Neurotrauma & Critical Care NEWS

American Association of Neurological Surgeons

CNS

AANS/CNS Section on Neurotrauma & Critical Care

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Editor: Laura B. Ngwenya, MD, PhD

In This Issue...

CHAIR'S MESSAGE

Dear Colleagues,

Julian Bailes, Jr., MD, FAANS

There are many new and emerging technologies for the delivery of care and achievement of better outcomes for traumatic brain injury (TBI) patients. These include assessment and imaging of cerebrovascular functioning, inpatient and outpatient rehabilitation and resource utilization, implementation of the electronic medical record in the trauma setting and others. An estimated 50 million people in the United States live one hour or more from a trauma center, so access to specialty care remains paramount.

Clinical research continues to be active and relevant for concussion, as it continues to remain an important and current topic in civilian life, the military and athletics. The diagnosis remains elusive, as a concussion is ordinarily a subjective presentation and there are no outward or visible signs of injury. The diagnosis of concussion remains one of the most challenging tasks facing a clinician, and emerging technologies are implementing oculomotor function assessment, electroencephalography network patterns, brain pulsatility and other methods. A recent study by Adrian et al. utilized the biomarkers UCHL1 and GFAP to predict the presence of intracranial lesions on CT scans, representing the first FDA-approved blood test to document a mild TBI. However, this technology is not a concussion test, nor is it approved for use in pediatric patients.

These developments remind us that the pursuit of science in neurotrauma is vitally important for advances in the field as well as for optimal patient care and outcomes. There has been pessimism in the past on the heels of innumerable failed clinical trials for TBI intervention. New thinking has led to efforts for more individualized approaches, which resemble the personalized care and genetic analysis that has led to advances in other areas of medicine. Recently, there has been over $100 million dollars committed to conducting large studies, including the NCAA-U.S. Department of Defense Concussion Assessment, Research and Education (CARE) Consortium, which is the largest concussion and repetitive head impact study ever undertaken. Funded jointly by the NCAA and DOD, it began in 2014 and now includes subjects across the U.S. on 30 college campuses. The CARE Consortium is part of the broader NCAA-DOD Grand Alliance and consists of two parts: (1) a clinical study aiming to define neurological symptoms and signs as well as how they are expressed and

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Chair's Message

evolve, representing the natural history of concussion and (2) an advanced research project with the goal to better understand the neurobiology of concussion and repetitive head impact exposure.

Another large study, the NINDS-funded, multicenter Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) is a public-private partnership, which is collecting and evaluating clinical data from 18 U.S. medical centers, including detailed neuroimaging, blood samples for biomarkers and clinical outcomes, with a goal of enrolling 3,000 subjects. Geoffrey Manley, MD, PhD, FAANS; David Okonkwo, MD, PhD, FAANS, and other neurosurgeons have been actively involved in this cutting-edge research. In my lab, we are working with an in-vitro assay using patient-specific neurons created through stem cells from blood samples. The ability to analyze the patients' genotypes, clinical phenotypes and response to in-vitro assessments should usher in a new era of looking at the heterogeneous TBI problem through a personalized approach. The Section on Neurotrauma and Critical Care continues to strive to be on the cutting edge and relevant to our members and the public which we serve.

Julian E. Bailes, Jr., MD, FAANS
Chairman, AANS/CNS Section on Neurotrauma & Critical Care

Editor's Corner

Laura B. Ngwenya, MD, PhD

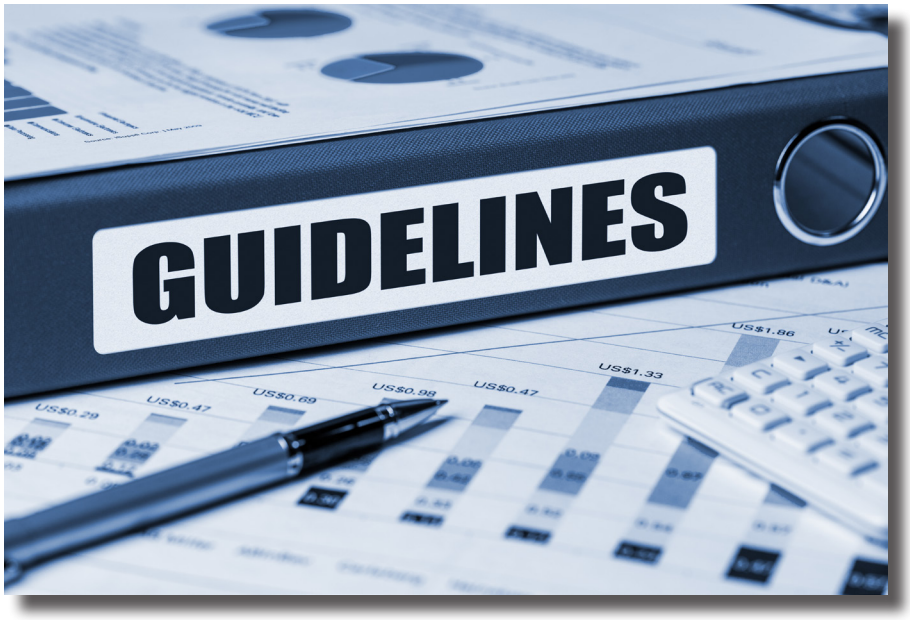
In this issue, we expand on the 2019 AANS Annual Scientific Meeting theme of The Science of Practice. We focus on an evaluation of the science that contributes to the practice of neurotrauma. We explore an upcoming clinical trial for TBI and discuss the future of SCI guidelines. In addition, we discuss evidence-based medicine and the possibilities of learning health systems. If you have an idea for a future issue theme, an article suggestion or would like to otherwise contribute, please contact us at Laura.Ngwenya@uc.edu. And remember to follow us on twitter: @AANSCNStrauma

Is the Clock Ticking on "Why Don't You Hang Some Phenylephrine and Call Me in the Morning?"

