Spontaneous Intracerebral Hemorrhage

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ICH Is Common
Incidence Predicted to Increase

ICH Proportion of Strokes (US)

ICH 9%
SAH 3%

700,000 Total Strokes Annually

No. of Persons

ICH Ischemic

Proportion of patients (%)

Dead
Dependent
Independent

Mortality
– 6-month, 30%-50%
– 1-year, 50%

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

Medical costs
– US$125,000 lifetime cost per person (1990)
– Direct and indirect costs (lost productivity + caregiver burden)

High-Risk Populations

- Hypertensive patients (especially poorly controlled)
- Anticoagulant users
- Patients with multiple comorbid risk factors
- Age >55 years
- Patients with cerebral microangiopathy (eg, cerebral amyloid angiopathy)
- Patients with dementia
- Certain ethnic populations – African Americans – Hispanics – Asians (especially Japanese)
- Alcohol abusers
- Smokers
- Patients with renal or liver failure

Traditionally High Mortality and Limited Recovery

Predictors of Outcome

- Hematoma volume
- GCS
- Intraventricular hemorrhage
- Age
- ICH location (deep)
- Increased cerebral edema (midline shift, herniation)

Sites of Spontaneous ICH

Lobar Subcortical Hemorrhage (25%)
Putaminal Hemorrhage (25%)
Thalamic Hemorrhage (25%)
Pontine Hemorrhage (7%)
Cerebellar Hemorrhage (5%)

Recurrence Risk Distinguishes Lobar from Deep ICH

Viswanathan Neurology. 2006;66:206

Mechanisms of Injury

Early hematoma growth
- Hematoma enlargement
- Increase in ICP, tissue disruption and shear forces

Edema and toxic effects of blood products
- Osmotically active serum products
- Thrombin
- Inflammatory response


Hematoma Expansion

- 72% have some hematoma expansion over the first 24 hours
- 36% have significant (>33%) expansion over 24 hours
- In 26% of these cases, the enlargement is within 1 hour


Hematoma Expansion

Contrast extravasation is independently associated with hematoma expansion and worse outcomes!

Patient with spot sign, demonstrating extravasation and hematoma expansion

Wada, R. et al. Stroke 2007;38;1257-1262

Common Etiologies of ICH

Primary Hypertension
Features and Characteristics

- Typical sites
  - Putamen - 50%
  - Thalamus - 15%
  - Lobar - 15%
  - Cerebellum - 10%
  - Pons - 10%

- Typically more severe than cerebral amyloid angiopathy-related ICH
- Risk of recurrence ~2% annually (if BP controlled)


Cerebral Amyloid Angiopathy
Features and Characteristics

- Location
  - Lobar hemorrhage
  - Multiple, bilateral
  - Pareto-occipital location
- Associated with dementia/AD
- Elderly patients (>70 years)
- Typically less severe than HTN-related ICH
- Risk of recurrence 0%-15% annually
- Microbleeds on gradient-echo MRI

### Common Etiologies of ICH

**Acquired Coagulopathy – Anticoagulation**

- Warfarin indicated in DVT, PE, AF
- Incidence of anticoagulant-associated ICH rise from 5% to 18% of cases of spontaneous ICH in 1990s
- INR 2.5-4.5 increases risk of ICH 10X
- Associated with longer duration of ICH expansion
- Doubles ICH mortality!


### Common Etiologies of ICH

**Acquired Coagulopathy – Thrombolytic Therapy**

- tPA increases risk of ICH (6% absolute risk in NINDS trial)
- 18.5% of bleeds at sites distant from stroke
- Risk factors
  - Age >70 years
  - Serum glucose >300 mg/dL
  - NIHSS >20
  - Early ischemic changes detected on CT
  - Not time to treatment!


### Other Etiologies of ICH

**Drug-related**

- Cocaine
- Amphetamines
- Other illicit drugs (eg, talwin-pyribenzamine, phencyclidine)
- MAO inhibitors

### Other Etiologies of ICH

**Vascular lesions**

- Cerebral aneurysm
- Arteriovenous malformations
- Dural A-V fistulas
- Cavernous malformation
- Venous angioma/capillary telangiectasia

### Other Etiologies of ICH

**Hemorrhagic conversion of ischemic stroke**

Neoplasms
Melanoma
Renal Cell Ca
Thyroid Ca
ChorioCa
Lung Ca

### Other Etiologies of ICH

**Cerebral aneurysm**

Pial Arteriovenous Malformations

61 y/o man p/w acute onset of speech difficulties and right HH in the setting of a left tempo-occipital ICH
45 YEAR OLD MAN PRESENTS WITH HEADACHES AND CONFUSION

BASELINE ANGIOGRAM

SCREENING FOR ICH
Clinical Symptoms

The likelihood of ICH doubles* when one of the following is present:

- Impaired level of consciousness
- Vomiting
- Severe headache
- Warfarin therapy
- SBP >220 mm Hg
- Hyperglycemia (glucose >170 mg/dL) in non-diabetic patients

*Likelihood ratio 2.4; 95% CI, 1.8-3.2.

