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REVIEW CLINICAL STUDIES

Pediatric Moderate and Severe Traumatic Brain Injury: A Systematic Review of Clinical Practice Guideline Recommendations

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Abstract

Traumatic brain injury (TBI) is the leading cause of death and disability in children. Many clinical practice guidelines (CPGs) have addressed pediatric TBI in the last decade but significant variability in the use of these guidelines persists. Here, we systematically review CPGs recommendations for pediatric moderate-to-severe TBI, evaluate the quality of CPGs, synthesize the quality of evidence and strength of included recommendations, and identify knowledge gaps. A systematic search was conducted in MEDLINE®, Embase, Cochrane CENTRAL, Web of Science, and Web sites of organizations publishing recommendations on pediatric injury care. We included CPGs developed in high-income countries from January 2012 to May 2023, with at least one recommendation targeting pediatric (≤ 19 years old) moderate-to-severe TBI populations. The quality of included clinical practice guidelines was assessed using the AGREE II tool. We synthesized evidence on recommendations using a matrix based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. We identified 15 CPGs of which 9 were rated moderate to high quality using AGREE II. We identified 90 recommendations, of which 40 (45%) were evidence based. Eleven of these were based on moderate to high quality evidence and were graded as moderate or strong by at least one guideline. These included transfer, imaging, intracranial pressure control, and discharge advice. We identified gaps in evidence-based recommendations for red blood cell transfusion, plasma and platelet transfusion, thromboprophylaxis, surgical antimicrobial prophylaxis, early diagnosis of hypopituitarism, and mental health mangement. Many up-to-date CPGs are available, but

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there is a paucity of evidence to support recommendations, highlighting the urgent need for robust clinical research in this vulnerable population. Our results may be used by clinicians to identify recommendations based on the highest level of evidence, by healthcare administrators to inform guideline implementation in clinical settings, by researchers to identify areas where robust evidence is needed, and by guideline writing groups to inform the updating of existing guidelines or the development of new ones.

Keywords: clinical paractice guidelines; neurology; pediatrics; systematic review; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children in the United States,[1] with 16,070 TBI-related hospitalizations and 2774 TBI-related deaths reported in 2019 and 2020 in children and adolescents <18 years old.[2] Hospital charges for pediatric TBI accounted for more than one billion dollars in 2006[3] and are probably much higher now.

In the last decade, many clinical practice guidelines (CPGs) have been published specifically addressing pediatric TBI.[4–8] Despite the fact that adherence to evidence-based CPGs in pediatric TBI has been shown to reduce mortality with possibly a favorable impact on hospital length of stay and functional outcomes[9] and no increase in hospital costs,[10] significant variability in the use and implementation of pediatric TBI guidelines persists.[11,12] Difficulty integrating information from multiple CPGs with heterogeneous development methods may explain some of this variability.

Three systematic reviews have analyzed the quality of pediatric and/or adult TBI guidelines,[13–15] another has reviewed pre-hospital recommendations,[16] and a fifth reviewed CPGs for concussion in both adults and children.[17] However, none of these reviews focused on recommendations for moderate-to-severe pediatric TBI, associated with the greatest mortality and morbidity.[13–17] A synthesis of recommendations and supporting evidence in pediatric TBI may increase adherence to evidence-based care and could identify gaps to guide future research.

We aimed to systematically review CPG recommendations for pediatric moderate-to-severe TBI. Specific objectives were to evaluate the quality of CPGs, synthesize the quality of evidence and strength of included recommendations, and identify knowledge gaps.

Methods

This review is part of a series of systematic reviews of CPG recommendations for pediatric injury care; detailed methodology was published previously.[18] The protocol was registered on International Prospective Register of Systematic Reviews (PROSPERO #CRD42021226934).[18] We followed methodological guidelines for systematic reviews of CPGs[19] and Cochrane guidelines.[20] Results are reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA 2020) statement.[21] This review was designed and conducted with a multidisciplinary advisory committee including emergency department physicians, critical care physicians, a neurosurgeon, trauma surgeons, a neuropsychologist, a physiotherapist, a trauma program manager with training as a nurse practitioner, a pharmacist, and methodological specialists in evidence synthesis. Members of the advisory committee are researchers and clinicians from five Canadian provinces, the United Kingdom, and Australia with recognized expertise in pediatric and injury research. They were recruited prior to the development of our study protocol and were involved in all stages of this review.

Eligibility

We included CPGs containing at least one recommendation targeting pediatric (≤ 19 years old) moderate-to-severe TBI (Glasgow Coma Scale [GCS] 3–12) populations on any diagnostic or therapeutic intervention during the acute phase of care developed in high-income countries during the last 10 years. CPGs are defined as ''statements that include recommendations intended to optimise patient care that are informed by systematic review of evidence and an assessment of benefits and harms of alternative care options.''[22] Acute care refers to emergency department (ED) or inpatient care treatment received immediately after the onset of injury.[23] Country income levels were defined using the latest World Bank country classifications.[24] We restricted our review to CPGs published since 2012, because those published >10 years ago were considered unlikely to represent current evidence. CPGs that target TBI care for mixed populations (adults and children) were considered if they include at least one recommendation specific to children. No language restrictions were applied, and CPGs were translated to English when necessary. Publications describing the implementation of CPGs or adherence to TBI recommendations were used to identify any additional CPGs but were not included. We did not include CPGs specifically targeting child protection, as a high-quality systematic review had been recently published on the subject.[25] Mild TBI, with distinct management strategies from moderate-to-severe TBI, will be covered in a separate review.