Investigating Evidence Beyond the Guidelines for Acute Management of Spinal Cord Injury

Uzma Samadani, MD, PhD, FAANS

The views reflected in this article are solely the views of the author and do not necessarily represent the views, opinions or positions of either the AANS or the CNS.



In the third period of a Friday night game a young standout athlete was hit from behind and toppled. He immediately lost sensation and motor strength from below the elbows. Imaging would later reveal C5-6 perched facets. The patient was placed in a halo and ultimately went to the operating room five days later. At a press conference the day after surgery, his surgeon stated that the spinal cord damage of this type is irreparable and the athlete will not able to walk again. Seven years later, he was finally able to wiggle his toes, a detail so important to his community that it was featured on the front page of his local paper.

The 2013 CNS guidelines for acute management of cervical spinal cord injury state, "There is Class III medical evidence that supports early closed reduction of cervical fracture/dislocation injuries with respect to neurological recovery." The guidelines also advocate surgery, stating that there is level III evidence to suggest "closed or open reduction of subaxial cervical fractures or dislocations is recommended. Decompression of the spinal cord/restoration of the spinal canal is the goal." However, the 2013 guidelines stopped short of recommending a timeline for surgery, reflecting insufficient evidence to support such a recommendation.

An update to the guidelines in 2017 was the first to suggest that there may be "low" quality of evidence and a "weak" recommendation for surgery less than 24 hours after injury in adult patients with acute cervical spine injury. (Fehlings et al, Global Spine J, 2017). The "low" quality indicates a reliance on retrospective data, since the ethics of a randomized trial investigating early vs. late intervention for spinal cord injury may be questioned. We would never consider running such a trial for evacuation of epidural hematoma.

When I began my neurosurgery residency in 1999 at the University of Pennsylvania, my department chair M. Sean Grady, MD, FAANS, who was president of the ABNS at that time, instilled in us a sense of urgency with regards to acute spinal cord injury. With incomplete cases we were made to understand these constituted surgical emergencies. While complete cases were generally afforded a poor neurologic prognosis, I came to understand that 'completeness' was not something that could always be ascertained with 100 percent certainty objectively in all circumstances and therefore, if the patient was hemodynamically stable, one ought to consider early rather than late decompression and fixation. I have very clear memories of Penn spine surgeon Paul Marcotte, MD, FAANS, telling a family he was consenting for surgery something to the effect of, "The odds are not in his favor at all. He has a chance in a million of being able to walk again, but we want to give him that chance."

Tarlov and Tator: The Sooner the Better

Even 20 years ago, these ideas were not novel; on the contrary, they are deeply rooted in neurosurgical history. Famed Canadian neurosurgeon Charles Tator, MD, PhD, FAANS(L), delivered a rousing address at the International Neurotrauma Society

Dr. Uzma Samadani

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Meeting in Toronto on Aug 12, 2018, reviewing his life's work on spinal cord injury in the context of those who came before him. In summarizing the work of Isadore Tarlov, MD, he stated, "Paralysis is reversible. Reversibility depends on the speed, force and duration of compression. If the duration of compression is too long, reversibility is not possible. If the force is too high and the speed too great, reversibility is not possible."

Dr. Tator's next slide was even more succinct: "For all ASIA A-D levels, at all spinal cord levels, decompress the sooner the better."

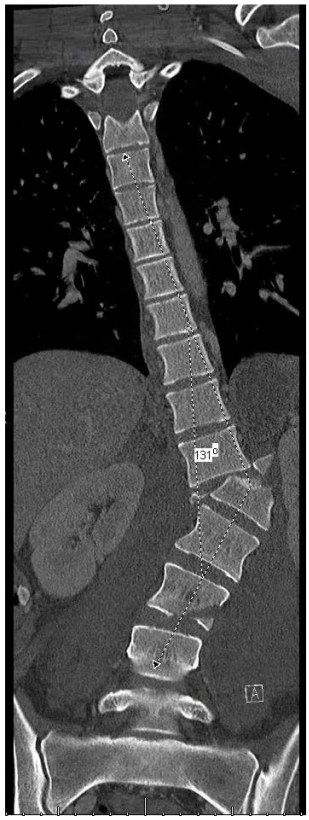
Michael Fehlings: "Time is Spine."

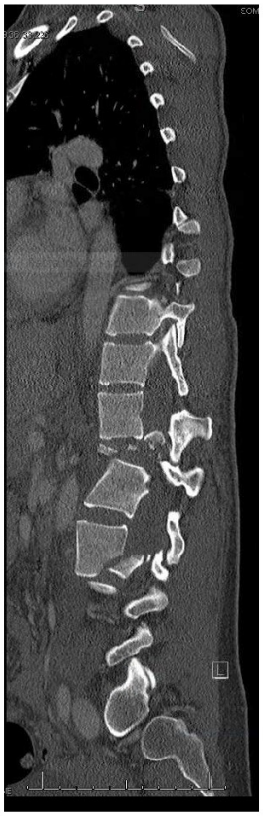
In the summer of 2017 at the National Neurotrauma Symposium in Snowbird, Utah, Michael Fehlings', MD, PhD, FAANS, talk was subtitled "Time is Spine". He subsequently published these ideas, along with a review of evidence supporting other treatments for acute spinal cord injury, in the Journal of Neurosurgery: Spine in December 2018. This review cited eight studies that demonstrate improved outcomes with earlier decompression of acute spinal cord injury (Badhiwala et al J Neurosurg Spine. 2018 Dec 20;30(1):1-18).

