Update on Neurocritical Care

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First known description of status epilepticus
(Sakikku cuneiform, ca. 700 B.C.)

Neurocritical Care Highlights
- Ischemic Stroke Treatment
  - Acute intervention
  - When acute doesn’t work
- Treating Global Cerebral Ischemia (GCI)
- Intracerebral hemorrhage – hematoma expansion
- Advanced Neuromonitoring for Secondary Brain Injury
- Ventilation in Neuromuscular Disease
Acute Ischemic Stroke 2009

- 67 yo woman
- Acute onset dense right hemiparesis and aphasia
- ED arrival at 4 ¾ hours after last seen normal
CT Perfusion

Perfusion mismatch
Green = good
(salvagable brain)
Red = bad
(dead brain)

Intra-arterial Therapy

MERCI embolectomy device
Acute Ischemic Stroke Treatment

- Recanalization is the strategy
  - Options
    - IV t-PA – window now 4 ½ hours
    - Intra-arterial thrombolysis
    - Embolectomy
      - MERCI retriever
      - PENUMBRA clot extraction
  - Use advanced neuroimaging for triage
  - Clinical trials ongoing and planned to eval
    - Comparison of treatments
    - Use of imaging to expand (remove?) time window

Large Hemispheric Infarction

- Case – 43 yo man with acute complete L MCA ischemic stroke
  - Received IV t-PA w/in 3 hours of onset
  - 12 hours later, deteriorated to deep coma
Options?

1. Let him go
2. ICP monitoring
   - Mannitol, etc
3. Hypothermia
4. Decompressive hemicraniectomy
   - Evidence?

European Pooled Trial Results

• Prospective pooled analysis of 3 ongoing (at the time) trials of decompressive surgery in malignant MCA infarction

• DECIMAL, DESTINY, HAMLET
• Patient criteria
  - Age 18-60
  - Rx w/in 48 hrs of stroke onset
  - Randomized to surgery or conservative Rx
  - 93 patients
Number Needed to Treat (NNT)

Alive but unable to walk
NNT=2

Alive, disabled but able to walk
NNT=4

Side of stroke (e.g., dominant hemisphere) didn’t matter

Treating post-arrest global cerebral ischemia

- Old way
  - Wait 3 days and prognosticate
  - “Levy criteria”
  - JAMA, 1985

- New way
  - Mild hypothermia (neuroprotection)
Hypothermia – clinical trials

- European study – NEJM 2002; 346:549-56
  - V fib arrest; still comatose after resuscitation
  - 24 hours of external cooling (special mattress) – 33°C
  - 6 month outcome (NNT=number needed to treat)
    - Hypothermia 55%
    - Normothermia 39% (RR 1.4 (1.08-1.81))

- Australian study – NEJM 2002; 346:557-63
  - V fib arrest; still comatose after resuscitation
  - 12 hours of surface cooling; often started prehospital
  - Outcome at hospital discharge (NNT=4)
    - Hypothermia 49%
    - Normothermia 26% (P=0.046)

2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

- Unconscious adult patients with return of spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours when the initial rhythm was ventricular fibrillation (Class IIA).

- Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb).

Circulation November 28, 2005
Lost in Translation?


Cooling after Cardiac Arrest

- Hypothermia as neuroprotective
- Perfusion has been restored to brain

- Many methods
  - Surface blankets
  - Endovascular
  - Cold saline

- You need a protocol
  - http://www.med.upenn.edu/resuscitation/hypothermia/protocols.shtml

Non-Traumatic Intracerebral Hemorrhage (ICH)

- 10-15% of all strokes
- High morbidity and mortality
  - 35-52% 90-day mortality
  - 20% of ICH patients independent at 6 mo
- 34% of years of potential life lost to stroke
- Lifetime cost per case ~ $124,000
- Total lifetime cost for annual US cases >$4B

