CRITICAL CARE OF THE TRAUMATIC BRAIN INJURY

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1. Intro

Despite advances in both prevention and treatment, traumatic brain injury (TBI) remains one of the most pervasive health care issues worldwide. According to the Centers for Disease Control (CDC), 1.7 million American sustain a TBI annually, and 52,000 of these patients die as a result of their injuries[1]. While prevention remains key to reducing the morbidity and mortality associated with TBI, acute care of the TBI patient is crucial to improving the outcomes in injured patients.

2. Classification of traumatic injury

TBI may be classified into three categories guided by initial presenting Glasgow Coma Score (GCS)[2]. Mild TBI is defined by a presenting GCS of 13-15, moderate requires a GCS of 8-12 and severe is dictated by a GCS of 3-8[3]. Lower initial GCS is correlated with poor outcome[4]. Etiology of the head trauma should also be considered in the management of the TBI patient. Classically, head trauma has been divided into closed or blunt, and penetrating mechanisms of injury. However, blast injury is increasingly recognized as a unique and distinct entity, likely related to the involvement of the United States (US) military in modern conflicts in Iraq and Afghanistan [5]. Regardless, mechanism of injury has consequences on the nature and degree of complications suffered as a result of the primary injury. Patients suffering from blast neuro-trauma are at significant risk of developing traumatic vasospasm and pseudoaneurysms compared with their non-blast counterparts[5,6].

A head injury is described as closed if the skull and dura remain intact during the injury. Overall, closed head injuries account for 75% of all TBI encountered in the US[1]. Most mild TBI falls into this category, with the notable exception of mild blast injury in combat veterans. These injuries, which are more common in men, result from motor vehicle accidents, falls, acts of violence and sports-related injuries[7]. In adults, there is a bi-modal distribution in age of onset, specifically with peaks between the ages of 15-24, and those aged 75 or older[7]. Patient presentations encompass a wide range of possibilities, from the conscious patient complaining of confusion to the comatose patient exhibiting signs of brain herniation. For this reason, approach to management of the closed head injury varies greatly depending on the severity of presentation. One potential exception to this principle in closed head injury is the concept of second impact syndrome. The hallmarks of second impact syndrome include two mild to moderate impacts occurring within minutes to hours of each other producing rapidly progressive, malignant brain edema without associated hematoma[8]. The end result is coma, and even death, from seemingly mild impacts. It is for this reason that the American Academy of Neurology has issued guidelines regarding the timing of return to work or play following mild head injury[9].

Penetrating brain injury frequently represents the more severe end of the spectrum of TBI in that it requires sufficient force to compromise the skull and dura. Penetrating gunshot and stab wounds to the head are an all too common example of this type of trauma, although not the only examples of this classification. It is beyond the scope of this review to discuss in detail the properties of ballistics. Suffice it to say that properties of a projectile dictate the degree of damage it causes. Factors such as kinetic energy, velocity, mass, shape and potential for fragmentation all play a role in the severity of the injury sustained[10]. Penetrating missiles cause injury by traversing and shearing tissue as well as via the pressure waves from their kinetic energy. Thus, tissues not directly penetrated may be injured as a result of the expansion and compression of the shock waves that a projectile creates[11].

Blast injury is a unique third mechanism of injury, though it does share some of the characteristics of both blunt and penetrating trauma. Like penetrating trauma with high kinetic energy projectiles, blast injury produces damage via high-pressure waves that disrupt the intracranial contents. These “shock waves” are produced when a high-energy gas rapidly expands compressing the surrounding air. The positive phase of this pressure wave has a shattering effect, termed “brisance”. When the blast wave hits the body, relatively high frequency stress waves and low frequency shear waves emerge, producing damage scaled to the force of the blast[12]. Practitioners subdivide blast injury into four categories; (1)Primary-caused by barotrauma, (2)Secondary-caused by penetrating projectiles, (3)Tertiary-caused by displacement of the entire body, usually in those close to the blast source, and (4)Quaternary- caused by miscellaneous environmental problems like burns from associated chemicals[13]. There is evidence that injury sustained from blast trauma is more complex than simply the shock waves blasts produce, but our understanding is incomplete at present[5]. Just as in closed head injury, concussions are a frequent bi-product of mild blast injury. A unique feature to blast injury (bTBI) is the disorder’s overlap with post-traumatic

stress disorder (PTSD). Both mild bTBI and PTSD manifest as difficulty in concentration, sleep disturbance and mood alteration. While both disorders can occur concomitantly, they are distinct entities. Headache is more common in bTBI, for example[14].

