

Traumatic brain injury

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Purpose of review

Management of the patient with traumatic brain injury is a rapidly advancing field, characterized in recent years by an improved understanding of intracranial pathophysiology and ways in which outcomes can be improved. Many traditional therapies, such as fluid restriction and hyperventilation, have been called into question and are no longer recommended. Other proposed therapies, such as deliberate hypothermia, remain controversial. This detailed review of the recent literature helps the reader come to an understanding of current scientific and evidence-based practices in this area, with emphasis on those therapies most likely to be of use to the practicing intensivist.

Recent findings

High-quality care of the traumatic brain injury patient demands the integrated activities of a number of different medical and nursing specialties. The best outcomes today are achieved by those systems that are able to focus as a team on the collective goal of minimizing secondary brain injury, and the respiratory therapist adjusting the patient's mechanical ventilation may be just as important to this effort as the attending neurosurgeon. Although the search for new diagnostic, prognostic, and therapeutic modalities continues (many of the more promising of which are reviewed in this article), it is clear that there exists no "silver bullet" therapy that will help all patients. Instead, it is the systematic integration and application of many small advances that will ultimately lead to better outcomes.

Summary

Some issues in traumatic brain injury have now been resolved, and specific recommendations can be made. Fluid therapy directed toward a euvoletic state is now universally recommended, for example, as is the role of intracranial pressure monitoring. Other areas, such as the use of hypertonic saline, remain controversial. In both cases the authors have made an effort to cite the most recent literature, so that readers can draw their own conclusions from the original source material.

Keywords

traumatic brain injury, fluid therapy, intracranial pressure monitoring, controversy

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Abbreviations

CPP	cerebral perfusion pressure
GOS	Glasgow Outcome Scale
HS	hypertonic saline
ICP	intracranial pressure
IL	interleukin
PEEP	positive end expiratory pressure
RSI	rapid sequence intubation
SjO ₂	jugular venous oxygen saturation
TBI	traumatic brain injury

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Introduction

Traumatic brain injury (TBI) affects 3 out of every 1000 Americans each year, and is the leading cause of morbidity and mortality after trauma, accounting for as many as 56,000 deaths per year and hundreds of thousands of ICU admissions [1]. The economic burden of TBI is staggering, with per-patient hospital costs for patients with severe disease (42% of those hospitalized) running as high as \$33,000 [2•]. Research into the pathogenesis, prognosis, and management of TBI is a fertile field. The following review of important findings was culled from more than 100 references published within the past 18 months.

Pathophysiology and prognosis

TBI begins with high-energy acceleration or deceleration of the brain within the cranium, typically caused by a motor vehicle collision, fall from a height, or assault. Penetrating trauma to the brain is less common, but more severe, with intracranial gunshot wound associated with a very high mortality. The complex molecular mechanisms in the pathogenesis of TBI are well elucidated in a recent review by Ray *et al.* [3]. Primary cellular injury is followed by a secondary response that includes changes in cerebral blood flow, local and systemic inflammation, alterations in oxygen delivery and metabolism, and both ischemic and apoptotic death of neural cells. Intravascular clot formation is common in TBI, and contributes to local ischemia; consumption of clotting factors can lead to systemic coagulopathy [4•]. Mussack *et al.* [5•] demonstrated that biochemical markers of both brain injury (S-100B) and systemic inflammation (interleukin [IL]-8) increase after TBI, and that this increase correlates with the patient's degree of neurologic dysfunction 12 months later. Singhal *et al.* [6•] studied IL-6 levels and outcome after TBI. Higher peak IL-6 levels in the cerebrospinal fluid and serum were associated with improved clinical outcome at 3 months. That IL-6 should correlate positively with outcome, and IL-8 negatively, is not surpris-

ing. The inflammatory cascade after acute injury can be both beneficial, to the extent that it is a necessary part of healing, and harmful, to the extent that it is inappropriately exaggerated. The challenge for future researchers is to determine which balance of mediators indicates an appropriate response, and how an individual patient can be moved in this direction.

The diagnosis of TBI hinges on the neurologic examination and on anatomic data derived from imaging studies. Improvement in CT and MRI technology have enabled greater diagnostic specificity in recent years, with Englander *et al.* [7•] reporting this year on those CT findings most associated with a poor prognosis on long-term follow-up. The presence of a midline shift, subcortical contusion, or evidence of bilateral injury were all predictors of decreased functional status 1 year later. The ability to diagnose diffuse axonal injury has been improved by quantification of changes in cellular water diffusion determined from early MRI, as reported by Chan *et al.* [8•]. The clinical significance of this is uncertain. MRI remains logistically cumbersome in most centers.

