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TRAUMATIC BRAIN INJURY – MODERN APPROACHES OF TREATMENT

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ABSTRACT

Traumatic brain injury is a major public health problem both in developed economies and developing countries contribute to a substantial number of deaths and cases of permanent disability. It has been called the 'silent epidemic' of modern times, and is the leading cause of mortality and morbidity in children and young adults. TBI is a diagnostic and therapeutic challenge. There is no Food and Drug Administration (FDA)-approved treatment for TBI yet. It took about 16 years of preclinical research to develop accurate and objective diagnostic measures for TBI. The World Health Organization predicts that TBI and road traffic accidents will be the third greatest cause of disease and injury worldwide by 2020. We searched the literature for articles on severe TBI, abstracting numbers of patients studied, numbers of deaths, and years of patient entry. Mortality rates were calculated for each study, and meta-regression used was to pool data and to test for significant temporal trends. We reviewed 207 case series comprising more than 140,000 cases of severe closed TBI admitted to hospital over a span of almost 150 years. Continuous attempts have been made worldwide to discover the best possible treatment, but an effective treatment method is not yet available. Improved treatment will come through understanding the physical changes in the brain that occur at the microscopic and molecular levels when the brain is subject to trauma. Appropriate targeting of prevention and improving outcome requires a detailed understanding of incidence, causes of injury, treatment approaches and outcome results.

KEYWORDS

Traumatic brain injury; Diagnosis; Treatment.

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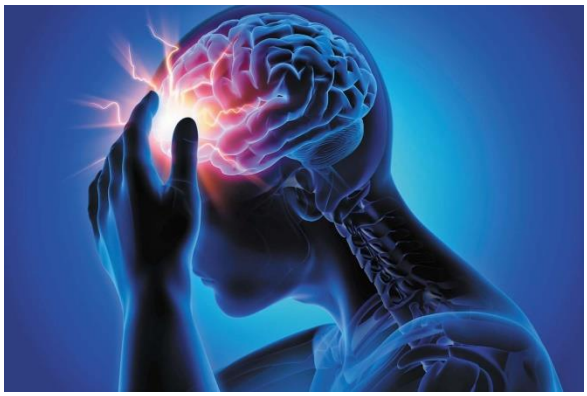


INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of mortality and morbidity in patients in the age group of 18–45 years[1]. Traumatic brain injury (TBI) is a common, preventable, and disabling health condition with heterogeneous aetiology, type, severity, and outcomes. Ongoing challenges in TBI care are reflected by rapidly growing literature in the prevention, assessment and treatment of TBI, especially in sports concussion and blast-related TBI[2]. Post-acute Traumatic Brain Injury differs from that of other neurological disabilities and most TBI patients have seemed to benefit from at least some level of specialized, interdisciplinary, rehabilitation[3-4]. Head injuries can be typically classified as closed or penetrating. A closed head injury is normally used to describe automobile accidents, assaults, and falls, while a penetrating injury usually results from gunshot or stab wounds. The use of explosive devices in military conflict has generated a category known as blast injury, which is rare in injury pattern and consideration [5]. The early injury resulting from an external force creates brain tissue destruction with parenchymal impairment, intracerebral hemorrhage, and axonal cutting. Likewise, the primary insult provokes secondary neurometabolic and neurochemical events, including inflammation, cerebral edema, disruption of the blood–brain barrier (BBB), oxidative stress, excitetoxicity, and mitochondrial and metabolic dysfunctions, that can extremely modify the outcome and the recovery patterns, persisting for months to years post-injury [6]. In comparison, there is a lack of clarity and standardization in the diagnostic criteria, severity grading, and nomenclature to describe TBI, which could improve many aspects of TBI care, especially in developing targeted therapies for TBI [7].

There is no standardized nomenclature of TBI subtype, which may be based on the history, clinical features and imaging findings and treatments for TBI patients are varied and complex [8]. The golden age of TBI research has been encouraged, thanks to the prominence of repetitive concussions or mild TBIs (mTBIs). Because of the failure of translational therapies focused on moderate to severe TBI, novel therapies have developed, defining two typical approaches. The traditional neuroprotection-based approach is based on the identification of key actions implicated in the advancement of secondary injury whether in mild or severe TBI. In this method, treatment is started as soon as possible after injury [9, 10].

