Chapter 17. Antiseizure prophylaxis

I. RECOMMENDATIONS

Strength of Recommendation: Weak.

Quality of Evidence: Low, from one poor-quality class III study.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

Prophylactic treatment with phenytoin may be considered to reduce the incidence of early posttraumatic seizures (PTS) in pediatric patients with severe traumatic brain injury (TBI).

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Posttraumatic seizures are defined as occurring early, within 7 days of injury, or late, beyond 8 days of recovery (1). Risk factors associated with the occurrence of PTS include location of the lesion, cerebral contusions, retained bone and metal fragments, depressed skull fracture, focal neurologic deficits, loss of consciousness, Glasgow Coma Scale (GCS) score <10, severity of injury, length of posttraumatic amnesia, subdural or epidural hematoma, penetrating injury, chronic alcoholism, and age. Infants and children have lower seizure thresholds (2), adding to the challenge of recognition of subtle clinical seizures (3) in critically ill children.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 15 potentially relevant new studies, no new studies were used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

One class III study met the inclusion criteria for this topic and provides evidence to support the recommendation. Data from a single center retrospective cohort study of children ages 3 months to 15 yrs identified by International Classification of Diseases, 9th Revision code were reported by Lewis et al (4). This study reported a significant reduction in early PTS rate in the severe TBI cases treated with prophylactic phenytoin compared with patients with severe TBI who were not treated prophylactically (15% vs. 53%, $p = .04$, one-tailed Fisher's exact test). Limitations of this study include the small size of the severe TBI group, the decision to treat based on individual physician preference, and the absence of data on long-term outcome, phenytoin levels, or complications of anticonvulsant therapy.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

Based on data from five studies, the adult guidelines for the prevention of PTS provide a level II recommendation for the use of anticonvulsants to decrease the incidence of early PTS (3). Among these studies, three compared phenytoin with placebo, one compared phenobarbital with placebo, and one compared phenytoin with valproate. The use of either phenytoin or valproic acid as prophylaxis to reduce the incidence of late PTS is not recommended. Similar recommendations have been published elsewhere (5). There are no data to show that early PTS are associated with worse outcomes.

A prospective study by Temkin et al (6) was performed as a double-blind, placebo-controlled study to determine the effect of treatment with phenytoin on early and late PTS in 404 patients. Importantly, dosages were adjusted to maintain therapeutic levels. In the treated group, the incidence of early PTS was 3.6%, a significant reduction ($p < .001$) compared with placebo (14.2%) (risk ratio, 0.27; 95% confidence interval [CI], 0.12–0.62). Treatment with phenytoin had no effect on either late PTS or survival compared with placebo.

A randomized, double-blind trial to evaluate the effect of valproic acid on the incidence of PTS compared phenytoin with valproic acid (7). One hundred thirty-two patients were randomized to 1-wk treatment with phenytoin, 120 to 1 month of valproic acid, and 126 to 6 months of valproic acid. The rates of early PTS did not differ between treatment groups (1.5% for the phenytoin group and 4.5% for both arms of the valproic acid group) and there were also no differences in the rate of late PTS. There was a trend toward higher mortality rate in patients treated with valproic acid compared with phenytoin (13.4% vs. 7.2%, $p = .07$; risk ratio, 2.0; 95% CI, 0.9–4.1).

B. Information Not Included as Evidence

To address the question about whether prophylactic treatment reduces seizures, various questions/issues need to be considered. For example: 1) What is the incidence of PTS? 2) What is the right anticonvulsant medication? 3) What is the appropriate dose? 4) What is the risk–benefit of the drug in the context of other morbidities after TBI? 5) Can and should the drug therapy be targeted to a high-risk group?

The following studies provide information about these questions but do not constitute evidence. It is important to keep in mind that the various studies have different case definitions when discussing PTS: 0–24 hrs, 0–48 hrs, 0–7 days, or 0–2 yrs.

