



Original Contribution

A review of research efforts to address the 2008 ACEP guideline for mild traumatic brain injury



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ARTICLE INFO

Article history:

Received 2 January 2018

Received in revised form 25 April 2018

Accepted 26 April 2018

Keywords:

Traumatic brain injury

Research gaps

Clinical practice guidelines

Emergency medicine

ABSTRACT

Background: The objective of this study was to evaluate the temporal relationship between clinical practice guideline development and subsequent research performed, with the goal of providing more data on areas of sparse evidence that serve to underlie guideline recommendations. We aimed to assess the quality of current research efforts to address the American College of Emergency Physicians guideline and to provide suggestions for future research of mild traumatic brain injury.

Methods: We identified clinical practice guideline recommendations with low levels of underlying evidence and searched ClinicalTrials.gov and the World Health Organization's International Clinical Trial Registry Portal to determine whether subsequent research has reflected an effort to address guideline recommendations.

Results: Few currently registered clinical trials attempt to focus on clinical practice guideline recommendations where the basis of evidence is weak, and even fewer might benefit future iterations of the guideline due to multiple problems in study design and reporting.

Conclusions: The amount of research dedicated to investigation of mild traumatic brain injury continues to be sparse and of poor quality. Study results should always be posted, even if the null hypothesis is confirmed. Efforts to improve the evidence base of a guideline should be realized by designing studies that directly assess and speak to the questions posed by guideline authors.

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1. Background

In the United States, every year more than one million emergency department visits are due to traumatic brain injury, 70–90% of which are considered “mild” [1–4]. Inclusion criteria created by the American College of Emergency Physicians (ACEP) guideline for adult mild traumatic brain injury (TBI) defines adult mild TBI as individuals at the age of 16 years or older presenting to the emergency department within 24 h of any non-penetrating head trauma with a Glasgow Coma Scale (GCS) of 14 or 15 on initial evaluation [5]. While most patients with mild traumatic brain injury can be safely discharged, 5–15% have

intracranial complications [6,7]. These intracranial lesions can be devastating, so emergency physicians need to be able to identify them quickly and treat them correctly [8,9]. The protocol and procedure upon which most physicians rely to make these important decisions are clinical practice guidelines [10,11]. These guidelines consist of recommendations for clinical care that are based on synthesis of the best current evidence [12]. Owing to their high importance and effect on clinical decision making, clinical practice guidelines and their recommendations need to be rooted in strong, reliable evidence. However, recent studies suggest that many guideline recommendations rely on weak or minimal evidence [13–17].

Poorly supported recommendations highlight the areas where more research needs to be focused. While more research is being done, with research funding exceeding \$240 billion in 2010, one estimate suggests that as much as 85% of research is wasted or does not provide new, clinically relevant data [18,19]. This huge portion of research is investigating sufficiently answered questions, clarifying clinically unimportant distinctions, or answering questions patients do not want answered

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[19–21]. Efforts should be focused on remedying gaps in clinical research, the products of which should ultimately provide physicians with more objective, evidence-based clinical recommendations.

Our study focused on analyzing the research landscape in the area of adult mild traumatic brain injury through the lens of the guideline: *Clinical Policy: Neuroimaging and Decisionmaking in Adult Mild Traumatic Brain Injury in the Acute Setting* [5]. Some controversy does exist regarding the use of this particular guideline in clinical practice. Other decision making tools such as the Canadian Head CT Rule and New Orleans Head CT Rule have been more widely accepted and are easier to implement. The goal of this study, however, was not to evaluate the validity of the recommendations which followed the critical questions, but instead made the assumption that the critical questions themselves were worth answering, that the conclusions substantiating recommendations directly addressed those questions, and that the recommendations were based on best evidence. Research gaps were identified based upon the GRADE system of the guideline, which evaluates each recommendation based on the level of evidence. Current or ongoing studies registered in ClinicalTrials.gov or the World Health Organization's International Clinical Trial Registry Portal (ICTRP) after publication of the guideline were evaluated to determine the extent to which research efforts are working to address both those critical questions which currently have no recommendations as well as those recommendations which are based on low-quality evidence.

