JOURNAL OF NEUROTRAUMA 35:1407–1418 (July 1, 2018)

DOI: 10.1089/neu.2017.5345

Review

Adherence to Brain Trauma Foundation Guidelines for Management of Traumatic Brain Injury Patients and Its Effect on Outcomes: Systematic Review

Yahya Hadi Khormi,[1,2] Ibrahim Gosadi,[3] Sandy Campbell,[4] Ambikaipakan Senthilselvan,[5] Cian O'Kelly,[6] and David Zygun[7]

Abstract

Traumatic brain injury (TBI) management based on Brain Trauma Foundation (BTF) guidelines is widely accepted and thought to improve outcome. The objectives of this study are to provide an overview of adherence to BTF guidelines and to explore which factors influence adherence. We conducted a search of relevant electronic bibliographic databases. Twenty articles met inclusion/exclusion criteria out of 666 articles screened. All were cohort studies. Wide variation in adherence to BTF guidelines was observed with a median of 66.2% (range 0–100%). The lowest median adherence was observed with surgical management (14%), whereas the highest was observed with oxygenation (100%), steroid (97.8%), and blood pressure recommendation (92.3%). Variability was primarily explained by the variation in the strength of evidence of each recommendation. Treating patients with higher severity of injury as well as treatment in a Level I trauma center positively influenced adherence. Overall, adherence to BTF guidelines varies. Further research is required to strengthen the current evidence and to identify factors related to adherence to guidelines from a professional prospective.

Keywords: brain injury guidelines; Brain Trauma Foundation guidelines; TBI

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability around the world. In the United States, the prevalence of TBI is estimated to be 2% in the general population,[1] and the reported mortality rate is 18.4 per 100,000 persons, with an annual average of 53,014 deaths.[2] A Canadian Institute for Health Information (CIHI) report indicated that there were 16,811 hospitalizations annually for TBI, with 1368 (8%) related deaths.[3] Among residents in the Calgary Heath Region in Alberta, Canada, the annual incidence of severe TBI was 11.4 per 100,000 persons, with a mortality rate of 5.1 per 100,000 persons per year.[4]

Clinical practice guidelines are mostly developed and distributed by well-recognized organizations to improve quality of care, to decrease discrepancy in practice, and to ensure that evidence is followed.[5] Guideline recommendations, defined as ''any statement that promotes or advocates a particular course of action in clinical care,''[6] are systematically developed recommendations to guide practitioners in choosing the appropriate healthcare decision for specific clinical circumstance.[7] In the treatment of TBI, guidelines are proposed to be an important aspect of patient management.

There are many published guidelines in the management of TBI that are released from different countries, which target different aspects of TBI management. These include but are not limited to, pre-hospital, emergency department, in-hospital, intensive care unit, surgical management, and indication for CAT scan of the head.[8–12]

Internationally, Brain Trauma Foundation (BTF) guidelines are widely disseminated. They have been translated into >15 different languages and applied in Europe, South America, and parts of China. The BTF maintains and revises some of the following TBI guidelines: Guidelines for Prehospital Management of Traumatic Brain Injury; Guidelines for the Management of Severe Traumatic Brain Injury; Guidelines for the Surgical Management of Traumatic Brain Injury; Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents; Guidelines for the Field Management of Combat Related Head Trauma; and Early Indicators of Prognosis of Severe

[1]Division of Neurosurgery, Department of Surgery, University of Alberta and the University of Alberta Hospital, Edmonton, Alberta, Canada.
[2]Faculty of Medicine, Jazan University, Jazan, Saudi Arabia.
[3]Department of Family and Community Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia.
[4]John W. Scott Health Sciences Library, Walter C. Mackenzie Health Sciences Centre, [5]School of Public Health, Edmonton Clinic Health Academy, [6]Division of Neurosurgery, Department of Surgery, and [7]Department of Critical Care Medicine, University of Alberta, Edmonton, Alberta, Canada.

Traumatic Brain Injury. Some of these guidelines are developed and maintained in collaboration with the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Section on Neurotrauma and Critical Care, European Brain Injury Consortium, and other stakeholders in TBI patient outcome.[11]

Guidelines for Management of Severe Traumatic Brain Injury address key topics that are useful for in-hospital medical management of severe TBI in adult patients with a Glasgow Coma Scale (GCS) score of 3–8. These include blood pressure (BP) and oxygenation, hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, intracranial pressure (ICP) monitoring, cerebral perfusion thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics and sedatives, nutrition, antiseizure prophylaxis, and hyperventilation through steroids use. These guidelines were published in 1995, 2000, and 2007.[4,11,13] with a fourth edition released in 2017.[14] Guidelines published in 2006 for the Surgical Management of Traumatic Brain Injury address important issues in acute surgical management of TBI, which include: acute epidural and subdural hematomas, parenchymal mass lesions, and depressed skull fractures through posterior fossa lesions, with a focus on indications and technique and timing of surgery.[12]

Studies suggest that implementation and strict adherence to BTF guidelines results in improvement in neurological outcomes and reduction in mortality from severe TBI.[15,16] However, there is still significant variability and inconsistency in management of traumatic TBI.[17,18]

Objectives

The first objective of this study is to present a systematic review of practitioners' adherence to the BTF guidelines for the management of severe TBI. The second objective is to explore which factors influence adherence to the guidelines. Identification of these factors may provide valuable insight into the development of strategies to increase adherence.

Methods

Protocol and study overview

The methods of this systematic review and meta-analysis have been developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) guidelines[19] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE).[20] We assembled a comprehensive database containing all published literature that addresses adherence to BTF guidelines in management of severe TBI. The goals of this study are to comprehensively and critically analyze the world's relevant literature in order to evaluate the utilization of BTF guidelines in clinical practice, and to study the factors that influence guideline utilization. This protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42015017794) and published in Systematic Reviews as ''Adherence to Brain Trauma Foundation Guidelines for Management of Traumatic Brain Injury Patients: Study Protocol for a Systematic Review and Meta-Analysis.[21] Detailed descriptions of methods can be found in these two sources.

Search strategy

The primary search strategy was developed by the primary investigator (Y.H.K.) in collaboration with an expert searcher/librarian (S.C.). We searched eight electronic bibliographic databases.

Study selection

All titles, abstracts and articles were screened to identify studies addressing the adherence to BTF guidelines for in-hospital management of adult civilian patients with TBI who were >17 years of age. Our search included in-hospital guidelines regarding BP and oxygenation, hyperosmolar therapy, prophylactic hypothermia, infection prophylaxis, deep vein thrombosis prophylaxis, indications for ICP monitoring, ICP monitoring technology, ICP thresholds, cerebral perfusion thresholds, brain oxygen monitoring and thresholds, anesthetics, analgesics, sedatives, nutrition, antiseizure prophylaxis, hyperventilation, and steroids. We also included guidelines for surgical management for acute epidural and subdural hematomas, parenchymal lesions, posterior fossa mass lesions, and depressed cranial fractures in our search.