Search strategy

We conducted our search using MEDLINE®, Embase, Cochrane CENTRAL, and Web of Science from January 2012, to May 2023. A list of Web sites of organizations publishing recommendations on pediatric injury care was established with the help of our advisory committee (Table S1) and searched for any additional CPGs. Members of our advisory committee were also consulted for any additional CPGs that were not identified by our search strategy.

We developed our search strategy with an information specialist using the 2015 Peer Review of Electronic Search Strategies (PRESS) statement (Table S2).[26] Keywords covering combinations of search terms under the themes of pediatrics, injury, and clinical practice guidelines as well as MeSH (MEDLINE) or Emtree (Embase) terms, when appropriate, were used.

Study selection

EndNote (version X9.3.3, Thomson Reuters, New York, NY, 2018) software was used for the management of citations. Titles and abstracts were independently assessed by pairs of reviewers for eligibility, and full texts were subsequently reviewed to determine suitability for final inclusion. Reasons for exclusion were documented. If more than one version of a CPG was identified, only the most recent version was included. For each CPG, supporting documents (e.g., methodological details, systematic review results) were independently retrieved by two reviewers.

Data extraction

First, we developed and pilot tested a standard electronic data abstraction form. Second, pairs of reviewers with methodological and content expertise independently extracted the following data from eligible CPGs: first author, title, country of origin, organization, target users, patient population, and focus. Third, for CPGs rated as being of moderate to high quality (described in the next section), we extracted eligible recommendations and information on associated quality of evidence and strength of recommendations.

Quality

The quality of included CPGs was assessed independently by two reviewers using the AGREE II tool, which is validated and recommended by the Cochrane group.[27] AGREE II comprises 23 items divided into six domains: (1) scope and purpose (objectives, health questions, and population to whom the CPG described applies specifically), (2) stakeholder involvement (development group includes all relevant professionals, views of target population [e.g. patients, public] sought, target users clearly defined), (3) rigor of development (systematic methods used to search for evidence; criteria for selecting evidence, strengths, and limitations of body of evidence, methods for formulating recommendations clearly described; health benefits, side effects, and risks considered; explicit link between evidence and recommendations; external review by experts; process for updating the CPG provided), (4) clarity of presentation (recommendations specific and unambiguous, different management options clearly presented, key recommendations easily identifiable), (5) applicability (barriers to and facilitators of application described, advice and/or tools for implementation provided, potential resource implications considered, monitoring/auditing criteria presented), and (6) editorial independence (views of the funding body did not influence the content, competing interests reported and addressed).[27]

We used recently published guidelines on conducting systematic reviews of CPGs to assess the overall quality of the guidelines (high, moderate, or low).[19] CPGs were considered of high quality if they scored ≥60% in at least three of six AGREE II domains, including domain 3 (rigor of development). If three domains or more scored ≥60%, and domain 3 (rigor of development) scored <60%, the CPG was considered of moderate quality. CPGs scoring <60% in two or more domains and scoring <50% in domain 3 were considered of low quality.[19]

Synthesis of recommendations

We synthesized evidence on recommendations from CPGs that were rated as being of moderate or high quality according to the AGREE II tool using a matrix based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence-to-Decision framework. The matrix, developed *a priori* with advisory committee members, includes the following elements: quality of evidence, strength of recommendation, and an indication of whether the recommendation appears in multiple eligible CPGs. CPGs used different methods to rate the quality of evidence and strength of recommendations. To facilitate comparisons across CPGs, we developed a unified grading system based on the GRADE method[28,29] in consultation with our advisory committee (Table S3). Original ratings of the quality of evidence and strength of evidence were thus matched to GRADE categories; very low, low, moderate, and high for the former and weak, moderate, and strong for the latter. For quality of evidence, we added the rating ''consensus'' for recommendations uniquely based on expert consensus.

We identified the following key areas of management to classify recommendations: stabilization, consultation, and transfer; neuroimaging (initial and repeat); neuromonitoring; interventions (hyperosmolar therapy, seizure prophylaxis, thromboprophylaxis, barbiturates, corticosteroids, mechanical ventilation, temperature management, red blood cell transfusion, plasma and platelet transfusion, antifibrinolytic agents, vasoactive/inotropic

drugs, neurosurgical interventions, surgical antimicrobial prophylaxis, pain management, nutrition, and early diagnosis of hypopituitarism); mental health management; discharge planning; and patient and family support.

The recommendations matrix was piloted on a random sample of CPG recommendations until acceptable agreement ($\kappa \geq 0.8$) was obtained. Discrepancies in all phases of the review were resolved by discussion with a senior member of the research team followed by consensus among members of the project advisory committee, when necessary.