2. Methods

This study was not subject to Institutional Review Board oversight because it did not meet the regulatory definition of human subject research as defined in 45 CFR 46.102(d) and (f) of the Department of Health and Human Services' Code of Federal Regulations [22]. We applied relevant Statistical Analyses and Methods in the Published Literature reporting guidelines for reporting descriptive statistics [23]. The following PICO question formatting, search string development, data extraction, and screening methods were used in previous studies on analyzing the research pipeline in other disciplines [24,25].

We retrieved the guideline for clinical management of adult mild traumatic brain injury from the ACEP website. For each recommendation rated as moderate, limited, inconclusive, or consensus, we constructed at least one research question using the population, intervention, comparator, outcome (PICO) format. This method identifies clinical components for systematic reviews, and it is endorsed by the Cochrane Collaboration [26].

Our definition of a search strategy is that defined by Gillespie and Gillespie [27]. We consulted a published protocol to ensure that the search strings were sensitive enough to maximize inclusion of potentially relevant studies [28]. This protocol also served as our guide in creating analogous search strings for both ClinicalTrials.gov and ICTRP.

2.1. Search string development and data extraction

PICO questions (in supplementary data) were drafted using the ACEP guideline by four investigators (AMM, DS, MS, JG) and submitted to MF, a medical research librarian and investigator. MF formulated seven search strings (in supplementary data) for the four critical questions and five recommendations listed in the guideline, using Boolean search operators and parenthetical groupings on ClinicalTrials.gov and ICTRP in a previously published protocol [29]. The critical questions and the associated recommendations and PICO question numbers are listed in [Table 1](#). All available data fields for all search results were extracted from the clinical trial registries and evaluated by two investigators (JM, TC).

2.2. Data extraction and screening

Data were independently extracted from each search engine by two investigators (JM, TC) in parallel, blinded fashion, and were compiled into a single spreadsheet for each investigator. After duplicate elimination, trials ending before the guideline publication date were excluded using the reason "date". Next, trials that did not include adults (16 years and above) in their population were excluded using the reason "Population: Age". Remaining registered trials were evaluated for pertinence to the recommendations within the guideline on the basis of whether their PICO criteria addressed the critical questions proposed in the recommendations. [Fig. 1](#) provides a detailed, hierarchical list of reasons for which studies were excluded from further consideration.

The purpose of using the PICO format for exclusion criteria was to minimize any ambiguity about which studies warranted further consideration. Where it was unclear which guideline recommendations correlated with a trial's PICO criteria, it was flagged and discussed with those investigators who drafted the PICO questions (AMM, DS, MS, JG). Owing to limitations in the design of one search portal, the only data fields extracted for the ICTRP search results were trial identification number, trial name, and trial status. As a result, these studies had to be individually assessed in greater detail. To further clarify reasons for inclusion, all relevant trials included in our analysis were noted for those guideline

Table 1
Results for each recommendation of the American College of Emergency Physicians *Clinical Policy: Neuroimaging and Decisionmaking in Adult Mild Traumatic Brain Injury in the Acute Setting*.

No	Critical question	Recommendation	Grade/level	PICO questions	Trials completed (n)	Trials not completed (n)
1	Which patients with mild TBI should have a noncontrast head CT scan in the ED?	A noncontrast head CT should be considered in head trauma patients with no loss of consciousness or posttraumatic amnesia if there is a focal neurologic deficit, vomiting, severe headache, age 65 years or greater, physical signs of a basilar skull fracture, GCS score less than 15, coagulopathy, or a dangerous mechanism of injury	B	1–26	4	0
2	Is there a role for head MRI over noncontrast CT in the ED evaluation of a patient with acute mild TBI?	N/A	N/A	27–31	0	0
3	In patients with mild TBI, are brain-specific serum biomarkers predictive of an acute traumatic intracranial injury?	Recommendations: In mild TBI patients without significant extracranial injuries and a serum S-100B level less than 0.1 µg/L measured within 4 h of injury, consideration can be given to not performing a CT	C	32–35	1	0
4	Can a patient with an isolated mild TBI and a normal neurologic evaluation result be safely discharged from the ED if a noncontrast head CT scan shows no evidence of intracranial injury?	Patients with an isolated mild TBI who have a negative head CT scan result are at minimal risk for developing an intracranial lesion and therefore may be safely discharged from the ED Mild TBI patients discharged from the ED should be informed about postconcussive symptoms	B C	36 37, 38	0 0	0 1