Taylor et al. Stroke 26:1459-1466, 1996
Hematoma Expansion in ICH

- Previously suggested as
  - rare
  - suggestive of underlying AVM, coagulopathy

- Studies of early serial CT show as common
  - 72% of patients have some hematoma expansion over initial 24 hrs
  - 38% have significant (>33%) expansion over 24 hrs, usually clinically significant
    - within 1 hr in 26% of cases

- Hematoma expansion worsens outcome

Davis et al. Neurology 2006
Brott et al. Stroke 1997

Hematoma Expansion in ICH

Initial CT

2' 45" later

Images Courtesy of Jonathan Rosand, MD

FAST Trial

- Phase III Trial of rFVIIa in acute ICH
- FAST trial conducted globally from May 2005 to November 2006
  - >120 global sites; ~70 US sites
  - 841 patients randomized; 821 patients dosed
- Largest ICH medical trial ever conducted
- Protocol similar to phase IIb trial which showed
  - Less hematoma expansion
  - Improved clinical outcomes
  - Slight increase in arterial thrombotic events
- rFVIIa 80 µg/kg vs 20 µg/kg vs placebo

FAST: Primary Results

<table>
<thead>
<tr>
<th>Hematoma Growth at 24 hrs</th>
<th>Placebo</th>
<th>20 μg/kg</th>
<th>80 μg/kg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % change</td>
<td>26%</td>
<td>18%</td>
<td>11%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Absolute difference</td>
<td>7.8 ± 18.7</td>
<td>4.7 ± 14.8</td>
<td>3.9 ± 15.3</td>
<td>0.009</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Outcome at 90 days</th>
<th>Placebo</th>
<th>20 μg/kg</th>
<th>80 μg/kg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Score &gt; 5</td>
<td>24%</td>
<td>26%</td>
<td>29%</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>19%</td>
<td>18%</td>
<td>21%</td>
<td>NS</td>
</tr>
</tbody>
</table>


FAST Trial: What Happened?

• Many patients with severe ICH at baseline “unable to be saved”?
  – Elderly, large ICH volume, large IVH volume, poor GCS
• Lack of clinical benefit does not seem (on initial analysis) to be a result of arterial thrombotic events (4% v. 8%)
• Subgroup benefit? (Stroke 2009)
  – Example: patients age < 70, hematoma volume < 60 ml, IVH volume < 5 ml, treated w/in 2.5 hrs
  – 19% of FAST population
    » Beneficial effect of reducing hematoma expansion with rFVIIa irrespective of baseline ICH volume and IVH volume (OR 0.28)
• But rFVIIa clearly reduces hematoma expansion (which is bad)
• So where to go from here?

CT “spot sign” in ICH

Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage

J.N. Goldstein, MD, PhD; S.R. Ponce, MD; B. Smith, PA; X. Seifert, MD; O.M. Grievezini, MD, PhD; J.E. Towbin, MD, PhD; J.L. Brott, MD; and J. Ronen, MD, PhD
NEJM 2007;357:2590-2598
Multivariable analysis of predictors of hematoma expansion

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast extravasation</td>
<td>18 (2.1-162)</td>
<td>0.009</td>
</tr>
<tr>
<td>ICH volume (per 10cc)</td>
<td>0.8 (0.6-1.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Time to CTA&lt; 3hours</td>
<td>3.4 (0.5-22)</td>
<td>0.2</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.2 (0.6-2.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>SBP (per 10mmHg)</td>
<td>0.94 (0.8-1.1)</td>
<td>0.5</td>
</tr>
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What's next? (studies ongoing or planned)
- Prospective validation of spot sign
- Use of spot sign to select patients for hemostatic therapy (rFVIIa?)

Neuromonitoring in NICU

Monitoring of neurologic function in patients at high risk for

- Primary brain injury from procedure or condition
- Secondary brain injury after a prior neurologic insult

The primary focus of Neurocritical Care for CNS problems is the prevention, identification, and treatment of secondary brain injury.