ICH MANAGEMENT IN ED
Assessment and Stabilization

Activate Stroke Team Prior to Arrival

Immediate General Assessment/Stabilization

- Assess ABCs/vital signs, monitor BP closely
- O2 (if hypoxic)
- IV access and labs (coagulation, platelets, CBC, electrolytes)
- Check glucose and treat (if indicated)
- Quick history
- Neurologic screening assessment (GCS, NIHSS)
- Emergent CT scan of brain (ASAP)
- 12-lead ECG

**Diagnosis of ICH**

**AHA Guidelines (2007)**

- Vomiting, early change LOC, and ↑ BP suggest ICH
- CT or MRI are both first choice for initial evaluation
- MRI and MRA in selected patients
  - Suspected cavernous malformation in normotensive surgical candidates with lobar hemorrhage
- Consider angiography (CTA or angiogram)
  - All surgical candidates without clear cause
  - Particularly young, clinically stable patients
  - Timing depends on factors including clinical state

**Diagnostic Imaging**

“Blood in the Brain” – What Type of Hemorrhage?

- Intracerebral hemorrhage (ICH)
- Intraventricular hemorrhage (IVH)
- Subarachnoid hemorrhage (SAH)

**Images courtesy of ITAM Scientific Committee.**

**General Management of ICH**

**Goals**

- Provide general supportive care in the ED and ICU/NICU to manage the primary brain injury and limit the secondary brain injury

  - Continue to support ABCs
  - Monitoring (BP, fever, ICP, labs)
  - Intubation
  - BP management
  - Seizure management
  - Reverse anticoagulation immediately

**Should BP Be Lowered in ICH?**

- Current data are inconclusive as to whether BP lowering is useful and about defining a target

  - **Potential benefits**
    - Limit hematoma growth
    - Decrease perihematoma edema
    - Isolated ICH with no stenosis and no temporal relationship
    - Baseline BP not associated with ICH growth in the largest prospective study of ICH growth

  - **Potential downside**
    - Create or exacerbate perihematoma ischemia
    - No significant change was observed in either global CBF or percent CBF as measured by PET after 15% MAP reduction

- Even if BP lowering isn’t harmful, does it help?
  - Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) Study
  - INTERACT study (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage)

- Different approaches based on ICH etiology (AVM, aneurysm, CAA)

**ICH Mortality Rate Is Reduced With Admission to an NICU**

- Non-NICU admission is associated with increased in-hospital mortality (OR, 3.4; 95% CI, 1.65-7.6)

**Images courtesy of ITAM Scientific Committee.**

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**Images courtesy of ITAM Scientific Committee.**

**Tables**

**TABLE 3.** Suggested Revascularization Guidelines for Treating Ischemic Cerebral Infarctions Due to Intracranial Aneurysm and Dural Arteriovenous Fistulae

<table>
<thead>
<tr>
<th>Type</th>
<th>Antihypertensive Drugs</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH</td>
<td>Olmesartan 10 mg daily</td>
<td>40 mg/day 5%</td>
</tr>
<tr>
<td></td>
<td>Captopril 12.5 mg daily</td>
<td>15 mg/day 5%</td>
</tr>
</tbody>
</table>

**TABLE 4.** Intravenous Medications That May Be Considered for Control of Elevated Blood Pressure in Patients With ICH

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug Name</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH</td>
<td>Labetalol</td>
<td>50-100 mg IV bolus</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>80-160 mg IV bolus</td>
</tr>
</tbody>
</table>

**Images courtesy of ITAM Scientific Committee.**
Seizures and ICH

- Seizures are more frequent in ICH than in ischemic stroke
- Seizure risk is 8% after ICH
- Most seizures at onset or ≤24 h of ICH
- More commonly associated with lobar than deep ICH

- Poorer outcomes
  - Neuronal injury and destabilization of critically ill patient
  - Nonconvulsive seizures may contribute to coma
  - Seizures associated with deterioration of NIHSS and increase in midline shift

Management of Seizures

- AHA guidelines recommend administering anticonvulsants for seizure at onset of ICH
- Consider anticonvulsants for ≤1 month in selected patients with lobar hemorrhage

ICH Expansion

ED Management:
Preventing Hematoma Expansion

- Warfarin reversal
- Hemostatic therapy (clinical trial)
- Blood pressure control (clinical trial)

Reversing Warfarin Effect: Time Counts!

