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SPEAKER SERIES

Advances in traumatic brain injury – evaluation and management

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About the speakers

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Jeffrey Bazarian is Professor of Emergency Medicine and Neurology at the University of Rochester, New York, USA. In 2010, Professor Bazarian joined the University of Rochester Sports Concussion Clinic, providing outpatient concussion care to area high school and collegiate athletes. Professor Bazarian's research is focused on developing neuroimaging and blood-based biomarkers of axonal injury after concussion and repetitive head hits, and the pathophysiologic mechanisms of recovery. He, along with Professor Welch, were lead authors on the 2018 *Lancet Neurology* publication detailing results of the ALERT-TBI study, which was used to support approval of the first blood-based biomarker test for traumatic brain injury in the US.

Robert Welch
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Robert Welch is Professor - Clinical Educator, in the Department of Emergency Medicine and is the Director of the Biostatistics and Epidemiology Research Design Group at Wayne State University, Michigan, USA. He is also a member of the Cardiovascular Research Institute and an Associate in the Department of Physical Medicine and Rehabilitation at Wayne State University. He was the Program Director of the Wayne State University Neurological Emergencies Treatment Trials Network from 2007 – 2018 and held numerous clinical research contracts with foundations and industry. Professor Welch's research interests include neurological emergencies, clinical trials methodology and heart disease.

This publication summarises a webinar held on 23 July 2020, featuring Professor Jeffrey Bazarian from the University of Rochester, New York, USA and Professor Robert Welch from Wayne State University, Michigan, USA. The webinar reviewed the current approach to management of concussion/mild traumatic brain injury, including the use of clinical decision rules. It also detailed the latest research on use of blood-based biomarkers for predicting the absence of intracranial injury on head CT scan. The webinar was sponsored by Abbott.

Advances in Concussion Management

Professor Bazarian

Challenges in concussion management

Concussion/mild traumatic brain injury is difficult to diagnose, and largely relies on self-reported or witness-reported brief loss of consciousness, amnesia, confusion or headache at the time of an injury or deceleration event to the head. Several tools have been developed to aid in diagnosis of concussion, including The Sport Concussion Assessment Tool – 5th Edition (SCAT5) and the Military Acute Concussion Evaluation (MACE) tool.[1,2] However, these tools still rely on patient reporting.

Another challenge in concussion management is determining which patients are at risk of persistent post-concussive symptoms, including headache, difficulty concentrating, dizziness and mood changes. Knowing the risk of post-concussive symptoms has implications for decisions regarding ongoing patient care upon discharge from the emergency room.[3]

Finally, it is very hard to predict long-term outcomes in patients with concussion, the most concerning aspect of which is cognitive decline. A link has also been reported between repeated mild or concussive traumatic brain injury and chronic traumatic encephalopathy.[4]

Current approach to concussion management in the emergency department

Current management of concussion in the emergency setting is guided by recommendations recently published in *Annals of Emergency Medicine*.[5] The most important task for emergency physicians is to perform all key components of the Emergency Department Concussion Assessment, and in particular to assess for traumatic intracranial injury risk factors, obtaining a head computed tomography (CT) scan when appropriate.[5]

In the US, because of the medico-legal environment, there is no tolerance for missing any bleeds associated with traumatic brain injury. However, judicious use of CT technology is pertinent. There are clinical decision rules for determining which patients are candidates for a head CT scan, but these are not widely used.[3]

Canadian CT Head Rule

One of the first decision rules was the Canadian CT Head Rule, published in 2001, which applies to patients with a Glasgow Coma Scale (GCS) score of 13-15.[6] It excludes patients aged <16 years, those on blood thinners, or those who have experienced seizure after injury. The decision rule specifies high risk criteria:[6]

- GCS score <15 at 2 hours post-injury
- Suspected open or depressed skull fracture
- Any sign of basilar skull fracture
- Haemotympanum, raccoon eyes, Battle's sign, cerebrospinal fluid oto-/rhinorrhoea
- Vomiting ≥2 episodes
- Age ≥65 years

And medium risk criteria:[6]

- Retrograde amnesia to the event ≥ 30 minutes
- "Dangerous mechanism" – e.g. pedestrian struck by motor vehicle, occupant ejected from motor vehicle, or fall from >3 feet or >5 stairs.