Protocol deviations

We initially planned to use the AGREE Recommendations Excellence (AGREE-REX) instrument[30] to evaluate the clinical applicability and implementability of guidelines. The advisory committee considered AGREE-REX to be more appropriate in the situation in which the goal was to adapt guidelines to a specific context. The AGREE II tool was therefore considered sufficient to assess the quality of included CPGs.[19] We also intended to include all CPGs published in the previous 15 years.[18] However, after identifying CPGs published in the past 10 years, we concluded that those published earlier without a recent update were no longer relevant because of recent therapeutic and surgical advances in the management of moderate-to-severe TBI.

Results

Characteristics of CPGs

Overall, 31,820 records were retrieved from databases and 95 were retrieved from Web sites of relevant healthcare organizations (Fig. S1). Thereafter, 483 reports were assessed for eligibility, of which 311 dealt with other types of injuries and 146 were not full guidelines (i.e., did not correspond to our definition of a CPG). A total of 26 CPGs included at least one recommendation on the management of pediatric TBI regardless of severity. Of these, two were excluded because they were limited to child protection,[31,32] one was a duplicate of another CPG,[33] seven focused on mild TBI only,[4,5,8,34–37] and one CPG remained inaccessible despite several attempts to contact the authors.[38] Ultimately, 15 CPGs were included in this review. A list of articles excluded at the full text stage is given in the Supplementary References 1.

Included CPGs were developed in the United States,[7,39–42], Italy,[6,43,44] France,[45,46] the United Kingdom,[47] and Germany[48] (Table 1). Three CPGs were published by organizations representing multiple countries.[49–51] Nine (60%) CPGs had been published in the previous 5 years. The oldest CPG was the American College of Surgeons guideline published in 2015.[39] The development groups were professional associations,[39,40] scientific groups/societies,[6,7,43–46,48–51] national institutes,[47] and children's hospitals.[41,42] The target users were physicians and other healthcare professionals. Six CPGs did not report the target population.[41,42,45,46,48,51] Patients and their families were involved in the development of recommendations for three (20%) CPGs.[43,47,49] Eleven (73%) CPGs focused only on pediatric populations[6,7,40–44,48–51] and four (27%) contained recommendations for both adults and children.[39,45–47] The definition of the pediatric population in terms of age was highly variable among CPGs: ≤18 years of age,[7] <18 years of age,[42,43,50] from 2 to 18 years of age,[41] ≤ 16 years of age,[6] and <16 years of age.[47] For eight CPGs, the target age was not defined.[39,40,44–46,49,51,52] Eight CPGs focused on severe TBI,[7,41,43–46,48,49] two focused on moderate-to-severe TBI,[50,51] and five focused on mild, moderate, or severe TBI.[6,39,40,42,47]

The identified CPGs focused on stabilization, consultation, and transfer;[6,39,46,47,49] neuroimaging;[6,7,40–43,46,47] neuromonitoring;[7,39,41,43,46] interventions;[6,7,39,41,43–48,50,51] discharge planning;[6,47] and patient and family support[47] (Table 1).

Quality appraisal of CPGs using AGREE II

Six CPGs were rated as high quality,[7,40,45,47,49,50] three as moderate quality,[6,44,51] and six as low quality[39,41–43,46,48] (Table 2). For low-quality CPGs, almost all domains, but particularly rigor of development, were rated <50%. These CPGs rarely specified the criteria for selecting the evidence, described the strengths and limitations of the body of evidence, submitted the CPG for external review, or provided a procedure for updating the CPG. For moderate-quality CPGs, rigor of development was rated >50% but <60%, mainly because they lacked details regarding the criteria for selecting the evidence and a description of its strengths and limitations. In addition, these CPGs were not externally reviewed by experts prior to publication and no update procedure was provided. For high-quality CPGs, scope and purpose, rigor of development, and clarity of presentation were rated high (≥60%), but stakeholder involvement and applicability were rated <50% for four out of six CPGs. This was mainly because the views and preferences of patients and families were not considered; the definition of target users was unclear; facilitators, barriers, and resource implications were not addressed; or implementation tools were not provided.

CPG recommendations

Methods used to grade the quality of evidence and the strength of recommendations were highly variable among CPGs (Table S3). The GRADE method was adopted for two CPGs.[45,49] One CPG used the Research and Development Corporation (RAND)/University of California, Los Angeles (UCLA) appropriateness method.[44] Three CPGs combined the GRADE approach and the

