New Hanover Regional Medical Center
Intracerebral Hemorrhage

James S. McKinney, MD, FAHA
Medical Director, NHRMC Stroke Center
Wilmington, NC

Disclosures

• I have no financial disclosures.
• Off label medications
  – Intrathecal administration of alteplase (rt-PA)

ICH Burden in Adults

• Primary ICH
  – Etiology
  – Incidence
  – Outcome

• Treatment
  – Anti-edema/ICP measures
  – Surgical evacuation
  – IVH and EVD
  – AED prophylaxis
  – Halting hematoma expansion

• 10-15% of all strokes
• 37,000-52,000 cases per year in U.S.
• Incidence expected to double in next 50 years
  • Aging of population
  • Changes in demographics

Age and ICH Etiology

- Prospective study of 206 ICH patients
  - aged 5 to 79 years (mean 42 years)
- Positive angiography was associated with:
  - Age < 45 (53/105, 50%, versus 18/101, 18%; P < .001)
  - No history of HTN (64/145, 44%, versus 5/58, 9%; P < .001).
- Angiographic findings included:
  - AVM 73%  
  - Aneurysm 14%  
  - Moyamoya 6%  
  - Venous sinus thrombosis 7%


Incidence of ICH by Age

Etiology of Adult ICH

- Spontaneous primary intracerebral hemorrhage
  - No underlying vascular malformation
  - No trauma, ischemia, vein thrombosis, vein thrombosis, etc
  - Generally due to HTN, cerebral amyloid angiopathy, cryptogenic

Outcome of ICH
• Mortality
  - 6-month, 30-50%
  - 1-year, 50%

• Only 20% of ICH patients are independent at 6 months vs 60% of ischemic stroke patients


• Two prospective, population-based cohorts: Primary ICH (n=60) and AVM (n=90)

• Outcome at 1 year
  - Mortality
    - Primary ICH ~60%
    - AVM ICH ~10%
  - Modified Rankin score ≥ 3
    - Primary ICH ~80%
    - AVM ICH ~40%


Predictors of Outcome in Primary ICH
- Age
- Neurologic status at presentation
  - Glasgow Coma Scale or NIHSS
- ICH location
  - Supratentorial vs infratentorial
  - Lobar vs deep
- ICH Volume
- Presence of IVH
- Anticoagulation

The ICH Score
Validated to Predict 30 day mortality and long term functional outcome

- Age
  - ≥ 80 = 1
- Location
  - Infratentorial = 1
- IVH
  - Yes = 1
- GCS
  - 3-4 = 2
  - 5-12 = 1
- Volume of ICH
  - ≥ 30 mL = 1

Predicting Outcome from ICH: Size Matters

- Major predictor of outcome is ICH volume
- Large ICH associated with mass effect and midline shift -> herniation -> death

ICH Volume
Powerful Determinant of 30-day Outcome

<table>
<thead>
<tr>
<th>ICH Volume (cm³)</th>
<th>Condition at 30 days (Oxford Handicap Scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>Recovery</td>
</tr>
<tr>
<td>30-60</td>
<td>2</td>
</tr>
<tr>
<td>≥ 60</td>
<td>4</td>
</tr>
</tbody>
</table>


ICH (N=188)

Overall mortality

0-29 cm³ Mortality 19%
30-60 cm³ Mortality 20%-55%
≥ 60 cm³ Mortality 91%

Only 1 of 71 patients with ICH volume ≥30 cm³ functioned independently at 30 days (Oxford Handicap Score ≤3)

ICH Volume Predicts Outcome

Ping-pong ball 28.0 mm 28.0 mL
Golf ball 1.68 in 40.8 mL

Estimating Size of ICH

ABC/2
- A= longest diameter
- B= diameter perpendicular to A
- C= height (n slices x slice thickness)

ICH seen on 11 slices x 3 mm slice thickness
- C = 3.3
- Volume = 3.3 x 2.5 x 3.3 /2 = 13.6 mL

Early Hemorrhage Expansion

Prospective study of 103 ICH pts with CT within 3 hours of onset (Brott, Stroke 1997)

