Article:
Moore, L., Tardif, P.-A., Lauzier, F. et al. (11 more authors) (2020) Low-value clinical practices in adult traumatic brain injury : an umbrella review. Journal of Neurotrauma, 37 (24). ISSN 0897-7151

https://doi.org/10.1089/neu.2020.7044

Final publication is available from Mary Ann Liebert, Inc., publishers
https://doi.org/10.1089/neu.2020.7044

LOW-VALUE CLINICAL PRACTICES IN ADULT TRAUMATIC BRAIN INJURY: AN UMBRELLA REVIEW

Acknowledgement relative to iThenticate process: The protocol of this manuscript was published in BMJ Open: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6797405/

First and corresponding author

Lynne Moore, PhD

Department of Social and Preventative Medicine, Université Laval, Québec (Qc), Canada;

Population Health and Optimal Health Practices Research Unit, Trauma – Emergency – Critical Care Medicine, Centre de Recherche du CHU de Québec (Hôpital de l'Enfant-Jésus), Université Laval, Québec (Qc), Canada

lynne.moore@fmed.ulaval.ca

Phone : (418) 525-4444

Fax : (418) 649-5733

2325, Rue de l'Université, Québec, G1V 0A6

Co-authors

Pier-Alexandre Tardif, MA MSc

Population Health and Optimal Health Practices Research Unit, Trauma – Emergency – Critical Care Medicine, Centre de Recherche du CHU de Québec (Hôpital de l'Enfant-Jésus), Université Laval, Québec (Qc), Canada

Pier-alexandre.tardif@crchudequebec.ulaval.ca

Phone : (418) 525-4444

Fax : (418) 649-5733

2325, Rue de l'Université, Québec, G1V 0A6

François Lauzier MD MSc

Department of Social and Preventative Medicine, Université Laval, Québec (Qc), Canada; Population Health and Optimal Health Practices Research Unit, Trauma – Emergency – Critical Care Medicine, Centre de Recherche du CHU de Québec (Hôpital de l'Enfant-Jésus), Université Laval, Québec (Qc), Canada

francois.lauzier@fmed.ulaval.ca

Phone : (418) 525-4444

Fax : (418) 649-5733

2325, Rue de l'Université, Québec, G1V 0A6

Melanie Bérubé PhD inf

Department of Social and Preventative Medicine, Université Laval, Québec (Qc), Canada; Population Health and Optimal Health Practices Research Unit, Trauma – Emergency – Critical Care Medicine, Centre de Recherche du CHU de Québec (Hôpital de l'Enfant-Jésus), Université Laval, Québec (Qc), Canada

melanie.berube@fsi.ulaval.ca

Phone : (418) 525-4444

Fax : (418) 649-5733

2325, Rue de l'Université, Québec, G1V 0A6

Patrick Archambault MD MSc

Population Health and Optimal Health Practices Research Unit, Transfert des connaissances et évaluation des technologies et modes d'intervention en santé, Centre de Recherche du CHU de Québec (Hôpital St François d'Assise), Université Laval, Québec (Qc), Canada

Patrick.m.archabault@gmail.com

Phone : (418) 525-4444

Fax : (418) 649-5733

2325, Rue de l'Université, Québec, G1V 0A6

François Lamontagne MD MSc

Department of Medicine, Université de Sherbrooke,

francois.lamontagne@usherbrooke.ca

Phone: (819) 821-8000

Fax: (819) 821-8295

3001, 12th Avenue North, Sherbrooke, Québec, Canada

Michael Chassé MD PhD

Department of Medicine, Université de Montréal CRCHUM, Montréal, Québec, Canada

michael.chasse@umontreal.ca

Phone : (514) 890-8000

Fax : (514) 343-5834

275, Av Viger Est, Montréal (Québec) H2X 3S7

Henry T Stelfox MD PhD

Departments of Critical Care Medicine, Medicine and Community Health Sciences, O'Brien Institute for Public Health, University of Calgary, Calgary, Alberta, Canada

tstelfox@ucalgary.ca

Phone: (403) 220-6354

Fax: (403) 289-0693

2500, University Drive NW Calgary, AB T2N 1N4

Belinda Gabbe PhD

School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, Farr Institute, Swansea University Medical School, Swansea University, Swansea, UK

belinda.gabbe@monash.edu

Phone: +61 3 9902 6011

Fax: N/A

Wellington Rd, Clayton VIC 3800, Australia

Fiona Lecky MD MSc

School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom; Trauma Audit and Research Network, United Kingdom

f.e.lecky@sheffield.ac.uk

Phone: +44 114 222 2000

Fax: N/A

Broomhall, Sheffield S10 2TG, United Kingdom

John Kortbeek MD

Department of Surgery, University of Calgary, Calgary, Alberta, Canada

john.kortbeek@albertahealthservices.ca

Phone: (403) 220-6354

Fax: (403) 289-0693

2500, University Drive NW Calgary, AB T2N 1N4

Paule Lessard Bonaventure MD MSc

Population Health and Optimal Health Practices Research Unit, Trauma – Emergency – Critical Care Medicine, Centre de Recherche du CHU de Québec – Université Laval (Hôpital de l'Enfant-Jésus), Université Laval, Québec (QC), Canada, Department of Surgery, Division of Neurosurgery, Université Laval, Québec (QC), Canada

paule.lessard-bonaventure.1@ulaval.ca

Phone : (418) 525-4444

Fax : (418) 649-5733

2325, Rue de l'Université, Québec, G1V 0A6

Catherine Truchon PhD

Institut national d'excellence en santé et en services sociaux, Québec (QC), Canada

catherine.truchon@inesss.qc.ca

Phone: (418) 643-1339

Fax: N/A

2535, Boulevard Laurier, Québec, QC G1V 4M3

Alexis F Turgeon MD MSc

Department of Social and Preventative Medicine, Université Laval, Québec (Qc), Canada; Population Health and Optimal Health Practices Research Unit, Trauma – Emergency – Critical Care Medicine, Centre de Recherche du CHU de Québec (Hôpital de l'Enfant-Jésus), Université Laval, Québec (Qc), Canada

alexis.turgeon@fmed.ulaval.ca

Phone : (418) 525-4444

Fax : (418) 649-5733

2325, Rue de l'Université, Québec, G1V 0A6

on behalf of the Canadian Traumatic Brain Injury Research Consortium (ctrc.cihr@gmail.com)

Word Count: 3850 words.

Funding: This research was supported by the *Canadian Institutes of Health Research* (Foundation grant, #353374 and Embedded Clinician Researcher (PA)). Drs Moore, Lauzier, Archambault, Lamontagne and Chassé are recipients of a research salary Award from the *Fonds de Recherche du Québec – Santé* (FRQS). Dr Turgeon is the Canada Research Chair in Critical Care Neurology and Trauma. The funders had no role in developing this protocol.

ABSTRACT

Despite numerous interventions and treatment options, the outcomes of traumatic brain injury (TBI) have improved little over the last three decades, which raises concern about the value of care in this patient population. We aimed to synthesize the evidence on 14 potentially low-value clinical practices in TBI care. Using umbrella review methodology, we identified systematic reviews evaluating the effectiveness of 14 potentially low-value practices in adults with acute TBI. We present data on methodological quality (AMSTAR-2), reported effect sizes and credibility of evidence (I to IV). The only clinical practice with evidence of benefit was therapeutic hypothermia (credibility of evidence II to IV). However, the most recent meta-analysis on hypothermia based on high-quality trials suggested harm (credibility of evidence IV). Meta-analyses on platelet transfusion for patients on antiplatelet therapy were all consistent with harm but were statistically non-significant. For the following practices, effect estimates were consistently close to the null: CT in adults with mild TBI who are low-risk on a validated clinical decision rule; repeat CT in adults with mild TBI on anticoagulant therapy with no clinical deterioration; antibiotic prophylaxis for external ventricular drain placement; and decompressive craniectomy for refractory intracranial hypertension. We identified five clinical practices with evidence of lack of benefit or harm. However, evidence could not be considered to be strong for any clinical practice as effect measures were imprecise and heterogeneous, systematic reviews were often of low quality and most included studies had a high risk of bias.

