

Neurotrauma Literature Review

Original Articles

01. Past, Present, and Future of Traumatic Brain Injury Research.

Hawryluk GW, Bullock MR. *Neurosurg Clin N Am.* 2016 Oct;27(4):375-96. doi: 10.1016/j.nec.2016.05.002. Epub 2016 Aug 9.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/27637391>

Traumatic brain injury (TBI) is the greatest cause of death and severe disability in young adults; its incidence is increasing in the elderly and in the developing world. Outcome from severe TBI has improved dramatically as a result of advancements in trauma systems and supportive critical care, however we remain without a therapeutic, which acts directly to attenuate brain injury. Recognition of secondary injury and its molecular mediators has raised hopes for such targeted treatments. Unfortunately, over 30 late-phase clinical trials investigating promising agents have failed to translate a therapeutic for clinical use. Numerous explanations for this failure have been postulated and are reviewed here. With this historical context we review ongoing research and anticipated future trends which are armed with lessons from past trials, new scientific advances, as well as improved research infrastructure and funding. There is great hope that these new efforts will finally lead to an effective therapeutic for TBI as well as better clinical management strategies.

02. Synthesis of Findings, Current Investigations, and Future Directions: Operation

Brain Trauma Therapy.

Kochanek PM, et al. *J Neurotrauma.* 2016 Mar 15;33(6):606-14. doi: 10.1089/neu.2015.4133.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/26671284>

Operation Brain Trauma Therapy (OBTT) is a fully operational, rigorous, and productive multicenter, pre-clinical drug and circulating biomarker screening consortium for the field of traumatic brain injury (TBI). In this article, we synthesize the findings from the first five therapies tested by OBTT and discuss both the current work that is ongoing and potential future directions. Based on the results generated from the first five therapies tested within the exacting approach used by OBTT, four (nicotinamide, erythropoietin, cyclosporine A, and simvastatin) performed below or well below what was expected based on the published literature. OBTT has identified, however, the early post-TBI administration of levetiracetam as a promising agent and has advanced it to a gyrencephalic large animal model--fluid percussion injury in micropigs. The sixth and seventh therapies have just completed testing (glibenclamide and Kollidon VA 64), and an eighth drug (AER 271) is in testing. Incorporation of circulating brain injury biomarker assessments into these pre-clinical studies suggests considerable potential for diagnostic and theranostic utility of glial fibrillary acidic protein in pre-clinical studies. Given the failures in clinical translation of therapies in TBI, rigorous multicenter, pre-clinical approaches to therapeutic screening such as OBTT may be important for the ultimate translation of therapies to the human condition.

03. Global neurotrauma research challenges and opportunities.

Rubiano AM, et al. *Nature.* 2015 Nov 19;527(7578):S193-7. doi: 10.1038/nature16035.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/26580327>

Traumatic injury to the brain or spinal cord is one of the most serious public health problems worldwide. The devastating impact of 'trauma', a term used to define the global burden of disease related to

all injuries, is the leading cause of loss of human potential across the globe, especially in low- and middle-income countries. Enormous challenges must be met to significantly advance neurotrauma research around the world, specifically in underserved and austere environments. Neurotrauma research at the global level needs to be contextualized: different regions have their own needs and obstacles. Interventions that are not considered a priority in some regions could be a priority for others. The introduction of inexpensive and innovative interventions, including mobile technologies and e-health applications, focused on policy management improvement are essential and should be applicable to the needs of the local environment. The simple transfer of a clinical question from resource-rich environments to those of low- and middle-income countries that lack sophisticated interventions may not be the best strategy to address these countries' needs. Emphasis on promoting the design of true 'ecological' studies that include the evaluation of human factors in relation to the process of care, analytical descriptions of health systems, and how leadership is best applied in medical communities and society as a whole will become crucial.

04. A Review of the Effectiveness of Neuroimaging Modalities for the Detection of Traumatic Brain Injury.

Amyot F, et al. *J Neurotrauma*. 2015 Nov 15;32(22):1693-721. doi: 10.1089/neu.2013.3306. Epub 2015 Sep 30.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/26176603>