All mechanisms of injury produce both a primary injury and the potential for secondary injury. Primary injury occurs at the time of insult, and producing neuronal injury via tearing, shearing and stretching of neurons. Additionally, vascular beds are often disrupted, producing hemorrhaging. These phenomena occur acutely at the time of injury. Secondary injury may occur hours, days or even weeks remotely from injury as a result of a myriad of processes indirectly related to the trauma including but not limited to ischemia, hypoxia, inflammation, and excitotoxicity. These abnormalities can be produced or exacerbated by brain edema, arterial hypotension, acidosis, infection and/or elevated intracranial pressure (ICP). While primary insult may not be altered, the goal of critical care is to limit the effects of secondary injury.

3. Non-Invasive Imaging of the injured brain

Diagnosis of TBI relies on history and physical exam, and supplemented with neuroimaging. Neuroimaging provides a window on the evolving neural pathology after TBI. One of the unique challenges in TBI is the heterogeneity of the lesions encountered in this disorder. Sheer-strain injury that occurs during TBI produces injury on three topographic levels (1) cell bodies (gray matter) creating contusion, (2) axons (white matter) creating DAI, and (3) deep nuclei of the brain stem[15]. The specifics and severity of the pattern of injury depends on the details of the trauma sustained. Contusions are large, ill-defined hemorrhagic lesions. They tend to be superficial, multiple, bilateral and involve the frontal and temporal lobes[16]. These characteristics are to be contrasted with DAI, which is defined as diffuse degeneration of the white matter following axonal sheering. Classically, DAI was diagnosed at autopsy with its characteristic axon retraction balls and numerous perivascular hemorrhages[17]. However, with the advent of more sophisticated sequences and techniques, the hallmarks of DAI can be evident on MRI. DAI is most likely to occur in three areas: (1) deep white matter of the frontal and temporal lobes, (2) corpus callosum, (3) brain stem, but is certainly not limited to those distributions[17]. Extra-axial hemorrhages such as subdural hematomas (SDH), epidural hematomas, traumatic subarchnoid hemorrhages (tSAH) may be uncovered with neuroimaging in association with the trauma. Clinicians must also have a high index of suspicion for vascular injuries such as arterial dissection, fistulas, pseudoaneurysms, and venous sinus thrombosis, particularly in penetrating trauma. Vascular imaging with contrasted CT (CT-angiogram) or MR-angiograms versus conventional angiograms may be warranted once a patient is clinically stable to undergo this type of imaging.

Non-contrast head computed tomography (CT) remains the standard in the acute setting for patients sustaining TBI presenting with a GCS less than 15. The need for imaging in mild TBI with an intact GCS is not always straightforward. In an effort to clarify this issue, the American College of Emergency Physicians addressed the need for imaging in adult patients with mild closed head injury in a set of guidelines published in 2008. They recommend:

> "A noncontrast head CT is indicated in head trauma patients with loss of consciousness or posttraumatic amnesia only if one or more of the following is present: headache, vomiting, age greater than 60 years, drug or alcohol intoxication, deficits in short-term memory, physical evidence of trauma above the clavicle, posttraumatic seizure, GCS score less than 15, focal neurologic deficit, or coagulopathy. A noncontrast head CT should be considered in head trauma patients with no loss of consciousness or posttraumatic amnesia if there is a focal neurologic deficit, vomiting, severe headache, age 65 years or greater, physical signs of a basilar skull fracture, GCS score less than 15, coagulopathy, or a dangerous mechanism of injury[18]."

