ICU Management Protocols

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Disclosures

- Grants / Research
  - NIH, DoD
  - UCB Pharma

- Consultant
  - Codman / J&J
Objectives

- Discuss TBI specific management protocols
- Review general critical care protocols
Management of Severe TBI

Part 1: Guidelines for the Pre-hospital Management of Severe Traumatic Brain Injury
Part 2: Guidelines for the Management of Severe Traumatic Brain Injury

- Initially published in 1995, 2\textsuperscript{nd} 2000, 3\textsuperscript{rd} 2007
- A Joint Project of
  - The Brain Trauma Foundation
  - American Association of Neurological Surgeons (AANS)
  - Congress of Neurological Surgeons (CNS)
  - AANS/CNS Joint Section on Neurotrauma & Critical Care
  - www.braintrauma.org

\textit{TBI Guidelines; J Neurotrauma May 2007}
Topics

- Blood Pressure & Oxygenation
- ICP Monitoring Indications
- ICP Monitoring Technology
- ICP Thresholds
- CPP Thresholds
- Brain Oxygen Monitoring & Thresholds*
- Hyperosmolar Therapy*

- Anesthetics, Analgesics, and Sedatives*
- Hyperventilation
- Prophylactic Hypothermia*
- Steroids
- Antiseizure Prophylaxis
- Infection Prophylaxis*
- DVT Prophylaxis*
- Nutrition

* New in 2007

TBI Guidelines; J Neurotrauma May 2007
Anesthetics, Analgesics, & Sedatives**

- **Level II:**
  Prophylactic administration of barbiturates to induce burst suppression EEG is not recommended.

High dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy.

Propofol is recommended for the control of ICP, but not for improvement in mortality or 6 month outcome. High dose propofol can produce significant morbidity (PRIS).

*TBI Guidelines; J Neurotrauma May 2007*
Pearls: Anesthetics

- Short acting agents become long acting with time
  - Narcotics: morphine, fentanyl
  - Sedatives: diazepam, midazolam, propofol* (PRIS)
    - remember effect on BP & CPP
  - Paralytic agents: vecuronium, cistacuronium
    - use sparingly, document time given, Train of 4

- Propofol Infusion Syndrome
  - Greatest risk in children and young adults
  - Associated with high doses & long-term use
    - >4 mg/kg/hr / >67 µg/kg/min; >48 hours
  - Characterized by severe metabolic acidosis, rhabdomyolysis, hyperkalemia, lipemia, renal failure, hepatomegaly, and cardiovascular collapse.
    - Monitor triglycerides
Pearls: Barbiturates

- Do not use prophylactically
  - Hypotension, hypoxia & secondary ischemia
  - No benefit on GOS at 1 year

- Refractory ICP elevations
  - Lower mortality rates, better outcome if respond
  - Trial test dose for response

- Pentobarbital used most often:
  - Loading dose = 10 mg/kg over 30 minutes
  - Maintenance = 1 mg/kg/hr infusion
  - Need an EEG to monitor (issues in brain death)
  - Contraindicated in hypotensive patients
Newer Concepts

- Delirium in ICU
  - Hypoactive versus hyperactive
  - Avoid benzodiazepines

- Dexmedetomidine
  - 2-adrenergic agonist
  - Compared to midazolam
    - Similar sedation effects
    - Shortened time to extubation → decreased costs
    - Associated with less delirium, tachycardia & hypertension; more bradycardia
  - May have anti-inflammatory effects
Hyperosmolar Therapy

- **Level II:**
  Mannitol is effective for control of raised intracranial pressure (ICP) at doses of 0.25g/kg to 1g/kg body weight. However, arterial hypotension should be avoided.

- **Level III:**
  Restrict mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes.

Note: Data on hypertonic saline still limited

*TBI Guidelines; J Neurotrauma May 2007*
Osmotic Therapy in Neurosciences

- Reduction of brain water content is thought to be an effective means of controlling ICP
  - Led to dehydrating patients with fluid restriction / diuretics
  - Osmotic therapy became the cornerstone of management in early 1960s, use is controversial & poorly understood.