Table 1. Characteristics of Included Clinical Practice Guidelines

Title, year	*Country*	*Organization*	*Target users*	*Patient population*	*Focus*
Head injury: assessment and early management, 2023[47]	United Kingdom	National Institute of Health and Care Excellence (NICE)	Healthcare professionals, patients, their families, and carers	Adults and children (<16 years) with mild, moderate, or severe TBI	Pre-hospital management, stabilization, consultation and transfer, neuroimaging, interventions, discharge planning, and patient and family support
Plasma and platelet transfusion strategies in critically ill children following severe trauma, traumatic brain injury, and/or intracranial hemorrhage, 2022[50]	International	The Transfusion and Anemia EXpertise Initiative-Control/Avoidance of Bleeding (TAXI-CAB)	Pediatric intensivists	Children (<18 years) with moderate or severe TBI or other critical conditions	Plasma and platelet transfusions
Surgical antimicrobial prophylaxis in neonates and children undergoing neurosurgery, 2022[44]	Italy	Peri-Operative Prophylaxis in Neonatal and Paediatric Age (POP-NeoPed) Study Group	Clinicians	Children undergoing neurosurgery (severe TBI or other major neurological disorders)	Surgical antimicrobial prophylaxis
Closed head injuries presenting to the emergency center within 24 hours, 2022[42]	USA	Texas Childrens Hospital	Unclear	Children (<18 years) with mild, moderate, or severe TBI	Neuroimaging
The management of pediatric severe TBI: Italian guidelines, 2021[43]	Italy	Italian scientific societies	Physicians	Children (<18 years) with severe TBI (GCS 3-8)	Neuroimaging, neuromonitoring and interventions
European Resuscitation Council guidelines 2021: paediatric life support, 2021[49]	Europe	European Resuscitation Council (ERC)	Lay persons, first aiders, healthcare professionals, paramedics, and decision makers	Children, before, during and after cardiac arrest (including children with severe TBI)	Pediatric life support
ACR appropriateness criteria head trauma-child, 2020[40]	USA	American College of Radiology (ACR)	Radiologists, radiation oncologists, and referring physicians	Children with mild, moderate, or severe TBI	Neuroimaging
Guidelines for the management of pediatric severe traumatic brain injury, third edition, 2019[7]	USA	Brain Trauma Foundation (BTF)	Clinicians	Children (≤18 years) with severe TBI (GCS <9)	Neuroimaging, neuromonitoring, and interventions
Severe traumatic brain injuries – evidence-based guideline, 2019[41]	USA	Texas Childrens Hospital	Unclear	Children (2-18 years) with severe TBI (GCS <8)	Neuroimaging, neuromonitoring, and interventions
Italian guidelines on the assessment and management of pediatric head injury in the emergency department, 2018[6]	Italy	Italian Society of Pediatric Emergency Medicine (ISPEM)	Pediatric and adult physicians who care for children	Children (≤16 years) with mild, moderate, or severe TBI	Stabilization, consultation and transfer, neuroimaging, interventions, and discharge planning
Management of severe traumatic brain injury (first 24 hours), 2018[46]	France	French scientific societies	Unclear	Adults and children with severe TBI (GCS <9)	Pre-hospital management, stabilization, consultation, and transfer, neuroimaging, neuromonitoring, and interventions
Recommendations on RBC transfusion in critically ill children with acute brain injury, 2018[51]	International	Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI)	Unclear	Children with moderate or severe TBI	Red blood cell transfusion
Recommendations on temperature management after cardiopulmonary arrest and severe traumatic brain injury in childhood beyond the neonatal period, 2017[48]	Germany	Society for Neonatology and Pediatric Intensive Care Medicine (SNPICM) and the scientific Working Group for Pediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care (GSAIC)	Unclear	Children with severe TBI (GCS <9) or cardiopulmonary arrest	Temperature management
Targeted temperature management in the ICU: guidelines from a French expert panel, 2017[45]	France	The French Intensive Care Society and the French Society of Anesthesia and Intensive Care Medicine: French expert panel (FEP)	Unclear	Critically ill adults and children (cardiac arrest, severe TBI, stroke, intra-cerebral hemorrhage)	Temperature management
Best practices in the management of traumatic brain injury, 2015[39]	USA	American college of surgeons (ACS)–Trauma Quality Improvement Program (TQIP)	Health care professionals	Adults and children with mild, moderate, or severe TBI	Stabilization, consultation, and transfer, neuromonitoring, and interventions

TBI, traumatic brain injury; GCS, Glasgow Coma Scale; RBC, red blood cell; ICU, intensive care unit.

Table 2. Clinical Practice Guideline (CPG) Quality According to AGREE II Domains and Total Scores (%)

Guideline	Scope and purpose[a]	Stakeholder involvement[b]	Rigor of development[c]	Clarity of presentation[d]	Applicability[e]	Editorial independence[f]	Global score[g]	Overall quality[h]
NICE-Head Injury[47]	100.0%	77.8%	93.8%	94.4%	70.8%	66.7%	86.2%	High
ERC[49]	94.4%	54.2%	89.1%	75.0%	63.5%	95.8%	79.3%	High
ACR[40]	72.2%	75.0%	97.9%	100.0%	41.7%	50%	78.1%	High
BTF[7]	80.6%	41.7%	77.1%	88.9%	37.5%	66.7%	63.2%	High
TAXI-CAB[50]	72.2%	55.5%	66.6%	77.7%	29.1%	58.3%	60.1%	High
FEP[45]	69.4%	19.4%	68.8%	81.9%	34.4%	58.3%	58.3%	High
ISPEM[6]	77.8%	72.2%	59.4%	77.8%	37.5%	79.2%	63.9%	Moderate
TAXI[51]	77.8%	38.9%	54.2%	83.3%	39.6%	66.7%	57.6%	Moderate
POP-NeoPed[44]	72.2%	44.4%	52.0%	72.2%	29.1%	75%	54.3%	Moderate
Texas Children Hospital[42]	61.1%	50.0%	47.9%	72.2%	12.5%	58.3%	47.9%	Low
Texas Children Hospital[41]	55.6%	44.4%	47.9%	72.2%	12.5%	58.3%	46.4%	Low
French scientific societies[46]	52.8%	44.4%	45.8%	77.8%	8.3%	37.5%	43.5%	Low
Italian scientific societies[43]	63.9%	41.7%	36.5%	55.6%	6.3%	58.3%	40.3%	Low
SNPICM- GSAIC[48]	50.0%	36.1%	29.2%	69.4%	4.2%	33.3%	34.4%	Low
ACS-TQIP[39]	72.2%	27.8%	4.2%	44.4%	0.0%	0.0%	20.8%	Low