Non-contrast Head CT confers several advantages. It readily identifies bony and soft tissue lesions including fractures and edema. Blood, air and foreign bodies are well visualized. However, CT does exhibit some weaknesses. Acute blood may be low or iso-dense in anemia or diffuse intravascular congestion (DIC). Head CT is inferior to Magnetic Ressonance Imaging (MRI) for diffuse axonal injury (DAI), cortical contusion, and posterior fossa pathology. It is possible to miss fractures at the vertex of the skull due to the single plane of imaging and traumatic aneurysms due to the lack of contrast[19]. The head CT is most useful to aid decision making in the acute setting, informing triage and need for consultation to other services, such as neurosurgical consultation.

While not essential in every trauma patient, MRI is helpful in visualizing parenchymal injury. MRI may provide prognostic information when the clinical exam is equivocal. While many scanners in clinical use are 3-Tesla, using 1.5-T MRI imaging sequences, MRI is up to 30% more sensitive than CT scanning in detecting acute traumatic intracranial injury in patients with mild TBI[20]. One of the strengths of MRI is the differing sequences that give the clinician access to different aspects of anatomy and pathology. The fluid attenuated inversion recovery

(FLAIR) sequence, for example, is sensitive to white matter integrity and can reveal the affects of sheared axons. The gradient echo (GRE) or susceptibility weighted image (SWI) is displays hemosiderin deposition presumably from blood products[21]. SWI is particularly sensitive to parenchymal damage[22]. Taken together, these findings might be consistent with DAI. An MRI displaying severe, diffuse DAI may help to explain why a comatose patient has not regained consciousness after TBI. However, severity on MRI is not always proportional to clinical exam, thus clinical exam should always take precedence over imaging findings when there is discordance. At present, there are no guidelines about which TBI patients require MRI either acutely or as part of routine clinical care[18].

In addition to diagnosis and management, imaging has been used to inform prognosis following TBI. The Marshall[23] and the Rotterdam[24] scores are two widely used scoring systems that describe severity of injury on Head CT. The Rotterdam score is essentially a refinement of the older Marshall score, however both scales award increasing points for compression of the basal cisterns, midline shift and mass lesions. As the score climbs, the mortality associated increases. CT may also address physiologic parameters, not just anatomic ones, when CT-perfusion is used. This technique utilizes intravenous (IV) contrast to highlight intracranial vascular structures to illuminate cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) which is the time it takes for blood to perfusion a region of tissue[25]. Normal or elevated (hyperemia) perfusion portended a better prognosis than low perfusion (oligemia)[26]. The same group found CT-perfusion helpful in establishing a quantitative assessment of cerebral vascular autoregulation[27]. Cerebral autoregulation is the ability of the cerebral vascular bed to react to changes in ICP or arterial pressure to provide a steady perfusion to neural tissues. Failure of cerebral autoregulation is independently associated with poor outcome after brain injury[28]. The limitation of this technique is one intrinsic to imaging: CT provides a snapshot in time, rather than a continuous measure. While prognostic information may be obtained, the dynamic nature of brain injury should be appreciated.

A subset of patients with normal CTs fair poorly after TBI, remaining comatose throughout the acute period. MRI may prove helpful in these scenarios, particularly when the damage incurred has not hemorrohagic. Not surprisingly, increased lesion burden on FLAIR and T2 weighted imaging is associated with poor outcome[22]. However, some newer techniques have become of interest, including diffusion tensor imaging (DTI), which has the ability to encode diffusion information in more than the conventional three directions diffusion weighted imaging (DWI) utilizes. This additional information is used to model white matter fiber tracts in a more complete, three-dimensional manner. DAI disrupts the cytoskeletal network and axon membranes, thus DAI is associated with decreased fractional anisotropy (FA), making DTI a powerful tool in identifying DAI after TBI[29]. Investigators have used FA values obtained via DTI in various regions of interest (especially the brainstem) and correlated decreased FA values in certain regions with poor outcome after TBI[30,31]. Likeweise, Magnetic Ressonance Spectroscopy (MRS) is another non-invasive technique utilizing MRI that provides a window into pathology at a molecular level. MRS can demonstrate cellular injury by detecting metabolites that indicate hypoxia, energy dysfunction, neuronal injury, membrane turnover and inflammation[32]. The technique phase encodes chemicals in regions of interest, termed “voxels”, much as conventional MRI encodes space. Four main resonances are revealed: (1)Choline [Cho] (2)Creatine [Cr] (3)*N*-acetylaspartate [NAA] (4) Lactate[Lac], each corresponding to different chemical processes in neuronal tissue[33]. Cho marks several processes including membrane synthesis, inflammation, or demyelination. Normal levels of Cr indicate intact brain energy metabolism. NAA decreases with neuronal loss or dysfunction[34]. Lac accumulates as a result of anaerobic glycolysis[35]. Small studies have correlated levels of metabolites and outcome after TBI, for example levels of central brain Lac corresponding to Glasgow Outcome Scale[36]. MRI combined with MRS may be helpful in determining outcome in vegetative states after TBI[37]. The weaknesses of this approach at present are the small area in which the MRS samples (~1cm^3), lack of standard protocol (brain location, timing, etc.), and the lack of wide availability which has limited its study in large clinical trials. See section 9 regarding prognosis below.