Frequency of posttraumatic seizures in pediatric TBI. A number of studies that report the inclusion of pediatric

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Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Study from previous guidelines			
Lewis et al, 1993 (4)	Design: retrospective cohort study N = 194; 31 with severe traumatic brain injury Age: ranged from 3 months to 15 yrs; median, 6 yrs GCS: 3–8 (31 [16%]); 9–15 (163 [84%]) Protocol: phenytoin within 24 hrs of hospital admission or no prophylactic anticonvulsant medication Purpose: to determine factors associated with early PTS Outcome: occurrence of any seizure during hospitalization	Class III Poor quality: for comparison of groups based on anticonvulsant medication use; moderate for prognostic factor analysis: control for confounders only in analysis of predictors of seizure, not for comparison of groups based on seizure prophylaxis	For children with GCS 3–8, treatment with prophylactic phenytoin was associated with a reduced rate of seizures (2 of 13 [15%]) compared with patients not treated with prophylactic medication (9 of 17 [53%]) ($p = .04$ one-tailed Fisher's; $p = .057$ two-tailed) Rate of seizures in total group of 194 was 9.3% In 14 of these 18 cases (78%), seizures occurred within 24 hrs of injury GCS of 3–8 ($p < .01$) and abnormal computed tomography ($p = .02$) associated with increased risk of early PTS Logistic regression performed to account for contribution of abnormal computed tomography, loss of consciousness, and GCS score to risk for PTS showed only association with GCS of 3–8 ($p < .001$)

GCS, Glasgow Coma Scale; PTS, posttraumatic seizures.

cases have examined the frequency of early and late PTS after severe TBI.

In a four-center study, subjects >6 yrs admitted between 1993 and 1998 with computed tomography evidence of TBI or a GCS less ≤10 24 hrs postinjury with negative computed tomography were studied to determine the natural history of later PTS in moderate and severe TBI (8). The subjects were followed for 2 yrs or until the first seizure >8 days after TBI, death, or treatment with an anticonvulsant. Among the 647 subjects, 43% were <30 yrs. Sixty-six (10%) of subjects had a late PTS, although 26% of the total were lost to follow-up. The probability of developing late PTS at 2 yrs after TBI was 13.8% (66 of 480). The majority (79%) of these seizures were generalized. The length of initial anticonvulsant prophylaxis correlated with a greater frequency of late PTS. The relative risk of seizures at 2 yrs after treatment with phenytoin on days 1–7 was 1.56 compared with 4.27 in the subjects treated up to 30 days after injury. It is possible this difference reflects differences in the severity of injury between these groups.

The incidence of late PTS was examined in two populations in Italy, a retrospective study of 55 cases and a prospective study of 82 subject all with severe TBI (9). In the retrospective group (age range, 14–62 yrs), ten patients (18%) had PTS of whom half had been treated with an anticonvulsant (phenobarbital) and half had not. In the prospective part of the study, 84% of the subjects were treated with prophylactic anticonvulsants during 2-yr follow-up and 39% experienced PTS. There were no PTS in the subjects who were not treated with an anticonvulsant. This counterintuitive finding may again reflect the clinical assessment of the need for treatment in the more severely impaired subjects.

A retrospective study from two hospitals in Turkey examined the risk factors for PTS in children <16 yrs (10). There were 149 cases of PTS (8.4%) in the 1785 patients in this series. Young age (<3 yrs), severity of injury, cerebral edema, depressed skull fracture, and hemorrhage were more common in the cases with PTS. A retrospective review of traumatic intracranial hemorrhage confirmed by computed tomography scan at three centers in Israel identified 52 cases (mean age, 50 yrs; range, 8–85 yrs) with recurrent seizures (11). Only five cases were <19 yrs, all of whom were reported as mentally handicapped. The patients with seizures or epilepsy were identified only by International Classification of Diseases, 9th Revision code and the majority of cases (44) were male. This study did not define risk factors for seizures after traumatic intracranial hemorrhage, but rather provided a description of the characteristics of patients with traumatic intracranial hemorrhage leading to recurrent seizures.