The incidence of traumatic brain injury (TBI) in the United States was 3.5 million cases in 2009, according to the Centers for Disease Control and Prevention. It is a contributing factor in 30.5% of injury-related deaths among civilians. Additionally, since 2000, more than 260,000 service members were diagnosed with TBI, with the vast majority classified as mild or concussive (76%). The objective assessment of TBI via imaging is a critical research gap, both in the military and civilian communities. In 2011, the Department of Defense (DoD) prepared a congressional report summarizing the effectiveness of seven neuroimaging modalities (computed tomography [CT], magnetic resonance imaging [MRI], transcranial Doppler [TCD], positron emission tomography, single photon emission computed tomography, electrophysiologic techniques [magnetoencephalography and electroencephalography], and functional near-infrared spectroscopy) to assess the spectrum of TBI from concussion to coma. For this report, neuroimaging experts identified the most relevant peer-reviewed publications and assessed the quality of the literature for each of these imaging techniques in the clinical and research settings. Although CT, MRI, and TCD were determined to be the most useful modalities in the clinical setting, no single imaging modality proved sufficient for all patients due to the heterogeneity of TBI. All imaging modalities reviewed demonstrated the potential to emerge as part of future clinical care. This paper describes and updates the results of the DoD report and also expands on the use of angiography in patients with TBI.

05. Management of moderate and severe traumatic brain injury.

Abdelmalik PA, et al. *Transfusion*. 2019 Apr;59(S2):1529-1538. doi: 10.1111/trf.15171.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/30980755>

Traumatic brain injury (TBI) is a common disorder with high morbidity and mortality, accounting for one in every three deaths due to injury. Older adults are especially vulnerable. They have the highest rates of TBI-related hospitalization and death. There are about 2.5 to 6.5 million US citizens living with TBI-related disabilities. The cost of care is very high. Aside from prevention, little can be done for the initial primary injury of neurotrauma. The tissue damage incurred directly from the inciting event, for example, a blow to the head or bullet penetration, is largely complete by the time medical care can be instituted.

However, this event will give rise to secondary injury, which consists of a cascade of changes on a cellular and molecular level, including cellular swelling, loss of membrane gradients, influx of immune and inflammatory mediators, excitotoxic transmitter release, and changes in calcium dynamics. Clinicians can intercede with interventions to improve outcome in the mitigating secondary injury. The fundamental concepts in critical care management of moderate and severe TBI focus on alleviating intracranial pressure and avoiding hypotension and hypoxia. In addition to these important considerations, mechanical ventilation, appropriate transfusion of blood products, management of paroxysmal sympathetic hyperactivity, using nutrition as a therapy, and, of course, venous thromboembolism and seizure prevention are all essential in the management of moderate to severe TBI patients. These concepts will be reviewed using the recent 2016 Brain Trauma Foundation Guidelines to discuss best practices and identify future research priorities.

06. A State-of-the-Science Overview of Randomized Controlled Trials Evaluating Acute Management of Moderate-to-Severe Traumatic Brain Injury.

Bragge P, et al. J Neurotrauma. 2016 Aug 15;33(16):1461-78. doi: 10.1089/neu.2015.4233. Epub 2016 Mar 18.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/26711675>

Moderate-to-severe traumatic brain injury (TBI) remains a major global challenge, with rising incidence, unchanging mortality and lifelong impairments. State-of-the-science reviews are important for research planning and clinical decision support. This review aimed to identify randomized controlled trials (RCTs) evaluating interventions for acute management of moderate/severe TBI, synthesize key RCT characteristics and findings, and determine their implications on clinical practice and future research. RCTs were identified through comprehensive database and other searches. Key characteristics, outcomes, risk of bias, and analysis approach were extracted. Data were narratively synthesized, with a focus on robust (multi-center, low risk of bias, $n > 100$) RCTs, and three-dimensional graphical figures also were used to explore relationships between RCT characteristics and findings. A total of 207 RCTs were identified. The 191 completed RCTs enrolled 35,340 participants (median, 66). Most (72%) were single center and enrolled less than 100 participants (69%). There were 26 robust RCTs across 18 different interventions. For 74% of 392 comparisons across all included RCTs, there was no significant difference between groups. Positive findings were broadly distributed with respect to RCT characteristics. Less than one-third of RCTs demonstrated low risk of bias for random sequence generation or allocation concealment, less than one-quarter used covariate adjustment, and only 7% employed an ordinal analysis approach. Considerable investment of resources in producing 191 completed RCTs for acute TBI management has resulted in very little translatable evidence. This may result from broad distribution of research effort, small samples, preponderance of single-center RCTs, and methodological shortcomings. More sophisticated RCT design, large multi-center RCTs in priority areas, increased focus on pre-clinical research, and alternatives to RCTs, such as comparative effectiveness research and precision medicine, are needed to fully realize the potential of acute TBI research to benefit patients.

07. Long-Term Consequences of Traumatic Brain Injury: Current Status of Potential Mechanisms of Injury and Neurological Outcomes.