4. Physiology of the normal brain

Management of TBI in the acute phase is informed by the understanding of intracranial physiology. The Monro-Kelly doctrine states that the skull is a rigid container[38], which is fixed in volume and contains three major components: (1) Brain, (2) Cerebrospinal fluid (CSF), and (3) Blood. Almost incompressible, the brain accounts for 80-90% of the 1500 milliliters (mL) intracranial volume that is typical for adults. As any of these components increases in volume (brain swelling with edema, for example), then these must be a compensatory reduction in one of the other components or intracranial pressure will rise. This concept of the interdependence of intracranial volume and intracranial pressure (ICP) is termed “compliance”. A compliant system is able to accept increases in volume without sharp rises in pressure, usually to a certain threshold. This threshold is lowered after brain injury. Likewise, under normal circumstances (MAP between 60 to 150 mmHg and ICP between 5 to 15 mmHg), the brain is exposed to relatively constant blood flow. This consistency is achieved via “autoregulation”, which

refers to the compensatory mechanisms that allow for little variation in cerebral blood flow or cerebral perfusion pressure (CPP); like those seen throughout the cardiac cycle, for example[39]. Normal CPP ranges between 60-85 mmHG, but is variable across individuals (Cerebral Perfusion Pressure= Mean Arterial Pressure – Intracranial Pressure or CPP= MAP - ICP). Poor autoregulation and loss of pressure-reactivity are independent predictors of fatal outcome following head injury [28]. Pressure reactivity (PRx) is the ability of the cerebral vessels to respond to changes in transmural pressure. PRx may be quantified as an index using a moving correlation coefficient between mean intracranial pressure (ICP) and mean arterial blood pressure, which can be calculated and continuously compiled with computer software[40].

Physiology forms the foundation of intervention in TBI. Our goals remain centered on preserving CPP while protecting the brain from elevated ICP, as we learn more about emerging targets for therapy.

5. Monitoring the Injured Brain

Monitoring neurologic progression and detecting deterioration in a timely fashion are critical in TBI. Serial physical examinations focused on the neurologic aspects are the cornerstone of neurologic critical care. No monitoring device may substitute for a careful bedside examination. However, the bedside exam may be augmented with monitoring, particularly when a patient is comatose. The updated 4th edition of the Brain Trauma Foundation Guidelines now recommend: "Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality," dropping the previous GCS, age, and Head CT parameters[41]. The ICP threshold for intervention varies, but is generally accepted at >20 mmHg. However, this is evidence suggesting using 20mmHg as a rigid threshold for all patients is not superior to protocols driven by clinical exam and imaging alone.[42]

Over the past two decades, awareness has increased that managing ICP alone might not prevent secondary brain injury. In fact, cerebral tissue may become ischemic or hypoxic at ICP values within the accepted normal range[43]. Either process is extremely deleterious, and must be avoided[44]. Cerebral oxygenation may be used as a marker for hypoxia, and can measured in a few different ways. Jugular bulb oxygen saturation from a central venous catheter ($SjvO_2$) or brain tissue oxygenation (PbO_2) from a parenchymal sensor are both used frequently in clinical practice to quantify brain tissue oxygenation. Episodes of jugular venous desaturation (SjvO2 < 50% for more than 10 min) or hypoxic tissue PbO_2 (<10 mmHg) reflecting cerebral ischemia is strongly associated with a poorer outcome[44,45]. It remains to be definitively shown if protocols targeting brain tissue oxygenation along with ICP and CPP will improve outcome over traditional ICP/CPP management[46,47]. Large clinical trials are currently in progress to settle lingering controversies regarding patient selection, anatomical placement of sensor, and impact on long term outcome (specifically BOOST 3).

