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TITLE: The Development of Best Practice Penetrating TBI Guidelines for Military and Civilian Patients

PRINCIPAL INVESTIGATOR: Dr. Bradley Dengler

CONTRACTING ORGANIZATION: Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD

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14. ABSTRACT

This 2021 study was undertaken in response to the dearth of clinical algorithms for the management of penetrating TBI (pTBI) despite the wide availability of algorithms/guidelines for blunt TBI management noted in the literature^{1, 2, 3}. To correct this disparity, Project Convenor Dr. Randy Bell (USUHS) together with representatives from the leading global organizations for clinical practice guideline generation² Dr. Jamshid Ghajar of the Brain Trauma Foundation, Stanford University and Dr. Gregory Hawryluk of the Seattle International Brain Injury Consensus Conference (SIBICC) effort^{1, 4} thus, submitted proposal Log no. BA200139, “The Development of Best Practice Penetrating TBI Guidelines for Military and Civilian Patients” which was awarded contract # W81XWH21C0102 by USAMRAA effective Sep 15, 2021. The proposal which aimed for an international and multidisciplinary effort to generate new evidence and consensus-based clinical practice guidelines for pTBI also led to the formation of a steering committee made up of the previously mentioned authors who delineated key topics related to penetrating pTBI. The committee formed a body which has grown to 40 Subject Matter Experts (SMEs) drawn worldwide based on their experience with pTBI management. The SMEs consisted of 24 neurosurgeons aided by the remaining Emergency Room physicians, General and Plastic surgeons, Anesthesiologists, Psychiatrists and Informaticists (see Appendix C, List of SMEs p.117-121). By Oct 2021, the SMEs had developed lead questions called “PICOT*” questions (*Mnemonic derived from clinical research question elements: Patient, Intervention, Comparison, Outcome and Time) from which to frame a literature search strategy enumerated in our Yr. 1 Qtr. 1 report. Drawing from their initial series of meetings using the Delphi method of consensus, a publication titled “Rationale and Methods for Updated Guidelines for the Management of Penetrating TBI” (Hawryluk G et al, 2022)⁵ (Annex F, Methods paper, pp 128-130) was produced as one of the first deliverables. The subaward agreement between co-investigators from Stanford Univ. and Oregon Health Sciences Univ. (OHSU) was finalized on June 15, 2022, which decided on a Statement A (public) distribution of the resulting recommendations in line with their institutions’ research efforts to perform the systematic literature review. This was followed by a similar agreement between Stanford Univ. and the Brain Trauma Foundation establishing the project’s (4) multisite collaborative setup. Forty-six Key Questions (KQs) on pTBI were identified and Section Leads assigned to initiate discussions while the Methodologists from site 3 (OHSU) exercised oversight on the objectivity of the consensus-forming process where an 80% majority vote would determine acceptability in resolving a Key Question (Appendix D, p.121-123). The deliberative process culminated in an In-Person Meeting held last Sept 4-8, 2023, at the Henry M Jackson Foundation (Collaboratorium) conference venue in Bethesda, MD where the remaining contentious KQs were tackled and on which this report will focus. The final evidence will then form the basis for the best practice guidelines to be eventually recommended and disseminated to civilian and military neurosurgical communities.

15. SUBJECT TERMS

Penetrating Traumatic Brain Injury, Clinical Practice Guidelines, Algorithms, Subject Matter Experts

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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The first surgical clinical practice guidelines published¹ were those for the management of traumatic brain injury (TBI) and their implementation has been credited with an approximate 50% reduction in mortality². The Brain Trauma Foundation's (BTF) whose guidelines are mandated for US trauma centers to maintain trauma accreditation, has published adult^{3, 6, 8} and pediatric severe TBI⁹ management guidelines as well as those related to combat TBI (<https://www.braintrauma.org/coma/guidelines>), pre-hospital care¹⁰ and prognosis¹¹. Although these guidelines have in most cases been modernized, Guidelines for penetrating TBI have not been updated for almost 20 years. With the evolution of guideline methodology, increased rigor has diminished the role of expert opinion alone in the generation of clinical practice guidelines. Concurrently, modern evidence-based guidelines have excluded consensus-based algorithms because the methodology used to generate them is unique requiring more validation. This has led to a void in the literature leaving non-expert practitioners without guidance and insufficient attention to advances emanating from recent studies. As such, management algorithms based on expert opinion must now bridge published evidence and its limitations with the realities of patient care. By implementing the proposal under this study, "The Development of Best Practice Penetrating TBI Guidelines for Military and Civilian Patients", (Award # W81XWH21C0102), or the pTBI Guidelines Study (short title) we will unite key military and civilian resources and investigators with long-standing experience and successful track-records in developing and disseminating clinical practice guidelines with the concerted effort using a consensus-based process towards generating evidence-based clinical algorithms. The convening neurosurgeons for this project (PI, Dr. Bradley Dengler, former PI and Chief, WRNMMC-Neurosurgery Dr. Randy Bell ; Dr. Jamshid Ghajar of the Brain Trauma Foundation⁶, an organization with world-wide experience in disseminating Clinical Practice Guidelines for Traumatic Brain Injury (TBI) and Dr. Gregory Hawryluk, a convenor himself of the Seattle International Severe Traumatic Brain Injury Convention (SIBICC)⁷, an allied organization) have joined forces not only to update the BTF 4th Edition guidelines⁸ but also to form and lead a body of Subject Matter Experts (SMEs) to address the risks they saw for Penetrating TBI specially the challenge its traumatic vascular problem posed to the population at large. Their journey, which has led them through administrative hurdles, funding and organizational buildup has culminated to this moment when international SMEs would gather for 4 days in September to finalize the updates for the pTBI Management Guidelines that will benefit both civilian and military providers for years to come.

2. Keywords:

Penetrating Traumatic Brain Injury, Clinical Practice Guidelines, Algorithms, Subject Matter Experts

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

A. What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The major goals of the pTBI Guidelines project are bold-highlighted in the list depicted below and gray-highlighted in the table that follows showing the Statement of Work (SOW) which also identifies the significant changes that affected the study to include the milestones reached during its 2 -year period of operation.

The goals are as follows:

- 1) **Establish governance for the project** consisting of a Steering Committee which will:
 - (a) refine the scope of the work and key clinical topics related to management of pTBI in military and civilian patients.
 - (b) provide oversight to ensure timely completion of high-quality work and will provide a mechanism for dispute resolution.
- 2) **Complete a thorough systematic literature review on pTBI** topics identified by the Steering Committee along with grading of identified evidence for quality and risk of bias. This will create a body of evidence for the generation of recommendations.
- 3) Using this body of evidence, **generate evidence-based best practice recommendations, or clinical practice guidelines**, aimed at identifying and encouraging best practices in military and civilian environments.
- 4) **Using a Delphi consensus-based approach, generate management algorithms for key subclasses of pTBI.** Where appropriate we will create distinctions relevant to the care of military and civilian patients.
- 5) **Widely disseminate guidelines and treatment algorithms** using multiple means, including the United States Army Institute of Surgical Research Clinical Practice Guidelines and the civilian Brain Trauma Foundation, which has been responsible for the issuance of previous Clinical Practice guidelines for Traumatic Brain Injury.

STATEMENT OF WORK – 09/15/2021
PROPOSED START DATE – 6/01/2021

Site 1: Uniformed Services University
4301 Jones Bridge Road
Bethesda, MD 20814
PI: Bradley Dengler, MD
Co-I: Gregory Hawryluk, MD

Site 2: Stanford University
314 Galvez St.,
Stanford, CA 94305
Sub PI: Odette Harris, MD
Co-I: Angela Lumba-Brown, MD
Co-I: Gerald Grant, M.D.

Site 3: Oregon Health & Science University
Pacific Northwest – Evidence Based
Pacific Center
3181 SW Jackson Park Road
Portland OR 97239
Sub PI: Shelley Selph, MD, MPH
Annette M. Totten, PhD
Co-I: Marian McDonagh, PharmD

Site 4: Brain Trauma Foundation
228 Hamilton Ave., 3rd Floor
Palo Alto, CA 94301
Sub PI: Jamshid Ghajar, MD

Specific Aim 1: Project Governance	Timeline	Site 1	Site 2	Site 3	Site 4	Status
Major Task 1: Creation of steering group for project governance (Complete)	1-9 mos					Completed
Subtask 1: Determine steering group membership (Complete)	1-3	X				Completed
Subtask 2: Secure WRNMMC IRB ruling (complete)	3-6	X	X	X	X	Completed
Subtask 3: Establish legal framework among sites (Complete)	6-9	X	X	X	X	Completed 6/23/22
<i>1st publication on Methodology delivered 6/11/22. Milestone Achieved: steering group chartered</i>	Month 9	X	X	X	X	Completed 6/23/22
Specific Aim 2: Systematic Literature Review (complete)	9-24 mos					Completed
Major Task 1: Perform a literature search of studies pertaining to the management of penetrating TBI (Complete)	Mos 9-24	X	X	X	X	Completed
Subtask 1: Draft Lit. abstracts	9-12	X	X	X	X	Completed
Subtask 2: Review Abstracts	9-12	X	X	X	X	Completed
Major Task 2: Full Text Review	12-18	X	X	X	X	Completed
Subtask 1: Designation of Teams w Section Leads for Full Text Review	12-18	X	X	X	X	Completed
Subtask 2: Full text review report	18-24	X	X	X	X	Completed
<i>Milestone(s) Achieved: Research outcomes and Full text review complete</i>	Month 24	X	X	X	X	Completed 9/8/23

Specific Aim 3: generate evidence-based best practice recommendations or Clinical Practice Guidelines (CPG)	18-24 mos	X	X	X	X	Completed 9/8/23
Major Task 1: Draft evidence-based recommendations	18-24 mos	X	X	X	X	
Subtask 1: allow for periods. of interaction bet. teams and Methodologist	18-24 mos	X	X	X	X	
Major Task 2: Finalize full evidence-based. recommendations	18-24 mos	X	X	X	X	Completed 9/8/23
Specific Aim 4: Delphi consensus-based approach used to generate management algorithms for pTBI						Completed
Major Task 1: Algorithm development	Month 24	X	X	X	X	Completed
Subtask 1: Draft Consensus-based algorithm	17-20	X	X	X	X	Completed
Subtask 2: Finalize Consensus- based. algorithm	20-23	X	X	X	X	Completed 9/8/23
<i>Milestone(s) Achieved: structure of consensus-based Algorithm Toolkit</i>	20-24	X	X	X	X	Completed 9/8/23
<i>Milestone(s) Achieved: Evidenced-based CPG and treatment algorithms drafted by Delphi Consensus</i>	Month 24	X	X	X	X	Completed 9/8/23
Specific Aim 5: Dissemination of final product						ongoing
Major Task 5: Final Report and Results Dissemination	Month 24	X	X	X	X	ongoing
Presentation and National conferences, website publication	12-24	X	X	X	X	ongoing
Final report and manuscript publication	12-24	X	X	X	X	ongoing
Milestone(s) Achieved: Final reports and final pTBI Guidelines published	Month 24					in progress

A. What were accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

The progress so far are summarized as follows (phrases pertaining to specific aims/ goals are underlined):

1. We have been able to accomplish Specific Aim # 2 which is completing a thorough systematic literature review on pTBI. The 40 corresponding Subject Matter Experts (SMEs), 35 of which were able to make it to our in-Person Meeting at the Henry M Jackson Foundation for Military Medicine Collaboratorium in Bethesda, MD, during Sep 4-8 were also able to diligently participate in reviewing the 295 identified articles assigned to their individual PICOT* question which leads us to a key issue in the management of pTBI which may be critical to the decision-making of the practitioner as he encounters pTBI. *As previously defined, PICOT is a mnemonic derived from clinical research question elements: Patient, Intervention, Comparison, Outcome and Time, that was used to frame a literature search strategy. Since PICOTs lead to the practical Key Question (KQ) informing the provider on-the-scene with the evidence-based recommendation (meaning, distilled from scientific literature by SMEs whose practice have weighed heavily on pTBI exposure/encounters), we have gathered 46 KQs organized in the sequential order of emergency events anticipated in a pTBI setting: Prehospital KQs, Critical Care KQs and Surgery KQs and can be found in Appendix D, p.191-193 for reference. We have also prioritized PICOT questions based on overall impact and available literature.
2. Algorithms. We have generated algorithms in the form of diagrams for the global progression of the patient through the different levels of care following PTBI: a) Initial Assessment and Survivability, (b) Acute Cerebrovascular Injury (c) Chronic Cerebrovascular Injury, (d) Major pTBI Management and (e) Non-Missile Foreign Body Removal. Each section of SME body has been assigned to review at least two algorithms which resulted in very thoughtful revisions. In making a collection of pTBI algorithms available as toolkits online, have fulfilled Specific Aims # 4 and 5. (Pls see Appendix E, P. 194-197 for reference)

PICOT questions. Dr. Selph and team [Site 3, Oregon State Health University (OHSU)] have reviewed 4 PICOT questions so far and provided a written summary of the evidence with evidentiary tables. OHSU staff has taken the role of providing oversight for the deliberations for both the consensus-based and the literature review processes of the SME group as a guardrail that it stays within the confines of scientific rigor. Since PICOT questions act as a gateway to generating evidence-based best practice recommendations, or clinical practice guidelines, it is also in fulfillment of Specific Aim # 3 and in adhering to oversight both in the Scientific review (Specific Aim # 2) and the consensus-gathering process, we accomplish part of Specific Aim # 1 (Governance) as well.

3. The 2 preliminary surveys undertaken at the end of the first year showed a scientific path in ascertaining that a chosen norm or algorithm chosen for pTBI management is reproducible in resulting to satisfactory outcomes when a consensus is arrived at. The bar (set at 80% and above) is high enough to dissuade doubts. Used in addressing the issues raised by the KQs, surveys mark the appropriate feedback mechanism in generating evidence-based clinical practice guidelines, which fulfills Specific Aim # 3
4. Mention was made of some of the outstanding presentations carried out remotely by some of the SMEs, notably Dr. Kitagawa, Dr. Stein on the management of cerebrovascular injury and on the use of MRI in pTBI by Dr. Rosenfeld which informed and helped solidify the decision of the SME members during consensus gathering for the said topics. As this report narrates on how the daily deliberations and voting for and against a crucial KQ unfolds, we will try to use the presentations/lectures mentioned as a contextual backdrop for the reader based on relevance and availability. Since we would unavoidably mention some of the personalities among the SMEs, it is also best for the reader to be acquainted with the extent and diversity of this collegial body of pTBI providers (see Annex C, p.117-121) to appreciate their output.
5. The pTBI Guidelines project held its first In-Person Meeting for the pTBI SMEs last Sept 4-8 using as its venue, the Henry M Jackson Collaboratorium provided at the HJF Headquarters in Bethesda, MD. Done under the auspices of the Uniformed Services University and directly overseen by the Military Traumatic Brain Injury Initiative (MTBI²) under its wings, the event served as the culmination of 2 years of correspondences and remote meetings from the SMEs tapped to accomplish the guidelines from their places of work dispersed all around the globe. This is the first time a recommendations and algorithm consensus was accomplished simultaneously and is the reason for the In-Person nature of the conference and its duration. This report (Appendix B, In-Person meeting report, p.25-116) will focus on the work done during this event, citing the relevance of deliverables previously accomplished.

What opportunities for training and professional development has the project provided?

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Participation in the first In-Person Meeting of Subject Matter Experts (SMEs) chosen world-wide for their wealth of experience in the management of penetrating TBI (pTBI) for the purpose of updating the Guidelines for Clinical Best Practices in managing pTBI provides a master’s class level of training for Health Policy formulation. The writing of Clinical Best Practices Guidelines are often left to the senior more experienced members of a specialty and in this particular event focusing on a neurosurgical problem, the convenors of the project have taken the added measure of adding 15 non-neurosurgeons (Epidemiologists, Informaticists, General surgeons, Emergency Room physicians, Neurointensivist, Anesthesiologists, Orthopedic and Plastic surgeons) for their input to the 25 neurosurgeons who have actively corresponded in previous remote meetings. The lectures provided in the intervening remote conferences provided by the SME on different but relevant topics (Methodology, Acute and chronic vascular problems, Critical care for the SME attendees ensured a high-quality output for the final pTBI Guidelines. (Refer to Appendix C, p. 117-121), for the diversity of specialties among the attendees).

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

The results of the In-Person Meeting will be compiled and organized together with the sequential topics covering the Prehospital, the Critical Care and Surgical phases covering the 46 Key Questions on pTBI resolved in previous meetings through the consensus voting process and submitted to the respective neurosurgical societies (e.g., American Association of Neurosurgical Surgeons, Congress of Neurological Surgeons and the World Federation of Neurosurgical Societies) and other related specialties (e.g., Emergency Medicine, Anesthesiology, Rehab Medicine, General Surgery) for publication and dissemination to the communities of interest. The target audience (non-neurosurgeon practitioner) will also be provided with actionable algorithmic toolkits he may use upon emergency encounter with a pTBI case. An early deliverable on the methodology used in coming out with the pTBI Guidelines (Hawryluk, GH et al, 2022) is already widely circulated. The main public health organizations for civilian (World Health Organization) and military (Defense Health Agency through the Department of Defense) communities will also be contacted for widest dissemination of the pTBI Clinical Best Practices Guidelines.

What do you plan to do during the next reporting period to accomplish the goals?

If this is the final report, state “Nothing to Report.”

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

As of this reporting, simultaneous editorial and organizational (continued resolution of remaining contentious issues) work are being done to ensure that the Clinical Best Practices Guidelines on Penetrating Traumatic Brain Injury be ready for publication before its target date(s) (the year’s end). We will be reviewing the resolutions and final recommendations documented for the covered Key Questions (KQs), aware that the final guidelines on pTBI will be included in the Final Report.

- 4. IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The result from this study directly impacts Neurosurgery as it fills the void of knowledge on penetrating TBI, which is still wanting in the aspect of management. There is currently an agreement on the urgency and lethality of pTBI as a surgical disease among neurosurgical practitioners themselves and even an acceptable mode of response based on the latest developments of neuroendovascular surgery which addresses traumatic cerebrovascular problems, which is one of the cases within pTBI having the highest mortality. However, the availability of this learned neuroendovascular skill has not been sufficiently communicated to the non-neurosurgical practitioners (e.g., Emergency room physicians, anesthesiologists, general surgeons, ENT, plastic surgeons, critical care physicians) whose cooperation in the care of the pTBI patient could result in a safe outcome.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

This Guidelines study which is intended to bridge the communication gap between the neurosurgical practitioner and other non-neurosurgical practitioners who may encounter pTBI necessarily impacts the allied medical disciplines involved in the Pre-Hospital, Critical, Perioperative and even surgical care of the pTBI patient. The pTBI Guidelines distribution plan to reach the allied surgical and medical societies is basically because they form part of the health communities critically impacted by these Guidelines.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Since the emergency scenarios envisioned for pTBI cases as they are encountered by non-neurosurgical practitioners equip the Guidelines with actionable algorithmic toolkits as to their next step of action, it is expected that an appropriate mobile app can be developed to help translate these ‘next step’ tips towards pTBI management into effective appropriately rapid life-saving responses. The Guidelines project is likely to make an impact on commercial technology upon regularity of use in the civilian Emergency room settings or Med-Evac settings to a Military Treatment Facility (MTF).

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- improving public knowledge, attitudes, skills, and abilities;*
- changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- improving social, economic, civic, or environmental conditions.*

Interaction of practitioners in general with the pTBI Guidelines will increase public awareness as well on the needs of pTBI management and a change of attitude towards a less nihilist, more rational and team-building approach to medical emergencies in general.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:*

Due to the magnitude of work required in gathering and organizing the Key Questions (KQs) and their corresponding recommendations in a concise, reader-friendly compilation to guide practitioners in general on pTBI management and drawing from the input of 40 corresponding SMEs of different views, it is anticipated that the planned publication of the Guidelines for Clinical Best Practice in the Management of Penetrating Traumatic Brain Injury may require an adjustment in meeting its targeted schedule before the end of 2023. Despite this awareness, the Project facilitators, (GH, RB) have enjoined their fellow authors to stick to their assigned deadlines.

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

As reflected in our previous Annual reporting, a significant portion of work period (3-6 months) had to be allotted to give way to the legal concerns of the 3 sites ([2] OHSU, [3] Stanford U and the Brain Trauma Foundation for which a renewed contract had to be redrawn. This involved the Distribution Statement wherein the Universities were insistent on using Distribution Statement A which was inherent in their research activities. The other reason involved a reorganizational modification, forming 4 sites from the original 3. Internally, a PI change had to be addressed as the original PI, Dr. Randy Bell, had to retire from the military, but the administrative change was well-documented and went smoothly, having been anticipated. Dr. Bradley Dengler serves as the incoming PI.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve

The reported delay in addressing the legal concerns of the three study sites, as previously mentioned, was resolved by directly addressing the relevant parts of the contract that would accommodate the permissible changes needed for a smoother inter-site working relationship. This was handled by the legal department of the contracting organization (Henry M Jackson Foundation).

them.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

The In-Person Meeting part of the pTBI study had an impact on expenditures since it required transportation and lodging expenses for the Subject Matter Experts (SMEs) who were based in different states, if not parts of the globe for the 4-day event. This was offset by the incoming PI Dr. Bradley Dengler, who by virtue of being the Director of Military Traumatic Brain Injury Initiative (MTBI²) under the Uniformed Services University and host of the event was able to work out the permissions necessary to make the use of the Collaboratorium conference facilities at HJF, Bethesda, MD free of charge for the conference attendees.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or

No human subjects, vertebrate animals, biohazards and/or select agents were used in this study.

Significant changes in use or care of human subjects

Not Applicable.

Significant changes in use or care of vertebrate animals

Not Applicable.

Significant changes in use of biohazards and/or select agents

Not Applicable.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

The most important product from the pTBI study is the manuscript for publication: “Clinical Best Practices in Managing Civilian and Military Patients with Penetrating Traumatic Brain Injury” (2023).

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

1. Hawryluk, GWJ; Selph, S; Lumba-Brown, A; Totten, AM; Ghajar, J; Aarabi, B; Ecklund, J; Shackelford, S; Adams, B; Adelson, D; Armonda, RA; Benjamin, J; Boone, D; Brody, D; Dengler, B; Figaji, A; Grant, G; Harris, O; Hoffer, A; Kitigawa, R; Latham, K; Neal, C; Okonkwo, DO; Pannell, D; Rosenfeld, JV; Rosenthal, G; Rubiano, A; Stein, DM; Stippler, M; Talbot, M; Valadka, A; Wright, DW; Davis, S; Bell, R. Rationale and Methods for Updated Guidelines for the Management of Penetrating Traumatic Brain Injury. *Neurotrauma Reports*. Vol 3, No. 1, 21 Jun 2022, <https://doi.org/10.1089/neur.2022.0008>

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

The manuscript for publication: “Clinical Best Practices in Managing Civilian and Military Patients with Penetrating Traumatic Brain Injury” (2023) is undergoing editorial work as of this writing.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Conference Papers from this pTBI study based on prerecorded videoconferences will be made available as a separate publication.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Not Applicable.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

The Algorithm Toolkit will be provided as a corollary reference to the pTBI Guidelines publication. (Refer to Appendix

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Not Applicable as of this writing.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury, or condition, or to improve the quality of life. Examples include:

- *data or databases.*
- *physical collections.*
- *audio or video products.*
- *software.*
- *models.*
- *educational aids or curricula.*
- *instruments or equipment.*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models).*
- *clinical interventions;*

- *new business creation; and*
- *other.*

Videoconferences are a major part of the pTBI study products which document the important interchanges, discussions and/or presentations which offer insights or rationales for the recommendations which will ensue from the published Guidelines.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

7. KEY PERSONNEL

<u>Name</u>	<u>Role</u>	<u>Specialty</u>	<u>Country</u>
Bradley Dengler, M.D.	PI (6/30/22 – present)	Neurosurgeon	USA
Randy Bell, M.D.	PI (9/15/21 – 6/30/22) Co-PI (6/30/22 – present)	Neuroendovasc. surgeon	USA
Jamshid Ghajar, M.D.	Co-PI BTF, Stanford U	Neurosurgeon	USA
Gregory Hawryluk, M.D.	Co-PI (SIBICC) Cleveland Clinic	Neurosurgeon	Canada
Shelley Selph, M.D., MPH	AI OHSU	Medical Informatics	USA
Annette Totten, Ph.D.	AI OHSU	Epidemiology	USA
Marian McDonagh, PharmD	AI OHSU	Pharmacist	USA
Angela Lumba-Brown, M.D.	Stanford U	Neurosurgery	USA
Gerald Grant, M.D.	AI Duke U	Neurosurgery	USA
Odette Harris, M.D.	AI Stanford U	Neurosurgery	USA

SUPPORTING PERSONNEL

Teodoro Tigno Jr., M.D.	Scientific Coordinator	Scientist II	USA
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*For list of attendees to the In-Person Meeting, pTBI Guidelines Study, 2023, pls refer to Appendix C, p. 117-121.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

<u>Organization Name</u>	<u>contribution to the project</u>	<u>Location</u>
Military Traumatic Brain Injury Initiative (MTBI ²)	In-kind support	MD, USA
Uniformed Services University of the Health Sciences	In-kind support	MD, USA
Henry M Jackson for the Advancement of Military Medicine	facilities,	MD, USA
U.S. Army Medical Research and Development Command	Financial support	MD, USA

8. Special Reporting Requirements (Refer to separate file for Quadchart)

9. APPENDICES

APPENDIX A. REFERENCES

References:

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Stein D, Stocchetti N, Taccone FS, Timmons S, Tsai E, Ullman JS, Vespa P, Videtta W, Wright DW, Zammit C, Chesnut RM. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). *Intensive Care Med.* 2019 Dec;45(12):1783-1794. doi: 10.1007/s00134-019-05805-9. Epub 2019 Oct 28. PMID: 31659383; PMCID: PMC6863785.

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APPENDIX . B. pTBI In-Person Meeting Report

The BTF pTBI In-Person Guidelines and Algorithm Consensus Meeting September 4th – 8th, 2023

Meeting

Day 1. Monday, September 4th, 2023:

The opening day of the 4-day event was initially left loosely structured, owing to the majority of the participants [35 of 39 corresponding Subject Matter Experts (SMEs)] having to settle in after their transport from abroad or from different states. Section Leads who were able to make it to the first day (Labor Day) (Angela Lumba-Brown (AL), Bizhan Aarabi (BA), Hal Mangat (HM) (BTF) who planned to meet one-on-one with any of their working groups, later joined the assembled delegates present who took turns introducing themselves to the rest of the group, some of whom they have previously interacted with only remotely. Each SME would state their designated Key Questions (KQs) and receive feedback from Project Facilitator Randy Bell(RB)/ (GH) as to the availability of the complementary work files for their topic. Gregory Hawryluk (GH) and RB serve as facilitators for the group . The session is documented in the following sequence showing both the efforts at implementing a work strategy of roll call, assignment check and the human communication sharing insights among SMEs as this first In-Person meeting unfolds :

<u>SME</u>	<u>Group</u>	<u>KQ Assigned</u>	<u>Thoughts/</u>
<u>Questions/Issues</u>			

Deb Stein (DS)	Critical Care	4, 13, 20, 30	(all done); (RB: praises work ethic of DS) involved w 41. I need help w 4 (Vasc. Imaging)
Kerry Latham (KL)	Cranioplasty	38, 40, 41	
Max Talbot (MT) (CAF*, Ortho)	“	33, 40	Timing of surgery
Darrel Boone(CAF)	Critical Care	6, 16	(RB: 21 not done yet)
Dylan Pannel (CAF)	Critical Care	4, 30, 32	(RB Reply: work w Guy Rosenthal & Ross on KQs)
Guy Rosenthal	Critical Care		
Andres Soriano (AS) Colombia	PreHospital		relates experience in Colombia (RB reply: suggest looking at KQ2)

The pace quickens and restarts with the reintroductions by facilitators RB and GH. GH engages Shelley Selph (SS) reminding of her coming presentation on Methodologies both for scientific literature review and for the consensus process to the audience. Small group breakout is encouraged.

Day 2. Tuesday, September 5th, 2023

A. continuation of Introductions and presentation of purpose (GH/RB/others)

The following SMEs indicated their presence and specialties: RA, BD JB, DW, KL, AL, GG, OH, MT, RK, DB (GS/Critical Care), Danielle Dang (Inova), JE(Critical Care), DA, DS, BA, GR, DP AV, JG, HM (Neurointensivist, Kansas), Annette Totten, Shelley Selph (Pls see ANNEX C, List of SMEs, p. 117 - 121 for reference)

GH continued with stressing the importance of focusing on pTBI acknowledging its 90% mortality, which held true also for civilian cases. Acknowledging Jamshid Ghajar's (JG) contribution for the Brain Trauma Foundation (BTF) Guidelines which reduced mortality for pTBI by 50%, as proven by the comparison of population groups using pTBI guidelines compared to those without. Rare pTBI guidelines – not well known to the public – were used in the comparison of groups managed via Guidelines showing economic advantage on general health savings. Although the 4th Edition of the BTF Guidelines received criticisms regarding employing more Expert opinion per se rather than consensus from experts, the BTF side did agree to an update of these Guidelines but the plan did not push through as of this writing. The BTF did publish a “Combat “ Guidelines attuned to the medic warfighter at the forefront. Representations have been made to Bev Walters of the BTF if the pTBI Guidelines project can take over the plan for the update, making the endproduct guideline, a useful and timely one..

GH constantly gave the reminder to consult the group's 'Models' paper which was basically the 2022 article published by Neurotrauma Reports (<http://online.liebertpub.com/doi/10.1089/neur.2022.0008>), Herein is sectioned the relevant excerpt which addresses: definition of pTBI, differences, and the types of TBI (Penetrating, Tangential and Perforating, among other topics determining risk of bias in determining the bases of evidence in literature..

Table 1. Key Definitions

Penetrating traumatic brain injury (pTBI): a head injury with violation of, at minimum, the skull and likely dura and brain by a foreign body. Linear non-displaced skull fractures alone will NOT be included.

pTBI encompasses penetrating, tangential, and perforating injuries as follows:

- Penetrating: a foreign object penetrates skull and dura and remains within the skull. This wounding mechanism lacks an exit wound.
- Tangential: a foreign object glances off the skull, which often drives skull fracture fragments into the brain.
- Perforating: a "through-and-through" injury, characterized by entry and exit wounds. Of these three, perforating brain injuries are associated with a worse outcome.

_ pTBI will be subclassified as:

- Missile injuries (such as gunshot wounds)
- Blast fragment injuries (such as type II blast injury—blast overpressure plus fragment injury)
- Low-velocity injuries (such as knives) numbers enrolled and analyzed, relevant outcomes (i.e., mortality, neurological function, selected morbidities, and cost), and funding source.

All included studies will be assessed for risk of bias using criteria specific for the type of study design. Randomized trials will be assessed for risk of bias based on the randomization process, method for allocation concealment, similarity of baseline characteristics, blinding, missing data overall and differences between groups, whether intent-to-treat analysis was used, and possible reporting bias. Assessment of non-randomized studies with a comparison group will include selection of participants, whether differences in prognostic factors between groups were present, missing data, PR specification of outcomes, whether ascertainment of outcomes was unbiased, and adjustment for potential confounding.

Assessment of single-group trials will include selection of participants, pre-specification of outcomes, whether ascertainment of outcomes was unbiased, and assessment of missing data. Case series and case reports are studies with high risk of bias and will not be individually assessed. Study risk of bias will be assessed by two independent reviewers. Data synthesis and quality of the body of evidence. When there is more than one study of an intervention, data will be synthesized quantitatively if a meta-analysis is appropriate (i.e., when studies are clinically homogeneous enough to provide meaningful combined estimates). When statistical heterogeneity is present in a pooled analysis, we will explore the reasons for this using stratified analysis and sensitivity analysis, as appropriate. We will also consider the potential effects of various participant subgroups (e.g., based on demographic characteristics, severity of injury, and injury mechanism) on intervention effects. When data cannot be pooled, we will provide a qualitative summary and analysis of findings.