Articles were included if they reported adherence rates and factors influencing adherence. We excluded: (1) animal studies, (2) studies with a majority of pediatric patients, (3) case reports and non-original articles, (4) studies that included <10 patients, (5) studies addressing adherence to pre-hospital guidelines, and (6) studies focused on military/combat-related TBI. Studies related to pre-hospital management were excluded because failure to achieve target recommendation might be an indicator of severe injury. Studies focused on military/combat-related TBI were excluded because the results would not be generalizable to the study population of civilian patients with TBI.

Data extraction and synthesis

Data were extracted from eligible studies using a predesigned and pilot-tested standardized electronic data extraction form. Narrative synthesis and quantitative analysis were used. Synthesis was based on clustering of selected studies by type of recommendation. Adherence to BTF-based protocol was extracted as a separate category if the full description of the protocol and the protocol adherence rate were reported. Data synthesis included description of study characteristics such as design, year and language of publication, publishing journal, country (mono-center/multicenter), study period, professionals studied for adherence, number of participants, median age, GCS, injury severity score, and quality assessment measure. From each article, adherence percentages for each recommendation were extracted. These indicate the number of patients managed based on guidelines divided by all patients managed. In the case of a pre and post-intervention design for evaluation of an intervention (for example, introducing a protocol or teaching program), only the post-intervention percentages were extracted, because we wanted to assess the current clinical practice. The median percentage of adherence for each recommendation was calculated. Additionally, factors influencing adherence were extracted when a statistically significant relationship between the factor and adherence was demonstrated in the article. Analysis was performed using Stata Statistical Software version 13.1. (StataCorp LP, College Station, TX).

Quality assessment

The quality of reporting of observational studies was assessed using a checklist, which is based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Study selection, as well as data extraction, synthesis, and quality assessment were performed by two independent investigators (Y.H.K., I.G). Differences of opinion were resolved by discussion with other researchers (C.O. and D.Z.). To assess inter-rater reliability, the percent agreement was calculated on adherence percentage for number of guideline recommendations by the third investigator (A.S.).

Results

Study selection

In total, 666 studies were identified. Initial title screening identified 228 ineligible studies, which were excluded. Next, 438 abstracts were evaluated based on inclusion/exclusion criteria, and 377 studies were excluded. The full texts of the remaining 61 studies were subjected to detailed evaluation. Based on inclusion/exclusion criteria, 41studies were excluded and 20 studies were included in the analysis (Fig. 1). Authors of 24 abstracts presented in a conference were e-mailed; we only received one response indicating that their result has not been finalized. The overall inter-rater agreement between the two investigators was moderate (κ statistic = 0.402).

Description of the studies

The studies that were included were observational (cohort studies) and are summarized in Table 1. The majority of the studies included were retrospective cohort studies. Only three studies collected data prospectively, and one study utilized both prospective and retrospective approaches to collecting the data. The majority of the studies were conducted in multi-center settings, whereas six studies were based on a single center. Included studies were conducted in North America, ($n = 13$, 12 in the United States and 1 in Canada), Europe ($n = 5$) and Asia ($n = 2$) and the Middle East ($n = 1$, from Saudi Arabia). Table 2 summarizes the recommendations assessed, level of evidence, and the number of studies that addressed each recommendation.

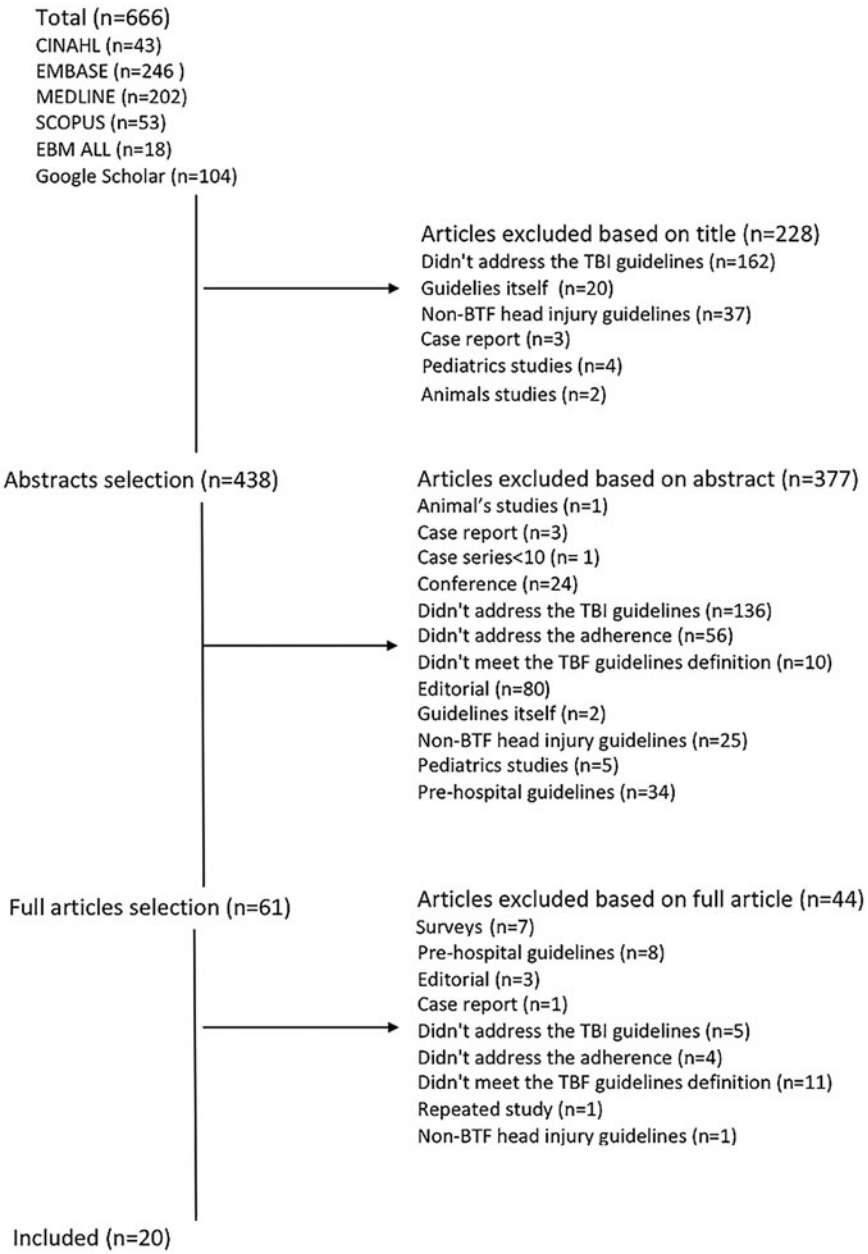

FIG. 1. Study selection process.