The management of severe TBI (featuring compromised cranial vault/space-occupying lesions, medically refractory intracranial hypertension) starts with surgical debridement, and despite its effectiveness in increasing survival, there is no clear correlation with improving outcomes[11, 12]. The Brain Trauma Foundation published guidelines on the management of severe TBI, accepted by the American Association of Neurosurgeons and endorsed by the World Health Organization Committee in Neurotraumatology. Although many of the recommendations from these guidelines are incorporated into protocols for the management of head-injured patients in individual ICU, there is still wide variation between Units. This article outlines the basic principles of the general [13]. Although many studies have recently supported the use of CAM in TBI treatment, especially Chinese traditional medicine, no studies have been conducted on the effectiveness of Avicenna's suggestions on TBI [14].

DIFFERENT PHASES OF TRAUMATIC BRAIN INJURY

According to history and accurate clinical examination of patients, TBI divided into four phases. Treatment for certain phase and emphasizes that treatments should be done exactly at the appropriate time[15].The four TBI phases have been described as following:

Phase I: Immediately after the trauma, that may be compatible with the primary injury in modern medicine.

Phase 2: The severity of the injury is constantly increasing which is possibly similar to secondary brain damage in modern medicine.

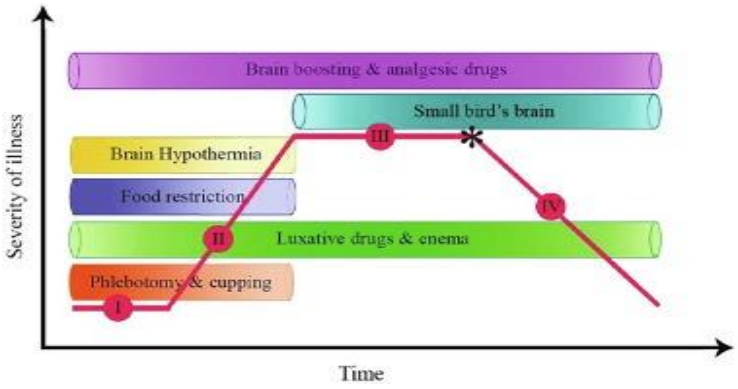
Phase 3: In this phase, the severity of the injury has reached a plateau and there is no further development.

Phase 4: The end of phase III which is called crisis point is followed by two different outcomes: worsening the severity of the injury [16, 17].

Fig.2. Four phases of the TBI

PATHOPHYSIOLOGY

Damages of neuronal tissues associated with TBI fall into two categories: (i) primary injury, which is directly caused by mechanical forces during the initial insult; and (ii) secondary injury, which refers to further tissue and cellular damages following primary insult.



1. Primary Brain Injuries:

The immediate impact of different mechanical insults to the brain can cause two types of primary injuries: focal and diffuse brain injuries. Studies have demonstrated that the co-existence of both types of injuries is common in patients who suffered from moderate to severe TBI [18]. However, diffuse axonal injury (DAI) accounts for approximately 70% of TBI cases. As a consequence of lacerations, compression and concussion forces, closed head TBI and penetrating TBI exhibit focal brain damage with evidence of skull fracture and localized contusion at the core of injury site [19]. Necrotic area of neuronal and glial cells is concentrated at the coup with compromised blood supply, causing the occurrence of hematoma, epidural, subdural and intracerebral hemorrhages at confined layers of the brain. Secondary contusion may develop in tissues opposite to or surrounding the coup (contre-coup) due to secondary impact

when the brain rebounds and strikes the skull [19]. Depending on the severity of the injury, it can lead to cognitive deficits, behavioral changes and hemiparesis. In contrast to focal injury, the main mechanism of diffuse brain injury is non-contact forces of rapid deceleration and acceleration which cause shearing and stretching injury in cerebral brain tissues. The strong tensile forces damage neuronal axons, oligodendrocytes and blood vasculature, leading to brain edema and ischemic brain damage [20].

2. Secondary Brain Injuries:

The biochemical, cellular and physiological events that occur during primary injury often progress into delayed and prolonged secondary damages which can last from hours to years. Mechanistically, a number of factors contribute to secondary injuries, which include excitotoxicity, mitochondrial dysfunction, neuroinflammation [21].