B. Welcome speech from Dean Elster (USU)

Dean Eric Elster (USU)
guest speaker

USU-School of Medicine (SOM):

Dean Elster gave an overview of the USU School of Medicine by introducing its pillars: its students: both undergraduate and Graduate students, its Faculty and

- Innovation (Great Faculty, students & Faculty funding resources for research
- (Research: Basic, Translational, Clinical,
- Breaking the academic Silos by engaging bridging areas: (Polytrauma, Brain Health, Infectious Disease, Sequencing Center, Craniofacial and MTBI², formerly CNRM)
- Bottomline, USU wholly supports the pTBI Guidelines project initiative

C. Resumption of Purpose and Methodologies,

Before introducing the speaker, GH reminds the audience of the 2 streams: **algorithms & evidence**, which he stated, the participants will be meeting up with in intervals as the general meetings break out into smaller groups in the coming days.

Shelley Selph, M.D., MPH from Oregon Health Sciences University, is one of the Section Leads assigned specifically to oversee that the groups 'Methods' on evaluating both data and the consensus process are within the bounds of scientific rigor. The other Methods person is Annette Totten, Ph.D., also from OHSU.

In introducing her review team, Shelley made mention of one neurosurgeon (Dr. Wright) who served as the review group's resource for neurosurgical procedures they may not be familiar with.

Most complex KQs are surgical for evaluation, preferred cases nearer to injury or recent Rate of study based on 'risk of bias; blinding', morbidity/mortality – telling of possible bias. Limitations? More mortalities, more bias, confidence level, the tighter Confidential Interval results w other studies, the less bias. -took best evidence approach (RCTs)

The Methodology group reviewed 6093 abstracts, 1,921 full txt publications, 124 studies, 188 citations to date and committed to 31 KQs; Why is this review unique? Normally, we would favor the ideal RCTs and ignore the case reports/ case series but because of the nature of the body of evidence, we are left to having to evaluate what cases there are, even inferior ones to make a headway for this project. Large no. of KQs, paradigm different; Trim and remove overlap of KQs. Process works. Identified appropriateness of KQs using specialists, usually 2, to lessen the bias.

KQs: 3 big buckets : PreHospital, Critical Care and Surgical We have mostly encountered case reports or case series for pTBI but at times what are being presented is a mixed bag, say only 75% pTBI. If we can screen for the pTBIs, we do and present them, but if this is not well defined and it is difficult to distinguish the pTBIs, we present the case series to the end user so that he could weigh his decision. This explains why there are different number of citations to the studies at times.

Limitations. Comment from Shelley Selph, Lead Methodologist: One topic left out was: facial injury and reconstruction. The other is polytrauma studies wherein pTBIs died but we failed to capture which of the mortalities were pTBIs.

In the presentation of PICOT question, it is recommended that the background should include:

- relevance and controversies of the PICOT question

- mention should be made about what the First edition Guidelines mention about this topic?
- overview of evidence to include:
 - study design
 - findings
 - limitations
 - quality and level of evidence for each included study
 - noteworthy studies not meeting inclusion i.e., relevant case reports
 - Correct assignment of the level of evidence for each study ?
 - Review of the strength of the body of evidence for the PICOT (High , Moderate, Very Low Low strength)

GH: interjected to be wary of helpful cases in the literature and not dismiss some cases outright. (exemplified case of patient with an aneurysm clip who died at the MR scanner. Be cognizant of things we may miss in the literature that may be helpful (i.e, patient with an aneurysm clip who dies at MRI scanner)

Break...photo-op.

RB: summarizes the progress so far since his conversations w GH and JG, when they agreed to apply to MRMC to start the pTBI Guideline project. RB received funding approval in Aug 2020 but execution delayed until June 2021, in time for the Methodology manuscript which was ready for publication by then..

1) Practicing with KQs

In emphasizing pTBI as a surgical disease, in contrast to closed head injuries, RB also wanted to put into perspective how evidence and algorithm intersect by way of giving as examples of actual cases he met up with (the evidence) and citing with each case the relevant Key Question (KQ) it invoked (algorithm).

Case 1 was a 18 yr. old boy who came in with a metallic foreign body in his head who deteriorated and died within 5 hours. KQs 5, 9 and 10 came into mind. Reviewing the KQs, KQ5 referred to patient characteristic (here injury characteristic) indicating diagnostic accuracy(bullet wound), KQ9 here refers to salvageability. What characteristic could have indicated that the patient was salvageable or non-salvageable.? KQ10 refers to a pTBI mechanism with a poorer outcome. In general, a Gunshot wound clues us in to a poorer outcome. (For reference, pls refer to Annex D, PICOTs and KQs, p.38)

Case 2. Patient comes in w pieces of glass in his brain as foreign body but this was missed on examination. Difficult to see glass on CT scan except in MRI. KQs are: 1,7,10,12

Case 3. Bullet not operated on with first OR. Later scanning revealed bullet migrating posteriorly. KQ: 34, 35, 37

Case 4. Patient underwent a standard-sized craniotomy but GCS decreased from 14 to 8, requiring a Decompressive Craniectomy in the end. KQ 38, 39, 42

Key Questions (KQs) are framed to solve a problem and the provider who meets up with the case is obliged to answer them to provide a solution. This can only come about if the provider has prior knowledge of the algorithm tying the condition to its solution. In a sense, the guideline familiarizes the provider with a valid working algorithm that will be useful for him during emergencies.

2) Practicing with Consensus

A session was devoted for the SMEs to familiarize themselves with the remote device used in registering one's vote on the screen, including how to change your answer, This was led by

Brandon Russell HJF(IT) and GH using the session to practice on old Guideline question
As an example , several old guidelines question were used to test the audience.c/o GH.

<u>Questions from previous Guideline</u>	<u>Audience Result</u>	<u>Qualifier</u>
Perforating injuries correlate w poorer outcome when compared w either penetrating/tangential injuries	(Y >80%)	
Effect of caliber of weapon affect prognosis: <i>rephrase</i> the higher the caliber, the higher impact energy <i>impact</i>	(Y >80%)	(GR: “caliber” w ‘higher energy’)
Is HPN a prognostic factor? (Y)	(Y >80%)	
Is Coagulopathy prognostic factor?	(Y 65%) (N 35%)	
Is GCS prognostic ? Y	(Y >80%)	
Are bil. fixed pupil reflexes prognostic ?		direct orbital Trauma also affects pupillary response and size
Is ICP prognostic of outcome ?	(100%\	
Is Cisternal effacement on imaging prognostic?	(Y >80%)	
Are IVH and SAH pronostic ? Y	(Y >80%)	
Is age a factor for incr. mortality for pTBI ?	(Y >80%)	

3) Discussing one’s differences. Pointers stressed during the meetings.

OH: Linking Level I-IV recommendation: w Level IV– the word ‘strongly’ recommended might add

confusion.

JG: language can conflict w evidence. (RB: consensus statement should not contradict existing evidence)

AH: ex. Antibiotic prophylaxis will not help

HM:given that a lot of recommendations might be Level III-IV,

JG: There is insuff. evidence to support antibiotic prophylaxis

GR: only in instances where evidence is marginal

AL: Level I evidence

JG; conclusion should be an action statement (recommendation)GH summarizing

JE: a commitment to strong wording may affect how “future investigations” – come into play.

GH: Take a vote: no video on how question is phrased

Penetrating Traumatic Brain Injury Guideline *Prehospital* Section

PREHOSPITAL CHAPTERS & SUB-CHAPTERS

- 1. Triage and Diagnosis of pTBI (Britton Adams, Darrell Boone, Deb Stein, Brad Dengler, Angela Lumba-Brown)**
 - a. Definition of pTBI: Primary and Secondary Survey Considerations
 - b. Field Assessments: Scales (including GCS) and Pupil Response
 - c. Mechanisms of Injury
 - d. Prehospital Triage and other Clinical Care Considerations
 - e. Emergent Imaging
 - f. Prognostic Strategies for pTBI in the Prehospital Setting

- 2. Early Clinical Management of pTBI (Stacy Shackelford, Brad Dengler, David Wright, Gerry Grant, Angela Lumba-Brown)**
 - a. Resuscitation Considerations for pTBI
 - b. Indications for Emergent Ventilation, Airway Adjuncts, Intubation, and Sedation
 - c. Prehospital Treatments and Strategies to Prevent Secondary Brain Injury
 - d. On-scene Wound Care and Hemostatic Treatments
 - e. Assessment of Salvageability
 - f. Emergency Department Treatments and Strategies to Prevent Secondary Brain Injury

For pre-Hospital, KQs are 1-23.

Reminder: The most important and complex topics should be prioritized first for in-person discussion (Stacey Shackelford (SSh) interjected def. of prehospital question).

Definition used for 'Pre-Hospital' definition: event that occurs outside of Inpatient/Hospitalization

* from earlier teleconference (led by AL, RB): 300 manuscripts met inclusion -exclusion criteria reviewed (includes case reports & case series)

Screening cohort literature focusing on **Diagnosis, Prognosis** and **Initial Management**

Prehospital Workgroup Members

Angela Lumba Brown (lead)	Emergency Medicine
Stacey Shackelford (lead)	Trauma Surgery
David Wright	Emergency Medicine
Brad Dengler	Neurosurgery
Britton Adams	Prehospital Care
Michael Remley	Prehospital Care
Darrell Boone	Trauma Surgery
Andres Rubiano	Neurosurgery
Deb Stein	Trauma Surgery
Gerry Grant	Neurosurgery
Dylan Pannell	Trauma Surgery

PreHospital Key Questions: Diagnosis

-referring to Diagnosis/ Diagnostic accuracy:

KQ 1: In patients with head, injury, what is the accuracy of diagnosis of pTBI using (e.g., Glasgow Coma Scale, pupil response/size/symmetry, biomarkers [e.g.s100b, UCH-L1, GFAP, tau, NSE, neurofilament/NF-1, cytokine, SNP, EEG]), Clinical exam, imaging techniques (MRI, CT, plain films)?

KQ2: In patients with pTBI, what is the diagnostic accuracy of imaging to detect pseudoaneurysms?

KQ3: In patients with pTBI, what are the benefits and harms and diagnostic accuracy of screening with cerebral angiography to diagnose Traumatic Intracranial arterial aneurysm (TICA) and cerebral vasospasm?

KQ4: In patients with pTBI, when should cerebral angiography best occur and is it preferred over CT angiography (CTA)?

KQ5: Does the diagnostic accuracy of screening for pTBI differ based on patient characteristics (e.g., age, gender, military status) of injury characteristics (e.g., mechanism of injury, location of injury)?

KQ6: In patients with head injury and no obvious penetration of the skull, what are the benefits and harms of screening for pTBI versus no screening?

KQ7: In patients with pTBI and the possibility of metal within the skull, what is the safety of MRI

PreHospital Key Questions: Prognosis

KQ8: In patients w pTBI, what factors related to the scene of injury (e.g, distance /time to trauma centers including rural and austere settings, prolonged field care, transport mode/factors, expertise of pre-hospital providers) impact morbidity and mortality ?

KQ9:What clinical characteristics (oe.g., demographics, mechanism of injury, characteristics of geographic site of injury, vital signs, blood loss, neurological deficit, location of head injury, other injuries) of patients with pTBI, are associated with salvageability or non-salvageability (patients or organs)that can be determined in early clinical settings including the field, the emergency departments and austere environments?

KQ10: What mechanisms of pTBI place a patient at higher risk for poor outcome?

KQ11: In patients with head injury, does on-scene trauma triage and assessments correctly identify pTBI patients with better or worse outcomes including death within 24 hours?

KQ12: In patients with pTBI, what imaging finding are associated with morbidity, mortality, quality of life and function ?

KQ13: What is the diagnostic accuracy of instruments and models (e.g, SPIN Score ?) in predicting survival in pTBI?

PreHospital Key Questions: Initial Management

KQ14: In patients with pTBI, what are the benefits and harms of pre-hospital and emergency department strategies (e.g., CPR, air maneuvers, oxygen administration, cervical spine immobilization, specific fluid administration including hypertonic saline, mannitol administration, pain management, hyperventilation) including the prevention of secondary injury (e.g, cerebral edema, diffuse axonal injury)

KQ15: In patients with p TBI, what patient and scene-related factors indicate a definitive airway is needed compared with no or non-invasive ventilation ?

KQ16: In patients with pTBI, who require intubation, what are the benefits and harms of sedation and analgesia ?

KQ17: on-scene wound care of head injury?

On a shared Google drive, attention to members were drawn to viewing pdf cohort literature list ignoring case reports and case series which were screened out. Directions :Must consider RELEVANCE.

Reminder from Greg Hawryluk, be PRACTICAL. Since preceding Guidelines were criticized for not being practical. Pls review Methods paper before proceeding. And pls be familiar with the guidelines of 2001 since we'll be building up on those.

Assignments were prioritized first on (a) volunteers (b) assignment by Section Lead (c) assignment by designee of Section Lead, until all PreHospital KQs would be covered.

<u>Key Question</u>	<u>Assignment</u>	
KQ1 –	BD, AL	
KQ2 –	DP, GG	
KQ3 –	AR, GG	
KQ4 –	DP, DS	
KQ5 –	BS, BD	
KQ6-	DB, AR	
KQ7 -	DW, AL	
KQ8 –	BA, DP	
KQ9 -	SS, DW	(Salvageability or non salvageability)
KQ10-	DB, GG	
KQ11 –	BA, SS	
KQ12 –	AL, AR	
KQ13 -	BD, DS	(Spin Score)
KQ14 -	BD, DW	
KQ15 –	SS, DP	
KQ16 -	AL, DB	
KQ17 –	BA, GG	
KQ18 -	BD, SS	(antibiotics)
KQ19 –	AL, GG	
KQ20 –	BD, DS	
KQ21 –	AR, DB	
KQ22 -	AL, SS	
KQ23 -	BA, AL	

Reminders from Dr. Greg Hawryluk: differences of opinion still exists among and between experts on: Safety of MRI and management of TICAs, as exemplified in the following KQs

KQs 2-4, 30 questions re. Diagnostic cerebral angio
KQ6 screening of skull perforation
KQ7 safety of MRI in the presence of metallic fragments
KQ 12 imaging findings w morbidity/ mortality
KQ13 diagnostic accuracy of screening. Instruments

Ballistic objects at 1.5-,3- and 7-Tesla



- Lab investigation, *ex-vivo*
- No steel → No movement
- Bullet with steel core and steel pellets moved to an unsafe degree (includes armour piercing bullets which have a steel core)
- At 3T - 5 bullets tested reached 1.7°C degrees. This is not a problem even for ferromagnetic bullets. Background Heat 1.5°C
- Artefact
 - No steel → small signal void
 - Steel bullet → large signal void

Dedini RD et al. Spine J. 2013;13(&):815-22.

Dr. JV Rosenfeld: MRI w metal (fear due to fatal case of Titanium clip aneurysm moving during MRI) how about metal from bullets ? ferromagnetic?

- Factors: variability in manufacture of bullets. Not all steel is ferromagnetic
- Proximity of metal to vital structures
- Artifact-distortion > w ferromagnetic frag. -difficult to do OR w MRI in situ due to artifact-distortion generated.
- In bullets, heating not a problem but movement

Day 3. Wednesday, September 6th, 2023

Critical Care Section. Hal Mangat, Section Lead

1500 – 1530: Critical Care Section Overview (Hal) review topics, scope, progress, points for discussion, points of controversy

1530 – 1730: Presentation, discussion, voting on select Critical Care section KQ's. Assigned question SME's to present.

1. KQ 24: ICP Monitoring

KQ 24: In patients with penetrating TBI, what are the benefits and harms of intracranial pressure

monitoring?

KQ 25. In patients with penetrating TBI, what ICP thresholds should be used for perfusion?

I.

RECOMMENDATIONS

Level I

There is insufficient evidence to support a Level I recommendation for this topic.

Level II

There is insufficient evidence to support a Level II recommendation for this topic.

Level III

Pediatric and adult severe pTBI patients should be managed using ICP monitoring to reduce mortality

Level IV

ICP should be maintained below 20 mmHg in pediatric and adult severe pTBI patients to reduce mortality and improve 6-month neurological outcomes.

EXPERT CONSENSUS:

In the absence of sufficient evidence

EXPERT CONSENSUS conditionally recommends cerebral perfusion pressure should be managed as per non-penetrating TBI recommendations:

The recommended target cerebral perfusion pressure (CPP) value for survival and favorable outcomes is between 60 and 70 mm Hg. Whether 60 or 70 mm Hg is the minimum optimal CPP threshold is unclear and may depend upon the patient's autoregulatory status

II. QUALITY OF BODY OF EVIDENCE AND APPLICABILITY

In patients with pTBI, what are the benefits and harms of intracranial pressure monitoring?

The data on benefits and harms of intracranial pressure (ICP) monitoring in penetrating traumatic brain injury (pTBI) is sparse. We identified one non-randomized study from the National Trauma Data Bank (NTDB; 2017 to 2019) in adults (N=466, mean age 32 years) with primarily gunshot wounds to the head (**Table**).¹ This study used propensity-score matching to compare outcomes in patients who underwent ICP monitoring with patients who did not receive ICP monitoring, and found a lower mortality rate with ICP monitoring (30.9% vs. 40.8%, odds ratio [OR] 0.65; 95% confidence interval [CI], 0.44 to 0.95), but twice the length of intensive care unit (ICU) stay with ICP monitoring (median 15 days vs. 7 days, $p<0.001$).

We also identified one non-randomized study of pediatric patients (aged 0 to 18 years) from the NTDB (2014 to 2017) that examined the association of clinical and treatment variables on outcomes in a population of pediatric patients with cranial gunshot wounds (N=209). ICP monitor placement occurred in 25.8% of the study population (N=54). Regression analyses were performed with covariates: age, presence of shock, ICP monitor placement, craniotomy, sex, ethnicity, and insurance status to determine impact on mortality. The authors report a lower risk of mortality with ICP monitor placement (OR 0.267; 95% CI, 0.082 to 0.864). This association was not present on subgroup analysis in patients presenting with Glasgow Coma Scale (GCS) scores of 9 to 15 (OR 0.65; 95% CI, 0.038 to 11.054). Discharge disposition was also examined and the authors reported that no

association was present between ICP monitor placement and discharge disposition for the entire group (OR 0.707; 95% CI, 0.196 to 2.551) or on subgroup analysis for patients with a GCS of 9 to 15 (OR 0.596; 95% CI, 0.089 to 3.998, **Table**).²

We identified one non-randomized study in an adult population (aged 18 to 90 years) that aimed to determine the rate and risk factors for central nervous system (CNS) infection after pTBI and to examine the impact of antibiotic prophylaxis on those outcomes.^{3,4} The authors reported an association of ICP monitor placement with development of CNS infection. Twenty nine percent of patients (N=223/763) in the study underwent ICP monitor placement after pTBI. The authors reported an increased proportion of infections in the ICP monitor group compared with those without a monitor placed (N=540, 12% vs. 4%, $p<0.0001$). On multivariable analysis ICP monitor placement was associated with an infection OR of 2.27 (95% CI, 1.18 to 4.4, $p=0.01$, **Table**). However, infections were determined clinically and supported by CSF cultures, only available with ventricular CSF ICP monitors, and wound swabs when available, which occurred in 74% of reported cases.

These studies provide low-strength evidence that ICP monitoring is associated with lower mortality, increased length of stay; and no difference in discharge disposition compared with no ICP monitoring.

Table. Outcomes associated with ICP monitoring in penetrating traumatic brain injury

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Mansour, 2023* (NRS) United States Civilian GSW: 93.6% Low-velocity mechanisms: 6.4%	Male: 85% Mean age: 32 years ISS median: 25.0 GCS 3: 60.1% GCS 4: 6.7% GCS 5: 4.5% GCS 6: 10.3% GCS 7: 10.9% GCS 8: 7.5%	ICP monitor placement: 50% (N=233, propensity- score matched) No ICP monitor placement: 50% (N=233, propensity- score matched)	Mortality rate with use of ICP monitor vs. no monitor: 30.9% vs. 40.8%, OR 0.65; 95% CI; 0.44 to 0.95 ICU days with ICP monitor vs. without monitor: 15 vs. 7 days, $p<0.001$ Discharge disposition was not associated with ICP monitoring	Moderate
Lannon, 2022 (NRS) United States Civilian GSW: 100%	Male: 86% Mean age: NR (range 0-18 years) GCS 3: 48% GCS 4-8: 21% GCS 9-12: 11% GCS 13-15: 20%	ICP monitor placement: 25.8% (N=54/209) No ICP monitor placement: 74.2% (N=155/209)	Risk of mortality with the use of ICP monitors vs. no monitor: OR 0.267; 95% CI, 0.082 to 0.864 Mortality benefit was not present in subgroup analysis for patients GCS 9-15 ICP monitor use not associated with discharge disposition (OR 0.707; 95% CI, 0.196 to 2.551)	Moderate

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Harmon, 2019 (NRS) United States Civilian GSW: 90% Knife: 6% Nail gun/hammer/ arrow: 4%	Male: 85% Mean age: 35 (range 18-90 years) <u>CNS Infection vs. no CNS Infection:</u> ISS 0-8: 2% vs. 3% ISS 9-15: 10% vs. 13% ISS 16-24: 39% vs. 29% ISS ≥25: 45% vs. 53%	ICP monitor placement: 29% (N=223/763) No ICP monitor placement: 71% (N=540/763)	<u>ICP monitor placement</u> CNS infection: N=27 (12%) No CNS infection N=196 (88%) <u>No ICP monitor placement</u> CNS Infection: N=24 (4%) No CNS infection N=516 (96%) p <0.0001 Risk of infection with ICP monitor placement vs. no monitor: OR 2.27; 95% CI, 1.18 to 4.4, p=0.01	Moderate

*The results section states that there was no difference in “favorable discharge disposition” between ICP and no ICP monitoring and refers to Table 2 in the text. However, the same data in Table 2 is listed under “unfavorable outcome”. Because of this discrepancy, we do not report data for discharge disposition for this study.

CNS=central nervous system; GCS=Glasgow Coma Scale; GSW=gunshot wound; ICP=intracranial pressure; ISS=Injury Severity Score; NR=not reported; NRS=non-randomized study

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KQ27. In patients with penetrating TBI, what are the benefits and harms of seizure prophylaxis, either initiated or continued, in the critical care setting?

RECOMMENDATIONS

Level I

There is insufficient evidence to support a Level I recommendation for this topic.

Level II

There is insufficient evidence to support a Level II recommendation for this topic.

Level III

There is insufficient evidence to support a Level III recommendation for this topic.

Level IV

There is insufficient evidence to support a Level IV recommendation for this topic.

Level C (achieved by DELPHI consensus)

- *In the absence of evidence, EXPERT CONSENSUS recommends the use of anti-seizure prophylaxis in patients with pTBI to reduce early post-traumatic seizures. (100% consensus)*
- *In the absence of evidence, EXPERT CONSENSUS recommends prophylactic anti-seizure treatment is to be given for a minimum of 7 days in the pTBI population. (100% consensus)*
- *In the absence of evidence, EXPERT CONSENSUS cannot recommend a specific anti-epileptic drug in preventing early post-traumatic seizures. (100% consensus)*

INTRODUCTION

Post-traumatic seizures following penetrating traumatic brain injury are relatively common, especially following transcranial gunshots and intraventricular injury. The risk for seizures decreases over time, in the absence of any evidence of infection.

Prior Guidelines Recommendations

The prior penetrating head injury guidelines addressed “Antiseizure Prophylaxis for Penetrating Brain Injury.”¹⁴ Recommendations created in this edition were based on 9 articles with 4 defined as Class I and 5 defined as Class III. Three general levels of recommendations were utilized in this edition and are related to the current edition as follows: “Standard” is now “Level I”; “Guideline” is now “Level

II”; “Option” is “Level III and IV”. No Level I or Level II recommendations on this subject were provided. Level III/IV recommendations stated antiseizure medication in the first week following pTBI was recommended, and subsequent prophylaxis could not be recommended. Direct evidence supporting this recommendation was lacking, however. None of the Class I studies met inclusion criteria for the updated pTBI guidelines because most of the studied patients had closed TBI.

QUALITY OF BODY OF EVIDENCE AND APPLICABILITY

The data on benefits and harms of administering seizure prophylaxis in penetrating traumatic brain injury (pTBI) is sparse. The actual rate of post injury seizures is difficult to ascertain due to virtually all studied patients receiving some form of anticonvulsant and the heterogeneous nature of the population with regards to the type of injury and the composition and size of any retained material. While mortality rates were reported, it is unclear if seizures contributed to poor outcome independently versus being a marker of extent of injury. In one small study, seizures were more frequently associated with transcranial gunshot wounds than blast injury².

Early vs Late Posttraumatic Seizures

While there is consensus that a posttraumatic seizure occurring in the first week after injury is considered “early” and subsequent episodes are “late” seizures, this is largely based on non-penetrating TBI literature. Of the 13 articles used to support this update, early seizures were defined by two studies as occurring within the first week and the remaining 11 failed to stratify events using any temporal sorting.

Prophylactic Use of Anticonvulsants

We identified no studies that compared seizure prophylaxis with no seizure prophylaxis or a different seizure prophylaxis in patients with pTBI.

We identified 11 noncomparative studies (N=1227) that reported the rate of seizures after seizure prophylaxis.¹⁻¹¹ Sample sizes ranged from 21 to 520, with most studies having fewer than 100 patients. Six studies were in civilians,³⁻⁸ while the other five were in military or war-affected populations. Seizure prophylaxis was mainly phenytoin (or diphenylhydantoin) 300 to 500 mg/day for adults and 4 to 7 mg/kg/day in children, when it was reported. One study administered levetiracetam² and one study reported administering barbiturates (drug not specified) for seizure prophylaxis,¹¹ while three studies did not report the type of seizure prophylaxis used.^{5,8,9}

Four studies (N=207) reported no deaths occurred,^{4,7,9,10} one study (N=99) reported 5% of patients died within 10 and 15 days of injury¹, one study (N=36) reported that five patients died but it was unclear the proportion of patients that died with penetrating injuries,² four studies (N=709) reported between 13% and 23% of patients died within 0 to 3 months,^{3,5,6,8} and one study (N=176) did not report deaths.¹¹

Four studies (N=354) reported that no seizures occurred with diphenylhydantoin or barbiturates given prophylactically,^{1,4,10,11} while other studies reported low rates of seizures (6 studies [N=795] reported 5% to 14% of patients developed a seizure after prophylaxis,^{2,3,5-7,9} 1 study [N=78] reported a 28% posttraumatic seizure rate⁸). Three of the studies indicated seizure prophylaxis was continued from the emergency department,^{1,8,10} while one study initiated seizure prophylaxis in the emergency room

only in ventilated individuals.⁵ Three studies reported initiating seizure prophylaxis in the intensive care unit (ICU),^{3,7,9} while the remaining four were unclear when the medications were initiated.^{2,4,6,11}

Only one small study (N=27) of patients with gunshot wounds to the head reported not giving seizure prophylaxis; one patient had symptomatic convulsions after cranial reconstructive surgery, which occurred 6 months after the initial injury, with no seizures experienced in the remaining patients.¹² The majority of patients had a Glasgow Coma Scale score of 3 to 8 (70%), and the overall mortality was 47%. The authors conclude from this small study that only patients with retained fragments and evidence of epileptiform activity on EEG should receive anticonvulsants.

One study (N=36) that administered levetiracetam for seizure prophylaxis in Iraq and Afghanistan war veterans, reported two patients with pTBI (5.5%) had a posttraumatic seizure.² Both patients suffered a transcranial gunshot wound, whereas most patients who did not have a seizure suffered a blast injury. Both patients who had a posttraumatic seizure eventually died. Although this study did include patients who did not receive seizure prophylaxis, these patients were cleared by neurosurgery for no prophylaxis or had isolated subarachnoid hemorrhage and likely did not have a penetrating injury.

Safety of Anticonvulsants

One large study (N=400) reported harms after prophylactic phenytoin which was administered using an 11 mg/kg intravenous (IV) and a 13 mg/kg intramuscular (IM) parenteral loading dose, and oral maintenance dose (therapeutic blood concentrations of 10-20 mcg/mL) and were followed for 12 to 36 months after surgery.¹³ A skin reaction occurred in 11% of patients between 5 and 70 days after surgery, and of those, two patients developed exfoliative dermatitis.

Table. Studies of seizure prophylaxis after penetrating traumatic brain injury

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Amirjamshidi, 2003 (NRS) Iran Military Blast: 100%	Total population (N=99) Male: 100% Age range: 13-55 Admission GCS: 12 ISS: Not provided	All patients received Diphenylhydantoin 250mg upon admission and Diphenylhydantoin 125mg twice a day for at least one year	No incidences of seizure within the first year	High
Atwood, 2023 (NRS) United States Military	Total population (N=71) Male: 100% Average age: 25 GCS: 13 (ED)	Patients received either Levetiracetam (86%), Phenytoin (3%), or no anticonvulsant (11%)	Two study patients experienced early (within 1 week) seizures -Both had GSW injuries and received Levetiracetam	High

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Blast: 76% GSW: 21% Blunt: 4%	ISS: 27			
Darwazeh, 2018 (NRS) Palestine Civilian Metallic bullets: 68% Rubber bullets: 27% Blast: 6%	Total population (N=520) Male: 90% Age: 6mo to 75 years Adults: 380 (73%, mean 33.5y) Children: 140 (27%, mean = 10.2y)	All study patients received phenytoin for 2 years post injury and then discontinued of no evidence of seizures	Seizure rates were 20% (N=42) in surgically treated patients and 14% (N=29) in conservatively treated patients No distinction between early or late presentation of seizures	High
Dosoglu, 1999 (NRS) Turkey Civilian GSW	Total population (N=47) Male: 87% (N=41) Age: 11mo to 74 years (mean = 27 years)	All patients received diphenylhydantoin (dose and duration not described)	No report of seizures in the postoperative period, one patient experienced delayed seizures (no time frame provided)	High
Khan, 2013 (NRS) Pakistan Civilian GSW	Total population (N=51) Male: 84% (N=43) Age: 28.9 +/- 12 years GCS: 13-15: N=23 9-12: N=6 3-8: N=22	Patients received anticonvulsants, although type and duration and not defined. Text is unclear regarding universality of prophylaxis.	14% (N=7) experienced seizures, no comment on timing or correlation to GCS	High
Malav, 2015 (NRS) India Civilian GSW: 58% Sharp weapon: 17% Machine: 17% Other: 8%	Total Population (N=60) Male Mean age: 27 years (2-60 years old) GCS: 3-8 (30%) 9-12 (25%) 13-15 (45%)	All patients received antiepileptics upon admission and for at least 6 months. Text alludes to phenytoin as anticonvulsant used.	Eight patients (13%) developed seizures in “perioperative period.” Seizures were more common in low GCS group (17% in GCS 3-8, 7% in GCS 9-12, 15% in GCS 15%), although numbers did not rise to significance).	High

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Ozkan, 2002 (NRS) Turkey Civilian GSW	Total Population (N=107) Male Age: 30 (range 5-75)	All patients received phenytoin upon arrival and continued for 1 year unless seizure activity reported.	Six patients (6%) experienced seizures with no elaboration of post-injury timing.	High
Singh, 2015 (NRS) India Civilian GSW or blast	Total Population (N=86) Male: 74 (86%) Female: 12 (14%) Age: Mean 26 (5-68)	All patients started on antiepileptics upon presentation. Presumably phenytoin with additional clobazam for breakthrough seizures.	Seizure rates were not consistently presented in the article and varied between 22 (28%), 15 (18%), and 43 (50%)	High
Splavski, 1998 (NRS) Croatia Civilian and military GSW= 38% Blast= 62%	Total Population (N=21) Male: 17 (81%) Female: 4 (19%) Age: 14-55 years GCS: 3-8: 33% 9-11: 48% 12-15: 19%	Prophylactic anticonvulsants administered to all patients after surgery.	One patient developed seizures “in the acute phase.” Authors noted the patient did not have retained fragments.	High
Taha, 1991 (NRS) Lebanon Civilian GSW= 16% Blast= 84%	Total Population (N=32) Age: 23 (3-51)	All patients received diphenylhydantoin upon presentation and maintained on med for at least one year.	Two seizures were reported, both in patients with penetrating shrapnel injuries.	High
Tudor, 2005 (NRS) Croatia Civ/Mil: NR	Total Population (N=176) Male: 165 (94%) Female: 11 (6%) Age: 29 (mean) GCS: ≥ 8: 91 (54%) <8: 77 (46%)	Barbiturates were given to all patients for an undefined period of time.	Nine (5%) early (1 st week) seizures reported and no late epilepsy.	High

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Petridis, 2011 (NRS) Germany Civilian GSW	Total Population (N=30) Male: 27 (90%) Female: (10%) Age: 49 (13-84) GCS: 3-8: 17 9-15: 13 Non-surgical: 12 (40%)	No prophylactic anticonvulsants used.	One case of seizures reported in the surgically treated group, no cases in the conservatively managed patients.	High
Cosar, 2005 (NRS) Turkey Civilian GSW	Total Population (N=400) Male: 397 (99%) Female: 3 (1%) Age: 23 (4-52) GCS: <5: 7 5-7: 90 8-10: 151 11-13: 125 14-15: 27	Post-operative phenytoin started on all patients and discontinued after 2 years.	Antiepileptic drug reaction was reported in 45 (1%) and 7 seizures noted without timeframe. Authors state no correlation between seizures and mortality.	High

Limitations

The benefit of anticonvulsant medications in the early post injury period with pTBI patients is universally accepted; therefore, there is little chance a randomized control study will be undertaken. The evidence presented in the previous guidelines is supported in the subsequent literature. While this consisted entirely of case studies, the data continue to substantiate administering anticonvulsants to pTBI patients in the first seven days post injury. No new evidence was reviewed to recommend anticonvulsants after one week. In addition, only one study utilized levetiracetam for most patients and had a low incidence of early post-injury seizures; therefore, while there isn't evidence to favor utilizing one medication over another, levetiracetam may be included as initial seizure prophylaxis.