The Canadian CT Head Rule was derived from a study of 3121 patients, of whom 2078 (67%) were scanned.[6] High risk criteria were found to be 100% sensitive (95% confidence interval [CI] 92%-100%) for predicting the need for neurological intervention, and 98.4% sensitive (95% CI 96%-99%) for predicting "clinically important" brain injury.[6] The rule identified 320 out of 348 patients with any injury on CT, including "clinically unimportant" injuries (sensitivity 92.0%; 95% CI 88%-94%).[6] When considered separately, the rule identified 70 of 94 "clinically unimportant" injuries (sensitivity 74.5%; 95% CI 64.4%-82.9%).[6]

Two studies have assessed the impact of the Canadian CT Head Rule on clinical practice. A matched-pair cluster-randomised trial compared the outcomes of 4531 patients with minor head injury, before and after strategies to actively implement the Canadian CT Head Rule.[7] This trial found that CT use increased by 6.7% after implementation of the Canadian Head CT Rule.[7] However, a larger trial of 44,947 encounters found that there was 5.3% absolute reduction in CT use after implementation of the Canadian CT Head Rule.[8]

Clinical decision rules summary

- There is persistent variability in CT use despite the availability of clinical decision rules
- There is a lack of understanding among clinicians regarding clinical decision rules
- There is variability in sensitivity and specificity of clinical decision rules under different practice conditions
- It is difficult to implement clinical decision rules in some clinical practices
- More objective tests are needed.

Possible role for blood-based biomarkers

Concussion leads to 3 key pathophysiological events: axonal stretch, vascular stretch and neuro-inflammation. These events lead to the release of proteins that can be detected in the blood, including ubiquitin c-terminal hydrolase (UCH-L1), S100 calcium-binding protein B (S100B), caplain-derived αII-spectrin N-terminal fragment (SNTF), glial fibrillary acidic protein (GFAP), tau, phosphorylated tau (P-tau), amyloid-β 1-42 (Aβ42), 120 kDa spectrin breakdown product (SBDP120), myelin basic protein (MBP) and neurofilament light chain (NFL) [see **Figure 1**].[3]

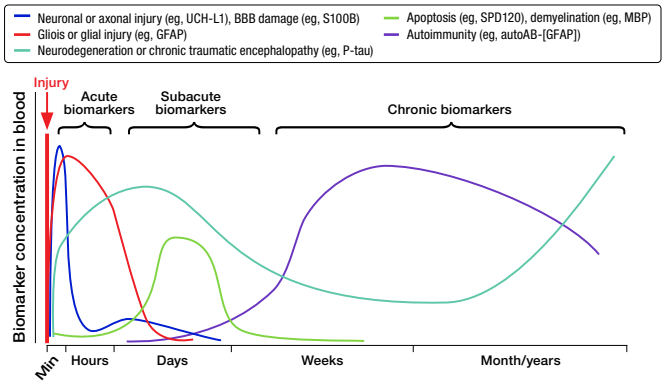

Figure 1. Acute, subacute and chronic biomarkers after traumatic brain injury.[3]

Biomarkers have been studied in two major areas:

- For classification/diagnosis, to separate patients with mild traumatic brain injury from those with moderate or severe injury
- For the prediction of traumatic intracranial injury on CT scan.

Figure 2 shows how well various biomarkers have performed at classifying injury, across a variety of studies.[3] A perfect test would have an area under the curve (AUC) value of 1.0. However, it is important to note that these tests have been compared to the current subjective reference standard of patient-reported symptoms. In the future, diffusion tensor imaging may serve as an objective reference standard. Further work is required before biomarkers can be successfully used as diagnostic aids in patients with traumatic brain injury.