A. Excitotoxicity:

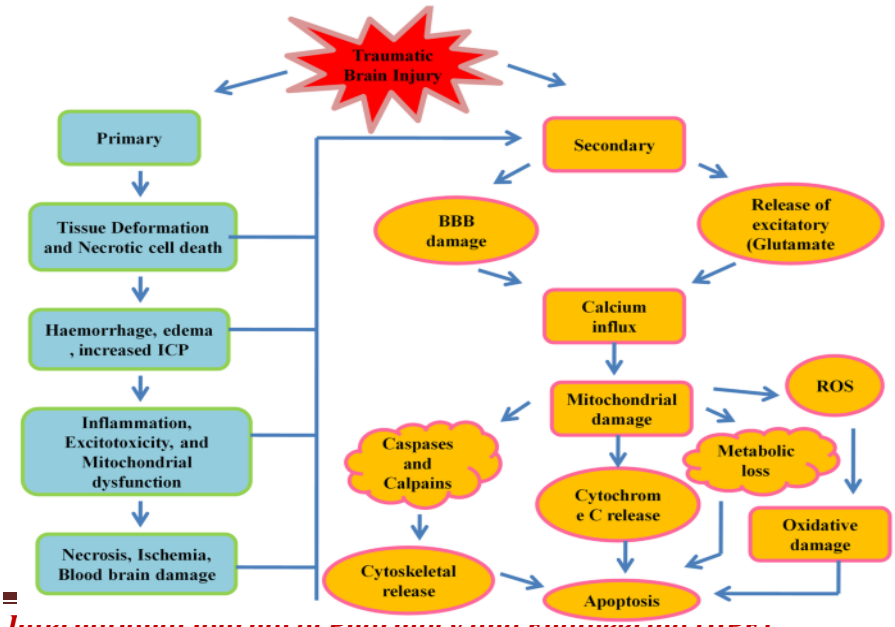
Studies in humans have demonstrated that BBB breakdown and primary neuronal cell death during TBI induce excessive release of excitatory amino acids such as glutamate and aspartate from presynaptic nerve terminals [22]. The presence of excessive glutamate during TBI is also contributed by a failure of glutamate re-uptake due to the dysfunction of glutamate transporters. There has been evidence that shows a 40% decline in the expression of astrocytic sodium-dependent glutamate transporters GLAST (EAAT1) and GLT-1 (EAAT2) within 24 h following TBI, leading to a significant decrease in the resorption of glutamate [23]. These excitatory amino acids activate both ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). Members of iGluRs such as N-methyl-d-aspartate (NMDA) receptor and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor are ligand-gated ion channels that allow Na+, K+ and Ca2+ ionic flux upon binding to glutamate, causing membrane depolarization in neurons [24]. NMDA receptor is peculiar in that it is also voltage-gated and is permeable to Ca2+ ions. Hyperactivation of AMPA and NMDA receptors by excessive glutamate has been shown to alter ion homeostasis in postsynaptic neurons by allowing influx of extracellular Ca2+ and Na+ ions [25]. NMDA-induced surge in intracellular Ca2+ initiates the activation of various downstream signaling molecules, including Ca2+/calmodulin-dependent protein kinase II [26], Protein kinase C is also activated to couple to NMDA receptors, thereby enhancing Ca2+ influx into postsynaptic neurons [27].

B. Mitochondrial Dysfunction:

Mitochondrial dysfunction is one of the hallmark events of TBI (Xiong et al., 1997), which contributes to metabolic and physiologic deregulations that cause cell death. The sequestration of intracellular Ca2+ and influx of excessive ions into mitochondria results in the production of ROS, depolarization of mitochondrial membrane and inhibition of ATP synthesis [28]. This leads to the breakdown of electron transport chain and impairment of oxidative phosphorylation processes, thus disrupting the restoration of metabolic reactions for cell survival and regulation

of calcium cycle. Mitochondrial permeability transition pore (mPTP) is also activated under these conditions. Conformational change of an inner membrane protein adenine nucleotide translocator (ANT) upon binding to cyclophilin D leads to the opening of mPTP and an increase in inner membrane permeability[29], further contributing to mitochondrial pathology. Electron microscopy analysis of mitochondria has revealed significant swelling and structural damages such as disruption of cristae membrane and loss of membrane potential. Furthermore, mitochondrial proteins such as cytochrome c and apoptosisinducing factor (AIF) which play crucial roles in apoptotic cell death are released into the cytosol [30].