Prognosis in TBI may be predicted by a number of variables, including the patient's age, initial Glasgow Coma Scale score, and pupillary response. The presence of hypoxia, hypotension, hyperthermia, and elevated intracranial pressure (ICP) are predictive of poor outcome [9•]. Gender does not appear to play a role in outcome [10]. Comerford *et al.* [11•] reported the effects of mild TBI, noting that even patients who are "normal" at discharge on gross examination (by Glasgow Outcome Scale [GOS]) may have significant deficits in cognitive functions such as short-term memory, information processing, and new learning. Elderly patients are at particular risk from TBI, with worse outcomes than younger patients after identical injury [12•]. Interestingly, the presence of coexisting injuries, although highly significant in the short term, appears to have little impact on the functional status of long-term survivors. Lippert-Gruner *et al.* [13••] studied a population of survivors of severe TBI and found that function at 1 year was not affected by the presence or absence of additional organ injury.

Early management of traumatic brain injury

Because of the well-established association between hypoxemia and worsened outcome after TBI, early airway management has been recommended for these patients, with many jurisdictions now endorsing prehospital rapid sequence intubation (RSI). This practice has been called into question in a pair of recent publications. Davis *et al.* [14] evaluated the association between prehospital RSI and GOS in a prospective series of TBI patients and matched historical control subjects, finding that paramedic RSI was associated with an increase in mortality and a decrease in good outcomes. Boichichio *et al.* [15] reported a prospective comparison of a cohort of

patients with severe TBI intubated either in the field or on arrival to the trauma center, finding that the group intubated in the field had increased mortality and morbidity compared with those intubated in the hospital. The authors of both studies cite the delay in transport produced by RSI and the variable experience level of field practitioners as an explanation for their findings. Biochemical alterations associated with early intubation may also play a role. Laboratory evidence is emerging to suggest that high levels of brain oxygenation may encourage free radical formation, and may be just as bad as low levels, although this theory has yet to be tested in humans. Hyperventilation after RSI may also be deleterious because of its vasoconstrictive effect on the cerebral circulation. Marion *et al.* [16•] used microdialysis catheters placed in close proximity to injured brain tissue to document an increase in mediators of secondary brain injury (lactate and glutamate) associated with even short periods of hyperventilation. Hyperventilation as a technique to reduce ICP is therefore recommended only in patients with a mass lesion and impending herniation, and only during the interval (hopefully short) between diagnosis and surgical relief.

Early hemodynamic management of the patient with severe TBI has been the focus of a number of recent studies, with the therapeutic goal being to detect and manage reductions in cerebral perfusion pressure (CPP) at the earliest possible moment. Detection of intracranial hypertension requires placement of an invasive pressure monitor, the cornerstone of modern care for patients with severe TBI [17]. Once an ICP monitor is in place, therapy is directed toward maintenance of an adequate CPP, either by a reduction of ICP or an increase in mean arterial pressure. Hlatky *et al.* [18••], in an excellent review article, extends this concept one step further, advocating determination of the optimal CPP for each individual patient and situation. In this scheme CPP is compared with the adequacy of cerebral blood flow, determined by global or local markers of cerebral ischemia (jugular bulb oxygen saturation or tissue oximetry) and adjusted accordingly. Xenon-enhanced CT is advocated as a means of discriminating between diffuse and local ischemia.

The ability to maintain CPP greater than 50 mm Hg was demonstrated as an important prognostic factor in the retrospective review by Hackbarth *et al.* [19•] of outcomes from TBI in a pediatric population. Unfortunately, aggressive early therapy aimed at increasing mean arterial pressure may have a deleterious effect on the patient's other injuries, interfering with efforts to achieve hemostasis. Shackford [20] has conducted a number of studies in a swine model of shock plus severe TBI to elucidate the optimal fluid resuscitation strategy in this difficult clinical situation. Low-volume resuscitation with hypertonic saline and dextran or a hemoglobin-

based oxygen carrier was shown to be superior to conventional crystalloid therapy in preserving cerebral oxygenation and limiting secondary ischemia. Future human trials of these agents are likely.

A final point of controversy in early management concerns the use of deliberate mild hypothermia (33 to 35°C) to limit cerebral oxygen demand and to reduce the potential for secondary ischemia. Although clearly beneficial in controlled animal models, results in human trials have been confounded by the potentially deleterious effects of hypothermia and subsequent rewarming on coagulation and myocardial performance. Yamamoto *et al.* [21•] reported a small group of TBI patients treated with deliberate mild hypothermia who had improved neurologic outcomes at 3 months compared with control subjects. In a survey of British neuroanesthesiologists reported by Pemberton and Dinsmore [22•], 41% reported using deliberate mild hypothermia to treat severe TBI. Future trials of this therapy are also likely, and will be required before it can become a recommended component of the standard of care.