A study of 102 children aged 1.3–15.2 yrs with severe TBI, of which 85% required mechanical ventilation, all of whom received inpatient rehabilitation therapy between 1991 and 1998, examined the prevalence of posttraumatic epilepsy (12). Follow-up in this study ranged from 19 months to 7 yrs, during which nine subjects (9%) developed posttraumatic epilepsy. The interval from insult to first seizure onset ranged from 0.7 to 5.2 yrs (median, 2.9 yrs). The presence of early (within the first week post-TBI) seizures ($p = .002$) and GCS score ($p = .043$) were the only factors at the time of injury related to the development of posttraumatic epilepsy. A series of 318 children ages 1 month to 17 yrs treated between 1965 and 1991–with an average follow-up of 8 yrs, 9 months–reported early seizures in 19.8% and an incidence of late seizures of 29.6% after open head injury compared with 20.2% after closed head injury (13).

Effects of treatment with anticonvulsants. In a randomized, double-blind, placebo-controlled study of the efficacy of phenytoin in preventing late PTS in 41 patients, Young et al (14) found no difference in rate of PTS in the treated group (12%) compared with control subjects (6.2%). All seizures occurred within the first year after injury. Compliance was poor, and by 6 months,

serum levels of phenytoin were available on only 15 (60%) of the treatment group. Among this group, six subjects (40%) had a measured serum drug level of ≤10 μg/mL. Notably, no patients with a serum level >10 μg/mL had a seizure. The study is limited by the small size, poor compliance, unclear criteria for randomization, and lack of clarity over association between GCS and outcome. Sixteen (39%) of the subjects had a GCS of ≤7. Because the analysis combined severe and moderate patients, it did not meet criteria for inclusion as evidence for this topic.

In a prospective cohort study of children admitted to the pediatric intensive care units at three centers, Tilford et al (15) identified 138 cases of severe TBI among the 477 children admitted with a diagnosis of head trauma. There was a significant variation in anticonvulsant use (range, 10% to 35%) among the three centers with an overall incidence of early PTS of 9.4%. The type of anticonvulsant used was not specified. The indications for such use, either prophylaxis or in response to a clinical or electrographic seizure, were also not specified. In a stepwise logistic regression model (accounting for GCS, the participating site, other therapies), the use of an anticonvulsant medication was associated with a significant reduction in risk of mortality ($p = .014$; odds ratio, 0.17; 95% CI, 0.04–0.70), but the analysis was not limited to patients in the severe TBI group.

A study by Young et al (16) reported no reduction in the rate of PTS within 48 hrs of injury in a randomized, double-blind, placebo-controlled trial of phenytoin in children with moderate to severe blunt head injury. Children <16 yrs with a GCS of ≤9 (<4 yrs) or ≤10 (>4 yrs) were enrolled by deferred consent within 40 mins of presentation to the emergency department and drug or placebo administered within 60 mins of presentation. Phenytoin dose was 18 mg/kg followed by 2 mg/kg every 8 hrs for the 48 hrs of the study. Subjects were stratified by age and GCS. One hundred three subjects were randomized with 33% lost at 48-hr follow-up and 36% lost at 30-day follow-up. In the phenytoin-treated group, three patients (7%) had a seizure during the 48-hr observation period compared with three (5%) in the placebo group. Six patients (one phenytoin, five placebo) had an electroencephalogram performed. None showed nonconvulsive seizures. Over 30 days recovery, there was no difference in mortality in the treatment group (20% [six of 30]) compared with placebo (39% [14 of 36]). The major limitations of this study are the low seizure rate and the small sample size resulting from early loss of subjects and decrease in enrollment after ceasing to waive consent.