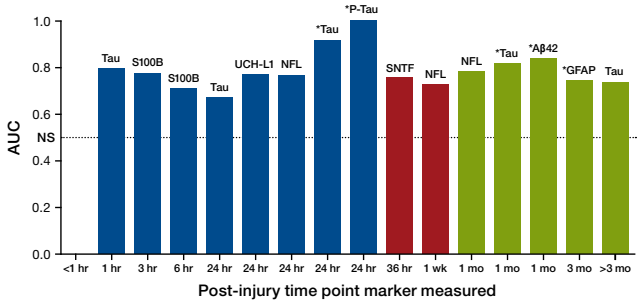

Figure 2. Performance of blood-based biomarkers for classification/diagnosis of patients with traumatic brain injury.[3]

* Includes complicated mild traumatic brain injury and/or moderate-severe traumatic brain injury. **AUC** = area under the curve; **NS** = not significant.

Figure 3 shows the performance of biomarkers across various studies for the prediction of traumatic intracranial injury.[3] Given the current reference standard is head CT scan, these findings can be considered robust. Indeed, the recommendations for management of concussion recently published in *Annals of Emergency Medicine* include a section on the use of ancillary tests as alternatives to clinical decision rules for risk stratification of intracranial injury, including blood-based biomarkers.[5]

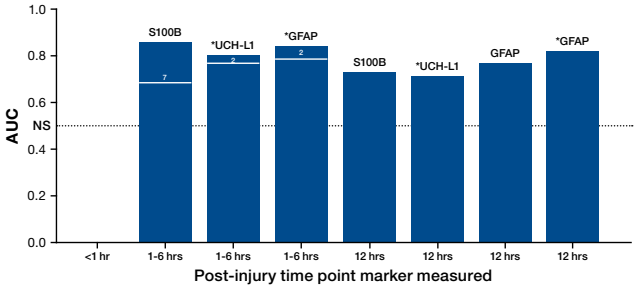

Figure 3. Performance of blood-based biomarkers for prediction of traumatic intracranial injury.[3]
* Includes complicated mild traumatic brain injury and/or moderate-severe traumatic brain injury. **AUC** = area under the curve; **NS** = not significant.

Conclusions

- Concussion/mild traumatic brain injury can be difficult to diagnose and prognose
- There are potential short- and long-term consequences of concussion
- Clinical decision rules for emergent head CT have been developed
  - Must consider those who can be included using the Canadian CT Head Rule
  - Will miss small or "non-clinically significant" bleeds
  - Difficult to widely implement
- Blood biomarkers may offer an objective and discriminatory test to determine the need for head CT in patients with mild traumatic brain injury.

Blood biomarkers to determine the need for head CT scan

Professor Welch

Performance of clinical decision rules in clinical practice

Although the Canadian CT Head Rule showed high sensitivity and specificity for detecting intracranial bleeds in initial Canadian studies,[7,9] an external validation study from the Netherlands demonstrated that the rule does not always perform so well in clinical practice.[10] In this prospective cohort study of 4557 patients with minor head injury (GCS score 13-15), 3742 (82%) received a CT scan.[10] The Canadian CT Head Rule was 80.3% (95% CI 76.1%-84.2%) sensitive and 44.2% specific (95% CI 42.7%-45.9%) for any traumatic finding.[10] In the same study, the New Orleans Criteria showed higher sensitivity (98.8%; 95% CI 97.6%-99.8%) but much lower specificity (4.4%; 95% CI 3.8%-5.1%).[10] Other rules examined included the National Institute for Health and Care Excellence rule and the CT in Head Injury Patient rule. However, the Canadian CT Head Rule is by far the most commonly used in the US.

What blood biomarker tests are currently available?