Intensive care unit management of traumatic brain injury

After the initial diagnostic workup, early resuscitation, and any necessary surgical intervention, the patient is admitted to the ICU. This is the location where the most rigorous and continuous monitoring and treatment occur, with the sole objective of minimizing secondary brain insult. The ideal neurointensive care unit includes physician, nursing, and support staff (respiratory, physical, and occupational therapy) who are trained in the subtleties of managing patients with TBI. Although multiple published guidelines exist to direct the management of patients after severe TBI [17,23], there are still a large number of institutions around the world that do not comply with these suggested therapies.

Elf *et al.* [24••] described a standardized treatment protocol for TBI patients admitted over a 2-year period to a neurosurgical ICU. They compared recent mortality to two previous study periods: from 1980 to 1981, before the availability of a neurointensive care unit, and from 1987 to 1988, after the establishment of a basic neuro-ICU. Each time period with each intervention showed a decrease in mortality, from 40% to 27% to 2.8%. In addition, the incidence of good functional outcome improved from 40% to 68% to 84%. The success of this unit was attributed to a number of factors. The first step was an educational program that defined the role of each team member in preventing secondary brain injury. Then, a standardized protocol that included intubation, optimization of gas exchange, control of fever, analgesia, and sedation was implemented. The goal was to maintain ICP less than 20 mm Hg and CPP more than 60 mm

Hg at all times. Patients were maintained in a normovolemic state, with infusions of 20% albumin as necessary to maintain intravascular volume and colloid oncotic pressure. Crystalloid infusions were minimized. For elevations of ICP uncontrolled by these measures, cerebrospinal fluid drainage was instituted, followed by barbiturate infusions as needed. Variations in this protocol are now common in tertiary care hospitals around the world. Any of a number of fluids may be used to support CPP, with the emphasis on preserving adequate intravascular volume. Euvolemia, rather than deliberate dehydration, is now the primary resuscitative goal for patients with severe TBI.

Diagnostic techniques

Patients with severe head injury (defined as a Glasgow Coma Scale score < 8 points) and abnormal head CT (hematoma, contusions, edema, or compressed basal cisterns) should undergo ICP monitoring, as should patients with severe TBI and normal head CT with any of the following: age more than 40 years, motor posturing, or systolic blood pressure less than 90 mm Hg [17]. Impairment of normal cerebral autoregulation is known to follow TBI, but is difficult to quantify clinically because direct measurement of cerebral blood flow is impossible outside of elaborate research protocols. Several recent publications suggest that early noninvasive assessment of cerebral autoregulation may soon be feasible. The first, by Lang *et al.* [25•], reports the development and validation of a moving correlation index of CPP and middle cerebral artery blood flow measured by transcranial Doppler ultrasonography. The presence or absence of autoregulation correlated well with GOS, even when arterial blood pressure rather than CPP was used to derive the index. Minassian *et al.* [26•] used norepinephrine infusions to determine the autoregulation index (percent change cerebrovascular resistance divided by percent change in cerebral perfusion pressure) with changes in mean arterial pressure. They were able to identify preserved versus perturbed autoregulation, and found that changes in ICP varied linearly with the strength of the autoregulation index. Although autoregulation is damped and shifted to higher CPP values in most patients with head trauma [27], alterations in autoregulation did not cause a significant change in the expected qualitative relation between ICP and mean arterial pressure during CPP management of patients with severe TBI.

In a preliminary report based on data from 30 patients, Dutton *et al.* [28•] described a noninvasive brain acoustic monitor capable of directly examining the quality of global cerebral blood flow. A simple pass/fail scoring system based on brain acoustic monitor data correlated well with GOS. van Santbrink *et al.* [29•] studied the correlation between transcranial Doppler-derived large-vessel blood flow and cerebral ischemia, as measured by brain

tissue oxygen saturation derived from invasive intraparenchymal monitoring. Low flow ipsilateral to the injury was a common finding, and correlated with increased tissue ischemia and worsened outcome.