A study of 318 cases of severe TBI from a single center in Germany with mean follow-up of 8 yrs, 9 months identified 68 cases (21%) of late seizures with a mean latency of 2 yrs, 5 months (17). Approximately half of these cases were resistant to anticonvulsant therapy, although the details of therapy are not given. The children with PTS had a worse outcome in this series with 60% having disabilities compared with 17% in the other patients.

In a single-center, prospective study during the war in Bosnia, 310 patients between 0 and 18 yrs with severe TBI were treated with either intravenous phenytoin or phenobarbital, depending on the availability of each drug (18). The primary outcome was the frequency of seizure in the first 24 hrs after admission. This was low, occurring only in two cases (0.64%). Although the criteria for classification of cases as severe are not specified, skull fracture was present in 85% of cases. The frequency of seizures is low and there is no detail on the process for monitoring for seizures, suggesting this may be an underestimate.

Pharmacokinetic considerations. TBI results in an increase in hepatic metabolism and decrease in protein binding of drugs including anticonvulsants (19), resulting in an increase in plasma clearance. The free fraction of phenytoin is elevated (20). The altered pharmacokinetics of phenytoin and other drugs may result in levels considered to be subtherapeutic. As part of a clinical trial evaluating the use of valproic acid for prophylaxis of posttraumatic seizures, the time-dependent effects of TBI on the pharmacokinetics of total and unbound valproic acid were evaluated (21). In the trial, 158 adult TBI cases (mean age, 36 yrs; mean GCS, 10; range, 3–15) were treated with a loading dose of valproic acid (20 mg/kg) followed by a maintenance dose. TBI resulted in an average 75% increase in drug clearance by 2 and 3 wks of recovery, which was associated with increased TBI severity, lower albumin concentration, tube feeding, and the presence of ethanol on admission. In general, there are limited data (22) on the effect of early age, genetic factors, and other drug interactions affecting pharmacokinetics of anticonvulsants after TBI and the contribution of these factors to neurologic outcomes.

Mechanisms of epileptogenesis relevant to pediatric TBI. Studies of the mechanisms of posttraumatic epilepsy traditionally were limited by the lack of animal models; however, recent studies have begun to focus on PTS in developing animals after experimental TBI (23–25). A number of mechanisms of posttraumatic epilepsy have been investigated; many focused on pathophysiological changes in the hippocampus including axonal sprouting, impaired K+ buffering by glia, saturation of synaptic long-term potentiation of Schaffer collaterals, hilar neuron loss, and activation of hippocampal TrkB-ERK1/2-CREB/ELK-1 pathways (23, 26). Recent studies have suggested a role for albumin-induced changes in the electrophysiological properties of astrocytes mediated by the transforming growth factor-β receptor and leading to accumulation of extracellular potassium (27, 28).

VII. SUMMARY

The incidence of early PTS in pediatric patients with TBI is approximately 10% given the limitations of the available data. Based on a single class III study (4), prophylactic anticonvulsant therapy with phenytoin may be considered to reduce the incidence of early posttraumatic seizures in pediatric patients with severe TBI. Concomitant monitoring of drug levels is appropriate given the potential alterations in drug metabolism described in the context of TBI. Stronger class II evidence is available supporting the use of prophylactic anticonvulsant treatment to reduce the risk of early PTS in adults. There are no compelling data in the pediatric TBI literature to show that such treatment reduces the long-term risk of PTS or improves long-term neurologic outcome.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Investigation of the frequency of early PTS in the setting of contemporary

management and their association with acute pathophysiology and long-term neurologic sequelae.
- Investigation of the efficacy, safety, and drug levels required for the prevention of early posttraumatic seizures.
- Investigation of the efficacy and safety of new anticonvulsants for the treatment of early and late posttraumatic seizures.
- Identification of neuroimaging, electroencephalography, or serum biomarkers, which serve to predict patients at increased risk for late posttraumatic seizures.
- Elucidation of the mechanisms of epileptogenesis after TBI and identification of new therapeutic targets based on understanding these mechanisms.
- Improvement in the classification of early and late seizures, including the use of electroencephalography, to detect and classify posttraumatic seizures.
- Evaluation of the effect of TBI on changes in dosage requirements for anticonvulsant drugs and the contribution of age and genetically determined differences in hepatic and renal drug metabolism to the efficacy of anticonvulsants in the treatment of posttraumatic seizures.

