Management of Spontaneous Intracerebral Hemorrhage (ICH)

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Objectives

1. Define ICH
2. Discuss the incidence/prevalence of acute, spontaneous ICH
3. Identify the most common causes of ICH
4. Describe the pathophysiology of the two most common causes: HTN and Cerebral Amyloid Angiopathy (CAA).
5. Analyze current recommendations of both medical and surgical management of acute, spontaneous ICH.

Definition

Spontaneous, Nontraumatic Intracerebral Hemorrhage...

...occurs when a diseased blood vessel within the brain bursts, allowing blood to leak inside the brain.
Incidence / Prevalence

“An estimated 6.6 million Americans ≥ 20 years of age have had a stroke (extrapolated to 2012 by use of NHANES 2009-2012). Overall stroke prevalence during this period is an estimated 2.6% (NHANES, NHLBI).”

NHANES = National Health and Nutrition Examination Survey
NHLBI = National Heart, Lung, and Blood Institute


Incidence / Prevalence

• “By 2030, projections show an additional 3.4 million people aged > 18 years will have had a stroke. A 20.5% increase in prevalence from 2012.”

• “Highest increase (29%) is projected to be in Hispanic men.”


Incidence / Prevalence

• Average age affected lower than that of ischemic stroke victims.

• ICH makes up approx 12% of all strokes

• Incidence 10-20/100,000

Highest Risk Factors

- Advanced age (>70)
- HTN
- Kidney Disease
- Heavy ETOH use
- Substance abuse (cocaine, amphetamines)
- Very low cholesterol

Causes of Spontaneous ICH

Primary:
- Hypertension (35%)
- Amyloid angiopathy (20%)
- Antiplatelet use and bleeding diathesis (5%)
- Drug/substance abuse

Secondary:
- Vascular Anomalies (5% overall but ~ 38% in ICH < 45 yrs of age):
  - Arterio-Venous malformation
  - Aneurysm
  - Cavernoma
  - AV fistula, etc.
- Anticoagulation (14%)
- Trauma
- Tumors
- Infection
- Hemorrhagic transformation of cerebral infarct
- Moyamoya disease
- Cerebral venous thrombosis

Causes remains undetermined in approximately 21% of spontaneous ICH.
Causes of Spontaneous ICH


Hypertension induced ICH

Chakrabarty, A., Shivane, A. 8(1), 2008

- Hyperplasia of the media in artery walls due to proliferation of reactive smooth muscle cells die → cells replaced by collagen fibers → brittle vessel wall

Pathophysiology Overview

Hypertension induced ICH

- Lipohyalinosis: Small vessel disease. Lipid accumulation in vessel wall causing narrowed lumen.
- Fibrinoid Necrosis: Accumulation of amorphous, basic, proteinaceous material in the tissue matrix with a staining pattern reminiscent of fibrin. NOT FIBRIN!
  - Antigen-Ab complexes stick to vessel wall → attract inflammatory cells → activate compliment leading to cell wall damage and necrosis.
- Hyperplasia of the media in artery walls due to proliferation of reactive smooth muscle cells die → cells replaced by collagen fibers → brittle vessel wall

Chakrabarty, A., Shivane, A. 8(1), 2008
Hypertension induced ICH:

- Charcot-Bouchard aneurysms: lenticulostriates, thalamoperforators, paramedian branches of the basilar artery, superior cerebellar arteries, and anterior inferior cerebellar arteries.

Cerebral Amyloid Angiopathy (CAA):

- Deposition of insoluble amyloid-beta peptides in the walls of leptomeningeal and cortical arteries, arterioles, and capillaries.
- Hemorrhages are superficial, lobar and commonly breach the cortical surface with associated subarachnoid hemorrhage.
- Can be multiple and recurrent
- Most commonly in age > 70
- Associated with Alzheimer's

Case Report:

This is a 57 y/o female with PMHx significant for HTN and Afib who presents approx 1 hour after acute onset of HA, right-sided weakness, dysarthria, and associated N/V.