Future Research:

Further high-quality studies are required pertaining to the use of anti-seizure prophylaxis based on injury mechanism and neurological injury, as well as duration of use.

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KQ 28: Antibiotic prophylaxis

KQ 28. In patients with penetrating TBI, what are the benefits and harms of antibiotic prophylaxis, either initiated or continued in the critical care setting?

RECOMMENDATIONS

Level I

There is insufficient evidence to support a Level I recommendation for this topic.

Level II

There is insufficient evidence to support a Level II recommendation for this topic.

Level III

Evidence neither supports nor refutes the benefits of routine use of prophylactic antibiotics in patients with pTBI

Level IV

In pTBI patients treated with routine prophylactic antibiotics, there is insufficient evidence to support any specific antibiotic regimen or duration of treatment supported by evidence.

Level C (achieved by DELPHI Consensus)

- *In the absence of sufficient evidence, based on EXPERT CONSENSUS, it is reasonable to treat pTBI patients who have violation of the dura or who are undergoing invasive procedures with prophylactic antibiotics. (87.5% consensus)*
- *In the absence of sufficient evidence, based on EXPERT CONSENSUS, pTBI related to blasts, air sinus penetration, retained bone fragments from grossly contaminated objects are at higher risk of infections (95.8% consensus).*
- *In the absence of sufficient evidence, based on EXPERT CONSENSUS, in pTBI patients at higher risk of intracranial infections it is reasonable to administer broad-spectrum antibiotic prophylaxis (95.8% consensus) including anaerobic coverage (81.8% consensus) for duration of up to 5 days. (91% consensus)*
- *In the absence of sufficient evidence, based on EXPERT CONSENSUS, in patients who are NOT at higher risk of intracranial infections it is reasonable to administer antibiotic prophylaxis (87.5% consensus) for duration of up to 3 days (100% consensus)*
- *In the absence of sufficient evidence, based on EXPERT CONSENSUS, when prophylactic antibiotics are administered, they should be administered as soon as possible. (100% consensus)*

INTRODUCTION

Intracranial infection following pTBI is not uncommon. Historically, infection rates were high, and led to routine prophylactic use of antibiotics in such patients. However, with improving surgical debridement techniques, and cleaner wounds, rates of infection have been decreasing overall since earlier studies from the world wars. Moreover, bacteria identified in infections are different from

those obtained by routine initial wound swabs. With rising rates of antimicrobial resistance, it is of utmost importance to be very rigorous about the routine use of antibiotic prophylaxis.

Prior Guidelines Recommendations

In the prior edition of the guidelines (2001), an ‘optional’ recommendation (Level III/IV) was made supporting the prophylactic use of antibiotics in patients with pTBI. There were increased rates of infection in pTBI patients with associated CSF leak, air sinus penetration, or retained bone fragments. Use of prophylactic antibiotics for patients with pTBI was option based on the decrease in infection rate after the onset of routine antibiotic use for these injuries and extrapolation from data on clean, elective neurosurgical cases.

QUALITY OF BODY OF EVIDENCE AND APPLICABILITY

There is scant for the benefit of the use of prophylactic antibiotics in the setting of penetrating traumatic brain injury (pTBI). We identified no trials that evaluate the use of prophylactic antibiotics, antibiotic regimen, or duration of antibiotics in this setting. One study assessed whether the duration of prophylactic antibiotics affected outcomes. All were conducted in civilian populations, three in the United States, and one each in South Africa and Colombia.

The largest study was a retrospective review of 11 years (2006 to 2016) of records from 17 trauma centers in the United States that identified 763 adult patients with penetrating brain injuries, including 62% (N=475) who were treated with antibiotics within 24 hours of admission.¹ The overall rate of central nervous system infections was 7% and this was not statistically significantly different for patients who did or did not receive antibiotics. Another large study of 192 non missile penetrating head injuries treated in one medical center in South Africa focused on categorizing management and complications of these injuries and how they differed from gunshot wounds.² The authors reported that 33% of the patients received no antibiotics, 52% received antibiotics in less than 24 hours from the time of injury, and 15% received antibiotics more than 24 hours after injury. The rate of infections was significantly lower among patients who received antibiotics at any time compared with those who did not (8% vs. 26%, $p=0.002$) in both univariate and adjusted models. However, the characteristics of the patients who did and did not receive antibiotics and the variables used in the adjusted model were not reported, as this was not the focus of the study.

Three studies were limited to patients with gunshot wounds. One study of 75 patients over 16 years old treated in a single U.S. civilian hospital for gunshot wounds to the head and survived over 48 hours were compared based on antibiotic regimen: no antibiotics, a single agent, or multiple antibiotics.³ In cases from 6 years (2012 to 2018), there were 8 (10.7%) intracranial infections documented over 1 week to 3 years from injury. There were more infections in patients who received the multiple antibiotics in unadjusted analyses, but in the adjusted analysis, neither the antibiotic group (single antibiotic or multiple antibiotics) nor duration of antibiotic prophylaxis were statistically significant. There were also 13 nosocomial infections reported in this study, but these were also not different across the antibiotic groups and were not associated with later intracranial infections. A study in Columbia followed 160 adult patients with gunshot wounds to the head who did or did not receive prophylactic antibiotics at the discretion of the treating neurosurgeon.⁴ A higher proportion of the patients who received antibiotics (33.9%) developed infections than those who did not (19.8%), but this difference was not statistically significant, and receipt of antibiotics was not included in multivariate analysis of risk factors for infection. Another study of patients treated for gunshot wounds to the head in a single trauma center in the United States identified 59 patients who

survived more than 48 hours.⁵ Thirty-eight (64%) were given systemic antibiotics within 36 hours of admission; 26 as preparation for a surgical procedure and 12 without surgery. Twenty-nine percent of these patients developed infections (N=11), while none of the patients who did not receive antibiotics developed infections.

The one study on the duration of antibiotics that was identified, used a registry from one trauma center to identify a small sample (N=22) of adult patients with penetrating gunshot wounds to the head who received short-term prophylactic antibiotics, for 48 hours or less (N=9). or extended treatment for over 48 hours (N=11).⁶ In follow-up that lasted for a mean of 15 months, no infections occurred in the patients with short-term treatment and four patients (30.8%) developed infections in the extended treatment group. One patient in each group died within 30-days of any cause and neither infection nor mortality were statistically significantly different, however, the study was not sufficiently powered to detect a difference in infection rates.

These studies provide low strength of evidence for the finding across most of the studies that prophylactic antibiotics as part of critical care make no significant difference in infection rates compared with no antibiotics for patients with penetrating brain trauma.

Table. Antibiotic prophylaxis in critical care

Author, Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Effectiveness of Antibiotic Prophylaxis				
Harmon, 2019 (NRS) United States 17 trauma centers Civilian GSW: 90% Knife: 6% Nail gun/hammer/ arrow: 4%	N=763 Survived >48 hours Male: 85% Mean age: 35 years (range: 18 to 90) White: 45% Black: 42% Hispanic: 5% Asian: 1% Other: 7: Mean ISS: 24 (range: 1 to 75) Retained foreign body: 63% Dural penetration	Prophylactic antibiotics: 62% (N=475) within 24 hours of admission Duration of antibiotics: None: 36% <24 hours: 14% 24 to 72 hours: 21% 3 to 7 days: 19% >7days: 10%	CNS Infections Total: 7% (n=51) Antibiotics vs. none: 7% vs. 6%, p=0.50 Mortality Total: 71% (N=541) CNS infection Died: 8% Lived: 92% No CNS infection Died: 75% Lived: 25% p=0.006 Timing of infection diagnosis 8% 1 to 4 days (N=4) 21% 5 to 10 days (N=11) 63% >10 days (N=8) 8% unknown (N=4)	Moderate

Author, Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
	Diffuse: 60% Local: 40%			
Harrington, 2020 (NRS) South Africa Civilian Assault: stab wounds Knife: 81% Screwdriver: 9% Nail gun: 0.5% Garden fork: 0.5% Barbeque fork: 0.5% Unknown: 8%	N=192 Male: 96% Mean age: 26.2 years (range: 18 to 58) GCS 15: 37% GCS 12 to 14: 34% GCS 9 to 11: 14% GCS 7 to 8: 8% GCS 4 to 6: 6% GCS 3: 1% Weapon in situ: Yes: 18% No: 82%	Prophylactic antibiotics None: 33% (N=64) <24 hours: 52% (N=99) >24 hours: 15% (N=29) Time from injury to antibiotic administration, as presented in article	Infections Total: 14% (N=27) Antibiotics vs. none Univariate: 8% vs. 26%, p=0.002 Adjusted (variables included not specified): OR 0.3 (95% CI, 0.1 to 0.8), p=0.02 Types of infections Abscess: 41% Meningitis: 30% Empyema: 15% Wound infection: 7% Abscess/empyema: 4% Ventriculitis 4%	High
Johnson, 2021 (NRS) United States Civilian GSW: 100%	N=75 Survived >48 hours Males: 84% Median age: 30 years (IQR: 20 to 45) White: 48% Black: 48% Other, not specified: 4% Median GCS (IQR): 10 (6 to 15) Median ISS (IQR): 25 (13 to 30) CSF leak: 8%	Prophylactic antibiotics 18% None (N=13) 37% Single (N=28) 45% Multi agent (N=34) 5-day median duration Most common 69% cephalosporins 43% vancomycin Initial GCS Median (IQR) None: 15 (13 to 15) Single: 10.5 (6.8 to 15)	Intracranial infections (N=8) None vs. single vs. multi Unadjusted: 1 vs. 1 vs. 6, p=0.019 Antibiotic duration, p=0.42 Survival at 6-months: 53.8% (N=7) vs. 67.9% (N=19) vs. 44.1% (N=15), p=0.422 Multivariable logistic regression (included demographics, GCS, ISS, Injury characteristics, comorbidities) Antibiotic group and duration: NS Infection associated with CSF leak and diabetes 75% gram positive	Moderate

Author, Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
	Surgery: 41.3% Tangential injuries: 32%	Multiple: 8 (6 to 13.8) Surgical Intervention None: 7.7% Single: 28.6% Multiple: 64.7%	Nosocomial infections (N=13): 1 vs. 6 vs. 6, p=0.556 Agent used p=0.8, duration p=0.18 Nosocomial not related to later intracranial infection, p=0.621	
Jimenez, 2013 (NRS) Colombia Civilian GSW: 100%	N=160 Male: 91% Mean age: 29 years (range 15 to 61) Rural: 26% GCS ≥ 9 : 66% GCS ≤ 8 : 34%	Prophylactic antibiotics: 36.8% (N=59) No antibiotics: 63.2% (N=101) Based on decision of treating neurosurgeon; all surgery patients 36% Ceftriaxone 19% Cephadrine 19% Ampicillin/Sulbactam Mean follow-up: 39 months (range: 3 to 92)	Intracranial infections: 25% (N=40) With antibiotics vs. without Intracranial infections: 33.9% (20/59) vs. 19.8% (20/101), NS (not included in multivariate analysis) Good (GOS 4 to 5): 59% vs. 54% Bad (GOS 1 to 3): 41% vs. 46% 3 variables significantly associated with infection 1. Presence of fragments post-surgery on CT 2. Projectile trajectory through natural orifices 3. Hospital stay >4.5 days 95% of infections emerged within 30 days	Moderate
Doherty, 2004 (NRS) United States Civilian GSW: 100%	N=59 survived >48 hours Male: 86% Mean age: 29 years (range 2 to 76) GCS 3 to 5: 10%	Prophylactic antibiotics within 36 hours of admission (N=38): 26 (44%): related to a surgical procedure 12 (20%): without surgery	0 infections in 11 patients with no antibiotics 29% Infections in 38 patients with prophylactic antibiotics: 3 CNS 2 IVC 1 initial wound 5 type not reported	High

Author, Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
	GCS 6 to 8: 12% GCS 9 to 12: 17% GCS 13 to 15: 61% 40 (68%) local irrigation, debridement 11 (19%): craniotomy, local debridement 4 (7%) craniotomy, extensive debridement 4 (7%) craniotomy, hematoma evacuation	53 (90%): any antibiotics 10 additional >36 hours after admission 5: topical only Cefazolin was most common (numbers not reported)	8 infections in the 10 patients who received later antibiotics: 4 IVC infections total 2 prophylactic antibiotics 2 none 7 injuries to air sinuses (risk factor for infection) 2 required Camino catheter monitors Both treated with antibiotic 2 to 7 days (unclear if both prophylaxis and treatment) 1: tracheobronchitis 1: died intraabdominal abscess and sepsis	
Duration of Prophylactic Antibiotics				
Etheridge, 2017 (NRS) United States Civilian GSW: 100%	N=22 Male: 95% Mean age: 28.3 years (range: 18 to NR) Mean GCS: 10.15 Mean ISS: 18.98 77.3% urgent operation 22.7% managed medically	Short-term ≤48 hours: Mean 1.2 days (N=9) Extended >48 hours: Mean 6.3 days (N=13)	Short-term vs. extended CNS infections: 0 vs. 30.8% (N=4), p=0.066 1 meningitis, 1 intracranial abscess, and 2 suspected meningitis 30-day all-cause mortality: 11.1% (1) vs. 7.7% (1), p=0.784 No multidrug resistant infections	Moderate

CI=confidence interval; CNS=central nervous system; CSF=cerebrospinal fluid; CT=computed tomography; d=days; GCS=Glasgow Coma Scale; GOS=Glasgow Outcome Scale; GSW=gunshot wound; IQR= interquartile range; ISS=Injury Severity Score; IVC=intravascular catheter; MOI=mechanism of injury; NR=not reported; NRS=non-randomized study; NS=not significant; OR=odds ratio; US=United States

Limitations

All studies that have attempted to look at rates of infection and use of prophylactic antibiotics in pTBI were all retrospective. The heterogeneity of injuries, the process of decision-making for the administration of antibiotics, and which antibiotics were selected for use are all significant sources of bias in these studies. Whether the patients who received prophylactic antibiotics were actually at high risk of infections remains undetermined. For example, pTBI from blast injuries as opposed to gunshot injuries are at high risk of contamination, retained fragments, and resulting infection. This additional selection bias must also be taken into account when considering the results of these studies, as they limit the external validity of some findings. Of note, in the main supportive study, there was a significant delay in presentation for many of these patients. Furthermore, no study described complication rates specifically associated with antibiotic use. While some patients with pTBI may have other systemic injuries that could predispose to sensitivity to toxicity of antibiotics, there is no reason to assume that the head injury itself would do so.

Future Research:

In the face of critically rising antimicrobial resistance, and the balance of immediate benefit to patient but delayed societal harm, further research into the routine prophylactic antibiotic use in pTBI patients is required. Key elements are classification of contamination in civilian and combat settings, which constitute different phenotypical injuries. Given incidence civilian pTBI from firearms is rising, cohort or comparative effectiveness studies must be planned to provide higher level of evidence.

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Possible 15 Minute Break here
KQ 29: DVT prophylaxis

KQ 29: In patients with penetrating TBI, what are the benefits and harms of venous thromboembolism prophylaxis?

RECOMMENDATIONS

Level I

There is insufficient evidence to make a Level I recommendation about this topic.

Level II

There is insufficient evidence to make a Level II recommendation about this topic.

Level III

There is insufficient evidence to make a Level III recommendation about this topic.

Level IV

- Early initiation of pharmacological VTE prophylaxis may be considered in adult patients with penetrating TBI who have not suffered increase in incident hemorrhage, without increasing the risk of consequent intracranial hemorrhage, emergent reoperation, or death.
- There is insufficient evidence to make recommendations regarding the utilization of VTE chemoprophylaxis or mechanical VTE prophylaxis for pediatric patients.
- There is insufficient evidence to make recommendations about the choice of pharmacologic agent, time to initiation, dosage, and duration for VTE prophylaxis.

Level C (achieved by DELPHI consensus)

- *In the absence of evidence, EXPERT CONSENSUS recommends, when feasible, the utilization of mechanical VTE prophylaxis for all adult patients with pTBI. (95.8% consensus)*
- *In the absence of evidence, EXPERT CONSENSUS recommends, when feasible, the utilization of VTE chemoprophylaxis for all adult patients with pTBI 24 - 48 hours after stable hemorrhage on CT scan. (100% consensus)*

INTRODUCTION

Venous thromboembolism is an underexplored area of critical care amongst pTBI patients. Traumatic injury is well known to activate tissue factor and induce coagulopathy, whereas confinement in intensive care unit, limits mobility and can increase risk of deep venous thrombosis and venous thromboembolism. For defense forces who must be transported long distances in acutely injured conditions, this poses an additional and frequently undertreated condition.

Prior Guidelines Recommendations

There were no recommendations on this topic in the prior edition of the guidelines (2001).

QUALITY OF BODY OF EVIDENCE AND APPLICABILITY

The data on venous thromboembolism (VTE) prophylaxis in penetrating traumatic brain injury (pTBI) is sparse. We identified one small retrospective study (N=67) that compared early VTE chemoprophylaxis in military patients injured in Afghanistan with no prophylaxis (**Table**).[†] The authors defined early prophylaxis as within 48 hours post-injury and the majority of patients received enoxaparin (91%). Early prophylaxis was not associated with either an increased incidence of hemorrhage expansion or VTE. There was also no association with increased rates of need for emergent reoperation or 30-day mortality. This study provides very low strength evidence that early deep vein thrombosis (DVT) prophylaxis results in little change in likelihood of VTE incidence, while 30-day mortality, likelihood of intracranial hemorrhage, and likelihood of emergent reoperation were not increased. This cohort was 100% male and military which limits generalizability. Additionally, the study was underpowered to demonstrate a difference between early prophylaxis and no prophylaxis for these outcomes and a larger study may have different findings.

Table. Study comparing early DVT prophylaxis with no prophylaxis

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Meyer 2017 (NRS) Afghanistan Military GSW: 22% Blast: 78%	Male: 100% Mean age: 25 (range 19-38) GCS: 10.3 vs. 8.3 ISS: 24.8 vs. 27.7 AIS: 3.8 vs. 4.1	DVT prophylaxis (N=32), 91% received enoxaparin 30 mg twice daily; 7% received UFH 5000 U thrice daily; time to first dose 24.5 hours and 17.7 hours, respectively No DVT prophylaxis (N=35)	<u>30-day mortality</u> : 3% vs. 9%, aRR* 1.50, 95% CI 0.07 to 34.0 <u>DVT or PE</u> : 12% vs. 17%, aRR* 0.88, 95% CI 0.20 to 3.93 <u>Worse ICH</u> : 16% vs. 29%, aRR* 0.56, 95% CI 0.17 to 1.85 <u>Incident-worsened ICH</u> : 16% vs. 17%, aRR* 0.76, 95% CI 0.21 to 2.79 <u>Non-elective reoperation</u> : 3% vs. 9%, aRR* 0.72, 95% CI 0.06 to 8.71	High

* adjusted for GCS, ISS, AIS; AIS=Abbreviated Injury Scale; aRR=adjusted relative risk; DVT=deep vein thrombosis; GCS=Glasgow Coma Scale; GSW=gunshot wound; ICH=intracranial hemorrhage; ISS=Injury Severity Score; NRS=non-randomized study; PE=pulmonary embolism; U=units; UFH=unfractionated heparin

Limitations

As demonstrated above, data on VTE prophylaxis specific to pTBI is minimal. Only one study is detailed above. As a retrospective study, it is biased; it is unknown whether the patients who received VTE prophylaxis were deemed low risk for intracranial hemorrhagic complications. The sample size is small and underpowered. Furthermore, the study includes only male patients. Use of oral contraceptives is associated with increased thrombotic events, and it is quite possible the risk-benefit profile for females is quite different than men.

Future Research

VTE prophylaxis is a low-cost high impact area of research. Such a study can be easily powered and recruited to, with rather uncomplicated outcome measures. Given the rising rates of pTBI, such a prospective study is not only feasible but essential.

Reference

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KQ 31: Organ donation

Critical Care KQ 31:

31. In patients with head injury, when should organ donation occur?

Recommendations

Level I

There is insufficient evidence to support a strong recommendation for the timing of organ donation after pTBI

Level II

There is insufficient evidence to support a moderate recommendation for the timing of organ donation after pTBI

Level III

There is insufficient evidence to support a weak recommendation for the timing of organ donation after pTBI

Level IV

There is insufficient evidence to support a very weak recommendation for the timing of organ donation after pTBI

Level C (achieved by DELPHI consensus)

Based on EXPERT CONSENSUS, after declaration of death by neurologic criteria following pTBI, organ donation should proceed as soon as organ function has been optimized to maximize organ function in recipients.

Introduction

The Uniform Determination of Death Act was approved by the American Medical Association in 1980 and the American Bar Association in 1981.¹ It defines death as either the irreversible cessation of all brain functions, including the brain stem, or the irreversible cessation of circulatory and

respiratory functions. Though the law has been adopted in all states, medical standards used to determine neurologic brain death vary slightly amongst jurisdictions and institutions.

Organ donation from deceased donors is an important source of viable organs for transplantation. There are a number of physiological derangements that occur following progression to death by neurologic criteria or so-called “brain death” however (PMID 28620674, 28822390). In order to optimize recipient outcomes, the process of organ donor management is recommended whereby specific goals for organ function are attempted (15616207). There are also several variations in donor management goals, which may be based on organ procurement organization or medical institution policy.^{2,3} One example of donor management goals are:³

- Mean arterial pressure, mm Hg: 60-110
- Central venous pressure, mm Hg: 4-12
- Ejection fraction, %: ≥ 50
- Low-dose vasopressors (dopamine at 10 $\mu\text{g/kg/min}$ or less, neosynephrine at 60 $\mu\text{g/min}$ or less, and norepinephrine at 10 $\mu\text{g/min}$ or less) No. of agents: ≤ 1
- Arterial blood gas, pH: 7.3-7.5
- PaO₂:FIO₂ ratio: ≥ 300
- Serum sodium, mEq/L: ≤ 155
- Urine output, mL/kg/h over 4 hours: ≥ 0.5
- Glucose, mg/dL: ≤ 150

Optimization of the organ donor following declaration of death by neurologic criteria in a patient with TBI can take time however and the optimal timing of organ donation and procurement is unknown.

Prior Guidelines Recommendations

The previous guidelines do not provide any recommendations for timing of organ donation following pTBI.

Methodology

To be provided by OHSU writers.

Scientific Foundation

We found no studies that specifically addressed this question in patients with penetrating TBI. However there were a few studies that attempted to address the issue of timing of organ donation following declaration of brain death in broader populations that included penetrating TBI. Two non-randomized studies mentioned the timing of organ donation or interventions to stabilize patients for better outcomes of organ donation prior to death by neurologic criteria caused by a head injury.

One non-randomized study of 173 brain dead donors which included TBI patients prospectively followed heart transplant recipients for 10 years after receiving the organ donation in Israel over a 20-year period (1997 to 2017).⁵ The study reported 10-year survival of recipients was similar between short and long time interval groups based on the median time from injury to brain death, from brain death to aortic cross-clamp in donors, and time from donor aortic cross-clamp to unclamping in the recipient. The study reported no differences in the rate of 10-year survival and no major adverse events when the time from injury to declaration of brain death was less than 97 hours or 97 hours and longer. For these groups, the study also reported no differences in in-hospital mortality or the mean

total rejection score of recipients. In addition, the study reported there were no differences in the rate of survival without rejection in any of the groups, but did not report the specific data. This study does suggest that delaying donation until the patient is hemodynamically stable may not worsen recipient outcomes.

Another non-randomized study of nearly 300 brain dead donors retrospectively reviewed the Gift of Life database, which serves parts of Pennsylvania, New Jersey, and all of Delaware, for organ donors between 2011 and 2015 who progressed to brain death after a head trauma.⁶ Twenty-eight per cent had a penetrating injury. The aim of the study was to determine if organ procurement should be delayed allowing for more donor management goals to be met. Based on the stated national goal for organ donation to be 3.75 organs transplanted per donor, the study compared characteristics of donors who donated more than four organs with those who donated four or less organs. For the donor management goals, four of the seven goals showed no differences between groups in the percent who met that goal. The study reported significantly shorter mean time, for those who donated more than four organs, from admission to declaration of brain death and between admission and organ procurement with those who donated four or less organs, however there was no difference in the time between declaration of brain death and organ procurement. This study suggests that a shorter time from admission to brain death and from admission to organ procurement is associated with a greater number of organs donated, but numbers of organs donated was not associated with time from brain death to organ procurement.

Discussion of Recommendations and Limitations:

As there is no data to guide the timing of organ donation following declaration of brain death in patients with penetrating TBI, extrapolation from other donor populations implies that organ donor management should be attempted and that longer times from declaration of death to donation do not result in adverse outcomes for recipients. These recommendations are limited to expert opinion.

Expert Opinion

Based on EXPERT CONSENSUS, after declaration of death by neurologic criteria following pTBI, organ donation should proceed as soon as organ function has been optimized to maximize organ function in recipients. This opinion is consistent with other published guidelines on organ donor management.

Future Directions:

Optimization of recipient outcomes should always be the goal once declaration of death occurs and the decision is made to proceed with donation. There is a large body of literature that addresses newer and novel techniques to improve organ function and maximize recipient outcomes, such as continual renal replacement therapy, direct personal resuscitation, etc. There is no reason to believe that these strategies would be applied any differently to the patient population with penetrating TBI and therefore are likely applicable to this patient population as well.

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Day 4. Wednesday, September 7th, 2023

Surgical Section Overview – Bizhan Aarabi, M.D., Section Lead

– Review of topics, scope, progress, points for discussion, points of controversy

Case presentations for the KQs
Levels of care: multidisciplinary
I
II Neurovasc.

Guest Patient: Josh Cooley; w/ Ms. Christine Cooley's (Mother's). post Blast (IED) patient w neurovascular complications for 1000/1030
0900-1200: Presentation, discussion, voting on select Surgical section KQ's. Assigned SME's to present. This section may go over and will move to the afternoon.

KQ 34: Surgical decompression vs. observation

KQ34. In patients with pTBI, what are the benefits and harms of urgent surgical decompression/craniectomy versus a period of observation prior to decompression?

Recommendations:

Level I

There is insufficient evidence to support a strong recommendation for urgent surgical decompression/craniectomy versus a period of observation prior to decompression.

Level II

There is insufficient evidence to support a moderate recommendation for urgent surgical decompression/craniectomy versus a period of observation prior to decompression.

Level III

There is insufficient evidence to support a recommendation for urgent surgical decompression/craniectomy versus a period of observation prior to decompression.

Level IV

In severely injured patients we recommend early decompression / craniectomy to reduce the likelihood of death or poor outcome.

LEVEL C: (By Delphi Consensus)

In the absence of sufficient evidence, EXPERT CONSENSUS recommends that patients with pTBI with surgical indications have surgery performed as soon as possible, ideally within 5 hours. (100%).

There is no evidence or expert opinion to support distinct recommendations based on patient gender, age, wounding mechanism, or military vs. civilian context.

Introduction

Patients with craniocerebral TBI due to GSW or blast fragment injuries, where surgery, including debridement and dural repair, is indicated, are operated emergently. Patients with pTBI caused by impalement of sharp foreign bodies usually also have emergent surgery to remove the foreign body, and debride and close the wound. (Rosenfeld, Bell, & Armonda, 2015)

Could surgical exploration, debridement, decompression and repair of dura be delayed if the injury is not immediately life-threatening and would this delay be inconsequential, considering CSF fistulas, infection rate and quality of life? Minor or superficial wounding from GSW, shell fragments or blast may only require a superficial limited debridement and dural repair and skin closure which could be delayed if OR and staff are not available. Delays to reach a neurosurgeon or a Level I trauma center are common for casualties in war and disaster zones and in remote or resource-poor environments. Does a delay in neurosurgery in these environments increase the risk of infection including CSF leaks, deep CNS infections, and increase the risk of poor outcome or death?

Timing of surgery for pTBI also depends on the general status of the patient, hemodynamic stability, other injuries, and physician judgment. Severe life-threatening polytrauma may be caused by multiple GSW or blast injuries. The blast trauma includes injury from the blast energy, penetrating injury from projectiles, blunt injuries from secondary impacts and burns. These complex and challenging injuries affecting multiple body regions demand multidisciplinary care led by a general trauma surgeon. Delay in surgery may also result from initial determination of poor prognosis. Following a mass casualty event in military or civilian hospitals, the timing of surgery also depends on the availability of the operating rooms and staff. The trauma surgeon triages the urgency of the patients for the OR. It is often advantageous for the patient to have damage control laparotomy or orthopedic surgery for limb trauma and craniotomy/craniectomy performed simultaneously by two teams, thus conforming to the principles of damage control neurosurgery.(Moore et al., 2016)
A literature review was conducted to compare outcomes of early versus delayed therapy and has identified six relevant studies.

Prior Guidelines Recommendations

The prior penetrating head injury guidelines addressed “Surgical management of Penetrating brain injury.” (“Surgical management of penetrating brain injury,” 2001b)

Timing is not specifically addressed for military trauma. Using mortality as the dependent variable when comparing different treatment methods was thought to be even less reliable in the military setting than in the civilian setting. It was suggested that a lower mortality rate reflects early triage and survivability decisions as much as treatment effectiveness.

For civilian trauma (S19), it was difficult to differentiate the effects on outcome of the timing of surgery from those resulting from rapid field triage and resuscitation. Although authors often state that early surgery is desirable, no solid evidence supports this practice.