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APPENDIX A

Publications from the First Edition Not Included in the Second Edition

Topic	Reference	Reason(s) for Exclusion
Indications for ICP monitoring	Cho, 1995	Data not relevant to this topic
	Taylor, 2001	GCS range exceeds 8 with no separate analysis of severe
	Sharples part I, 1995	No direct correlation between ICP and outcome
	Eder, 2000	Retrospective, N = 21
	Peterson, 2000	Treatment study about effect of hypertonic saline on ICP
ICP thresholds	Cho, 1995	Data not relevant to this topic
	Shapiro and Marmarou, 1982	Data not relevant to this topic
	Sharples part I, 1995	No direct correlation between ICP and outcome
Cerebral perfusion pressure thresholds	Elias-Jones, 1992	GCS range exceeds 8 with no separate analysis of severe
	Sharples part III, 1995	No association between ICP/CPP and outcome
Hyperosmolar therapy	James, 1980	Mean age 42 yrs, with no separate analysis of pediatric patients
	Miller, 1993	4 of 16 patients are children and relevant data are not provided by age
	Khanna, 2000	Prospective cohort, N = 10
Temperature control	Gruszkiewicz, 1973	Randomized controlled trial, N = 20
Decompressive craniectomy	Polin, 1997	Average age 18.7 ± 12.6 yrs with no separate analysis of pediatric patients
	Taylor, 2001	GCS range >8 with no separate analysis of severe
Hyperventilation	Stringer, 1993	Case series, N = 3
Corticosteroids	Gobiet, 1977, Advances in . . .	GCS not reported
	Gobiet, 1977, Monitoring of . . .	Sample includes adults with no separate analysis of pediatric patients
	Hoppe, 1981	No comparison group
	Kretschmer, 1983	27% penetrating brain injury without separate analysis
	James, 1979	Retrospective, N = 9
	Cooper, 1979	Prospective cohort, N = 10
Analgesics, sedatives, and neuromuscular blockade	Vernon and Witte, 2000	Includes patients with pathologies other than traumatic brain injury without separate analysis
Glucose and nutrition	Phillips, 1987	No analysis of association between any nutritional parameter and any clinical outcome
	Moore, 1989	Age range is 3–67 yrs with no separate analysis of pediatric patients
Antiseizure prophylaxis	Tilford, 2001	Does not analyze the effect of anticonvulsants within the severe group
	Young, 1983	GCS range >8 with no separate analysis of severe

ICP, intracranial pressure; GCS, Glasgow Coma Scale; CPP, cerebral perfusion pressure.

APPENDIX B

Literature Search Strategies

Indications for Intracerebral Pressure Monitoring

Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 head injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 brain Injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 intracranial pressure.mp. or Exp Intracranial Pressure/
6 intracranial hypertension.mp. or exp Intracranial Hypertension/
7 5 or 6
8 4 and 7
9 Limit 8 to "all Child (0 to 18 Yrs)"
10 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.
11 10 and 9

Intracerebral Pressure Thresholds

Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 head injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 brain injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 intracranial pressure.mp. or exp Intracranial Pressure/
6 intracranial hypertension.mp. or exp Intracranial Hypertension/
7 5 or 6
8 4 and 7
9 limit 8 to "all child (0 to 18 yrs)"
10 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.
11 10 and 9

Cerebral Perfusion Pressure Thresholds

Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 head injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 brain injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 cerebral perfusion pressure.mp.
6 cerebrovascular circulation/and blood pressure/
7 5 or 6
8 4 and 7
9 Limit 8 to "all child (0 to 18 Yrs)"
10 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.
11 10 and 9