- ICH expansion (>33% increase in volume) in patients
  - 26% in first 1 hour post CT
  - 12% between hour 1 and 20

Portends a worse outcome

General Management Principles

- Keep patient euthermic, euglycemic, euvoletic
- HOB at 30 degrees, head midline
- Maintain ICP < 20, CPP > 60-70
- Monitor and provide aggressive treatment of ICP if suspected to be high, consider surgery in select patients
- Avoid common medical complications

Blood Pressure Reduction to Lower Risk of Hematoma Expansion

- If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 min.
- If SBP is >180 mm Hg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure 60 mm Hg.
- If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of elevated ICP, then consider a modest reduction of BP (e.g., MAP of 110 mm Hg or target BP of 140/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically reexamine the patient every 15 min.

Aggressive BP Reduction

- **INTERACT II** – Anderson NEJM 2013
  - RCT of intensive BP lowering (goal reduction to SBP < 140 within 1 hour) vs standard practice (AHA guideline driven, SBP < 180)
  - 2794 patients SE Asia & Australia
  - Primary outcome – Death or Disability (DR 0.87, CI 0.75-1.01)

- **ATACH II Trial**
  - RCT 1000 subjects with ICH
  - Target SBP 110-139 vs. Target SBP 140-179

AHA Guidelines 2010
Blood pressure management-ICH

Level of evidence

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  - In patients presenting with a systolic BP of 150 to 220 mm Hg, acute lowering of systolic BP to 140 mm Hg is probably safe

Morgenstern et al. Stroke. 2010 Sep;41(9):2108-29

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Seizures in ICH

- Seizures are more frequent in ICH than in ischemic stroke
- Seizure risk ~8% in first few days after ICH
- Most seizures at onset or ≤ 24 h of ICH
- More commonly associated with lobar than deep ICH
- Potential for worse outcomes
  - Neuronal injury and destabilization of critically ill patient
  - Nonconvulsive seizures may contribute to coma
  - Seizures associated with deterioration of NIHSS and increased midline shift
  - However, no association with worse long term outcome after adjusting for other predictors


Prophylactic AEDs in ICH

- Cerebral Hemorrhage and NXY-059 Trial (CHANT)
  - RCT of a putative neuroprotectant
  - 303 patients received placebo
- 23 placebo patients (8%) were initiated on AEDs without documented seizure
- Initiation of AEDs was robustly associated with poor outcome (OR 6.8; 95%CI: 2.2-21.2, p=0.001) after adjustment for other known predictors of outcome after ICH (age, initial hematoma volume, presence of intraventricular blood, initial Glasgow Coma Score, and prior warfarin use)

Messe et al. Neurocrit Care. 2009;11(1):38-44
Prophylactic AEDs in ICH

- A second prospective cohort of 98 ICH patients
  - 7% had a seizure
  - Phenytoin was associated with more fever and worse modified Rankin Scale at 3 months
  - Levetiracetam use was not associated with any difference in outcome


AHA Guidelines 2010 Seizures in ICH

Level of evidence

A
- Clinical seizures should be treated with antiepileptic drugs

B
- Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury
- Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs

C
- Prophylactic anticonvulsant medication should not be used

Interventions for High ICP

- Treat edema/mass effect
  - Hyperventilation, steroids, mannitol, hypertonic saline
- Reduce ICH size directly
  - Surgery?

Edema and Mass Effect

- Hyperventilation provides a short lived effect and is generally only helpful as a bridging measure to definitive therapy
- Steroids have been shown to be ineffective (with increased adverse events)
- Mannitol and hypertonic saline have limited evidence that they can reduce edema and temporarily reverse herniation
  - They are both reasonable to use as bridging therapies
  - Invasive ICP monitoring should be considered to guide therapy