Protocol registration: PROSPERO: CRD42019132428

Keywords: Low-value clinical practices, traumatic brain injury, umbrella review

INTRODUCTION

Traumatic brain injury (TBI) is the main cause of mortality from injury in people under 45 years of age[1] and leads to US$60 and €33 billion in medical costs in the USA[2] and Europe[3] each year. Moreover, outcomes following TBI have not improved significantly in the last four decades.[4, 5] Treatment options for TBI are multiple, but many lack robust evidence of their effectiveness.[6, 7]

Low-value clinical practices, defined as '*a test or procedure that is not supported by evidence and/or could expose patients to unnecessary harm*'[8-15] consume up to 30% of healthcare resources.[9, 16] In the past decade, the medical community has turned towards the de-adoption of low-value practices as a promising means to reduce the strain on healthcare budgets, free-up resources and reduce harm to patients.[17] Physicians report using low-value practices because of a lack of alternative treatment options, fear of legal consequences, and a lack of guidelines on low-value care.[15, 18] The *Brain Trauma Foundation*, among others, publishes guidelines on TBI care.[19] However, emphasis is on practices that should be adhered to rather than practices that should be avoided. *Choosing Wisely* publishes recommendations specifically targeting low-value practices, but few pertain to TBI care and many are based uniquely on expert consensus.[11] A previous scoping review and expert consultation survey identified 14 potentially low-value clinical practices in acute TBI care.[20] These practices represent potential targets for guidelines, overuse metrics and de-adoption interventions. However, before recommendations can be made, we need to synthesize the evidence base for these practices. The objective of the present study was to synthesize the evidence on potentially low-value intra-hospital clinical practices in acute TBI in adults.

METHODS

Given the multitude of systematic reviews available for the clinical practices identified as potentially low-value,[20] we opted to conduct an umbrella review (a review of systematic reviews).[21] Our umbrella review was conducted according to published guidelines.[22-24] In the absence of reporting guidelines for umbrella reviews, we used applicable Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[25] The protocol was published[26] and registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42019132428). An ethics waiver was obtained from the CHU de Québec – Université Laval research ethics board.

Eligibility criteria

We considered systematic reviews of original studies evaluating the effectiveness of any of the 14 clinical practices previously identified in a scoping review and expert consultation study [20] in acute TBI in adults (exclusively ≥ 16 years old or less than 20% <16 years old). We limited the search to systematic reviews published in English since 1990, in line with umbrella review guidelines.[23, 24] The project steering committee comprising clinicians (two emergency physicians, seven critical care physicians, and one neurosurgeon), four methodologists, and three health system managers used the Population, Intervention, Comparator, Outcome and Study design (PICOS) framework to develop specific research questions for each of the 14 clinical practices (Additional file 1).[20, 27]

We used the Cochrane definition to identify systematic reviews; we considered a review to be systematic if it clearly stated a set of objectives and reported explicit eligibility criteria, an

extensive search strategy (a refined search strategy ran on MEDLINE or the Cochrane Library and at least one other database)[28, 29] and reproducible methods to identify, select, and critically appraise the findings of the included systematic reviews.[22]

Outcomes

Primary and secondary outcomes were identified for each of the 14 clinical practices by the project steering committee and are described in PICOS format in Additional file 1. The most common were intracranial injury for diagnostic interventions and the Glasgow Outcome Scale (GOS) or the GOS-Extended (GOS-E) for therapeutic interventions.

Search strategy

We developed comprehensive literature search strategies separately for each clinical practice on consultation with an information specialist (see Additional file 2 for PubMed search strategies). We searched systematic reviews using the Cochrane Library, Excerpta Medica Database (EMBASE), Epistemonikos,[30] Medical Literature Analysis and Retrieval System Online (MEDLINE) and the International Prospective Register of Systematic Reviews (PROSPERO)[31] from 1990 to up to six months prior to submission for publication. Using a snowball approach, we then screened the references of included studies in addition to previous reviews on this subject.[7, 32-35]

Selection process

We managed all citations with EndNote software (version X8.2, Clarivate Analytics, 2014). We identified and removed duplicates using electronic and manual screening.[36] To ensure reliability when selecting studies for a given practice, two sets of 100 citations were independently

evaluated and then discussed by the reviewers. Pairs of reviewers (PAT, LM, IF) independently screened all identified records using titles, abstracts and full texts, consecutively. Any disagreement was resolved through discussion between reviewers and, if necessary, consultation with a senior author (AFT).

Data items and abstraction process

Using a standardized data abstraction form piloted on a representative sample of 5 systematic reviews, pairs of experienced reviewers (PAT, LM, IF) independently extracted the following data: first author, title, year of publication, databases used and date of the last search; population(s), intervention(s), comparator(s), outcome(s) and study designs included; measures of association and their respective measures of heterogeneity; risk of bias in original studies; and GRADE rating, when available. Any disagreement was resolved through discussion between reviewers and, if necessary, consultation with a senior author (AFT). When information was unclear or unavailable, we contacted systematic review authors with up to three email attempts.

Methodological quality assessment

Two reviewers (PAT, LM) independently critically appraised the quality of systematic reviews using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR-2) tool. Methodological quality was categorised as critically low, low, moderate or high.[37]

Synthesis

Results are presented according to current recommendations for umbrella reviews.[38] For each low-value practice and each review, we present the number of studies according to their design, the sample size, the quality of the reviews (AMSTAR-2), measures of association for primary

and secondary outcomes with their measures of heterogeneity, reported risk of bias for included studies, and reported strength of evidence (GRADE).[26] As GRADE was only used in 6/44 systematic reviews, we also evaluated evidence with credibility of evidence criteria used in previous umbrella reviews.[39, 40] These criteria class evidence from meta-analyses into four categories: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV) and non-significant (NS), based on statistical significance, sample size, heterogeneity and risk of bias.

RESULTS

Of 8,455 citations identified in the initial search, we assessed 212 full texts for eligibility (Figure 1). Of these, 44 were deemed eligible and included in the synthesis (Additional file 3). Details of excluded systematic reviews are provided in Additional file 4.

Description of included reviews

At least one systematic review was identified for ten out of 14 targeted low-value practices (Table 1). Systematic reviews conducted within the last five years were available for nine clinical practices and meta-analyses were available for eight practices. The number of systematic reviews varied from one for plasma transfusion and neuromuscular blocking agents to 19 for hypothermia. Reviews on imaging mostly defined primary outcomes as intracranial injury, neurological deterioration or neurosurgical intervention, and their population as patients with mild or mild complicated TBI. Systematic reviews on therapeutic interventions mainly focussed on the GOS or GOS-Extended, mortality, or adverse events in patients with moderate to severe TBI. Most systematic reviews restricted their population of interest to adults but some included pediatric patients. Nine systematic reviews did not specify targeted study designs in their PICOS.

In 20 other systematic reviews, only RCTs were included and in 14 both randomized controlled trials and observational studies were considered.

Methodological quality of systematic reviews

Of the 44 included systematic reviews, two[41, 42] were rated high quality and eight[43-50] moderate quality (Additional file 5). All but two reviews[51, 5251 52](51, 52)[51,52][51, 52] used a comprehensive research strategy (95%), 17 (38%) established methods prior to the review and reported significant deviations from the study protocol, 34 (76%) used a satisfactory technique for reporting risk of bias, 20 (45%) accounted for risk of bias in individual studies when interpreting/discussing results, 33 out of the 34 reviews (97%) performing meta-analyses used appropriate analytic methods, and 20 (59%) investigated the presence of publication bias and discussed its potential impact on the results of meta-analyses.