Advanced Neuromonitoring

Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

1 Exp Craniocerebral Trauma/
2 ((head or brain$ or cereb$ or cerebell$) adj3 (wound$ or traum$ or injur$ or damag$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 1 or 2
4 exp Monitoring, Physiologic/
5 exp Intensive Care Units/or Exp Intensive Care/
6 4 and 3 and 5
7 exp Oxygen/bl, an [Blood, Analysis]
8 licox.mp.
9 pbto2.mp.
10 ((oxygen$ or o2 or hypoxi$) adj3 (concentrat$ or level$ or monitor$ or pressur$)).mp.
11 exp Oximetry/
12 8 or 11 or 7 or 10 or 9
13 ((transcrani$ adj3 (doppler or ultrasono$)) or tcd).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
14 ((near infrared adj3 spectrosc$) or nirs).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
15 exp Phosphopyruvate Hydratase/
16 exp Nervous System/
17 exp Nervous System Diseases/
18 17 or 16
19 18 and 15
20 neuron specific enolase$.mp.
21 nse.mp.
22 21 or 20 or 19
23 exp S100 Proteins/
24 (s100b or S100 β).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
25 24 or 23
26 exp Myelin Basic Proteins/
27 (Myelin basic protein$ or mbp).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
28 26 or 27
29 glutamat$.mp.
30 xenon.mp. or exp Xenon/
31 ((brain$ or cereb$ or cerebell$) adj5 ((interstitial$ or extracellul$) adj3 (fluid$ or space$))).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
32 exp Extracellular Space/or exp Extracellular Fluid/
33 exp Brain/
34 32 and 33
35 34 or 31
36 microdialysis.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
37 exp Biological Markers/
38 (biomarker$ or biological marker$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
39 37 or 38
40 3 and 5
41 40 and 12
42 13 and 40
43 14 and 40
44 22 and 40
45 25 and 40
46 28 and 40
47 29 and 40
48 30 and 40
49 35 and 40
50 36 and 40
51 39 and 40
52 50 or 51 or 41 or 48 or 47 or 42 or 49 or 46 or 45 or 43 or 44
53 52 or 6 (333)
54 limit 53 to "all child (0 to 18 yrs)"
55 limit 54 to English language

Neuroimaging

Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 ((head or brain$ or cereb$ or cerebell$) adj3 (wound$ or traum$ or

injur$ or damag$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 1 or 2
4 exp Tomography, X-Ray Computed/
5 exp Magnetic Resonance Imaging/
6 ((t2 or t1 or diffusion or susceptibility) adj weight$ adj3 imag$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
7 exp Magnetic Resonance Spectroscopy/
8 (magnetic$ adj resonan$ adj2 spectroscop$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
9 8 or 7
10 apparent diffusion coefficient$.mp.
11 exp Tomography, Emission-Computed/
12 (positron$ adj emission$ adj2 spectroscop$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
13 (positron$ adj emission$ adj3 tomogra$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
14 pet scan$.mp.
15 11 or 13 or 12 or 14
16 6 or 4 or 10 or 9 or 15 or 5
17 3 and 16
18 Limit 17 to (English Language and Humans)
19 Limit 18 to "all child (0 to 18 yrs)"
20 exp Intensive Care Units/or exp Intensive Care/
21 ((intensiv$ or critical$) adj2 (care or cared or caring or treat$ or therap$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
22 (icu or ccu).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
23 22 or 21 or 20
24 23 and 19
25 exp Emergency Treatment/
26 exp Emergency Service, Hospital/
27 25 or 26
28 27 and 19
29 28 or 24

Hyperosmolar Therapy
Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 head injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 brain injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 hyperosmolar therapy.mp.
6 hyperosmolar treatment.mp.
7 fluid therapy.mp. or exp Fluid Therapy/
8 Saline Solution, Hypertonic/
9 Osmolar Concentration/
10 5 or 6 or 7 or 8 or 9
11 4 and 10
12 limit 11 to (English language and humans)
13 limit 12 to "all child (0 to 18 yrs)"
14 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.
15 13 and 14