- An ideal osmotic agent does not cross the cell membrane or blood-brain barrier (BBB)
  - Thus promotes movement of water from intracellular to extracellular compartment

- After neurological injury the BBB is disrupted
  - This impacts on effectiveness of any osmotic agent
Mannitol for ICP

Effects:

- Plasma expander - ↓ hematocrit, ↑ blood flow, ↑ cerebral oxygen delivery
- Osmotic effect delayed for 15 to 30 minutes while gradients established between plasma and cells
  - “opening of BBB” → mannitol accumulation → reversed osmotic shift → ↑ brain osmolality → exacerbates ICP by ↑ brain edema = Rebound ICP
- Never subjected to randomized, PCT in TBI
- One study (n=28) looked at a dose response curve
  - 85 doses of 50 gm; 50 doses of 100 gm
  - Dose dependent changes; higher dose more durable
Hypertonic Saline

- Establishes osmotic gradient
- Volume expander w/ minimal renal effects, thus maintains MAP
- Less tendency to cross BBB than mannitol, thus less rebound cerebral edema
- Vascular endothelial effects may reverse vasospasm & related hypoperfusion
- Modulation of inflammatory response
  - ↓ WBC adherence, migration & prostaglandin production
- NMDA receptor effects
HTS in TBI

- Limited studies to date with small numbers
- Resuscitation fluid
  - 7.5% HTS with or without dextran
  - Increased survival in TBI patients
- ICP control
  - Early or as rescue therapy
  - Variable concentrations (1.7% - 29.2%)
  - Bolus therapy or continuous infusions
  - Goal: Na\(^+\) levels of 145 – 160
  - Results generally show a ↓ in ICP as Na\(^+\) rises
- Pearl:
  - pick a method, work w/ your pharmacist, stay consistent
Mannitol vs HTS (7.5%)

- N=12; severe TBI with refractory ICP treated with
  - Mannitol (25%, 0.75 g/kg) or HTS (7.5%, 250 ml)
- Results: 42 episodes treated: mannitol (n=28); HTS (n=14)

<table>
<thead>
<tr>
<th></th>
<th>Mannitol</th>
<th>HTS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29 ± 8</td>
<td>27 ± 8</td>
<td>0.40</td>
</tr>
<tr>
<td>30 min</td>
<td>21 ± 8</td>
<td>17 ± 7</td>
<td>0.15</td>
</tr>
<tr>
<td>60 min</td>
<td>23 ± 12</td>
<td>15 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>120 min</td>
<td>24 ± 9</td>
<td>15 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CPP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>60 ± 17</td>
<td>63 ± 15</td>
<td>0.56</td>
</tr>
<tr>
<td>30 min</td>
<td>71 ± 16</td>
<td>78 ± 18</td>
<td>0.32</td>
</tr>
<tr>
<td>60 min</td>
<td>67 ± 20</td>
<td>76 ± 16</td>
<td>0.05</td>
</tr>
<tr>
<td>120 min</td>
<td>65 ± 19</td>
<td>76 ± 17</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Oddo, et al. JNNP 2009; Mar 16 epub
Mannitol vs HTS effect on PbtO$_2$

Oddo, et al. JNNP 2009; Mar 16 epub
Mannitol vs HTS (23.4%)

- Retrospective; severe TBI w/ mean ISS 28 ± 11
  - n = 22; 210 doses of mannitol (n=102) or HTS (n = 210)

- Data assessed for 60 minutes after infusion
  - ICP; ICP reduction after treatment; CPP
  - Serum sodium, osmolality, & dose response

- Results
  - HTS patients had significantly higher ICP at start of therapy (31 vs. 28 mm Hg). CPP similar.
  - Mean ICP reduction was greater with HTS (9.3 vs. 6.4 mm Hg; p = 0.0028)
  - More responded to HTS (93% vs. 74%; p = 0.0002).
  - No difference in the duration of ICP reduction
  - No adverse events identified with either

UC Continuous Infusions HTS Protocol

- Protocol designed using 3% NaCl for ICP control
  - Goal serum Na\(^+\) = 145 – 155 mEg/L
  - Baseline based bolus then continuous effusion adjusted every 6 hours