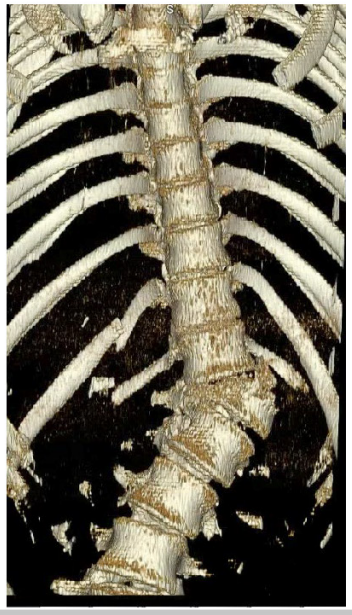
The more recent literature advances the evidence considerably. A retrospective analysis of 48 cases by Burke et al (Neurosurgery, 2018 Nov 28) demonstrates that surgical decompression occurring within 12 hours after acute spinal cord injury leads to relatively improved neurologic recovery compared to surgery that takes place after 12 hours. Eighty-nine percent of cases treated within 12 hours of injury converted from complete to incomplete spinal cord injury, versus 34 percent of those treated later.

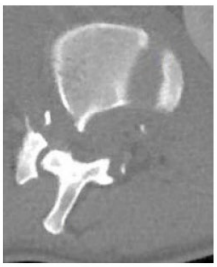
Ultimately, the application of this evidence is that if a patient comes in with acute spinal cord injury, the surgeon who does not offer early surgery will have to justify why he or she believed the risk outweighed the benefit.

As Dr. Fehlings has noted in his review, the implications of these studies are profound and affect the entire health care system. They require changes in patient transport, surgeon availability, training of nursing staff and operating room availability. "There is hence a need to study and modify healthcare system infrastructure and logistics to permit a streamlined path to a specialized acute care center for patients with an acute spinal cord injury" (Badhiwala et al J Neurosurg Spine. 2018 Dec 20;30(1):1-18).

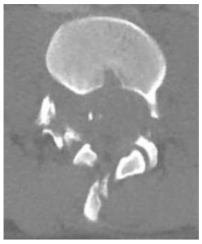




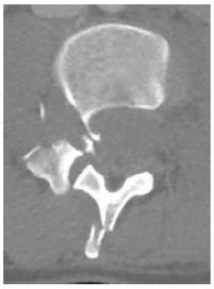




L1



L2



L3

Impression:
1. Severe fracture dislocation at T12-L1. T12 is dislocated anteriorly and to the right with respect to L1 with 50 degrees levoconvex scoliosis. There is severe central canal stenosis at T12-L1 due to retropulsion of L1 vertebral body fragments.
2. Severely comminuted posterior element fractures of L1, L2 and L3 with bilateral pedicle fractures. There is grade 1 posttraumatic anterolisthesis at L3-4 with moderate central stenosis due to retropulsion of L3 vertebral body fragments. There are also multiple transverse process and spinous process fractures throughout the lumbar spine.
3. Right-sided rib fractures at T9, T11, and T12. Thoracic spine is process fractures between T3 and T7. Please see chest CT report for other findings.