- 69 consecutive patients with warfarin-related ICH
- All patients had repeated INR measures and were treated aggressively for ICH in the MGH ED

INR reversed at 24 hours

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (N=12)</th>
<th>Yes (N=57)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to CT (min)</td>
<td>62 (30-90)</td>
<td>45 (25-45)</td>
<td>0.5</td>
</tr>
<tr>
<td>CT to FFP (min)</td>
<td>210 (100-375)</td>
<td>90 (60-205)</td>
<td>0.02</td>
</tr>
<tr>
<td>FFP dose (units)</td>
<td>2 (1-5)</td>
<td>4 (2-8)</td>
<td>0.1</td>
</tr>
<tr>
<td>CT to Vitamin K (min)</td>
<td>246 (37-361)</td>
<td>87 (25-210)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Should All Patients Be Reversed?

Because of the high mortality of OAT-ICH and high risk of hematoma expansion, ALL OAT-ICH patients should receive rapid and complete reversal of anticoagulant effect in the Emergency Department.
Reversing Warfarin Effect in the Emergency Department

Current MGH Guidelines for ICH patients

- Vitamin K 10 mg IV over 10 minutes STAT
- FFP 10 ml/kg over 90 minutes (Prothrombin Concentrate may be substituted for FFP.)
- Team must designate a single physician to take personal responsibility for ensuring that these therapies are administered as fast as possible.
- As soon as FFP ordered, “runner” dispatched to blood bank to collect FFP.

www.stopstroke.org

Reversing Anticoagulation (cont.)

- ASA-related coagulopathy
  - Platelet transfusion
- No antidote for clopidogrel-related coagulopathy
- Thrombolytic therapy-related coagulopathy
  - Stop thrombolytic agent
  - 6-8 units of cryoprecipitate containing factor VIII
  - 6-8 units of platelets
- Heparin- and enoxaparin-induced anticoagulation
  - Protamine sulfate

Reducing Hematoma Expansion

Many Potential Hemostatic Agents

- Aminocaproic acid
- Prothrombin-complex concentrates
  - Concentrated vitamin K–dependent factors (factors II, VII, IX, X)
- Recombinant factor VIIa
- DDAVP (Desmopressin)
- Tranexamic acid
- Cryoprecipitate
- Aprotinin (Trasylol)

Reversing Anticoagulation

ICH in any patient on warfarin (with INR ≥1.5) should be considered life-threatening

Goal → Normalize INR to <1.4 ASAP

- Time until initiation of warfarin reversal is the strongest predictor of 24-h coagulation reversal
- Reversal may not occur in 1 of 6 patients

Reducing Hematoma Expansion Early Hemostatic Therapy With Factor VIIa

- Currently approved for use in hemophiliacs; initiates hemostasis
- Well suited for limiting early hematoma growth in ICH
- Local effects in endothelial disruption and vascular injury
- Reduces bleeding in patients without coagulopathy
- Rapidly normalizes INR in anticoagulant-associated ICH
- Has been studied as a therapy for ICH in:
  - 2 phase IIa dose-escalation studies
  - Phase IIb global dose-response study
  - Phase III

Reducing Hematoma Expansion


**rFVIIa Phase Ib Dose-Response Study**

**Change in Hematoma Volume at 24 Hours**

Percent Change in ICH Volume: Baseline → 24 Hours

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Increase</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>rFVIIa 40 µg/kg</td>
<td>16%</td>
<td>0.07</td>
</tr>
<tr>
<td>rFVIIa 80 µg/kg</td>
<td>14%</td>
<td>0.049</td>
</tr>
<tr>
<td>rFVIIa 160 µg/kg</td>
<td>14%</td>
<td>0.015*</td>
</tr>
<tr>
<td>Combined Treatment</td>
<td>16%</td>
<td>0.012*</td>
</tr>
</tbody>
</table>

*ICTR values

**Functional Outcome at 90 Days**

Modified Rankin Scale

- 0-1: no significant disability
- 2-3: slight to moderate disability
- 4-5: moderate–severe to severe disability
- 6: dead

For rFVIIa 160 µg/kg:

- 38% survival

**Conclusions**

- Compared with placebo, rFVIIa treatment:
  - Significantly reduced hematoma growth (P=.01)
  - Significantly reduced mortality: 38% decrease (P=.02)
  - Significantly improved patient outcome
- Thromboembolic serious adverse events, mainly myocardial and cerebral infarction, occurred in 7% of rFVIIa patients compared with 2% of placebo patients (P=.12)
- Thromboembolic serious adverse events that were possibly or probably related to treatment and that were fatal or disabling occurred in 2% of rFVIIa-treated patients and in 2% of the placebo group.