Poungvarin, NEJM 1987
AHA Guidelines 2010 – ICP Management

Reduce ICH Size Directly:
Surgical Evacuation

Meta-Analysis of Surgical Rx

Meta-analysis of 7 RCTs for surgical treatment of ICH shows no benefit

Comparison: surgery v control
Outcome: death or disability

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI Fixed)</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKissock (1961)</td>
<td>2.00 [1.04,3.83]</td>
<td>2.00 [1.04,3.83]</td>
</tr>
<tr>
<td>Auer (1989)</td>
<td>0.46 [0.20,1.04]</td>
<td>0.46 [0.20,1.04]</td>
</tr>
<tr>
<td>Juveis (1989)</td>
<td>4.39 [0.81,23.65]</td>
<td>4.39 [0.81,23.65]</td>
</tr>
<tr>
<td>Batjer (1990)</td>
<td>0.55 [0.06,4.93]</td>
<td>0.55 [0.06,4.93]</td>
</tr>
<tr>
<td>Chen (1992)</td>
<td>1.66 [0.82,3.34]</td>
<td>1.66 [0.82,3.34]</td>
</tr>
<tr>
<td>Morgenstern (1998)</td>
<td>0.53 [0.13,2.21]</td>
<td>0.53 [0.13,2.21]</td>
</tr>
<tr>
<td>Zuccarello (1999)</td>
<td>0.48 [0.09,2.69]</td>
<td>0.48 [0.09,2.69]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1.20 [0.83,1.74]</td>
<td>1.20 [0.83,1.74]</td>
</tr>
</tbody>
</table>

Chi-square 13.41 (df=6) Z=0.96

“Ultra-Early” Surgery (< 4 hours)

- Surgical evacuation vs medical therapy
- Treatment < 4 hours from onset
- Study stopped after 11 patients treated surgically:
  - High rate of rebleeding (40%) in surgically treated patients
  - High mortality in those who rebled (75%)
Surgical Evacuation for Cerebellar Hemorrhage

- Comprises ~10% of ICH
- Non-randomized prospective study of 75 patients with cerebellar hemorrhage > 40 mm and GCS < 13
- Good outcome occurred in 58% with surgery and in 18% with conservative medical therapy
- Subsequent studies consistent
  - EVD alone is not recommended

Kobayashi, Stroke 1990

I-STICH
International-Surgical Treatment for Intracerebral Hemorrhage

- 1033 patients enrolled from > 20 countries
  - Nearly double the total # pts enrolled (561) in all prior trials combined
- Early surgical evacuation vs. medical therapy
  - 25% of medical group declined and had late surgery
- Enrollment based on surgeon being “uncertain about the benefits of either treatment”
- Treatment < 72 hours from onset
  - median 30 hours, IQR 16-49 hours
- Patients with GCS ≥ 5
- Surgery via craniotomy 75%, stereotactic 25%

Mendelow AD, Lancet 2005

I-STICH: ICH Size/Location
International-Surgical Treatment for Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Size/Location</th>
<th>Favorable</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early surgery</td>
<td>26.1%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Medical</td>
<td>36.3%</td>
<td>37.1%</td>
</tr>
</tbody>
</table>

• Outcome determined by prognosis based GOS (taking into account age, admission GCS, and ICH volume)
• Analysis using Rankin and Barthel similar

Mendelow AD, Lancet 2005
Pre-specified subgroup analysis
(Mendelow AD, Lancet 2005)

STICH II - Baseline Hematoma
Early Surgery vs. Initial Conservative Medical Treatment in Patients with Spontaneous Supratentorial Lobar Intracerebral Hematomas

<table>
<thead>
<tr>
<th></th>
<th>Early surgery group (n=305)</th>
<th>Initial conservative treatment group (n=292)</th>
<th>p value</th>
<th>Absolute difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognosis based</td>
<td>207</td>
<td>241</td>
<td>0.367</td>
<td>3.7% (-6.3 to 11.4)</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>178 (51%)</td>
<td>178 (51%)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Favorable</td>
<td>129 (40%)</td>
<td>163 (52%)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 6 months</td>
<td>0.085</td>
<td>0.085</td>
<td>..</td>
<td>5.8% (-1.6 to 12.2)</td>
</tr>
<tr>
<td>Dead</td>
<td>54 (18%)</td>
<td>58 (19%)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Alive</td>
<td>244 (82%)</td>
<td>232 (75%)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Prognosis-based modified Rankin</td>
<td>0.436</td>
<td>0.436</td>
<td>..</td>
<td>3.2% (-5.0 to 11.2)</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>155 (51%)</td>
<td>158 (51%)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Favorable</td>
<td>140 (45%)</td>
<td>124 (43%)</td>
<td>..</td>
<td>..</td>
</tr>
</tbody>
</table>