Bramlett HM, Dietrich WD. J Neurotrauma. 2015 Dec 1;32(23):1834-48. doi: 10.1089/neu.2014.3352. Epub 2014 Dec 19.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/25158206>

Traumatic brain injury (TBI) is a significant clinical problem with few therapeutic interventions successfully translated to the clinic. Increased importance on the progressive, long-term consequences of TBI have been emphasized, both in the experimental and clinical literature. Thus, there is a need for a better understanding of the chronic consequences of TBI, with the ultimate goal of developing novel therapeutic interventions to treat the devastating consequences of brain injury. In models of mild, moderate, and severe TBI, histopathological and behavioral studies have emphasized the progressive nature of the initial traumatic insult and the involvement of multiple pathophysiological mechanisms, including sustained injury cascades leading to prolonged motor and cognitive deficits. Recently, the increased incidence in age-dependent neurodegenerative diseases in this patient population has also been emphasized. Pathomechanisms felt to be active in the acute and long-term consequences of TBI include excitotoxicity, apoptosis, inflammatory events, seizures, demyelination, white matter pathology, as well as decreased neurogenesis. The current article will review many of these pathophysiological mechanisms that may be important targets for limiting the chronic consequences of TBI.

09. The Impact of Traumatic Brain Injury on Later Life: Effects on Normal Aging and Neurodegenerative Diseases.

Griesbach GS, et al. *J Neurotrauma*. 2018 Jan 1;35(1):17-24. doi: 10.1089/neu.2017.5103. Epub 2017 Oct 27.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/28920532>

The acute and chronic effects of traumatic brain injury (TBI) have been widely described; however, there is limited knowledge on how a TBI sustained during early adulthood or mid-adulthood will influence aging. Epidemiological studies have explored whether TBI poses a risk for dementia and other neurodegenerative diseases associated with aging. We will discuss the influence of TBI and resulting medical comorbidities such as endocrine, sleep, and inflammatory disturbances on age-related gray and white matter changes and cognitive decline. Post mortem studies examining amyloid, tau, and other proteins will be discussed within the context of neurodegenerative diseases and chronic traumatic encephalopathy. The data support the suggestion that pathological changes triggered by an earlier TBI will have an influence on normal aging processes and will interact with neurodegenerative disease processes rather than the development of a specific disease, such as Alzheimer's or Parkinson's. Chronic neurophysiologic change after TBI may have detrimental effects on neurodegenerative disease.

10. Chronic Aspects of Pediatric Traumatic Brain Injury: Review of the Literature.

Babikian T, et al. *J Neurotrauma*. 2015 Dec 1;32(23):1849-60. doi: 10.1089/neu.2015.3971.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/26414654>

Traumatic brain injury (TBI) in children, while the brain is in a state of rapid change and development, can adversely impact their development, their extended environment, and their families. The extant literature has identified several physiological, genetic, and environmental variables that predict outcomes after pediatric TBI; nonetheless, the individual course of recovery and later development of a given child is uniquely shaped by injury-related factors (e.g., nature and extent of the injury itself, the developmental status of the child) as well as a number of personal and family variables (e.g., pre-injury cognitive, genetic, and psychological status of the child, family functioning and resources, coping style). Further, the effects of a brain injury during development may or may not become evident immediately after injury depending on a number of factors. Instead, observing trajectories of development over time may allow for a better understanding of the long-term consequences in many functional domains that interest researchers, clinicians, and families. The current

article reviews the chronic aspects of medical/health, cognitive/academic, emotional/behavioral, and family/social outcomes after pediatric TBI, with the goal of providing monitoring and treatment strategies for affected children and their families, as well as serving as a resource for researchers designing studies to better understand this heterogeneous population.

11. The Role of Surgical Intervention in Traumatic Brain Injury.

Adams H, et al. *Neurosurg Clin N Am*. 2016 Oct;27(4):519-28. doi: 10.1016/j.nec.2016.05.007. Epub 2016 Aug 10.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/27637401>

The general consensus to optimize the care for severe TBI patients is management at specialized neurotrauma centers with neurosurgical and neurocritical care support and the use of guidelines-based standardized protocols. Over the last decade, significant efforts have been made to define neurotrauma treatment guidelines. However, it is important to recognize the heterogeneity of TBI and that the "one-size-fits-all approach" may not always be appropriate for these patients. Knowledge synthesis activities in neurotrauma are important to define future research agendas. Clinical and research advances have influenced neurotrauma as it continues to mature into a distinct subspecialty of neurosurgery.