Management of Increased ICP

**Treatment Options**

- **Osmotherapy**
  - 3% or 23.4% saline
  - Mannitol bolus
    - 0.25-0.5 g/kg q4h
    - Target 3-10 mOsm/L
  - Avoid hypo-osmolar fluids
  - Maintain euolemia
- **Positional factors**
  - Raise head of bed 30°
  - Keep head at midline
  - Avoid head and neck positions that compress jugular veins
  - Avoid flat-supine position
  - Tracheostomy/ETT ties loose
- **Sedation, short-term neuromuscular paralysis**
- **Ventricular drain.** (especially for hydrocephalus)

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**Other Issues in Medical Management**

- **Steroids** – No
- **Fever is bad**
  - Does controlling fever help?
  - Important in first 24 hours
- **Hyperglycemia**
  - Insulin infusions are en vogue in ischemic stroke
  - Little data for ICH either way
- **Don’t forget DVT prophylaxis**
  - When can heparin be started?
    - Some say never and to use TEDS/SCDs
    - Others start SQ heparin or LMWH sometime after 48 hours
  - DVT = IVC Filter
- **Don’t forget nutrition!**
- **Start rehab early**
  - Begin range-of-motion exercises in ICU, even in comatose patients
  - Extent of rehab activities will depend on patient’s condition

**Surgical Intervention in ICH**

**Goal**

- Remove as much blood clot as possible, as quickly as possible, with the least amount of brain trauma

**Surgical Modalities: Craniotomy, Stereotactic**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open craniotomy</strong></td>
<td>+ Gets all the blood</td>
</tr>
<tr>
<td></td>
<td>– Invasive, disrupts tissue</td>
</tr>
<tr>
<td><strong>Endoscopic aspiration</strong></td>
<td>+ Visualization</td>
</tr>
<tr>
<td></td>
<td>– Slow, leaves volume</td>
</tr>
<tr>
<td><strong>Stereotactic evacuation</strong></td>
<td>+ No disruption</td>
</tr>
<tr>
<td></td>
<td>– Slow, leaves volume</td>
</tr>
<tr>
<td><strong>Intra-hematoma thrombolysis?</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Surgical Issues**

- Evidence that it works?
- Careful diagnosis
- Timing of intervention: ultra-early, early, late
- Site of hemorrhage
- Technique – craniotomy, stereotactic
- Consistent, good medical management
  - Monitoring
  - Preventing re-bleeding
  - Managing BP
- Understand pathophysiology

**Restarting Anticoagulation After ICH ACC/AHA 2006 Guideline**

- Discontinue anticoagulants and antiplatelets ≥1-2 weeks
- Reverse anticoagulation as soon as possible (vitamin K, FFP)
- If required, resume oral anticoagulation after 3-4 weeks (rigorous monitoring, INR in lower range); if anticoagulation is needed sooner after ICH, IV heparin (with PTT 1.5 to 2.0 times normal) or LMWH may be better acute therapy than oral warfarin
- Higher risk of recurrent ICH if anticoagulation resumed in lobar ICHs, microbleeds, and suspected CAA on MRI

**Adapted from Sacco RL et al. Stroke. 2006;37:577-587.**


**STICH**

International Surgical Trial in Intracerebral Hemorrhage

- Randomized prospective trial
- N=1033
- Early surgery (24 h to surgery; >96 h from onset) vs initial conservative treatment
- GCS >5 and ICH diameter ≥2 cm
- 1st outcome = death or disability


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**Surgical Guidelines**

AHA Guidelines (2007)

- Cerebellar hemorrhage ≥3 cm with neurological deterioration or brain stem compression and/or hydrocephalus should have surgical removal of the hemorrhage ASAP (Class I, Level of Evidence B).
- Lobar clots within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered (Class IIb, Level of Evidence B).
- No clear evidence indicates that ultra-early craniotomy improves functional outcome or mortality rate. Operative removal within 12 hours, particularly by less-invasive methods, has the most supportive evidence, but the number of subjects treated within this window is very small (Class IIb, Level of Evidence B).
- Very early craniotomy may be associated with an increased risk of recurrent bleeding (Class IIb, Level of Evidence B).


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**Treatment of ICH**

- Prevention
  - Modify risk factors
  - Control hypertension
  - Limit anticoagulation
- Acute intervention when it occurs
  - After hemostasis
    - rFVIIa for acute ICH
    - Rapid reversal of coagulopathy in warfarin-related ICH
  - Surgery
    - Alternatives to craniotomy
    - Neuroprotection, rehabilitation, etc.
Thank you for your attention!