Hypoxia and ischemia are interrelated but distinct mechanisms of secondary brain injury. Microdialysis has come to the fore at a tool to uncovering ischemic changes in brain parenchyma. Cerebral microdialysis endeavors to monitor the extracellular chemistry with an intraparenchymal probe in hopes of detecting early metabolic derangements associated with adverse events like ischemia. Substances that might be measured with such a catheter are seemingly innumerable, but commonly studied microdialysis markers include glucose, lactate, pyruvate, glutamate, glycerol and the lactate/pyruvate ratio. Extracellular metabolic markers are independently associated with outcome following traumatic brain injury[48]. Not unlike cerebral oxygenation, whether intervention to improve biochemical markers will produce better outcome remains to be established.

6. Medical Interventions

Pre-hospital management of TBI is outside the scope of this chapter. Suffice it to say that hypotension (SBP<90 mmHg) and hypoxia (Oxygen saturation<90%) must be avoided as both are associated with poor outcome[49]. Attention to the "ABCs" (Airway, Breathing, Circulation) is crucial in the first moments after a trauma occurs. The goal is to ensure a smooth transition from pre-hospital to the emergency care arena and then to the intensive care unit (ICU) for moderate to severe injuries. Limited available data suggests that outcomes may be improved in severe TBI patients by receiving care in a specialized neurologic critical care unit with protocol driven therapy[50].

In the emergency or ICU setting, endotracheal intubation to improve oxygenation should be performed early if the patient's efforts are insufficient. Head should be maintained midline to enhance cranial venous drainage. A cervical collar, which may already be in place as a precaution for cervical spinal injury, may facilitate this goal. Head of bed should be maintained at 30-45 degrees unless contraindicated[51]. As previously discussed, early neuroimaging is key for rapid neurosurgical intervention, should surgical management be required. Diffuse or disseminated injuries, like DAI or contusions, do not generally warrant surgical intervention. Depressed skull fractures and expanding intracranial hematomas (epidural, subdural, intraparenchymal) may require immediate attention. Vigorous effort should be made to avoid hypotension. Hypotension (SBP<90 mmHg) is independently

associated with poor outcome after TBI. Interestingly, ICP can rise sharply when blood pressure is modestly lowered while increasing blood pressure modestly has little effect on ICP if autoregulation is intact. If autoregulation is defective, ICP will vary directly blood pressure[52]. For these reasons, attention to systemic circulation is essential.

If there is any indication of neurologic deterioration rapid evaluation, preferably with neuroimaging is advised. Cerebral edema is one of the most important causes of secondary injury that must be considered after TBI. The peak time period for the development of cerebral edema after brain injury is 48 to 96 hours after injury, but may develop rapidly after injury in some cases. Cerebral edema, with or without elevated ICP, may progress to brain herniation (central, uncal, tonsillar) if left untreated. It is important to note that a patient may display signs of herniation in the absence of elevated ICP as a result of differential ICP gradients. ICP is not always uniform in all intracranial compartments, accounting for this difference. Therefore, it is critical to combine the clinical exam with information gained from neuromonitoring.

The mainstays of medical therapy for cerebral edema and/or elevated ICP include hyperventilation, osmotic agents, sedation and hypothermia. These therapies are often offered in a tier approach, with more invasive therapies following less invasive therapies for refractory intracranial hypertension.

Reduction of ICP can be achieved rapidly by reducing the blood volume component of the intracranial contents. This is achieved by reducing the arterial carbon dioxide ($PaCO_2$) by increasing the respiratory rate, thereby promoting arterial vasoconstriction. However, practitioners should keep in mind vasoconstriction, particularly prolonged vasoconstriction, may promote ischemia. Prophylactic or prolonged hyperventilation is not recommended[53]. Patients receiving prophylactic hyperventilation to prevent neurologic deterioration have fewer good outcomes than those receiving normal ventilation[54].