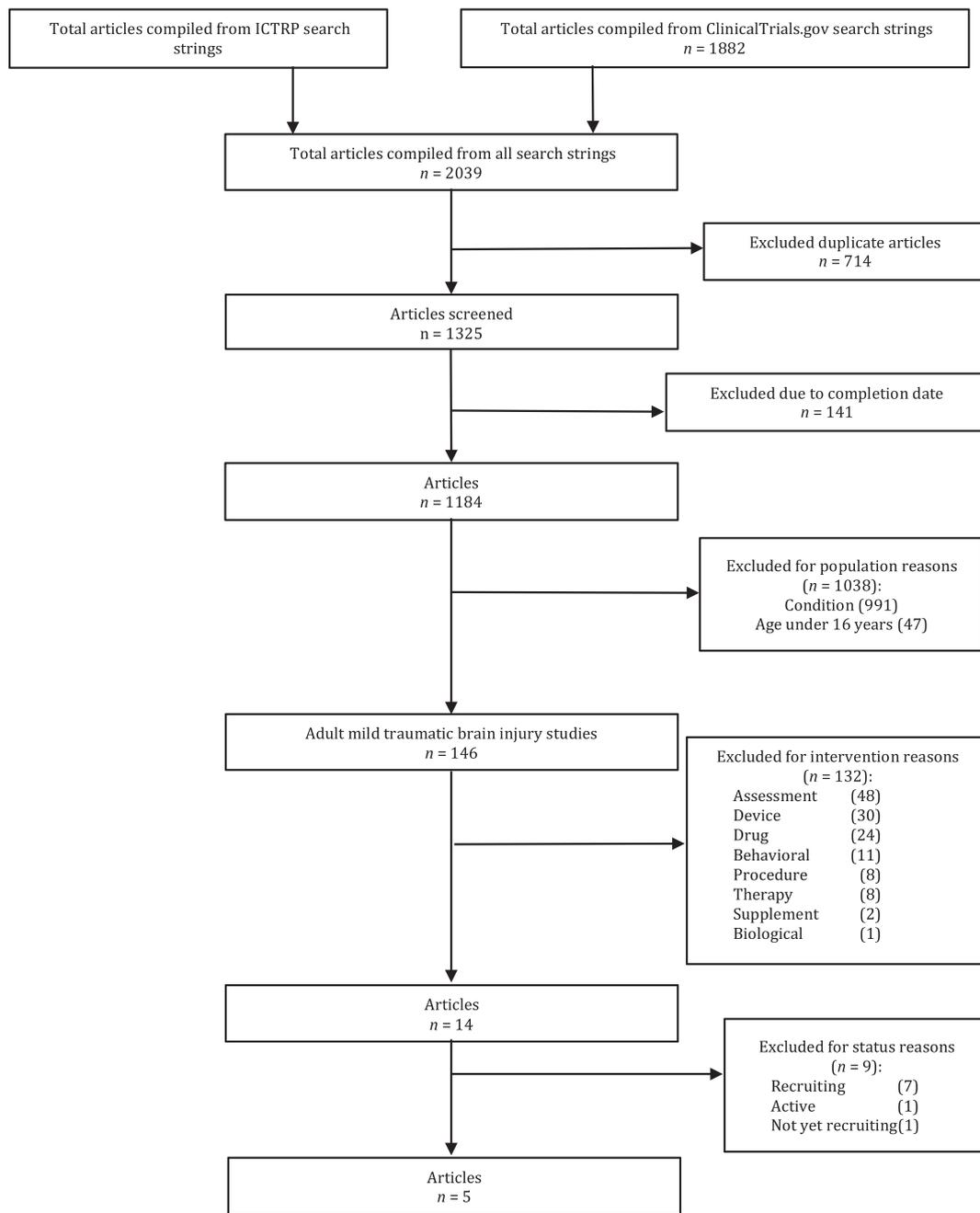


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses for the World Health Organization International Clinical Trial Registry Portal (ICTRP) and [ClinicalTrials.gov](https://www.clinicaltrials.gov).

critical questions (and recommendations, if existent) that they address. All disagreements about eligibility were resolved by consensus.

We applied the ACCP (American College of Chest Physicians) adaptation of the GRADE system [30]. Studies could be of low, moderate, or high evidence quality and have weak, moderate, or strong recommendations associated with them. The quality of evidence can be assessed for any study and is dependent on the nature of the study design, whereas recommendation strength is made based on the difference in treatment effect of an intervention versus other interventions or placebo. The recommendation strength takes into consideration both the potential benefits and harm demonstrated by the results in the trial population, so recommendation strength may only be determined from completed studies. For completed studies, we assigned both evidence quality judgments (A, B or C) and recommendation strength (1 or 2). For ongoing studies, we assigned a quality of evidence rating but were not able to assess recommendation strength.

3. Results

The combined [ClinicalTrials.gov](https://www.clinicaltrials.gov) and ICTR search strings resulted in 2039 articles; 714 duplicates were removed, yielding 1325 articles. These 1325 articles were screened for eligibility. Of the 1325 articles, 146 (11%) were studies included in our analysis.

Critical Question 1 concerns which patients need to receive a computed tomography (CT) scan in the emergency department. According to the guideline, current evidence suggests that noncontrast CT should be considered in head trauma patients with no loss of consciousness if they present with a variety of symptoms (e.g., focal neurologic deficit, vomiting, severe headache, dangerous mechanism of injury) (Recommendation 1) [5]. From our screening, a total of four completed studies addressed Recommendation 1. According to GRADE system, it was determined that one of the four completed studies had strong recommendations but low-quality evidence (1C) due to the observational study

