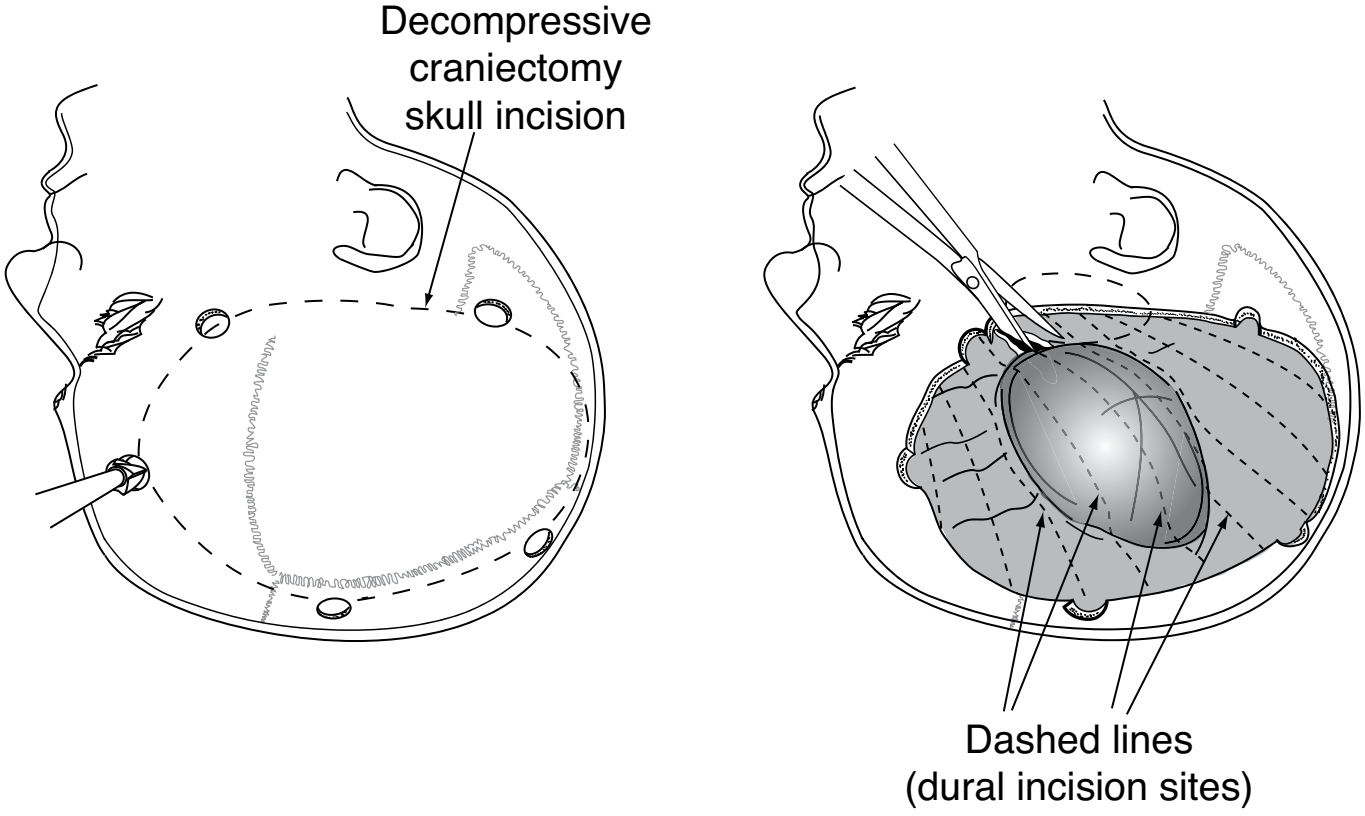

Figure 18. *Decompressive craniectomy bone flap and exposed hematoma. Bone may be cut using a power craniotome, or a Hudson brace and Gigli saw. Adapted image courtesy of the Borden Institute, Office of The Surgeon General, Washington, DC. Illustrator: Bruce Maston.*

to be beneficial in reducing the risk of seizures during the first week after TBI.[170] Carbamazepine, phenobarbital, and valproate are also effective antiepileptic drugs.[171] Unfortunately, no antiepileptic drug has been shown to prevent the development of late post-traumatic seizures. Studies have shown that when followed for 15 years after significant TBI, approximately 50 percent of patients will develop late seizures.[172] As 50 percent will not, the recommended approach is to stop antiepileptic drug therapy after the first seven days, and only reinstitute treatment should late seizures manifest.[173] The potential for cognitive side effects of phenytoin make prolonged prophylactic use of this medication less attractive.[174] If a patient is unable to take medications orally, alternatives to phenytoin and fosphenytoin are valproate and levetiracetam, as all are available in intravenous form. Levetiracetam has not undergone rigorous human clinical TBI trials but has been shown to be effective in preclinical TBI models.[175]

There is little evidence to support or refute the use of antiepileptic drugs for prevention of post-penetrating TBI seizures. The risk of seizure following penetrating TBI is much higher than nonpenetrating TBI, and thus antiepileptic drugs are prescribed by most providers.[176] Management options include the use of antiepileptic drugs during the first seven days after penetrating TBI and then to discontinue their use.[177] Should the patient suffer a late seizure, the antiepileptic drug therapy can be restarted. Therapeutic options are phenytoin, fosphenytoin, carbamazepine, valproate, or phenobarbital.[173]

The risk of seizures following penetrating TBI is much higher than nonpenetrating TBI. Hence, antiepileptic drugs, such as phenytoin, are frequently administered for at least the first seven days following injury.