12. Traumatic Brain Injury Advances.

Stein DM, et al. *Crit Care Clin*. 2017 Jan;33(1):1-13. doi: 10.1016/j.ccc.2016.08.008.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/27894490>

There have been many recent advances in the management of traumatic brain injury (TBI). Research regarding established and novel therapies is ongoing. Future research must not only focus on development of new strategies but determine the long-term benefits or disadvantages of current strategies. In addition, the impact of these advances on varying severities of brain injury must not be ignored. It is hoped that future research strategies in TBI will prioritize large-scale trials using common data elements to develop large registries and databases, and leverage international collaborations.

13. Advances in Intracranial Pressure Monitoring and Its Significance in Managing Traumatic Brain Injury.

Kawoos U, et al. *Int J Mol Sci*. 2015 Dec 4;16(12):28979-97. doi: 10.3390/ijms161226146.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/26690122>

Intracranial pressure (ICP) measurements are essential in evaluation and treatment of neurological disorders such as subarachnoid and intracerebral hemorrhage, ischemic stroke, hydrocephalus, meningitis/encephalitis, and traumatic brain injury (TBI). The techniques of ICP monitoring have evolved from invasive to non-invasive-with both limitations and advantages. Some limitations of the invasive methods include short-term monitoring, risk of infection, restricted mobility of the subject, etc. The invasiveness of a method limits the frequency of ICP evaluation in neurological conditions like hydrocephalus, thus hampering the long-term care of patients with compromised ICP. Thus, there has been substantial interest in developing noninvasive techniques for assessment of ICP. Several approaches were reported, although none seem to provide a complete solution due to inaccuracy. ICP measurements are fundamental for immediate care of TBI patients in the acute stages of severe TBI injury. In severe TBI, elevated ICP is associated with mortality or poor clinical outcome. ICP monitoring in conjunction with other neurological monitoring can aid in understanding the pathophysiology of brain

damage. This review article presents: (a) the significance of ICP monitoring; (b) ICP monitoring methods (invasive and non-invasive); and (c) the role of ICP monitoring in the management of brain damage, especially TBI.

14. Brain Death.

Drake M, et al. *Surg Clin North Am.* 2017 Dec;97(6):1255-1273. doi: 10.1016/j.suc.2017.07.001.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/29132508>

Death determined by neurologic criteria, commonly referred to as "brain death," occurs when function of the entire brain ceases, including the brain stem. Diagnostic criteria for brain death are explicit but controversy exists regarding nuances of the evaluation and potential confounders of the examination. Hospitals and ICU teams should carefully consider which clinicians will perform brain death testing and should use standard processes, including checklists to prevent diagnostic errors. Proper diagnosis is essential because misdiagnosis can be catastrophic. Timely, accurate brain death determination and aggressive physiologic support are cornerstones of both good end-of-life care and successful organ donation.

15. Trauma: Spinal Cord Injury.

Eckert MJ, Martin MJ. *Surg Clin North Am.* 2017 Oct;97(5):1031-1045. doi: 10.1016/j.suc.2017.06.008.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/28958356>

Injuries to the spinal column and spinal cord frequently occur after high-energy mechanisms of injury, or with lower-energy mechanisms, in select patient populations like the elderly. A focused yet complete neurologic examination during the initial evaluation will guide subsequent diagnostic procedures and early supportive measures to help prevent further injury. For patients with injury to bone and/or ligaments, the initial focus should be spinal immobilization and prevention of inducing injury to the spinal cord. Spinal cord injury is associated with numerous life-threatening complications during the acute and long-term phases of care that all acute care surgeons must recognize.

16. Spinal Cord Injury and Related Clinical Trials.

Kim YH, et al. *Clin Orthop Surg.* 2017 Mar;9(1):1-9. doi: 10.4055/cios.2017.9.1.1. Epub 2017 Feb 13.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/28261421>

Spinal cord injury (SCI) has been considered an incurable condition and it often causes devastating sequelae. In terms of the pathophysiology of SCI, reducing secondary damage is the key to its treatment. Various researches and clinical trials have been performed, and some of them showed promising results; however, there is still no gold standard treatment with sufficient evidence. Two therapeutic concepts for SCI are neuroprotective and neuroregenerative strategies. The neuroprotective strategy modulates the pathomechanism of SCI. The purpose of neuroprotective treatment is to minimize secondary damage following direct injury. The aim of neuroregenerative treatment is to enhance the endogenous regeneration process and to alter the intrinsic barrier. With advancement in biotechnology, cell therapy using cell transplantation is currently under investigation. This review discusses the pathophysiology of SCI and introduces the therapeutic candidates that have been developed so far.