Temperature Control
Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 head injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 brain injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 Hypothermia, Induced/
6 4 and 5
7 limit 6 to "all child (0 to 18 yrs)"
8 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.
9 8 and 7

Line Search

1 Exp Craniocerebral Trauma/
2 ((brain$ or cereb$ or cerebell$ or head) adj3 (traum$ or damag$ or injur$ or wound$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier]
3 1 or 2
4 exp Fever/
5 Fever$.mp.
6 4 or 5
7 3 and 6
8 limit 7 to "all child (0 to 18 yrs)"
9 limit 8 to English language
10 hypertherm$.mp.
11 1 and 10
12 limit 11 to "all child (0 to 18 yrs)"
13 limit 12 to English language
14 9 or 13

Cerebrospinal Fluid Drainage
Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 head injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 brain injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 lumbar drain$.mp.
6 lumbar shunt$.mp.
7 exp Cerebrospinal Fluid Shunts/
8 *Drainage/
9 5 or 6 or 7 or 8
10 4 and 9
11 limit 10 to "all child (0 to 18 yrs)"
12 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.

Decompressive Craniotomy
Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 head injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 brain injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 intracranial hypertension.mp. or Exp Intracranial Hypertension/
6 4 and 5
7 limit 6 to "all child (0 to 18 yrs)"
8 limit 7 to English language
9 su.fs.
10 drain$.mp.
11 cerebrospinal fluid shunts.mp. or exp Cerebrospinal Fluid Shunts/
12 neurosurgery.mp. Or Neurosurgery/
13 shunt$.mp.
14 9 or 10 or 11 or 12 or 13

15 8 and 14
16 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.
17 16 and 15

Hyperventilation
Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 exp ISCHEMIA/
3 exp Jugular Veins/
4 exp Regional Blood Flow/
5 exp PERFUSION/
6 Exp HYPERVENTILATION/
7 2 or 3 or 4 or 5 or 6
8 1 and 7
9 limit 8 to "all child (0 to 18 yrs)"
10 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.

Corticosteroids
Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 head injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 brain injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 exp Steroids/or steroids.mp.
6 synthetic glucocorticoids.mp.
7 5 or 6
8 4 and 7
9 limit 8 to "all child (0 to 18 yrs)"
10 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.
11 10 and 9

Analgesics, Sedatives, and Neuromuscular Blockade
Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

1 exp Analgesics/
2 exp "Hypnotics and Sedatives"/
3 propofol.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 exp phenothiazines/
5 exp central nervous system depressants/
6 1 or 2 or 4 or 5
7 exp Craniocerebral Trauma/
8 6 and 7
9 Limit 8 to (English language and humans)
10 limit 9 to "all child (0 to 18 yrs)"

Glucose and Nutrition
Database: Ovid Medline <1950 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 ((head or brain$ or cereb$ or cerebell$) adj3 (wound$ or traum$ or injur$ or damag$)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 1 or 2
4 exp Glucose/
5 exp hyperglycemia/or exp hypoglycemia/
6 exp Insulin/
7 exp diet/
8 exp Nutrition Therapy/
9 exp nutritional status/
10 exp nutritional requirements/
11 exp Enteral Nutrition/
12 exp Intubation, Gastrointestinal/
13 exp Feeding Methods/
14 exp Gastrostomy/
15 exp Energy Metabolism/
16 Exp Energy Intake/
17 harris-benedict equation.mp.
18 exp Nutritional Requirements/
19 intralipid.mp. or exp Fat Emulsions, Intravenous/
20 (metaboli$ adj3 (cart or carts)).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
21 4 and 3
22 3 and 5
23 6 and 3
24 3 and 7
25 3 and 8
26 3 and 9
27 3 and 10
28 3 and 11
29 12 and 3
30 3 and 13
31 3 and 14
32 15 and 3
33 3 and 16
34 3 and 17
35 3 and 18
36 3 and 19
37 3 and 20
38 24 or 25 or 26 or 27 or 35 or 33 or 36 or 29 or 34 or 21 or 28 or 30 or 22 or 32 or 23 or 31 or 37
39 limit 38 to English language
40 limit 39 to humans
41 limit 40 to "all child (0 to 18 yrs)"