Synthesis of results

Primary outcomes

Diagnostic interventions

We identified two reviews for CT in adults with mild TBI (both without meta-analyses),[44, 53] but only one presented data allowing us to calculate point estimates for our primary outcome;[44] less than 5% of patients who were classed as low-risk (any decision rule) had intracranial injury (Table 2). Sample sizes were large for studies using the Canadian CT Head Rule (CCHR), the CT in Head Injury Patients (CHIP) rule and National Emergency X-Radiography Utilization Study (NEXUS) rule, but none of the included studies were at low risk of bias. In adults with acute mild complicated TBI (abnormal initial CT) with no neurological deterioration, routine repeat CT detected progression of intracranial hemorrhage in around 20% of patients. Routine repeat head

CT led to the detection of delayed intracranial in only 0.6% of adults with mild TBI on anticoagulant or antiplatelet therapy.[54]

Therapeutic interventions

We identified two systematic reviews with meta-analyses on platelet transfusion in adults with TBI on antiplatelet therapy, which suggested increased risk of mortality in patients receiving the intervention, but estimates were imprecise and all CIs included the null value.[46, 55] The systematic review on antibiotic prophylaxis for basal skull fracture suggested that the intervention is associated with reduced odds of meningitis, but again the estimates were imprecise and covered the null value.[47] A systematic review by the same group reported no benefit of antibiotic prophylaxis for external ventricular drain placement in severe TBI in terms of risk of infection.[41] We identified four systematic reviews with meta-analyses on seizure prophylaxis extended for more than one week after injury.[48, 56-58] Odds ratio (OR) and risks ratio (RR) varied from 0.40 to 1.28 across systematic reviews. The most widely studied drug, levetiracetam, was associated with a potential reduction in late seizures, but with confidence intervals (CI) covering the null value. Fifteen out of the nineteen systematic reviews identified for therapeutic hypothermia performed meta-analyses with the GOS as the primary outcome.[42, 43, 49, 52, 59-69] OR/RRs varied between 0.61 and 1.16 with 11 suggesting significant benefit (credibility of evidence 3 class II,[42, 43, 69] three class III[65, 67, 68] and 5 class IV[42, 61-64]) and one[69] (the most recent) suggesting significant harm (class IV). In five meta-analyses on high-quality studies, OR/RR either covered the null value (n=3),[49, 64, 65] suggested significant harm (n=1)[69] or suggested significant benefit (n=1).[42] Finally, we identified six systematic reviews on decompressive craniectomy,[70-75] of which four presented quantitative synthesis on GOS.[70, 71, 74, 75] All were based exclusively on RCTs but were of low or critically low quality and had highly heterogeneous point estimates ($I^2 \geq 72\%$). Effect estimates

were consistently close to one with CI covering the null value, suggesting no significant difference in outcome between intervention and control groups.

Secondary outcomes

Close to 0% of adults with mild TBI who were at low risk on a clinical decision rule for head CT required neurosurgical intervention (Additional file 6).[44] Routine repeat head CT in mild complicated TBI without neurological deterioration led to a neurosurgical intervention in between 0.6 and 2.4% of patients,[76-78] a change in clinical management in between 0.6[77] and 3.9%[78] and a change in intracranial pressure (ICP) monitoring in 1.2%.[78] Less than 0.2% of adults with mild TBI on anticoagulant or antiplatelet therapy with a routine repeat CT required neurosurgical treatment or died in hospital.[54]

Authors of the single systematic review on antibiotic prophylaxis in adults with basal skull fractures reported no reduction in all-cause or meningitis-related mortality.[47] In, eight of the 15 systematic reviews on hypothermia, a statistically significant reduction in the risk or odds of mortality was observed whereas one review observed an increase.[43, 50, 61, 64, 65, 67-69] Five out of seven reviews that looked at pneumonia suggested higher risk/odds of this adverse event in adults receiving therapeutic hypothermia.[49, 59, 64, 67, 69] All of the four systematic reviews on decompressive craniectomy looked at mortality;[71, 73-75] three observed a statistically lower risk in the intervention group at 6 months.[73-75] Finally, two systematic reviews on decompressive craniectomy observed significantly lower mean intracranial pressure and shorter length of stay in the intervention group but significantly higher risk/odds of complications.[73, 75]

DISCUSSION

In this umbrella review on potentially low-value clinical practices in acute TBI care, the only clinical practices with any evidence of clinical benefit were routine repeat CT in mild complicated TBI (detection of progression of intracranial hemorrhage around 20%) and hypothermia (credibility of evidence II to IV). However, the most recent review for hypothermia based on high-quality trials suggested harm (credibility of evidence IV).[69] Meta-analyses on antibiotic prophylaxis in basal skull fractures all reported effect estimates consistent with clinically significant benefit but were statistically non-significant.[47] Meta-analyses on anti-platelet transfusion for adults with acute TBI on antiplatelet therapy all reported effect estimates consistent with clinically significant harm but were again statistically non-significant.[46, 55] For the following practices, effect estimates were consistently close to the null value suggesting no clinical benefit: CT in adults with mild TBI who are at low-risk on a validated clinical decision rule;[44] repeat CT in adults with mild TBI on anticoagulant or antiplatelet therapy with no clinical deterioration;[54] antibiotic prophylaxis for external ventricular drain placement;[41] and decompressive craniectomy for patients with refractory intracranial hypertension.[68, 71, 74, 75] However, confidence intervals were all wide.

Three clinical practices pertained to low-value imaging, which leads to increased costs, delays in care for other patients who require diagnostic imaging and is associated with an increased lifelong risk of cancer.[79-81] The review on CT in adults with mild TBI suggested less than 5% of patients who are at low-risk on a validated clinical decision rule had intracranial injury and less than 0.04% required neurosurgical intervention.[44] These results are in line with the inclusion of this practice as low-value in internationally recognized guidelines (*National Institute for Health and Care Excellence* [NICE], *Choosing Wisely*).[11, 82] Less than 1% of adults with mild TBI on anticoagulant or antiplatelet therapy showed progression of hemorrhage on repeat CT or had poor

outcomes.[54] However, the only systematic review on the subject was of very low quality. Evidence of low-value care for routinely repeating head CT in mild complicated TBI was less convincing with around one in five patients showing progression of hemorrhage.[76, 77, 83] This suggests the need to develop predictive models to more accurately identify patients at low risk of progression to avoid unnecessary repeat head CT scans in this population. It may also suggest that progression of intracranial hemorrhage is not the most clinically relevant outcome; repeat CT led to a change in clinical management (i.e. change in ICP monitoring, drug therapy or neurosurgical intervention based on CT results) in less than 4% of patients (secondary outcome).[76-78] This observation also brings up the question of how our threshold of tolerance for false negatives should vary according to the severity of the consequences of missing a case.

In terms of therapeutic interventions, evidence for platelet transfusion in adults on antiplatelet therapy suggested low-value care, with a non-significant increase in mortality in all systematic reviews.[46, 55] Antiplatelet therapy was used in between 3% to 42% of these patients and given the adverse events associated with this practice, its de-adoption has the potential to improve patient outcomes in addition to freeing-up resources. However, reviews were based on retrospective cohorts and evidence was graded as very low in all cases. A systematic review of moderate quality based on RCTs suggested a possible beneficial effect of antibiotic prophylaxis in adults with basal skull fractures with or without CSF leakage with evidence of moderate strength according to GRADE.[47] However, OR were imprecise with 95% CI covering the null value. The only review on antibiotic prophylaxis for external ventricular drain placement included one RCT which suggested no benefit in terms of infection incidence but this was based on a very imprecise pooled estimate and unclear risk of bias.[41] Evidence on extended antiseizure prophylaxis was inconsistent; most point estimates suggested a protective effect, but all CI covered the null value.

The review including the most RCTs (n=6; also with the highest methodological quality) observed a null effect and graded the evidence as very low regarding carbamazepine and phenytoin whereas the most recent review (critically low quality) observed a non-significant protective effect and graded evidence as high for levetiracetam and phenytoin.[48]

For therapeutic hypothermia, multiple large RCTs have been conducted (the most comprehensive systematic review included 22 RCTs)[69] and targeted populations and interventions have changed over the years. The latest high-profile trials evaluated therapeutic hypothermia in all adults admitted to the ICU after a closed TBI with ICP>20 mm Hg for at least 5 minutes after stage I treatments (Eurotherm3235 Trial)[84] and prophylactic hypothermia in adults with severe TBI regardless of ICP prior to randomisation (POLAR-RCT).[85] POLAR-RCT was not included in any systematic review we identified. Recruitment in the Eurotherm3235 Trial was stopped early since preliminary results suggested harm in the intervention arm (6-month mortality, hazard ratio: 1.45 [95 % CI: 1.01-2.10]). Moreover, results from the POLAR-RCT were compatible neither with harm nor benefit on six-month GOS-E (RR: 0.99 [95 % CI: 0.82-1.19]) and six-month mortality (RR: 1.15 [95 % CI: 0.80-1.64]. In line with these two RCTs, the most recent meta-analyses on RCTs with a low risk of bias suggest that therapeutic hypothermia is associated with no benefit or harm.[69] Among changes in these recent trials which may explain observed differences are the application of a normotherapy protocol in the control group.