type. Another completed study had weak recommendations but moderate quality evidence (2B) because of its randomized study type. The other two completed studies were observational study types (C) but had no results posted and were therefore not graded further (Table 2).

Critical Question 2 addresses whether use of magnetic resonance imaging (MRI) has any advantages over CT. The current guideline iteration has no recommendations to address this question [5]. From the analysis, it was determined that no studies directly concerned Critical Question 2 (Table 2).

Critical Question 3 asks whether there are any serum biomarkers in patients with mild traumatic brain injury that could be measured to predict intracranial injury. According to the guideline, current evidence suggests that a serum S-100B concentration of less than 0.1 µg/l in patients with mild traumatic brain injury indicates consideration for not performing a CT scan (Recommendation 2) [5]. One completed study addressed this recommendation. This study had strong recommendations but had an observational study type and therefore was graded as a level 1C study with low quality evidence (Table 2).

Critical Question 4 addresses whether patients can be safely discharged if noncontrast CT shows no signs of intracranial injury. Current evidence suggests that patients who have a negative CT scan have a minimal risk for developing an intracranial lesion and therefore can be safely discharged (Recommendation 3) [5]. The guideline also provided evidence for educating patients on postconcussive symptoms before discharge (Recommendation 4) [5]. No studies addressed Recommendation 3; however, one “not completed” study addressed Recommendation 4. The “not completed” study is an interventional, randomized study where the outcomes assessor was blinded (Table 2).

Overall, 6 (4.11%) of 146 studies addressed critical questions and recommendations from the guideline. Five of these studies were completed at the time of our assessment.