In contrast, ICP may be reduced by extracting water from the edematous brain with osmotic agents, namely mannitol or hypertonic saline. Mannitol is an osmotic diuretic which both promotes mild vasoconstriction[55] as well as by creating an osmotic gradient between blood and brain, allowing for the extraction of water. Mannitol is generally dosed 0.5-1.0 g/kg. Fluid balance should be monitored closely as mannitol may cause significant diuresis, as well as reducing serum sodium by as much as 10 miliequivalents. Serial serum sodium and plasma osmolarity should be monitored. Like mannitol, Hypertonic saline has been shown to produce a biphasic reduction in ICP first by way of rheology followed by osmotic activity across the blood-brain barrier[56,57]. However, hypertonic saline has the added theoretical benefit of a higher reflection coefficient, translating in to less permeablity than mannitol across the blood-brain barrier[58]. Hypertonic saline is available in a variety of concentrations and amounts, which complicate dosing regimens. Bolus dosing of both agents is advised over continuous infusions in order to discourage re-establishment of a new osmotic set point, such that the intracellular and extracellular compartments re-equilibrate. No further water extraction can occur once this re-equilibration occurs. Target serum sodium and osmolality values have yet to be definitely determined, but therapeutic goals are often serum sodium concentrations of 150-160 mEq/L, and plasma osmolality between 300-320mOsm[59]. Several case series have shown the effectiveness of boluses of mannitol and hypertonic saline for the reduction of ICP in TBI. Despite the promise of hypertonic saline in a trauma population, superiority of one agent over the other has not been definitively shown[60–63].

Hypothermia may also be used to reduce cerebral edema or help control ICP, though there is no robust evidence for improvement in outcome[64]. Recently, a large, multicenter randomized controlled trial addressed the issue of hypothermia to treated elevated ICP. In the Eurotherm 3235 Trial, severe TBI patients with raised ICP (>20mmHg) were randomized to receive standard of care interventions or standard of care with therapeutic hypothermia (32-35°C). The investigators found that therapeutic hypothermia plus standard care to reduce intracranial pressure did not result in outcomes better than those with standard care alone[65]. The trial protocol introduced hypothermia in the intervention group after Stage 1 interventions for ICP, namely sedation and CSF drainage, excluding osmotherapy. This practice varies from many centers in the US where osmotherapy is usually introduced earlier, often before deep sedation or temperature control. Thus, early application of hypothermia for ICP control is not supported. However, hypothermia may have a role as a later tier therapy once osmotherapy and sedation have failed.

Finally, deep sedation may be required if the interventions listed above prove ineffective or loose their effectiveness over time. Deep sedation may be achieved with a variety of different agents, but all with the goal of reducing cerebral metabolism ($CMRO_2$), which both reduces cerebral blood flow and tissue oxygen demand. The most commonly used agent, certainly historically, is pentobarbital. Pentobarbital should be administered as a loading dose followed by two continuous infusions, for example: 5mg/kg bolus, followed by 5 mg/kg/h for 3 hours, and finally 1mg/kg/hr thereafter. The target is usually burst suppression on electroencephalogram (EEG). An alternative agent is propofol, loaded at 2mg/kg followed by an infusion of up to 200 micrograms/kg/min[66]. Barbiturates should not be used in a prophylactic fashion to prevent neurologic deterioration in TBI[67]. However,

their role in refractory intracranial hypertension is integral when other agents fail[68]. Initiating pharmacologic coma is not without risk. Patients in barbiturate coma are more susceptible to hypotension, infection and end organ failure. Hypotension reducing CPP may offset reduction in ICP[69]. Propofol carries a special set of risks, specifically propofol infusion syndrome[70]. Thus, pharmacologic coma is not elected unless less invasive options have been exhausted.