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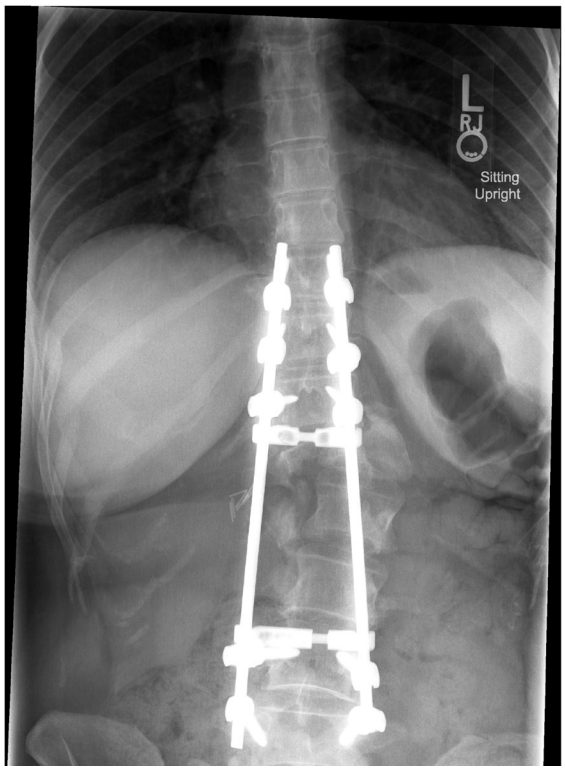
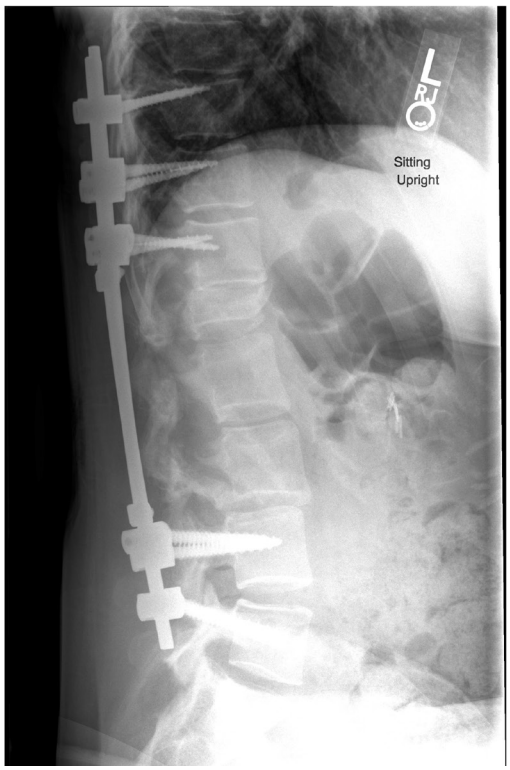
While no surgeon would choose to spend their night or weekend repairing a complex spine trauma (see figure), the ethics of awaiting a randomized trial and higher level of evidence are unjustifiable given the relative risks of surgical complications weighed against the possibility of functional recovery. Greater understanding of neurogenic and spinal shock with better blood pressure and heart rate control through the use of pacing wires, pressors and other agents has rendered acute spine surgery safer than in past eras. I would argue that it is the responsibility of surgeons to be the drivers of change in this arena. Just as neurosurgery has moved towards specialization in the fields of pediatrics, vascular and functional, there needs to be a recognition that complex spine trauma is a subspeciality requiring a unique skillset. More importantly, hospitals need to decide if they can meet the needs of these patients or if they cannot. They must be willing to stock instrumentation enabling complex spine repair and staff accordingly. If they cannot, acute spine trauma patients should be directed elsewhere. The alternative is that the medicolegal system will drive the change that needs to happen. No surgeon would enjoy such an exercise.

A young athletic person who sustains an injury on a Friday night should not be resigned to the fate of quadriplegia to convenience the lifestyle of the surgeon on call, but be granted his shot at recovery; however, long that shot may be. Had the fourth period of that sporting event been held in the operating room, one wonders if that athlete might have celebrated the seventh anniversary of his injury engaged in teaching his children the sport of his choice rather than merely wiggling his toes.

Miraculously, [redacted] has regained some neurological function in her legs and she is now able to walk with a walker. She also has intact bowel and bladder function, according to her report. That is really quite amazing given the severity of her injury.



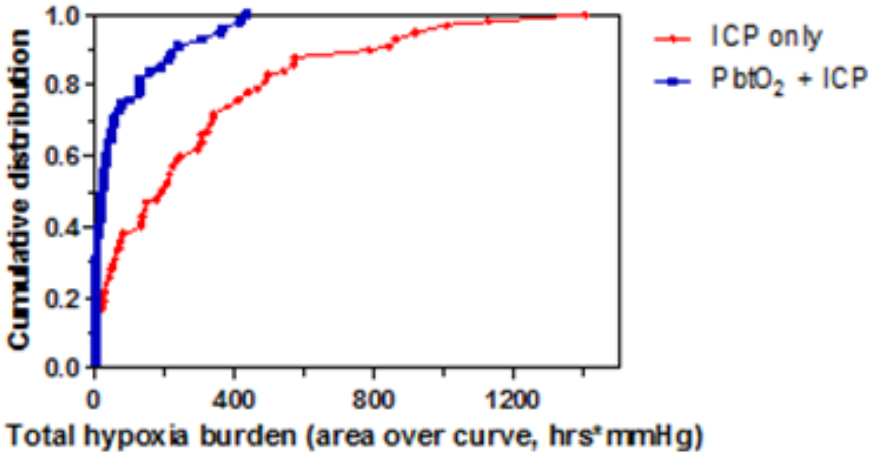


Brain Oxygen Optimization in Severe Traumatic Brain Injury (BOOST) Phase-III: A Promising Future

Enyinna L. Nwachuku, MD | Lori A. Shutter, MD, FNCS, FCCM

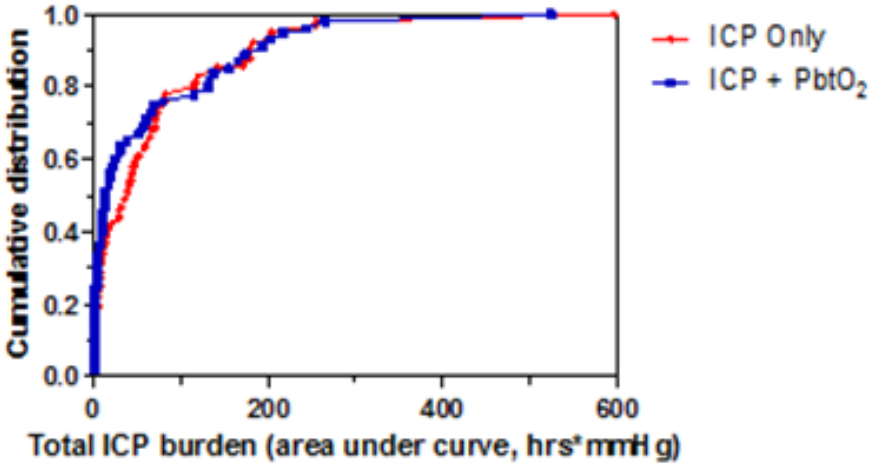
Effective management against secondary injury in patients with severe traumatic brain injury (TBI) continues to plague the current health care system. Acute management of severe TBI aims to treat intracranial mass lesions and minimize secondary brain injury. Traditionally, increased intracranial pressure (ICP) has been considered the most important contributing force leading to the formation of free radicals and neuro-inflammatory processes that result in secondary injury. In the late 1990s and early 2000s, small studies suggested that treatment paradigms incorporating optimization of brain tissue oxygenation showed improved patient outcomes.[1,2,3]