Blood biomarker tests have the potential to reduce the use of head CT scans and associated radiation risk. The S100B test is currently available in the UK and several European countries, but not the US. In 2018, Banyan's Brain Trauma Indicator (BTI™), a biomarker utilising serum GFAP and UCH-L1, was cleared in the US.[11] This biomarker was validated for the prediction of absence of intracranial injuries on head CT in the ALERT-TBI study.[12]

ALERT-TBI study methods

ALERT-TBI was a prospective study undertaken in 15 US and 7 European emergency departments between Dec 2012 and March 2014.[12] It was funded by the US Army Medical Research & Materiel Command and Banyan Biomarkers.[12] Patients in the study were aged ≥18 years with suspected non-penetrating traumatic brain injury

and had a GCS score of 9-15.[12] A head CT scan was performed on all patients as part of clinical care, and blood was drawn within 12 hours of injury.[12] UCH-L1 and GFAP were measured in serum and analysed using pre-specified cut-off values of 327 pg/ml and 22 pg/ml, respectively.[12]

UCH-L1 and GFAP assay results were combined into a single test result, positive or negative (Banyan BTI™).[12] The test was considered positive if either biomarker was above the pre-specified cut-off value.[12] Test results were correlated to the presence or absence of CT-detected traumatic intracranial injury to determine accuracy.[12] Injuries were defined as subdural haematoma, epidural haematoma, subarachnoid haemorrhage, intraventricular haemorrhage, contusion or oedema.[12]

ALERT-TBI study results

There were 2011 eligible participants, with 52 excluded due to missing serum or head CT data.[12] Out of the 1959 subjects who were analysed, 6% had a positive CT scan and 66% had a positive biomarker test.[12] Mean age of participants was 48.9 years, and the vast majority had a GCS score of 15 on presentation.[12] More than 30% of patients had post-traumatic amnesia, and more than 40% had loss of consciousness.[12] Falls accounted for more than 50% of injury.[12] Most patients were White, and there were more males than females.[12]

Scatterplots of UCH-L1 and GFAP assay results among patients with a GCS score of 14-15 (n= 1920) showed many patients with low assay values in the CT negative group (see **Figure 4**).[12] However, a number of patients who were CT negative had high values, indicating some level of brain injury not apparent on CT.[12]

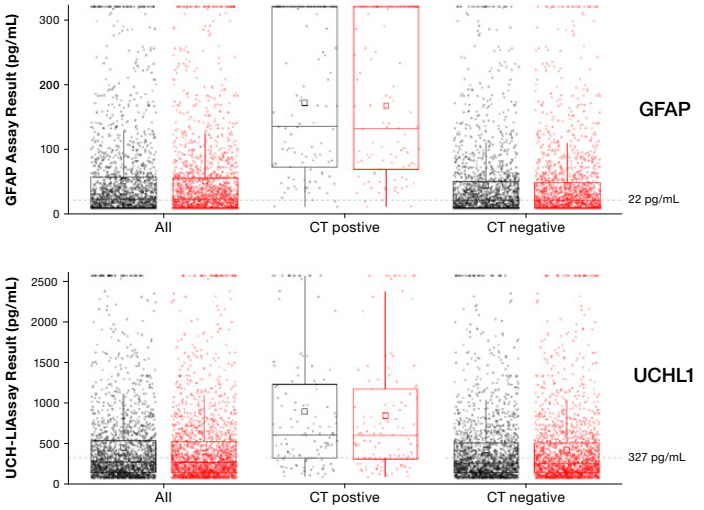

Figure 4. GFAP and UCH-L1 assay results in patients with mild traumatic brain injury and GCS score of 14-15 in the ALERT-TBI study.[12]

Among all 1959 patients, only 3 with a positive CT scan had a negative Banyan BTI™ test, which corresponded to a sensitivity of 0.976 with a negative predictive value of 0.996 (see **Table 1**).[12] Among patients with a GCS score of 14-15, the sensitivity of the Banyan BTI™ test was 0.973 with a negative predictive value of 0.995.[12]

Table 1. **Performance of the Banyan BTI™ biomarker test for predicting the absence of intracranial injury on head CT scan in patients with mild traumatic brain injury.[12]**

	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)
Banyan BTI™ test			
GCS score 9-15 (n =1959)	0.976 (0.931-0.995)	0.364 (0.342-0.387)	0.996 (0.987-0.999)
GCS score 14-15 (n=1920)	0.973 (0.924-0.994)	0.367 (0.345-0.390)	0.995 (0.987-0.999)

CI = confidence interval; **GCS** = Glasgow Coma Scale; **NPV** = negative predictive value.