4. Discussion

Practitioners rely on timely guideline development and frequent updates to ensure that the standard of care reflects the state of the art of medical research. For this to occur, research efforts must align with relative knowledge gaps in the literature, as identified by their lower recommendation strength. According to the GRADE guidelines [30], those recommendations based on lower levels of evidence are most likely to benefit from further research efforts.

We identified a number of inconsistent or inefficient current research practices that may be hindering further development of the guideline (Table 3) [5]. For example, some studies were confounded by mixed populations (both children and adults) being assessed for traumatic brain injury. Currently, the ACEP guideline for adult mild traumatic brain injury includes patients 16 years and older. While there may

be an argument for stratifying groups of patients into different age brackets than those currently used, research efforts moving forward should be designed in accordance with the current criteria for age stratification to maximize the potential for a study to contribute to guideline recommendations.

We found little evidence to evaluate the role of particular physical signs as predictors of the need for a CT or neurosurgical intervention. Two studies evaluated the efficacy of decision tools like the Canadian CT Head Rule and the New Orleans Criteria in Minor Head Trauma [31,32]. Two studies directly evaluated risk factors for intracranial bleeding but in one the population was primarily paediatric [33], and in the other the focus was primarily geriatric patients and looked at the use of anticoagulants affecting the risk of intracranial bleeding (Table 3) [34]. Thus, the few studies found that addressed Critical Question 1 offer limited additional insight that may benefit ED physicians.

In another example, which perhaps illustrates the degree to which research efforts can become disconnected from the data needed to produce clinical guidelines, consider the ACEP’s position on the use of plain film radiographs as a screening test for CT. Since 2002, ACEP has recommended not using plain film as a screening test for suspected mild traumatic brain injury, as negative results may mislead clinicians. Despite this, in 2004 a study was launched to evaluate the role of plain film as a screening test [35], while no studies were conducted to further evaluate the predictive value for CT indication of physical signs and symptoms that are associated with mild TBI.

Some studies addressed the various MRI modalities in question (Critical Question 2), but either failed to perform, or report performance of, baseline measurements in the acute setting [36–39]. Three others were terminated [40–42], and two others are currently (July 2017) recruiting to evaluate a population of collegiate football players [43,44]. The last two studies evaluate a population with a specific mechanism of injury, which may limit their interpretive value as a whole, and to date these trials have reported no results (Table 3). As the guideline suggests, many possibilities exist for the role of MRI technologies in evaluation of mild traumatic brain injury, but our analysis largely confirms that little has been done to employ its use in the acute evaluation of adults presenting to emergency departments with minor head injuries.

In studies evaluating the role of biomarkers such as S-100B as screening tests for CT [45–51], applicability to guideline recommendations was weakened by variable measurement windows specified in each study. Such measurement windows for S-100B ranged from three hours post-injury [45] to seven days post-injury [49] with the guideline-specified timeframe of four hours post injury being an uncommon measurement cutoff point. Some studies evaluated proprietary biomarkers other than S-100B [52,53]. Only one study evaluating S-100B [54] reflected a clear effort to provide evidence on the use of

Table 2
Studies addressing research gaps based upon the ACCP adaptation of the GRADE system.

Trial title	Registry number	Recruitment status	Critical questions addressed	Recommendation addressed	Study type	Study design	Strength of study	Evidence quality
Risk factors of minor head injury	NCT00451789	Completed	1	1	Observational	Defined population, natural history, longitudinal, prospective	1C	Low
Diagnostic algorithm in patients with minor head injury	NCT00452036	Completed	1	1	Observational	Cohort, retrospective	C	Low
Canadian computed tomography (CT) head rule study	NCT00993252	Completed	1	1	Interventional	Matched-pair, cluster-randomized	2B	Moderate
The value of the Canadian CT head rule and the New Orleans criteria in minor head trauma	NCT01619943	Completed	1	1	Observational	Cohort, prospective	C	Low
S-100B as pre-head CT scan screening test after mild traumatic brain injury	NCT00717301	Completed	3	2	Observational	Cohort, prospective	1C	Low
SWIFT Study in the ED	NCT01893970	Recruiting	4	4	Interventional	Randomized, parallel assignment, single blind (outcomes assessor)	B	Moderate