- Retrospective study for safety & efficacy
  - N = 41 pts (34 sTBI, 3 ICH, 2 SAH, 1 CVA, 1 tumor)
  - 80% males; Median age = 38 (Range 15 – 68)
  - Median GCS = 7

- Median # of rescue interventions for ↑ ICP was 2.0
  - Mannitol, hyperventilation (pCO\(^2\) < 35), surgery

- No adverse events were noted

Sangha & Shutter. Am Coll Clin Pharm Research Forum 4/06
TUH 3% Saline Protocol for ICP

- Four levels of therapy
  1. Hyponatremia goal = 135 –145
  2. At risk for ICP goal = 140 –150
  3. ICP goal = 145 –155
  4. Refractory ICP goal = 150 –160

- Start with 3% saline at 30 cc/hr via CVL
  - Increase in increments of 5 –10 ml / hr to goal
  - There is a 2% option if no central access

- Lab assessments
  - Follow Na & S osm
  - Levels every 6 hours while Na > 130 or < 150
  - Increase to every 4 hours when Na <130 or >150
PbtO₂ Monitoring

- **Location**
  - Placed in white matter (~35mm)
  - Normal tissue or pericontusional?
- **Measures O₂ partial pressure (mmHg) in interstitial space**
- **Values:**
  - Normal > 20 mmHg
  - Ischemia: 8 - 12 mmHg
  - Critical: 5 - 8 mmHg
What does PbtO$_2$ represent?

- Prospective observation study; n = 14 sTBI
  - PbtO$_2$ & CBF monitoring with FiO$_2$, MAP, CO$_2$ challenges
  - Measured: PaO$_2$, CaO$_2$, PVO$_2$, CVO$_2$, AVDO$_2$, locCMRO$_2$
- Best association: CBF x (PaO$_2$-PvO$_2$)
  - Thus may represent diffusion of dissolved plasma O$_2$ across BBB and reflect O$_2$ accumulation in brain

Is PbtO₂ Important?

- Prospective observational cohort; sTBI; n = 123
  - Simultaneous ICP, CPP, PbtO₂ management = 70
  - ICP / CPP management = 53
- Outcome @ 3 months:

  *p<0.05

  **p=0.01

PbtO2 Research

- **BOOST II**
  - Randomized controlled trial of PbtO2 vs ICP driven management to assess safety & feasibility
  - Sites: UTSW, UMiami, UWash, UPenn
  - New Sites: Temple, UCinn, UPitt, Duke, OSU, Jefferson
  - > 20 patients enrolled

- **BOOST III**
  - Multicenter, randomized controlled trial of PbtO2 vs ICP based care in TBI phase III trial planning grant
  - Lead Site: UPenn, PI: Le Roux
Fever in the NSICU

- Definition: T \( \geq 101.5^\circ F \) or \( \geq 38.5^\circ C \).
  - “central fevers” is a diagnosis of exclusion

- Natural response to inflammation and infection

- Injured brain cells have reduced tolerance to heat.
  - Fever / ↑ temperature associated with worse outcomes

### Causes of Fever in NSICU

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Non-infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infections</td>
<td>Deep venous thrombosis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Vasospasm</td>
</tr>
<tr>
<td>Line infections</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Septicemia</td>
<td>Central etiology</td>
</tr>
<tr>
<td>Meningitis / ventriculitis</td>
<td></td>
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<tr>
<td>Wound infection</td>
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</tr>
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</table>

UC Neuroscience Institute
Temperature Control

- Comparative cohort study; n = 42
  - Normothermia (36 – 36.5°C) by endovascular device
  - Historical sTBI controls w/ fever & conventional therapy
  - End points: Fever (rectal temp > 38°C); ICP in first 72 hrs

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
<th>Historical controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever burden (%)</td>
<td>1.6</td>
<td>10.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean ICP (mm Hg)</td>
<td>12.74</td>
<td>16.37</td>
<td>0.027</td>
</tr>
<tr>
<td>% time ICP &gt; 25</td>
<td>2.3</td>
<td>9.4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Puccio AM, et al. Neurocrit Care 2009;11:82-87

- Role of temperature control for treatment of refractory ICP elevations?
Management of Refractory ICP

- Decompression
  - Acute worsening never occurs at convenient times

- Barbiturate coma
  - Works in some patients, doesn’t in others
  - Associated with risks – use sparingly

- Hypothermia
  - May be very effective, more data is needed

- Look for underlying causes
  - Sinus thrombosis
  - Vasospasm
  - Seizures
  - Fever
Antiseizure Prophylaxis

- Level II:
  Prophylactic use of phenytoin or valproate is not recommended for preventing late posttraumatic seizures. Anticonvulsants are indicated to decrease the incidence of early PTS (within 7 days of first drug administration). However, early PTS is not associated with worse outcomes.

