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Objectives

- Defining the problem
- IOM 2011 Recommendations
- Nutrient Interventions for TBI
- Pharmaceutical vs. Nutriceutical
- Summary & Conclusions
Defining the problem: Incidence in the USA

Concussion Rates among US high school athletes

- Boys' Soccer: 51%
- Girls' Soccer: 2%
- Volleyball: 13%
- Boys' Basketball: 8%
- Girls' Basketball: 10%
- Wrestling: 4%
- Baseball: 3%
- Softball: 2%
- Football: 1%

DoD Numbers for TBI

- Penetrating: 6%
- Severe: 1%
- Moderate: 10%
- Mild: 82%

- TBIs account for approximately 2.5M emergency department visits, hospitalizations & deaths in the U.S./yr.
- Of these, approximately 87% (2,213,826) are treated in EDs, and released; 11% (283,630) are hospitalized and discharged, and 2% (52,844) die.
- DoD data from 2000 - 2017, indicate 379,519 service members were diagnosed with a TBI (dvbic.dcoe.mil).
- The numbers do not account for persons who did not receive medical care, or had outpatient visits.
Defining the problem: US Warfighter incidence


Source: [www.afhsc.mil/msmr](http://www.afhsc.mil/msmr) [2015 Vol 22 (2)].
## Classification of TBI by Injury Severity

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS 13-15</td>
<td>GCS 9-12</td>
<td>GCS &lt;9</td>
</tr>
<tr>
<td>Altered or LOC &lt; 30 min with normal CT and/or MRI</td>
<td>LOC &lt; 6 hours with abnormal CT and/or MRI</td>
<td>LOC &gt; 6 hours with abnormal CT and/or MRI</td>
</tr>
<tr>
<td>PTA &lt; 24 hrs</td>
<td>PTA &lt; 7 days</td>
<td>PTA ≥ 7 days</td>
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Source: dvbic.dcoe.mil
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IOM 2011 Recommendations: Reliance on Evidence-Based Reviews

Nutrition and Traumatic Brain Injury

Improving Acute and Subacute Health Outcomes in Military Personnel

Committee on Nutrition, Trauma, and the Brain Food and Nutrition Board
John Erdman, Maria Oriio, and Laura Pillsbury, Editors

INSTITUTE OF MEDICINE
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Summary of Recommendations
Recommendation 6-1:

- Evidence-based guidelines should include the provision of early (within 24 h after injury) nutrition (more than 50% of total energy expenditure and 1-1.5 g/kg **protein**) for the first 2 weeks after injury.
- Intervention will limit the intensity of the inflammation response due to TBI, and improve outcome.
Recommendation 5-1: DoD should conduct *dietary intake assessments* in different military settings (e.g. when eating in military dining facilities or when subsisting on a predominantly ration-based diet) both pre-deployment and during deployment to determine the nutritional status of Soldiers as a basis for recommending increases in intake of specific nutrients that may provide resilience to TBI.

Recommendation 5-2: Routine *dietary intake assessments* on TBI patients in medical treatment facilities should be undertaken as soon after hospitalization as possible to estimate pre-injury nutrition status, and to provide optimal nutritional intake throughout the various stages of treatment.
IOM (2011): Most Promising Research Recommendations

**Recommendation 6-2:** DoD should conduct human trials to determine appropriate levels of blood glucose (BG) following TBI to minimize morbidity & mortality. These should be clinical trials of early feeding using intense insulin therapy to maintain BG concentrations at less than 150-160 mg/dl versus current usual care of acute TBI in ICU settings for the first 2 weeks.

**Recommendation 6-3:** DoD should conduct clinical trials of the benefits of insulin therapy for care of acute TBI in inpatient settings with total parenteral nutrition (TPN) alone (or plus enteral feeding) versus enteral feeding alone. The goals for BG in the TPN group should be lower (e.g. < 120 mg/dl) than in the enteral group (e.g. < 150-160 mg/dl). Variables to measure include clinical outcomes and incidence of hypoglycemia.

**Recommendation 8-1:** DoD should continue to monitor the literature on the effects of nutrients, dietary supplements, and diets on TBI, particularly those that may emerge as potentially effective in the future.
Recommendation 9-1:

- DoD should monitor the COBRIT trial that is examining the effect of CDP-choline and genomic factors on cognition & functional measures in severe, moderate, and complicated mild TBI.
- If successful, DoD should conduct animal studies to define the optimal dose & duration of treatment following TBI, as well as to explore choline’s potential to promote resilience to TBI when used pre-injury.
Citicoline, an intermediate in the generation of phosphatidylcholine from choline, is found in eggs, beef liver, milk, yogurt and cruciferous veggies.

The COBRIT Trial (Citicoline Brain Injury Treatment) Trial was a phase III, double-blind study comparing citicoline vs placebo. 1,213 study participants with complicated mild, moderate, or severe TBI were randomized to receive 2,000 mg of citicoline or placebo daily for 90 days. This 4-yr trial (2007-2011) was terminated early due to futility. Among patients with TBI, the use of citicoline compared with placebo did not result in improvement in functional and cognitive status (1).