Mendelow et al. Lancet 2013

STICH II - Surgery Details
Early Surgery vs. Initial Conservative Medical Treatment in Patients with Spontaneous Supratentorial Lobar Intracerebral Hematomas

<table>
<thead>
<tr>
<th>Surgery details</th>
<th>Early surgery group (n=288)</th>
<th>Initial conservative treatment group (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniotomy</td>
<td>284 (99%)</td>
<td>59 (95%)</td>
</tr>
<tr>
<td>Craniectomy</td>
<td>1 (&lt;1%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Minimally invasive*</td>
<td>3 (1%)</td>
<td>..</td>
</tr>
</tbody>
</table>

Mendelow et al. Lancet 2013

STICH II - RESULTS
Early Surgery vs. Initial Conservative Medical Treatment in Patients with Spontaneous Supratentorial Lobar Intracerebral Hematomas
AHA Guidelines 2010

Level of evidence B

- For most patients with ICH, the usefulness of surgery is uncertain with the follow exceptions:
  - Patients with cerebellar hemorrhage who are deteriorating or have hydrocephalus should undergo evacuation as soon as possible. EVD alone is not recommended in these patients
  - For patients with lobar clots >30 mL and within 1 cm of the surface, evacuation might be considered
  - Minimally invasive clot evacuation is considered investigational
  - Very early craniotomy may be harmful due to increased risk of recurrent bleeding

Morgenstern et al. Stroke. 2010 Sep;41(9):2108-29

Minimally Invasive Surgery

MISTIE II
- Medical Management + Clot Drainage Catheter with tPA vs. Medical Management alone
  - Inclusion: Spontaneous, supratentorial Intracerebral hemorrhage >20 mL with a GCS <14 or NIHSS >6
  - N= 96 patients randomized
  - Therapy: 1mg of rtPA administered via drainage catheter every 8 hours up to 72 hours

Hanley D. ISC 2013

Minimally Invasive Surgery

MISTIE II Long Term Outcomes

Hanley D. ISC 2013
Minimally Invasive Surgery

- New Technologies
  - Apollo-Penumbra
  - Vycor
  - BrainPath-Nico
  - Viket Medical
  - Tres Medical
  - Stryker

Minimally Invasive Clot Evacuation

- BrainPath™ Approach

- BrainPath™ Clinical Outcomes

- ENRICH Trial Now Recruiting
Intraventricular Hemorrhage
- IVH may occur in isolation
- ICH is associated with IVH in ~40% of cases
- May result in hydrocephalus and increased ICP
- Portends a worse outcome

Ventriculostomy Drainage and IVH
- Never studied prospectively
- Generally associated with poor outcome
- Main risks are hemorrhage and infection
- Preliminary data suggested EVD + tPA improved clearance of IVH
  - CLEAR IVH: A randomized controlled trial of intraventricular tPA to expedite clearance of IVH and improve outcome
    - Prelim data: 1mg Q8h resulted in fewer VPS (22% vs 50%) and shorter LOS in ICU (7.5 vs 12)


CLEAR III Study - A randomized controlled trial of intraventricular tPA to expedite clearance of IVH and improve outcome

- Outcome mRS ≤ 3 at 180 days
  - tPA 47.6% vs. saline 44.9%, p=0.554
- Mortality
  - tPA 18.5% vs. saline 29.1%, p=0.006
- VPS
  - tPA 18.5% vs. saline 17.5%, p=784
- No difference in hospital or ICU LOS

CLEAR III trial – clinicaltrials.gov

Thank You
james.mckinney@nhrmc.org