[a]Objectives, health questions, and population to whom the CPG applies are specifically described.
[b]Development group includes all relevant professionals, views of target population (patients, public) are sought, target users are clearly defined.
[c]Systematic methods used to search for evidence; criteria for selecting evidence, strengths, and limitations of body of evidence, methods for formulating recommendations are clearly described; health benefits, side effects, and risks are considered; there is explicit link between evidence and recommendations; externally reviewed by experts; process for updating the CPG is provided.
[d]Recommendations are specific and unambiguous, different management options are clearly presented, key recommendations are easily identifiable.
[e]Barriers and facilitators to application are described, advice and/or tools for implementation, potential resource implications are considered, monitoring/auditing criteria are presented.
[f]Views of the funding body have not influenced the content, competing interests are reported and addressed.
[g]Calculated as (obtained score in all domains-minimum score in all domains)/(maximum score in all domains-minimum score in all domains) × 100.
[h]High: ≥ 60% in at least three domains, including rigor of development. Moderate: three domains ≥60% but <60% for domain 3. Low: <60% in two or more domains and <50% in domain 3.

AGREE, Appraisal of Guidelines for Research & Evaluation; NICE, National Institute of Health and Care Excellence; ERC, European Resuscitation Council; ACR, American College of Radiology; BTF, Brain Trauma Foundation; TAXI-CAB, The Transfusion and Anemia EXpertise Initiative-Control/Avoidance of Bleeding; FEP, French expert panel; ISPEM, Italian Society of Pediatric Emergency Medicine; TAXI, Pediatric Critical Care Transfusion and Anemia Expertise Initiative; POP-NeoPed, Peri-Operative Prophylaxis in Neonatal and Paediatric Age Study Group; SNPICM-GSAIC, Society for Neonatology and Pediatric Intensive Care Medicine and the Scientific Working Group for Pediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care; ACS-TQIP: American College of Surgeons–Trauma Quality Improvement Program.

RAND/UCLA method.[40,50,51] One CPG used the American Academy of Pediatrics system for grading recommendations.[6] For one CPG, the development group adopted their own grading methods.[7] The 2023 National Institute for Health and Care Excellence (NICE) CPG[47] included not only new recommendations but also older ones from earlier versions (2003, 2007, and 2014) which were amended or updated, but which were based on a different grading system (Table S3).

We identified 90 recommendations from moderate to high quality CPGs targeting the acute phase of care of children with moderate-to-severe TBI, of which 40 (45%) were based on evidence (Table 3 and Table S4) and 50 (55%) were based solely on expert opinion or consensus (Table S5). Thirty-one evidence-based recommendations (78%) targeted increased use of high-value practices and nine targeted decreased use of low-value practices.

Eleven recommendations (28%) were derived from moderate to high quality evidence and were graded as moderate or strong by at least one CPG (Table 3) including transfer of children with moderate-to-severe TBI to centers with neurological capability (high quality of evidence and strong recommendation according to the Italian Society of Pediatric Emergency Medicine [ISPEM][6] and NICE[47]), indications for initial head computed tomography (CT) (high quality of evidence and strong recommendation according to ISPEM[6]), using hyperosmolar therapy to control intracranial pressure (moderate quality of evidence and strong recommendation according to ISPEM[6]), avoiding corticosteroids (moderate quality of evidence and strong recommendation according to ISPEM[6]), avoiding permissive hypercapnia in severe TBI (high quality of evidence and strong recommendation according to the European Resuscitation Council [ERC][49]), avoiding moderate hypothermia to control intracranial hypertension (high quality of evidence and strong recommendation according to the French Expert Panel [FEP][45]), and giving spoken and printed discharge advice to children with TBI and their caregivers (moderate quality of evidence and strong recommendation according to ISPEM[6]). These 11 recommendations constitute those with the highest levels of evidence among the 90 recommendations identified.

Twenty-nine recommendations were based on low quality of evidence or were graded weak (Table S4). They focused on several key areas of management including stabilization, consultation, and transfer (2); initial and repeat neuroimaging (7); neuromonitoring (5); and interventions (hyperosmolar therapy [3], seizure prophylaxis [1], barbiturates [2], mechanical ventilation [2],

Table 3. Matrix of Recommendations Based on Moderate to High Level of Evidence and Graded Moderate to Strong by at Least One Clinical Practice Guideline (CPG)