Critical Care and Air Evacuation

After initial emergency care, patients with moderate and severe TBI require close neurological and physiological monitoring. This is best done in the ICU of a Level III care facility, where monitors and advanced clinical practice nurses are present. Evidence demonstrates improved outcomes when specialized neurological intensive care teams, employing evidence-based clinical care, guide management.[178] The presence of other traumatic injuries may require additional care from trauma, orthopedic, craniofacial and other specialists. In this critical injury period, the best measure of efficacy of treatment or worsening of condition is the neurologic examination. Thus, regular clinical neurological examination by skilled practitioners is needed. In the acute period, it may be as often as every hour and then less frequently if the patient remains stable. Intracranial pressure and CPP measurements should be made continuously if an ICP monitor is indicated. However, even in the presence of ICP monitoring, the importance of the clinical examination and neurological assessment cannot be overstated. The highest risk period for deterioration is in the first few days after TBI. The majority of conversion to traumatic intracerebral hemorrhage occurs usually within the first nine hours, and generally the peak period of cerebral edema is from 48 to 96 hours after TBI.[53] Thereafter, these processes wane, and there is clinical improvement with better ICP control.[76]

Evidence demonstrates improved outcomes in patients with moderate and severe TBI when specialized neurological intensive care teams apply evidence-based clinical care. This is best done in the ICU of Level III care facilities.

Current military policy supports the principle of rapid out-of-theater evacuation to fixed medical facilities, although the decision to transfer the severely injured soldier with TBI via air evacuation may still

be difficult. As discussed above, both the peak period of cerebral edema, as well as the likely conversion of TBI to traumatic intracerebral hemorrhage will occur in the hours and days after the initial trauma. For this reason, it is wise to have the injured service member out-of-theater and en route to a medical center that is part of the casualty evacuation system. Although the risk of transferring a patient who may become unstable during air evacuation is disconcerting, a recent review of the Air Force Critical Care Air Transport Team's (CCATT) safety record and census of trauma and nontrauma-related air evacuations is reassuring.[179] During the period of study, air evacuations via CCATT teams from OIF to Landstuhl, Germany, no inflight or 24-hour post-flight fatalities were reported among flights occurring over a one-year period for the flight time of approximately five hours. In this study, 17 percent of combat casualties had neurologic injury, and 9 percent of these patients had an ICP monitor in place with resultant increases in ICP during flight occurring in 3 percent of patients. Although the authors of this study credit the in-theater medical teams with proper preparation of trauma-related casualties for air evacuation, there is data to support the current doctrine of rapid removal of casualties from theater.[179] This policy has been credited with improved rates of fatalities of soldiers wounded in combat during the conflicts in Iraq and Afghanistan.[180]

Other Management Considerations

Other important considerations include preventing secondary complications of critical illness including venous thromboembolism, gastric stress ulcers, and decubitus ulcers. Injured and immobilized patients are at high risk for developing deep venous thrombosis with subsequent venous thromboembolism. The optimal approach in severe TBI with intracranial hemorrhage is uncertain. Sequential compression devices on the lower extremities are minimally invasive and are not associated with worsening intracranial hemorrhage. Thus, they should be placed as soon as possible. The optimal timing of introduction of unfractionated or low molecular weight heparin for venous thromboembolism prophylaxis in head trauma is less clear.

However, if there are no contraindications to heparin use (e.g., ongoing coagulopathy, worsening thrombocytopenia, or ongoing hemorrhage) then treatment should be started as soon as possible, ideally within the first 36 hours of injury.[181] A practical guide is to obtain CT imaging of the brain after a period of 24 to 36 hours, and if no increase in hemorrhage or new hemorrhage has occurred, then subcutaneous heparin can be started. In the setting of any degree of increasing traumatic intracerebral hemorrhage, the risks and benefits of heparin must be weighed on an individual basis. The routine placement of inferior vena cava filters is controversial, and placement is currently supported only by a low-level recommendation in patients with a GCS score of less than 8 and contraindications to anticoagulation.[181,182]

Gastric stress ulcers may be prevented using either H2-receptor antagonists or proton-pump inhibitors.[183] Either one of these medications should be routinely used for gastric stress ulceration prophylaxis in severe TBI patients, although the tendency for H2-receptor antagonists to cause thrombocytopenia may limit their usefulness.[184] Prevention of skin breakdown is a concern in all severely injured trauma patients, and care must be taken to reduce the likelihood of decubitus ulcers through frequent repositioning, vigilant nursing care, and good skin hygiene practices.

Summary

Medical management of the combat TBI patient is challenging. The field and hospital care of TBI is largely confined to supportive efforts to minimize secondary brain injury for optimal neurologic recovery. This is accomplished through maintaining cerebral perfusion, controlling ICP, and preventing morbidity associated with critical illness. Routine or prolonged hyperventilation, as discussed previously, is harmful and should be avoided.[27] As new pharmacologic and medical approaches are introduced, there will be increasing opportunity to better manage these patients and enhance their long-term neurologic outcomes.

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