*TBI Guidelines; J Neurotrauma May 2007*
Incidence of EPTSz

- Peak incidence in initial 48 – 72 hrs
  - high risk period up to 1 week
- Incidence using continuous EEG in TBI patients (all with therapeutic anticonvulsant levels)
  1. 94 patients with GCS ≤ 12; 21 (24%) had seizures.
     - Non-convulsive in 57%
  2. 51 TBI patients; 9 (18%) had seizures.
     - All were non-convulsive.
  3. 46 severe TBI patients; 8 (17%) had seizures.
     - All were non-convulsive

Do Seizures Matter?

- Prospective monitoring; retrospective data analysis.
  - 20 mod - severe TBI (GCS = 3–13)
  - Continuous EEG & microdialysis for 7 days after injury.
  - Seizures occurred in 10 (SE in 7)
  - Patients were compared with a matched cohort of TBI patients without seizures.

- Results: Patients with PTSz had:
  - Episodic increases in ICP (22 vsv 13 mm Hg; $p < .001$) and L/P ratio (49 vs. 24; $p < .001$)
  - Higher mean ICP (18 vs. 12 mm Hg; $p < .001$) and L/P ratios (39 vs. 27; $p < .001$)
  - ICP & L/P ratio elevations for > 5 days ($p < 0.02$)

TBI - with seizures

TBI - no seizures
Do Seizures Matter?

- Prospective monitoring; retrospective data analysis.
  - 10 mod - severe TBI (GCS = 3–13)
  - Continuous EEG & MD for 7 days after injury.
  - Seizures occurred in 5 (SE in 7)
  - MRI on day 7 & at 6 months

- Results in pts with PTSz:
  - ICP elevations & MD markers of cellular distress
  - 1st ADC & GRE images: no primary hippocampal injury
  - MRI @ 6 months:
    - global atrophy = 7.8 ± 4.4%
    - hippocampal atrophy = 32% vs 10% (p<0.001)

LEV vs PTN for Seizure Prophylaxis

- Study was an IIR project funded by UCB Pharma
- LAS
  - Research support – DOD, NIH
  - Speaker bureau/consultant – Integra, BTF
- JS
  - Research support – NIH, AAN, Davis Phinney Foundation / Sunflower Revolution, UCB Pharma, UC Research Council
  - Speaker bureau/consultant - Abbott, AAN, Pfizer, UCB Pharma

Prospective, Randomized, Single-Blinded Comparative Trial of Intravenous Levetiracetam Versus Phenytoin for Seizure Prophylaxis

Jerzy P. Szaflarski · Kiranpal S. Sangha · Christopher J. Lindsell · Lori A. Shutter
Methods: General Design

- **Investigator initiated trial**
  - Original design: enroll 104 patients (52 SAH; 52 sTBI)
  - Recruitment and funding issues prompted a change: focus on sTBI; stop enrollment at 52.

- **Prospective, randomized, single-blinded trial comparing IV LEV to PHT**
  - 2:1 ratio; NCT00618436
  - Enrollment within 24 hours after admission

- **Blinding**
  - Electrophysiologist was blinded to group assignment & diagnosis; reported EEG results to PI daily
  - Managing physicians were partially blinded
  - Research coordinators were blinded to treatment group
Results

- 52 patients randomized (LEV=34; PHT=18)
  - 89 % with TBI
  - Median duration of AED use = 7 days
  - Hospital LOS: PHT = 15 days; LEV = 14 days
  - No difference in neurosurgical interventions