- Initial Vitals:
  - BP 185/112, HR 115 bpm, RR 22, SpO2 99% on 2Lpm per NC
- Home medications: Lisinopril 20 mg QD, ASA 81 mg QD, and coumadin 5 mg Tu/Thurs and 2.5 mg on M/W/F/Sat
- Negative UDS
Radiographical Imaging

CT reveals a left thalamic, intracranial hemorrhage with intraventricular extension.

Radiographical Imaging for ICH:

• Initial – CT scan
  – Repeat imaging for assessment of expansion should be CT for accurate comparison...
    “Apples to apples…”

• Diagnostic evaluation
  – Vascular lesions: Angiography
  – Tumors / Infections: MRI w/wo contrast
  – Trauma: CT good for blood but MRI best for prognostication

Hemorrhage Assessment:

Location

• Supratentorial: Cerebrum, Lateral and third ventricle

• Infratentorial: Brain stem, Cerebellum, Fourth ventricle
Hemorrhage Assessment:

Size of hemorrhage:
A: Length (cm) x B: Width (cm) x C: Depth (# of slices) x slice thickness / 2

\[ \frac{5.2 \text{ cm} \times 5.8 \text{ cm} \times 6 \times 0.5}{2} = 45.2 \text{ ml ICH} \]

The ICH Score

Purpose: A clinical grading scale for ICH for accurate and rapid assessment of 30-day mortality.

Hemphill, et al. 2001 Stroke
This is a 57 y/o female with PMHx significant for HTN and Afib (on coumadin), who presents approx 1 hour after acute onset of HA, right-sided weakness, dysarthria, and associated N/V. Found per CT to have a hypertensive, left thalamic hemorrhage with intraventricular extension.

Supratentorial hematoma volume of 42 ml
ICH score of 3, predicting a 72% 30-day mortality
Medical Management

1st and utmost important...

Correction of Coagulopathy!!!

Coagulation Cascade
Correction of Coagulopathy

**Heparin / LMWH**

Mechanism: Binds to the enzyme inhibitor antithrombin III (AT) → inactivates thrombin, factor Xa and other proteases

Treatment:
- Ascertain last dose
- Reversal: Protamine sulfate
- May consider rFVIIa in LMWH if protamine contraindicated or continued hemorrhage despite protamine.

Frontera, et al. Neurocritical Care, 24, 2016
**Correction of Coagulopathy**

**Warfarin (Coumadin)**

Mechanism: "Vitamin K Antagonist" but rather antagonizes vitamin K1 recycling, depleting active vitamin K1.

Depletes factors II, VII, IX, and X ("27, 910")

Reversal: Vitamin K → (INR > 2) FFP or Prothrombin Complex Concentrate (PCC)

INR correction with FFP + Vit K ~ 4-5 times slower than with PCC.


**Coagulation Cascade**

**Direct Thrombin Inhibitors (Dabigatran)**

Bivalent: Hirudin, Bivalirudin, Desirudin, Lepirudin

Univalent: Argatroban

Mechanism: Directly inhibits the enzyme thrombin (factor II)

Treatment:
- Ascertain time of last dose
- If < 2 hrs since ingestion, administer activated charcoal
- Reversal: idarucizumab (Praxbind) – Adheres to thrombin binding sites
- Administer PCC
- Approx 50% dialyzable

Frontera, et al. Neurocritical Care, 24, 2016
Direct Xa Inhibitors
(Rivaroxaban, Apixaban, Edoxaban)

Mechanism: Inhibits factor Xa thereby interrupting the intrinsic and extrinsic pathway → inhibits thrombin formation

Treatment:
- Ascertain time of last dose
- If < 2 hrs, administer 50 g activated charcoal
- Prothrombin Complex Concentrate (PCC)
- Reversal: Andexanet – alfa may be a future option.

Anti-Platelet Agents
ASA/Plavix
- Platelet function testing if able
- Single dose desmopressin (DDAVP) = 0.3 mg/kg
- Platelet transfusion = inferior to standard of care
  Worsened outcomes!