The study patients undergoing late surgery were so different from the other two groups that no solid conclusions could be made about the actual timing of surgery. The question of timing of surgery was not adequately studied to make evidence-based recommendations.

Clearly, the general practice is to operate as soon as the indications for surgery are recognized. If simple wound care is elected, this should be performed expediently to prevent the complications associated with CSF contamination. If intracranial surgery is indicated, this should be performed promptly. If intra-cranial findings are equivocal regarding need for immediate neurosurgical intervention, follow-up CT scanning and intracranial pressure monitoring should be strongly considered as adjuncts to determining the need for and timing of surgical intervention.

Methodology

To be provided by OHSU writers.

Scientific Foundation

For patients with closed or blunt TBI, early evacuation of acute subdural hematoma (ASDH) has become standard practice. The ‘four-hour rule’ has developed from a series of 82 patients with closed TBI and ASDH. The mortality increased to 90% compared with 30% if surgery was delayed >4 hours. Functional survival was achieved in 65% patients (GOS $\geq$ 4) in patients having surgery <4 hours. (Seelig et al., 1981) Sizeable or expanding acute epidural hematoma (EDH) in patients with closed TBI are also managed emergently to prevent coning and death.

Evidence based guidelines have been published for the surgical management of TBI. It is recommended that patients with acute subdural hematoma (ASDH) and acute epidural hematoma (EDH), where surgery is indicated, are operated as soon as possible. (Bullock et al., 2006a, 2006b, 2006c; Bullock et al., 2006d, 2006e) However, these guidelines do not include pTBI.

Patients with severe closed or ‘blunt’ TBI, without an intracranial hematoma requiring urgent evacuation, are frequently managed with an initial period of intensive medical management in an intensive care unit with ICP monitoring. A delayed (or secondary) decompressive craniectomy is performed for intractable intracranial hypertension. (Cooper et al., 2011; Hawryluk et al., 2020; Hutchinson et al., 2016) These management paradigms for closed TBI are not directly applicable to patients with pTBI because pTBI is distinct from blunt TBI.

Patients with craniocerebral pTBI are usually treated acutely because the patient arrives in the ER acutely; there is an open wound which requires early debridement and closure; there is often significant brain swelling with pathological midline or transtentorial/foramen magnum shifts; CSF leaks require acute repair to prevent infection; and early decompression of large or expanding hematomas may be indicated.

Acute hypoxia and hypotension should be urgently corrected. The neurosurgeon must also assess the pTBI patient following resuscitation, including a review of their radiological imaging (including angiography, if indicated), and laboratory investigations, and decide whether they are likely to benefit from surgery and indeed ongoing active treatment. Patients with fixed dilated pupils and GCS 3 to 4 following adequate resuscitation, patients with severe bi-hemispheric trauma, a projectile trajectory traversing the brain stem or thalami/basal ganglia, are not survivable injuries and should be managed expectantly. (Rosenfeld, Bell, & Armonda, 2015)

Despite the poor outcomes of many patients with craniocerebral GSW, (Aarabi et al., 2014) the remarkable recovery in the high profile case of the life-threatening cerebral GSW injury to Congresswoman Gabrielle Giffords in the USA in 2011 which Lin et al call the ‘Gifford factor’, has likely encouraged more urgent and aggressive surgery in patients with severe craniocerebral GSW. Lin et al give practical technical advice to enable rapid and successful surgery in patients with pTBI. (Lin et al., 2012; Rosenfeld, Bell, & Armonda, 2015) Their mantra for treating GSW to the brain is “time is brain”. (Lin et al., 2012) Giffords was operated about 38 minutes after arrival at the hospital. (Lin et al., 2012)

Experience of surgeons with ‘damage control surgery’ and its extension, ‘damage control neurosurgery’, has also encouraged neurosurgeons to operate more acutely in patients with craniocerebral pTBI, including decompressive craniectomy, where brain swelling and/or mass lesion is present. During the surgery, deranged physiology including acidosis, hypoxia, hypothermia and coagulopathy continue to be corrected.(Rosenfeld, 2004) (Rubiano et al., 2019)

As a result of experience of the US military neurosurgeons with blast and penetrating TBI in the recent wars in Iraq and Afghanistan, acute decompressive craniectomy has become the standard treatment with intracranial mass lesions.(Bell et al., 2010) Shackelford et al reported a series of 486 military combat casualties from Iraq who had a craniectomy, and found that postoperative mortality was significantly lower when craniectomy was initiated within 5.33 hours of injury.(Shackelford et al., 2018) The outcomes of combat casualties with pTBI have demonstrated significant improvement in functional status up to 2 years from discharge with a large proportion of patients sustaining severe TBI attaining functional independence. (Weisbrod et al., 2012) These results have also encouraged the aggressive surgical management of combat casualties with pTBI.

Aarabi et al in a series of 964 patients from the Iran-Iraq war, reported that the incidence of infection was lower when surgery was carried out in the first 24 hours rather than no surgery or evacuation to a more distant base hospital with further delay.(Aarabi et al., 1998)

A total of 6 studies were determined to be of sufficient quality for inclusion in the evidentiary base.

One non-randomized study was identified in civilian/military patients in China with cranial gunshot wounds (GSW) and blast injuries.(Wei et al., 2013) The authors identified 56 patients from 1966 until May 2009 and performed a retrospective analysis of outcomes. Surgical intervention in this cohort included debridement, hematoma evacuation, and decompressive craniectomy and the authors noted this was performed as early as possible. Surgical intervention was performed within 8 hours of injury in 39 patients (69.6%) and beyond 8 hours of injury in 15 (8.9%). Two of the 56 patients died (1 extensive brain injury, 1 multiple organ failure). The authors report that patients who underwent surgical intervention within 8 hours of injury were more likely to recover (undefined) than those who received debridement after 8 hours (82.1% vs. 26.7%, $p<0.001$).

A second non-randomized study performed in the United States (2 urban trauma centers in Kansas City, Missouri) examined the association of early surgery (ES), late surgery (LS), and no surgery (NS) with outcomes in a population of patients ($N=89$) with cranial penetrating GSW.(Helling et al., 1992) Early and late surgery were defined as less than 24 hours and greater than 24 hours, respectively. Reasons provided for delayed surgery were an initial determination of poor prognosis or that of minor injury. The study period spanned 1987 to 1989 and was retrospective by design. Twenty-seven patients underwent early surgery, six underwent late surgery, and 56 underwent no surgery due to clinical findings and presumptive poor prognosis as determined by local neurosurgeons. The authors report a statistically significant difference in mortality for the groups (ES [$N=10$, 37%], LS [$N=0$, 0%], NS [$N=46$, 82%], $p<0.001$). It should be noted that the mean Glasgow Coma Scale (GCS) score of the groups differed ES (7.86 $\pm$ 4.72), LS (12.17 $\pm$ 4.10), and NS (5.59 $\pm$ 4.42). Patients in the NS group were the most severely injured and were the least severely injured in the LS group. There were fewer patients with GCS scores 3 and 4 in the ES group ($N=11/27$) compared with the NS Group ($N=37/56$). However, there were more survivors in the ES Group ($N=4/11$) compared with the NS group ($N=1/37$) amongst those patients with GCS 3 or 4 ($p=0.007$). No patients in the LS group died, however, the mean GCS of this cohort was much higher at presentation. There was one infection (brain abscess) and this occurred in a patient who underwent LS.

A third non-randomized study examined the impact of early versus delayed decompressive bilateral or bicompartamental craniectomy in a U.S. military population ($N=33$). (Ecker et al., 2011) The median age of the population was 24 years (range 19 to 46 years) and median GCS 5 (range 3 to 14). Nineteen patients underwent bifrontal decompression (58%), eight underwent bihemispheric decompression (24%), and six underwent both supra- and infratentorial decompression (18%). Eighty-eight percent of injuries in this cohort were due to blast injury and 12% from GSW. All but three patients underwent early decompression prior to evacuation. Poor outcome was defined as Glasgow Outcome Score (GOS) 1 to 3 at 6 months and at 1 to 5 years. At 6 months, 16 patients in the ES group had poor outcomes as compared with none in the LS group. Among good outcomes at 6 months, three (18%) patients underwent delayed surgery and 14 (82%) underwent early surgery ($p=0.10$). Among patients for whom GOS were available at 1 to 5 years, 12 patients had a poor outcome and 18 had good outcome. Of the patients with poor outcome, 100% underwent early surgery ($N=12$). Of those patients with good outcome 16 (89%) underwent early surgery and two

(11%) underwent delayed surgery ($p=0.36$). No time from injury to surgery were defined for early or delayed surgery by the authors.

A fourth non-randomized study of civilian injuries in Iraq ($N=39$) examined the association of surgical timing with outcomes.(Dolachee et al., 2019) Time to surgery from injury was defined as less than 5 hours ($N=10$), 5 to 8 hours ($N=22$), and 9 hours or more ($N=5$). Surgical intervention included craniotomy or craniectomy, debridement, hemostasis, and watertight dural repair. The authors report good outcome for five patients (50%) in the less than 5 hours cohort, 14 (63%) in the 5 to 8 hours cohort, and one (20%) in the 9 hours or more cohort. Poor outcomes were reported in five patients (50%) in the less than 5 hours cohort, eight (36%) in the 5 to 8 hours cohort, and four (80%) in the 9 hours or more cohort ($p=0.2$). It should be noted that no clear definition was provided for good or poor outcome, although GOS was referenced.

A fifth non-randomized study examined time to surgery from injury in a population of civilians ($N=44$) in Italy with GSW.(Siccardi et al., 1991) Time intervals from injury to surgery were within 3 hours, within 6 hours, and greater than 6 hours. Surgical intervention included debridement of necrosis, removal of in-driven fragments, evacuation of hematoma, hemostasis, and watertight dural closure. Of patients who underwent surgery within 3 hours ($N=2$), one patient survived and one patient died (50% mortality). Of patients who underwent surgery within 6 hours ($N=33$), 19 survived and 14 died (mortality 42.4%). Of patients who underwent surgery greater than 6 hours from time of injury ($N=9$), six survived and three died (mortality 33.3%).

A sixth non-randomized study was identified that examined the impact of duration of time between injury and surgery on morbidity and mortality in a military/civilian (civil war) population in Libya with craniospinal GSW.(Sertbaş & Karatay, 2020) Data for morbidity was reported in aggregate for cranial and spinal GSW and could not be included. The association of time to surgery on mortality for patients with cranial GSW ($N=35$) was examined. Surgical intervention included duraplasty ($N=29$, 82%), decompressive craniectomy ($N=21$, 60%), hematoma evacuation ($N=20$, 57%), and bone fragment removal ($N=20$, 57%). The mortality for the overall cohort was 22.8% ($N=8$). Time intervals from injury to surgery which were examined were less than 24 hours, 24 to 72 hours, greater than 72 hours. Mortalities by time from injury to surgery were: one in less than 24 hours, three in 24 to 72 hours, and four in greater than 72 hours. For patients with cranial GSW the authors report a significantly lower mortality when operated on within 24 hours ($p=0.044$).

These studies provide very low strength of evidence that early surgical intervention may reduce the likelihood of death/other poor outcome in more severely injured patients compared with delayed surgery and highlight a lack of agreement for what timeframe constitutes early versus delayed. Associations with other outcomes could not be determined due to the methods of reporting data (not by time to surgery) in the included studies.

Table. Outcomes of early and late decompression/craniectomy in penetrating traumatic brain injury

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Wei, 2013 (NRS) China Military/Civilian Blast: 33.9% GSW: 66%	Total population ($N=56$) Male: 89% Mean age: 24.1 (range: 2 to 52) years Admission GCS GCS 3-5: 8.9% GCS 6-8: 80% GCS 9-12: 7.1%	Surgery ($N=54$, 96.4%) Surgery <8 hours of injury: $N=39$, 68.9% Surgery >8 hours of injury: $N=15$, 8.9% Debridement and foreign body removal: $N=40$, 71.4%	Total cohort mortality: $N=2$, 3.5% Patients receiving debridement within 8 hours more likely to recover (undefined) than those receiving debridement >8 hours after injury (82.1% vs. 26.7%, $p<0.001$).	High

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
	GCS 13-15: 3.6% Penetrating wound: N=11 (19.6%) Blind tract wound: N=41 (73.2%)	Debridement and partial foreign body removal: N=12, 21.4%		
Helling, 1992 (NRS) USA Civilian GSW: 100%	N=89 Male: 91% Mean age: 31 (range: 13 to 73) years GCS: ES: 7.86 +/- 4.72 LS: 12.17 +/- 4.10 NS: 5.59 +/- 4.42	ES (<24 hours), LS (>24 hours), NS	Mortality ES: 10/27, 37% LS: 0/6, 0% NS: 46/56, 82% p<0.001	High
Ecker, 2011 (NRS) United States Military GSW: 12% Blast: 45% Projectile: 48%	Male: 100% Median age: 24 (range: 19 to 46) years Median GCS 5 (range: 3 to 14)	Early (not defined) vs. delayed (not defined) decompressive craniectomy (N=33) Bifrontal: N=19, 58% Bihemispheric: N=8, 24% Supra+Infratentorial: N=6, 18%	6-month GOS Poor (GOS 1-3): N=16 Good: (GOS 4-5): N=17 Poor Outcome (GOS 1-3) Early Surgery: N=16, 100% Delayed Surgery: N=0 Good Outcome (GOS 4-5) Early Surgery: N=14, 82% Delayed Surgery: N=3, 18% p=0.10 1 to 5 years GOS Poor: N=12 Good: N=18 Poor Outcome (GOS 1-3) Early Surgery: N=12, 100% Delayed Surgery: N=0 Good Outcome (GOS 4-5) Early Surgery: N=16, 89% Delayed Surgery: N= 2 11% p=0.36	High
Dolachee, 2019 (NRS)	Male 90% Mean age: NR	Association of surgical timing with good and poor outcome in pTBI at time points from injury:	Good Outcome (not defined) <5 hours: N=5, 50%	High

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Iraq Civilian Blast/shrapnel: 18% GSW: 61% Other: 20%	GCS 13-15: 41% GCS 9-12: 43% GCS 5-8: 13% GCS Unavailable: 3%	<5 hours (N=10) 5-8 hours (N=22) >9 hours (N=5) Craniotomy: 7.7% Craniectomy: 92.3%	5-8 hours: N=14, 63% >9 hours: N=1, 20% Poor Outcome (not defined) <5 hours: N=5, 50% 5-8 hours: N=8, 36% >9 hours: N=4, 80% p=0.2	
Siccardi, 1991 (NRS) Italy Civilian GSW: 100%	Characteristics of 314 patients report but not for the 44 included patients who had surgery	Surgical Intervention (N=44): debridement of necrosis, removal of in-driven fragments, evacuation of hematoma, hemostasis, watertight dural closure.	Mortality: 40.1%, N=18/44 Time to surgery from injury: # cases, survived, died: Within 3 hours: 2,1,1, mortality 50% Within 6 hours: 33, 19, 14, mortality 42.4% >6 hours: 9,6,3, mortality 33.3%	High
Sertbas, 2020 (NRS) Libya Civilian/Military (Civil War) GSW: 100%	Male: 100% Mean age: 27 years GCS 12-15: 37% GCS 7-12: 34% GCS 3-7: 28%	N=35 Surgical intervention: Duraplasty: N=29, 82% Decompressive craniectomy: N=21, 60% Hematoma evacuation: N=20, 57% Bone fragment removal: N=20, 57%	Mortality: N=8, 22.8% Time To Surgery from Injury and Mortality <24 hours: N=1 24-72 hours: N=3 >72 hours: N=4 Lower mortality when operated on within 24 hours (p=0.044)	High

ES=early surgery; GCS=Glasgow Coma Scale; GOS=Glasgow Outcome Score; GSW=gunshot wound; LS=late surgery; NRS=non-randomized study; NS=no surgery; pTBI=penetrating traumatic brain injury

Discussion of Recommendations and Limitations

Add: It is recommended that patients with pTBI who do not require urgent decompressive surgery may have surgery >5 hours from the time of injury, where there is systemic constraint or no neurosurgeon available. Effort should still be made to perform the surgery as soon as possible.

Patient outcome depends on many variables including the mechanism of injury, ballistics, proximity

of the victim to the weapon or the epicenter of the explosion, the age and general condition of the patient including other injuries, their neurological status, the level of resuscitation, the degree of contamination of the wound at scalp level and within the brain, the duration from the time of the injury to reaching a neurosurgeon and getting into the OR and the postoperative ICP. This heterogeneity extends to the pattern of injury which can include a mass lesion, presence of a foreign body, vascular injury, and/or diffuse edematous injury. The type of injury, age, neurological status, and postoperative ICP strongly influence outcome.

As discussed, the literature that exists is not of ideal quality to lend a confirmatory statement. When considering pTBI, however, we can consider other similar traumatic pathologies to help guide decision making.

When considering timing of intervention, the presence or absence of elevated intracranial pressure (ICP) also dictates surgical management and, if so, per what etiology. If there is a mass lesion present, it is recommended that emergent intervention be pursued. If there is no mass lesion but clear evidence of elevated ICP, decompressive craniectomy is recommended. There is no data to support the superiority of either bifrontal or bilateral hemicraniectomies – this should be tailored to the patient (i.e., are the concomitant frontal bone fractures that also need repair). Based on the included studies reviewed and Shackelford et al, it is recommended this be performed acutely, or within 5.33 hours.[Shackelford, 2018] If the clinical picture is unclear, an ICP monitor can be considered prior to intervention. If there is no mass lesion and no evidence of elevated ICP, but there are bony fractures that require repair, it is recommended these be addressed as a typical depressed skull fracture to prevent infection and neurologic worsening.

A paucity of high-quality evidence regarding timing of surgery in pTBI has been published since the last management guidelines were published in 2001. The current iteration of guidelines are, at their core, the same. Briefly, for a surgical indication in the pTBI population, it is recommended to operate as soon as possible. When considering operations purely for wound debridement/wash-out without intracranial extension of foreign bodies, this should be performed in a timely manner to prevent CNS infection, although this is not as emergent as a patient with cerebral herniation or intracranial foreign bodies.

Guidelines are based on the level of evidence supporting recommendations. The point should be made that, not only will creating a prospectively randomized controlled trial be difficult and unethical, one could argue it also is unnecessary. Although the mechanism of pTBI is different from other traumatic or neurologic injuries, the questions we are asking ourselves are not. For example, it has been studied and makes intuitive sense to intervene as soon as possible in the presence of a mass lesion causing compression/herniation. Similarly, if there is not a mass lesion/hematoma, but the patient's clinical exam indicates elevated intracranial pressure and there are radiographic findings to support that diagnosis including herniation and/or loss of cisterns, emergent decompressive craniectomy is recommended. In the case of no mass lesion and an unclear ICP crisis, active observation with an ICP monitor +/- multimodal monitoring is recommended to guide treatment. However, earlier surgery is recommended to prevent CSF leakage and chances of infection.

If we were to design a randomized trial (with minimal bias) in patients with pTBI to compare urgent surgical decompression with a period of observation, it would be fraught with difficulty. For a start, there is unlikely to be clinical equipoise in early versus delayed surgery, when the neurosurgeon is faced with an acute pTBI victim. It should be noted that all these non-randomized observational studies had a high risk of evidentiary bias because of variability in the cohort size and composition, the non-standardized definition of early surgery and some patients being relegated to have no surgery. Surgical techniques were also not standardized. Studies conducted in war zones and low- and middle-income countries, (Dolachee et al., 2019; Sertbaş & Karatay, 2020; Wei et al., 2013) cannot be compared to studies conducted in high income civilian trauma systems. (Ecker et al., 2011; Helling et al., 1992; Siccardi et al., 1991)

There does appear to be equipoise in two scenarios regarding timing of surgical intervention: 1) presence of an open wound and retained foreign body in a neurologically intact patient, and 2) the patient who presents with no intracranial pathology (for example, from a tangential penetrating injury) and need for wound washout. In both of these scenarios, prompt but not emergent interventions seems reasonable. There is not adequate data to provide a “safety cutoff” time. In these cases, it would be recommended to intervene as soon as safe and clinically feasible.

Variables in these six studies include military versus civilian populations, different trauma systems, variable quality of prehospital resuscitation and treatment, delays in reaching medical care, inhomogeneous patient populations, different mechanisms of injury (eg projectile (GSW), blast injury, non-ballistic pTBI), and the variable extent of craniectomy and debridement. Combining different surgical techniques in the same study may also confound results. It is unsurprising, therefore, that no randomized trials of the timing of surgical technique in pTBI have been identified in the literature and the studies consist of non-uniform cohorts in early and late surgical groups. One study included cranial and spinal injuries.(Sertbaş & Karatay, 2020)

The six studies identified consisted of GSW and blast injury,(Dolachee et al., 2019; Ecker et al., 2011; Wei et al., 2013) and GSW alone (Helling et al., 1992; Sertbaş & Karatay, 2020; Siccaldi et al., 1991). Assessment of outcome is confounded when cranial blast injury and GSW are both included in the study because of different wounding mechanism, extent and fragment size, pathophysiology and expected outcomes. Three of these studies are civilian (Dolachee et al., 2019; Helling et al., 1992; Siccaldi et al., 1991), two are mixed civilian and military,(Sertbaş & Karatay, 2020; Wei et al., 2013) and one is military (Ecker et al., 2011). Military and civilian trauma systems are different particularly in the prehospital resuscitation and evacuation systems, and therefore are not equivalent when assessing medical evidence. As a result, generalizations on outcome may not apply.

Decompressive craniectomy (DC) in civilian and military practice is most commonly a unilateral frontal-temporo-parietal (FTP) DC. Bifrontal DC is indicated when there is bi-frontal injury including swelling and hemorrhage. Bilateral pathology including intracranial hemorrhage may require bilateral FTP craniectomies as described in Ecker et al,(Ecker et al., 2011) and the need for both supra- and infra- tentorial decompression described in Ecker et al is infrequently performed.(Ecker et al., 2011)

The decision for early versus late surgery in these review articles varies. Some patients with severe pTBI were deemed to have a poor prognosis and were relegated to late or no surgery.(Helling et al., 1992) This skew results in favor of performing early surgery for better outcomes. Patients with higher mean GCS were relegated to the late surgery group and this also skews the results.(Helling et al., 1992) In the military setting, delays in casualties reaching neurosurgical care also resulted in late surgery being performed. The timing of surgery in these six articles varies considerably. What is characterized as early surgery in these six articles ranges from <3 hours to <24 hours, and in Ecker et al is undefined.(Ecker et al., 2011)

Current military casualty care positions surgical facilities within the area of combat operations such that early surgery (within 3 to 4 hours) is undertaken. The injured soldier, once stabilized, is then evacuated to a facility with a higher level of care. Delays in transporting the injured soldier for neurosurgery may occur due to various operational constraints. These may include damage control general surgery in a forward hospital where there is no neurosurgery or restrictions in aeromedical transport opportunity or availability. Performing a decompressive craniectomy on a soldier with pTBI reduces the risk of uncontrollable intracranial hypertension developing during aeromedical evacuation (Bell et al., 2010; Roberts et al., 2016)

Civilian trauma systems have evolved to transport a casualty rapidly to a trauma center where early surgery including neurosurgery can be achieved.

Conclusion: There is Level IV evidence of weak strength to recommend early versus delayed decompression.

Future Directions:

There is a need to define early surgery versus late surgery.

There is a need to define low versus high velocity wounding in patient populations.

There is a need to define trauma systems including extent of prehospital resuscitation to compare early with late decompression.

There is a need to better classify and stratify pTBI patients to compare early with late decompression.

There is a need to define surgical techniques with more precision so that comparisons can be made.

There is a need to better standardize outcomes -eg GOS; other rating scales such as Modified Rankin; PTE; infection; and duration of follow-up,

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KQ 35: Local debridement and closure

35. In patients with pTBI, what are the benefits and harms of local debridement and closure?

Recommendations

Level I

There is insufficient evidence to support a strong recommendation.

Level II

There is insufficient evidence to support a moderate recommendation.

Level III

There is insufficient evidence to support a weak recommendation.

Level IV

There is insufficient evidence to support a weak recommendation.

Level C is recommended to be achieved by DELPHI consensus

In the absence of sufficient evidence, EXPERT CONSENSUS recommends that local debridement is a treatment option for pTBI patients who meet the following criteria (100% consensus):

1. Entry wound < 2 cm
2. No exit wound.
3. Absence of neurological decline
4. No operative intracranial lesion

Introduction

A definition of **local debridement and closure** is needed for evaluation of the evidence in the literature. Our definition of local debridement is a superficial operation with wound washout, minimal debridement and wound closure. Loose superficial bone fragments and debris are removed. The dura does not require wider opening. The scalp is closed primarily.

Local debridement should be differentiated from **conservative debridement surgery** which includes craniotomy/craniectomy and surgery for accessible pathology-hematoma evacuation, superficial debridement of devitalized-necrotic brain, removal of superficial bone and metal fragments and water-tight closure.

Radical debridement surgery includes surgery for deeper inaccessible pathology eg debridement irrigation of missile track and removal of deep fragments.

The extent of craniectomy/craniotomy is a separate issue in relation to the need for exposure of pathology and the degree of decompression required.

The range of pathology to be considered in the selection of patients for local debridement and closure includes:

- Superficial trauma to the scalp/skull
- +/-Depressed fracture
- Minimal underlying brain injury
- +/-Open dura with CSF leak
- Superficial fragments/bullet (location: subgaleal, bone, intracerebral)
- The presence of intracerebral fragments per se does not rule out local debridement.

Other systemic factors for decision on local debridement and closure:

- Trauma system-e.g. long delays to reach a neurosurgeon.
- Location of injury - remote, rural versus metropolitan
- Availability of CT
- Patient having simple wound closure in the ER and deliberate planning for secondary surgery.

This Key Question 35 is framed as ‘benefits and harms of local debridement’.

These parameters may include length of stay, death, neurological status, posttraumatic epilepsy, infection-meningitis abscess and wound infection.

Prior Guidelines Recommendation

All available studies were classified as Class III evidence.

Military

Vietnam War-vigorous debridement was the practice for US neurosurgeons and reoperation for retained bone fragments. Six non-US studies concerned less aggressive approaches. In five of these CT was available. Gonul et al local debridement (more extensive than our definition?) and dura closed. Mortality 8%, Infection 6%. Brandvold et al and Levi et al studied the same cohort of patients and were the first to use CT for combat casualties. They included evacuation of hematomas (therefore more extensive than local debridement). 10% patients did not undergo craniotomy-local wound closure only. Mortality 26% including 7% who were judged not salvageable did not undergo surgery. Taha et al reported on 32 patients treated with simple wound closure in the ER. There were no deaths and one brain. Abscess(3%). They tried to eliminate patients with significant amounts of devitalized tissue and excluded those with exit wounds ie high velocity gunshot injuries.

Civilian

Studies on limited debridement were published in the 1970s, a decade before the military literature. Limited debridement was performed in the absence of CT, and on patients with potential for functional recovery. PTE 13% Infection 4% Mortality 33% (Lillard). Potapov et al- initial limited debridement then transfer to neurosurgery center for CT and more extensive surgery if required. Infection 18% (Potapov). Hubschmann mortal 22% in those who had surgery and 92% in those selected not to have surgery. Infection 4%.

[Suddaby 1987 .22 caliber weapons ‘relatively neurologically intact who deteriorate or who had hematomas’. (But hematomas require craniotomy) Local wound care in the ER. Similar complications compared with more aggressive surgery.] Sarnaik et al Pediatric study with all calibers of bullets. Limited debridement, ICP monitoring and delayed more extensive surgery and hematoma evacuation. Shoung et al Local wound care, debridement and dural closure unless expanding hematoma. Mortality 35%.

The conclusion was these studies ‘raise the question of the need for debridement (presumably cerebral) in addition to careful wound care and watertight closure’

Methodology

To be provided by OHSU

Scientific Foundation

Background

For this key question we included studies when local debridement and closure of wounds were done in an emergency room, bedside, or the field, but not in an operating room as part of a surgical intervention. We also included studies where this was presumed to be curative treatment and excluded studies where local debridement and closure were only used for patients who were not expected to survive.

Literature

There were no randomized trials or comparative cohort studies identified that addressed the benefits and harms of local debridement and closure as treatment for penetrating traumatic brain injuries (pTBI). We identified four non-randomized studies that provide information about the indications for this treatment strategy and patient outcomes when it was used. In two studies, local debridement was the focus of the studies and all included patients received this course of treatment.^{1,2}

One non-randomized study reported the outcome data of patients with pTBI from explosive fragments treated with local wound care during the Iran-Iraq War. Only patients with ≥ 12 months of follow-up were included in the study.² Ninety-nine males between the ages of 13 and 55 years met this criteria. All had small entrance wounds (<3 cm), an absence of exit wound, a GCS ≥ 8 , and no rapid neurological deterioration. Treatment was either simple dressing application or wound debridement and closure (suture) performed by a consultant neurosurgeon under local or general anesthesia within 24 hours of wounding. Patients were referred to a higher echelon of care where they were re-examined by a neurosurgeon. Sixty wounds were found to have CSF leakage or were “under tension” and required re-operation which consisted of “superficial debridement of the skin, bones, and local contused brain”. These patients were then admitted and received IV antibiotics for at least two weeks. The long-term functional outcome was good for 90 patients who were able to return to work. Four patients had severe disability and five died of meningitis. No brain abscess were detected during follow-up.

In a second series, 32 patients injured the Lebanese Civil War were treated with superficial wound care at the American University of Beirut Medical Centre between 1981 and 1988.¹ The injury was caused by explosive fragments in 27 cases and missiles (bullets) in 5 cases. The criteria for local debridement and closure included (1) a GCS > 10 (2) evaluation < 6 hours after wounding (3) an entry wound < 2 cm (4) no exit wound (5) trajectory not crossing the sylvian fissure (6) no epidural or subdural hematoma and (7) no enlarging intraparenchymal hematoma and (8) no intraparenchymal hematoma > 4 cm. The mean GCS in the emergency room was 14 and the mean wound size was 0.7 cm. All patients received IV antibiotics and had a wound débridement and single layer closure in the emergency room. Patients were admitted for two weeks and received antibiotics during this period. All patients survived. One patient developed epilepsy secondary to a brain abscess. The other patients experienced no complications at an average follow-up of 45 months.

In two other studies where inclusion was limited to specific types of injuries, the majority of patients were managed with local debridement and closure.^{3,4} One non-randomized study reported care and outcomes for 30 patients treated for falling bullets injuries (celebratory gunfire).³ Patients were treated at teaching hospital in Bagdad, Iraq. The median age was 17.5 years; 63% of patients were males. The majority of patients ($n=20$) had an admission GCS ≥ 13 . Nineteen patients were treated with simple local wound care. Their outcomes included death ($n=4$), GOS of 3 ($n=2$), GOS of 4 ($n=5$), and a GOS of 5 ($n=8$). Three of the patients who died had an admission GCS of 5 while one had a GCS of 6. No CSF leaks or infections were detected, but only 50% of patients had any follow-up after hospital discharge. Only one patient had a documented complication, focal seizures.

The fourth series included 49 patients treated for .22 caliber gunshot wounds in Edmonton, Canada.⁴ The majority were suicide attempts (88%). The mean age was 30.4 years old and 88% of patients were males. Patients were assessed in the emergency department and 36 were provided local wound care and then admitted, while 13 were taken to the operating room for surgical interventions (Max: I have a different understanding of the results. I think six patients had craniotomies, and 43 had local wound care). The study authors did not report patient outcomes separately by type of treatment. We include the outcomes and the study in the table as it was included in the prior guideline and to highlight that this study included patients that are more seriously injured (64.5% have GCS ≤ 7) and had a much higher mortality rate (61%). However, as the results are not separated, we did not include it in our Strength of the Body of Evidence assessment.