FIG 3- Schematic representation of pathophysiology of traumatic brain injury (TBI)



Diagnostic Criteria

Many patients with mild TBI in whom CT scans are normal show abnormalities on subacute MRI. Such abnormalities are strong predictors of poor neurocognitive and neuropsychiatric outcomes [31]. MRI may provide useful confirmatory evidence that the symptoms are attributable to an earlier TBI. These emerging technologies offer opportunities for improved disease characterization in TBI, which will aid 'precision medicine'—a concept recently advocated by the US National Academy of Science that will facilitate targeted management and individualized approaches to treatment of patients with TBI [32]. The initial GCS score and, therefore, the severity of the TBI help to predict the likelihood of death from the injury. The mortality rate is high in severe TBI and is low in moderate TBI [33]. Acute and long-term risk factors associated with youth and sports-concussions are a major concern, and there is increasing evidence that multiple mild TBIs may pre-dispose to early onset dementia, later substance-use disorders and mental illness [34, 35]. In the United States, research shows that receiving care at a Level I trauma center can decrease the risk for

death among seriously injured patients by 25 percent. New technology in CT and MRI is allowing the acquisition of more accurate and detailed information on cerebral pathology post-TBI. This has greatly improved prognostic ability in TBI and enables earlier identification of pathology, making it potentially amenable to therapeutic intervention. Several MRI methods have excellent potential to help visualize metabolic, microstructural and functional network changes related to resting and cognitive states in addition to allowing better detection of microhemorrhage. Multimodal techniques may emerge helpful orthogonal approaches to enhance the diagnostic precision of abnormalities. Neuroimaging is an essential tool to assist clinicians in diagnosis of TBI. Early imaging reduces time to detection of life-threatening complications and is associated with better outcomes. Advanced MRI (diffusion tensor imaging) allows visualization of white matter tracts and quantification of axonal damage [36].

MODERN APPROACHES OF THE TREATMENT

There are various methods for the treatment of TBI, such as, Airway Control and Ventilation, Blood Pressure and Cerebral Perfusion Pressure (CPP), Fluid Management, ICP Monitoring and Management, Osmotherapy, Anticonvulsant Therapy, Antibiotic Therapy.

A. AIRWAY CONTROL & VENTILATION:

Several studies have shown a correlation between hypoxemia and poor outcomes. Although airway control may be our primary concern in these patients, studies have reported poorer outcomes for TBI patients who were intubated at the site of trauma [37]. ntubation by inexperienced providers showed a four-fold increase in death and a significantly higher risk of worse functional outcomes when compared to patients whose airway was secured in the emergency department. In 2013[38]. Risk factors include a motor vehicle accident and a GCS less than 8. Therefore, all attempts at intubation should include in-line neck stabilization to reduce the chance of worsening a neurological injury until radiological clearance is obtained. Pre-existing hypoxia, intracranial hypertension, full stomach, and coexisting injuries, such as cervical spine trauma and maxillofacial injuries, may be present that predisposes a patient to difficult airway management. Thus, careful preparation and preoxygenation is mandatory. Anesthetic drugs that allow for rapid control of the airway while avoiding an increase in intracranial pressure (ICP) and providing hemodynamic stability are preferred. Propofol and thiopental are the most commonly used drugs, but they may cause hypotension. Etomidate has advantages in terms of cardiovascular stability, but the possibility of adrenal suppression exists. Ketamine is popular in trauma patients and recent evidence suggests that its effect on ICP may be limited [39]. For rapid sequence intubation, succinylcholine or rocuronium may be used. Although succinylcholine may produce a small increase in ICP, this has to date not proven to be clinically significant. A retrospective study in 2016 compared rocuronium and succinylcholine in brain injured patients undergoing rapid sequence intubations in the emergency department. It reported an increased risk of mortality with succinylcholine; however, similar data from prospective studies are lacking. To obtain a response to laryngoscopy, an opiate such as fentanyl (1 µg/kg) may be used,