Correction of Coagulopathy
Frontera, et al. Neurocritical Care, 24, 2016
Correction of Coagulopathy

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Reversal strategy</th>
<th>Mechanism</th>
<th>Approval status</th>
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<tbody>
<tr>
<td>Heparin, LMWH</td>
<td>protamine</td>
<td>Binding and inactivation of heparins</td>
<td>FDA-approved</td>
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<tr>
<td>Warfarin</td>
<td>Vitamin-K</td>
<td>Overwhelm warfarin inhibition of VKOR-C1</td>
<td>FDA-approved</td>
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<tr>
<td>Dabigatran</td>
<td>Idarucizumab (Praxbind®)</td>
<td>Monoclonal antibody that binds dabigatran</td>
<td>FDA-approved</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Kcentra® (4-factor PCC)</td>
<td>Factor replacement</td>
<td>Not-FDA approved (use based on very low quality and inconsistent evidence)</td>
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<td>Apixaban</td>
<td>Kcentra® (4-factor PCC)</td>
<td>Factor replacement</td>
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<tr>
<td>Edoxaban</td>
<td>Andexanet-alfa</td>
<td>Decoy Xa molecule</td>
<td>Under FDA review</td>
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Medical Management:

Next most important... Blood Pressure Control

Blood Pressure Goals

What are we trying to achieve?

...Maximal cerebral perfusion of both global parenchyma AND local, perihematomal tissue being compressed...
Blood Pressure Goals

What are we MOST afraid of?

MORE BLOOD!!!!

Blood Pressure Goals

So what SBP is best to obtain maximal perfusion with the least risk of worsening hemorrhage?

120???
140???
180???
160???

What do the studies show?

- Vemmos et al evaluated the relationship between SBP and DBP on admission and early or late mortality in acute stroke patients
- Prospective study of hospitalized, first-ever stroke patients over 8 yrs
- N = 1,121
- Admitted within 24 hrs of stroke onset
- Followed for 12 months
- Main outcome measures were mortality at 1 month and 12 months after stroke.

Results

Both high and low admission BP values are associated with poor outcome.


Is early, intensive BP-lowering safe?

INTERACT2 Trial
N = 2,794
Randomized to SBP < 140 mmHg or < 180 mmHg
Intensive lowering of blood pressure did not result in a significant reduction in the rate of death or severe disability.
Significantly better functional outcomes, as well as, better physical and psychological well-being among patients who received intensive treatment.
While poor eGFR predicts poor outcome, intensive BP reduction does not affect this.

Anderson, et al. NEJM, 368(25), 2013

Is early, intensive BP-lowering efficacious?

INTERACT2 Trial
• Did not significantly reduce death or disability.
• Trend toward improved functional outcomes
• No significant difference in size of hematoma between two groups.
Primary Outcome: Death or disability at 3 months after randomization.

N = 1000 (500 to each group)
Standard group (SBP 140 – 179 mmHg)
Intensive group (SBP 110 – 139 mmHg)

Eligibility:
ICH volume < 60 ml
GCS > 5

Conclusions:
Target SBP 110 – 139 mmHg did not result in lower rate of death or disability compared to the standard treatment group 140 – 179 mmHg.
Stopped early due to futility and adverse events (ie. renal injury)

So now we know that rapid, intensive, BP-lowering to 140 vs 180 is safe and potentially efficacious...

However, closer to 120 has worsened adverse events...

...but does a SBP of < 140 mmHg provide enough cerebral perfusion?
“A randomized clinical trial using CT perfusion in primarily small and medium ICH found no clinically significant reduction in cerebral blood flow within the perihematomal region related to early intensive BP lowering to an SBP target of <140 mm Hg within several hours of ICH.”

AHA / ASA Recommendation:

For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe (Class I; Level of Evidence A) and can be effective for improving functional outcome (Class IIa; Level of Evidence B)

(Revised from the previous guideline)

For ICH patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring.