Table 3
Trials identified that address research gaps

Trial title	Registry number	Recruitment status	Critical questions addressed	Recommendations addressed	PICO questions addressed	Challenges
Risk factors of minor head injury	NCT00451789	Completed	1	1	2, 3, 7, 8	N/A
Diagnostic algorithm in patients with minor head injury	NCT00452036	Completed	1	1	1	N/A
Canadian computed tomography (CT) head rule study	NCT00993252	Completed	1	1	3, 6, 7, 9, 26	N/A
The value of the Canadian CT head rule and the new Orleans criteria in minor head trauma	NCT01619943	Completed	1	1	3, 4, 6, 7, 9	N/A
Traumatic brain injury - knowledge translation	NCT01453621	Completed	1	N/A	N/A	Age
Is a two-film skull X-ray series as sensitive as a four-film series in the diagnosis of skull fractures in paediatric patients	NCT01448473	Completed	1	N/A	N/A	Age
Infant minor head trauma clinical decision rule	NCT03050970	Recruiting	1	N/A	N/A	Status, age
A prospective observational study to assess the diagnostic accuracy of clinical decision rules for children presenting to emergency departments after head injuries: The Australasian Paediatric Head Injury Rules Study (APHIRST)	ACTRN12614000463673	Recruiting	1	N/A	N/A	Status, age
Longitudinal study of Traumatic Brain Injury (TBI) in (University of Florida) UF athletes	NCT01890304	Enrolling	2	N/A	28, 30	Status, assessment
Objective brain function assessment of mTBI from initial injury to rehabilitation and treatment optimization	NCT02477943	Ongoing, but not recruiting	2	N/A	28, 30	Status, assessment
Advanced MRI applications for mild traumatic brain injury-phase 2	NCT02556177	Recruiting	2	N/A	28, 30	Status, assessment
Advanced MRI applications for mild traumatic brain injury – UCSF	NCT02141360	Terminated	2	N/A	28, 30	Status, assessment
TBI MR study 3 Houston methodist	NCT02218216	Terminated	2	N/A	28, 30	Status, assessment
Advanced MRI applications for mild traumatic brain injury	NCT02070588	Terminated	2	N/A	28, 30	Status, assessment
Objective brain function assessment of mTBI from initial injury to rehabilitation and treatment optimization in high school athletes	NCT02661633	Ongoing but not recruiting	2	N/A	N/A	Status, age
Identification of biomarkers that correlate with clinical features and outcomes following concussion	ACTRN12615000543583	Recruiting	2, 3	N/A	N/A	Status, assessment
Evaluation, pathogenesis, and outcome of subjects with or suspected traumatic brain injury	NCT01132937	Recruiting	2, 3	N/A	N/A	Status, assessment
S-100B as pre-head CT Scan screening test after mild traumatic brain injury	NCT00717301	Completed	3	2	32, 33	N/A
Immunomodulation in patients with minor head injury	NCT00622778	Completed	3	N/A	N/A	Assessment
Biomarkers of mild and moderate traumatic brain injury	NCT01295346	Completed	3	N/A	N/A	Assessment
Introduction of protein S100 in diagnostics in minor brain injury patients at our hospital	NCT01122212	Completed	3	N/A	N/A	Assessment
'CHIP REfinement STudy (CREST)' prospective refinement study of the CHIP (CT in head injury patients) prediction rule for patients with minor head injury	NTR5409	Not yet recruiting	3	N/A	N/A	Status, assessment
S100 biomarker in the acute management of mild head injuries	NCT02650765	Recruiting	3	N/A	N/A	Status, assessment
Concussion in rugby players: a pilot study of neural recovery using fMRI	NCT02988609	Recruiting	3	N/A	N/A	Status, assessment
The clinical relevance of micro RNAs in mild traumatic brain injury	NCT02639923	Recruiting	3	N/A	N/A	Status, assessment
SWIFT study in the ED	NCT01893970	Recruiting	4	4	37, 38	Status

biomarkers as screening tests in mild head injuries (Table 3). There are challenges to the use of serum biomarkers in the ED secondary to multiple factors including: availability of test, delay in results, cost and, for the studies that have been conducted, exhaustive lists of exclusion criteria (e.g., recent use of any number of legal or illicit substances) severely limit the external validity of such studies in the ED setting [55].