but there is no evidence to support the use of lidocaine. Adequate sedation and muscle relaxation tends to reduce the cerebral metabolic oxygen requirement (CMRO2), optimize ventilation, and prevent coughing or straining. Ventilation of patients with severe TBI aims to maintain PCO2 within a normal range of 34–38 mmHg. Hypoventilation should be avoided, as increased PCO2 levels may lead to cerebral hyperemia with an increase in blood volume and ICP. Hyperventilation, on the other hand, results in an increased risk of vasoconstriction and increased tissue hypoxia, especially in the penumbra zone, so it is best avoided. The ongoing EPIC trial in Arizona focuses on avoidance of hyperventilation in TBI patients in a prehospital setting because it may lead to an approximately six-fold increase in poor outcomes. Hyperventilation up to a PaCO2 of 25 mmHg for the purpose of reducing ICP is still accepted in the BTF Guidelines from 2016 for a brief period of time. Volume-guaranteed modes of ventilation may be a rational choice in these patients to minimize variations in PaCO2. Fraction of inspired oxygen (FiO2) settings on a ventilator should be adjusted to achieve a PaO2 of ~90 mmHg, which can oxygenate the penumbra zone. High PaO2 should be avoided, considering the risk of hyperoxic cerebral vasoconstriction and hypertoxic lung injury. PEEP of 5–10 cmH2O may be administered to prevent atelectasis and has been proven to be safe in these patients [40]. Consequently, the BTF has recommended that early tracheostomy should be performed to reduce ventilation days when the overall benefit outweighs the complications associated with the procedure (Level IIA).

B. BLOOD PRESSURE & CEREBRAL PERFUSION PRESSURE (CPP):

Despite consensus on the principles of early management, there is no widespread agreement on resuscitation goals as various expert bodies have offered different management guidelines. Initially, the recommendation was to keep CPP above 70 mmHg with vasopressors if needed. However, a subsequent study showed that outcomes were better with a relatively lower CPP, possibly because of a reduced incidence of acute respiratory distress syndrome secondary to reduced vasopressor usage[41]. Although there is minimal evidence to support the use of one vasopressor agent over another, a recent study suggested that phenylephrine may be associated with improved parameters.

The 4th edition of the BTF guidelines recommend:

Maintaining SBP at ≥ 100 mmHg for patients 50 to 69 years old or at ≥ 110 mmHg or above for patients 15 to 49 or over 70 years old to decrease mortality and improve outcomes (Level III).

The recommended target CPP value for survival and favorable outcomes is between 60 and 70 mmHg. Whether 60 or 70 mmHg is the minimum optimal CPP threshold is unclear and may depend upon the patient's autoregulatory status (Level IIB).

Avoiding aggressive attempts to maintain CPP above 70 mmHg with fluids and pressors may be considered [42].

C. ICP MONITORING & MANAGEMENT:

The indications of ICP monitoring in TBI from the latest edition of the BTF guidelines are as follows:

Management of severe TBI patients based on ICP monitoring may reduce in hospital and two-week post-injury mortality;

The guidelines no longer include a recommendation regarding patients that should be chosen for monitoring because of insufficient high-quality evidence;

Clinical judgement should be used to initiate intracranial monitoring in patients who are at a high risk of clinical deterioration.

Updated BTF guidelines state that ICP monitoring is a level IIB recommendation, and recommend treatment of ICP > 22 mmHg to reduce mortality. The management of increased ICP includes standardized strategies that use a "staircase approach" with an escalating treatment intensity.The American College of Surgeons TBI Guidelines recommend a three-tier approach for the management of increased ICP [43]. Invasive monitoring using the external ventricular drain (EVD) technique, in which a catheter is placed into one of the ventricles through a burr hole, is considered to be the gold standard of ICP monitoring. In addition to measuring ICP, this technique can also be used to drain cerebrospinal fluid and administer medicine intrathecally, such as for antibiotic administration in cases of ventriculitis. Additionally, EVD placement may be indicated to drain post-traumatic hemorrhage.

D. OSMOTHERAPY:

Osmotherapy with mannitol has been used since the 1960s as the main treatment for raised ICP and remains a component of TBI management guidelines. Hypertonic saline has become an alternative during the last 20 years, but controversy remains regarding which solution is the best agent and regarding the best method of administration. Mannitol increases CBF by plasma expansion, decreasing the blood viscosity via deformed erythrocytes, and promoting osmotic diuresis. Hypertonic saline promotes the flux of water across the BBB and improved blood flow by expanding the plasma volume. Cottenceau and colleagues compared equiosmolar doses of mannitol and hypertonic saline in the treatment of increased ICP [44].