Recommendations	*CPG*	*Quality of evidence*	*Strength of recommendation*
Stabilization, consultation, and transfer			
Arrange transfer to a suitable hospital for people with indications for a CT scan who present to a hospital where CT scans are not available	ISPEM	High	Strong
	NICE	High	Strong
Neuroimaging			
Perform a head CT in all brain-injured children presenting to the ED with a GCS <14	ISPEM	High	Strong
	ACR	Low	Moderate
	NICE	Low-high	Moderate
Interventions			
Hyperosmolar therapy			
Bolus HTS (3%) is recommended in patients with intracranial hypertension for ICP control. Recommended effective doses for acute use range between 2 and 5 mL/kg over 10–20 min.	ISPEM	Moderate	Moderate
	BTF	Moderate	Weak
Corticosteroids			
The use of corticosteroids is not suggested to improve outcome or reduce ICP in children with severe blunt head trauma	ISPEM	Moderate	Strong
	BTF	Low	Weak
Mechanical ventilation			
Permissive hypercapnia is not recommended in severe traumatic brain injury (TBI)	ERC	High	Strong
Temperature management			
In children with severe TBI, we do not recommend using TTM at 32–34 °C to control intracranial hypertension	FEP	High	Strong
Prophylactic moderate (32–33°C) hypothermia is not recommended over normothermia to improve overall outcomes	FEP	Consensus-high	Strong
	ISPEM	Moderate	Strong
	BTF	Moderate-high	Moderate
If hypothermia is used and rewarming is initiated, it should be carried out at a rate of 0.5–1.0°C every 12–24 h or more slowly to avoid complications	BTF	High	Moderate
Moderate (32–33°C) hypothermia is suggested for ICP control	BTF	Moderate	Moderate
Discharge planning			
Patients admitted after a brain injury may be discharged after resolution of all significant symptoms and signs providing they have suitable supervision arrangements at home	ISPEM	Consensus-high	Strong
	NICE[a]	Consensus	Weak
Give spoken and printed discharge advice to children with head trauma and their caregivers upon discharge from the ED or ED observation unit, including: signs and symptoms that warrant medical review; recommendation that a responsible adult should monitor the patient for the first 24 h after trauma; details about the possibility of persistent or delayed symptoms following head trauma and whom to contact if they experience ongoing symptoms; information about return to school and return to sports for children who sustain a concussion	ISPEM	Moderate	Strong
	NICE[b]	Moderate	Moderate

[a]2003 recommendation included in 2023 NICE CPG.
[b]2014 recommendation included in 2023 NICE CPG.
ISPEM, Italian Society of Pediatric Emergency Medicine; ACR, American College of Radiology; NICE, National Institute of Health and Care Excellence; BTF, Brain Trauma Foundation; ERC, European Resuscitation Council; FEP, French expert panel; ED, emergency department; CT, computed tomography; GCS, Glasgow Coma Scale; HTS, hypertonic saline; ICP, intracranial pressure; TTM, targeted temperature management.

antifibrinolytic agents [1], vasoactive/inotropic drugs [1], neurosurgical interventions [2], pain management [1] and nutrition [2]).

Eleven (28%) evidence-based recommendations were reported by more than one CPG (Table 3 and Table S4). However, gradings of quality of evidence were often heterogeneous across CPGs for the same recommendation, such as indications for initial head CT (quality of evidence graded low by the American College of Radiology (ACR),[40] high by ISPEM,[6] and low to high by NICE[47]) and avoiding the use of corticosteroids to improve outcome/reduce intracranial pressure (quality of evidence graded low by the Brain Trauma Foundation [BTF][7] and moderate by ISPEM[6]).

Gaps in CPGs

Nearly half of recommendations pertained to interventions ($n=42$, 47%); 53% of these ($n=22$) were evidence based (Fig. 1a, b). Almost one third of recommendations pertained to stabilization, consultation, and transfer ($n=25$, 28%); 12% of these ($n=3$) were based on evidence. Neuromonitoring, discharge planning, and patient and family support all had five or fewer recommendations. We identified no recommendations based on evidence for red blood cell transfusion, plasma and platelet transfusion, thromboprophylaxis, surgical antimicrobial prophylaxis, early diagnosis of hypopituitarism, or mental health management.

Discussion

In this systematic review, we identified 15 CPGs, including 9 that were rated of moderate to high quality with at least one recommendation on the management of moderate-to-severe pediatric TBI. Stakeholder involvement and applicability were noted as specific areas for improvement in CPG quality. Within these CPGs, we identified 90 recommendations, of which 40 (45%) were evidenced based. Of the evidence-based recommendations, 11 (28%) were based on moderate to high quality evidence and were graded moderate to strong by at least