For decompressive craniectomy, point estimates for unfavorable outcome were close to the null value and statistically non-significant indicating no significant benefit of the intervention in terms of reduction in unfavorable outcome (GOS 1-4) at 6 months. Results are mostly driven by two large high-profile RCTs (DECRA[86] and RESCUE-ICP[87]) that were both included in three of the

four systematic reviews we identified. In the DECRA trial, decompressive craniectomy was conducted as a second-tier therapy; a statistically non-significant increase in unfavorable outcome at six months for the intervention group and no difference in mortality were observed. In the RESCUE-ICP trial, decompressive craniectomy was conducted as a third-tier therapy; the intervention group had significantly lower mortality at 6 months but no difference in unfavorable outcome was observed (gains in survival translated into more patients with severe disability). The systematic reviews we identified for this clinical practice had critical methodological flaws. Of note, Lu and colleagues[75] considered the GOS-E at 6 months for DECRA but at 12 months for RESCUE-ICP whereas Tsaousi[74] and Zhang[73] considered a GOS-E of three and less as an unfavorable outcome, therefore considering upper severe disability as favorable. This led to an overestimation of the benefit of the intervention in both cases. Since the publication of DECRA and RESCUE-ICP, a consensus statement has been published recognizing the lack of evidence of effectiveness for improving patient outcome but recommending (based solely on consensus) decompressive craniotomy in specific situations, often dictated by physician gestalt and physician-family shared decision-making.[88]

Limitations

This review does have limitations which should be considered in the interpretation of results. First, to ensure the feasibility of the review, we restricted our search to the 14 low-value practices identified previously in a scoping review and expert consultation study,[20] which may have led us to miss some low-value practices. However, given the exhaustive search strategy used in the scoping review and the fact that experts were asked to add any other practices they considered low-value, it is unlikely that important low-value practices have been missed. Second, by targeting systematic reviews rather than original studies, we may have missed some evidence. For

three clinical practices, we did not identify any systematic reviews, namely ICU admission in adults with acute mild complicated TBI who are not on direct oral anticoagulants, neurosurgical consultation in adults with acute mild TBI with normal head CT and albumin administration in severe TBI. In addition, for plasma transfusion and neuromuscular blocking agents, all identified studies were qualitative. Furthermore, systematic reviews may not convey the most up-to-date evidence (there are substantial delays between conduct of primary studies and publication of systematic reviews). We did search for RCT published after the date of the last search of the most up-to-date systematic reviews; only the POLAR study was identified.[85] Additionally, systematic reviews may not meet high quality standards; reviews on decompressive craniectomy all had critical methodological flaws.[85] Fourth, meta-analysis results may not convey heterogeneity in effects, as indicated by the high heterogeneity of pooled estimates in many systematic reviews. For example, we may have missed differential effects of decompressive craniectomy as a second-tier or third-tier therapy or of therapeutic hypothermia according to timing and target temperature. Unfortunately, low numbers of studies precluded subgroup analyses for these factors. Fifth, all included reviews/studies aimed to demonstrate effectiveness (superiority trials) and were therefore not designed to formulate conclusions on low-value care (i.e. lack of effectiveness or harm). For this, inferiority trials would be necessary. Finally, for feasibility reasons, we limited this umbrella review to systematic reviews published in English since 1990 as per recommendations for umbrella reviews.[23, 24] These limitations should have a negligible impact on results since no systematic reviews were published prior to 1990 (the first review identified was published in 2001) and most published reviews are written in English.[23, 24] Among the 23 studies excluded based on language, only two were eligible based on the English abstract (published in Mandarin and Romanian) and their reported results (again from the abstract) were concordant with those of reviews included in our study.

CONCLUSIONS

We found low-grade evidence that the following clinical practices are either not beneficial or harmful: CT in adults with mild TBI who are at low-risk on a clinical decision rule; repeat CT for adults with mild TBI on anticoagulant or antiplatelet therapy prior to injury; platelet transfusions in adults on antiplatelet therapy; antibiotic prophylaxis for external ventricular drain placement; and decompressive craniectomy in patients with refractory intracranial hypertension. In addition, the most recent systematic review on high quality trials suggest that hypothermia is associated with harm when compared to normothermia. More rigorous evaluations will be needed to draw strong conclusions on the value of these practices. We should also strive to measure the prevalence of these practices and assess inter-provider variation. Conditional on the results of future research, they may represent targets for de-adoption interventions to improve value in care for adults with acute TBI. The reduction of low-value clinical practices in this patient population has the potential to reduce pressure on strained healthcare budgets, free up resources, reduce adverse events and improve patient outcomes.

Acknowledgements: Not applicable

Author Disclosure Statement

No competing financial interests exist

REFERENCES

1. The American Association for the Surgery of Trauma (AAST) (December 1999). Traumatic Brain Injury in the United States: A Report to Congress, CDC,.

2. Coronado, V.G., Haileyesus, T., Cheng, T.A., Bell, J.M., Haarbauer-Krupa, J., Lionbarger, M.R., Flores-Herrera, J., McGuire, L.C. and Gilchrist, J. (2015). Trends in Sports- and Recreation-Related Traumatic Brain Injuries Treated in US Emergency Departments: The National Electronic Injury Surveillance System-All Injury Program (NEISS-AIP) 2001-2012. J Head Trauma Rehabil 30, 185-197.

3. Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.U., Jonsson, B., group, C.s. and European Brain, C. (2012). The economic cost of brain disorders in Europe. Eur J Neurol 19, 155-162.

4. Rosenfeld, J.V., Maas, A.I., Bragge, P., Morganti-Kossmann, M.C., Manley, G.T. and Gruen, R.L. (2012). Early management of severe traumatic brain injury. Lancet 380, 1088-1098.

5. Maas, A.I.R., Menon, D.K., Adelson, P.D., Andelic, N., Bell, M.J., Belli, A., Bragge, P., Brazinova, A., Buki, A., Chesnut, R.M., Citerio, G., Coburn, M., Cooper, D.J., Crowder, A.T., Czeiter, E., Czosnyka, M., Diaz-Arrastia, R., Dreier, J.P., Duhaime, A.C., Ercole, A., van Essen, T.A., Feigin, V.L., Gao, G., Giacino, J., Gonzalez-Lara, L.E., Gruen, R.L., Gupta, D., Hartings, J.A., Hill, S., Jiang, J.Y., Ketharanathan, N., Kompanje, E.J.O., Lanyon, L., Laureys, S., Lecky, F., Levin, H., Lingsma, H.F., Maegele, M., Majdan, M., Manley, G., Marsteller, J., Mascia, L., McFadyen, C., Mondello, S., Newcombe, V., Palotie, A., Parizel, P.M., Peul, W., Piercy, J., Polinder, S., Puybasset, L., Rasmussen, T.E., Rossaint, R., Smielewski, P., Soderberg, J., Stanworth, S.J., Stein, M.B., von Steinbuchel, N., Stewart, W., Steyerberg, E.W., Stocchetti, N., Synnot, A., Te Ao, B., Tenovuo, O., Theadom, A., Tibboel, D., Videtta, W., Wang, K.K.W.,

Williams, W.H., Wilson, L., Yaffe, K., In, T.P. and Investigators (2017). Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 16, 987-1048.

6. Maas, A.I., Roozenbeek, B. and Manley, G.T. (2010). Clinical trials in traumatic brain injury: past experience and current developments. Neurotherapeutics 7, 115-126.

7. Bragge, P., Synnot, A., Maas, A.I., Menon, D.K., Cooper, D.J., Rosenfeld, J.V. and Gruen, R.L. (2016). A State-of-the-Science Overview of Randomized Controlled Trials Evaluating Acute Management of Moderate-to-Severe Traumatic Brain Injury. J Neurotrauma 33, 1461-1478.

8. Boat, T.F., Chao, S.M. and O'Neill, P.H. (2008). From waste to value in health care. JAMA 299, 568-571.

9. Reilly, B.M. and Evans, A.T. (2009). Much ado about (doing) nothing. Annals of internal medicine 150, 270-271.

10. Berwick, D.M. and Hackbarth, A.D. (2012). Eliminating waste in US health care. JAMA 307, 1513-1516.

11. Choosing Wisely Canada (2015).

12. Morgan, D.J., Dhruva, S.S., Wright, S.M. and Korenstein, D. (2016). 2016 Update on Medical Overuse: A Systematic Review. JAMA Intern Med 176, 1687-1692.

13. Berwick, D.M. (2017). Avoiding overuse-the next quality frontier. Lancet 390, 102-104.

14. Brownlee, S., Chalkidou, K., Doust, J., Elshaug, A.G., Glasziou, P., Heath, I., Nagpal, S., Saini, V., Srivastava, D., Chalmers, K. and Korenstein, D. (2017). Evidence for overuse of medical services around the world. Lancet 390, 156-168.