Sources:
**Recommendation 10-1:** Based on the evidence supporting the effects of creatine on brain function and behavior after TBI in children & adolescents, DoD should initiate studies in adults to assess the value of creatine for treating TBI patients.

**Update:** there have been no human trials to date and currently there are not any human trials in the process of evaluating the effects of creatine and concussion/mild TBI.
Recommendation 13-1:

- DoD should conduct animal studies that examine the effectiveness of pre-injury and post-injury oral administration of commercial purified n-3 fatty acids on TBI outcomes.

- As fish oil decreases inflammation within hours of continuous administration, human clinical trials that investigate fish oil as a treatment for TBI are recommended.

- Continuous enteral feeding with a formula containing fish oil should provide equivalent effects for this purpose in the early phase of severe TBI when enteral access becomes available.
Currently, there are 3 double-blind randomized control trials examining DHA supplementations and concussions.

- East Carolina University – 62 NCAA division 1 athletes supplemented with **2200 mg of DHA for 30 days** after onset of a concussion and measured the number of days to full, unrestricted participation and the number of days for balance and cognition to return to baseline. Study ended July 2017, with no preliminary data to share (1).

- University of Texas Southwestern Medical Center – kids ages 14-18 years supplemented with **2 g of DHA daily for 12 weeks** and measuring the time to return to competitive play and resolution of balance impairment. Study is expected to end June 2018 (2).

- University of Michigan – the OPTIMA-TBI Pilot study will enroll 50 adult subjects with mild TBI to receive **6 g DHA+EPA for one month** followed by 1.2 g DHA+EPA for two months. Capsules contain fish oil 1000 mg (contains 500 mg DHA & 100 mg EPA) or placebo. Study is expected to end July 2019 (3).

Sources:
1. [http://clinicaltrials.gov/show/NCT01814527](http://clinicaltrials.gov/show/NCT01814527)
2. [http://clinicaltrials.gov/show/NCT01903525](http://clinicaltrials.gov/show/NCT01903525)
Recommendation 16-1:

- DoD should conduct animal studies to determine the best practices for zinc administration after concussion/mild, moderate, and severe TBI, such as determining the therapeutic window for Zn administration, the length of treatment time for greatest efficacy, and the optimal level of Zn to improve outcomes.
- These trials should also evaluate concerns about Zn toxicity and overload.
- Results should be used to design human clinical trials using Zn as a treatment for TBI.
Zinc update

- Preclinical studies indicate that after an initial period of total parenteral nutrition, dietary Zn supplementation of 22 mg/day using Zn-gluconate significantly increases visceral protein mass in post-TBI patients, is associated with improved GCS’s, as well as mortality decrease from 26% to 12% (1).

- With the recommended upper limit of dietary Zn being 40 mg/day, further clinical studies will clearly define the optimal doses/timing to improve post-TBI deficits and prevent neurotoxicity and undesired effects to other organs (2).

Sources:
**IOM (2011): Other Research Recommendations**

**Recommendation 7-1**: DoD should consider a clinical trial with TBI patients using an array of antioxidants in combination (e.g. vitamins E and C, selenium, beta-carotene).

**Recommendation 11-1**: DoD should conduct animal studies to examine the specific effects of ketogenic diets, other diets (e.g. structured lipids, low-glycemic index carbohydrates, fructose), or precursors of ketones bodies that affect energetics and have potential value against TBI. Results from these studies should be used to design human studies with these various diets to determine if they improve outcome against severe TBI.

**Recommendation 14-1**: Based on positive outcomes in animal models of TBI with curcumin and resveratrol, DoD should consider conducting human trials. In addition, other flavonoids (e.g. isoflavones, flavanols, epicatechin, theanine) should be evaluated in preclinical models.
Curcumin (Turmeric) update

- Animal-based studies have shown that supplementation with curcumin before sustaining a concussion resulted in improved balance as well as transduction and monitoring of cellular energy compared with controls (1).

- Supplementation with curcumin after a concussion has been shown to improve membrane function, restoration of homeostasis, neuronal plasticity (2), synaptic plasticity, and neuronal signaling as well as significantly reduced neural inflammation by decreasing the levels of microglia and macrophages that aid in neuronal apoptosis (3).

- However, there have been no human trials to date and currently there are not any human trials in the process of evaluating the effects of curcumin and concussion.

Sources:
Resveratrol update

- The two animal studies evaluating resveratrol in regard to treatment of concussions report that supplementation with resveratrol after a concussion increased cell survival by suppressing autophagy and apoptosis that are mediated by a pathway induced by glutamate toxicity (1) as well as improve motor performance, visual spatial memory, and behavior (2).