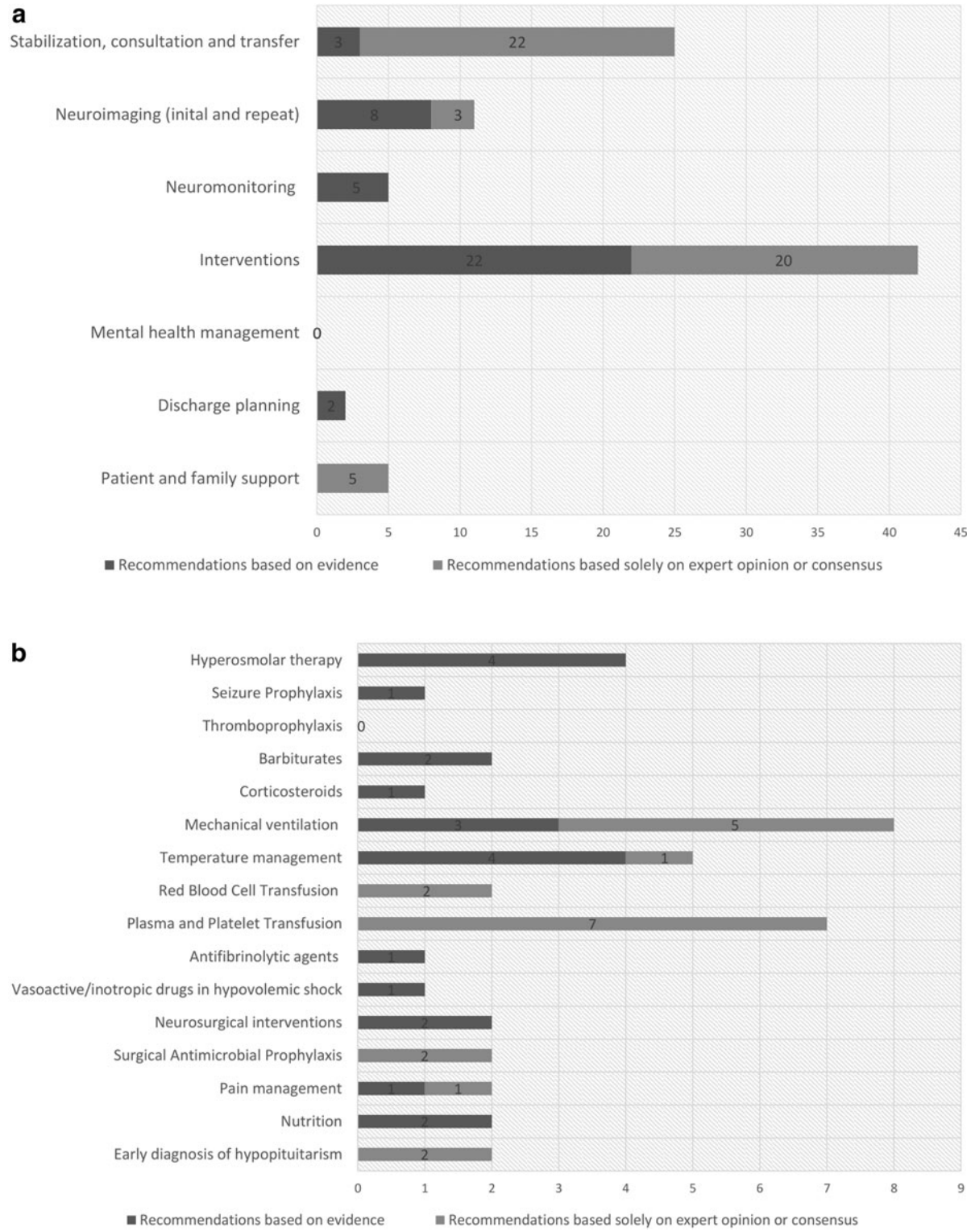

FIG. 1. **(a)** Shows the classification of recommendations according to key areas of management. Nearly half of recommendations pertained to interventions. One third of recommendations pertained to stabilization, consultation, and transfer. Neuromonitoring, discharge planning, and patient and family support all had five or fewer recommendations. No recommendations were identified for mental health management. **(b)** Presents the recommendations pertaining to the different categories of interventions. No recommendations based on evidence were identified for red blood cell transfusion, plasma and platelet transfusion, thromboprophylaxis, surgical antimicrobial prophylaxis, and early diagnosis of hypopituitarism.

one CPG. These recommendations focused on transferring children with moderate-to-severe TBI to centers with neurosurgical capability, indications for head CT, using hyperosmolar therapy to control intracranial pressure, avoiding corticosteroids, avoiding permissive hypercapnia, avoiding moderate hypothermia, and giving spoken and printed discharge advice to children with TBI and their caregivers. We identified gaps in evidence-based recommendations for red blood cell transfusion, plasma and platelet transfusion, thromboprophylaxis, surgical antimicrobial prophylaxis, early diagnosis of hypopituitarism, and mental health management. These results may be used by clinicians to identify recommendations based on the highest level of evidence, by healthcare administrators to inform guideline implementation in clinical settings, by researchers to identify areas where robust evidence is needed, and by guideline-writing groups to inform the update of existing guidelines or the development of new ones.

Similarly to our study, other systematic reviews of CPGs in pediatric TBI have identified issues with CPG quality using the AGREE II tool.[13–15] In line with our findings, scope and purpose and clarity of presentation of the CPGs received the highest scores, and applicability and stakeholder involvement received the lowest.[13–15] In our study, the views and preferences of patients and families with lived experience were rarely considered, despite the growing recognition that patient and public involvement is an essential element in the development process of CPGs, with a significant impact on implementation success.[53,54] We also found that facilitators and barriers and resource implications were rarely addressed and that implementation tools were rarely provided. The need to improve the applicability of pediatric CPGs has been reported by others.[55]

Similarly to our review, many other studies have highlighted the paucity of high quality of evidence for pediatric TBI care.[56,57] Systematic reviews that have synthesized recommendations for the prehospital management of pediatric TBI[16] and the management of concussion and mild TBI for adult and pediatric populations[17] also reported that recommendations were mostly low grade. These results likely reflect the fact that many of the recommendations are based on indirect evidence from adult or mixed populations,[56] which may explain the poor adherence to CPGs for pediatric TBI care.[11,12] The GRADE group recommends publishing *good practice statements* instead of recommendations when no direct evidence is available,[58] which could constitute a solution to be adopted by future CPGs developers, highlighting issues for which more clinical research is needed. Additionally, in the future, barriers to robust evidence, mostly related to insufficient sample sizes, may be addressed by innovations such as clinical trial platforms, multi-site/multi-national integration of data through cloud applications, and machine learning applied to electronic medical data.