Of the 3 patients whose intracranial injury was not detected by the Banyan BTI™ test, 2 had a tiny subdural haematoma that would be considered insignificant by the Canadian CT Head Rule, and 1 had a cavernous sinus malformation unrelated to the traumatic event.[12]

How do biomarkers compare with clinical decision rules?

A recently published study compared the performance of S100B and clinical decision rules for the prediction of intracranial injury on head CT scan after mild traumatic brain injury.[13] A total of 679 emergency department patients aged ≥16 years were assessed, of whom 5.7% had some type of intracranial haemorrhage on CT scan.[13] In this study, the Canadian CT Head Rule had a sensitivity of 0.795 for predicting the absence of intracranial injury (see **Table 2**).[13] While sensitivity of the New Orleans Criteria was higher than that of the Canadian CT Head Rule at 0.923, specificity was lower.[13] The S100B test had a sensitivity of 0.846 and the highest negative predictive value of all 3 tests.[13]

Table 2. **Performance of the S100B biomarker test vs clinical decision rules for predicting the absence of intracranial injury on head CT scan in patients with mild traumatic brain injury.[13]**

	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)
Canadian CT Head Rule	0.795 (0.632-0.898)	0.283 (0.248-0.318)	0.958 (0.929-0.986)
New Orleans Criteria	0.923 (0.839-1.00)	0.138 (0.111-0.164)	0.967 (0.930-1.00)
S100B test	0.846 (0.703-0.928)	0.336 (0.300-0.373)	0.973 (0.942-0.988)

CI = confidence interval; **NPV** = negative predictive value.

A study presented at the 2019 Annual Meeting of the Society for Academic Emergency Medicine compared the Banyan BTI™ test with the Canadian CT Head Rule for prediction of intracranial injury on head CT scan.[14] This secondary analysis of the ALERT-TBI study included 919 patients with a GCS score of 14-15 who met criteria for Canadian CT Head Rule determination.[14] GCS score was 15 in 94% of patients.[14] When significant CT findings in all patients were considered, the Canadian CT Head Rule was only 71.2% sensitive for predicting the absence of traumatic intracranial injury, with a negative predictive value of 97.0% (see **Table 3**).[14] The Banyan BTI™ test was 96.2% sensitive, with a negative predictive value of 99.4%.[14] When all study-defined CT findings in patients with a GCS score of 14-15 were considered, sensitivity was 70.1% for the Canadian Head CT Rule and 95.5% for the Banyan BTI™ test.[14] While the sensitivity of the Canadian CT Head Rule in this study was lower than that observed in other studies, the upper 95% confidence interval was in line with previous results.[14]

Table 3. **Performance of the Banyan BTI™ biomarker test vs the Canadian CT Head Rule for predicting the absence of intracranial injury on head CT scan in patients with mild traumatic brain injury.[14]**

	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)
Significant CT findings			
Canadian CT Head Rule	71.2% (56.9-82.9%)	55.1% (51.8%-58.5%)	97.0% (95.0-98.3%)
Banyan BTI™ test	96.2% (86.8%-99.5%)	38.8% (35.0-41.6%)	99.4% (97.9-99.9%)
All study-defined CT findings			
Canadian CT Head Rule	70.1% (57.7-80.7%)	55.5% (52.1-58.9%)	95.5% (93.8-97.5%)
Banyan BTI™ test	95.5% (87.5-99.1%)	38.8% (35.6-42.2%)	99.1% (97.4-99.8%)

CI = confidence interval; **NPV** = negative predictive value.