- University of Texas Southwestern Medical Center - the REPAIR study evaluated the use of 500 mg resveratrol in 30 boxers who have sustained a mild to moderate concussion. The study was a double-blind, placebo-controlled RCT measuring cognitive performance with ImPACT testing and axonal injury via MRI. This study has been completed, but not published (3).

Sources:
IOM (2011): Other Research Recommendations

Recommendation 15-1:

- Conduct more animal studies to determine if vitamin D enhances the beneficial actions of progesterone in the treatment of TBI.
- If this synergistic effect is confirmed in animals, then studies in humans should be conducted to evaluate the extent to which vitamin D supplementation might improve the efficacy of progesterone treatment.
Vitamin D3 update

Clinical studies using vitamin D

- By itself, vitamin D has not shown great promise for TBI, though in combination with progesterone, there are some promising results.

- In rodent studies, the combination of progesterone and vitamin D showed significantly reduced neuronal loss & proliferation of reactive astrocytes after a TBI (1).

- In the two human-based Phase II studies, the combination of progesterone and vitamin D in patients with sTBI resulted in significantly improved Glasgow Outcome Scale scores, a better recovery rate (2), and a greater efficacy in reducing neuroinflammation (3).

- However, the ProTECT (Progesterone for the Treatment of TBI) and SyNAPse (Efficacy and Safety Study of Progesterone in Patients with Severe TBI) trials were large Phase III clinical trials that were SUSPENDED due to lack of efficacy.

Sources:
Recommendation 2-1:
Evidence-based nutrition guidelines specific to severe TBI should be updated.

- Guidelines should address unique nutritional concerns of severe TBI when different from generic critical illness nutrition guidelines (e.g. meeting energy needs and benefits of specific nutrients, food components, or diets).

- Current guidelines to manage mild and moderate TBI should include recommendations for nutritional interventions. The guidelines should be developed in collaboration with the various key stakeholders (e.g. American Dietetic Association, Department of Veterans Affairs, DoD).
Common mTBI/Postconcussive Symptoms

- Immediately post mild TBI, 80-100% describe one or more symptoms
- Most individuals return to baseline functioning within a year

• Headache
• Memory difficulty
• Fatigue
• Anxiety
• Light sensitivity
• Poor concentration
• Irritability
• Depression
• Dizziness
• Sound sensitivity

Research Gaps:
• The interventions should be selected to address symptomology;
• Combination nutrients may be more effective than single-nutrient interventions.

Source: Ferguson et al. 1999, Carroll et al. 2004; Levin et al. 1987
Objectives

- Defining the problem
- IOM 2011 Recommendations
- Nutrient Interventions for TBI
- Medicinal Food vs. Nutriceutical
Why no pharma?

Number of clinical trials initiated over the past 30 years, differentiated by studies of neuroprotective agents (n=24) vs. therapeutic strategies (n=13)
Medicinal Food vs. Nutriceutical

- **Variability of active ingredients**: only 1/3 of vitamin D supplements tested met the US Pharmacopeial Convention standards requiring pills to contain between 90-100% of the active ingredient. Active ingredients ranged from 9% to 146% (1).

- **Inconsistent recommendations**: the benefits of n-3 intake have resulted in intake recommendations ranging from 250 to 500 mg/d from various professional organizations, including the AHA and the International Society for the Study of Fatty Acids & Lipids (2). Current estimates of dietary DHA and EPA intake for Americans are 90–120 mg/d for females and males aged ≥ 20 y, which is less than 50% RDA.

Sources:
Summary of Nutrition for TBI, based on site of injury

- **Parietal Lobe**
  - Nutrition: currently unknown.

- **Occipital Lobes**
  - Nutrition: currently unknown.

- **Temporal Lobes**
  - Nutrition: increase protein intake, B-6, magnesium, folate, zinc, copper, DHA, vitamin D3, vitamin C, bifidobacterium.

- **Anterior Cingulate Gyrus**
  - Nutrition: increase B-6, B-12, vitamin D3, magnesium, DHA, inositol.

- **Prefrontal Cortex**
  - Nutrition: avoid gluten, increase protein intake, B-6, magnesium, folate, zinc, copper, DHA, vitamin C, probiotics.

- **Limbic System**
  - Nutrition: B-6, magnesium, folate, zinc, vitamin C, DHA.

Conclusions

- The chronic neurological deficits of TBI are complex and clinical treatments are limited.
- Several clinical trials have failed because heterogeneous TBI patients with a wide range of injury severities were grouped together in the same studies.
- Ongoing failure of clinical trials for TBI treatment has questioned the direction of therapy.
- Combination therapies of dietary supplementation and pharmaceutical agents are likely to yield the best results.
mTBI is a significant source of morbidity in deployed U.S. service members. No in-field ration component exists to enhance recovery from cognitive, sensory or motor deficits following exposure to mTBI.

• **Hypothesis**: Pre-injury and/or post-injury dietary supplementation will improve resiliency to concussion/mild TBI, and post-concussive syndrome.