Table 1. Summary of Included Studies

Study	*Language of the publication*	*Publishing journal*	*Number of centers*	*Country*	*Study type and temporality*	*Study period, start*	*Study period, end*	*Inclusion/Exclusion criteria*	*Number of patients*
Talving et al.[18]	English	Journal of Neurosurgery	2 centers	United States	Prospective cohort	January 1, 2010	December 30, 2011	Inclusion: GCS ≤8, head AIS ≥3, met the BTF criteria for ICP monitoring, admitted to the surgical ICU Exclusion: age <18years, moribund patients, and those who were not expected to improve prior to the decision of whether an ICP monitoring device would be placed	216
Biersteker et al.[17]	English	Critical Care Medicine	5 (Level I trauma center)	Netherlands	Prospective cohort	June 1, 2008	May 31, 2009	Inclusion**:** patients met BTF criteria for ICP monitoring Exclusion**:** age <16 years and hospital admission >72 h after the injury was sustained	265
Farahvar et al.[25]	English	Journal of Neurosurgery	22 trauma centers (20 Level I and 2 level II)	United States	Prospective cohort	June 6, 2000	December 31, 2009	Inclusion: patients met BTF criteria for ICP monitoring and at least one of the following ICP treatment regimens was administered in the first 2 days following admission: mannitol, hypertonic saline, barbiturates, drainage of CSF, or decompressive craniectomy Exclusion: nonparalyzed patients on day 1 or 2 following trauma, with a GCS score of 3 or 4, and with fixed and dilated pupils	1307
Shafi et al.[33]	English	The Journal of Trauma Injury, Infection, and Critical Care	Participating trauma centers nationally	The National Trauma Data Bank of the American College of Surgeons (USA)	Retrospective cohort	1994	2001	Inclusion: admission to a designated Level I or II trauma center, blunt mechanism, age 20–50 years, admission to an intensive care unit for at least 3 days, and met the BTF criteria for ICP monitoring. Exclusion: patients with AIS of <3, patients who died within 48 h of admission, and those who were admitted to a trauma center 24 hours after sustaining the injury	1646
Barmparas et al.[22]	English	The American Surgeon	2 centers	The National Trauma Data Bank research data sets (USA)	Retrospective cohort	2007	2008	Inclusion: patients met the BTF criteria for placement of an ICP monitor, blunt mechanism of injury, admission to a Level I or a Level II trauma center, and age >14 years Exclusion: AIS in any body region = 6, had missing head AIS or GCS scores, died in the emergency room	15,921

(*continued*)

Table 1. (Continued)

Study	Language of the publication	Publishing journal	Number of centers	Country	Study type and temporality	Study period, start	Study period, end	Inclusion/Exclusion criteria	Number of patients
Tang et al.[34]	English	Journal of Surgical Research	Monocenter	United States	Retrospective cohort	2010	2012	Inclusion: patients who met the BTF guidelines for placement of an ICP monitor Exclusion: Patients transferred from other institutions and patients with unsalvageable brain injury were excluded	194
Shafi et al.[32]	English	Journal of the American College of Surgeons	5 centers	United States	Retrospective observational	Center A: January 1, 2006 Centers B, C, D, and E: January 1, 2009	Center A: December 31, 2008 Centers B, C, D, and E: December 31, 2010	Inclusion: age >16, GCS ≤8 intracranial bleed on head CT and endotracheal intubation Exclusion: time from injury to arrival in emergency department of >1 day; burns, poisoning, drowning, hanging, submersion, or asphyxiation; gunshot wounds to the head; and dead on arrival in emergency department	831
Mauritz et al.[28]	English	European Journal of Public Health	13 centers	Europe (Austria, Bosnia, Croatia, Macedonia, and Slovakia)	Retrospective cohort	January, 2001	June, 2005	Inclusion: GCS ≤8 after resuscitation or a GCS score deteriorating to ≤8 within 48 h of injury and survived at least until admission to the ICU were enrolled into this study Exclusion: GCS of 3	1172
Bulger et al.[24]	English	Critical Care Medicine	28 (Level I trauma centers) and 6 (Level II trauma centers)	United States	Retrospective cohort	May 1, 1998	December 31, 1998	Inclusion: GCS of 8 or less and has a fracture of the tibia, fibula, or femur. Exclusion: burn injury, pregnancy, spinal cord injury with paralysis and patients transferred from another institution >24 h after injury	182
Gerber et al.[27]	English	Journal of Neurosurgery	22 (20 are Level I trauma centers and 2 are Level II trauma centers)	United States	Retrospective cohort	2007	2009	Inclusion: isolated or multi-trauma TBI, arrival at the participating trauma center within 24 h of injury, GCS <9 with a GCS motor score <6 for at least 6 h after injury and after resuscitation Exclusion: Patients with severe TBI who died in the emergency department or were admitted with the diagnosis of brain death	1133
English	Wiener	Klinische Wochenschrift	5 centers	Austria	Retrospective cohort	2007	2009	Inclusion: fulfilled the criteria for severe brain trauma Exclusion: Patients who died at the scene, during transport to the hospital, or immediately after admission to the emergency room were excluded	415

(*continued*)

Table 1. (Continued)

Study	Language of the publication	Publishing journal	Number of centers	Country	Study type and temporality	Study period, start	Study period, end	Inclusion/Exclusion criteria	Number of patients
Thompson et al.[35]	English	Intensive and Critical Care Nursing	Monocenter	United States	Retrospective cohort	2000	2002	Inclusion: patients admitted to a Level I trauma center following a primary diagnosis of severe TBI	108
Griesdale et al.[37]	English	Journal of Critical Care	Monocenter	Canada	Retrospective cohort	2006	2012	Inclusion: all patients who were admitted to the ICU if they had an admission diagnosis of TBI and had an ICP monitor inserted during their stay Exclusion: ICP monitor inserted for reasons other than a closed TBI or penetrating TBI	127
Neumann et al.[29]	English	Journal of Intensive Care Medicine	22 centers	Europe	Retrospective cohort	July, 2003	June 2005	Inclusion: all TBI patients with a known time of trauma and at least one record ABG	151
Frohlich et al.[26]	English	Irish Journal of Medical Science	Monocenter	Ireland	Retrospective cohort	2005	2007	Inclusion: all TBI patients	46
Shafi et al.[31]	English	Journal of Neurosurgery	11 Level I trauma centers	United States	Retrospective cohort	January 1, 2008	September 9, 2009	Inclusion: GCS ≤8 Exclusion: unsurvivable brain injuries (AIS of 6) patient age >99 years	2056
Bhullar et al.[23]	English	Journal of Trauma and Acute Care Surgery	Level 1 trauma centers	National Trauma Registry of the American College of Surgeons (USA)	Retrospective cohort	January, 2008	January, 2010	Inclusion: age >18 years, blunt severe TBI (positive CT scan of the head and GCS of 3–8) and remained in the hospital at least 7 days after injury Exclusion: antiseizure prophylaxis with levetiracetam, seizure before possible AED loading opportunity, and death within 72 h of hospital admission	93
Tsai et al.[36]	English	Surgical Neurology	6 medical centers	Taiwan	Retrospective cohort	January, 1, 2003	June 31, 2003	Inclusion: ≥18 years of age, sustained brain injury with a post resuscitation GCS of 3–8, and required mechanical ventilation Exclusion: lost to follow-up at 6 months after the injury.	94
Arabi et al.[40]	English	Journal of Critical Care	Monocenter	Saudi Arabia	Retrospective cohort	March, 1999	December, 2006	Inclusion: patients >12 years of age with severe TBI (GCS ≤8) Exclusion: brain death on admission	434
Palmer et al.[15]	English	Journal of Trauma Injury Infection and Critical Care	Monocenter	United States	Combined retrospective and prospective cohort	1994	1999	Inclusion: GCS 3–8, CT scan had findings indicative of brain injury, age >8 years, closed head injury and patient had to have ICP monitor Exclusion: dead within 24 h of admission.	93

GCS, Glasgow Coma Scale; BTF, Brain Trauma Foundation; ICP, intracranial pressure; ICU, intensive care unit; CSF, cerebrospinal fluid; TBI, traumatic brain injury; ABG, arterial blood gas; AIS, American Spinal Injury Association (ASIA) Impairment Scale; AED, antiepileptic drug.