15. Saini, V., Brownlee, S., Elshaug, A.G., Glasziou, P. and Heath, I. (2017). Addressing overuse and underuse around the world. Lancet 390, 105-107.

16. Fisher, E.S., Wennberg, D.E., Stukel, T.A., Gottlieb, D.J., Lucas, F.L. and Pinder, E.L. (2003). The implications of regional variations in Medicare spending. Part 2: health outcomes and satisfaction with care. Annals of internal medicine 138, 288-298.

17. Niven, D.J., Mrklas, K.J., Holodinsky, J.K., Straus, S.E., Hemmelgarn, B.R., Jeffs, L.P. and Stelfox, H.T. (2015). Towards understanding the de-adoption of low-value clinical practices: a scoping review. BMC Med 13, 255.

18. Emanuel, E.J. and Fuchs, V.R. (2008). The perfect storm of overutilization. JAMA 299, 2789-2791.

19. Carney, N., Totten, A.M., O'Reilly, C., Ullman, J.S., Hawryluk, G.W., Bell, M.J., Bratton, S.L., Chesnut, R., Harris, O.A., Kissoon, N., Rubiano, A.M., Shutter, L., Tasker, R.C., Vavilala, M.S., Wilberger, J., Wright, D.W. and Ghajar, J. (2017). Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery 80, 6-15.

20. Moore, L., Lauzier, F., Tardif, P.A., Boukar, K.M., Farhat, I., Archambault, P., Mercier, E., Lamontagne, F., Chasse, M., Stelfox, H.T., Berthelot, S., Gabbe, B., Lecky, F., Yanchar, N., Champion, H., Kortbeek, J., Cameron, P., Bonaventure, P.L., Paquet, J., Truchon, C., Turgeon, A.F. and Canadian Traumatic brain injury Research, C. (2019). Low-Value Clinical Practices in Injury Care: A Scoping Review and Expert Consultation Survey. J Trauma Acute Care Surg.

21. Fusar-Poli, P. and Radua, J. (2018). Ten simple rules for conducting umbrella reviews. Evid Based Ment Health 21, 95-100.

22. Higgins, J., Green, S. and (editors). (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration.

23. Smith, V., Devane, D., Begley, C.M. and Clarke, M. (2011). Methodology in conducting a systematic review of systematic reviews of healthcare interventions. BMC Med Res Methodol 11, 15.

24. The Joanna Briggs Institute (2014). Joanna Briggs Institute Reviewers' Manual: 2014 edition / Supplement. The Joanna Briggs Institute.

25. Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. and Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6, e1000097.

26. Tardif, P.A., Moore, L., Lauzier, F., Farhat, I., Archambault, P., Lamontagne, F., Chasse, M., Stelfox, H.T., Gabbe, B.J., Lecky, F., Kortbeek, J., Lessard-Bonaventure, P., Truchon, C. and Turgeon, A.F. (2019). Low-value clinical practices in adult traumatic brain injury: an umbrella review protocol. BMJ Open 9, e031747.

27. Stone, P.W. (2002). Popping the (PICO) question in research and evidence-based practice. Appl Nurs Res 15, 197-198.

28. Marshall, I., Marshall, R., Wallace, B., Brassey, J. and Thomas, J. (2018). Rapid reviews may produce different results to systematic reviews: a meta-epidemiological study. J Clin Epidemiol.

29. Bramer, W.M., Rethlefsen, M.L., Kleijnen, J. and Franco, O.H. (2017). Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Systematic reviews 6, 245-245.

30. Epistemonikos Epistemonikos n.d.

31. Centre for Reviews and Dissemination PROSPERO.

32. Horton, L., Rhodes, J. and Wilson, L. (2018). Randomized Controlled Trials in Adult Traumatic Brain Injury: A Systematic Review on the Use and Reporting of Clinical Outcome Assessments. J Neurotrauma 35, 2005-2014.

33. Lei, J., Gao, G.Y. and Jiang, J.Y. (2012). Is management of acute traumatic brain injury effective? A literature review of published Cochrane Systematic Reviews. Chin J Traumatol 15, 17-22.

34. Lu, J., Gary, K.W., Copolillo, A., Ward, J., Niemeier, J.P. and Lapane, K.L. (2015). Randomized controlled trials in adult traumatic brain injury: a review of compliance to CONSORT statement. Arch Phys Med Rehabil 96, 702-714.

35. Synnot, A., Bragge, P., Lunny, C., Menon, D., Clavisi, O., Pattuwage, L., Volovici, V., Mondello, S., Cnossen, M.C., Donoghue, E., Gruen, R.L. and Maas, A. (2018). The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: A comprehensive evidence map. PLoS One 13, e0198676.

36. Bramer, W.M., Giustini, D., de Jonge, G.B., Holland, L. and Bekhuis, T. (2016). De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc 104, 240-243.

37. Shea, B.J., Reeves, B.C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E. and Henry, D.A. (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 358, j4008.

38. Lunny, C., Brennan, S.E., McDonald, S. and McKenzie, J.E. (2018). Toward a comprehensive evidence map of overview of systematic review methods: paper 2-risk of bias assessment; synthesis, presentation and summary of the findings; and assessment of the certainty of the evidence. Syst Rev 7, 159.

39. Theodoratou, E., Tzoulaki, I., Zgaga, L. and Ioannidis, J.P. (2014). Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 348, g2035.

40. Li, X., Meng, X., Timofeeva, M., Tzoulaki, I., Tsilidis, K.K., Ioannidis, J.P., Campbell, H. and Theodoratou, E. (2017). Serum uric acid levels and multiple health outcomes: umbrella

review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. BMJ 357, j2376.

41. Ratilal, B., Costa, J. and Sampaio, C. (2006). Antibiotic prophylaxis for surgical introduction of intracranial ventricular shunts. Cochrane Database Syst Rev, CD005365.

42. Crossley, S., Reid, J., McLatchie, R., Hayton, J., Clark, C., MacDougall, M. and Andrews, P.J. (2014). A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury. Crit Care 18, R75.

43. Fox, J.L., Vu, E.N., Doyle-Waters, M., Brubacher, J.R., Abu-Laban, R. and Hu, Z. (2010). Prophylactic hypothermia for traumatic brain injury: a quantitative systematic review. CJEM 12, 355-364.

44. Pandor, A., Goodacre, S., Harnan, S., Holmes, M., Pickering, A., Fitzgerald, P., Rees, A. and Stevenson, M. (2011). Diagnostic management strategies for adults and children with minor head injury: a systematic review and an economic evaluation. Health Technol Assess 15, 1-202.

45. Yang, L., Stanworth S Fau - Hopewell, S., Hopewell S Fau - Doree, C., Doree C Fau - Murphy, M. and Murphy, M. (2012). Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials.

46. Kumar, A., Mhaskar, R., Grossman, B.J., Kaufman, R.M., Tobian, A.A., Kleinman, S., Gernsheimer, T., Tinmouth, A.T., Djulbegovic, B. and Panel, A.P.T.G. (2015). Platelet transfusion: a systematic review of the clinical evidence. Transfusion 55, 1116-1127; quiz 1115.

47. Ratilal, B.O., Costa, J., Pappamikail, L. and Sampaio, C. (2015). Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. Cochrane Database Syst Rev, CD004884.

48. Thompson, K., Pohlmann-Eden, B., Campbell, L.A. and Abel, H. (2015). Pharmacological treatments for preventing epilepsy following traumatic head injury. Cochrane Database Syst Rev, CD009900.

49. Zhu, Y., Yin, H., Zhang, R., Ye, X. and Wei, J. (2016). Therapeutic hypothermia versus normothermia in adult patients with traumatic brain injury: a meta-analysis. Springerplus 5, 801.

50. Olah, E., Poto, L., Hegyi, P., Szabo, I., Hartmann, P., Solymar, M., Petervari, E., Balasko, M., Habon, T., Rumbus, Z., Tenk, J., Rostas, I., Weinberg, J., Romanovsky, A.A. and Garami, A. (2018). Therapeutic Whole-Body Hypothermia Reduces Death in Severe Traumatic Brain Injury if the Cooling Index Is Sufficiently High: Meta-Analyses of the Effect of Single Cooling Parameters and Their Integrated Measure. J Neurotrauma 35, 2407-2417.