7. Surgical Interventions

Occasionally surgical options may augment medical therapy or serve as rescue when medical options for cerebral edema fail. Surgery may either reduce the intracranial contents (ex: hematoma evacuation) or open the cranial vault, relieving intracranial pressure. Surgery should be considered sooner rather than later when confronting an expanding epidural or subdural hematoma. Often, patients with small epidural/subdural hematomas (EDH/SDH) can be managed conservatively (lesions <10 mm of thickness, midline shift <5 mm). If surgery is contemplated for a larger hemorrhage, operations occur either within 24 hours from injury (acute EDH/SDH) or later (parenchymal hematomas)[71]. Hemicraniectomy represents a more definitive option for reduction of ICP, as the cranial vault is opened, and edematous brain is allowed to swell outwardly without rigid confines. While hemicraniectmy can be lifesaving[72], its role in outcome after TBI is not completely clear. Studies have reported conflicting results. One report of young patients (<50 years of age) cited good outcome (social rehabilitation) after hemicraniectomy for cerebral edema in just over half of patients receiving hemicraniectomy[73]. In contrast, the DECRA trial randomized 155 patients (age 15-59) with diffuse axonal injury from severe TBI and elevated ICP to receive either early bifrontotemporal decompressive craniectomy or standard of care. Early craniectomy decreased intracranial pressure and the length of stay in the ICU but was associated with more unfavorable outcomes[74]. Perhaps lack of agreement of these trials rests on differences in surgical technique (release of dura, timing of operation) and patient selection (contusions versus diffuse axonal injury may behave differently)[75]. Decompressive hemicraniectomy may have no role in elderly patients[76]. Newer evidence from the rigorous RESCUEicp trial performed in the UK suggests that unilateral decompressive hemicraniectomy for refractory elevated ICP reduces mortality but increases severely disabled survivors[77].

8. Complications

Just as any critical illness, TBI patients are at risk for a myriad of complications. Infection, deep vein thrombosis (DVT), decubitus ulcers, and gastric stress ulcers must all be actively prevented in this population in the usual fashion. Hyperthermia should be aggressively treated as hyperpyrexia may exacerbate or even cause secondary injury.

Some complications are unique to brain injury. Patients may develop post-traumatic seizures. Phenytoin has proven beneficial in reducing the risk of post-traumatic seizure in the first seven days after TBI, but not thereafter[78]. Late seizures (> 7 days after trauma) occur in approximately 10% of severe TBI and can be more difficult to prevent than early seizures[79]. A variety of anti-epileptic drugs may be used in the chronic setting, though providers must weigh the cognitive side effects of long-term anti-epileptic use with indication for seizure prophylaxis[80].

Traumatic vasospasm may occur after TBI, particularly after blast trauma, and is an independent predictor of poor outcome[81]. Port-traumatic vasospasm in under-recognized, and management of the condition is not well established. Perhaps as many as half of blast-TBI patient experience traumatic vasospasm[6]. Traumatic vasospasm may develop earlier than vasospasm associated with aneurismal SAH—as early as 48 hours in some cases[82], and as late as 10 or more days after injury. Fever on admission, younger age, lower admission GCS, and quantity of cisternal or intracerebral hemorrhage appear to be risk factors[81,83], while traumatic subarachnoid blood does not always increase the risk. Transcranial Doppler (TCD) may have a role in vasospasm surveillance. It remains to be shown if traditional hypervolemia, hypertension, and hemodilution (‘‘triple H’’) therapy or calcium channel blockers (systemic or intra-arterial) are helpful in this condition[84].

Both blast TBI and penetrating TBI may be associated with pseudoanuerysm formation[85]. Diagnosis with non-invasive neuroimaging may be challenging in the penetrating trauma population due to retained projectiles. Thus, diagnosis may be confirmed with conventional four-vessel angiogram. Fractures crossing over the middle meningeal artery and its branches seem to be a risk factor for the development of traumatic vascular abnormalities[86]. While intravascular therapies are occasionally an option[87], craniotomy and clipping can be required[6].