E. ANTICONVULSANT THERAPY:

Subsequent to TBI, convulsive activity results in increased ICP and altered oxygen supply to the injured brain. To prevent secondary brain injury, many studies have attempted to study the benefit of seizure prophylaxis [45]. It showed that treatment with phenytoin was effective in

decreasing the rate of posttraumatic seizures in the first 7 days of injury, but had no significant role in prevention of posttraumatic seizures after the first week of injury. Clinical comparisons of levetiracetam and phenytoin in prevention of early posttraumatic seizure prophylaxis have found no significant difference in rates of early posttraumatic seizures among patients treated with phenytoin compared with patients treated with levetiracetam. The current BTF Guidelines recommend treatment with anticonvulsants within 7 days of injury. No randomized controlled studies have been performed till date to prove that one antiepileptic drug is better than another in this setting [46].

F. ANTIBIOTIC THERAPY:

Since TBI patients are more likely to receive invasive monitoring and therapeutic treatments, including mechanical ventilation, they are also more likely to be at increased risk for the development of infections. Sources of potential infections need to be identified and appropriate therapy should be instituted. A common source of infection is invasive monitoring of ICP. The incidence of ICP device infection has been reported to range from 1% to 27% [47]. Most studies cited by the BTF guidelines that evaluated prophylactic antibiotic coverage in patients with TBI have shown little significant differences in infection rates. Another study that evaluated patients who received bacitracin flushes showed a higher rate of infection among the intervention group. The current guidelines suggest the use of antibiotic-impregnated catheters to reduce infection rates, although this is only a Level III recommendation [48].

DISCUSSION

Research in traumatic injuries in the CNS has significantly expanded our understanding of the underlying pathophysiology and molecular mechanisms. While primary injuries in TBI are largely irreversible, the ensuing secondary damages that develop and progress over months to years are amenable to therapeutical interventions. Since this delayed phase of injury involves a plethora of events, which include excitotoxicity, apoptotic cell death, inhibition of axonal regeneration, neuroinflammation and oxidative stress, the devise of efficacious therapeutic strategies will need to target multiple mechanisms over an extended period. The availability of depot systems for regulated and sustained delivery of therapeutic agents that are capable of entering cells by permeating the plasma membrane will apparently allow further improvement of the bioavailability of existing drugs. More importantly, it will offer the opportunity to explore the therapeutic potential of novel agents against druggable targets. In fact, this therapeutic approach has been applied in the treatment of many neurodegenerative disorders such as Alzheimer's disease, Huntington's disease and Parkinson's disease. While the feasibility of this strategy in the

management of TBI has yet to be established, it seems promising due to the slow progression of events during secondary damages in TBI, which require continuous availability of therapeutic agents in bioactive form at non-cytotoxic concentration. TBI has become a major health and socioeconomic problem throughout the world, which imposes a significant healthcare burden to modern societies that call for more effective therapeutic means. It also represents a valid issue in defense science because of a drastic increase in subtle CNS injuries among the military when they are better protected from fatality by modern technologies [50].

CONCLUSION

Recent reviews of the literature have suggested that modern research may not have significantly improved outcomes in patients with severe TBI, although progress has been made in understanding the mechanism of injury and general hospital care. A lack of convincing evidence remains for many of the therapeutic approaches used in various guidelines, even after several randomized controlled trials have evaluated specific components of these guidelines. The intent of establishing guidelines is to use evidence-based therapeutic approaches to reduce variations in patient management and improve functional outcomes. There is substantial evidence that the treatment of these patients in centers with protocol-driven management is associated with better outcomes [51]. The BTF guidelines, which are most widely used for the management of severe TBI patients, are a constantly evolving set of recommendations based on meta-analysis approaches and systematic reviews originating from clinical outcome studies. A study of severe TBI patients in which the patients were treated according to the BTF guidelines has shown improvements in outcomes between 2001 and 2009. Better clinical outcomes are likely to be a consequence of a combination of improved prehospital and critical care. Prompt interventions to limit secondary brain injury are essential to improve the longterm outcomes in this patient population [52].

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