Table 2. Brain Trauma Foundation (BTF) Recommendations Being Evaluated for Adherence in Included Studies

Guideline	*Recommendations*	*Number of studies (Reference)*
Pre and post guidelines based protocol implementation	Levels I, II, and III all guidelines	2 (15,40)
Indication for intracranial pressure (ICP) monitoring	Level II ICP should be monitored in all salvageable patients with a severe traumatic brain injury (TBI) (Glasgow Coma Scale [GCS] score of 3–8 after resuscitation) and an abnormal CT scan. An abnormal CT scan of the head is one that reveals hematomas, contusions, swelling, herniation, or compressed basal cisterns. Level III ICP monitoring is indicated in patients with severe TBI with a normal CT scan if two or more of the following features are noted at admission: age >40 years, unilateral or bilateral motor posturing, or systolic blood pressure (BP) <90 mm Hg.	15 (18,17, 22, 23,24, 25, 26,27,28, 30, 31,32,33, 34, 36)
ICP thresholds	Level II Treatment should be initiated with ICP thresholds >20 mm Hg.	3 (30,34, 36)
BP	Level II BP should be monitored and hypotension (systolic BP <90 mm Hg) avoided.	5 (26,27,30, 31, 34)
Oxygenation	Level III Oxygenation should be monitored and hypoxia (PaO_2 < 60 mm Hg or O_2 saturation <90%) avoided.	2 (26, 30)
Cerebral perfusion thresholds	Level II Aggressive attempts to maintain cerebral perfusion pressure (CPP) >70 mm Hg with fluids and pressors should be avoided because of the risk of adult respiratory distress syndrome (ARDS). Level III CPP of <50 mm Hg should be avoided. The CPP value to target lies within the range of 50–70 mm Hg. Patients with intact pressure autoregulation tolerate higher CPP values. Ancillary monitoring of cerebral parameters that include blood flow, oxygenation, or metabolism facilitates CPP management.	6 (27,30, 31,34, 36, 37)
Hyperventilation	Level II Prophylactic hyperventilation ($PaCO_2 \leq 25$ mm Hg) is not recommended. Level III Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP. Hyperventilation should be avoided during the first 24 h after injury when cerebral blood flow (CBF) is often critically reduced. If hyperventilation is used, jugular venous oxygen saturation (SjO_2) or brain tissue oxygen tension ($PbrO_2$) measurements are recommended to monitor oxygen delivery.	2 (26, 29)
Steroids	Level I The use of steroids is not recommended for improving outcome or reducing ICP.	4 (26, 27, 28, 30)
Antiseizure prophylaxis	Level II Prophylactic use of phenytoin or valproate is not recommended for preventing late post-traumatic seizures (PTS). Level III Anticonvulsants are indicated to decrease the incidence of early PTS (within 7 days of injury). However, early PTS is not associated with worse outcomes.	3 (23, 26, 30)
Nutrition	Level II Patients should be fed to attain full caloric replacement by day 7 post-injury.	3 (26, 27, 32)
Temperature	Normothermia	1 (35)
Surgical management of acute subdural hematoma (SDH)	Acute SDH with a thickness >10 mm or a midline shift >5 mm on CT scan should be surgically evacuated, regardless of the patient's GCS score. All patients with acute SDH in coma (GCS score <9) should undergo ICP monitoring.	1 (26)
Surgical management of traumatic parenchymal lesion	Signs of progressive neurological deterioration referable to the lesion, medically refractory intracranial hypertension, or signs of mass effect on CT scan should be treated operatively. Patients with GCS scores of 6–8 with frontal or temporal contusions >20 cm^3 in volume with midline shift of at least 5 mm and/or cisternal compression on CT scan, and patients with any lesion >50 cm^3 in volume should be treated operatively.	1 (26)

Level of recommendations based on third edition of BTF Guidelines for the Management of Severe TBI.

Adherence to BTF Guidelines for management of TBI

Eighteen studies reported adherence to the BTF guidelines. These studies mostly assessed the adherence of neurosurgeon and intensivist.[17,18,22–37] Adherence by critical care nurses to the recommendation to normothermia was assessed in one study.[35]

Agreement between investigators was high (93.8% for guideline adherence percentage). The median percentage of adherence to the BTF guidelines for management of TBI was 60.7%, ranging from 0 to 100%. Upon investigating the adherence level according to the location of the study, there was no significant difference in adherence level between the studies conducted in North America (59.2%) and those conducted in other countries (67.1%). The adherence level in North American centers had less variability than studies conducted in other countries, ranging between 13.5% and 55.9% and between 0 and 100% respectively. Overall adherence to BTF guidelines was 40% in 1997. An increase in the adherence to the guidelines was observed, reaching 60% in 2002. Nonetheless, it seems that no further improvement in the median adherence has been observed since 2002.

Adherence to BTF guidelines for medical management of severe TBI

Eighteen studies reported adherence for 10 different medical management guidelines for severe TBI, as illustrated in Table 2. The most commonly studied recommendation for medical management of severe TBI was indication for ICP monitoring. This was reported in 15 of the studies. The remaining recommendations were reported less frequently as follows: cerebral perfusion threshold, BP and oxygenation, steroid use, ICP threshold, nutrition, antiseizure prophylaxis, and hyperventilation.

Overall median percentage of adherence was 66.2%, varying from 0 to 100%. Figure 2 demonstrates the median percentage adherence and interquartile range of different recommendations. Smaller median adherence percentages (31% and 40.1%) were reported in two studies for normothermia and cerebral perfusion thresholds (CPT) recommendations, whereas higher median adherence percentages (100%, 97.8%, 92.3%) were reported in three studies with recommendations of oxygenation, steroids, and BP, respectively. These were followed by the adherence to nutrition, ICP threshold, and hyperventilation, which were 79% 78.4%, and 70%, respectively. Moderate adherences were reported in two studies for antiseizure prophylaxis and indication for ICP recommendation, which were 58.1% and 46.4% respectively. One study reported the adherence for six different guidelines, including the indication for ICP monitoring, BP, and CPT, which was 73%. Another study reported the adherence to oxygenation and BP recommendation combined, which was 79.2%.