These case series provide very low strength evidence that local debridement and closure are associated with benefits for patients, which we are inferring from consistently reported good

outcomes. However, the rigor of the studies is extremely limited and little information is provided on potential harms. The small number of studies/reports suggest that there may be publication bias, that is it is at least possible that this approach to care has been tried more frequently, likely out of necessity, but that negative results have not been published.

Table. Benefits and harms of local debridement and closure for penetrating brain injury.

Author, Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Kadhim, 2020 Case Series Iraq Civilian Falling bullets: 100%	N=30 Median age: 17.5 years (range 7 to 55) Male: 63% GCS 13-15: 66% GCS 9-12: 10% GCS 6-8: 7% GCS 3-5: 17% Injury: -Unilobar: 13 -Multilobar or bihemispheric: 6 -Through deep midline structures: 10 -Transventricular with IVH: 7 -SAH: 4	19 local wound care 5 extraction of extra cranial bullets 6 more extensive surgery Indications - Local wound care unless surgery needed due to - Depressed fracture related to bullet - Indriven bone chips	Follow-up: 6 months after hospitalization. Reported for local wound care for this KQ GOS 5: 42% (8/19) -Initial GCS12-15 GOS 4: 26% (5/19) -Initial GCS: 4,5,8, 13,14 GOS 3: 11% (2/19) -Initial GCS: 12 GOS 1/died: 21% (4/19). -Initial GCS: 5-6	High
Amirjamshidi, 2003 Case Series Iran Military/civilian-battlefield areas Metal shrapnel: 98% Grenade fragments: 2%	N=99 patients treated for low-velocity wounds without surgery and followed for up to 9 years Mean age: NR (range 13 to 55 years) Male: 100% GCS 13-14: 48% GCS 10-12: 41% GCS 8-10: 10% Injury site: -Parietal: 31% -Temporal: 20% -Occipital: 5% -Suboccipital: 2% -Orbiofacial: 2%	Treatment (at field hospital) - wound cleaned, dressed or skin debrided, 2-4 stiches 1 dose antibiotic 250 diphenylhydantoin and 8 to 16 mg dexamethasone by IV Indications: Patients - with GSC $\geq$8 - no rapid deterioration in in consciousness - small entrance wound Treatment at secondary hospital - X-ray and CT 62 to OR for CSF leak or wound under tension - Superficial debridement of skin, bone and local contused brain tissue - IV antibiotics for 2 weeks $\geq$2 CT scans - Diphenylhydantoin 125 mg 2x day for 1 year	Mean follow-up: 98 months (range: 90 to 124) Outcome: 91% (90): Good = back to work 4% (4): Poor = severe disability 5% (5): Bad = Dead due to severity of injury and meningitis Mortality: 5% (5/99) No: hematoma, brain abscess, epilepsy Outcome did not vary by whether superficial debridement was needed at second hospital or not. (p=0.23)	High
Taha, 1991 ^a Case Series	N=32	Superficial entry wound debrided and closed without	Mortality: 0 Neurological deficits: 0	High

Author, Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Lebanon Civilian/Conflict zone (presumed, not specified) Shrapnel: 84% GSW: 16%	Mean age: 23 years (range 3 to 51) Male: 87.5% GCS 15: 19 GCS 14: 5 GCS 13: 3 GCS 12: 2 GCS 11: 2 Not reported: 1	drainage in ER within mean 3 hours (range 0.5 to 6) Indications: • GSC >10 • Exam within 6 hours of injury • Entry wound <2 cm with or without visible cerebral tissue and with or without indriven bone • No exit wound • Missile tract did not traverse the proximal sylvian fissure • No epidural or subdural hematoma • No intracerebral hematoma that enlarged on serial CT or 4 cm or more in diameter	Complications: 1 (3.1%) seizure and left hemiparesis 20 days after injury. Brain abscess, excised and 3 weeks of cefotaxime given. 2 month follow-up: no abnormalities. Mean follow-up: 3.5 years (range 1 to 7.5)	
Suddaby, 1987 ^a Case Series Canada Civilian GSW .22 caliber: 100% Suicide attempts: 88%	N=49 Mean age: 30.4 years (range 8 to 92) Male: 88% GCS 12-15: 20.4% GCS 8-11: 12.2% GCS ≤ 7: 65.4%	36: local superficial wound care in ER prior to admission 13: taken to OR 6: emergency craniotomy for ICH 4: surgery for intra cerebral hematoma (2 died) 2: craniotomy of subdural hematoma (2 died) 1: local wound debridement in OR	61% mortality rate (30/49) 18% complication rate: 1 brain abscess 5 CSF leaks 1 meningitis 1 hydrocephalus 1 late epilepsy	High

CSF=cerebrospinal fluid; CT=computed tomography; ER=emergency room; GCS=Glasgow Coma Scale; GSW=gunshot wound; hrs.=hours; ICH=intracerebral hemorrhage; IVH= intraventricular hemorrhage; OR= operating room; SDH=Subdural hematoma

^aincluded in 1st edition of guideline

^b text specifies 1 case with seizure, case 21; table 1 indicated case 7 also had a seizure.

^carticle says 16% in text; table suggests 9/49=18%

Discussion of Recommendations and Limitations

Insert discussion on

There is no evidence supporting local wound care as opposed to more extensive surgery in patients meeting these criteria in terms of benefits versus harms.

There are many reasons for significant bias in this limited body of evidence.

Variability of patient characteristics between studies and within a single study.

Wide age-range (8 to 92 years).

Studies reported over a long time from 1987 to 2020.

Civilian and military studies are not directly comparable because of differences in the trauma systems-one military/civilian study, three civilians.

Trauma system variance in Iraq, Iran, Lebanon, Canada

The ballistics in these studies vary, including falling bullets (Kahim et al), GSW and shrapnel. Some patients were not pTBI with no breach of the skull. None of these studies included foreign body sharp object pTBI. These tend to be single case reports (refs) but where local debridement is a common treatment where there is no intracranial mass lesion.

The Suddaby et al and Kahim et al studies included craniotomy/craniectomy, however the comparison of limited debridement versus more extensive exploration (craniotomy/craniectomy) or radical debridement was not the aim of these studies. Therefore, no conclusions can be drawn on the effect of local debridement on benefits and harms mortality, post-traumatic epilepsy, or infection in comparison with more extensive surgery.

Suddaby et al series included predominant suicides (88%) with 61% mortality.

Bias in comparing patients with low velocity injury in good neurological condition versus patients in poorer neurological condition.

Some patients fail local debridement and require a second unplanned operation (Amirjamshidi)

(‘Patients who were likely to die having simple wound closure were excluded in this literature review’. My comment: But patients in the Suddaby et al series include this type of patient?)

Synthesis and expert opinion:

- Local debridement and closure should be considered for patients with:
- Low velocity ballistic mechanism,
- Small entry wound (<2cm)
- neurologically stable
- +/- CSF leak
- Bullet, fragment under the scalp
- (Evaluation <6 hours post injury? - Taha et al)
- Small, depressed fracture. (Local wound care was excluded for patients with depressed fracture in the series of Kadhimi et al)

Local debridement and closure is contraindicated if there is:

- Progressive neurological deterioration
- CT shows epidural or subdural hematoma or extensive cerebral disruption-contusion, hematoma, edema.
- Exit wound present.

Relative contraindication: SXR/CT intracerebral fragments - depends on the patient’s condition.

There is an indication for reoperation if there is clinical deterioration and there is hematoma/ swelling on imaging, or ongoing CSF leak or wound under increasing tension (Amirjamshidi)

Unable to make a recommendation on ICP monitoring from these studies

Based on this evidence no recommendation can be made on whether local debridement with craniotomy has benefits and harms when compared with a more extensive exploration.

Future directions

Develop standard definitions and indications for limited debridement and closure based on clinical and imaging findings and the constraints of the trauma system.

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KQ 38: Water tight closure to prevent CSF leakage

KQ38: In patients with pTBI, what are the benefits and harms of water-tight closure of the dura, with or without graft, to prevent CSF leak in the setting of exposure of cisterns or the ventricular system?

RECOMMENDATIONS

Level I

There is insufficient evidence to make a recommendation.

Level II

There is moderate strength evidence that infection risk is greater when patients have a CSF fistula following penetrating traumatic brain injury (pTBI), and SHOULD be avoided or prevented. There is insufficient evidence to support or refute water-tight dural closure, with or without graft, as the preferred technique to prevent CSF leak.

Level III

There is insufficient evidence to make a recommendation.

Level C:

We recommend, by expert consensus, that available techniques to create an effective closure, potentially including CSF diversion, be employed during the primary operation to prevent CSF fistula (100%).

BACKGROUND

Human brain is an astonishingly privileged organ surrounded by pia, arachnoid, dura, skull and scalp blocking free communication of CSF with the outside environment and contamination. Penetrating traumatic brain injury (pTBI) violates this secure environment and results in leakage of CSF and contamination. Violation of air sinuses, skull base and the ventricular systems predispose to CSF fistulas. Discontinuous skull fractures resulting from sudden and precipitously elevated intracranial pressure expose basal cisterns and free flow of CSF into the nasal cavities or mastoid air cells. Direct CSF fistulas through the skin or in form of liquorrhea may result in nosocomial infections, increasing deep CNS infections and complications including mortality. Artful watertight closure of dural tears can prevent meningitis and dangerous complications. In the first iteration of pTBI CPGL (Supplement to the Journal of Trauma: 51 Number 2 S29-S33: Management and Prognosis of Penetrating Brain Injury, primary dural repair and surgical correction of CSF leaks that do not close spontaneously, or are refractory to temporary CSF diversion was recommended.

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SCIENTIFIC FOUNDATION

We identified no comparative studies where some patients received planned water-tight dural closure and other patients received planned no dural closure or less-than-water-tight dural closure. We identified 16 non-randomized studies (N=6,452) that reported outcomes in patients where water-tight dural closure was attempted, though not always successfully. Mean sample size was 403 (range 13 to 1,732), average study mean age was 24.6 years (range 21 to 37.8 years) in studies that reported age (9 studies), average study proportion males was 94% in studies that reported proportion of males (11 studies). Eight studies were in a military population, six in a civilian population, and two in mixed military and civilian population. The vast majority of penetrating injuries involved gunshot wounds or shrapnel. Three studies were conducted in Vietnam and Turkey; two studies were conducted in the United States, Croatia, and Korea; one study each was conducted in Brazil, India, Iran, and Iraq. No specific harms of watertight closure of the dura were reported.

Four non-randomized studies (N=2,206) reported infection rates in the proportion of patients with cerebrospinal fluid (CSF) fistula compared with those without fistula.¹⁴ The first study was in a military population (N=379) of cranial penetrating injuries during the Iran-Iraq War.¹ The authors reported watertight closure in all operative cases by the following means: primary closure (N=49, 13%), tensor fascia lata (N=288, 76%), and pericranium/temporalis fascia (N=41, 11%). In all patients in this series the dura was closed with 4-0 nylon monofilament suture and plastic surgeon assistance was utilized for complex scalp wounds. CSF fistulas occurred in 33 patients (8.7%). Of those, the most common locations were from the scalp (N=23), followed by orbit (N=7), nose (N=2), and ear (N=1). Twelve of the 33 patients (36%) developed central nervous system (CNS) infections compared with 1.7% (6/346) of patients without CSF fistula ($p<0.001$). Of patients with CSF fistula and positive CSF culture (50%), all were secondary to gram negative infections with *Klebsiella pneumonia*, *Enterobacter*, and/or *Pseudomonas aeruginosa*. The authors also noted that they were forced to perform daily lumbar puncture, insert lumbar drainage catheters, or place shunts to prevent CSF fistulae in select cases and in some patients, reoperation that entailed re-suturing dural or scalp fistulas several times before CSF leaks ceased was required. However, no data were provided for these. Site of injury was not a contributing factor to rate of infection in this series. The major contributors to infection in this series were due to CSF fistula and gram-negative bacterial meningitis. There were no complications reported

due to pericranium/tensor fascia Lata/temporalis graft harvest and no complications attributed to watertight dural closure in this series. There were 32 total deaths in this series. Deaths due to infection occurred in seven patients (18 total infections, 38.8%). The mortality rate for gram negative bacterial infection was 71% (N=5/7). The rate of gram-negative bacterial infection was higher in patients with CSF fistula (54%) than those without fistula (16.6%).

The second study was of military patients (N=1,133) in the Vietnam War who suffered missile injuries to the brain.² The authors reported an incidence of CSF fistula of 8.9% (N=101). Of these, 54 (53.4%) occurred at the vertex/wound site, 30 (29.7%) with rhinorrhea, and 23 (22.8%) with otorrhea. Two cases presented with rhinorrhea and a wound site fistula, while four cases presented with both otorrhea and a wound site fistula. There were 28 patients with presumptive transventricular wounds who developed CSF fistulas. The infection rate of the entire cohort was 8.6% (97/1,133). Of patients with and without CSF fistula, the rates of infection were 49.5% (50/101) and 4.6% (47/1,023), respectively. Of the patients with vertex/scalp CSF fistulas, 12 underwent initial attempted primary closure, 34 underwent grafted closure (graft type not described), two cases the closure type was unknown, and in six cases no closure of the dura was performed. Data for these patients were reported in aggregate. Of these patients (N=54), 57.4% (N=31) developed an infection. In the case of rhinorrhea 41.4% (12/30) developed an infection and for those with otorrhea 47.8% (11/23) developed infection. There were 11 patients in this series for which resolution of CSF leak was not achieved by surgery and they all died. The authors concluded that inadequate closure of the dura and scalp is a frequent cause of failure to prevent an infection. The mortality of patients with CSF fistula was 22.8% (23/101) compared with 5.1% (53/1032) in patients without CSF fistula. There were no adverse events reported secondary to graft harvest or watertight dural closure.

The third study that reported infection rates associated with CSF fistula was in a mixed military/civilian cohort (N=374) of patients with penetrating injuries in Turkey.³ All patients in this series underwent surgical intervention, which consisted of debridement and watertight closure of the dura by the following means: primary (N=59, 15.7%), pericranial/temporal fascia graft (N=285, 76.2%), tensor fascia lata graft (N=22, 5.9%), or cadaveric dural graft (N=8, 2.1%). Nineteen patients developed CSF fistulas in this series (5.1%), of these, 13 developed CNS infections (68.4%). There was one case of purulent ventriculitis (N=1/19, 5.3%), five cerebral abscesses (N=5/19, 26.3%), three subdural empyemas (N=3/19, 15.8%), three with meningitis (N=3/19, 15.8%), and one superficial infection (N=1/19, 5.3%). This is contrasted with an incidence of infection in the cohort without CSF fistulas (N=5/355, 1.4%). In this group there were no instances of purulent ventriculitis, subdural empyema, or meningitis. There were four instances of cerebral abscess (80%, N=4/5) and one superficial infection (20%, N=1/5). There were no adverse events of watertight dural closure reported.

The fourth study also reported infection rates in the setting of CSF fistula in a mixed military/civilian cohort (N=288) who underwent craniotomy, debridement, and watertight closure of the dura in Turkey.⁴ Watertight dural closure was obtained by the following means: primary (15%, N=45), pericranial/temporal fascia graft (76.4%, N=220), tensor fascia lata (5.9%, N=17), and cadaveric dural graft (2.1%, N=6). The authors reported an incidence of CSF fistula of 4.5% (N=13). There were 11 intracranial infections in the total study cohort with a majority occurring in patients with CSF fistulas (69.2%, N=9/13) compared with patients without CSF fistulas (0.73%, N=2/275). No adverse events of watertight closure or grafting were reported by the authors.

A pooled analysis of these four studies found a greatly increased risk of infection in the presence of CSF fistula compared with no fistula (relative risk 30.18, 95% CI, 14.34 to 63.53, Figure).¹⁴ This analysis provides moderate strength evidence that infection risk is greater when patients have a CSF fistula.

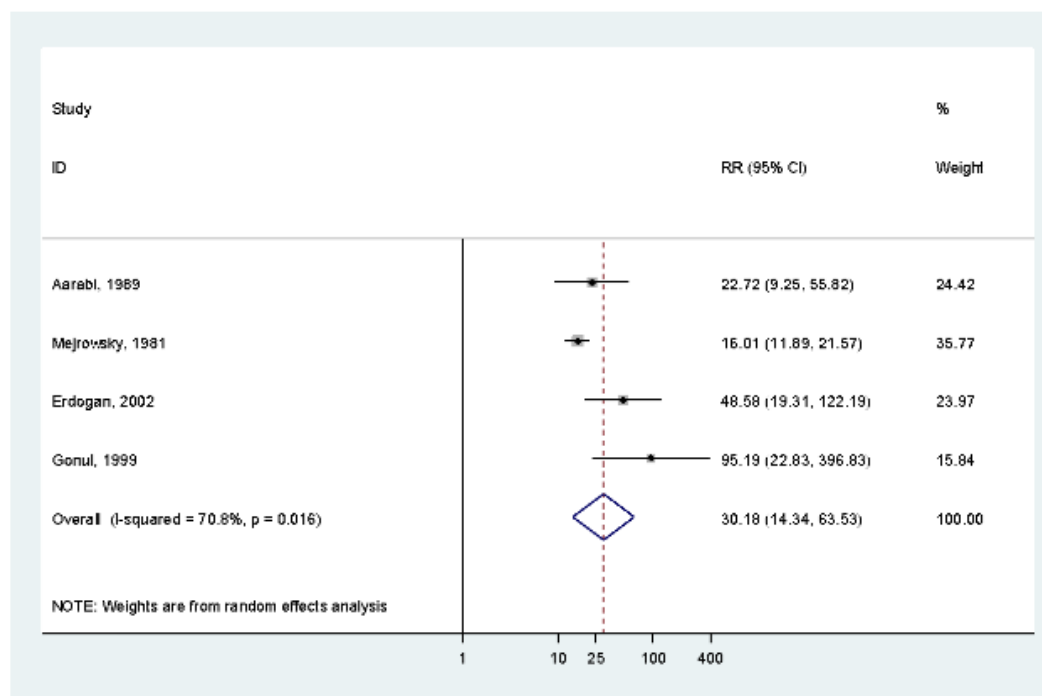


Figure. Pooled analysis of risk of infection in the presence of CSF fistula

CI=confidence interval; CSF=cerebrospinal fluid; RR=relative risk

An additional study (N=964) that also indicated a positive relationship between a CSF fistula and infection could not be added to the above analysis as raw data counts are not reported.⁵ In this study, 54.8% had penetrating injuries (N=528) and 7.5% had perforating injuries (N=72) due to military conflict. Primary radical procedures, including watertight closure, were performed in 414 patients. Univariate analysis indicated an association of development of CSF fistula and infection (53.13%, $\chi^2=187.75$, $p<0.0001$). On multivariable analysis development of CSF fistula remained associated with development of infection (Wald $\chi^2=46.5260$, OR 11.931, $p=0.0001$). It should be noted that data for patients with watertight closure were reported in aggregate with patients for whom closure type was

not available and variable treatments were performed for CSF fistulas including reoperation, lumbar punctures, and continuous CSF drainage.

Another study that could not be added to the above analysis because there were no patients with a CSF fistula was in a population of military patients (N=60) in India.⁶ Of 60 patients who were admitted with penetrating cranial wounds, 52 underwent acute surgical intervention including six who had previously undergone limited surgical procedures at forward operating bases. The authors reported that in all cases dural defects were closed with either a pericranial or temporal fascia graft to achieve a watertight closure. There were no CSF leaks in patients who underwent surgery and no patients developed brain abscesses. The authors attribute this to early surgical intervention (≤ 48 hours of injury) and the absence of CSF fistulas in this series. The average time to surgical intervention in this series was 36 hours post-injury (range 6 to 72 hours) and all patients were started on antibiotics within 6 hours of injury. There were no adverse events reported secondary to watertight closure of the dura.

The remaining 10 non-randomized studies reported other outcomes including rhinorrhea, otorrhea, reoperation, and overall mortality among others. These studies are further described below and in the table. Studies in a military population are presented first, followed by studies in a civilian population.

One study reported outcomes for a series of military patients with penetrating traumatic brain injury (pTBI) in the Vietnam War.⁷ The study cohort was comprised of 103 patients with gunshot wounds to the head who underwent surgical intervention, however, complications were only reported for survivors (N=91). The authors implied watertight dural closure was performed in all cases and noted an incidence of CSF leak of 2.1% (N=2). In both cases, re-exploration identified an absent or misplaced dural suture at the primary closure site and determined this as the etiology of the leak.

Another study in military patients (N=312) in Croatia reported surgical debridement and watertight dural closure in all patients when deemed appropriate.⁸ The incidence of CSF fistula was 14.4% (45/312). The incidence of fistula for the entire cohort by site were: 4.8% (15/312) at wound site, CSF rhinorrhea 7.4% (23/312), and CSF otorrhea 2.2% (7/312). Of fistulas identified: 33% occurred at site of injury (15/45), 51% (23/45) were via the nose, and 15% (7/45) were via the ears. All patients with wound site fistulas underwent surgical intervention and three required subsequent reoperation for persistent leak. The authors utilized patch grafting with muscle, tensor fascia lata, or alloplastic material/lyophilized dura and fibrin glue. The incidence of postoperative meningitis was 13.3% in patients with CSF fistula (6/45) and all instances occurred in patients with CSF rhinorrhea. It should be noted that it is unclear which patients underwent initial attempt at primary repair and which cases underwent a trial of spontaneous closure. It also should be noted that the cohort reported data in aggregate with 10 patients with closed head injuries.

One study in military patients (N=62) in Croatia with pTBI, reported four patients had primary closure of the dura, 45 patients underwent watertight closure with grafts and 53 total procedures were performed in these patients.⁹ The number of total procedures includes those with through and through/bilateral repair and eight patients who required reoperation. The authors separated the cohort into groups by graft type: fascia or temporalis muscle (Group 1), lyodura (Group 2), periosteum (group 3), tensor fascia lata (Group 4). Group 1 was comprised of only two patients and the mortality was 50%. Group 2 was comprised of six patients and mortality was 83.3% (N=5/6), and one patient developed CSF leak and meningitis. There were no intracranial infections identified on autopsy of those who died. Group 3 was comprised of 22 patients of which nine died (41%). Among those who survived there were three patients who developed CSF leak and meningitis, one who developed encephalitis, and three who required reoperation where periosteum was replaced with tensor fascia lata grafts. Among the nine deaths in this group there was one CSF leak and one instance of meningitis. Group 4 was comprised of 15 patients, four of whom died (mortality 26.7%). Among those who survived there

were no CSF fistulas. Among those who died (N=4), there were two instances of CSF leak, wound dehiscence, and meningitis. There were no adverse events reported by the authors due to type of graft utilized for watertight closure.

One study in military patients in Vietnam reported outcomes of 1,171 operative cases in the U.S. military and 561 cases in Vietnamese patients with pTBI in which watertight dural closure was achieved “in almost all cases” by dural grafting with muscle, fascia, or pericranium from the operative area.¹⁰ If sterile graft material was not available in the immediate exposed area the authors extended a limb of the incision and obtained tissue from another cranial site. The mortality of the operative U.S. military cohort was 9.74% (114/1,171). There were 104 deaths attributable to cerebral mortality (8.88%) in the U.S. military patients and 76 cerebral deaths in the Vietnamese cohort (13.55%). Postoperative CSF fistula requiring reoperation or additional surgery occurred in 0.63% of cases (N=11). Postoperative meningitis occurred in 0.63% of cases (N=11). There were no adverse events reported by the authors due to watertight closure or graft harvest.

Another study in military patients (N=540) in Korea reported outcomes of craniotomy/craniectomy, debridement, and watertight closure.¹¹ There were 167 transventricular wounds in this study cohort. Dural grafts were utilized for closure and a total of 590 grafts were utilized in the surgical cohort. There were 489 grafts inserted during primary craniectomy, 64 grafts inserted at secondary craniectomy/craniotomy, and in 37 instances grafts required reinsertion or replacement during secondary operations. The following grafts were used: tensor fascia lata (N=198), temporal/occipital fascia (N=186), pericranium (N=155), and gelfoam film (N=27). CSF fistulas occurred in 49 patients, 41 cases required secondary surgical closure of a dural defect. There were 144 cases of secondary surgical site exploration and graft viability was recorded: viable graft (N=90), viable graft with visible defect (N=25), non-viable graft (N=20), and gelfoam failure/migration (N=9). The authors did not report any adverse events secondary to dural graft harvest or watertight closure.

One study in a civilian population (N=39) in Iraq looked for an association with type of dural patch graft (pericranium vs. tensor fascia lata) and outcomes by the Glasgow Outcome Scale (GOS).¹² All patients underwent craniotomy or craniectomy with watertight dural closure by pericranium (64.1%) or tensor fascia lata (35.9%) graft. The authors reported an incidence of CSF leak of 12.8% in the entire cohort. There was no association with type of graft used for dural closure ($p=0.7$). Of the cohort of patients who developed CSF leak, 40% achieved a poor outcome and 60% achieved a good outcome. It should be noted that the authors utilized GOS for determination of quality of outcome, but no strict definition was provided. There were no reported complications secondary to graft harvest or watertight closure.

One study reported incidence of development of CSF fistula with duroplasty and watertight dural closure in a cohort of patients with cranial gunshot wounds to the head in a civilian population (N=110) in Brazil.¹³ The authors noted that duroplasty was performed in 73% (N=81) of patients in the cohort and indicated that watertight closure was attempted in all patients. The mortality of the cohort was 24.5% (N=27). Reoperation occurred in 8.2% of cases (N=9). Among 83 survivors a total of 15 patients developed CSF fistula (18%). No patients who expired developed CSF fistula prior to death ($p=0.0175$).

One study reported a single institution experience (N=442) with civilian pTBI in Turkey over a 16-year period.¹⁴ The authors reported that “in most cases” dura was closed primarily (15.1%, N=67). In cases where the dura could not be primarily closed, the authors performed duroplasty with pericranium or temporalis fascia (57%, N=252), tensor fascia lata (4.2%, N=19), or cadaveric dura (2%, N=9). The aggregate incidence of CSF fistula in this population was 4.5% (N=20) and was not stratified by closure type. There were no comparison groups and definitive closure attempt was implied in all cases.

One study in civilian patients (N=13) with gunshot wounds in Korea reported that watertight dural closure was performed in all cases.¹⁵ The incidence of CSF leak was 15.4% (N=2) and both cases resolved with CSF diversion without infection.

One study examined outcomes in civilian patients in the United States.¹⁶ The authors report operative outcomes for 79 patients who underwent operative intervention for gunshot wounds. In all cases dural closure was attempted. The authors reported a rate of CSF fistula of 10.1% for the entire study cohort. No leaks occurred at the surgical scalp wound or vertex. There were seven cases of CSF rhinorrhea and one case of CSF otorrhea. In these eight cases, five leaks resolved spontaneously and two required reoperation for definitive closure. One patient died with a persistent CSF fistula. The authors reported no adverse events from dural closure.

One study reported outcomes for 192 patients with penetrating brain injuries that survived to hospital admission across nine trauma centers in Maryland.¹⁷ Of the study cohort 15 patients underwent craniotomy with watertight dural closure. Of these patients there was one patient with CSF leak (CSF rhinorrhea) that required reoperation and dural repair and one epidural/subdural empyema that required washout. No description was provided for primary or grafted dural closure and no adverse events were reported secondary to watertight closure. Demographics for this subgroup were unable to be elicited.

One study in a military population with pTBI during the Croatian War looked for an association of infection and reoperation with presence of a CSF fistula.¹⁸ This study was not included in the Table due to lack of surgical description or granularity with respect to closure or non-closure of the dura. However, this work is contained within the text due to the findings of: presence of CSF fistula was associated with development of infection. CSF fistula occurred in 11% of patients (N=21). Of patients without CSF fistula, 12% developed infections. Of patients with CSF fistula, 47.6% developed infection ($\chi^2=15.33$, $p<0.001$). The authors also reported higher rates of reoperation in patients with CSF fistula (76%) compared with patients with deep seated infections (60%, $\chi^2=43.6$, $p=0.00001$) and patients without infections (8.4%, $\chi^2=56.95$, $p=0.00001$). It should be noted that no clear description of reparable or non-reparable (craniobasilar injuries) were given for this patient population. The authors defined watertight dural closure as “not allowing a CSF fistula to develop.”

Several other works were identified that support the above findings, but did not meet criteria for inclusion due to lack of granularity of injury patterns or procedures performed,¹⁹ or no clear description of dural closure were provided (watertight, primary repair, onlay only, combination).^{20,21}

One study was identified in a population of U.S. military patients that concluded that watertight closure, harvesting adjunct grafts (pericranium), or utilizing suturable grafts was time consuming and noted benefits were not apparent relative to the increased operative time in multiply injured patients.²² However, no objective measures were provided supporting this claim.

There were no harms reported secondary to watertight closure or associations with type of dural graft used.