17. A Review of Clinical Trials in Spinal Cord Injury Including Biomarkers.

Badhiwala JH, et al. J Neurotrauma. 2018 Aug 15;35(16):1906-1917. doi: 10.1089/neu.2018.5935.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/29888678>

Acute traumatic spinal cord injury (SCI) entered the arena of prospective, randomized clinical trials almost 40 years ago, with the undertaking of the National Acute Spinal Cord Study (NASCIS) I trial. Since then, a number of clinical trials have been conducted in the field, spurred by the devastating physical, social, and economic consequences of acute SCI for patients, families, and society at large. Many of these have been controversial and attracted criticism. The current review provides a critical summary of select past and current clinical trials in SCI, focusing in particular on the findings of prospective, randomized controlled trials, the challenges and barriers encountered, and the valuable lessons learned that can be applied to future trials.

18. Time is spine: a review of translational advances in spinal cord injury.

Badhiwala JH, et al. J Neurosurg Spine. 2018 Dec 20;30(1):1-18. doi: 10.3171/2018.9.SPINE18682.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/30611186>

Acute traumatic spinal cord injury (SCI) is a devastating event with far-reaching physical, emotional, and economic consequences for patients, families, and society at large. Timely delivery of specialized care has reduced mortality; however, long-term neurological recovery continues to be limited. In recent years, a number of exciting neuroprotective and regenerative strategies have emerged and have come under active investigation in clinical trials, and several more are coming down the translational pipeline. Among ongoing trials are RISCIS (riluzole), INSPIRE (Neuro-Spinal Scaffold), MASC (minocycline), and SPRING (VX-210). Microstructural MRI techniques have improved our ability to image the injured spinal cord at high resolution. This innovation, combined with serum and cerebrospinal fluid (CSF) analysis, holds the promise of providing a quantitative biomarker readout of spinal cord neural tissue injury, which may improve prognostication and facilitate stratification of patients for enrollment into clinical trials. Given evidence of the effectiveness of early surgical decompression and growing recognition of the concept that "time is spine," infrastructural changes at a systems level are being implemented in many regions around the world to provide a streamlined process for transfer of patients with acute SCI to a specialized unit. With the continued aging of the population, central cord syndrome is soon expected to become the most common form of acute traumatic SCI; characterization of the pathophysiology, natural history, and optimal treatment of these injuries is hence a key public health priority. Collaborative international efforts have led to the development of clinical practice guidelines for traumatic SCI based on robust evaluation of current evidence. The current article provides an in-depth review of progress in SCI, covering the above areas.

19. A Systematic Review of Experimental Strategies Aimed at Improving Motor Function after Acute and Chronic Spinal Cord Injury.

Gomes-Osman J, et al. J Neurotrauma. 2016 Mar 1;33(5):425-38. doi: 10.1089/neu.2014.3812. Epub 2016 Jan 20.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/26415105>

While various approaches have been proposed in clinical trials aimed at improving motor function after spinal cord injury in humans, there is still limited information regarding the scope, methodological quality, and evidence associated with single-intervention and multi-intervention approaches. A systematic review performed using the PubMed search engine and the key words "spinal cord injury

motor recovery" identified 1973 records, of which 39 were selected (18 from the search records and 21 from reference list inspection). Study phase (clinicaltrials.org criteria) and methodological quality (Cochrane criteria) were assessed. Studies included proposed a broad range of single-intervention (encompassing cell therapies, pharmacology, electrical stimulation, rehabilitation) and multi-intervention approaches (that combined more than one strategy). The highest evidence level was for Phase III studies supporting the role of multi-intervention approaches that contained a rehabilitation component. Quality appraisal revealed that the percentage of selected studies classified with high risk of bias by Cochrane criteria was as follows: random sequence generation = 64%; allocation concealment = 77%; blinding of participants and personnel = 69%; blinding of outcome assessment = 64%; attrition = 44%; selective reporting = 44%. The current literature contains a high proportion of studies with a limited ability to measure efficacy in a valid manner because of low methodological strength in all items of the Cochrane risk of bias assessment. Recommendations to decrease bias are discussed and include increased methodological rigor in the study design and recruitment of study participants, and the use of electrophysiological and imaging measures that can assess functional integrity of the spinal cord (and may be sufficiently sensitive to detect changes that occur in response to therapeutic interventions).

20. Traumatic Spinal Cord Injury-Repair and Regeneration.

Ahuja CS, et al. Neurosurgery. 2017 Mar 1;80(3S):S9-S22. doi: 10.1093/neuros/nyw080.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/28350947>

BACKGROUND:

Traumatic spinal cord injuries (SCI) have devastating consequences for the physical, financial, and psychosocial well-being of patients and their caregivers. Expediently delivering interventions during the early postinjury period can have a tremendous impact on long-term functional recovery.