Out of this data, the concept of BOOST II was born, which is a randomized prospective clinical trial conducted across 10 intensive care units at notable academic medical centers across the U.S. One hundred and nineteen patients were randomly selected for a treatment protocol of ICP management only, versus ICP plus brain tissue oxygenation (PbtO2) management. The study was a feasibility and safety trial with the primary goal of reducing brain hypoxia through a treatment paradigm focusing on managing PbtO2. Enrollment occurred from 2010 to 2013, and results published in 2017 show that reduction of brain hypoxia is both feasible and safe. The data also suggested that combined management of ICP and PbtO2 in severe traumatic brain injury may lower mortality and result in more favorable outcomes compared to ICP management alone.[4]



Cumulative distribution of total hypoxia burden in BOOST-2. Mean hypoxia burden was 74.9 (95% CI 43.9 – 105.9) in PbtO2 and ICP group (n=55) versus 285.8 (95% CI 202.0 – 369.7) p < 0.0001) in the ICP only group (n=58).

Okonkwo DO, et al. Crit Care Med 2017; 45(11):1907-1914.



Cumulative distribution of total ICP burden in BOOST-2. Mean hypertension burden was 61.1 (95% CI 35.0 – 87.9) in PbtO2 and ICP group (n=55) versus 67.9 (95% CI 42.5 – 93.4) p = 0.21) in the ICP only group (n=59)

Okonkwo DO, et al. Crit Care Med 2017; 45(11):1907-1914.

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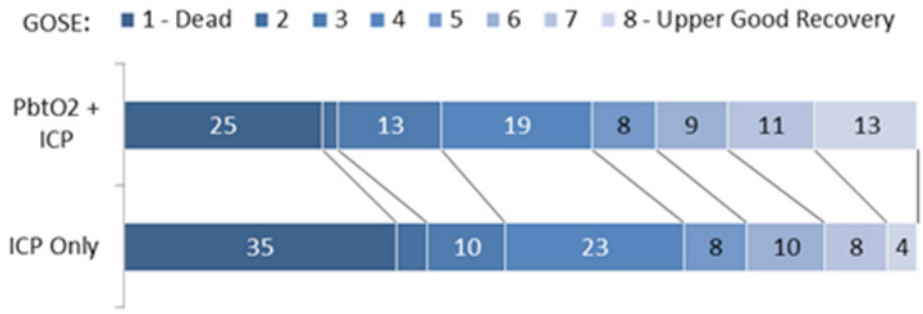

Glasgow Outcome Score Extended distribution between ICP only and ICP + PbtO2 groups.

Okonkwo DO, et al. Crit Care Med 2017; 45(11):1907-1914.

Brain Oxygen Optimization in Severe Traumatic Brain Injury – Phase 3 (BOOST-3), is a randomized clinical trial expanding the work accomplished in BOOST 2. BOOST-3, which will begin enrollment in spring 2019, evaluates whether a treatment protocol guided by PbtO2 + ICP monitoring, compared to treatment guided by ICP alone, results in improved neurologic outcome for severe TBI patients.

Dr. Enyinna L. Nwachuku

Dr. Lori A. Shutter

BOOST-3 is a two-arm, single blind, randomized, controlled, phase III, multi-center trial of the efficacy of PbtO2 monitoring and is designed to obtain data regarding efficacy of physiologic maneuvers aimed at normalizing PbtO2 in the first five days after injury. There will be 45 participating sites in the U.S. and Canada with an enrollment goal of 1,094 TBI patients who require ICP monitoring. The key inclusion and exclusion criteria are listed in Table 1. Informed consent will be obtained from legally authorized representatives (LAR) or via Exemption from Informed Consent (EFIC), if the patient's LAR is not present.

All eligible patients will have both an ICP and PbtO2 monitor placed within six hours of arrival at the enrolling hospital (but no later than 12 hours after injury) and be randomized into either the control group (ICP only) or active treatment group (ICP + PbtO2). Patients in the control group (ICP only) will be managed to maintain a goal ICP of < 22 mm Hg and those in the treatment group (ICP + PbtO2) will be managed to maintain both ICP < 22 mm Hg and PbtO2 of >/= 20 mm Hg. Study interventions will continue for five days, unless the monitors are removed early by the treating clinician based on the patient's clinical status or care needs. The primary outcome is neurological status based on the Glasgow outcome scale-extended (GOS-E) at 180 days after injury. The study schematic is provided in Figure 4. Results from BOOST-3 have the potential to change the standard of care for acute management of severe TBI patients by tailoring interventions to address both brain hypoxia and ICP to decrease secondary brain injury.