Cost-effectiveness of biomarker tests

A cost-effectiveness analysis of data from the ALERT-TBI study published in the *Journal of Neurotrauma* in 2019 found that for mild traumatic brain injury with a probability of intracranial bleed of 0.104, the Banyan BTI™ test is cost-effective at USD308.96 or less per test.[15] However, for moderate traumatic brain injury with a probability of 0.663, the test is only cost-effective at USD73.41 or less per test.[15]

Questions for clinical adoption of biomarker tests in the emergency department

- Will providers order the test (are there evidence-practice gaps)?
- Does testing impact emergency department operations and patient throughput (extra staff, device management, etc?)
- Are test results available in a timely fashion?
- How do results get into the emergency room?
- What do emergency physicians tell patients with a positive biomarker test and a normal head CT scan?
- Do patients like the test? Will they accept being told they don't need a head CT based on a blood test?
- Is the test cost effective?
  - How much will insurers reimburse for this test?
  - How many head CT scans are actually avoided?

Availability for clinical use

The Banyan BTI™ test has licensing agreements with companies including Abbott, for use of their point-of-care platform i-STAT and their laboratory platform ARCHITECT. The test is now available for clinical use in certain approved regions.

Conclusions

- The use of CT scans in patients with mild traumatic brain injury is still common but has relatively low yield
- Clinical decision rules may help reduce CT use but are variable in sensitivity and specificity
- Blood biomarkers may augment the clinician's ability to reduce CT use
- There is a need for a rapid test that is useful in the acute care setting
- A test that combines GFAP and UCH-L1 (Banyan BTI™) is the only blood test that has Food and Drug Administration approval for mild traumatic brain injury in the US.

Questions and answers

Do we need to look for every lesion after mild traumatic brain injury?

Professor Bazarian – we are now learning that so-called "clinically unimportant" lesions are surrogate markers for axonal injury, and can indicate poor outcome. Patients with these types of lesions on CT and magnetic resonance imaging are at higher risk of persistent post-concussive symptoms and persistent problems with cognition.

Do you see blood biomarker tests having a larger role in the emergency department in the next 5-10 years?

Professor Welch – a rapid test that can be performed point-of-care (such as i-STAT) will be very useful. The test would need to demonstrate a high negative predictive value and high sensitivity in clinical practice, and would need to be priced correctly. If these requirements are fulfilled, it is likely clinicians will adopt such a test in the next 4-5 years.

Is it possible to have biomarker tests sensitive enough to provide information within 2 hours of mild traumatic brain injury?

Professor Welch – it appears that levels of UCH-L1 rise rapidly after injury and then decrease rapidly, whereas GFAP levels rise more slowly but stay elevated for longer. This is one of the reasons for having both biomarkers in the Banyan BTI™ test. There is currently some limited data to suggest that the Banyan BTI™ test can be useful within 2 hours of injury, and this is being investigated further.

Do you have any data on combining clinical decision rules and biomarker tests?

Professor Bazarian – in the study we published comparing S100B with the Canadian CT Head Rule and New Orleans Criteria for predicting intracranial injury after mild traumatic brain injury, we found that incorporating clinical variables with S100B maximised prediction of intracranial injury.[12] However, we used selected decision rules, not all of them.

Professor Welch – in the ALERT-TBI study, combining the entire Canadian Head CT Rule with the Banyan BTI™ assay did not improve sensitivity of the biomarker test for predicting intracranial injury.[11]

Could a multi-modality system be used in the emergency department to determine who should receive a head CT scan?

Professor Bazarian – a multi-modality system, combining a biomarker test, cognitive test, and eye test, could be valuable for determining which patients are at risk of poor outcome, but not for determining which patients need a head CT scan.

How much time could be saved in the emergency department by introducing a biomarker test?

Professor Welch – the ALERT-TBI study data suggest that using the Banyan BTI™ test can reduce head CT scan use by over 30%,[11] so there is a lot of potential for improved workflow in the emergency department.

Professor Bazarian – the average wait time for a head CT scan in the US is approximately 3 hours. Patients who return a negative biomarker test can avoid this wait and reduce emergency department congestion.

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