TBI is often associated with a hyperadrenergic state accompanied by elevated levels of plasma catcholamines[88]. In its more severe presentation, the hyperadrenergic state presents as dysautonomia, which is characterized by paroxysmal alteration in vital signs not due to another underlying clinical entity other than neurologic injury. Dysautonomia is also known as sympathetic storms, paroxysmal autonomic instability with

dystonia (PAID), but paroxysmal sympathetic hyperactivity (PSH) is the preferred terminology[89]. PSH is usually recognized by episodes of hyperadrenergic alteration in vitals, including a constellation of tachycardia, hypertension, fever, posturing and diaphoresis, though not all signs need be present.[90] PSH is a diagnosis of exclusion. Patients with both TBI and PSH have worse Glasgow Outcome Scales (GOS), Functional Independence Measures (FIM), longer hospital courses and higher healthcare costs than their counterparts without PSH[91]. Emerging evidence suggests these patients have greater nutrition requirements than similarly injured TBI patients.[92] PSH occurs in 8-33% of patients with TBI, depending on how PSH is defined, but the true incidence is likely about 10% of moderate-severe TBI patients. Still, PSH is under-recognized, and often mistaken for other clinical problems. There is evidence that PSH after severe brain injury may occur due to loss of inhibitory input to the sympathetic autonomic nervous system producing tachycardia, hypertension, etc.[93] While imaging in this condition suggests a greater lesion burden in the white matter compared with non-PSH TBI controls, studies have failed to demonstrate consistent lesion localization[94,95]. Diffusion tensor imaging may provide greater insight into lesion localization than conventional imaging[96]. Early fever might herald its arrival[97]. It remains unclear if PSH is a marker for TBI severity or a reflection of a distinct anatomical injury. Opiods, benzodiazepines, beta-blockers and bromocriptine remain the mainstay in therapy to reduce the frequency and severity of the paroxysmal events.

9. Prognosis

Practitioners occasionally consult Neurologists to provide prognosis for recovery after TBI, particularly in persistent coma after a severe TBI. Clinicians are increasingly recognizing that prognosis after TBI is unique as compared with other sources of coma like anoxic brain injury or stroke. In parallel, investigators are exploring new ways to build on the clinical exam in order to provide more accurate prognostication. Recently, prognostic scores, advanced imaging techniques, and biomarkers lead active inquiry.

One of the most widely used scores in TBI prognostication is the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) score. Steyerberg and colleagues demonstrated that a prognostic model could be built from admission data. They used data collected in 11 clinical studies of TBI to build a prognostic model which was then validated using a dataset from a large European head injury trial: Corticosteroid Randomization after Significant Head Injury (CRASH). Their prognostic model parses patients with good and poor 6-month outcomes after TBI, especially if CT and laboratory findings are added to clinical exam features.[98] (see slide set)

Sophisticated MRI techniques including DTI, MRS, SWI (described above), along with high angular resolution diffusion imaging (HARDI) and functional MRI (fMRI) are used primarily in experimental protocols[99], but their use for prediction in clinical arena has not been well established. Despite the limited availability of the technology and lack of standardized software packages to interpret the data, these techniques hold promise in adding accuracy to clinical scores like IMPACT. An example of such strategy is Galanaud and colleagues who used fractional anisotropy values obtained in the acquisition of DTI to build their own prognostic model in TBI. They report that the "DTI score had a sensitivity of 64% and a specificity of 95% for the prediction of unfavorable outcome."[100] Work is ongoing to make these experimental observations clinically relevant in the form of predictive models for return of consciousness and outcome after severe TBI.

The list of biomarkers under study for post-TBI prognosis is lengthy, but Ubiquitin C-terminal hydrolase L1 (UCH-L1), glial fibrillary acidic protein (GFAP), Neuron-specific enolase (NSE), and S100 calcium binding protein B (S100B) are lead candidates. Emerging evidence suggests that each might foretell outcomes after TBI[101,102], but none are in widespread clinical use at present. Translating biomarkers into clinical care has suffered from lack of rigorous laboratory quality standards that might make such assays reproducible[103]. Lack of standardized techniques in the measurement of these markers (ELISA v. mass spectroscopy, lack of controls, etc.) are likely responsible for contradictory results between studies. Future work to eliminate inconsistencies may improve translation to the clinical realm.

10. Conclusion

TBI is a heterogeneous, complex disease requiring a multi-disciplinary approach to management. Outcomes continue to improve, particularly for young patients, as practioners refine management strategies. Minimizing secondary injury remains the cornerstone in critical care for the TBI patient. Early neuro-protection is an exciting, emerging field that will continue evolve in the coming decades. As we learn more about the mechanisms underlying secondary injury, monitoring and therapy will continue to gain sophistication and improve patient outcome.

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