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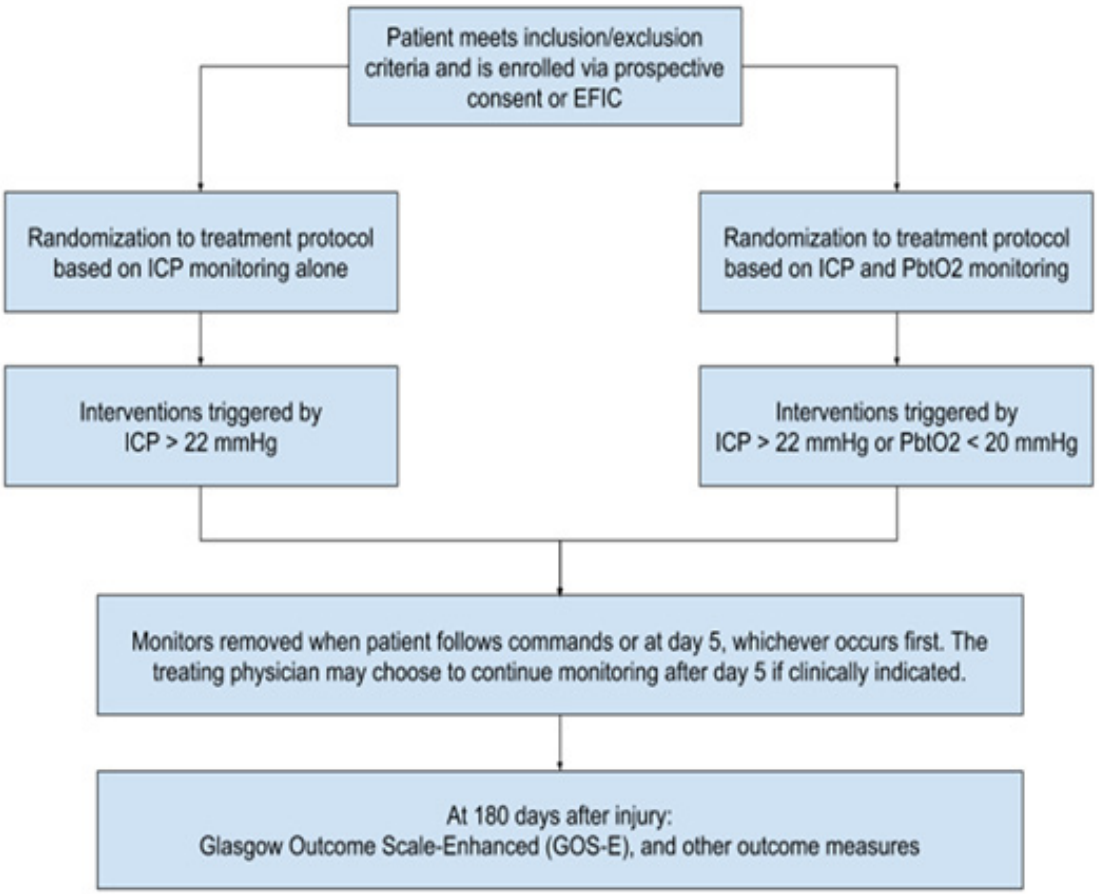
Table 1. BOOST-3 key inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Non-penetrating TBI	GCS motor score = 6
Males and females greater than or equal to 14 years of age	Bilaterally absent pupillary response in the absence of paralytic medication
Need for ICP monitoring	Contraindications to ICP monitor placement
Monitors placed within 6 hours of arrival (and within 12 hours from injury)	Pregnancy
	Difficulty in diagnosis, treatment or follow up
	Known active drug or alcohol dependence

Figure 5. Schematic of BOOST-3 enrollment and study flow-diagram



Does Neurotrauma Need Practice-based Medicine?

Laura B. Ngwenya, MD, PhD | Brandon Foreman, MD

As we continue to have heightened community awareness surrounding traumatic brain injury (TBI) and concussions, it is reasonable to take pause and consider our progress, or lack thereof, in advancing treatment. We have performed dozens of clinical trials involving patients with TBI with minimal advancements in patient care and no new therapeutic interventions. Current research is underway to collect information about patients with TBI to help better characterize and stratify patients and to identify enriched populations. The Transforming Research And Clinical Knowledge in TBI (TRACK-TBI) and the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) studies are spearheading efforts to advance how we think about TBI and how we design future TBI clinical trials. However, what is the future of TBI research? Should our pursuit of knowledge be confined to the next clinical trial?

Evidence-based medicine (EBM) has dominated our approach to teaching and delivering patient care since the late 20th century. In the mid-1990s, EBM became the buzzword that represented a way to overcome our "failures" in the medical community. EBM is defined as the "conscientious, explicit and judicious use of current best evidence in making decisions about care of individual patients"[1,2] and emphasizes a rigorous collection and evaluation of evidence to inform clinical decisions. Although clinical expertise and learned wisdom was not ignored, external evidence from research studies became the penultimate data with which to guide treatment decisions, with the randomized controlled trial (RCT) being the gold-standard of clinical research quality and excellence. An entire field emerged focusing on clinical data integrity, quality of evidence and the use of evidence to make recommendations for patient care guidelines.[3,4] However, overemphasis on the RCT and high-quality evidence has led to some recommendation gaps in TBI care.[5] This approach risks negating clinically proven management strategies as "ineffective" despite years of clinical experience, simply due to lack of external evidence proving their efficacy.