Because CPP values do not assess a physiologic end point, the ability to determine tissue oxygenation is a valuable measure in the management of patients with severe TBI. The current American Association of Neurologic Surgeons (AANS) guidelines do not make recommendations on the use of these technologies, but many institutions routinely use monitors of cerebral tissue O_2 utilization. Jugular venous oxygen saturation (SjO_2) represents venous drainage in the jugular bulb and may be used to guide therapy. In a recent retrospective review of SjO_2 measurements, patients were divided into two groups: those with abnormal SjO_2 values ($>75\%$ or $<55\%$) and those with normal values [30•]. Patients in the abnormal group had a significantly higher occurrence of intracranial hypertension ($P < 0.001$) and worse outcome as determined by GOS ($P < 0.005$). The events associated with SjO_2 desaturations were hyperventilation (41%), hypovolemia (28%), and anemia (21%). In the face of concurrent intracranial hypertension and abnormal SjO_2 , the risk of death increased 2.3 fold.

Near-infrared spectroscopy for determining cerebral oxygen saturation after head injury has not been shown to assess changes consistently as a result of CO_2 or fluctuations in arterial pressure [31] and brain tissue oxygen saturation techniques have not as yet demonstrated a definitive outcome benefit [32], but a novel use of brain tissue oxygen monitoring to elucidate autoregulation has been proposed. Lang *et al.* [33•] studied 14 patients prospectively with TBI who underwent pharmacologic manipulation of blood pressure in an effort to correlate cerebral tissue O_2 with CPP and blood flow velocity. They showed that a plateau phase of tissue oxygenation occurs at CPP values between 70 torr and 90 torr. CPP autoregulation was validated by transcranial Doppler, as described in the study cited earlier [25•]. A further finding was that static cerebral autoregulation (resulting from slow changes in blood pressure or CPP) was significantly correlated with cerebral tissue oxygen reactivity. Because cerebral autoregulation and tissue oxygen reactivity are mutually correlated, it may be possible in the future to delineate which patients would benefit from CPP-driven therapy; that is, elevating CPP by vasopressors in patients with marginal tissue oxygenation in whom no plateau exists.

Therapy

Although mannitol remains the recommended pharmacologic agent for treating elevations in ICP, recent studies investigating the use of hypertonic saline (HS) solutions in the treatment of TBI have been promising. The beneficial effects of HS are the result of several mechanisms. In addition to an osmotic effect on edematous

cerebral tissue, HS solutions exert hemodynamic, vaso-regulatory, immunologic, and neurochemical effects [34]. Increases in mean arterial pressure are the result only of plasma volume expansion but may also occur because of changes in circulating hormone levels [35]. Vasospasm that occurs after TBI may be counteracted by HS through vasodilatory actions [36]. The perturbations in extracellular sodium and excitatory neurotransmitters that occur after injury may be attenuated by HS, and depression of leukocyte adherence and neutrophil margination may offer protection from bacterial illnesses [37]. HS use in clinical trials ranges from 1.7 to 29.2% concentrations and consistently shows significant decreases in ICP, improvements in CPP, and enhanced hemodynamic function. A head-to-head comparison of HS and mannitol was recently published [38•]. Twenty consecutive patients who failed conventional treatment of increased ICP (sedation, analgesia, optimization of hemodynamics, and positional therapy) were randomized to either 7.5% HS or 20% mannitol. These doses were repeated until resolution of intracranial hypertension or treatment failure (defined as persistently elevated ICP despite two consecutive infusions of the same osmotic agent). Although there were no differences between the groups in the number of days monitored or the mean number of osmotic solute infusions administered, the number of intracranial hypertension episodes per day and the daily duration of episodes were significantly lower in the HS group ($P < 0.01$), as were the rates of clinical failure ($P < 0.01$). Mortality and GOS at 90 days were not different between the two groups. The osmotic load delivered with HS was greater than that with mannitol (361 mOsm *vs* 175 mOsm), and this may have accounted for the differences seen. In addition, as an osmotic diuretic, mannitol may lead to intravascular dehydration and subsequent decreased CPP. Although the authors do not remark on urine output, there were no differences in vasopressor use or episodes of CPP less than 70 torr between the groups.

Mechanical ventilation represents a necessary adjunct to the treatment of head-injured patients. Control of PaO_2 and $PaCO_2$ is mandatory and will affect both cerebral hemodynamics and ICP. Patients with isolated head injury can be managed with traditional ventilatory strategies, but those with chest trauma, aspiration, or massive resuscitation after shock are at high risk for developing acute lung injury. The classic teaching of no or low-level positive end expiratory pressure (PEEP) to prevent elevated ICP is inappropriate because it may fail to correct hypoxemia. With adequate volume resuscitation, PEEP does not increase ICP nor does it lower CPP [39,40], and it may actually decrease ICP as a result of improved cerebral oxygenation. Although earlier guidelines have suggested that increasing PEEP results in an increase in ICP, more recent data are consistent with the concept that in a euvolemic patient, an increase in mean airway

pressure is not detrimental but rather advantageous to care. Huynh et al. [41••] looked at the effects of increasing PEEP (0 to 5, 6 to 10, and 11 to 15 cm H₂O) on ICP and found that as PEEP increased, ICP decreased, without any effect on systemic oxygen delivery or consumption.