(Class IIIb; Level of Evidence C). (New recommendation)
Antihypertensive Pharmacotherapy:

Nicardipine hydrochloride (Cardene)
- Dihydropyridine class of CCB
- More selective for cerebral and coronary blood vessels
- Does not intrinsically decrease myocardial contractility

Avoid nitroprusside (Nipride) and nitroglycerin infusions due to cerebral vasodilatory effects

Antihypertensive Pharmacotherapy:

Hydralazine (Apresoline)
- Direct-acting smooth muscle relaxant
- Decreases PVR thereby lowering afterload
- May increase HR and CO due to reflex sympathetic stimulation (baroreceptor reflex)
- May increase plasma renin concentration → fluid retention
- Can be given in combo with B-Blocker and a diuretic
Antihypertensive Pharmacotherapy:

Labetalol hydrochloride (Normodyne)

- Mixed alpha/beta adrenergic antagonist
- Short-term → decreases SVR without effect on SV, HR, or CO
- Long-term → decreases HR while maintaining CO with an increase in SV
- SE = postural hypotension

Better BP control than HR control

Glucose Management:

- High blood glucose on admission predicts increased risk of mortality and poor outcome
- Aggressive glucose management leads to increased incidence of both systemic and cerebral hypoglycemic events = increased risk of mortality

AHA / ASA Recommendation:
Closely monitor glucose but avoid both hyperglycemia and hypoglycemia. Goal 140-180 mg/dL.

(Class I; Level of Evidence C).

Temperature Management:

- Fevers worsen outcome and increases cerebral metabolic demand
- Hypothermia thought to reduce perihematomal edema but no evidence
- Common in ICH, especially those with IVH, due to huge inflammatory response
- Goal should be normothermia

AHA / ASA Recommendation:
Treatment of fever after ICH is reasonable.

(Class IIb; Level of Evidence C). (New recommendation)
Seizures and Seizure Prophylaxis:

- Frequency of clinical sz within 1 week after ICH = up to 16%
- Despite prophylaxis, 28-31% still have electrographic seizures on continuous EEG
- Cortical involvement single highest predictor


Seizures and Seizure Prophylaxis:

Do seizures (clinical or electrographic) worsen outcomes?

Passero, et al (2002) performed study followed 761 patients with spontaneous, nontraumatic ICH in order to characterize seizures after ICH, evaluate risk for relapse, predisposing factors, prognostic significance, and to assess the utility of AED therapy.

“...short-term mortality was not affected, and the risk of epilepsy was lower than previously thought”


Seizures and Seizure Prophylaxis:

Purpose: Assess the occurrence of seizures and neurologic outcome in SICH patients randomized to either valproic acid (VPA) or placebo x 1 month after SICH.

N = 7

No benefit on mortality but could provide improve neurological outcomes.

"No statistical difference found for seizure prevention in those prescribed prophylactic anticonvulsants"


**AHA / ASA Recommendation:**
Clinical or subclinical seizures should be treated with anti-seizure drugs.

(Class I; Level of Evidence A)

Prophylactic anti-seizure medication is not recommended

(Class III; Level of Evidence B)

Consider continuous EEG when mental status disproportionate to degree of brain injury.

(Class IIa; Level of Evidence C)

**Great! Wait... so you want to start prophylaxis anyway?!?!**
Seizures and Seizure Prophylaxis:

So which drug is best?

Seizures and Seizure Prophylaxis:

Retrospective analysis

N = 85
(25 phenytoin vs 60 levetiracetam)

Found "levetiracetam is more effective than phenytoin for seizure prophylaxis without suppression of cognitive abilities in patients with ICH".
ICP Monitoring and Treatment

Ventricular drainage for hydrocephalus is reasonable, especially in the setting of decreased LOC.

(Class IIa; Level of Evidence B) (Revised from the previous guideline)

Those with extensive intraventricular hemorrhage with concern for developing hydrocephalus.

(Class IIb; Level of Evidence C)

GCS < 8 and/or evidence of transtentorial herniation.

(Class IIb; Level of Evidence C)

Corticosteroids should not be administered for treatment of elevated ICP in ICH.