Recently, there has been a trend to capitalize on the technological advances in electronic medical record systems, data capture opportunities and bioinformatics strategies to improve patient care with evidence outside that of the traditional EBM framework. This focus on Practice-based Medicine (PBM) emphasizes comparative effectiveness research, which includes real-world clinical practice, unselected patient populations and longer-term outcomes. PBM is actualized by the Learning Health System (LHS) framework – defined by the Institute of Medicine as a "system that learns from data collected at point-of-care and applies lessons [for] patient care improvement."[6] An LHS includes a plan-do-study-act approach to learning best practices, allows patients or caregivers to act as catalysts for change and takes advantage of data generated in the course of healthcare delivery (rather than in a controlled clinical trial). In a LHS, knowledge gained from research and patient care is reciprocal (Figure 1).[7]

The concepts of PBM and patient/caregiver engagement have proven effective in select settings. As an example, a collaborative group of pediatric gastroenterologists established the ImproveCareNow network. This network employed an LHS approach to the care and cost of treating children and adolescents with inflammatory bowel disease by engaging patients, families

Dr. Laura B. Ngwenya

Dr. Brandon Foreman

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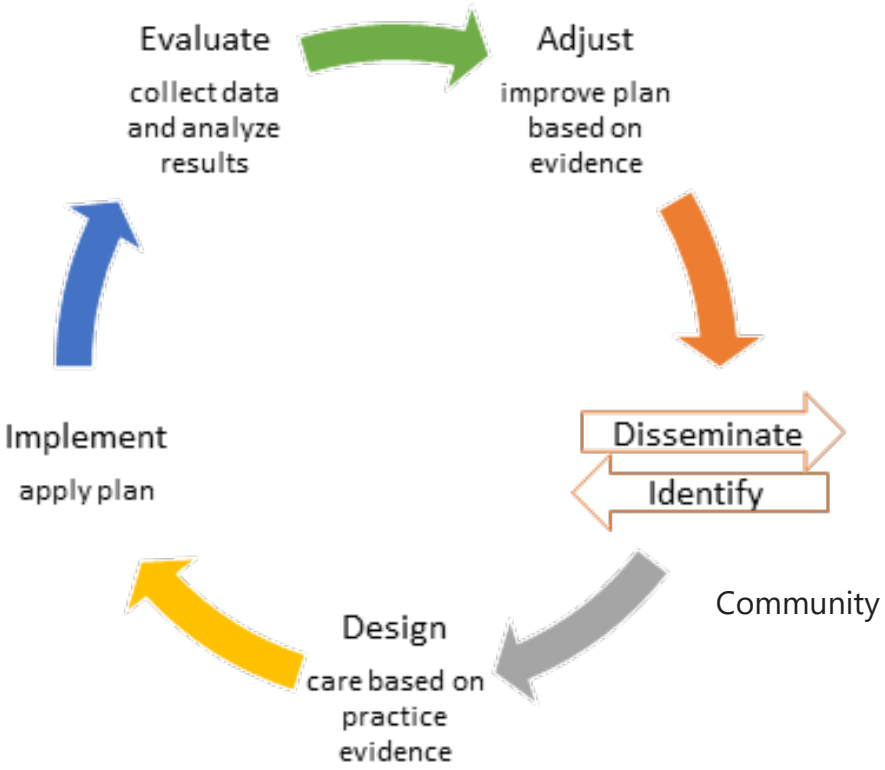

Figure 1: Phases of a learning health system. Research influences practice and practice influences research. Knowledge learned is disseminated to the community and the community (patients) help identify problems to be solved. Modified from Green, SM, Reid RJ, and Larson, EB 2012. Ann Intern Med. 157(3):207-210.

and clinicians. Ultimately, ImproveCareNow increased the proportion of patients in remission from 55 percent to 77 percent.[8,9] LHS approaches are gaining acceptance in many fields of medicine, including cardiology and internal medicine subspecialties.[10,11] Touted as a form of precision medicine, PBM has the potential to identify problems and solutions in patient care that have been otherwise unrecognized or poorly studied. As we near the completion of TRACK-TBI and CENTER-TBI and continue to look for new solutions and strategies to improve patient care, is it time for the neurotrauma community to leverage the insights of comparative effectiveness research and embrace a learning health system approach?

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Officer in the Spotlight
Martina Stippler, MD, FAANS

Dr. Martina Stippler is a practicing neurosurgeon at Beth Israel Deaconess Medical Center in Boston, Massachusetts. She is the director of Neurotrauma, co-director of the neuro-intensive care unit, and is a visiting assistant professor at Harvard Medical School. She serves on the executive committee of the Congress of Neurological Surgeons. Her clinical areas of expertise are neurotrauma, complex and minimally invasive spine surgery, brain tumors, and endoscopic pituitary surgery. Her research and education efforts are focused on using multimodality monitoring data to predict brain swelling, advanced imaging to triage mild TBI, and difficult conversations in emergency settings.

What do you think is the biggest unanswered question in TBI?
Nobody would obtain a CT scan of the heart to see how well it is working, but this is precisely what we do with the brain. We look at the CT scan and try to judge the extent of the injury, although we all know this is not always possible. You can have a patient with a large frontal contusion sitting up in bed asking for lunch and have another patient with the smallest traumatic SAH in a coma from DAI (diffuse axonal injury). I cannot wait for the day where we can use reliable biomarkers to tell us the extent of brain injury and how it is responding to our treatment.