Adherence to BTF guidelines for surgical management of severe TBI

Only one study[29] assessed the adherence to the surgical recommendation for management of acute subdural (ASD) hematoma and intraparynchemal lesions (IPL). In this study, the percentages of adherence to the recommendation for management of ASD hematoma and IPL were 13% and 14% respectively.

Adherence to BTF guidelines organized based on the level of evidence

Reported guidelines were organized based on the level of evidence in Table 2 to examine whether level of evidence could influence the level of adherence to the BTF guidelines. We observed that recommendations with the higher the level of evidence were associated with the higher median percentage of adherence, 96.9%, 79%, 32% and 13.5% for Levels I, II, III, and unclassified recommendations, respectively (Fig. 3).

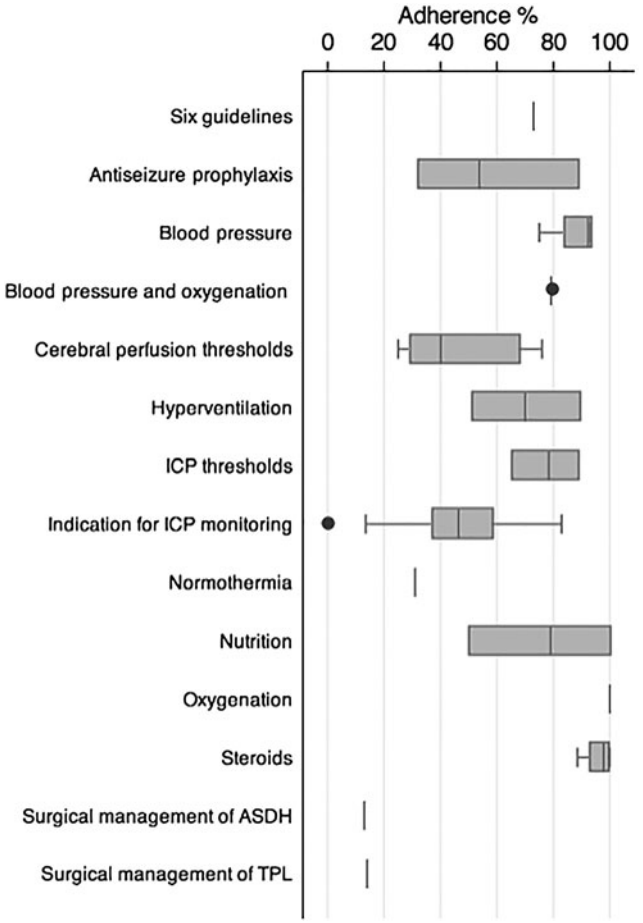

FIG. 2. Median percentage adherence and interquartile range for Brain Trauma Foundation (BTF) recommendations.

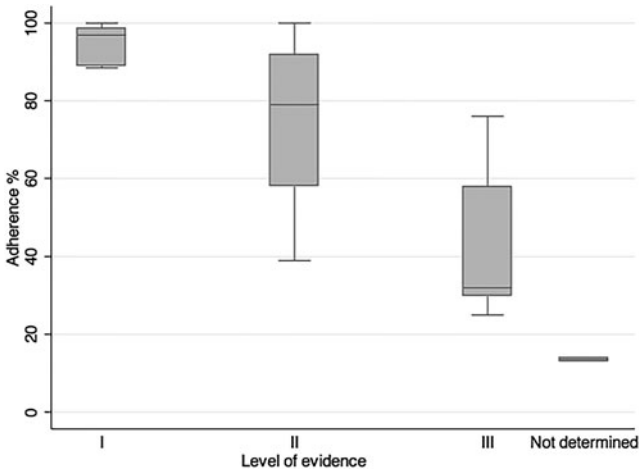

FIG. 3. Median percentage adherence and interquartile range for Brain Trauma Foundation (BTF) recommendations grouped by level of evidence.

Table 3. Factors Influencing Adherence with BTF Guidelines

	Adherence	
Influencing factors	*Increased*	*Decreased*
Patient characteristic		
Age	• Younger age[17,18,22,31]	
Sex		• Female sex[31]
Severity of Injury		
Neurological status	• Head AIS greater than 3[22,31]	• Improved neurological status within 24 h[18]
Systemic Injury	• Severe systemic injuries; high ISS,[17,22] extremity AIS score ≥3[18] • Higher SBP[31]	• Hypotension on admission[18,22] • Coagulopathy[18]
Management	• Decompressive craniectomy/craniotomy[18,22]	
Organizational factors	• Admission to a Level I trauma center[22] • Higher economic status countries[28]	• Lack of health insurance[31]

BTF, Brain Trauma Foundation; AIS, American Spinal Injury Association (ASIA) Impairment Scale; ISS, Injury Severity Score; SBP, systolic blood pressure.

Influencing factors

Six studies addressed factors influencing adherence in the context of indication for ICP monitoring, BP, and cerebral perfusion pressure management. These factors were clustered in relation to patient characteristics: age, sex, severity of injury, neurological status, systemic injury, management, and organization factors (Table 3).

Adherence to the indication for ICP monitoring was higher when treating younger patients.[17,18,22] patients with severe neurological injury,[22,31] and patients who underwent surgical treatment.[18,22] Adherence was lower for treatment of patients whose neurological status improved within 24 h or who were coagulopathic.[18]

Patients with lower systolic blood pressure (SBP) were less likely to be treated based on guidelines for ICP monitoring, despite the fact that the guidelines recommend ICP monitoring for these patients.[18,22]

Adherence to BP and cerebral perfusion pressure management guidelines was higher when treating younger patients and patients with higher severity of neurological injury.[31]

Findings related to adherence to recommendations concerning papillary abnormality were contradictory. Biersteker and coworkers reported that the presence of more pupillary abnormalities increased the adherence level,[17] whereas Farahvar and coworkers reported that more pupillary abnormality decreased the adherence to ICP monitoring.[25]

Two studies reported that more abnormality in the CT increased adherence, and normal CT scans decreased adherence.[17,18] Shafi and coworkers reported the opposite, with a Marshal score ≤2 associated with increased adherence.[31] These contradictions are most likely the result of not incorporating specific information on CT findings, and using different classifications for CT head findings.

As for organizational factors, treatment in a Level I trauma center and living in a country with a higher economic status positively influenced adherence,[22,28] whereas lack of health insurance negatively influenced adherence.[31]

Methodological quality; quality of reporting

Out of the 20 studies, 9 studies presented key elements of study design early in the article; 19 studies described the setting, location, and relevant dates, including period of recruitment; 19 studies gave the eligibility criteria, source, and method of selection; 17 studies gave the method of assessment for each variable; 4 studies described plans to address the potential sources of bias; 8 studies explained how study size was determined; 17 studies described statistical methods, including those used to control for confounding, and described any methods used to examine subgroups or interactions; 8 studies presented flow diagrams for participants; 17 studies adequately described their study populations (included information on exposure and potential confounders), 13 studies reported confounder-adjusted estimates and made clear for which confounders adjustments were made, subgroup analysis or sensitivity analysis; 15 studies discussed limitations; 13 studies discussed external validity; and 8 studies listed the sources of funding. Other items were reported by all studies. Tables 4 and 5 provide more details of the evaluation of the methodological quality of reporting.