PATHOPHYSIOLOGY:

This is largely due to the unique pathophysiology of SCI where the initial traumatic insult (primary injury) is followed by a progressive secondary injury cascade characterized by ischemia, proapoptotic signaling, and peripheral inflammatory cell infiltration. Over the subsequent hours, release of proinflammatory cytokines and cytotoxic debris (DNA, ATP, reactive oxygen species) cyclically adds to the harsh postinjury microenvironment. As the lesions mature into the chronic phase, regeneration is severely impeded by the development of an astroglial-fibrous scar surrounding coalesced cystic cavities. Addressing these challenges forms the basis of current and upcoming treatments for SCI.

MANAGEMENT:

This paper discusses the evidence-based management of a patient with SCI while emphasizing the importance of early definitive care. Key neuroprotective therapies are summarized including surgical decompression, methylprednisolone, and blood pressure augmentation. We then review exciting neuroprotective interventions on the cusp of translation such as Riluzole, Minocycline, magnesium, therapeutic hypothermia, and CSF drainage. We also explore the most promising neuroregenerative strategies in trial today including Cethrin™, anti-NOGO antibody, cell-based approaches, and bioengineered biomaterials. Each section provides a working knowledge of the key preclinical and patient trials relevant to clinicians while highlighting the pathophysiologic rationale for the therapies.

CONCLUSION:

We conclude with our perspectives on the future of treatment and research in this rapidly evolving field.

21. Spinal Cord Injury-What Are the Controversies?

Ahuja CS, et al. J Orthop Trauma. 2017 Sep;31 Suppl 4:S7-S13. doi: 10.1097/BOT.0000000000000943.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/28816870>

Traumatic spinal cord injuries have a tremendous impact on individuals, families, and society as a whole. Substantial heterogeneity in the patient population, their presentation and underlying pathophysiology has sparked debates along the care spectrum from initial assessment to definitive treatment. This article reviews spinal cord injury (SCI) management followed by a discussion of the salient controversies in the field. Current care practices modeled on the American Association of Neurological Surgeons/Congress of Neurological Surgeons joint section guidelines are highlighted including key recommendations regarding immobilization, avoidance of hypotension, early International Standards for Neurological Classification of SCI examination and intensive care unit treatment. From a diagnostic perspective, the evolving roles of CT, MRI, and leading-edge microstructural MRI techniques are discussed with descriptions of the relevant clinical literature for each. Controversies in management relevant to clinicians including the timing of surgical decompression, methylprednisolone administration, blood pressure augmentation, intraoperative electrophysiological monitoring, and the role of surgery in central cord syndrome and pediatric SCI are also covered in detail. Finally, the article concludes with a reflection on clinical trial design tailored to the heterogeneous population of individuals with SCI.

22. Neurotrauma.

Smith C. *Handb Clin Neurol*. 2017;145:115-132. doi: 10.1016/B978-0-12-802395-2.00008-0.

PDF: No PDF Available

URL: <https://www.ncbi.nlm.nih.gov/pubmed/28987162>

Traumatic brain injury remains a major cause of morbidity and mortality throughout the world, affecting young and old alike. Pathologic data have been developed through observations of human autopsies and developing animal models to investigate mechanisms, although animal models do not represent the polypathology of human brain injury and there are likely to be significant differences in the anatomic basis of injury and cellular responses between species. Traumatic brain injury can be defined pathologically as either focal or diffuse, and can be considered to be either primary, directly related to the force associated with the neurotrauma, or secondary, developing as a downstream consequence of the neurotrauma. While neuropathology has traditionally focused on severe head injury, there is increasing recognition of the long-term consequences of traumatic brain injury, particularly repetitive mild traumatic brain injury, and a possible long-term association with chronic traumatic encephalopathy.

23. Secondary Gains: Advances in Neurotrauma Management.

Long B, Koyfman A. *Emerg Med Clin North Am*. 2018 Feb;36(1):107-133. doi:

10.1016/j.emc.2017.08.007.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/29132572>

Neurotrauma is a leading cause of death and is associated with many secondary injuries. A balance of mean arterial pressure (MAP) and intracranial pressure (ICP) is required to ensure adequate cerebral blood flow and cerebral perfusion pressure. Evaluation and management in the emergency department entails initial stabilization and resuscitation while assessing neurologic status. ICP management follows a tiered approach. Intubation requires consideration of preoxygenation, head of bed elevation, first pass success, and adequate analgesia and sedation. Early consultation with neurosurgery is needed for definitive therapy. Focused evaluation and management play a significant role in optimizing patient outcomes.