In our systematic review, we identified important issues that have not been reported by others.[13–17] First, the reported level of evidence varied significantly across CPGs for the same recommendation. This situation may be explained by the lack of systematic approaches to searching for evidence and the low reliability of grading tools for complex bodies of evidence.[59] Second, the definition of the pediatric population in terms of age was highly variable among CPGs. Third, methods used to grade the quality of evidence and the strength of recommendations were highly variable among CPGs. The three aforementioned elements constitute barriers to the adherence to and the successful implementation of CPGs.[60,61] Finally, it seems important to mention that NICE's guideline, with the highest quality score on AGREE II, is the only one to have adopted a healthcare systems approach in the development process, which promotes the comprehensive management of TBI.[47]

Strengths and limitations

Our systematic review was conducted according to methodological guidelines for systematic reviews of CPGs and Cochrane guidelines, and our findings are reported according to the PRISMA 2020 statement. Our search strategy was designed to capture both peer-reviewed publications and unpublished CPGs from gray literature, through a thorough review of the Web sites of healthcare organizations with interest in pediatric injury care. Further, we created a unified grading system that allowed us to compare and contrast the level of evidence and the strength of recommendations from different CPGs. Finally, our review was supported by a multidisciplinary advisory committee including clinical experts in the field of pediatric injury care and methodologists specialized in knowledge synthesis.

Our systematic review has some limitations. First, the search strategy was not developed to identify CPGs that do not specifically target pediatric injury populations. Therefore, we may have missed recommendations if they were included in CPGs that target general pediatric populations or trauma populations of all ages. Nevertheless, these CPGs were probably identified by consulting professional organization Web sites or through consultation with our advisory committee. Second, we developed a unified grading system for levels of evidence and the strength of recommendations to facilitate their interpretation across CPGs, but this system was not validated. However, our system strongly adheres to the GRADE method.[28,29] Third, AGREE II is a subjective tool that may lead to bias in quality ratings.[13,16,62,63] Nonetheless, we did pilot the tool *a priori* among all reviewers until acceptable agreement was achieved. In addition, although cutoffs used to attribute an overall quality score were established *a priori* based on published recommendations, they have not been formally validated. Fourth,

pediatric patients with moderate-to-severe TBI often have concomitant injuries. Other systematic reviews of CPGs covering multi-system, solid organ, and orthopedic trauma should be consulted alongside this review.[18,64]

Conclusion

Pediatric TBI represents a challenge to healthcare providers and systems, but improving adherence to evidence-based CPGs has the potential to improve patient outcomes. High-quality, up-to-date CPGs are available, but they have weaknesses. The results of this review lead us to three important findings. First, we identified 11 recommendations based on high levels of evidence that may be implemented with a high level of confidence in clinical settings. We also identified 29 recommendations based on low levels of evidence. Despite limitations, they remain important issues in the management of children with moderate-to-severe TBI and may be used to guide clinical care. Second, our results highlight gaps in evidence in this population (red blood cell transfusion, plasma and platelet transfusion, thromboprophylaxis, surgical antimicrobial prophylaxis, early diagnosis of hypopituitarism, and mental health management) that can be used to guide research priorities. Third, we have identified potential areas for CPG improvement, including the need to involve patients and family representatives in the development process, provide information on barriers and facilitators and tools to support implementation, and better integrate resource considerations.

Transparency, Rigor, and Reproducibility Summary

This review is part of a series of systematic reviews of CPG recommendations for pediatric injury care; detailed methodology was published previously. The protocol was registered on International Prospective Register of Systematic Reviews (PROSPERO #CRD42021226934). Our systematic review was conducted according to methodological guidelines for systematic reviews of CPGs and Cochrane guidelines, and our findings are reported according to the PRISMA 2020 statement. Our review was supported by a multidisciplinary advisory committee including clinical experts in the field of pediatric injury care and methodologists specialized in knowledge synthesis. We found that many up-to-date clinical practice guidelines are available, but that there is a paucity of evidence to support recommendations, highlighting the urgent need for robust clinical research in this vulnerable population. Moreover, we identified potential areas for clinical practice guidelines improvement including involving patients and family representatives in the development process, providing tools to support implementation, and better integrating resource considerations. The data sets used and analyzed during the current study are available from the corresponding authors on request.

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Authors' Contributions

A.B.A. and L.M. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for the concept and design as well as the acquisition, analysis, or interpretation of data. A.B.A., L.M., G.C.F., N.Y., and A.F.T. were responsible for drafting of the manuscript. All authors were responsible for Critical revision of the manuscript for important intellectual content. L.M., G.C.F., A.F.T., M.B., T.S., S.B., F.L., R.Z., E.B., and N.Y. obtained funding. L.M., P.A.T., and A.B.A. provided administrative, technical, or material support.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

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