Table. Outcomes of water-tight closure of the dura to prevent CSF leak

Author Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Aarabi, 1989 (NRS) Iran Military GSW: 10.6% Shell Fragment: 72% NR: 17.4%	N=379 Male: 99.9% Mean age: 21 years (SD 6.1) Mean time since injury: 49 hours (range: 7 to 450)	Surgical debridement (Radical) with watertight dural closure Primary dural closure: N=49 (13%) Tensor Fascia Lata: N=288 (76%) Pericranium/Temporalis Fascia: N= 42 (11%)	CSF fistulas: N=33 (8.7%) Scalp: N=23 Orbit: N=7 Nose: N=2 Ear: N=1 12/33 Patients with fistulas (36%) developed CNS infections vs. 6/346 patients without CSF leakage and CNS infection (P<0.001) 50% (N=6) of patients with CSF leaks developed gram negative CNS infections (Klebsiella pneumonia, Enterobacter, and pseudomonas aeruginosa were highest frequency) The rate of gram-negative infection was higher in patients with CSF fistula than those without (54% vs 16.6%) Total deaths in series: 32 Deaths due to infection: 7/18 (38.8%) Mortality rate in gram- negative infection: 71% (5/7)	High
Singh, 2003 (NRS) India Military Shrapnel: 72% GSW: 20% IED: 8%	N=60 patients (52 surgical) Male: 98% Mean age: 25 years (range 19 to 40) GCS 3-5: 13% GCS 5-8: 23% GCS 8-12: 50% GCS 13-15: 13% Site of injury: -Frontal: 18% -Parietal: 33% -Temporal: 17% -Occipital: 7% -Orbito-cranial/ fasciocranial: 25%	Craniotomy, debridement: N=42 Craniectomy, debridement: N=10 Watertight dural closure performed in all cases with pericranium or temporal fascia	Among 52 operated patients 0 instances of CSF leak/fistula and 0 instances of brain abscess/deep seated infection.	High
Meirowsky, 1981 (NRS) Vietnam Military MOI: NR	N= 1,133 missile wounds to the brain Male: 100% Mean age: NR	Surgical debridement, dural closure (primary or graft)	CSF fistula: 101 (8.9%) Wound site/scalp: 54 (53.4%) Rhinorrhea: 30 (29.7%) Otorrhea: 23 (22.8%) Note: 2 cases presented with rhinorrhea and wound site fistula; 4 cases presented with otorrhea and wound site fistula Transventricular wounds with fistula: 8	High

Author Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
			Infection: 8.6% (97/1133) With CSF fistula: 49.5% (50/101) Without CSF fistula: 4.6% (N=47/1032) Mortality With CSF fistula: 22.8% (23/101) Without CSF fistula: 5.1% (53/1032) Wound site/scalp fistulas: Primary closure: 12 Grafted closure: 34 NR: 2 cases No attempt to close the dura in 6 cases. Of these (N=54) Infections: 57.4% (N=31) N=12/30 (41.4%) of cases of rhinorrhea developed an infection N=11/23 (47.8%) of patients with otorrhea developed an infection.	
Dolachee, 2019 (NRS) Iraq Civilian Shrapnel: 18% Bullets: 61% Others: 20%	N=39 patients Male: 90% Mean age: NR GCS 13-15: 41% GCS 9-12: 43% GCS 5-8: 13% GCS unavailable: 3%	Craniotomy or craniectomy, watertight dural repair with patch graft: Pericranium: 64.1% Tensor fascia lata: 35.9%	CSF leak incidence: 12.8% Of these patients: 40% poor outcome 60% good outcome Authors utilized GOS as measure of outcomes, however cut-off for good/poor was not reported. There was no association with good or bad outcome by type of graft used (pericranium, TFL), p=0.7	High
Carey, 1974 (NRS) Vietnam Military GSW: 100%	Total population (N=103), survivors N=91 Male: NR Mean age: NR Admission GCS NR	Surgical debridement, implied watertight closure	CSF fistula (N=2) 1 incisional CSF leak 1 incisional CSF leak plus sterile meningitis Intraoperative discovery of failure of primary closure	High
Ambrosi, 2012 (NRS) Brazil	Male: 93% Mean Age: 26.9	Surgical intervention including implied watertight closure of dura. Duroplasty: 73% (81/105 available OR records)	Reoperation: 8.2% (N=9) Mortality: 24.5% (N=27) 15/110 (13%) developed CSF fistula Survivors CSF fistula: 15/83 (18%)	High

Author Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Civilian GSW: 100%	GCS admission: 11.5 (SD 3.7) GCS Surgery: 10.8 (SD 3.7)		Non-survivors CSF fistula: 0/27 (0%) p=0.0175	
Solmaz, 2009 (NRS) Turkey Civilian Blast/shrapnel: 68% GSW: 32%	Male 99.3% Mean age: 22.3 years (range 4 to 54) GCS 8-15: 326 GCS 3-8: 116	Dural closure: primary: 15.1%, N=67 Duroplasty: pericranium/temporalis fascia: 57%, N=252 Tensor fascia lata: 4.2%, N=19 cadaveric dura graft: 2%, N=9	GCS 8-15 mortality: 6.1% (N=20) GCS 3-8 mortality: 23.3% (N=27) CSF Fistula: 4.5% (N=20)	High
Kim, 2007 (NRS) Korea Civilian GSW: 100%	Male: 84.6% Mean age: 24.1 years (range 8 to 39) Mean GCS: 10.6 (range 4 to 15) GCS 13-15: 7 (53.8%) GCS 9-12: 2 (15.4%) GCS 6-8: 3 (23.1%) GCS <5: 1 (7.7%)	Watertight dural closure (N=13)	Mortality: 7.7% CSF leak/fistula: 2 (15.4%)	High
Melada, 2002 (NRS) Croatia Military Shrapnel: 90% GSW: 10%	N=312 Male: 99.4% Mean age: NR (range 18 to 67 years)	Debridement, watertight dural closure	CSF fistula incidence: 14.4% (45/312) Wound site fistula: 4.8% (15/312) CSF Rhinorrhea: 7.4% (23/312) CSF Otorrhea: 2.2% (7/312) CSF fistulas Site of Injury: 33% (15/45) Rhinorrhea: 51% (23/45) Otorrhea: 15% (7/45) All patients with wound-site fistulas underwent surgery. 3 underwent reoperation for recurrent leak. Patch grafting: muscle, tensor fascia lata, or alloplastic material/lyophilized dura, fibrin glue Patients with CSF rhinorrhea: subfrontal approach (TSS: N=2) Incidence of postop meningitis: 13.3% (6/45) [only occurred in patients with CSF rhinorrhea]	High
Sherman, 1980 (NRS)	Male: 81%	N=79 operative patients.	Mortality: 23%	High

Author Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
United States Civilian GSW: 100%	Mean age: 21 years (range 15 months to 81 years)	Radical debridement with watertight closure	CSF fistula: 8 CSF rhinorrhea: 7 CSF otorrhea: 1 Meningitis: 2/8 Spontaneous resolution: 5/8 Reoperation 2/8 1 patient died with persistent fistula	
Vrankovic, 1992 (NRS) Croatia Military	Male: 87.1% No other demographics provided	Surgical patients: 62 Watertight dural closures with graft: 45 (53 total procedures) Primary closures: 4 Grafts Group 1 (fascia, temporalis muscle): 2 Group 2 (lyodura): 6 Group 3 (periosteum): 22 Group 4 (tensor fascia Lata): 15	Primary closures: mortality 50% (N=2), no evidence of intracranial infection Grafted closures: Group 1: mortality 50% (N=1) Group 2: mortality 83.3% (N=5), CSF leak/meningitis: N=1 Group 3: mortality 41% (N=9) Living (N=13): CSF Leak/meningitis: N=3 Encephalitis N=1 Reoperations N=3 Deaths (N=9) CSF leak/meningitis: 1 Group 4: mortality 26.7% (N=4) Living: No CSF leaks Deaths: CSF Leak/meningitis N=2	High
Hammon, 1971 (NRS) Vietnam Military GSW: 10.7% Shrapnel: 87.2% Other: 2.0%	No demographics provided	Watertight Dural closure with local grafts (muscle, fascia, galea)	Total operative mortality for U.S. military patients: 9.74% (114/1,171) Direct cerebral mortality for U.S. military patients: 8.88% (104/1171) Total operative mortality for Vietnamese: 14.9% (84/561) Mortality of entire operative cohort: 11.23% (198/1732) Among patients with craniectomy/debridement: Postoperative CSF fistulas requiring reoperation/further surgery: 0.63% (N=11) Postoperative meningitis: 0.63% (N=11)	High
Wallace, 1960 (NRS) Korea Military	No demographics provided	Craniotomy/craniectomy, debridement, watertight closure with: Fascia lata: 198 Temporal/occipital fascia: 186 Periosteum: 155	CSF fistula: 49 41 cases required secondary surgical closure 144 cases were secondarily explored. Viable graft: 90 Viable graft with defect 25	High

Author Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Shrapnel: 50% Missiles: 29.6% Various objects: 6.5% Unknown: 15.9%		Gelfoam/fibrin film: 27 489 grafts inserted at primary craniectomy. 64 grafts inserted at secondary craniectomy. 37 instances grafts had to be reinserted or replaced in secondary operations	Non-viable graft: 20 Gelfoam in place: 4 Gelfoam displaced: 5 1 case of seizures thought secondary to cerebral herniation through dural defect	
Aarabi, 2014 (NRS) United States Civilian GSW: 100%	Total sample (N=786) Male: 84.1% Mean age: 37.8 years No demographics for small subgroup analyzed (N=15)	Craniotomy/debridement, watertight dural closure (N=15 cases)	CSF leak/rhinorrhea: 1 (6.7%) [required reoperation for dural repair] Subdural/epidural empyema: 1 (6.7%)	High
Erdogan, 2002 (NRS) Turkey Military/Civilian GSW: 32.3% Shrapnel: 67.7%	Male: 100% Mean age: 22 years (range 4 to 48)	N=374 patients Watertight dural closure: Primary: 59 (15.7%) Pericranium/temporal fascia: 285 (76.2%) Tensor fascia Lata: 22 (5.9%) Cadaveric dural graft: 8 (2.1%)	CSF fistula: 19 (5.1%) Infections With CSF fistula: 13/19 (68.4%) Purulent ventriculitis: 1 (5.3%) Cerebral abscess: 5 (26.3%) Subdural empyema: 3 (15.8%) Meningitis: 3 (15.8) Superficial infection: 1 (5.3%) Infections in cases without CSF fistula: 5/355 (1.4%) Purulent ventriculitis: 0 Cerebral abscess: 4 (80%) Subdural empyema: 0 Meningitis: 0 Superficial infection: 1 (20%)	High
Gonul, 1999 (NRS) Turkey Civilian/Military Shrapnel: 65% GSW: 35%	Male: NR Mean age: 22 years (range 4 to 45)	Craniotomy, debridement, removal of superficial in-driven fragments, watertight dural closure Closure type Primary: 15.7% (N=45) Pericranium/temporal fascia: 76.4% (N=220) Tensor fascia lata: 5.9% (N=17) Cadaveric dural graft: 2.1% (N=6)	CSF fistula: 4.5% (N=13) Intracranial infection: With fistula: 69.2% (9/13) Without fistula: 0.73% (2/275) With CSF fistula Purulent ventriculitis: 1 Cerebral abscess: 3 Subdural empyema: 2 Meningitis: 2 Superficial infection: 1 Without CSF fistula Purulent ventriculitis: 0 Cerebral abscess: 2 Subdural empyema: 0	High

Author Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
			Meningitis: 0 Superficial infection: 0	

CNS=central nervous system; CSF=cerebrospinal fluid; GCS=Glasgow Coma Scale; GOS=Glasgow Outcome Scale; GSW=gunshot wound; IED=improvised explosive device; MOI=mechanism of injury; NR=not reported; NRS=nonrandomized study; TFL=Tensor Fascia Lata

DISCUSSION

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KQ 41: Early vs. delayed cranioplasty

41. In patients with pTBI, what are the benefits and harms of early versus delayed cranioplasty?

Recommendation:

Level I

There is insufficient evidence to support a strong recommendation for benefits and harms of early versus delayed cranioplasty.

Level II

There is insufficient evidence to support make moderate recommendation for benefits and harms of early versus delayed cranioplasty.

Level III

There is insufficient evidence to support make any recommendation for benefits and harms of early versus delayed cranioplasty.

(Level IV ?)

Level C

based on EXPERT OPINION Cranioplasties can be done safely within weeks after the craniectomy and may lead to functional improvement.

Introduction

Craniectomy is the preferred treatment option in patients with life-threatening pTBI. If the initial injury is survived, each of these patients will have to undergo a cranioplasty to restore the cranial vault's integrity. Delaying the cranioplasty too long can impede neurological recovery, makes the brain vulnerable to injury, and may delay the treatment of external hydrocephalus. However, the right timing for cranioplasty has not been determined. Some argue for at least 12 weeks between cranioplasty and craniectomy, while others perform cranioplasties as soon as the incision is healed and the brain swelling subsides.

Prior Guidelines Recommendations

None

Methodology

Provided by OHSU writers.

Scientific Foundation

Two non-randomized studies report outcomes of cranioplasties received by U.S. soldiers who sustained penetrating brain injuries in overseas actions.^{1,2} The repairs were conducted in the United States and the studies had medium to large sample sizes. The potential utility of the evidence these studies provide is lessened because the authors provided no or very limited information on the characteristics of patients who received cranioplasties at different times and any differences in the patients are not incorporated into the analyses. This makes it difficult to attribute differences in outcomes to the timing of the cranioplasty.

A retrospective review of cranioplasties performed at two U.S. military hospitals between April 2002 and October 2008 collected data on soldiers injured and initially treated in Iraq or Afghanistan and included 117 cranioplasties on 108 patients.³ Ninety-three of these patients had penetrating brain injuries, mostly from blasts. The patients were young, with a mean age of 26 years and only one was female. The time from injury to cranioplasty ranged from 7 to 546 days with a mean of 190 days. There was one death (0.9%) and 12 patients of the 29 patients who experienced complications required reoperation to remove the prosthesis. The mean Glasgow Outcome Score was 4.0 at 1 to 2 years post injury, but details on the follow-up period and the distribution of scores were not provided. As improvement often continues over longer periods, this may not be the definitive finding. Time to cranioplasty was stratified by 90-day intervals and the authors report they found no difference in complications or the need for reoperation across the time intervals (data was not provided in the article).

A registry was created by military surgeons in Vietnam of 1,030 cases of penetrating brain injury among soldiers treated from 1967 to 1970 and their records were reviewed by the National Research Council from 1976 to 1979 to obtain follow-up information.¹ They identified 491 cranioplasties conducted at military, Veterans Administration, and private civilian hospitals to repair these injuries. When cranioplasties were sorted by the time from initial operation, the rate of complications decreased as the time from injury increased and leveled out at under 5% after 12 months. When only cases with complications after the initial surgery are examined, the complication rate for cranioplasties done in the 2nd year after the original surgery was lower (4%) than the rate for patients with cranioplasties in the 1st year (20%).

Also included are two case series that provide some limited information about the timing of cranioplasty in pediatric patients.^{3,4} We included these since studies of pediatric patients with penetrating brain injury are limited. Both involve children injured in war zones. One study reported on all cases of children treated at the Multinational Medical Unit at Kandahar Airfield in Afghanistan by the only neurosurgeon in the region.³ During three periods totaling 237 days between September

2008 and April 2010 in which the unit could take local cases, 16 children under 15 years old treated for penetrating brain injuries were included and followed. In six cases the bone flap was left out and the patient discharged, with instructions about when to return for cranioplasty, based on both expectations of healing and operational availability. Four returned as scheduled 5, 8, and 10 weeks later, one patient returned early at 4 weeks and one patient did not return. All five of the cranioplasties were completed without difficulties and the patients were discharged with no focal neurological deficits. The other study was a prospective series of decompressive craniectomies to treat penetrating blast injuries in children treated in a 2-year period in Iran near the border with Iraq (dates and hospital location not reported).⁴ All three of the children who survived had cranioplasties 3 months later and all had good outcomes at 1 year with no major motor deficits and reports of excellent school performance.

These studies provide very low strength evidence that the timing of cranioplasty is associated with outcomes. This is based on the inconsistent findings and study risk of bias due to a lack of reporting and adjustment for patient characteristics by early and late cranioplasty that may have influenced findings.

Table. Early versus delayed cranioplasty

Author, Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Stephens, 2010 (NRS) United States Military Explosive blast injury: 67% GSW: 28% MVA: 2.8% Helicopter crash: 0.9% Falling: 0.9% Stabbing: 0.9%	N=108 patients 93 penetrating TBI 15 closed TBI Male: 99% Mean age: 26 yearsrs. Initial Presentation: Mean GCS: 7.5 Mean ISS: 33	Mean time injury to cranioplasty: 190 (sd 91) days (SD: 91) (range: 7 to -546 days) 117 Cranioplasties (N=117) MMaterial: 89 (82%) Polymethacrylate: N=89, 82% 19 (18%) Titanium mesh: N=19, 18%	Death: N=1, (0.9%) Prosthesis removal: N=12, (11%) 3 extra axial hematomas: N=3 9 Infections: N=9 Mean GOS 1 to -2 years post injury: 4.0 (sdSD 0.93) Total cComplications: N= Total: 29 ((24%)) Infection: N=13 ((12%)) -Skull base injury: 7 (54%) -Orbitofacial fracture: 5 (39%) -Sinus injury: 4 (31%) -Preexisting fluid collection: 1 (7.7%) -CSF leakage: 1 (7.7%)) Seizure: N=8 ((7.4%)) Extra axial hematoma: N=8 (7.4%) Characteristics associated with infectious complications: Skull base injury: N=7 (54%) Orbitofacial fracture: N=5 (39%) Sinus injury: N=4 (31%) Preexisting fluid collection: N=1 (7.7%) CSF leakage: N=1 (7.7%) Infection rate: 0-90 days: N=1 (7.7%)	Moderate

Author, Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
			90-180 days: N=4 ((31%)) 180-270 days: N=4 ((31%)) 270-360 days: N=1 ((7.7%)) >360 days: N=3 ((23%)) No significant difference in complications or need to revise or reverse when time to cranioplasty was stratified by 90-day intervals. Infection rate for 90 to 270 days approached significance (p=0.061). No factors were found to be associated with cranioplasty failure or GOS score.	
Rish, 1979 (NRS) United States Military (patients) Mixed (hospitals) Missile fragments: 76.4% GSW: 16.3% MVA: 4.1% Other: 3.2% (all pBlpTBI)	N=491 cranioplasties N=in 1,030 patients with pBlpTBI Mean age at injury (all pBlpTBI): 21.3 years	Cranioplasties performed at multiple facilities including military, VA and private civilian hospitals; numbers not reported Cranioplasties (N=491) Material: Acrylic: N=341 Metal: N= 71 Plastic: N= 12 Autogenous Bone: N=20 Unlisted: N=47	Time from injury to cranioplasty: Complications N (%) # cases, # complications: Months Complications 1-6 months: (N=89,) 7, complications ((7.9%)) 7-12 months: (N=187,) 10, complications ((5.3%)) 12-18 months: (N=132,) 6, complications ((4.5%)) >18 months: (N=83,) 4, complications ((4.8%)) Ten cases after 12 months: 4 minor complications 1 bone plate dislodged with trauma; 1 bone infected and resorbed. 4 infections with removal Complications from ilinitial surgery: had any complications subgroup # cases, # complications: Months Complications 1-12 months: (N=51,) 10, complications ((20%)) 13-24 months: (N=52,) 2, complications ((4%)) Death: N=1, 0.2% 1 death (0.2%) related to cranioplasty performed 3 months after initial injury. Patient developed CSFT rhinorrhea or died due to chronic meningitis.	High
Matthew, 2013 (NRS)	N= 6 Ppatients with DC, intended	5 of 6 Ccompleted cranioplasties: N=5/6	Time to cranioplasty after discharge:	High

Author, Year (Study Design) Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Afghanistan Civilian (patients) Trauma Center (military) Blast: 135 (83%) GSW: 3 (17%) Penetrating: 12 Perforating: 1 Tangential: 2 Cranial facial Degloving: 1	cranioplasty: N=6/16 Out of 16 children Demographics for N=6 Male: 67% Mean aAge: Mean 9 yearsrs. (rRange: 6 to 12) 5 Penetrating: N=5 1 Perforating: N=1	Bone was stored in a left anterior abdominal wall subcutaneous pocket.	4 as planned 8 weeks: N= 1 10 weeks: N= : 2 5 weeks: N=: 1 1 earlier than planned: 4 weeks All wounds were healed and reopening presented no technical difficulty. Discharge within 1 week: N=All 5 patients discharged within 1 week, fully conscious with no focal neurological deficits and not further follow-up. 1 patient who did not return for follow-up and cranioplasty. : Ooutcome for this patient is unknown.	
Javadi, 2021 (NRS) Iran Civilian Blast injury due to land mine: 100%	N=3 Ages: 7,8, and 9 years GCS on admission: 4 post decompressive craniectomy GCS 5 days post DC: 7 GCS 2 weeks post DC: 9 GCS 1One-month post DC: 14	Cranioplasty performed at 3 months	1-year: No major motor deficits Excellent school performance 1 case of contralateral dominancy and handedness	High

CSF=cerebrospinal fluid; DC=decompressive craniectomy; GOS=Glasgow Outcome Scale; GSC=Glasgow Coma Scale; GSW=guns: shotgun shot wound; GSC=Glasgow Coma Scale; ISS=Injury Severity Scale; MVA=motor vehicle accident; pBIpTBI=penetrating brain injury; SD=standard deviation; TBI=traumatic brain injury, VA=Veterans Administration

We set out to answer whether early or delayed cranioplasty is more beneficial for pTBI patients. A retrospective review of cranioplasties included 117 cranioplasties on 108 patients.² Ninety-three of these patients had penetrating brain injuries, mostly from blasts. The time from injury to cranioplasty ranged from 7 to 546 days. Time to cranioplasty was stratified by 90-day intervals, and the authors

found no difference in complications or the need for reoperation across the time intervals. This study did not provide any data on cranioplasties in pTBI on cranioplasties earlier than 90 days.

The studies available did not provide a consistent definition of early versus late cranioplasty. A registry-based study based on patient data from 1967 to 1970 demonstrated that cranioplasties two years after craniectomy have a lower complication rate than one year after craniectomy. One has to be careful to draw conclusions from this historical data as it would be outside of the current standard of care to wait 1 or 2 years for a routine cranioplasty.

It is essential to know that none of the studies available on this topic went as far as accounting for recovery speed and functional outcome in patients with early vs. late cranioplasty. It is known that the syndrome of the trephine can impede recovery after TBI, and improved neurological function has been described in patients after cranioplasty.

Studies in non-pTBI showed that early Cranioplasties (<12 weeks) after TBI compared to cranioplasties >12 weeks are safe and do not have a higher complication rate. A systematic review and meta-analysis from 2016 comparing cranioplasty in all TBI patients performed within (early) and beyond (late) 90 days. Found that early cranioplasty had significantly higher odds of hydrocephalus than late cranioplasty (Odds Ratio [OR] 2.38, 95% Confidence Interval [CI] 1.25-4.52, p=0.008). There was no difference in odds of overall complications, infections, reoperations, intracranial hemorrhage, extra-axial fluid collections, seizures, or bone resorption. This study did not account for rehabilitation needs and progress. The increased risk of hydrocephalus in the early group might be explained by the extra-axial fluid collection in a patient in the late group not been correctly diagnosed as external hydrocephalus.

Taking the negative impact of a prolonged defect in the cranial vault (aka syndrome of the trephine) into account and the fact that early (within 12 weeks) cranioplasty has not been associated with an increased risk of complication, lead to the following expert opinion.

Expert Opinion: Cranioplasties can be done safely within weeks after the craniectomy and may lead to functional improvement.

There is xxx consensus within the guidelines subject matter expert working group in this matter.

Future Directions for Research:

Our understanding of the ideal timing to perform a cranioplasty in the setting of pTBI remains to be determined. Additional work is needed to clearly identify the ideal time for cranioplasties ultra-early (within 4 weeks), early (4-12 weeks), or late (>12 weeks). Additionally, future studies should look beyond infection and other complication rates and include comprehensive outcome data, including speed of recovery and neurological status after cranioplasty.

References

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KQ43/44: endovascular and surgical management of TICA's

43. In patients with pTBI, what are the benefits and harms of endovascular coil occlusion to reduce risk of rupture, in the setting of a traumatic aneurysm?

Recommendations

Level I

There is insufficient evidence to support a strong recommendation for or against endovascular occlusion to reduce risk of traumatic aneurysm rupture resulting from pTBI.

Level II

There is insufficient evidence to support a moderate recommendation for or against endovascular occlusion to reduce risk of traumatic aneurysm rupture resulting from pTBI.

Level III*

There is insufficient evidence to support a weak recommendation for or against endovascular occlusion to reduce risk of traumatic aneurysm rupture resulting from pTBI.

Level IV

Endovascular treatment of traumatic aneurysms, which often requires re-treatment, is strongly recommended as a means of reducing the risk of aneurysm hemorrhage and the associated high rate of morbidity and mortality. There is, however, insufficient evidence to support superiority of endovascular aneurysm occlusion over open surgical parent vessel sacrifice despite a theoretical reduced risk of iatrogenic stroke with surgical intervention.

Level C (achieved by DELPHI consensus)

In the absence of sufficient evidence, based on EXPERT CONSENSUS, it is recommended that traumatic aneurysms which increase in size be treated with either open or endovascular means because of a presumed elevated risk for rupture (87.5% consensus).

In the absence of sufficient evidence, based on EXPERT CONSENSUS, it is recommended that larger traumatic aneurysms should be more strongly considered for treatment because of a presumed elevated risk for rupture (80.5% consensus). There is insufficient evidence or expert consensus to recommend a size threshold, however.

In the absence of sufficient evidence, based on EXPERT CONSENSUS, it is recommended that traumatic aneurysms treated endovascularly should be reassessed with cerebral angiography **within 8**

weeks after initial treatment because of a risk of treatment failure (i.e., aneurysm recurrence or regrowth) for which further therapeutic procedures may be necessary. (95% consensus)

In the absence of sufficient evidence, based on EXPERT CONSENSUS, it is recommended that in certain circumstances traumatic aneurysms may undergo a short period of conservative management with close observation. Reasons for observation may include the lack of available neuroendovascular expertise, or a perceived unfavorable risk:benefit ratio inherent to treatment (95% CONSENSUS).

No evidence or expert opinion supported distinct recommendations based on patient gender, age, wounding mechanism, or military vs. civilian context.

Introduction

Penetrating traumatic brain injury often injures the cerebral vasculature. Traumatic pseudoaneurysms can be caused by direct laceration of the arterial wall or by indirect mechanisms such as irritation from the fragment or missile cavitation wave. These aneurysms are highly unstable and unpredictable, and are associated with delayed development, growth, rupture, and in some cases spontaneous healing.¹⁻⁴ Other cerebrovascular pathologies associated with pTBI include traumatic cerebral vasospasm and arterio-venous fistula.^{5,6} While pathologic consequences and treatment paradigms for arterio-venous fistula are well established (references), the same is not necessarily true for traumatic cerebral vasospasm.^{5,6} Historically there has been uncertainty as to when and how to screen for traumatic aneurysms, and if, in what circumstances, and by what means they should be treated.²⁻⁴ Dogma has long held that because traumatic pseudoaneurysms lack a wall that can retain endovascular coils, traumatic aneurysms are not amenable to coiling. A growing body of experience and evidence has challenged this dogma, however.^{2,7-15}

Prior Guidelines Recommendations

The prior penetrating head injury guidelines addressed “Vascular Complications of Penetrating Brain Injury.”¹⁶ Recommendations created in this edition were based on 8 articles defined as Class III. Three general levels of recommendations were utilized in this edition and are related to the current edition as follows: “Standard” is now “Level I”; “Guideline” is now “Level II”; “Option” is “Level III and IV”. No Level I or Level II recommendations on this subject were provided. Level III/IV recommendations stated that surgical or endovascular management of traumatic aneurysms or arterio-venous fistula was recommended. Direct evidence supporting this recommendation was lacking, however. Of the 8 papers included, only four directly or indirectly addressed the issue of surgical management of TICA in pTBI.^{1,3,4,17} Of these, two studies shared populations,^{4,17} and one study did not include specific details concerning the outcomes of the patients treated³.

Methodology

To be provided by OHSU writers.

Scientific Foundation

Background

Traumatic cerebrovascular injury is central to the management of penetrating brain injury. The incidence of traumatic aneurysms resulting from pTBI in larger studies ranges from 3-40%^{2,17,18} Contrasting with spontaneous saccular aneurysms that have a dome comprised of connective tissue (adventitia), traumatic aneurysms lack such a dome. These traumatic “false” aneurysms are generally confined instead by organized blood clot within the subarachnoid space which is adjacent to the area of vessel damage.^{4,8} This results in an unpredictable natural history characterized by delayed formation and presentation, spontaneous healing, interval growth, and delayed rupture.^{1-4,7-15}

Traumatic pseudoaneurysm rupture has been associated with significant morbidity and mortality. In one study, delayed rupture was associated with a nearly 50% mortality rate.²

Physicians treating traumatic pseudoaneurysms have had to balance the risk of rupture with the risks of treatment. Historically, traumatic aneurysms were treated with open surgery, either at the time of initial presentation and surgical intervention, or in a delayed fashion after follow-up imaging based diagnoses.^{1,3,4} This has typically involved significant risk of intraoperative rupture and the near ubiquitous need for parent vessel sacrifice which can lead to an iatrogenic stroke – sometimes of eloquent brain.^{1,3,4}

Technological advancements in endovascular materials, including detachable coils and flow diverting devices, have made endovascular occlusion of traumatic aneurysms a viable alternative. In contrast to dogma which held pseudoaneurysms could not be coiled, experience and evidence has demonstrated that endovascular treatment is feasible. Given the inherent complexities and divergent expert opinions on the topic, the management of traumatic aneurysms is a pTBI subtopic which is particularly in need of evidence and consensus-based guidance which seek to identify and disseminate best care practices. Here we present evidence informing the endovascular treatment of traumatic pseudoaneurysms supplemented with expert consensus statements.

Endovascular Management of Traumatic Aneurysms

A total of 9 studies were determined to be of sufficient quality for inclusion in the evidentiary base. One non-randomized study of wartime traumatic aneurysms in Iraq reported outcomes in patients with penetrating traumatic brain injury (pTBI) and traumatic intracranial aneurysms (TICAs) treated with coil occlusion (N=12), and one additional treated with stent buttress coil occlusion.³ Most injuries were blast-related (67%), with gunshot wounds (25%) and knife wound (8%) the other mechanisms of injury. The anterior cerebral artery was the vessel most commonly affected (60% of patients) followed by the middle cerebral artery (25% of patients). In general, those traumatic aneurysms noted to increase in size or that were treated in this study were larger than those that were not treated. Following initial TICA treatment, 5/12 patients (42%) patients experienced aneurysm recurrence and required re-treatment with coil or stent-coil (3/5) or clip (2/5). There were no aneurysm ruptures that occurred following coil occlusion in this study. This compares with one recurrence/retreatment (20%) in the five pTBI patients with TICA treated with a clip, and one rupture (12.5%) in the eight pTBI patients whose TICA was not treated. However, the size/severity/location of the TICA was likely a confounding factor in the specific treatment or lack of treatment provided (**Table**).

In another non-randomized study (N=2) from a Level 1 trauma center in Jerusalem, two patients with pTBI and TICAs were treated with endovascular coils.⁷ One patient (17 years) suffered a missile wound in a bus bombing and following treatment had a Glasgow Outcome Scale (GOS) score of 5; the other patient (5 years) was stabbed with an umbrella (transorbital-transcavernous) with a post-treatment GOS of 4 (**Table**).

In a third non-randomized study (N=2) one adult patient with a nail gun injury and TICA was treated with endovascular coils and recovered without infarction (callosomarginal territory).⁸ The other adult patient in this study experienced a TICA due to a gunshot wound to the head. Follow-up angiography at 2 months indicated an enlargement of the TICA, which was then treated with detachable coils, sparing the parent artery (**Table**).

Other reports of treatment of TICA in pTBI with endovascular coiling were limited to case reports. Results were mixed (**Table**).¹⁰⁻¹⁵

These studies provide very low strength evidence that coil embolization of TICA in the setting of pTBI may reduce the risk of further bleeding outcomes or need for retreatment but do not provide evidence for endovascular coiling compared with other treatments in the absence of potential confounding factors.