<table>
<thead>
<tr>
<th>Demographics (All patients)</th>
<th>PHT (n = 18)</th>
<th>LEV (n = 34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35 (18-80)</td>
<td>44 (17-75)</td>
<td>0.805</td>
</tr>
<tr>
<td>Male</td>
<td>13 (72%)</td>
<td>26 (77%)</td>
<td>0.747</td>
</tr>
<tr>
<td>Female</td>
<td>5 (28%)</td>
<td>8 (23%)</td>
<td></td>
</tr>
<tr>
<td>TBI</td>
<td>16 (89%)</td>
<td>30 (88%)</td>
<td>1.000</td>
</tr>
<tr>
<td>SAH</td>
<td>2 (11%)</td>
<td>4 (12%)</td>
<td></td>
</tr>
<tr>
<td>GCS in ED</td>
<td>4</td>
<td>5</td>
<td>0.419</td>
</tr>
<tr>
<td>ISS</td>
<td>27</td>
<td>28</td>
<td>0.953</td>
</tr>
</tbody>
</table>
Results

- **Mortality**
  - Overall = 35%: PHT 4/18 vs. LEV 14/34 ($p = 0.227$)
  - Early death = 12%: PHT 2/18 vs. LEV 4/34 ($p = 1.00$)
  - Early withdrawal of care (< 30 days after injury):
    PHT 0/18 vs. LEV 5/34 ($p = 0.150$)
  - Late withdrawal of care (> 30 days after injury):
    PHT 2/18 vs. LEV 5/34 ($p = 1.00$)
  - Withdrawal of care was based on quality of life issues

- **Seizure occurrence: no difference**
  - Overall seizure incidence = 8/52 (15%; all TBI patients)
  - During cEEG: PHT 3/18 vs. LEV 5/34 ($p = 1.0$); all NCS
  - 6 months: PHT 0/14 vs. LEV 1/20 ($p = 1.0$)
<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>PHT (n = 18)</th>
<th>LEV (n = 34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>10 (56%)</td>
<td>18 (53%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Increased ICP</td>
<td>8 (44%)</td>
<td>13 (38%)</td>
<td>0.769</td>
</tr>
<tr>
<td>Stroke / expanding bleed</td>
<td>3 (17%)</td>
<td>7 (21%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Gen Neuro worsening</strong></td>
<td><strong>9 (50%)</strong></td>
<td><strong>6 (18%)</strong></td>
<td><strong>0.024</strong></td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (11%)</td>
<td>7 (21%)</td>
<td>0.470</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>6 (33%)</td>
<td>14 (41%)</td>
<td>0.766</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (22%)</td>
<td>17 (50%)</td>
<td>0.076</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (17%)</td>
<td>5 (15%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Liver test abnormalities</td>
<td>0 (0%)</td>
<td>2 (6%)</td>
<td>0.538</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (6%)</td>
<td>2 (6%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>GI issues</strong></td>
<td><strong>4 (22%)</strong></td>
<td><strong>1 (3%)</strong></td>
<td><strong>0.043</strong></td>
</tr>
<tr>
<td>Early death</td>
<td>2 (11%)</td>
<td>4 (12%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Care withdrawn early (&lt; 1 mo)</td>
<td>0 (0%)</td>
<td>5 (15%)</td>
<td>0.150</td>
</tr>
<tr>
<td>Care withdrawn late (&gt; 1 mo)</td>
<td>2 (11%)</td>
<td>5 (15%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
Results: Outcomes

- All patients: no differences between groups
- Survivors: LEV group had better outcomes
  – Persisted when controlled for admission GCS

<table>
<thead>
<tr>
<th>Survivors</th>
<th>PHT (n = 14)</th>
<th>LEV (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS, discharge</td>
<td>10 (3-15)</td>
<td>11 (6-15)</td>
<td>0.396</td>
</tr>
<tr>
<td>GOSE, discharge</td>
<td>3 (2-3)</td>
<td>3 (2-4)</td>
<td>0.545</td>
</tr>
<tr>
<td>DRS, discharge</td>
<td>22 (7-29)</td>
<td>22 (7-26)</td>
<td>0.436</td>
</tr>
<tr>
<td>GOSE, 3 mos</td>
<td>3 (2-5)</td>
<td>4 (2-7)</td>
<td>0.107</td>
</tr>
<tr>
<td>DRS, 3 mos</td>
<td>11 (5-23)</td>
<td>5 (0-23)</td>
<td>0.006</td>
</tr>
<tr>
<td>GOSE, 6 mos</td>
<td>3 (3-7)</td>
<td>5 (3-8)</td>
<td>0.016</td>
</tr>
<tr>
<td>DRS, 6 mos</td>
<td>6 (0-20)</td>
<td>3 (0-17)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Conclusion