51. Teasell, R., Bayona, N., Lippert, C., Villamere, J. and Hellings, C. (2007). Post-traumatic seizure disorder following acquired brain injury. Brain Inj 21, 201-214.

52. Leng, L. (2017). Hypothermia Therapy after Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Turk Neurosurg.

53. Easter, J.S., Haukoos, J.S., Meehan, W.P., Novack, V. and Edlow, J.A. (2015). Will Neuroimaging Reveal a Severe Intracranial Injury in This Adult With Minor Head Trauma?: The Rational Clinical Examination Systematic Review. JAMA 314, 2672-2681.

54. Chauny, J.M., Marquis, M., Bernard, F., Williamson, D., Albert, M., Laroche, M. and Daoust, R. (2016). Risk of Delayed Intracranial Hemorrhage in Anticoagulated Patients with Mild Traumatic Brain Injury: Systematic Review and Meta-Analysis. J Emerg Med 51, 519-528.

55. Leong, L.B. and David, T.K. (2015). Is Platelet Transfusion Effective in Patients Taking Antiplatelet Agents Who Suffer an Intracranial Hemorrhage? J Emerg Med 49, 561-572.

56. Temkin, N.R. (2001). Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. Epilepsia 42, 515-524.

57. Chang, B.S., Lowenstein, D.H. and Quality Standards Subcommittee of the American Academy of, N. (2003). Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 60, 10-16.

58. Wilson, C.D., Burks, J.D., Rodgers, R.B., Evans, R.M., Bakare, A.A. and Safavi-Abbasi, S. (2018). Early and Late Posttraumatic Epilepsy in the Setting of Traumatic Brain Injury: A Meta-analysis and Review of Antiepileptic Management. World Neurosurg 110, e901-e906.

59. Harris, O.A., Colford, J.M., Jr., Good, M.C. and Matz, P.G. (2002). The role of hypothermia in the management of severe brain injury: a meta-analysis. Arch Neurol 59, 1077-1083.

60. Henderson, W.R., Dhingra, V.K., Chittock, D.R., Fenwick, J.C. and Ronco, J.J. (2003). Hypothermia in the management of traumatic brain injury. A systematic review and meta-analysis. Intensive Care Med 29, 1637-1644.

61. McIntyre, L.A., Fergusson, D.A., Hebert, P.C., Moher, D. and Hutchison, J.S. (2003). Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. JAMA 289, 2992-2999.

62. Brain Trauma, F., American Association of Neurological, S., Congress of Neurological, S., Joint Section on, N., Critical Care, A.C., Bratton, S.L., Chestnut, R.M., Ghajar, J., McConnell Hammond, F.F., Harris, O.A., Hartl, R., Manley, G.T., Nemecek, A., Newell, D.W., Rosenthal, G., Schouten, J., Shutter, L., Timmons, S.D., Ullman, J.S., Videtta, W., Wilberger, J.E. and Wright, D.W. (2007). Guidelines for the management of severe traumatic brain injury. III. Prophylactic hypothermia. J Neurotrauma 24 Suppl 1, S21-25.

63. Peterson, K., Carson, S. and Carney, N. (2008). Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. J Neurotrauma 25, 62-71.

64. Sydenham, E., Roberts, I. and Alderson, P. (2009). Hypothermia for traumatic head injury. Cochrane Database Syst Rev, CD001048.

65. Georgiou, A.P. and Manara, A.R. (2013). Role of therapeutic hypothermia in improving outcome after traumatic brain injury: a systematic review. Br J Anaesth 110, 357-367.

66. Li, P. and Yang, C. (2014). Moderate hypothermia treatment in adult patients with severe traumatic brain injury: a meta-analysis. Brain Inj 28, 1036-1041.

67. Crompton, E.M., Lubomirova, I., Cotlarciuc, I., Han, T.S., Sharma, S.D. and Sharma, P. (2017). Meta-Analysis of Therapeutic Hypothermia for Traumatic Brain Injury in Adult and Pediatric Patients. Crit Care Med 45, 575-583.

68. Zang, Z., Xu, X. and Xu, S. (2017). The efficacy of therapeutic hypothermia in adult patients with traumatic brain injury: A systematic review and meta-analysis. International Journal of Clinical and Experimental Medicine 10, 8691-8699.

69. Watson, H.I., Shepherd, A.A., Rhodes, J.K.J. and Andrews, P.J.D. (2018). Revisited: A Systematic Review of Therapeutic Hypothermia for Adult Patients Following Traumatic Brain Injury. Crit Care Med 46, 972-979.

70. Barthelemy, E.J., Melis, M., Gordon, E., Ullman, J.S. and Germano, I.M. (2016). Decompressive Craniectomy for Severe Traumatic Brain Injury: A Systematic Review. World Neurosurg 88, 411-420.

71. Wang, J.W., Li, J.P., Song, Y.L., Tan, K., Wang, Y., Li, T., Guo, P., Li, X., Wang, Y. and Zhao, Q.H. (2016). Decompressive craniectomy in neurocritical care. J Clin Neurosci 27, 1-7.

72. Abraham, P., Rennert, R.C., Gabel, B.C., Sack, J.A., Karanjia, N., Warnke, P. and Chen, C.C. (2017). ICP management in patients suffering from traumatic brain injury: a systematic review of randomized controlled trials. Acta Neurochir (Wien) 159, 2279-2287.

73. Zhang, D., Xue, Q., Chen, J., Dong, Y., Hou, L., Jiang, Y. and Wang, J. (2017). Decompressive craniectomy in the management of intracranial hypertension after traumatic brain injury: a systematic review and meta-analysis. Sci Rep 7, 8800.

74. Tsaousi, G.G., Marocchi, L., Sergi, P.G., Pourzitaki, C., Santoro, A. and Bilotta, F. (2018). Early and late clinical outcomes after decompressive craniectomy for traumatic refractory intracranial hypertension: a systematic review and meta-analysis of current evidence. J Neurosurg Sci.

75. Lu, G., Zhu, L., Wang, X., Zhang, H. and Li, Y. (2019). Decompressive Craniectomy for Patients with Traumatic Brain Injury: A Pooled Analysis of Randomized Controlled Trials. World Neurosurg.

76. Stippler, M., Smith, C., McLean, A.R., Carlson, A., Morley, S., Murray-Krezan, C., Kraynik, J. and Kennedy, G. (2012). Utility of routine follow-up head CT scanning after mild traumatic brain injury: a systematic review of the literature. Emerg Med J 29, 528-532.

77. Almenawer, S.A., Bogza, I., Yarascavitch, B., Sne, N., Farrokhyar, F., Murty, N. and Reddy, K. (2013). The value of scheduled repeat cranial computed tomography after mild head injury: single-center series and meta-analysis. Neurosurgery 72, 56-62; discussion 63-54.

78. Reljic, T., Mahony, H., Djulbegovic, B., Etchason, J., Paxton, H., Flores, M. and Kumar, A. (2014). Value of repeat head computed tomography after traumatic brain injury: systematic review and meta-analysis. J Neurotrauma 31, 78-98.

79. Mathews, J.D., Forsythe, A.V., Brady, Z., Butler, M.W., Goergen, S.K., Byrnes, G.B., Giles, G.G., Wallace, A.B., Anderson, P.R., Guiver, T.A., McGale, P., Cain, T.M., Dowty, J.G., Bickerstaffe, A.C. and Darby, S.C. (2013). Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 346, f2360.

80. Pearce, M.S., Salotti, J.A., Little, M.P., McHugh, K., Lee, C., Kim, K.P., Howe, N.L., Ronckers, C.M., Rajaraman, P., Sir Craft, A.W., Parker, L. and Berrington de Gonzalez, A. (2012). Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 380, 499-505.

81. Stein, S.C., Hurst, R.W. and Sonnad, S.S. (2008). Meta-analysis of cranial CT scans in children. A mathematical model to predict radiation-induced tumors. Pediatr Neurosurg 44, 448-457.

82. National Institute for Health and Care Excellence (2019). Head injury: assessment and early management.

83. Marincowitz, C., Lecky, F.E., Townend, W., Borakati, A., Fabbri, A. and Sheldon, T.A. (2018). The Risk of Deterioration in GCS13-15 Patients with Traumatic Brain Injury Identified by Computed Tomography Imaging: A Systematic Review and Meta-Analysis. J Neurotrauma 35, 703-718.

84. Andrews, P.J., Sinclair, H.L., Rodriguez, A., Harris, B.A., Battison, C.G., Rhodes, J.K., Murray, G.D. and Eurotherm Trial, C. (2015). Hypothermia for Intracranial Hypertension after Traumatic Brain Injury. N Engl J Med 373, 2403-2412.