The only randomized study to date to evaluate the role of education in the emergency department to inform patients about postconcussive symptoms is currently under way [56], and comes on the heels of a 2014 published study suggesting that such education improves outcomes [57]. Two other studies dealt with postconcussive symptoms, but their interventions were behavioral rather than educational (Table 3) [58,59]. Despite limited number of studies on the subject, the role of education in ED cannot be overlooked. The current ACEP guidelines highlight the decision making and management of mTBI, and the education is considered to be a part of larger discharge instructions. A proportion of mTBI patients without identifiable bleeds develop long-term complications. This is particularly true in trauma and motor-vehicle

accidents but seen also in sports [60,61]. It may be worthwhile to consider research that inquires about the role of standardized educational process in ED, including the impact of education on the patient's ability to self-monitor and report, in a timely manner, any adverse and newly-occurring complications after mTBI, and the impact of education on the long-term outcomes.

Finally, a subset of studies are currently “in progress” as of their last status update on the clinical trial registries [40,49–51,56,58,62–64]. Some of these studies have the potential to provide evidence on various guideline recommendations, but to date have reported no results (Table 3). In summary, of the 2039 studies surveyed, few studies reflected a clear effort to directly answer a Critical Question [5]. Designing studies that directly answer questions posed by clinical practice guidelines can help to increase yield from basic research, which reduces research waste [65].

There are many factors to consider for the physician attending to a patient presenting to the emergency department with the potential for mild traumatic brain injury, including loss of consciousness, focal

neurological deficits, posttraumatic amnesia, vomiting, severe headache, coagulopathy, dangerousness of mechanism of injury and GCS score. In the absence of visible signs of a basilar skull fracture, the decision to perform CT and the decision to admit or discharge have profound implications for both patient and physician. While CT is the gold standard, it does expose patients to radiation, so viable screening alternatives like serum biomarkers and MRI need to be explored for economic prudence, emergency department efficiency and patient safety. In the same way, appreciation for better education practices, more advanced imaging modalities and affordable laboratory testing to mitigate the costs of imaging when level of suspicion is low can be realized by conducting bespoke studies that are purpose-built to address guideline recommendations. Finally, future clinical projects should consider the role of education in ED for mTBI with and without neuroimaging findings. The role of acute education in ED should be explored with respect to its short and long-term outcomes; future projects should also make an attempt to explore the education process with clearly assigned roles of educators, goals of education, and process.

4.1. Limitations

For some studies, the population, intervention, condition, or outcomes being evaluated were unclear to the extent that would be required to suggest its relevance to ACEP guideline recommendations. If we were unable to ascertain this information, the studies were eliminated from further consideration. Thus, it is possible that we eliminated studies which may yet come to benefit the guideline recommendations on account of poor stewardship of their clinical trial registry records. Another potential limitation is that infrequent reporting of results on clinical trial registries and observed difference in outcomes reported in subsequent publications suggests that our efforts to grade recommendation strengths of study results may be less than comprehensive if studies possess full data sets which could be graded but have not been released on the clinical trial registry websites.

5. Conclusions

We recommend that more research be devoted to improving clinical practice guideline recommendations for adults with mild traumatic brain injury, that this research should be shaped in the image of the critical questions posed by the guideline, and that efforts should be made to improve frequency and consistency of study result reporting on clinical trial registries.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

A copy editor of Monmouth Editorial reviewed our manuscript for grammatical errors and wording.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajem.2018.04.061>.

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