- LEV group had fewer episodes of
  - General worsening of neurological status
  - GI events
- Efficacy of seizure prevention was similar
- Outcome measures favored use of LEV
  - significantly improved GOSE and DRS at 3 & 6 months
- LEV appears to be an alternative to PHT for seizure prophylaxis in the ICU setting
AED Pearls

- Phenytoin is commonly used
  - Impaired liver or renal function & low albumin can impact on levels
  - Cognitive effects are detrimental

- Other agents are available
  - LEV: activating AED, may have fewer side effects than PHT

- Consider selection of medication based on side effect profile
  - Agitation: avoid LEV
  - Sedation: avoid PHT
Lung Injury

- Acute Lung Injury / Adult Respiratory Distress Syndrome
  - ALI: PaO$_2$/FiO$_2$ < 300; Mortality = 39%
  - ARDS: PaO$_2$/FiO$_2$ < 200; Mortality = 40 – 50%

- Incidence is 20 – 31% in TBI
  - Independent predictor of mortality, worse outcomes

- Etiology
  - Sepsis/SIRS
  - Inhalation injury
  - Pulmonary Trauma
  - Drug toxicity
  - Aspiration
  - Pancreatitis
  - *Transfusions (TRALI)

- Contributing factors: vasopressors, high Vt
Transfusion Related ALI (TRALI)

- **Definition (2003)**
  - New occurrence of acute onset ALI (hypoxemia, CXR w/ bilateral infiltrates, no evidence of left atrial hypertension) emerging during or within 6 hours of end of transfusion
  - No alternative ALI risk factors

- **Incidence rates per RBC unit = 1:5,000**

- **The number of TRALI-related fatalities reported has steadily risen from 1995**
  - Now the most frequently reported cause of transfusion-related death

Patient transfused with 1 U PRBC @ 2400
TRALI

Developed sudden increased O\textsuperscript{2} requirements
Pearls: Transfusions after TBI

- The concept that maintaining a HCT > 30% after TBI has little empirical supportive evidence.
- There is clear evidence that blood transfusions have an adverse impact on outcome.

Therefore present recommendation should be:
- Do not transfuse if Hgb > 9 g/dL
- Do transfuse if Hgb ≤ 7 g/dL
- For Hgb between 7 – 9 g/dL transfusion triggers should be based on physiological parameters
  - Volume status, hemodynamic state, EKG, cardiovascular disease, PbtO$_2$
Nutrition in TBI

- Retrospective review; prospectively collected multi-center data (n = 797)
  - Assessed calories fed per day. Controlled for age, GCS, hypotension, pupillary status, CT scan findings
  - Delayed nutrition increased mortality.
    - Not fed within 5 days = 2-fold & 7 days = 4-fold increase.
  - Amount of nutrition in first 5 days was related to death
    - Every 10 kcal/kg decrease in caloric intake associated with a 30 – 40% increase in mortality


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Glucose Control

- Intensive glucose control in severe TBI (n=63)
  - Reduced mean & max ICP (p=0.003; <0.0001); fewer seizures (p<0.0001); similar mortality, higher Karnofsky scores at 6 & 12 mos (Van den Berghe et al. Neuro 2005;64(8):1348-53)

- Loose vs tight control in severe TBI (n=47)
  - Tight control decreased cerebral glucose by 70% vs 33%.