85. Cooper, D.J., Nichol, A.D., Bailey, M., Bernard, S., Cameron, P.A., Pili-Floury, S., Forbes, A., Gantner, D., Higgins, A.M., Huet, O., Kasza, J., Murray, L., Newby, L., Presneill, J.J., Rashford, S., Rosenfeld, J.V., Stephenson, M., Vallance, S., Varma, D., Webb, S.A.R., Trapani, T., McArthur, C., Investigators, P.T. and the, A.C.T.G. (2018). Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients With Severe Traumatic Brain Injury: The POLAR Randomized Clinical Trial. JAMA 320, 2211-2220.

86. Cooper, D.J., Rosenfeld, J.V., Murray, L., Arabi, Y.M., Davies, A.R., D'Urso, P., Kossmann, T., Ponsford, J., Seppelt, I., Reilly, P., Wolfe, R., Investigators, D.T., Australian and New

Zealand Intensive Care Society Clinical Trials, G. (2011). Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 364, 1493-1502.

87. Hutchinson, P.J., Kolias, A.G., Timofeev, I.S., Corteen, E.A., Czosnyka, M., Timothy, J., Anderson, I., Bulters, D.O., Belli, A., Eynon, C.A., Wadley, J., Mendelow, A.D., Mitchell, P.M., Wilson, M.H., Critchley, G., Sahuquillo, J., Unterberg, A., Servadei, F., Teasdale, G.M., Pickard, J.D., Menon, D.K., Murray, G.D., Kirkpatrick, P.J. and Collaborators, R.E.T. (2016). Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. N Engl J Med 375, 1119-1130.

88. Hutchinson, P.J., Kolias, A.G., Tajsic, T., Adeleye, A., Aklilu, A.T., Apriawan, T., Bajamal, A.H., Barthelemy, E.J., Devi, B.I., Bhat, D., Bulters, D., Chesnut, R., Citerio, G., Cooper, D.J., Czosnyka, M., Edem, I., El-Ghandour, N.M.F., Figaji, A., Fountas, K.N., Gallagher, C., Hawryluk, G.W.J., Iaccarino, C., Joseph, M., Khan, T., Laeke, T., Levchenko, O., Liu, B., Liu, W., Maas, A., Manley, G.T., Manson, P., Mazzeo, A.T., Menon, D.K., Michael, D.B., Muehlschlegel, S., Okonkwo, D.O., Park, K.B., Rosenfeld, J.V., Rosseau, G., Rubiano, A.M., Shabani, H.K., Stocchetti, N., Timmons, S.D., Timofeev, I., Uff, C., Ullman, J.S., Valadka, A., Waran, V., Wells, A., Wilson, M.H. and Servadei, F. (2019). Consensus statement from the International Consensus Meeting on the Role of Decompressive Craniectomy in the Management of Traumatic Brain Injury : Consensus statement. Acta Neurochir (Wien) 161, 1261-1274.

Authors contributions:

LM contributed substantially to the conception and design of the study, the acquisition of data, the analysis, the interpretation of the data, and drafted the article

PAT contributed substantially to the conception and design of the study, the acquisition of data, the analysis, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

FL contributed substantially to the conception and design of the study, the interpretation of the data, the analysis critical revision of the article and provided final approval of the version submitted for publication

PA contributed substantially to the conception and design of the study, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

FL contributed substantially to the conception and design of the study, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

MC contributed substantially to the conception and design of the study, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

HTS contributed substantially to the conception and design of the study, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

BG contributed substantially to the conception and design of the study, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

FL contributed substantially to the conception and design of the study, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

JK contributed substantially to the conception and design of the study, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

PLB contributed substantially to the conception and design of the study, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

CT contributed substantially to the conception and design of the study, the interpretation of the data, critical revision of the article and provided final approval of the version submitted for publication

FL contributed substantially to the conception and design of the study, the interpretation of the data, the analysis, critical revision of the article and provided final approval of the version submitted for publication

Table 2. Synthesis of results for diagnostic interventions

First author and year of publication of review	Studies (n) (RCT; prospective; retrospective; other)	Patients (n)	AMSTAR-2[a]	Patients with primary outcome (%)[b]	Heterogeneity χ^2, Q or I^2	Studies at low risk of bias, n[c]
Head CT in adults with acute mild TBI at low-risk on a validated clinical decision rule						
Intracranial injury						
Pandor et al. 2011						
CCHR (high risk criteria)	0; 5; 1; 0	17,152		0 to 4.52%[g]		0/6[d]
CHIP	0; 1; 0; 0	3,181	Moderate	1.21%[g]	NA	0/1[d]
New Orleans Criteria	0; 5; 1; 0	13,334		0 to 2.89%[g]		0/6[d]
NEXUS-II	0; 2; 0; 0	21,683		0.46 to 0.90%[g]		0/2[d]
Routine repeat head CT in absence of neurological deterioration in adults with acute mild complicated TBI[e]						
Progression of intracranial traumatic hemorrhage on repeat CT						
Stippler et al. 2012	0; 8; 7; 4	1,630	Critically low	19.9%[h]	NR	0/19
Almenawer et al. 2013	0; 8; 4; 0	2,120	Critically low	22.4%[g]	NR	NR
Marincowitz et al. 2018	0; 2; 12; 0	NR	Critically low	20.4% (14.7-26.7)	I^2=97.9%	NR
Routine repeat head CT in absence of neurological deterioration in adults with acute mild TBI on anticoagulant or antiplatelet therapy[f]						
Delayed intracranial hemorrhage						
Chauny et al. 2016	0; 3; 4; 0	1,594	Critically low	0.6% (0.0-1.2)	NR	0/7

AMSTAR, Assessing the Methodological Quality of Systematic Reviews; CCHR, Canadian CT Head Rule; CHIP, CT in Head Injury Patients; CI, confidence intervals; CT, computed tomography; NA, not applicable; NEXUS-II, the National Emergency X-Radiography Utilisation Study II; NR, not reported; P, proportion; RCT, randomized controlled trials; TBI, traumatic brain injury

[a]Interpretation of AMSTAR-2: High: no or one non-critical weakness, Moderate: more than one non-critical weakness, Low: one critical flaw with or without non-critical weaknesses, Critically low: more than one critical flaw with or without non-critical weaknesses

[b]False omission rate, calculated as «1 – negative predictive value (i.e., true negatives / [true negatives + false negatives])»

[c]As reported in systematic review

[d]Number of studies ≥ 70% items

[e]Mild TBI with abnormal initial head CT

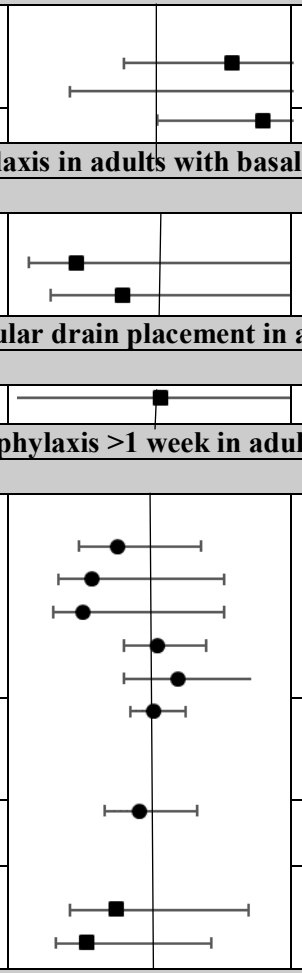
[f]Mild TBI with normal initial head CT

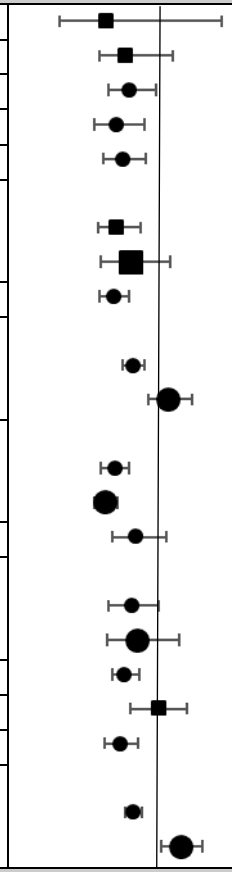
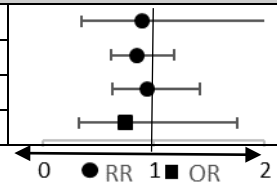
[g]Range of values from included studies