Discussion

This systematic review is the first to look at adherence to BTF guidelines for management of severe TBI. It is designed to provide an overview of professionals' adherence to BTF guidelines, and to explore factors influencing adherence to these guidelines. Eighteen articles reported adherence to medical management recommendations, and only one small-size study reported the adherence to surgical management recommendations.

Despite the urgency and life-threating nature of severe TBI, as well as the worldwide dissemination since 1996 of BTF guidelines for management of severe TBI, results show a wide variation in adherence even among the studies conducted in North America.

The adherence to recommendations related to steroids, oxygenation, and blood pressure was >88%. Adherence to nutrition, ICP threshold, and hyperventilation ranged from 70% to 79%. Moderate adherence (between 46% and 58%), was reported for antiseizure prophylaxis and indication for ICP recommendation. Lower adherence to guidelines for medical management was noted for normothermia and CPT recommendations ranging between 30% and 40%. The lowest adherence was for surgical recommendations, at ~14%. However, it is difficult to draw a valid conclusion based on adherence to specific recommendations, when study number and size are small, and studies are conducted in different settings and countries over different periods of time.

This review found that the level of adherence was proportionally associated with the strength of evidence. Level I evidence recommendations were associated with optimal adherence, Level II recommendations had reasonable adherence, suboptimal adherence was detected with Level III evidence recommendations, and very poor adherence was associated with unclassified recommendations (13.5%). These findings explain the large variation in adherence to BTF guideline recommendations, which might indicate a barrier

Table 4. Quality of Reporting of Observational Studies Based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement

Variable	*Title/abstract*	*Introduction*	*Background/rationale*	*Objectives*	*Methods*	*Study design*	*Setting*	*Participants*	*Variables*	*Data sources/measurement*	*Bias*	*Study size*	*Quantitative variables*
Talving et al.[18]	•		•	•		•	•	•	•	•	•		•
Biersteker et al.[17]	•		•	•		•	•	•	•	•			•
Farahvar et al.[25]	•		•	•		•	•	•	•	•			•
Shafi, et al.[33]	•		•	•			•	•	•	•			•
Barmparas et al.[22]	•		•	•			•	•	•	•			•
Tang, et al.[34]	•		•	•		•	•	•	•	•		•	•
Shafi, et al.[32]	•		•	•			•	•	•	•	•	•	•
Mauritz et al.[28]	•		•	•			•	•	•	•			•
Bulger et al.[24]	•		•	•			•	•	•	•			•
Gerber et al.[27]	•		•	•			•	•	•	•		•	•
Rusnak et al.[30]	•		•	•				•	•				•
Thompson et al.[35]	•		•	•			•	•	•	•			•
Griesdale et al.[37]	•		•	•		•	•	•		•		•	•
Neumannet al.[29]	•		•	•		•	•	•	•	•		•	•
Frohlich et al.[26]	•		•	•			•		•				•
Shafi et al.[31]	•		•	•			•	•	•	•	•	•	•
Bhullar et al.[23]	•		•	•		•	•	•	•	•		•	•
Tsai et al.[36]	•		•	•			•	•	•			•	•
Arabi et al.[40]	•		•	•		•	•	•	•	•			•
Palmer et al.[15]	•		•	•		•	•	•	•	•	•		•

Table 5. Quality of Reporting of Observational Studies Based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement

Variable	*Statistical methods*	*Results*	*Participants*	*Descriptive data*	*Outcome data*	*Main results*	*Other analyses*	*Discussion*	*Key results*	*Limitations*	*Interpretation*	*Generalizability*	*Funding information*
Talving et al.[18]	•			•	•	•	•		•	•	•	•	
Biersteker et al.[17]	•		•	•	•	•	•		•	•	•	•	•
Farahvar et al.[25]	•		•	•	•	•	•		•	•	•		•
Shafi, et al.[33]	•			•	•	•	•		•	•	•	•	
Barmparas et al.[22]	•			•	•	•	•		•	•	•		
Tang et al.[34]	•		•	•	•	•	•		•	•	•		
Shafi et al.[32]	•		•	•	•	•	•		•	•	•	•	
Mauritz, et al.[28]	•			•	•	•	•		•		•	•	•
Bulger et al.[24]	•			•	•	•	•		•	•	•	•	
Gerber et al.[27]	•			•	•	•	•		•		•	•	•
Rusnak et al.[30]	•				•	•	•		•	•	•		•
Thompson et al.[35]				•	•	•			•	•	•	•	
Griesdale et al.[37]	•		•	•	•	•			•	•	•		•
Neumann et al.[29]	•		•		•	•			•	•	•		
Frohlich et al.[26]	•				•	•			•		•	•	
Shafi, et al.[31]	•		•	•	•	•	•		•	•	•	•	•
Bhullar et al.[23]			•	•	•				•	•	•	•	
Tsai et al.[36]				•	•	•			•		•		•
Arabi et al.[40]	•			•	•	•			•	•	•	•	
Palmer et al.[15]	•			•	•	•	•		•		•	•	

specifically for individual recommendations rather than guidelines as a whole. Another explanation could be that guidelines containing a large number of recommendations would interfere with an appropriate level of adherence; therefore, translation of guidelines into more efficient, practical, and feasible protocols and algorithms would enhance adherence, as has been shown before.[38]

Factors influencing adherence were reported in six studies[17,18,22,25,28,31] These factors related to the patients and health institute. No factors related to profession were studied. More research focusing on the perspectives of professionals would be valuable. This systematic review demonstrates that stronger evidence would increase adherence to BTF guidelines as whole. Patients' characteristics were addressed mostly in the context of indication for ICP monitoring recommendation. Generally adherence was higher when treating surviving patients with more severe TBI. Patients with lower SBP were less likely to be treated based on guidelines for ICP monitoring, although low SBP is one of the indications for insertion ICP monitoring. This was reported in two studies,[18,22] which have insufficient information to make a solid conclusion. Either this was an indicator of lower adherence because this recommendation represents Level III evidence, or hypotension in this group of patients was a representative of devastating systemic injury (not survivable by the patient), which also decreases adherence.

The lack of agreement of the effect of pupillary abnormality on adherence between two studies[17,25] might be explained by the difference in the duration of the pupillary abnormality between the patients in the two studies, as neither study accounted for that in its analysis. It has been shown that bilateral pupillary abnormality and longer duration of the abnormality has a worse outcome.[39]

It is not possible to draw a conclusion about the effect of the CT findings on adherence, as only three studies reported on this variable,[17,18,31] and they each used different classifications of CT findings in their analyses.