What are the changes in clinical TBI research?
Again, heterogeneity of brain trauma; currently when a patient is enrolled in RCT, the stratifying criterion is the level of consciousness, in short, GCS score. But we all know that the underlying brain injury and pathophysiology in a patient with an epidural hematoma is much different from a patient with diffuse axonal injury. Until we can stratify these patients better, our attempts to improve TBI therapies with clinical trails will fail.

What TBI question did you set out to answer?
I am very interested in how we triage TBI, especially complicated mild TBI. Much of my work has focused on providing the evidence to stop the routine follow-up head CT scan in complicated mild TBI patients. In my institution now, we are following modified BIG (brain injury guidelines) criteria and do not perform this reflexive second head CT scan, which in the absence of neurological changes does not alter treatment. Lately, I also have become interested in how we surgeons can improve our communication of poor prognoses to loved ones and provide more goal-concordant care for the elderly population. Sometimes, doing nothing is harder than doing something.

What advice would you give to other neurosurgeons dealing with TBI patients?
Self-compassion. Be kind to yourself. Instead of mercilessly judging and criticizing yourself for various inadequacies or shortcomings, self-compassion means you are kind and understanding when confronted with a poor patient outcome and leave room to recover and learn.

What is your biggest challenge during your day-to-day work?
The endless flood of emails that pull you away from patient care. The more you write, the more come back.

Neurotrauma |

Saturday, April 13

8:00 am - 12:00 pm
008 Neurotrauma and Neurocritical Care for the Practicing Neurosurgeon: MOC Review and Update | PRACTICAL CLINIC

8:00 am - 5:00 pm
003 You Are Never Too Old for Surgery: Spine Management in an Aging Population | PRACTICAL CLINIC

1:00 pm - 5:00 pm
014 Neurosurgical Care of Athletes: Concussion, Spine, Peripheral Nerve and Return-to-play | PRACTICAL CLINIC

1:00 pm - 5:00 pm
016 Update on the Management of Spine and Spinal Cord Injury | PRACTICAL CLINIC

Sunday, April 14

7:30 am - 4:30 pm
NEW 027 Global Neurosurgical Practice | PRACTICAL CLINIC

7:30 am - 4:30 pm
028 Case-based Management of Traumatic Brain Injury | PRACTICAL CLINIC

12:30 pm - 4:30 pm
NEW 035 Neurosurgery Around the World: Education and Other Opportunities | PRACTICAL CLINIC

1:42 pm - 4:30 pm
International Symposium - Session VI: Neurotrauma

Monday, April 15

7:00 am - 9:00 am
109 Pediatric Neurosurgery for General Neurosurgeons | BREAKFAST SEMINAR

7:00 am - 9:00 am
111 Return-to-play After Sports Injury I: Spine Injury | BREAKFAST SEMINAR

7:00 am - 9:00 am
112 Cerebral Trauma: State-of-the-art Treatment | BREAKFAST SEMINAR

1:40 pm - 2:30 pm
Neurosurgery in Press: Latest Results of Clinical Trials in Neurosurgery and Allied Fields

2:30 pm - 6:00 pm
Scientific Session VI: Neurotrauma

Tuesday, April 16

7:00 am - 9:00 am
NEW 201 Precision Medicine for Individualized VTE Prophylaxis in the Neurosurgical Patient, Including Trauma and Critical Care | BREAKFAST SEMINAR

2:30 pm - 6:00 pm
Advancements in Neurotrauma Care

Wednesday, April 17

7:00 am - 9:00 am
301 Contemporary Management of Spinal Fractures | BREAKFAST SEMINAR

1:00 pm - 2:00 pm
Rapid Fire Abstracts: Neurotrauma; Pediatrics; Stereotactic and Functional

2:00 pm - 5:00 pm
AANS/CNS Section on Neurotrauma and Critical Care

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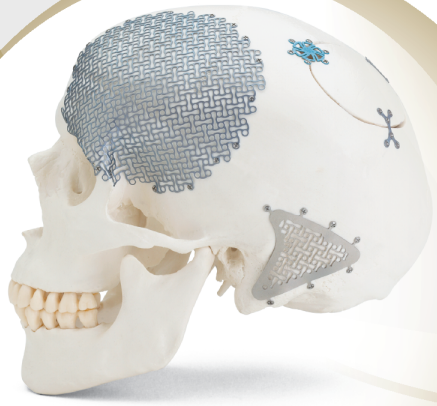

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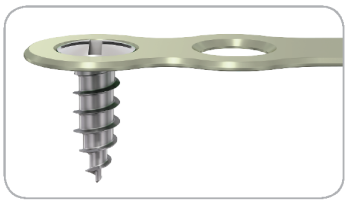

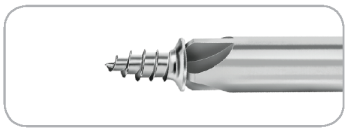

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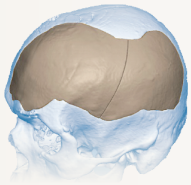

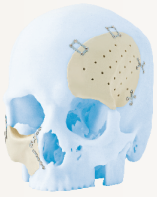

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1. Kamer, Lukas, MD, DDS, Noser Hansrudi, PhD, Hammer, Beat, MD, DDS; Anatomical Background for the Development of Preformed Cranioplasty Implants; The Journal of Craniofacial Surgery, 2013:264-268.
2. Internal Data, PSI Complaint History, July 2018.
3. Powered Driver User Experience Validation Study, Junicon, January 2017.

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