Categories of Neuromonitors

- Clinical
  - Neurologic examination
- Physiologic
  - Pressure - ICP, BP
  - Flow - CBF, TCD
  - Electrical - EEG, EP
- Metabolic
  - Oxygen
  - Metabolites - glucose, lactate, EAAs
FDA Approved Advanced Neuromonitoring Devices

- **Licox Brain Tissue Monitor**
  - PO₂, Temp (now in single probe)
  - Integra Neurosciences
- **Thermal-diffusion Perfusion Monitor**
  - Quantitative cerebral blood flow
  - Hemedex
- **Microdialysis**
  - Lactate, pyruvate, glutamate, other substances
  - CMA

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Intracranial Monitors - location

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UCSF PₜO₂ Monitoring
Cerebral Microdialysis

- Blood capillary
- Microdialysis catheter
- Extracellular fluid
- Cell

Cerebral Blood Flow

- Thermal Diffusion Flowmetry - TDF
- Less than 1 mm diameter flexible probe

Effects of Hyperventilation on $P_{bt}O_2$

- Secondary ischemia identified by advanced neuromonitoring
Current Approach at SFGH

- All patients with ICP monitor get
  - \(P_{\text{tO}}\), \(S_j\text{VO}_2\), CBF (if available)
  - Selective use of cEEG
- Start with standardized orders
  - CPP > 60, ICP < 20, \(P_{\text{tO}}\) > 15, \(S_j\text{VO}_2\) > 60%
- Test autoregulation (usually daily) and adjust CPP goal accordingly
- Metabolic monitors as
  - “early warning” signs
    - Guides to optimal “front-end” parameters (e.g. BP, ICP, CPP, ETCO\(_2\))
- Not currently using oxygen directed therapy if other parameters are acceptable

Neuromuscular Respiratory Failure

- Myasthenia gravis
- Guillain-Barré syndrome
- Botulism
- Acute myopathies
- Time course
  - Usually subacute – hours to days
  - Precipitous deterioration due to
    - Mucous plugging
    - Atelectasis
    - Aspiration
- Is it
  - Ventilatory failure?
  - Bulbar failure?

Non-invasive Ventilation

- Ventilatory support delivered without establishing an endotracheal airway
  - Negative pressure
  - Positive pressure
Preventing Intubation in MG?

- Rabinstein A and Wijdicks EFM. BiPAP in acute respiratory failure due to myasthenia crisis may prevent intubation. Neurology 58:1647-1649, 2002
- Used BiPAP as initial ventilatory support strategy in 9 patients (11 episodes) out of 36 patients with MG crisis and respiratory failure
- Prevented intubation in 7 of 11 cases
  - Bulbar weakness in 4 of these
- Mean BiPAP pressures 13/5 cm H2O
- Mean duration 5 days (4 hours – 16 days)
- All patients with hypercapnia (Paco2 > 50 mmHg) at BiPAP initiation required intubation

What about Guillain-Barré?

- Warning due to
  - Difficult to assess diaphragmatic weakness
  - Progressing disease course without usual rapid reversal
  - Precipitous (not progressive, linear, and predictable) deterioration

A Word of Caution

- This strategy might work in select patients
- Requires more vigilance than just intubating patient
- Use of BiPAP does not mean the patient is “not as sick”
- Patient must be in ICU
- Not appropriate if
  - Hypercapnic
  - Significant bulbar weakness
Update on Neurocritical Care

- Neurocritical Care is delivered in many different parts of the hospital (ED, NeuroICU, CCU, general/trauma ICU, Neuro angio suite, OR)

- Cerebral ischemia
  - Focal – open that vessel
  - Global – cool that brain (neuroprotection)

- How to prevent hematoma expansion in ICH patients who are still salvagable?

- Concepts of neuromonitoring for secondary brain injury
  - Relevant to TBI and stroke (ischemic/ICH/SAH)

- Respiratory management in acute neuromuscular disease
  - Be careful and don’t get too fancy