In terms of organizational factors, there are consistent patterns showing that treatment in a Level I trauma center or being in a higher economic status country positively influences adherence,[22,28] whereas lack of health insurance negatively influences adherence.[31]

This knowledge can be used to improve guidelines and to establish strategies to improve adherence. These strategies should also focus on individual guideline recommendations as well as on the guidelines as a whole.

Limitations of included studies

This study has a few limitations; first, the included studies were observational, and most used retrospective design and patient databases. These methods have high risk of bias. Second, only four studies described plans to address the potential sources of bias, indicating that the risk of bias might be high.

Review limitations

First, the differences in recommendations, settings, and patient characteristics do increase the generalizability of the results, but they also make the analysis and interpretation of the results extremely challenging. Second, although high methodological standards were followed in conducting this systematic review with good inter-rater reliability, the results are limited by the quality of the studies included.

Study strength

A very comprehensive systematic search was conducted based on established guidelines for systematic reviews. Fairly good inter-rater reliability was achieved. Finally, the standard protocol for reporting systematic reviews was followed.

Conclusions

Adherence to BTF guidelines shows high variability in the reported literature despite the wide dissemination of these guidelines, as well as the urgency needed in treating this life-threatening condition. The most likely explanations are the weakness of evidence for some recommendations. This emphasizes the need for more well-conducted research to strengthen the current evidence, to focus on the perspectives of professionals, and to develop strategies to increase adherence. These could include treating severe TBI patients in Level I trauma centers and supporting economic improvements to the health system.

Acknowledgments

Y.H.K. is not funded. I.G. is financially supported by the Vice Deanship of Research Chair, King Saud University, Riyadh, Kingdom of Saudi Arabia. S.C. is not funded. A.S. is not funded. C.O. is not funded. D.Z. is not funded for this project specifically, but is appointed to the Division of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta. Y.H.K. and D.Z. formulated the research question. Y.H.K., D.Z., and C.O. designed the study. Y.H.K. developed the preliminary search strategy. S.C. refined and executed the search strategy and exported the results. Y.H.K. and A.S. designed the statistical analysis plan. Y.H.K. and I.G. identified articles, performed data extraction, and assessed the risk of bias of individual studies. Y.H.K. and A.S. performed data analysis; Y.H.K. wrote the article. Y.H.K., D.Z., C.O., A.S., I.G., and S.C. critically reviewed the manuscript for content. All authors have approved the final version of the manuscript.

Author Disclosure Statement

No competing financial interests exist.

References

1. Langlois, J.A., Rutland-Brown, W., and Wald, M.M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. J. Head Trauma Rehabil. 21, 375–378.
2. Coronado, V.G., Xu, L., Basavaraju, S.V., McGuire, L.C., Wald, M.M., Faul, M.D., Guzman, B.R., Hemphill, J.D., and Centers for Disease Control and Prevention (2011). Surveillance for traumatic brain injury-related deaths—United States, 1997–2007. Morb. Mortal. Wkly. Rep. Surveill. Summ. 60, 1–32.
3. (2009) Head Injuries in Canada: A Decade of Change (1994–1995 to 2003–2004), in: *National Trauma Registry Analysis in Brief*. Canadian Institute for Health Information.
4. Zygun, D.A., Laupland, K.B., Hader, W.J., Kortbeek, J.B., Findlay, C., Doig, C.J., and Hameed, S.M. (2005). Severe traumatic brain injury in a large Canadian health region. Can. J. Neurol. Sci. 32, 87–92.
5. Thomas, L., Cullum, N., McColl, E., Rousseau, N., Soutter, J., and Steen, N. (2000). Guidelines in professions allied to medicine. Cochrane Database Syst. Rev. CD000349.
6. Lugtenberg, M., Burgers, J.S., and Westert, G.P. (2009). Effects of evidence–based clinical practice guidelines on quality of care: a systematic review. Qual. Saf. Health Care 18, 385–392.
7. Field, M.J. and Lohr, K.N. (1990). *Clinical Practice Guidelines: Directions for a New Program.* National Academy Press, Washington, DC.
8. Haydel, M.J., Preston, C.A., Mills, T.J., Luber, S., Blaudeau, E., and DeBlieux, P.M. (2000). Indications for computed tomography in patients with minor head injury. N. Engl. J. Med. 343, 100–105.
9. Badjatia, N., Carney, N., Crocco, T.J., Fallat, M.E., Hennes, H.M., Jagoda, A.S., Jernigan, S., Letarte, P.B., Lerner, E.B., Moriarty, T.M., Pons, P.T., Sasser, S., Scalea, T., Schleien, C.L., Wright, D.W., Brain Trauma, F. and Management, B.T.F.C.f.G. (2008). Guidelines for