24. Preclinical modelling of militarily relevant traumatic brain injuries: Challenges and recommendations for future directions.

Cernak I, et al. *Brain Inj.* 2017;31(9):1168-1176. doi: 10.1080/02699052.2016.1274779.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/28981339>

As a follow-up to the 2008 state-of-the-art (SOTA) conference on traumatic brain injuries (TBIs), the 2015 event organized by the United States Department of Veterans Affairs (VA) Office of Research and Development (ORD) analysed the knowledge gained over the last 7 years as it relates to basic scientific methods, experimental findings, diagnosis, therapy, and rehabilitation of TBIs and blast-induced neurotraumas (BINTs). The current article summarizes the discussions and recommendations of the scientific panel attending the Preclinical Modeling and Therapeutic Development Workshop of the conference, with special emphasis on factors slowing research progress and recommendations for ways of addressing the most significant pitfalls.

25. Metabolomics and Biomarker Discovery in Traumatic Brain Injury.

Banoei MM, et al. *J Neurotrauma.* 2018 Aug 15;35(16):1831-1848. doi: 10.1089/neu.2017.5326.

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/29587568>

Traumatic brain injury (TBI) is one of the leading causes of disability and mortality worldwide. The TBI pathogenesis can induce broad pathophysiological consequences and clinical outcomes attributed to the complexity of the brain. Thus, the diagnosis and prognosis are important issues for the management of mild, moderate, and severe forms of TBI. Metabolomics of readily accessible biofluids is a promising tool for establishing more useful and reliable biomarkers of TBI than using clinical findings alone. Metabolites are an integral part of all biochemical and pathophysiological pathways. Metabolomic processes respond to the internal and external stimuli resulting in an alteration of metabolite concentrations. Current high-throughput and highly sensitive analytical tools are capable of detecting and quantifying small concentrations of metabolites, allowing one to measure metabolite alterations after a pathological event when compared to a normal state or a different pathological process. Further, these metabolic biomarkers could be used for the assessment of injury severity, discovery of mechanisms of injury, and defining structural damage in the brain in TBI. Metabolic biomarkers can also be used for the prediction of outcome, monitoring treatment response, in the assessment of or prognosis of post-injury recovery, and potentially in the use of neuroplasticity procedures. Metabolomics can also enhance our understanding of the pathophysiological mechanisms of TBI, both in primary and secondary injury. Thus, this review presents the promising application of metabolomics for the assessment of TBI as a stand-alone platform or in association with proteomics in the clinical setting.

26. Critical Care of Traumatic Cervical Spinal Cord Injuries: Preventing Secondary Injury.

Schwartzbauer G, Stein DM. *Seminars in Neurology.* 2016;36(6):577-585. DOI: 10.1055/s-0036-1592189

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URL: <https://www.ncbi.nlm.nih.gov/pubmed/27907962>

The incidence of traumatic spinal cord injury (SCI) has not changed much over the years due to an aging population suffering falls, yet advances have been made in quality of life and survival time. In addition to initial medical and surgical stabilization, modern intensive care unit (ICU) care throughout the critical early period following SCI is essential to avoid continued secondary injury to the spinal cord. Cervical SCI patients are particularly prone and sensitive to periods of cardiovascular instability and respiratory failure directly resulting from their injuries. Preclinical and class III clinical data suggest improved outcomes by maintaining the mean arterial pressure > 85 mm Hg and avoiding

hypoxemia at least for 7 days following cervical SCI, and this level of monitoring and support should occur in the ICU.

27. AAST Geriatric Trauma/ACS Committee. Geriatric traumatic brain injury-What we know and what we don't.

Stein DM, et al. J Trauma Acute Care Surg. 2018;85(4):788-798. DOI: 10.1097/TA.0000000000001910

PDF: [Read PDF Here](#)

URL: <https://www.ncbi.nlm.nih.gov/pubmed/30256343>

Care of the geriatric patient with a TBI is a significant issue facing trauma care providers. The number of geriatric patients with TBIs continues to rise annually. There is, however, a shortage of literature on TBI in the elderly, representing a large void in our knowledge. High-quality research (Table 3) is needed to guide the development of geriatric-specific management guidelines for TBI and ultimately improve outcomes and decrease mortality in this vulnerable population.

Guidelines

28. Evaluation and management of mild traumatic brain injury: an Eastern Association for the Surgery of Trauma practice management guideline.