The use of corticosteroids after TBI has been studied extensively. The large, multicenter Corticosteroid Administration after Severe Head Injury (CRASH) trial in the United Kingdom has enrolled more than 3000 patients. Although the data from this study have not yet been published, a systematic review abstract of available data, covering 19 trials and more than 2000 patients is available [42•]. A small and statistically insignificant reduction in mortality suggests that there is currently no role for the use of steroids after TBI.

The need for antiseizure prophylaxis after severe TBI remains controversial. A search of multiple databases for prospective studies with class I data demonstrated a significantly lower risk of early posttraumatic seizures (those occurring within 7 days of injury) in patients treated with phenytoin compared with control subjects [43•]. There was no benefit past 7 days and, interestingly, patients who seized within the first week who had received prophylaxis were observed to have therapeutic levels at the time of their seizure. Beyond 7 days from injury there appears to be no benefit to prophylactic treatment.

Decompressive craniectomy is a surgical procedure used to control severely elevated ICP and to prevent herniation after stroke and subarachnoid hemorrhage, and is now more widely used for the same indications after severe TBI. In one retrospective review, younger patients and those who undergo early decompression seem to have a better functional outcome, but no survival advantage [44]. Decompressive craniectomy is indicated for selected anatomic patterns of TBI, when CPP cannot be maintained despite rigorous application of the previously described therapies, including barbiturate coma. There are no prospective, randomized trials of decompression, but recent evidence suggests that relieving ICP by removal of a piece of cranium may improve mortality and morbidity in patients who might not otherwise survive [45•]. Kontopoulos *et al.* [45•] report a series of nine patients who underwent this procedure as a result of failure of the ability to control ICP. In a cohort with a predicted mortality of between 84 to 100% mortality, actual mortality was 22%. The development of diffuse injury type III on CT (diffuse cerebral edema) and failure of medical management led to this "rescue" therapy. Follow-up of at least 2 years demonstrated severe disability in only 11% of patients and good recovery by GOS in 66%. Whether decompressive craniotomy should be performed in a protocol-driven manner or prophylacti-

cally has not yet been determined. Our own experience includes more than 60 patients who have undergone decompression after TBI to date. We are currently in the process of analyzing the outcomes of these patients and are attempting to predict prospectively which patients will benefit from this procedure.

Decompressive laparotomy may also be indicated in patients with severe TBI, if coexisting injuries or vigorous volume infusion have increased intraabdominal compartment pressure to more than 20 mm Hg. Intraabdominal hypertension worsens pulmonary mechanics, necessitating a higher mean airway pressure to maintain arterial oxygen saturation. This increase in ventilating pressure will increase intrathoracic pressure, impairing venous drainage from the head and thus decreasing CPP. Anecdotal experience has suggested a role for decompressive celiotomy in reducing ICP even when measured abdominal compartment pressures are not overly high [46•].

Few new drug therapies are currently under clinical investigation, even though development of pharmaceutical agents and "cocktails" continues in the laboratory. One such therapy is the use of amantadine in the treatment of diffuse axonal injury, some degree of which is believed to be present in any TBI in which the patient has lost consciousness. Diffuse axonal injury is associated with a reduction in dopamine turnover from midbrain cellular injury. Amantadine acts presynaptically to enhance dopamine release and to inhibit dopamine reuptake. In a randomized, prospective, crossover design, 35 patients with a Glasgow Coma Scale score of 10 points or less were given amantadine 200 mg versus placebo, each for 6 weeks (total, 12 weeks of study) [47]. Multiple test scores showed a consistent and more rapid improvement in functional recovery in patients receiving amantadine during a given 6-week course. Although this may be a promising new adjunct to therapy, amantadine is also known to lower the threshold for seizures.

Conclusion

The outcome of patients after severe TBI can be improved by following a systematic, stepwise approach to control of elevated ICP and maintenance of adequate CPP, directed at maintenance of adequate cerebral oxygen delivery and interruption of secondary insults. Future diagnostic and therapeutic interventions will be based on an improved understanding of the pathology of secondary brain injury, and the ways in which it can be minimized.

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