prehospital management of traumatic brain injury 2nd edition. Prehospital emergency care 12, Suppl. 1, S1–S52.
10. Shigemori, M., Abe, T., Aruga, T., Ogawa, T., Okudera, H., Ono, J., Onuma, T., Katayama, Y., Kawai, N., Kawamata, T., Kohmura, E., Sakaki, T., Sakamoto, T., Sasaki, T., Sato, A., Shiogai, T., Shima, K., Sugiura, K., Takasato, Y., Tokutomi, T., Tomita, H., Toyoda, I., Nagao, S., Nakamura, H., Park, Y.S., Matsumae, M., Miki, T., Miyake, Y., Murai, H., Murakami, S., Yamaura, A., Yamaki, T., Yamada, K., Yoshimine, T., and Guidelines Committee on the Management of Severe Head Injury, Japan Society of Neurotraumatology (2012). Guidelines for the Management of Severe Head Injury, 2nd Edition. Guidelines from the Guidelines Committee on the Management of Severe Head Injury, the Japan Society of Neurotraumatology. Neurologia medico–chirurgica 52, 1–30.
11. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS. (2007). Guidelines for the management of severe head injury. J. Neurotrauma 24, Suppl., S–1–S106.
12. Bullock M.R., C.R., Ghajar J., Gordon D., Hartl R., Newell D.W., Servadei F., Walters B.C., and Wilberger J.E. (2006). Guidelines for the surgical management of traumatic brain injury. Neurosurgery 58, 51–61.
13. Bullock, R.M., Chesnut, R., and Clifton, G.L., et al. (2000). The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Guidelines for the management of severe traumatic brain injury. J. Neurotrauma 17, 449–554.
14. Carney N., T.A.M., and O'Reilly C., et al. (2016). Guidelines for the management of severe traumatic brain injury. Neurosurgery 24, S1–106.
15. Palmer, S., Bader, M.K., Qureshi, A., Palmer, J., Shaver, T., Borzatta, M., and Stalcup, C. (2001). The impact on outcomes in a community hospital setting of using the AANS traumatic brain injury guidelines. American Association of Neurological Surgeons. J. Trauma 50, 657–664.
16. Vukić, M., Negovetić, L., Kovač, D., Ghajar, J., Glavić, Z. and Gopčević, A. (1999). The effect of implementation of guidelines for the management of severe head injury on patient treatment and outcome. Acta Neurochir. 141, 1203–1208.
17. Biersteker, H.A., Andriessen, T.M., Horn, J., Franschman, G., van der Naalt, J., Hoedemaekers, C.W., Lingsma, H.F., Haitsma, I. and Vos, P.E. (2012). Factors influencing intracranial pressure monitoring guideline compliance and outcome after severe traumatic brain injury. Crit. Care Med. 40, 1914–1922.
18. Talving, P., Karamanos, E., Teixeira, P.G., Skiada, D., Lam, L., Belzberg, H., Inaba, K., and Demetriades, D. (2013). Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. J. Neurosurg. 119, 1248–1254.
19. Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., and Thacker, S.B. (2000). Meta–analysis of observational studies in epidemiology: a proposal for reporting. Meta–analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283, 2008–2012.
20. Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J., and Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta–analyses of studies that evaluate health care interventions: explanation and elaboration. Ann. Intern. Med. 151, W65–94.
21. Khormi, Y.H., Gosadi, I., Campbell, S., Senthilselvan, A., O'Kelly, C., and Zygun, D. (2015). Adherence to Brain Trauma Foundation guidelines for management of traumatic brain injury patients: study protocol for a systematic review and meta–analysis. Syst. Rev. 4, 149.
22. Barmparas, G., Singer, M., Ley, E., Chung, R., Malinoski, D., Margulies, D., Salim, A., and Bukur, M. (2012). Decreased intracranial pressure monitor use at level II trauma centers is associated with increased mortality. Am. Surg. 78, 1166–1171.
23. Bhullar, I.S., Johnson, D., Paul, J.P., Kerwin, A.J., Tepas, J.J., 3rd, and Frykberg, E.R. (2014). More harm than good: antiseizure prophylaxis after traumatic brain injury does not decrease seizure rates but may inhibit functional recovery. J. Trauma Acute Care Surg. 76, 54–60.
24. Bulger, E.M., Nathens, A.B., Rivara, F.P., Moore, M., MacKenzie, E.J., Jurkovich, G.J., and Brain Trauma Foundation (2002). Management of severe head injury: institutional variations in care and effect on outcome. Crit. Care Med. 30, 1870–1876.
25. Farahvar, A., Gerber, L.M., Chiu, Y.L., Carney, N., Hartl, R., and Ghajar, J. (2012). Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. J. Neurosurg. 117, 729–734.
26. Frohlich, S., Johnson, P., and Moriarty, J. (2011). Prevalence, management and outcomes of traumatic brain injury patients admitted to an Irish intensive care unit. Ir. J. Med. Sci. 180, 423–427.
27. Gerber, L.M., Chiu, Y.L., Carney, N., Hartl, R., and Ghajar, J. (2013). Marked reduction in mortality in patients with severe traumatic brain injury. J. Neurosurg. 119, 1583–1590.
28. Mauritz, W., Wilbacher, I., Majdan, M., Leitgeb, J., Janciak, I., Brazinova, A., and Rusnak, M. (2008). Epidemiology, treatment and outcome of patients after severe traumatic brain injury in European regions with different economic status. Eur. J. Public Health 18, 575–580.
29. Neumann, J.O., Chambers, I.R., Citerio, G., Enblad, P., Gregson, B.A., Howells, T., Mattern, J., Nilsson, P., Piper, I., Ragauskas, A., Sahuquillo, J., Yau, Y.H., Kiening, K., and Brain, I.T.G. (2008). The use of hyperventilation therapy after traumatic brain injury in Europe: an analysis of the BrainIT database. Intensive Care Med. 34, 1676–1682.
30. Rusnak, M., Janciak, I., Majdan, M., Wilbacher, I., Mauritz, W., and Australian Severe, T.B.I.S.I. (2007). Severe traumatic brain injury in Austria VI: effects of guideline–based management. Wien. Klin. Wochenschr. 119, 64–71.
31. Shafi, S., Barnes, S.A., Millar, D., Sobrino, J., Kudyakov, R., Berryman, C., Rayan, N., Dubiel, R., Coimbra, R., Magnotti, L.J., Vercruysse, G., Scherer, L.A., Jurkovich, G.J., and Nirula, R. (2014). Suboptimal compliance with evidence–based guidelines in patients with traumatic brain injuries. J. Neurosurg. 120, 773–777.
32. Shafi, S., Barnes, S.A., Rayan, N., Kudyakov, R., Foreman, M., Cryer, H.G., Alam, H.B., Hoff, W., and Holcomb, J. (2014). Compliance with recommended care at trauma centers: association with patient outcomes. J. Am. Coll. Surg. 219, 189–198.
33. Shafi, S., Nathens, A.B., Parks, J., Cryer, H.M., Fildes, J.J., and Gentilello, L.M. (2008). Trauma quality improvement using risk–adjusted outcomes. J. Trauma 64, 599–604.
34. Tang, A., Pandit, V., Fennell, V., Jones, T., Joseph, B., O'Keeffe, T., Friese, R.S., and Rhee, P. (2015). Intracranial pressure monitor in patients with traumatic brain injury. J. Surg. Res. 194, 565–570.
35. Thompson, H.J., Kirkness, C.J., and Mitchell, P.H. (2007). Intensive care unit management of fever following traumatic brain injury. Intensive Crit. Care Nurs. 23, 91–96.
36. Tsai, M.D., Chiu, W.T., Lin, J.W., Chen, C.F., Huang, S.J., Chang, C.K., Chen, W.L., and Tsai, S.H. (2006). Current experiences in the use of the severe head–injury guidelines in Taiwan. Surg. Neurol. 66, Suppl. 2, S3–7.
37. Griesdale, D.E., Ortenwall, V., Norena, M., Wong, H., Sekhon, M.S., Kolmodin, L., Henderson, W.R., and Dodek, P. (2015). Adherence to guidelines for management of cerebral perfusion pressure and outcome in patients who have severe traumatic brain injury. J. Crit. Care 30, 111–115.
38. Krinsley, J.S. (2004). Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin. Proc. 9, 992–1000.
39. Martins, E.T., Linhares, M.N., Sousa, D.S., Schroeder, H.K., Meinerz, J., Rigo, L.A., Bertotti, M.M., Gullo, J., Hohl, A., Dal–Pizzol, F., and Walz, R. (2009). Mortality in severe traumatic brain injury: a multivariated analysis of 748 Brazilian patients from Florianopolis City. J. Trauma 67, 85–90.
40. Arabi, Y.M., Haddad, S., Tamim, H.M., Al–Dawood, A., Al–Qahtani, S., Ferayan, A., Al–Abdulmughni, I., Al–Oweis, J., and Rugaan, A. (2010). Mortality reduction after implementing a clinical practice guidelines–based management protocol for severe traumatic brain injury. J. Crit. Care 25, 190–195.

Address correspondence to:
Yahya Hadi Khormi, MD, FRCSC
Division of Neurosurgery
Department of Surgery
University of Alberta and the University of Alberta Hospital
8440 112th Street
Edmonton, Alberta T6G 2B7
Canada

E-mail: khormi@ualberta.ca;
khormins@gmail.com