Barbosa RR, et al. Eastern Association for the Surgery of Trauma.

J Trauma Acute Care Surg. 2012 Nov;73(5 Suppl 4):S307-14. doi: 10.1097/TA.0b013e3182701885.

PDF: [Read PDF Here](#)

URL: <https://www.ncbi.nlm.nih.gov/pubmed/23114486>

BACKGROUND:

An estimated 1.1 million people sustain a mild traumatic brain injury (MTBI) annually in the United States. The natural history of MTBI remains poorly characterized, and its optimal clinical management is unclear. The Eastern Association for the Surgery of Trauma had previously published a set of practice management guidelines for MTBI in 2001. The purpose of this review was to update these guidelines to reflect the literature published since that time.

METHODS:

The PubMed and Cochrane Library databases were searched for articles related to MTBI published between 1998 and 2011. Selected older references were also examined.

RESULTS:

A total of 112 articles were reviewed and used to construct a series of recommendations.

CONCLUSION:

The previous recommendation that brain computed tomographic (CT) should be performed on patients that present acutely with suspected brain trauma remains unchanged. A number of additional recommendations were added. Standardized criteria that may be used to determine which patients receive a brain CT in resource-limited environments are described. Patients with an MTBI and negative brain CT result may be discharged from the emergency department if they have no other injuries or issues requiring admission. Patients taking warfarin who present with an MTBI should have their international normalized ratio (INR) level determined, and those with supratherapeutic INR values should be admitted for observation. Deficits in cognition and memory usually resolve within 1 month but may persist for longer periods in 20% to 40% of cases. Routine use of magnetic resonance imaging, positron emission tomography, nuclear magnetic resonance, or biochemical markers for the clinical management of MTBI is not supported at the present time.

29. Brain Trauma Foundation Guidelines

Guidelines for the Management of Pediatric Severe TBI, 3rd Ed.
Guidelines for the Management of Severe TBI, 4th Ed.
Guidelines for Prehospital Management of TBI, 2nd Ed.
Early Indicators of Prognosis in Severe TBI
Guidelines for the Surgical Management of TBI (last updated in 2006)
Guidelines for Field Management of Combat-Related Head Trauma (last updated in 2005)
PDF: [Read PDF Here](#)
URL: <https://braintrauma.org/coma/guidelines>

30. TQIP - https://www.facs.org/-/media/files/quality-programs/trauma/tqip/tbi_guidelines.ashx

31. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC).

Hawryluk GWJ, et al. Intensive Care Med. 2019 Oct 28. doi: 10.1007/s00134-019-05805-9.

PDF: [Read PDF Here](#)

URL: <https://www.ncbi.nlm.nih.gov/pubmed/31659383>

BACKGROUND:

Management algorithms for adult severe traumatic brain injury (sTBI) were omitted in later editions of the Brain Trauma Foundation's sTBI Management Guidelines, as they were not evidence-based.

METHODS:

We used a Delphi-method-based consensus approach to address management of sTBI patients undergoing intracranial pressure (ICP) monitoring. Forty-two experienced, clinically active sTBI specialists from six continents comprised the panel. Eight surveys iterated queries and comments. An in-person meeting included whole- and small-group discussions and blinded voting. Consensus required 80% agreement. We developed heatmaps based on a traffic-light model where panelists' decision tendencies were the focus of recommendations.

RESULTS:

We provide comprehensive algorithms for ICP-monitor-based adult sTBI management. Consensus established 18 interventions as fundamental and ten treatments not to be used. We provide a three-tier algorithm for treating elevated ICP. Treatments within a tier are considered empirically equivalent. Higher tiers involve higher risk therapies. Tiers 1, 2, and 3 include 10, 4, and 3 interventions, respectively. We include inter-tier considerations, and recommendations for critical neuroworsening to assist the recognition and treatment of declining patients. Novel elements include guidance for autoregulation-based ICP treatment based on MAP Challenge results, and two heatmaps to guide (1) ICP-monitor removal and (2) consideration of sedation holidays for neurological examination.

CONCLUSIONS:

Our modern and comprehensive sTBI-management protocol is designed to assist clinicians managing sTBI patients monitored with ICP-monitors alone. Consensus-based (class III evidence), it provides management recommendations based on combined expert opinion. It reflects neither a standard-of-care nor a substitute for thoughtful individualized management.

Military Priorities

32. The Top 10 Research and Development priorities for battlefield surgical care

Martin, M. et al. 2019 Journal of Trauma and Acute Care Surgery

PDF: [Read PDF HERE](#)

URL: <https://www.ncbi.nlm.nih.gov/pubmed/31246901>