Open Surgical Management of Traumatic Aneurysms

Please see write up for KQ 46

Table. Studies of endovascular coil occlusion in TICA

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Bell, 2010 ² (NRS) Iraq Military Blast: 60% GSW: 25% Knife: 8%	Total population (N=187) Male: 99% Mean age: 26 years Admission GCS: 8.4 ISS: 24 Average time to Angio: 10 days Total patients w TICA , N=24 Total #TICA: 31	pTBI patients with TICA treated with coil (N=12) Surgery: N=5 patients, 9 TICA clip (N=9) No surgery (N=8) Note: 1 patient had 1 TICA (ACA) clipped and 1 TICA (MMA) not treated 2 patients had endovascular coil retreated with a clip and 1 patient had a clip retreated with a coil	<u>Initial Treatment:</u> TICA patients treated initially with coil (N=12): Rupture: 0% Parent artery preservation: 50% Recurrence: 27% Retreatment: 36% Retreatment was with coil or clip All TICA pTBI patients treated initially with clip (N=5): Rupture: Recurrence: 20% Retreatment: 20% All untreated pTBI patients with TICA (N=8) Rupture: 12.5% Resolved: 87.5% Average size ruptured TICA: 8.3 mm Average size not ruptured TICA: 3.2 mm Average time to rupture: 15 days (range 4 to 32 days)	High
Cohen, 2008 ⁷ (NRS) Israel Civilian Blast: 50% Umbrella: 50%	Total population: 25 pt. Total TICA's: 10 Male: 0% (2 patients both female) Age: 17 and 5 years GCS: 7 and 13	pTBI patients with TICA total treated (10); coil or stent coil (2); PAO with NBCA (8)	Coil results: 17-year-old (blast): GOS score 5 5-year-old (umbrella): GOS score 4 Noted complete occlusion	High
Hemphill, 1999 ⁶ (NRS)	Total patients: 4 Total with pTBI: 2	pTBI patients with TICA treated with coil (N=2)	39-year-old (nail gun): recovered without infarction (callosomarginal territory)	High

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
United States Civilian Nail gun: 50% GSW: 50%	Male: 50% (2 patients, 1 male, 1 female) Age: 39 and 33 years		33-year-old (GSW): angiography at 2 months showed worsening TICA treated with detachable coils sparing parent artery	
Aljuboori, 2020 ¹⁰ (Case report) United States Civilian GSW	Male Age: 19 years	pTBI patient with TICA treated with coil (N=1)	Treated with coil embolization, recurrence at 2 weeks , treated with a Pipeline Flex embolization device; patient remained neurologically intact, follow-up angiography at 6 months showed resolution	High
Hachemi, 2007 ¹³ (Case report) France Civilian GSW	Female Age: 10 years	pTBI patient with TICA treated with coil (N=1)	Aneurysm presented with rupture post injury day 7 prior to treatment. Good neurological recovery at 6 months	High
Darsaut, 2007 ¹¹ (Case report) Canada Civilian Knife	Male Age: 32 years GCS: 3	pTBI patient with TICA treated with coil (N=1)	Coil embolization was followed by knife removal which led to “contrast extravasation from the coiled vessel stump”, so additional coiling was deployed and extravasation stopped; in ICU patient died after removal of life support (patient had elevated intracranial pressure:70 mmHg)	High
Sirko, 2018 ¹⁴ (Case report) Ukraine Military Shrapnel	Male Age: NR GCS: 11	pTBI patient with TICA treated with coil (N=1) (Patient had comorbid injuries requiring thoracotomy and removal of foreign body from heart)	Middle cerebral artery bleeding was treated with clipping, bipolar coagulation, and Surgicel. At 3 months TICA was discovered and treated with detachable microcoils without further deterioration	High
Feng, 2018 ¹² (Case report) China Civilian Bamboo branch	Female Age: 62 years Stable vitals but fixed right pupil (transorbital penetration)	pTBI patient with TICA treated with coil (N=1)	Foreign body was surgically removed; 3 weeks after discharge the patient returned with swelling, pain, and bleeding from nose and mouth, CTA showed TICA of right ICA treated with coiling, patient followed up for 12 weeks and recovered except for loss of vision in Right eye	High
Yoon, 2022 ¹⁵ (Case report)	Gender: NR Age: NR	pTBI patient with TICA treated with coil (N=1)	Stable pseudoaneurysm on admission but expanded 27 days after admission treated with stenting and coiling; long-term outcomes NR	High

Author Year Country Civil/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
United States Civilian GSW				
Mansour, 2021 ^a (NRS) United States Civilian GSW: 100% Median Age: 26.5	Total patients: 128 with pTBI Total CTA: 72 patients 37 arterial injuries in 26 patients (11TICA, 7 occlusion, 8 transections, 6 dissections, 4 intimal injuries) 8 patients, 11 TICA's 1F, 7M Male: 87.5%% Mean age: 28 years GCS: 4T,3T,5T,5T, 3T (individual GCS scores)	Surgery N=1 patient, 1 TICA (GCS 5T) Endo coil: N=3 patients, 3 TICA (GCS8T, 15, and 3T) Observation: N=4 patients, 7 TICA (GCS 4T, 3T, 5T, 3T)	<u>Outcomes</u> Surgical: "unfavorable", (GOSE 3) Endo: 2 favorable (GOSE 4 and 6), one unfavorable (death) Observation: "Unfavorable": all 4 patients, discharge details not reported	High

CTA= computed tomography angiography; GCS=Glasgow Coma Scale Score; GOS=Glasgow Outcomes Scale Score; GSW=gunshot wound; ISS=Injury Severity Scale; MOI=mechanism of injury; NR=not reported; NRS=non-randomized study; pTBI=penetrating traumatic brain injury; TICA= traumatic intracranial aneurysms

Discussion of Recommendations and Limitations: Endovascular treatment

As has been previously discussed, penetrating brain injury is a highly lethal wounding mechanism that is very difficult to study with prospective, randomized trials. With this in mind, the body of literature in this area remains largely retrospective, observational, or case report in nature (Class III or IV), and therefore does not support Level I or II recommendations. That said, it is the lethal and unpredictable nature of penetrating brain injury in general, and traumatic aneurysms in specific, that support the nature of the above recommendations.

At the time of the creation of the prior pTBI guidelines in 2001, open surgical management of traumatic aneurysms was the primary means of treatment^{1,3,4} This was in part secondary to the early and somewhat rudimentary nature of the endovascular technologies available at that time as well as a concern that they would not be contained by the pseudoaneurysm clot. Specifically, at that time, aneurysm coils were still considered new technology, and neither aneurysm stents nor flow diverters were available. Since that time, endovascular technologies and techniques have exponentially advanced.^{2,7-15}

The purpose of treatment of traumatic aneurysms is not to reverse the primary injury, but to help reduce the risk of secondary brain injury, often catastrophic, from aneurysm rupture. Open surgical techniques remain a viable approach but can theoretically involve the morbidity of stroke in the distribution of the parent artery if sacrifice is necessary. From an algorithmic perspective, this approach may be preferred at the time of initial surgical intervention for superficial and active arterial bleeding. However, endovascular coil occlusion in the acute setting is a viable alternative that may 1) reduce the risk, at the time of open surgical decompression, of catastrophic hemorrhage from large, skull base arterial injury, 2) reduce the need for return to the operating room for clip reconstruction of an aneurysm in an injured and inflamed cortical environment, 3) identify, with the necessary pre-treatment gold standard cerebral angiogram, arterial injury (aneurysms, arteriovenous fistula, etc.) not visualized with CTA, 4) allow for treatment of arteriovenous fistula sub-optimally visualized on non-invasive imaging, and 5) provide a means of preserving the parent artery at the time of initial treatment.

The Level IV recommendation supporting endovascular occlusion of intracranial traumatic aneurysms in pTBI is based on the reported literature experience of 33 endovascularly treated aneurysms, with 25 treated with coil occlusion, and 8 treated with parent artery sacrifice. The rate of re-rupture following initial treatment was 1/25 4%. In this one case, the aneurysm was diagnosed at the time of patient presentation with a protruding foreign body (knife), the aneurysm coiled with the microcatheter left in place, and continued bleeding after the knife was removal immediately treated. Overall, while counterintuitive to coil a false aneurysm or blood clot, the data support this option as a means of preventing aneurysm rupture and preserving the parent artery. One study specifically noted a rate of parent artery preservation as high as 50%.² While this offers an advantage over surgery, the aneurysm recurrence rate is relatively high, necessitating early post intervention follow up angiography (preferably within approximately 4-8 weeks). Aneurysm re-treatment may be necessary should recurrence be noted. In these cases, technology that includes the use of one of the many flow diverters currently available may be a viable option, as was demonstrated in the case report by Aljuboori et. al. Flow diversion as a primary means of treatment may also be considered, depending on the location of injury and the need to preserve the parent artery (i.e. Internal carotid, proximal MCA/PCA/ACA). As flow diversion mandates the extended use of dual antiplatelet therapy (3 or more months), the timing of this intervention must take into account the need for additional open surgical intervention.

Expert Opinion

The available evidence does not, at this time, support definitive recommendations concerning the timing of initial diagnostic assessment and treatment of pTBI related traumatic aneurysms, whether observation or non-treatment of some traumatic aneurysms is warranted and the conditions where this might apply, the size threshold for mandatory treatment, and the frequency of follow up diagnostic imaging in the setting of observed or treated traumatic aneurysms. With this in mind, a DELPHI consensus model (>80%) was obtained through dedicated, in-person survey of the multi-disciplinary subject matter expert team during a 5 day guidelines consensus conference. Aneurysm treatment, timing of follow up evaluation for treated aneurysms, and conditions where observation may be warranted were addressed. While the diagnosis of pTBI associated vasospasm was addressed with evidence-based recommendations, endovascular treatment was not addressed in this guideline.

We are aware of diverse management strategies for traumatic pseudoaneurysms including some who currently favor conservative management of these lesions. It was, however, the strong opinion of our expert group that a failure to diagnose and treat these lesions can have catastrophic consequences. Our expert panel advocates aggressively screening for and treating traumatic pseudoaneurysms. These lesions require complex judgment individualized to specific patients and

circumstances, however. Clinicians caring for pTBI patients must have both a high index of suspicion in pTBI, and a low threshold for treatment. In short, all traumatic aneurysms should be considered for treatment, and consensus was achieved amongst our panelists that large aneurysms and those noted to increase in size must be treated with particular urgency (80.5% and 87.5% Consensus respectively). A consensus recommendation for minimum size threshold for aneurysm treatment was not obtained. While smaller aneurysms have been noted to heal on interval imaging, they have also been noted to grow, rupture, and result in death. It is with this in mind that the consensus recommendation for observation under certain specific conditions was made (95% Consensus). In this setting, early follow up cerebral angiography (within 4-8 weeks) should be considered.

It should be noted that aneurysm recurrence in the setting of endovascular occlusion of traumatic aneurysms was reported as high as 27%.² This is a significant limitation of this type of intervention and requires early follow up (4-8 weeks) cerebral angiography as noted above (95% consensus). Secondarily, it is also acknowledged that the full scope of endovascular treatment modalities, including aneurysm stents and flow diverters, may be considered too high risk in the acute setting secondary to the need for dual anti-platelet therapies with these interventions. These approaches may be best considered with delayed or recurrent traumatic aneurysm presentation.¹⁰

Future Directions:

Our understanding of how traumatic aneurysm characteristics influence risk of rupture and the risk:benefit of different treatment options is advancing but remains unclear. Additional work in characteristics associated with coiled traumatic aneurysm re-treatment, techniques to and the risks and benefits of different endovascular therapies would also be beneficial.

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Harms and benefits of endovasc. Management of endovasc. Traumatic Intracranial Aneurysms (TICAs)

40 studies

Evidence for open surgery vs. endovasc.

46. In patients with pTBI, what are the benefits and harms of surgery to reduce the risk of rupture and improve outcome, in the setting of a traumatic intracranial aneurysms (TICA)?

Recommendations:

Level I

There is insufficient evidence to support a strong recommendation for surgery to reduce the risk of TICA rupture and improve outcome.

Level II

There is insufficient evidence to support a moderate recommendation for surgery to reduce the risk of TICA rupture and improve outcome.

Level IV

Open surgery may be considered in the setting of traumatic intracranial aneurysms resulting from penetrating traumatic brain injury to reduce chance of rupture and improve outcome. There is insufficient evidence to support superiority of open surgical clip reconstruction over endovascular management of traumatic aneurysms.

Expert Consensus Opinion

In the absence of sufficient evidence, EXPERT CONSENSUS recommends a multi-disciplinary approach to vascular sequelae of pTBI (TICA, A-V fistula, vasospasm, etc.) for patients with traumatic vascular injury(ies) when feasible.(100%)

Introduction

Penetrating traumatic brain injury (pTBI) often injures the cerebral vasculature. Damage (including complete or partial transection) or irritation to the arterial wall can be associated with the formation of TICA. TICAs are highly unstable and unpredictable, and are associated with delayed development, growth, rupture, and in some cases spontaneous healing. Other cerebrovascular pathologies associated with pTBI include traumatic cerebral vasospasm, arterio-venous fistulas and complete occlusion of an arterial branch causing stroke. Historically there has been uncertainty as to when and how to screen for traumatic aneurysms, and if, in what circumstances and by what means they should be treated. Prior to the advent of specific endovascular techniques and technologies, open surgery following conventional angiography was the main treatment available.

Prior Guidelines Recommendations

The prior penetrating head injury guidelines addressed “Vascular Complications of Penetrating Brain Injury.” Recommendations created in this edition were based on 8 articles defined as Class III. Three general levels of recommendations were utilized in this edition and are related to the current edition as follows: “Standard” is now “Level I”; “Guideline” is now “Level II”; “Option” is “Level III and IV”. No Level I or Level II recommendations on this subject were provided. Level III/IV recommendations stated that surgical or endovascular management of traumatic aneurysms or arterio-venous fistula was recommended. Direct evidence supporting this recommendation was lacking, however. Since 2001, significant advances have been witnessed in endovascular management of both congenital aneurysms and TICAs.

Methodology

Provided by OHSU writers.

Scientific Foundation

Seven non-randomized studies (6 case series, and 1 case report, N=89) provided evidence on the risk of traumatic intracranial aneurysm (TICA) rupture following surgery compared with no surgery.^{1,7} All studies were rated high risk of bias due to study design. Injuries were due to high velocity missiles or stab wounds.

One study involved 187 patients (162 penetrating) who received cerebral angiograms an average of 10 days after their primary injury. A total of 31 TICA’s were diagnosed in 24 patients in this study (total of 64 vascular injuries in 48 patients). 9/31 aneurysms in 5/24 patients were treated with primary clip occlusion, and 3/31 aneurysms in 3/24 patients were treated with a combination of coil occlusion and clip ligation. No ruptures were observed in patients treated with primary or secondary clip reconstruction. 8 TICA’s in 8 patients were not treated, with rupture occurring in one of those patients resulting in death.⁷ Overall GOS was noted to be 3.1 in this study, without a specific outcome attributed to the TICA subgroup.

One study (N=15) described findings associated with traumatic aneurysms at presentation. 14 of 15 patients in this study presented in the pre-CT era.⁴ Four patients presented with subdural hematoma, all attributed by the authors to aneurysm rupture. 12 patients presented with intracerebral hemorrhage, 11 attributed to aneurysm rupture by the authors. Of specific note, 5 patients suffered

deterioration of clinical examination in a delayed fashion. One patient had a delayed headache and seizure, one a new hemiparesis, and three a deterioration of consciousness. While suspicious for delayed rupture, no specific conclusion can be made. Two of the five patients had what was described as a “good” outcome, one with “poor” outcome, and two with death. In all cases, surgical intervention (11 trapped and excised, 1 coagulated, 1 treatment completed but not specified) appeared in this study to occur after hemorrhage findings associated with the aneurysm. Outcomes in this study were attributed to the condition of the patient at presentation, without association specifically to the traumatic aneurysm. However, 2/13 surgical patients died. There were no reported aneurysm ruptures after treatment.

One study involved 255 patients with penetrating brain injury who received cerebral angiography an average of ~17 days after injury during the Iran-Iraq War.⁵ 8 of 255 patients presented with traumatic aneurysms. Two of 8 ruptured prior to treatment. 7 of 8 aneurysms were treated with surgery and clip exclusion of the aneurysm. Of those treated surgically, 2 patients died, and 5 recovered with varying degrees of outcome (confusing, as the study published what looks like the MRS outcome by score but referred to it as the GCO or Glasgow Coma Outcome). There was no reported rupture after surgical treatment. The patient not treated had a favorable long-term recovery at 47 weeks.

One study evaluated the incidence of vascular injury in 109 patients with cranial stab wounds with 79/109 receiving cerebral angiograms.⁶ A total of 11 aneurysms were noted in 11 patients. 6/11 patients received surgery described as “clip, trap, or excise”, without specific attribution of type of surgery to a specific patient. The paper reports good outcomes in all six of these patients, however it does note a delayed hemorrhage in a patient receiving a prior craniotomy and aneurysm clip at day 98 from a delayed rupture from a second aneurysm confirmed at autopsy (0 or 16% rupture risk after surgery). In this case, 1/6 patients is suspicious for delayed rupture after initial treatment. A total of 5/11 aneurysms were not treated, with aneurysm rupture and death occurring in 4/5 patients (80%).

One study evaluated the incidence of vascular injury in 250 patients stabbed in the head, with 181 patients receiving cerebral angiography. A total of 21 patients harboring 24 TICA’s were noted in this population. Of those patients, 16 patients received “surgery”, however the type of surgery was not specifically specified. Of the 5 patients not receiving surgery, 2 patients refused with outcomes not recorded, 2 patients aneurysms resolved on follow up angiogram, and 1 patient died. Of note, no patients who were treated surgically suffered a re-hemorrhage.

One study evaluated 128 patients with penetrating brain injury and included the 72 patients who received a CTA or within 72 hours. A total of 37 arterial injuries were noted in 26 patients, with 11 TICA’s noted in 8 patients. Of those patients, only one patient received surgery, 3 patients received coil occlusion, and 4 patients were observed. Outcomes in the observed population were noted to be unfavorable, with no reference to delayed hemorrhage in either the treated or untreated groups.

Other studies reported the quality of overall outcomes (e.g., good, fair, poor, unfavorable, died, did well, surgery successful) with surgery versus no surgery or reported Glasgow Outcome Scale score after surgery or at discharge (**Table**). Patients tended to do better with surgery compared with no surgery. However, individuals who did not have surgery may have been more gravely injured (likely not to survive anyway) or have smaller aneurysms (where watchful waiting may be an acceptable treatment) than individuals who underwent surgical clipping or other surgery.

One study evaluated the outcomes in 597 patients with transcranial stab wounds, specifically focusing on 17 with trans-brainstem penetrating injury. Within this population, 1 patient was diagnosed with a delayed basilar bifurcation aneurysm. This patient received craniotomy and

aneurysm clipping, but ultimately died. Autopsy revealed that the aneurysm was “well clipped”, and did not mention delayed hemorrhage. A ruptured posterior communicating artery aneurysm was discovered at autopsy in a second patient. This patient, by report did receive a cerebral angiogram prior to death which was negative. It is not clear from this study whether or not the rupture was the cause of death. However, the aneurysm was untreated, with a 100% incidence of rupture.

Overall, these studies provide very low strength evidence that surgery in the setting of TICA may reduce the risk of rupture and may lead to more favorable outcomes than no surgery.

Table. Surgery versus no surgery for TICA

Author Year (Study Design) Country Civilian/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Bell, 2010 (NRS) Iraq Military Blast: 60% GSW: 25% Knife: 8%	Total population (N=187) Average time to Angio: 10 days Total patients w TICA, N=24 Total #TICA: 31 Male: 99% Mean age 26 years Admission GCS: 8.4 ISS: 24	Interventions for TICA: Surgery: N=5 patients, 9 TICA clip (N=9) No surgery (N=8) Note: 1 patient had 1 TICA (ACA) clipped and 1 TICA (MMA) not treated 2 patients had endovascular coil retreated with a clip and 1 patient had a clip retreated with a coil	<u>Rupture:</u> 1/8 patients (12.5%) with untreated TICA *0/9 primary primary clip occlusion; 0/2 clip after coil occlusion; 0/1 coil after clip Overall GOS 3.1 at discharge, not stratified to TICA's.	High
Haddad, 1991 (NRS) Lebanon Military: 47% Civilian: 53% Shrapnel: 93% Bullet: 7%	Total Population: N=15 Number TICA: 17 Male: 100% Age military: 26 years (range: 18 to 35) Age civilian: 19 years (range: 6 to 57) Associated findings: SDH-4 ICH-12 (all prior to surgery)	Surgery (N=13 or 14) Trapped/excised 11 pts Coagulated 1 pt Not mentioned 1 pt (15/17 aneurysms treated) No surgery (N=2 pt) (2/17 TICA not treated) Note: Text indicates that 14 patients had surgery; Table 5 indicates that 13 patients had surgery	<u>Rupture (all occurred prior to treatment):</u> 5 cases of suspicious delayed rupture (**pre-CT, clinical deterioration). 2/5 “Good” outcome; 3/5 “poor” or “died.” <u>Outcome after trapping and excision:</u> Good: 45% (5/11) Fair: 18% (2/11) Poor: 9% (1/11) Died: 18% (2/11) <u>Outcome after unspecified surgery:</u> Poor: 100% (1/1) <u>Outcome after coagulation:</u> Died: 100% (1/1) <u>Outcome after no operation:</u> Fair: 50% (1/2) Poor: 50% (1/2)	High
Aarabi, 1988 (NRS) Iran	Total pop.: 255 patients Number patients w TICA: 8	Surgical (N=7) No surgery, no follow up angiogram (N=1 pt, 2 TICA)	Definitive hemorrhage prior to treatment: 2 *Definitive hemorrhage after treatment: none	High

Author Year (Study Design) Country Civilian/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Military High-velocity missile: 100%	Total #TICA's: 9 Male: NR (presume 100%) Mean age: 22 years. GCS: 9.9 Artery involved: Ophthalmic: 12.5% ACA: 37.5% MCA: 50%	(Delayed follow up with good outcome at 47 weeks) Types of surgery: Surgical Clip/trap: 7	GCO score after surgery: 2.8 (two deaths, 5 with varying recovery; note numbers look like MRS, reported as GCO) GCO score in patient who did not have surgery: 1	
Aarabi, 1995 Iran (2 addl cases) Military High velocity (19 shell fragments, one bullet)	964 pTBI dural violations 18 patients with TICA 2 add'l patients with pTBI outside of this population added. Total pts.: 21 Total TICA's: 22 Mean age: 20 years Arteries: MCA: 10 ACA: 6 ICA: 6	Surgical: Consisted of trap, excision, Clip (no comment on parent artery preservation), and Arutinov procedure (Bizhan?) Trap/excised: 14 TICA in 13 patients. Clip: 2 TICA in 2 patients AR: 1 TICA, 1 pt No treatment: 5	14 aneurysms discovered by cerebral angiogram 8 aneurysms discovered following rupture Average follow up: 71 days 5 deaths (GOS is backward in this paper): 4 of 5 in surgical patients, 1 of 5 in observation. Outcomes: Observation: GOS 4 or 5 in 3/5 patients, unknown in 1, 1 in 1 Surgical: GOS 4 or 5 in 12 patients, GOS 1 in 4 patients	high
Kieck, 1984 (NRS) South Africa Civilian Stabbing: 100%	Total population: 109 patients Total angio: 79 patients Total TICA: 11? Male: NR Age: NR Aneurysms: Cranial: 8 Orbital: 3	Cranial and orbital aneurysms: Surgery (N=6) (surgery described as "clip, trap, or excise". Specific number of each not specified) No surgery (N=5)	<u>Outcomes</u> Surgery: all 6 did "well" Hemorrhage: 0 or 1 out of 6 (0 or 16.6%) No surgery: 4 died of delayed SAH; 1 lost to follow-up. Hemorrhage without treatment: 80% *0 or 1 hemorrhage after first treatment	High
Du Trevou, 1992 (NRS) South Africa Civilian	Total pt: N-250 Total angio: N=181 Total pts w TICA: 21 Total TICAs: 24	130 pt. angiograms <7 days, 15 patients with TICA (14 surgery, 1 resolved) 51 pt. angiograms >7 days, 6 patients with TICA (2 surgery,	<u>Outcomes in patients with aneurysms</u> Surgery: "successfully operated on" with "good recovery" (16)	High

Author Year (Study Design) Country Civilian/Military MOI	Baseline Characteristics	Intervention	Results	Study Risk of Bias
Stabbing: 100%	Male: NR Age: NR Underwent angiography >7 days after surgery	2 refused, 1 rupture, 1 resolved) Surgery (N=16 patients); type of surgery not specified No surgery (N=5)	No surgery: (2 refused surgery – no outcomes reported); 1 patient died from brain damage; 2 traumatic aneurysms resolved *No hemorrhages reported after treatment	
Mansour, 2021 (NRS) United States Civilian GSW: 100%	Total patients: 128 with pTBI Total CTA: 72 patients 37 arterial injuries in 26 patients (11TICA, 7 occlusion, 8 transections, 6 dissections, 4 intimal injuries) 8 patients, 11 TICA's Male: 80% Mean age: 28 years GCS: 4T,3T,5T,5T, 3T (individual GCS scores)	Surgery N=1 patient, 1 TICA (GCS 5T) Endo coil: N=3 patients, 3 TICA (GCS8T, 15, and 3T) Observation: N=4 patients, 7 TICA (GCS 4T, 3T, 5T, 3T)	<u>Outcomes</u> Surgical: “unfavorable”, (GOSE 3) Endo: 2 favorable (GOSE 4 and 6), one unfavorable (death) Observation: “Unfavorable”: all 4 patients, discharge details not reported	High
Nathoo, 2000 (Case report) South Africa Civilian Stabbing: 100%	597 cranial stab wounds 17 patients with brainstem penetration 15/17 received DSA 1/17 with basilar TICA 1/17 postmortem ruptured TICA Male:100% (1/1) Age: 28 GCS: 9 Admitted 3 weeks after assault	Ventriculostomy, craniotomy for clipping of basilar bifurcation aneurysm	13/17 deaths Surgical: N=1, GOS 1 (autopsy confirmed no evidence of re-rupture) 1/17 patients with ruptured, untreated TICA at autopsy	High

ACA=anterior cerebral artery; GCO=Glasgow Coma Outcome; GCS=Glasgow Coma Scale;
GOS=Glasgow Outcome Scale; GOSE=Glasgow Outcome Scale-Extended; GSW=gunshot wound;
ISS=Injury Severity Score; MMA=middle meningeal artery; MOI=mechanism of injury; NR=not

reported; NRS=non-randomized study; SAH=subarachnoid hemorrhage; TICA= traumatic intracranial aneurysm

Discussion

As has been previously discussed, penetrating brain injury is a highly lethal wounding mechanism that is very difficult to study with prospective, randomized trials. With this in mind, the body of literature in this area remains largely retrospective, observational, or case report in nature (Class III or IV), and therefore does not support Level I or II recommendations. That said, it is the lethal and unpredictable nature of penetrating brain injury in general, and TICAs in specific, that support the nature of the above recommendations.

At the time of the creation of the prior pTBI guidelines in 2001, open surgical management of traumatic aneurysms (when feasible) was the primary means of treatment.³⁻⁶ This was in part secondary to the early and somewhat rudimentary nature of the endovascular technologies available at that time as well as a concern that they would not be contained by the pseudoaneurysm clot. Specifically, at that time, aneurysm coils were still considered new technology, and neither aneurysm stents nor flow diverters were available. Since that time, endovascular technologies and techniques have exponentially advanced.

The Level IV recommendation supporting consideration for open surgical management of traumatic intracranial aneurysms is based on a total of 89 patients who harbored 105 TICAs in the studies referenced.¹⁻⁷ Within this population, a total of 49 patients received surgery as the first operation to treat a total of 55 TICAs. Another two received a surgical clip after initial coil occlusion, and one received coil occlusion of a previously clipped aneurysm. There were no reported aneurysm re-ruptures after initial or secondary treatment in this group. In comparison, another 26 patients harbored 30 aneurysms that were observed or received no treatment. A total of 6 definitive ruptures in these 26 patients (23%) resulted in unfavorable outcomes including death. Concerning TICA's, and while the study risk of bias is considered high given the study designs, there appears to be a uniform effect with respect to protection from aneurysm rupture following treatment with either open surgery or endovascular occlusion. It should be noted that surgical management in the referenced studies was described in a number of ways, and almost always include parent artery occlusion with coagulation or aneurysm clip, often with resection of the traumatic aneurysm. There is no mention of parent artery preservation in any of the studies referenced. Neurologic outcomes, when included, are almost always attributed to the degree of underlying brain injury at presentation in those treated.

Expert Opinion

The addition of a recommendation to consider multi-disciplinary approach to traumatic intracranial aneurysms arises from the understanding that the treatment of cerebrovascular pathology of any kind requires consideration of open and endovascular surgical strategies. This recommendation also reflects the fact that endovascular techniques have advanced considerably over the past 22 years, making management of these highly complex and unstable conditions safer. *There was uniform consensus within the guidelines subject matter expert working group on this matter.* Additional expert opinion concerning TICA diagnosis, observation, and treatment are contained within KQ 43.

Future Directions for Research:

Our understanding of how TICA characteristics influence risk of rupture and the risk:benefit of different treatment options is advancing, but remains unclear. Additional work in characteristics associated with coiled traumatic aneurysm re-treatment, techniques to and the risks and benefits of different endovascular and open surgical therapies would also be beneficial. Of specific note, the

optimal timing of diagnosis and treatment, and characteristics associated with aneurysm healing, would be beneficial.

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Pointers gathered during discussion:

- **We do not know the natural hx of uncoiled aneurysms**
- **Do we upgrade a Level IV to Level III recommendation for endovasc. Tx for TICAs?**

Option to make it a strong Level IV but not upgrade it.

Voting results: Y 50% No 50%

- **Period of Reevaluation after initial coiling?** Within 8 weeks 95% consensus

KQ 45: Intraoperative cultures ?

KQ 45: In patients with pTBI, what are the benefits and harms of obtaining intraoperative cultures to determine appropriate antibiotic treatment?

RECOMMENDATIONS

10. Level I

There is insufficient evidence to support a recommendation.

B. Level II

There is insufficient evidence to support a recommendation.

C. Level III

There is insufficient evidence to support a recommendation.

D. Level IV

There is insufficient evidence to support a recommendation.

E. Level C (Consensus Recommendation)

Intra-operative cultures of the scalp, wound track, or bone/metal fragments should not be routinely performed to guide antibiotic treatment but can be considered in some circumstances such as delayed presentation.

INTRODUCTION

Intraoperative cultures are intended to guide antibiotic therapy by identifying the contaminating organisms. The objects responsible may be bone fragments, foreign bodies, or debris, and therefore several studies report culture results from these materials.

PRIOR GUIDELINES RECOMMENDATION

The prior guidelines reported studies of cultures of the offending objects. However, no recommendation was given regarding if this should routinely be done or should guide antibiotic therapies.

METHODOLOGY, SCIENTIFIC FOUNDATION, AND LIMITATIONS

Multiple retrospective reviews have been performed that looked at bacterial cultures. However, there was no standard method. In the Vietnam series, *Staphylococcus epi* was the primary organism isolated. In other studies of the Iran-Iraq war, included *Staphylococcus*, *Acinetobacter*, and other gram-negative organisms which is consistent with other studies. However, the identity of the offending bacterial in documented infections did not necessarily correlate with these cultured organism and mainly included *Staphylococcus* and gram negative organisms. Anaerobic organisms such as *Clostridium* were also identified. The assessment is limited by the lack of standard procedures or processes. There is no literature regarding if the cultures directed antibiotic choice and there is no literature if the changes to antibiotic therapy effected outcome.

Evidentiary Table: Wound, Brain track and Retained Bone and Metal Fragment Cultures

Author, Year clusions	Description	Level	Con
Aarabi B, NEUROSURGERY 1987 ¹	One study of 125 patients from the Iran war classified head wounds as penetrating (51.6%), perforating (7.4%), or tangential gutter type (22.4%), while 18.6% could not be classified. ¹ This study reported that out of 102 intraoperative	Low	Prolongation of time from injury to debridement did not have much effect on the rate of contamination or infection. While most of the contaminating

	brain cultures in 125 patients, 28% were positive and out of 95 intraoperative bone fragment cultures, 21% were positive. ¹ Gram-positive organisms were grown more frequently from both brain cultures (59%) and bone cultures (76%) compared with gram-negative organisms.		organisms were gram positive, the majority of infective organisms were gram negative.
Carey ME et al <i>J Neurosurgery</i> , 1971 ²	Forty-five war casualties from Vietnam with penetrating brain injuries had scalp wound, brain track and retained bone fragments cultured within 2-4 hours following trauma. Forty-four skin, five brain track and 44 retained bone fragments were positive predominantly with staphylococci.	Low	Although complete removal of all retained bone fragments is ideal, no attempts should be made to remove deep retained bone or metal fragments.
Ecker AD, <i>J Neurosurgery</i> , 1946 ³	Forty-two casualties who incurred penetrating injuries had wound cultures of which 32 had positive cultures mostly with gram positive (Staph). Of 11 brain track cultures 9 had positive cultures again primarily gram+ cocci.	Low	Most of deaths were from infective gram-negative organisms

DISCUSSION Two fundamental questions are always in the mind of a trauma surgeon which are challenged by the infectious team to begin with. Is there a relationship between contamination and deep CNS infection and can we prevent deep infections by knowing the contaminating organisms? There is growing evidence that prophylactic antibiotics cannot prevent deep nosocomial CNS infections.⁴ As such what are the indications for obtaining incurred head wound, brain track and retained bone fragment cultures? As the cultures organisms do not necessarily correlate with the infective organisms, routine cultures are not recommended. Some of the brain track and retained fragment cultures in Iran-Iraq war were due to *Acinetobacter species* which were experienced in the Gulf Wars. Therefore, obtaining cultures from scalp wound, brain track and retained bone fragment of neglected or older wounds with CSF fistulas may be considered under certain circumstances.

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Day 4. Thursday, September 7th, 2023

Algorithm discussion and voting

Large algorithm overview (Refer to Annex E, Algorithm diagrams, p.)