Antiseizure Prophylaxis
Database: Ovid Medline <1996 to 2010>
Search Strategy

Line Search

1 exp Craniocerebral Trauma/
2 head injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3 brain injur$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4 1 or 2 or 3
5 exp Seizures/or Seizures.mp.
6 exp Epilepsy/
7 exp convulsions/or convulsions.mp.
8 5 or 6 or 7
9 4 and 8
10 limit 9 to "all child (0 to 18 yrs)"
11 exp seizures/dt, pc or exp epilepsy/dt, pc or convulsions/dt, pc
12 4 and 11
13 limit 12 to "all child (0 to 18 yrs)"
14 exp Clinical Trials as Topic/
15 Exp Practice Guidelines as Topic/or practice guidelines.mp.
16 14 or 15
17 10 and 16
18 13 or 17
19 (2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.
20 18 and 19

APPENDIX C

Literature Search Yield

Topic	Search Results	Abstracts Read	Publications Read	Included First Edition Studies	Included New Studies
Indications for intracranial pressure monitoring	756	422	35	9	7
Intracranial pressure treatment threshold	756	422	60	6	5
Cerebral perfusion pressure thresholds	219	161	78	3	8
Advanced neuromonitoring	121	74	44	N/A	2
Neuroimaging	344	161	89	N/A	1
Hyperosmolar therapy	213	31	9	3	0
Temperature control	228	53	17	2	2
Cerebrospinal fluid drainage	136	32	6	3	1
Barbiturates	212	87	47	2	0
Decompressive craniectomy	160	83	18	1	7
Hyperventilation	295	141	16	1	1
Steroids	138	20	19	2	0
Analgesics, sedatives Neuromuscular blockade	699	121	44	0	2
Nutrition	593	182	113	0	1
Antiseizure prophylaxis	68	17	10	1	0

N/A, not applicable.

APPENDIX D

Mixed Patient Samples

Criteria for including a study in which the sample includes patients with TBI and patients with other pathologies, or pediatric and adult patients

If:

- the sample for a study includes patients with TBI as well as patients with other pathologies, pediatric as well as adult patients, or mild/moderate as well as patients with severe TBI,
- and the data are not reported separately,
- and there is an effect of the study,

then it cannot be known if the effect existed for the TBI group or if it was large in the non-TBI group and small in the TBI group. Similarly, it cannot be known if the effect existed for the pediatric group or if it was large in the adult group and small in the pediatric group. Therefore, we cannot know with confidence that the intervention had an effect for TBI in pediatric patients.

We have established the following criteria to minimize the uncertainty when including publications with mixed samples:

1. Sample size must be ≥25 patients.
2. ≥85% of the patients must have severe TBI.
3. ≥85% of the patients must be ≤18 yrs of age.
4. Such a study could never be used to support a level I recommendation.
5. Such a study can only support a level II or III recommendation. It cannot be used to support a level II recommendation if it is the only class II study available.
6. If a publication mixes the results of pediatric patients with those of adults, and the mean and standard deviation for age are provided, the mean and standard deviation can be used to calculate the proportion of pediatric patients, and if the proportion is ≥85%, the study can be used as evidence.
7. If the study does not report the percent of patients with TBI, it cannot be used as evidence at any level.

APPENDIX E

Evidence Table Template

Source	Study Design	Setting/Population	Sample	Intervention	Cointerventions	Confounding Variables
Length of Follow-Up	Measures	Analysis	Results		Caveats	Level of Evidence