- Loose vs tight control in TBI (n= 228; GCS 3 – 15)
  - 2 time periods: 90-144 mg/dl compared to 63-117 mg/dl
  - Lower glucose ↑ ICP in 1st wk (P < 0.001) & ↑ mortality in 1st 2 wks (25% vs 19%; NS) (Meier R, et al. Crit Care 2008;12:R98)

Pearl: Goal glucose = 110 – 150 mg/dl
NSICU protocol

- Goal: maintain glucose levels 110 –150
- Management guided by expected LOS in NSICU
  - If > 3 days, use an insulin drip
  - If < 3 days, start a basal bolus correction
- BBC issues
  - If on tube feeds: accuchecks q 6 hours; use NPH and regular insulin only
  - If taking po: accuchecks q ac & hs; may use lantus and novolog insulin
- HgbA1c
  - Measure in all patients with high daily insulin needs unless known diabetic
Reversal of Anticoagulation

- Discontinue warfarin; Target INR < 1.5
  - It may be difficult to achieve with FFP & vit K
  - FFP 15 – 20 mL / kg
  - Vitamin K, 10 mg IV. May repeat Q 8 – 12 hours for 1-2 days based on INR
  - Prothrombin Complex Concentrate (if available)
  - Recombinant Factor VIIa (selected patients?)

- If PTT > 50
  - Protamine 50 mg IV

- Platelet dysfunction
  - Thrombelastography testing
TEG

- Thrombelastography technology analyzes functional activities of blood
  - Coagulation & fibrinolytic factors, activators, inhibitors
  - TEG®; Haemonetics Corp

- Components
  - R value = time until first evidence of a clot
  - K value = time from the end of R until the clot reaches 20mm (speed of clot formation)
  - Angle = tangent of curve made as the K is reached and offers similar information to K
  - MA (maximum amplitude) = reflection of clot strength
## TEG

<table>
<thead>
<tr>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>4 – 8 min</td>
</tr>
<tr>
<td>k</td>
<td>0 – 4 min</td>
</tr>
<tr>
<td>angle</td>
<td>47 – 74 deg</td>
</tr>
<tr>
<td>MA</td>
<td>54 – 72 mm</td>
</tr>
</tbody>
</table>

### Normal
- R, k, MA: Angle = Normal

### Anticoagulants/Hemophilia
- Factor Deficiency
  - R, k: Prolonged
  - MA: Angle = Decreased

### Platelet Blockers
- Thrombocytopenia
  - MA = Decreased

### Fibrinolysis (UK, SK, or t-PA)
- Presence of t-PA
  - MA = Continuous decrease
  - LY30 > 7.5%; WBCLI30 < 97.5%
  - LY60 > 15.0%; WBCLI60 > 85%

### Hypercoagulation
- R, k: Decreased
  - MA: Angle = Increased

### D.I.C
- Stage 1
  - Hypercoagulable state with secondary fibrinolysis
- Stage 2
  - Hypocoagulable state
DVT Prophylaxis**

- Level III:
  Graduated compression stockings or intermittent pneumatic compression (IPC) stockings are recommended, unless lower extremity injuries prevent their use. Continue use until patients are ambulatory.

  LMWH or low dose unfractionated heparin should be used in combination with mechanical prophylaxis unless the patient has CT evidence of ICH.

  There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for DVT.
DVT Prophylaxis after TBI

- Retrospective study, 64 patients w/ severe TBI
  - Two groups:
    - Early: within 72 hours of admission (n=47)
    - Late: after 3rd day of hospitalization (n=17)
  - CTs to assess for intracranial bleeding
  - No ↑ in intracranial bleeding; Same VTE rates

- Prospective, observational study, 150 patients w/ hemorrhagic TBI lesions treated w/ enoxaparin @ 24 hrs
  - CTs at admission, 24 hours later and prn
  - 23% had worsening on CT; 19% worsened before, 4% worsened after enoxaparin (no deaths)
  - DVT identified in 2 of 106 patients.

NSICU DVT Prophylaxis

- **Timing**
  - Start 24 hr after admission or neurosurgical procedure
  - Exclusions:
    - Worsening contusions, unsecured AVM, planned surgical intervention within 24 hours, uncorrected coagulopathy, spinal surgery (wait until 72 hrs post-op)
    - Hold for 4 hrs prior to removal of ICP monitor, Licox monitor or lumbar drain

- **Method:**
  - Mechanical prophylaxis on everyone
  - SQ heparin for cranial patients; LMWH for spinal and trauma patients
  - Empiric IVC filters in: hypercoagulable states or bleeding disorders that limit use of heparin or LMWH
NSICU DVT Prophylaxis