- **Ongoing Algorithm discussion and voting**

Algorithms are the handy decision-making tools that will uniquely complement the pTBI Guidelines upon its dissemination. It is useful for visual learners who will need to keep apace of life-saving information and apply it to a fast-paced emergency scenario involving pTBI. Here, we will focus on some of the algorithms that received 100% consensus vote among the SMEs. The first algorithm is a general assessment of a pTBI patient as soon as he is attended to by emergency responders immediately after the incident trauma.



The green box (1A) alerts the responding provider on the crucial elements to note to consider the cranial injury a severe or a grave one. Since these visual targets are easily spotted, they are expected to be accomplished in split seconds before moving on to the next box. These visual targets to spot are: (a) anatomic skull barrier has been left open by trauma (b) direction of injury has crossed crucial barriers like crossing the sagittal or coronal plane of the skull; injuries at the skull base (c) cerebrospinal fluid (CSF) leak (d) neck injuries w bulging may denote carotid artery/jugular vein vessel injury (e) penetration of bony air sinuses (f) cerebral extrusion on the cranio-facial orifices or from main penetrating skull opening (g) embedded foreign body protruding from head (h) injury involving multiple compartments.

Once, majority of the elements in the green box are noted to be positive, move to the white box on the far right (1B) which will presume the case to be surgical unless proven otherwise. Immediately, the provider should consider the steps cited on the bigger box below it (1C): Presurgical Evaluation and Treatment. Here, the ABC's of emergency treatment take place: Airway evaluation and resuscitation, Breathing, Cardiac evaluation on whether the patient has a palpable pulse and adequate blood pressure are done. Intravenous fluid support is a given since the case we are evaluating and prepping is already considered to be a surgical one. Only when the conditions of adequate air exchange and circulatory support are provided does it make sense to focus on the Glasgow Coma Scale and a thorough neurological exam, to include the autonomic and brainstem reflexes (pupillary, gag, corneal, Babinski). The history of previous sedation and trauma on the orbit should always be ruled out Portable Lab works, X-rays and/or imaging (CTA/CT.) or angiography can also be done in this allotted time while awaiting the surgical team's definitive response. Cerebral angiography strongly recommended if with with embedded foreign body.

At this point, the surgical decision may still be only local debridement, but with all the crucial elements of a severe brain injury present, the case is brought to the Operating Room (OR) for definitive surgical care. In the OR setting, the case may show one of several possibilities: (a) one of having a mass lesion (hematoma) causing brain shift requiring a Decompressive Craniectomy, (for which a separate algorithm is provided). , or a vascular lesion (Traumatic Intracranial Aneurysm (TICA), or a foreign body, which may have embedded or migrated.in which the corresponding neurosurgical approach depicted in separate algorithms, whether involving neuroendovascular, will be adapted according to the requirements of the particular case. As the diagram depicts, the ICU and the OR are at the crossing of many decision points and the case, at this point may shift from one or the other based on the patient's progress.

The dangers in the management of the severe pTBI patient is illustrated in the red-highlighted box which lists the following pitfalls: (1) inaccurate neurologic exam (2) failure to identify priorities among other life-threatening injuries (3) failure to anticipate blood loss(4) failure to anticipate vascular injury (5) failure to

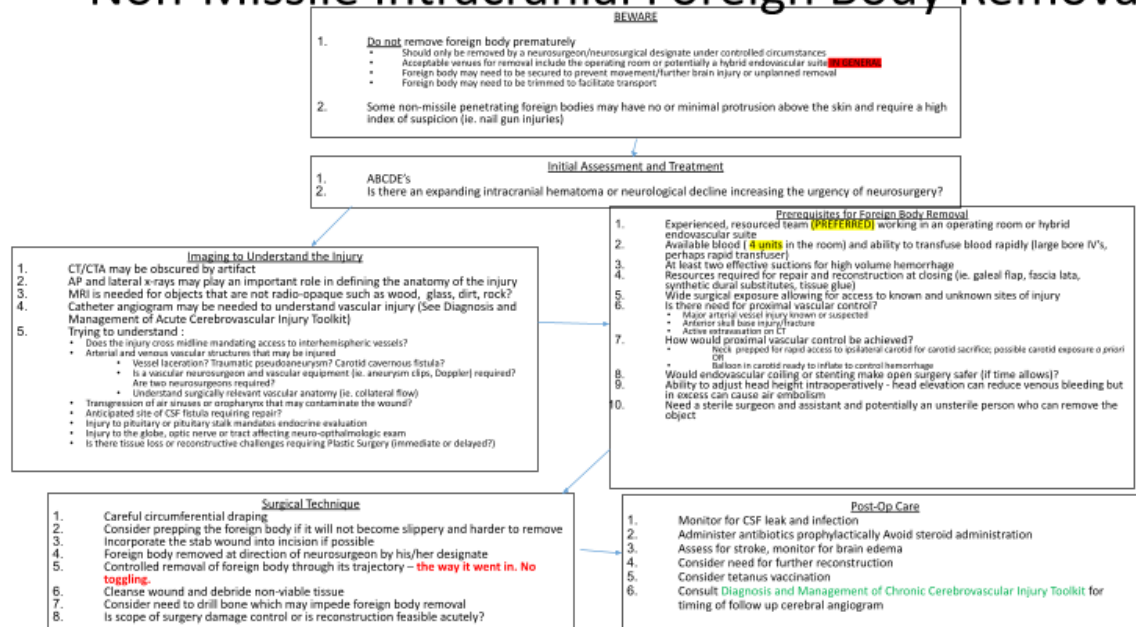
address skull base injuries leading to CSF leak and infections (6) intervention results in secondary injury.

The algorithm in meeting up with a patient having an embedded foreign body (non-missile) is also filled with a lot of important pitfall warnings. The front poster immediately shows a 'Beware' sign stating that a non-missile foreign body (FB) should not be removed prematurely. The cautionary notice lists the following:

1. FB should be removed by the neurosurgeon or neurosurgical designee under controlled circumstances.
2. Acceptable venues for removing FBs should be an Operating Room or a hybrid endovascular suite- OR
3. FB may need to be secured to prevent migration causing further brain damage.
4. FB may need to be trimmed to facilitate transport.

Depending on the FB, the patient may need the appropriate imaging (MRI can visualize glass/ wood better than CT scan/ x-ray films). Planned pre-removal vascular control always a factor. Some non-missile FBs may not have an obvious entry wound in the skin (e.g., nail gun FB)

Non-Missile Intracranial Foreign Body Removal



Day 5. Friday, September 8th, 2023

- Foreign Body removal
- Acute cerebrovascular Injury
 - 1200 – 1300: Lunch
 - 1300 - 1500:
- Chronic Cerebrovascular Injury
- Continued voting on any remaining topics
 - 1500: Review of Key Topics for Future Research
 - 1600: Plan for Unresolved Issues
 - 1630: Publication Plan
 - 1700: Concluding Remarks

The following topics were assigned to the following SMEs:

Surgery Key Questions:

Timing of Surgery

- In patients with pTBI who are neurological stable, what are the benefits and harms of delaying surgery for better operative conditions?
- In patients with pTBI, what are the benefits and harms of urgent surgical decompression/craniectomy versus a period of observation prior to decompression?

Assigned to :

Stippler / Talbot

Rosenfeld / Okonkwo

Type of Debridement

3. In patients with pTBI, what are the benefits and harms of local debridement and closure?
Figaji, / Rosenfeld
4. In patients with pTBI what are the benefits and harms of retained bone or metal fragments?
Neal / Rosenfeld
5. In patients with pTBI, what are the benefits and harms of radical (brain debridement, deep fragment removal) versus conservative debridement (local irrigation and closure)?
Okonkwo / Kitagawa

Prevention of CSF leaks

6. In patients with pTBI, what are the benefits and harms of water-tight closure of the dura, with or without graft, to prevent CSF leak in the setting of exposure of cisterns or the ventricular system?
In patients with pTBI, what are the benefits and harms of CSF diversion?
Ecklund/Aarabi/Latham

Cranioplasty/facial surgery

8. In patients with pTBI, what are the benefits and harms of autologous cranioplasty versus use of alloplastic implants (i.e., titanium, methyl methacrylate, polyetheretherketone [PEEK])?
Latham / Talbot
9. In patients with pTBI, what are the benefits and harms of early versus delayed cranioplasty?
Latham / Stippler
10. In patients with pTBI and facial injury, what are the benefits and harms of a multidisciplinary approach to pTBI surgery/management?
Kitagawa / Figaji

Traumatic cerebrovascular injury

11. In patients with pTBI, what are the benefits and harms of endovascular coil occlusion to reduce risk of rupture, in the setting of a traumatic aneurysm?
Bell / Armonda
12. In patients with pTBI, what are the benefits and harms of surgical or endovascular management of venous sinus injuries to prevent venous infarction?
Bell / Armonda

Other

13. In patients with pTBI, what are the benefits and harms of obtaining intraoperative cultures to determine appropriate antibiotic treatment?
Aarabi / Kitagawa

APPENDIX C: LIST OF SMES AND SPECIALTY / OTHER ATTENDEES LIST

ATTENDEES	With Room Reservations	ATTENDING VIRTUALLY
		Jamshid Ghajar
		Christopher Neal
		Rene Smith (USAMRAA)
Max Talbott	x	

Darrell Boone	x
Dylan Pannel	X
Jeff Rosenfeld	x
Angela Lumba-Brown	x
Gerald Grant	x
Odette Harris	
Randy Bell	x
Greg Hawryluk	x
Alex Valadka	x
Hal Mangat	x
Shelley Selph	x
Annette Totten	X
Bizhan Aarabi	x
Debra Stein	x
Andres Rubiano	x
David Wright	x
Alan Hoffer	x
Guy Rosenthal	x
Brandon Russell (IT)	x
David Okonkwo	x
David Adelson	x
Ryan Kitagawa	x

SPECIAL GUESTS

Joshua Cooley	x
Christine Cooley	x
Dolores Mills	x

LOCAL ATTENDEES

Bradley Dengler
Kerry Latham
John Benjamin
Ross Puffer
Shelton Davis
Rocco Armonda
James Ecklund
Martina Stippler

	SME	9/4/23	9/5/23	9/6/23	9/7/23	9/8/23	Institution	Specialty
1	Bizhan Aarabi , M.D.	X	X	X	X	X	UMD	Neurosurgery
2	Britton Adams, D.O.					X		Optometry
3	David Adelson, M.D.	X	X		X	X	WVU	Neurosurgery, Ped
4	Rocco Armonda, M.D.		X	X	X	X	MedStar GWUMC	Neurosurgery
5	Randy Bell, M.D.	X	X	X	X	X	AMHUHC (SD)	Neurosurgery
6	John Benjamin, M.D		X	X	X	X	WRNMMC	Anesthesiology
7	Darrel Boone, M.D.	X	X	X	X	X	CAF /Mem'rl Univ of Newfoundland, CN	Crit Care Med
8	Shelton Davis, M.D.		X		X	X	WRNMMC	Phys Med/ Rehab
9	Danielle Dang, M.D			X	X	X	Inova Fairfax	Neurosurgery
10	Bradley Dengler, M.D.	X	X	X	X	X	USUHS	Neurosurgery
11	James Ecklund, M.D.		X	X			Inova (VA)	Neurosurgery
12	Anthony Figaji, M.D.						UCT, SA	Neurosurgery
13	Jamshid Ghajar, M.D.,Ph.D.		X				BTF	Neurosurgery
14	Gerald Grant, M.D.	X	X	X	X	X	Duke U	Neurosurgery
15	Odette Harris, M.D.		X	X		X	Stanford U	Neurosurgery
16	Gregory Hawryluk, M.D.,Ph.D.	X	X	X	X	X	Cleveland Clinic (BTF)	Neurosurgery
17	S Alan Hoffer, M.D.		X	X	X	X	CWRU	Neurosurgery
18	Ryan Kitigawa, M.D.	X	X	X	X	X	UTSHCH	Neurosurgery
19	Kerry Latham, M.D.	X	X	X	X	X	USUHS	Plastic
20	Angela Lumba-Brown, M.D.	X	X	X		X	Stanford U	Neurosurgery
21	Halinder Mangat, M.D.	X	X	X	X	X	BTF	Neurointensivist
22	Chris Neal, M.D.						UMaine	Neurosurgery
23	David Okwonko, M.D., Ph.D.			X	X	X	UPMC	Neurosurgery
24	Dylan Pannell, M.D.	X	X				Univ of Toronto (CAF)	Gen. Surgery
25	Miranda Pappas						OHSU	Res. Associate
26	Ross Puffer, M.D.	X	X	X	X	X	WRNMMC	Neurosurgery
27	Patti Raksin, M.D.						Neurosurgeon	USA
28	Michael Remley, M.D.						MI	Emergency Care
29	Jeffrey Rosenfeld, M.D.	X	X	X	X	X	Monash U, AUS	Neurosurgery
30	Guy Rosenthal, M.D.	X	X	X	X	X	UCSF/Hadassah Med Ctr	Neurosurgery
31	Andres Rubiano, M.D.	X	X			X	Meditech, Colombia	Neurosurgery
32	Uzma Samadani, M.D.						UMinn	Neurosurgery
33	Shelley Selph, M.D., MPH	X	X	X	X	X	OHSU	Epidemiology
34	Stacey Shackelford, M.D.						DHA	Trauma
35	Deborah Stein, M.D.	X	X	X	X	X	UMD	General Surgery
36	Martina Stippler, M.D.				X		BIDMC (MA)	Neurosurgery

37	Max Talbot, M.D.	X	X	X	X	X	Canadian Armed Forces	Ortho
38	Annette Totten, Ph.D.	X	X		X	X	OHSU	Epidemiology
39	Alex Valadka, M.D.	X	X	X	X	X	UTSW, Dallas	Neurosurgery
40	David Wright, M.D.		X		X	X	EmoryU	Emergency Med.

APPENDIX D :PICOTS & KEY QUESTIONS (KQS)

Prehospital Key Questions (KQs):

Diagnosis / diagnostic accuracy

1. In patients with head injury, what is the accuracy of screening for diagnosis of pTBI (e.g., Glasgow Coma Scale, pupil response/size/symmetry, biomarkers [e.g., s100b, UCH-L1, GFAP, tau, NSE, neurofilament/NF-1, cytokine, SNP, EEG]), clinical exam, imaging techniques (e.g., MRI, CT, plain films)?
2. In patients with pTBI, what is the diagnostic accuracy of imaging to detect pseudoaneurysms?
3. In patients with pTBI, what are the benefits, harms and diagnostic accuracy of screening with cerebral angiography to diagnose traumatic intracranial arterial aneurysm (TICA) and cerebral vasospasm (VSP)?
4. In patients with pTBI, when should cerebral angiography best occur and is it preferred over CT angiography (CTA)?
5. Does the diagnostic accuracy of screening for pTBI differ based on patient characteristics (e.g., age, gender, military status) or injury characteristics (e.g., mechanism of injury, location of injury)?
6. In patients with head injury and no obvious penetration of the skull, what are the benefits and harms of screening for pTBI versus no screening?
7. In patients with pTBI and the possibility of metal within the skull, what is the safety of MRI?

Prognosis

8. In patients with pTBI, what factors related to the scene of injury (e.g., distance/time to trauma centers including rural and austere settings, prolonged field care, transport mode/factors, expertise of pre-hospital providers) impact morbidity and mortality?
9. What clinical characteristics (e.g., demographics, mechanism of injury, characteristics of geographic site of injury, vital signs, blood loss, neurological deficit, location of head injury, other injuries) of patients with pTBI are associated with salvageability or non-salvageability (patients or organs) that can be determined in early clinical settings including the field, the emergency department, and austere environments?
10. What mechanisms of pTBI place a patient at higher risk for poor outcomes?
11. In patients with head injury, does on-scene trauma triage and assessments correctly identify pTBI patients with better or worse outcomes including death within 24 hours?
12. In patients with pTBI, what imaging findings are associated with morbidity, mortality, quality of life, and function?
13. What is the diagnostic accuracy of instruments and models (e.g., SPIN score) in predicting survival in pTBI?

Initial Management

14. In patients with pTBI, what are the benefits and harms of pre-hospital and emergency department resuscitation strategies (e.g., correction of coagulopathy, CPR, airway maneuvers, oxygen administration, cervical spine immobilization, specific fluid administration including hypertonic saline, mannitol administration, pain management, hyperventilation, posture), including the prevention of secondary injury (e.g., cerebral edema, diffuse axonal injury)?
15. In patients with pTBI, what patient and scene-related factors indicate a definitive airway is needed compared with no or non-invasive ventilation?
16. In patients with pTBI who require intubation, what are the benefits and harms of sedation and analgesia?
17. In patients with pTBI, what are the benefits and harms of on-scene wound care of head injury?

18. In patients with pTBI, what are the benefits and harms of early initiation (prehospital and emergency department) of antibiotic prophylaxis?
19. In patients with pTBI, what are the benefits and harms of treatment in the prehospital and emergency department with tranexamic acid (TXA), antiseizure prophylaxis, and pressor support?
20. In patients with pTBI, what are the benefits and harms of routine evaluation with thromboelastography (TEG) and correction of coagulopathies?
21. In patients with pTBI, what are the benefits and harms of a 24-hour or more delay in evaluation by a neurosurgeon?
22. How should treatment be modified if field care is prolonged (>24 hours)?
23. Do the effects of treatment for pTBI differ based on patient characteristics (e.g., age, gender, military status) or injury characteristics (e.g., mechanism of injury, location of injury)?

Critical Care Key Questions:

Intracranial Pressure

24. In patients with pTBI, what are the benefits and harms of intracranial pressure monitoring?
25. In patients with pTBI, what blood pressure thresholds should be used for intracranial pressure and cerebral perfusion pressure?
26. In patients with pTBI, what are the benefits and harms of treating intracranial hypertension (e.g., hyperosmolar therapy, lumbar drainage, ventilation therapies) in the critical care (i.e., ICU) setting?

Prophylaxis

27. In patients with pTBI, what are the benefits and harms of seizure prophylaxis, either initiated or continued, in the critical care setting?
28. In patients with pTBI, what are the benefits and harms of antibiotic prophylaxis, either initiated or continued, in the critical care setting?
29. In patients with pTBI, what are the benefits and harms of deep vein thrombosis prophylaxis?

Other

30. In patients with pTBI, what are the benefits and harms of screening for delayed vascular complications? In patients with head injury, when should organ donation occur?
31. In patients with head injury, when should organ donation occur?
32. For patients with pTBI, what are the benefits and harms of rehabilitation (e.g., physical, speech, occupational therapy) and when should rehabilitation be started?

Surgery Key Questions:

Timing of Surgery

33. In patients with pTBI who are neurologically stable, what are the benefits and harms of delaying surgery for better operative conditions?
34. In patients with pTBI, what are the benefits and harms of urgent surgical decompression/craniectomy versus a period of observation prior to decompression?

Type of Debridement

35. In patients with pTBI, what are the benefits and harms of local debridement and closure?
36. In patients with pTBI what are the benefits and harms of retained bone or metal fragments, or removal of retained/embedded objects (e.g., blade)?
37. In patients with pTBI, what are the benefits and harms of radical (brain debridement, deep fragment removal) versus conservative debridement (local irrigation and closure)?

Prevention of CSF leaks

38. In patients with pTBI, what are the benefits and harms of water-tight closure of the dura, with or without graft, to prevent CSF leak in the setting of exposure of cisterns or the ventricular system?
39. In patients with pTBI, what are the benefits and harms of CSF diversion?

Cranioplasty/facial surgery

40. In patients with pTBI, what are the benefits and harms of autologous cranioplasty versus use of alloplastic implants (i.e., titanium, methyl methacrylate, polyetheretherketone [PEEK])?
41. In patients with pTBI, what are the benefits and harms of early versus delayed cranioplasty?
42. In patients with pTBI and facial injury, what are the benefits and harms of a multidisciplinary approach to pTBI surgery/management?

Traumatic cerebrovascular injury

43. In patients with pTBI, what are the benefits and harms of endovascular coil occlusion to reduce risk of rupture, in the setting of a traumatic aneurysm?
44. In patients with pTBI, what are the benefits and harms of surgical or endovascular management of venous sinus injuries to prevent venous infarction?

Other

45. In patients with pTBI, what are the benefits and harms of obtaining intraoperative cultures to determine appropriate antibiotic treatment?

Additional KQ

46. In patients with pTBI, what are the benefits and harms of endovascular coil occlusion to reduce risk of rupture, in the setting of a traumatic aneurysm?

ANNEX E : ALGORITHMS

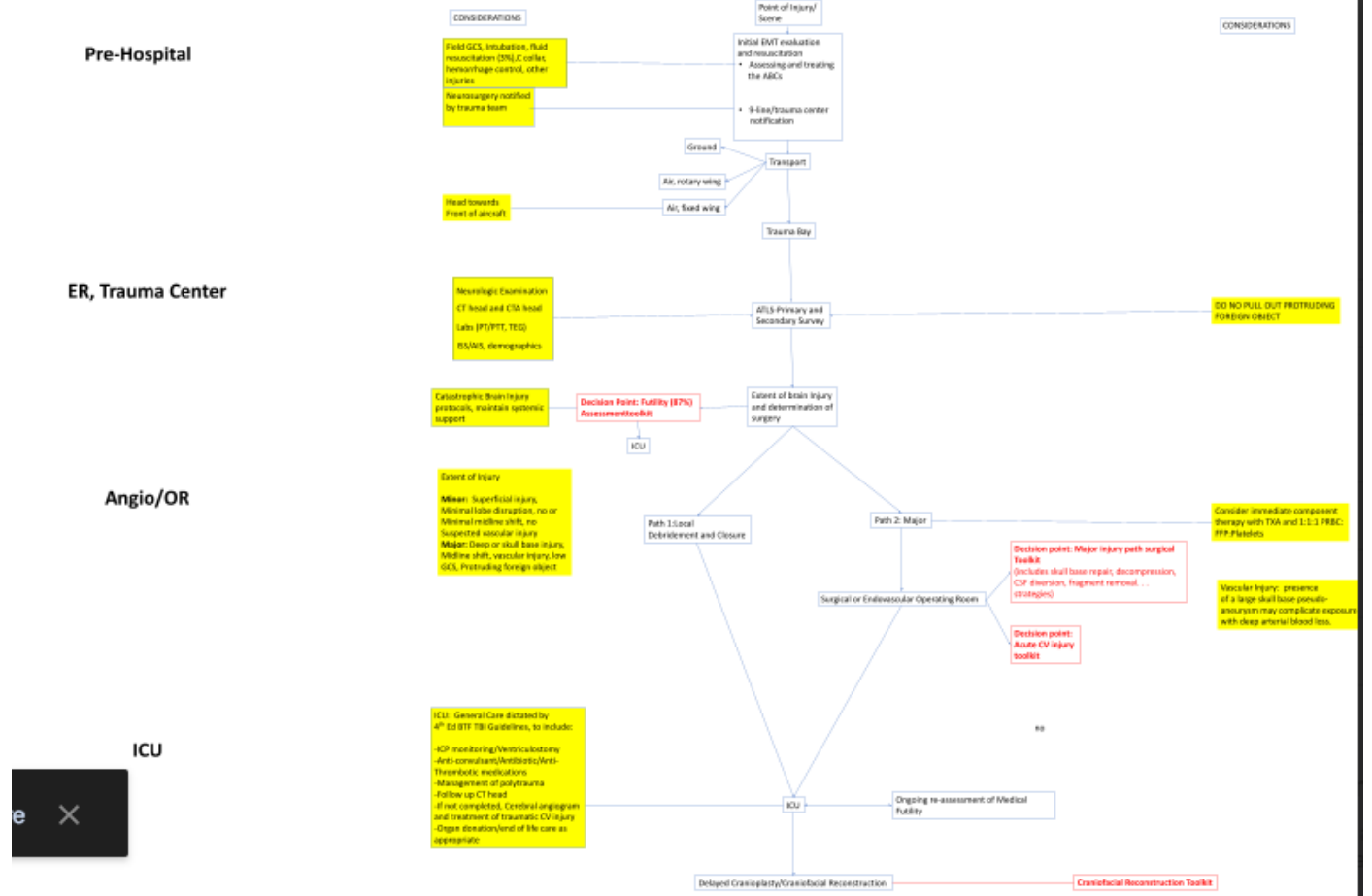
Algorithm Toolkits

The BTF pTBI 2nd Edition In-Person Guidelines Meeting
Bethesda, MD
Sept. 4 – 8, 2023



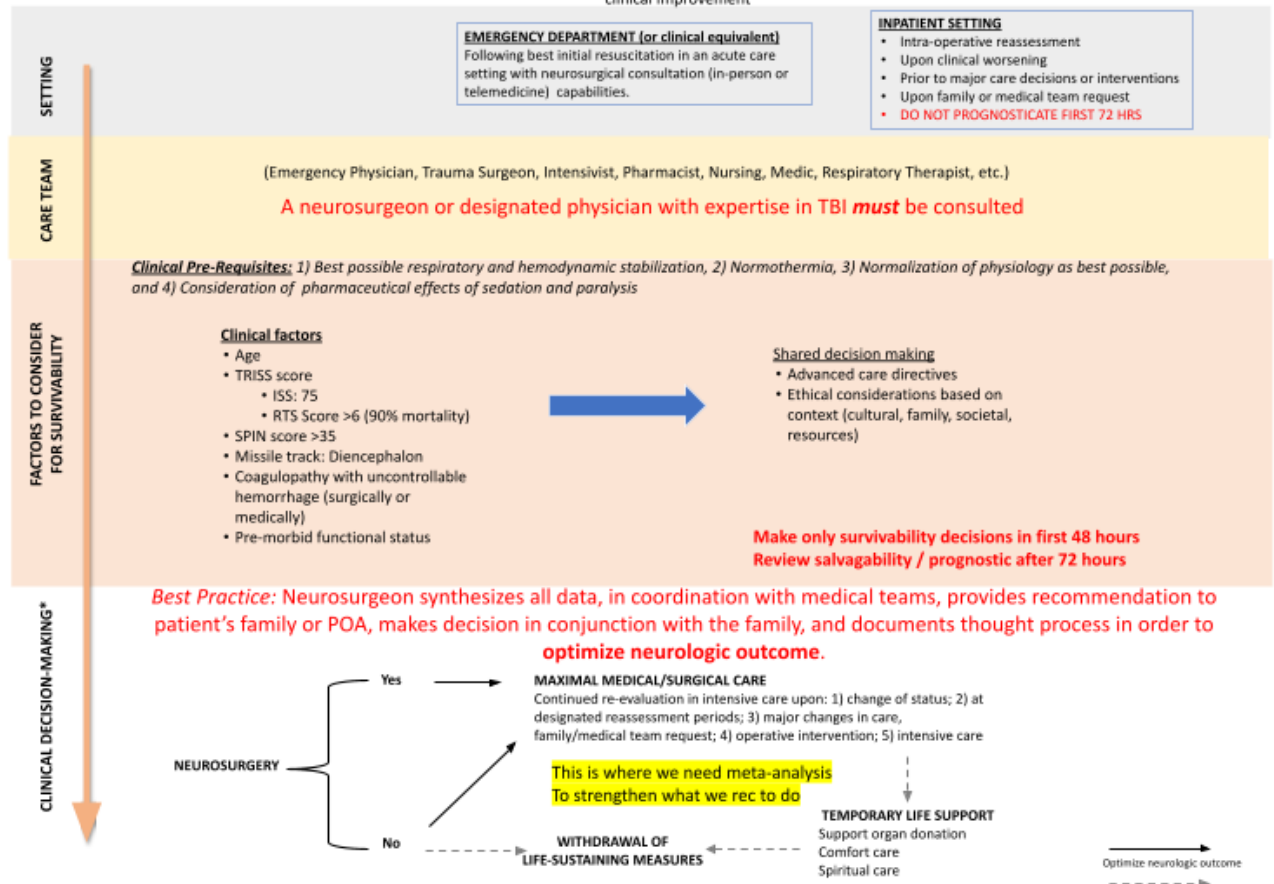
U.S. ARMY MEDICAL RESEARCH
AND DEVELOPMENT COMMAND



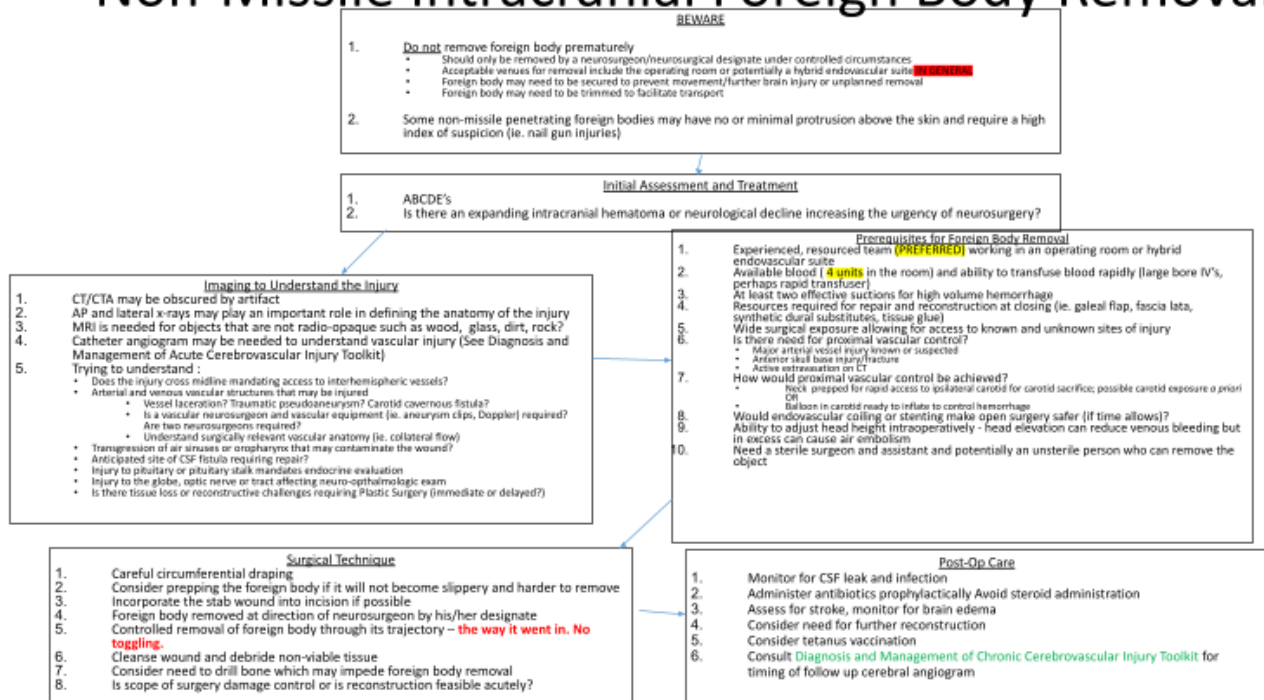


pTBI Futility Assessment

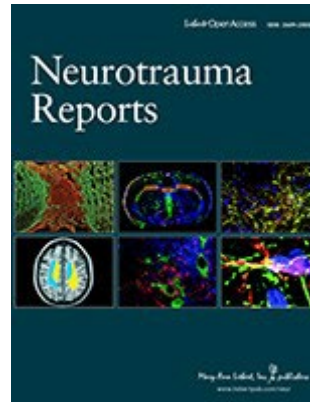
"pTBI Survivability" -- TBI expert assessment leading to optimal care that may minimize mortality before 72 hours and offer opportunity for meaningful clinical improvement



Non-Missile Intracranial Foreign Body Removal



APPENDIX F. METHODS PAPER



Rationale and Methods for Updated Guidelines for the Management of Penetrating Traumatic Brain Injury

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ORIGINAL ARTICLE

Open Access

Rationale and Methods for Updated Guidelines for the Management of Penetrating Traumatic Brain Injury

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