[h]Pooled estimate from included studies (CI not reported)

Table 3. Synthesis of results for therapeutic interventions

First author and year of publication of review	Studies, n (RCT; prosp.; retrosp.; other)	Patients (n)	AMSTAR-2[a]	OR or RR on primary outcome (95% CI)	Heterogeneity χ^2, Q or I^2	Low risk of bias (n)[b]	GRADE; Credibility of evidence[c]
Platelet transfusion in adults with acute traumatic brain injury on antiplatelet therapy							
Mortality							
Kumar et al. 2015			Moderate				
With thrombocytopenia	0; 0; 5; 0	804		OR: 1.55 (0.75-3.18)	I^2=68%	0/5	Very low; NS
Without thrombocytopenia	0; 0; 1; 0	108		OR: 7.59 (0.36-162)	NA	0/1	Very low; NS
Leong et al. 2015	0; 0; 4; 0	711	Critically low	OR: 1.77 (1.00-3.13)	I^2=36%	2/4[d]	NR; NS
Antibiotic prophylaxis in adults with basal skull fractures							
Meningitis							
Ratilal et al. 2015			Moderate				
With CSF leakage	3; 0; 0; 0	92		OR: 0.44 (0.09-2.15)	I^2=0%	2/3[d]	Moderate; NS
Without CSF leakage	2; 0; 0; 0	106		OR: 0.77 (0.25-2.41)	NR	1/2[d]	Moderate; NS
Antibiotic prophylaxis for external ventricular drain placement in adults with acute traumatic brain injury							
Infections							
Ratilal et al. 2010	1; 0; 0; 0	52	High	OR: 1.08 (0.06-18.3)	NA	NR	NR; NS
Extended seizure prophylaxis >1 week in adults with severe TBI							
Late seizures[e]							
Temkin et al. 2001			Critically low			NR	
Carbamazepine	1; 0; 0; 0	110		RR: 0.70 (0.33-1.50)	NR		NR; NS
Phenobarbital	1; 0; 0; 0	163		RR: 0.45 (0.12-1.73)	NR		NR; NS
Phenobarbital+Phenytoin	1; 0; 0; 0	148		RR: 0.36 (0.08-1.73)	NR		NR; NS
Phenytoin	4; 0; 0; 0	812		RR: 1.08 (0.76-1.55)	NR		NR; NS
Valproate	1; 0; 0; 0	344		RR: 1.28 (0.76-2.16)	NR		NR; NS
Chang et al. 2003 *Carbamazepine+phenytoin+valproate*	5; 0; 0; 0	1,312	Critically low	RR: 1.05 (0.82-1.35)	NR	2/5	NR; NS
Thompson et al. 2015 *Carbamazepine+phenytoin*	6; 0; 0; 0	1,029	Moderate	RR: 0.91 (0.57-1.47)	I^2=54%	2/6[d]	Very low; NS
Wilson et al. 2018			Critically low				
Levetiracetam	2; 0; 0; 0	164		OR: 0.69 (0.24-1.96)	NR	2/2	High; NS
Phenytoin	3; 0; 1; 0	716		OR: 0.40 (0.10-1.60)	NR	4/4	High; NS
Therapeutic hypothermia in adults with acute severe traumatic brain injury							



GOS or GOS-E – unfavorable outcome								
Harris et al. 2002	4; 0; 0; 0	499	Critically low		OR: 0.61 (0.26-1.46)	χ^2=6.9	0/4	NR; NS
Henderson et al. 2003	8; 0; 0; 0	748	Critically low		OR: 0.75 (0.56-1.10)	χ^2=16.6	3/8	NR; NS
McIntyre et al. 2003	10; 0; 0; 0	779	Low		RR: 0.78 (0.63-0.98)	Q=16.1	2/10	NR; IV
Bratton et al. 2007	6; 0; 0; 0	694	Critically low		RR: 0.68 (0.52-0.89)	I^2=48%	0/6[f]	NR; IV
Peterson et al. 2008	12; 0; 0; 0	1,294	Low		RR: 0.73 (0.59-0.90)	I^2=59%	1/12	NR; IV
Sydenham et al. 2009			Low					
All studies	20; 0; 0; 0	1,382			OR: 0.69 (0.55-0.86)	I^2=38%	8/20	NR; IV
Low risk of bias	8; 0; 0; 0	686			OR: 0.79 (0.57-1.08)	I^2=0%	8/8	NR; NS
Fox et al. 2010	10; 0; 0; 0	1,223	Moderate		RR: 0.66 (0.56-0.78)	I^2=34%	7/10	II
Georgiou et al. 2013			Low					
All studies	18; 0; 0; 0	1,733			RR: 0.81 (0.73-0.89)	I^2=63%	3/18	Low; III
Low risk of bias	3; 0; 0; 0	670			RR: 1.07 (0.92-1.24)	I^2=1%	3/3	Low; NS
Crossley et al. 2014			High					
All studies	20; 0; 0; 0	1,885			RR: 0.67 (0.78-0.57)	I^2=51%	16/20	NR; II
Low risk of bias	16; 0; 0; 0	964			RR: 0.60 (0.52-0.69)	I^2=0%	16/16	NR; IV
Li et al. 2014	10; 1; 0; 0	1,029	Critically low		RR: 0.83 (0.65-1.05)	I^2=61%	NR	NR; NS
Zhu et al. 2016			Moderate					
All studies	11; 0; 0; 0	1,651			RR: 0.80 (0.63-1.00)	I^2=78%	5/11	NR; NS
Low risk of bias	5; 0; 0; 0	781			RR: 0.84 (0.62-1.15)	I^2=76%	5/5	NR; NS
Crompton et al. 2017	20; 14; 1; 0	3,109	Critically low		RR: 0.74 (0.65-0.85)	I^2=53%	NR	NR; III
Leng et al. 2017	7; 0; 0; 0	1,324	Critically low		OR: 1.00 (0.79-1.21)	I^2=68%	NR	NR; NS
Zang et al. 2017	21; 0; 0; 0	2,302	Critically low		RR: 0.71 (0.60-0.84)	I^2=72%	10/21	NR; III
Watson et al. 2018			Low					
All studies	22; 0; 0; 0	2,346			RR: 0.81 (0.75-0.87)	I^2=71%	2/22	NR; II
Low risk of bias	2; 0; 0; 0	522			RR: 1.16 (1.02-1.32)	I^2=0%	2/2	NR; IV
Decompressive craniectomy in adults with severe traumatic brain injury								
GOS/GOS-E – unfavorable outcome								
Wang et al. 2016	2; 0; 0; 0	175	Critically low		RR: 0.89 (0.34-2.37)	I^2=81%	1/2	NR; NS
Zhang et al. 2017	4; 0; 0; 0	645	Critically low		RR: 0.85 (0.61-1.18)	I^2=73%	2/4	NR; NS
Tsaousi et al. 2018	3; 0; 0; 0	564	Low		RR: 0.94 (0.63-1.41)	I^2=75%	2/3	NR; NS
Lu et al. 2019	4; 0; 0; 0	622	Critically low		OR: 0.75 (0.32-1.75)	I^2=77%	0/4	NR; NS

AMSTAR, Assessing the Methodological Quality of Systematic Reviews; CI, confidence intervals; CSF, cerebrospinal fluid; CT, computed tomography; GOS-E, Glasgow Outcome Scale-Extended; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not applicable; NEXUS-II, the National Emergency X-Radiography Utilisation Study II; NR, not reported; OR, odds ratio; P, proportion; RR, relative risks; RCT, randomized controlled trials; TBI, traumatic brain injury; [a]AMSTAR-2 interpretations: High: no or one non-critical weakness, Moderate: more than one non-critical weakness, Low: one critical flaw with or without non-critical weaknesses, Critically low: more than one critical flaw with or without non-critical weaknesses; [b]As reported in systematic review

[c]II (Highly suggestive evidence): n>1000, $P < 0.000001$ for pooled estimate, largest study p<0.05; III (suggestive evidence): n>1000 and p<0.001 for pooled estimate; IV (weak evidence): p<0.05 for pooled estimate; NS (nonsignificant association): p>0.05 for pooled estimate; [d]Number of studies ≥ 70% items; [e]Antiepileptic drugs were compared to either placebo, no treatment or other pharmacologic agents; [f]Seven RCTs at high risk of bias were excluded