- **Surveillance:**
  - Duplex study of lower extremities on 3rd day after admission, then weekly OR anytime if clinical symptoms or suspicion are present

- **Treatment**
  - Below knee DVT: surveillance every 3 days to monitor propagation. If stable on 2 repeats, return to weekly
  - Above knee / propagating DVT or PE: therapeutic anticoagulation vs IVC filter

- **Duration:**
  - May be discontinued once ambulating >/= 150’
GI Bleeding

- Low incidence
- Prophylactic Antacids or H2 blockers
  - Decreased gastric acidity may reduce gastric erosions and aspiration acidic injury
  - Changes in gastric acidity may remove a barrier to nosocomial infection
  - Some older studies report that antacids are equal to H2 blockers in prevention
  - Sucralfate may be beneficial, but reduces absorption of medications
- Protocol for NSICU
  - Use is based on 1 major or 2 minor indications
Stress Ulcer Prophylaxis

- **ALL** patients **DO NOT** require SUP.
  - Who does? Those with 1 ‘Major’ or 2 ‘Minor’ indications

- **Major Indications**
  - Mechanically ventilated (predict > 48 hours)
  - Coagulopathy:
    - Plts < 50k/mm³; INR > 1.5; PTT > 2 x control

- **Minor Indications**:
  - Severe TBI; acute SCI; septic shock or pressors > 8 hrs; occult bleeding x 6d; MOF (>3); hx of GIB in last year; high dose steroids; major surgery; acute hepatic failure; acute renal insufficiency

- **Treatment**:
  - histamine-2 receptor antagonist (H2RA) (i.e. famotidine)
  - proton pump inhibitor (PPI)*
Cortical Spreading Depression

- Waves of tissue depolarization that mediate progressive development of cortical infarction
  - Have been seen in both animal models and patients with acute brain injury

- Subdural ECoG strip
  - Often used with other probes
    - PbtO2, CBF, MD, Surface vs depth EEG electrodes

- Possible sign of progressive metabolic failure leading to tissue death
Cortical Spreading Depression

- **Purpose / Hypothesis**
  - To determine if the occurrence or severity of CSD is related to worse neurological recovery after TBI
  - Should CSD monitoring be used as a treatment target

- **Outcomes**
  - Primary: Incidence of CSD; GOSE @ 6 mos
  - Secondary: Post-traumatic epilepsy questionnaire @ 6, 12, & 24 months after injury

- **Details**
  - Goal enrollment = 180
  - Start: 1/09
  - Projected primary completion: 9/12
  - Sites: UC, MCV, UPitt, UMiami, King’s College
Results

- **Enrollment**
  - 6 patients excluded due to poor quality of ECoG
  - 103 patients monitored for 72 hr (quartiles: 40,102)
  - surgery at 10 hr post-trauma (quartiles: 5, 26)

- **Depolarization Incidence**
  - Depolarizations observed in 58/103 monitored (56%)
  - total of 1,328 depolarizations (average: 23 / patient)
TBI case example

Licox $P_{br}O_2 > 20$ mm Hg throughout
ICP < 20 mm Hg throughout
GCS: 7T → 10T
Results

No differences in recording durations (p>0.50), timing of surgery (p>0.50), or prognostic scores (p=0.34).

Significant difference in outcome between depolarization categories
Conclusions

- Spreading depolarizations are robustly associated with worse outcomes
  - independent of baseline outcome predictors including age, GCS, and pupillary reactivity.
- Depolarizations account for 13% of outcome variance beyond that explained by established prognostic factors.
- Results suggest that depolarizations are a causal pathomechanism, with adverse effects on traumatically injured brain.
- The first pathomechanism, with demonstrated clinical relevance, that can be monitored in real-time and targeted in treatment of TBI.
Final Thoughts

- Guidelines are just that – guidelines
  - Explain / document your reasons to vary
- Standardized care does improve outcomes
  - Work with the intensivists
  - Develop protocols & encourage compliance
  - ‘Algorithm’ for care must be individualized

"Seat belts are not as confining as wheelchairs or caskets."
LA State Police 2009
Questions?

HELMMETS
There's no need when you have faith

http://www.ucneurocriticalcare.com/physicians