(Class III; Level of Evidence B) (New recommendation)

Intraventricular Hemorrhage (IVH)

- IVH occurs in ~45% of patients with spontaneous ICH
- Can lead to a clot in the CSF conduits blocking its flow and leading to obstructive hydrocephalus which may quickly result in increased ICP and death.
- Inflammatory response damages the arachnoid granulations, inhibiting the regular reabsorption of CSF and resulting in permanent non-obstructive hydrocephalus.

Intra-thecal tPA Administration

A multicenter, randomized, double-blinded, placebo-controlled phase III study of Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III)

- In IVH pts, rt-PA has been shown to reduce morbidity and mortality by accelerating blood clearance and clot lysis.
- CLEAR-IVH Trial: Patients treated with rtPA had significantly lower intracranial pressures, fewer VC obstructions that required replacement, and non-significantly shorter duration of VC requirement.
  1. Slightly increased risk of symptomatic bleeding
  2. Less need for permanent shunting
  3. No statistical difference in mRS or mortality
Conclusion

AHA / ASA Recommendations:
Although intraventricular administration of rtPA in IVH appears to have a fairly low complication rate, the efficacy and safety of this treatment are uncertain.

The efficacy of endoscopic treatment of IVH is uncertain.

(Class IIb; Level of Evidence B). (New recommendation)

Supratentorial Intracerebral Hemorrhage

• Above the tentorium
• Majority of intracranial hemorrhages
• High morbidity and mortality

Surgery vs Conservative Treatment

STICH Trial
Question: Does early surgery reduce mortality and improve neurological outcome compared with conservative management?

Answer: 26% vs 24% = No overall statistically significant difference in mortality or functional outcome.
Surgery vs Conservative Treatment

STICH II Trial
Question: Is early surgery would be beneficial for conscious patients with superficial lobar hemorrhage within 1 cm of the cortical surface?

Answer: 41% (early surgery group) vs 38% (medical arm) had favorable outcomes; this difference was not statistically significant.

Non-significant survival advantage

Conclusion

Study Findings:
Patients with spontaneous supratentorial intracerebral hemorrhage in neurosurgical units show no overall benefit from early surgery when compared with initial conservative treatment.

However, the STICH II results confirm:
1. That early surgery does not increase the rate of death or disability at 6 months
2. Early surgery might have a small but clinically relevant survival advantage for patients with spontaneous superficial intracerebral haemorrhage without intraventricular hemorrhage.

Supratentorial hematoma evacuation in deteriorating patients might be considered as a life-saving measure.

(Class IIb; Level of Evidence C). (New recommendation)

Minimally Invasive Clot Evacuation
Conclusion

**Preliminary Findings:**
Thus far study has demonstrated a **significant reduction in perihematomal edema** in the hematoma evacuation group with a **trend toward improved outcomes**.

**AHA / ASA Recommendations:**
The effectiveness of minimally invasive clot evacuation with stereotactic or endoscopic aspiration with or without thrombolytic usage is **uncertain**. *(Class IIb; Level of Evidence B)*

**Infratentorial Intracerebral Hemorrhage**
- Below the tentorium
- Narrow confines of the posterior fossa can quickly lead to deterioration in cerebellar hemorrhage caused by obstructive hydrocephalus or local mass effect on the brainstem.
Conclusion

AHA / ASA Recommendations:
Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible.

(Class I; Level of Evidence B)

Initial treatment of these patients with ventricular drainage rather than surgical evacuation is not recommended.

(Class III; Level of Evidence C)

Summary
Top 5 things to remember

1. Spontaneous, atraumatic ICH has significant impact on not only mortality, but also functional impairment.
2. Correction of coagulopathy and BP management (SBP < 140) are of utmost importance in the acute management phase.
3. Direct catheter injected tPA has shown promise in both IVH and IPH resolution.
4. Spontaneous, supratentorial, intracerebral hemorrhage show no overall benefit from early surgery when compared with initial conservative treatment.
5. Spontaneous, infratentorial hemorrhages should undergo emergent evacuation as soon as possible.