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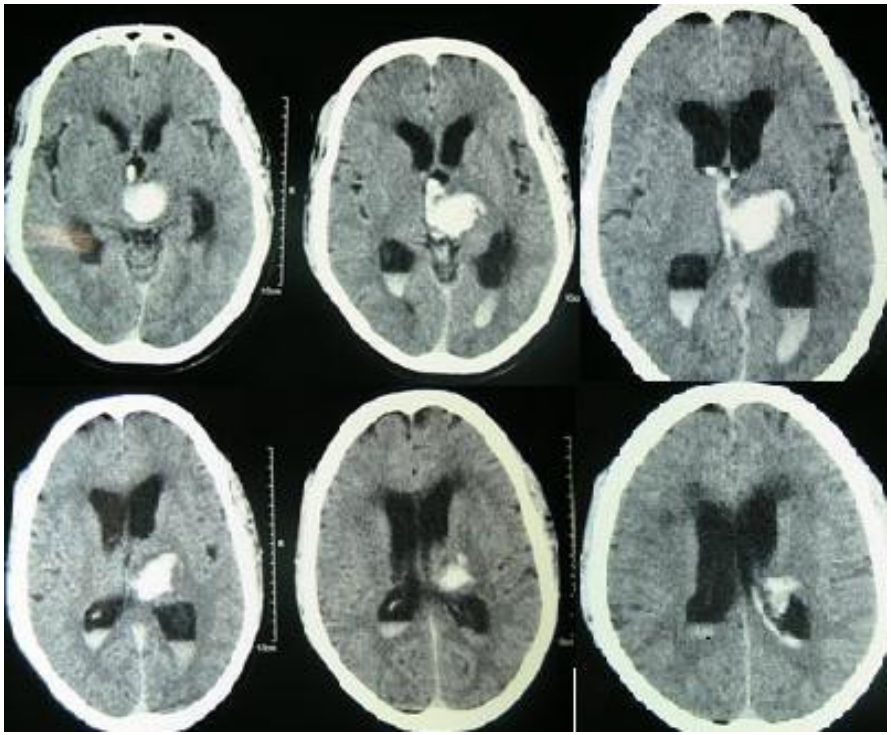
Intracerebral Hemorrhage (ICH)



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William Barsan, MD
Department of Emergency Medicine

Introduction

- Spontaneous (atraumatic) ICH: bleeding into the parenchyma of the brain that may extend into the ventricles and subarachnoid space.
- 10-15% of all cases of stroke
- Mortality
  - 6 month 30-50%
  - One year 50%

Intracerebral Hemorrhage

- Spontaneous, non-traumatic intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality throughout the world.

- Excellent medical care has a potent, direct impact on ICH morbidity and mortality, even before a specific therapy is found.

- The overall aggressiveness of ICH care is directly related to mortality from this disease.

- AHA has new guidelines for 2010, updated from 2007

Classification

- Primary (80-90%)
  - Spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy
- Secondary
  - Vascular abnormalities (AVM, aneurysm)
  - Tumor
  - Coagulopathy

Pathophysiological features

- Origin of hematoma
  - Degenerative changes in the vessel wall induced by chronic hypertension.
  - Dilatation in the walls of small arterioles. (microaneurysms)
  - Electron-microscopical study: most bleeding occur at the bifurcation of affected arteries.

Where do they occur?

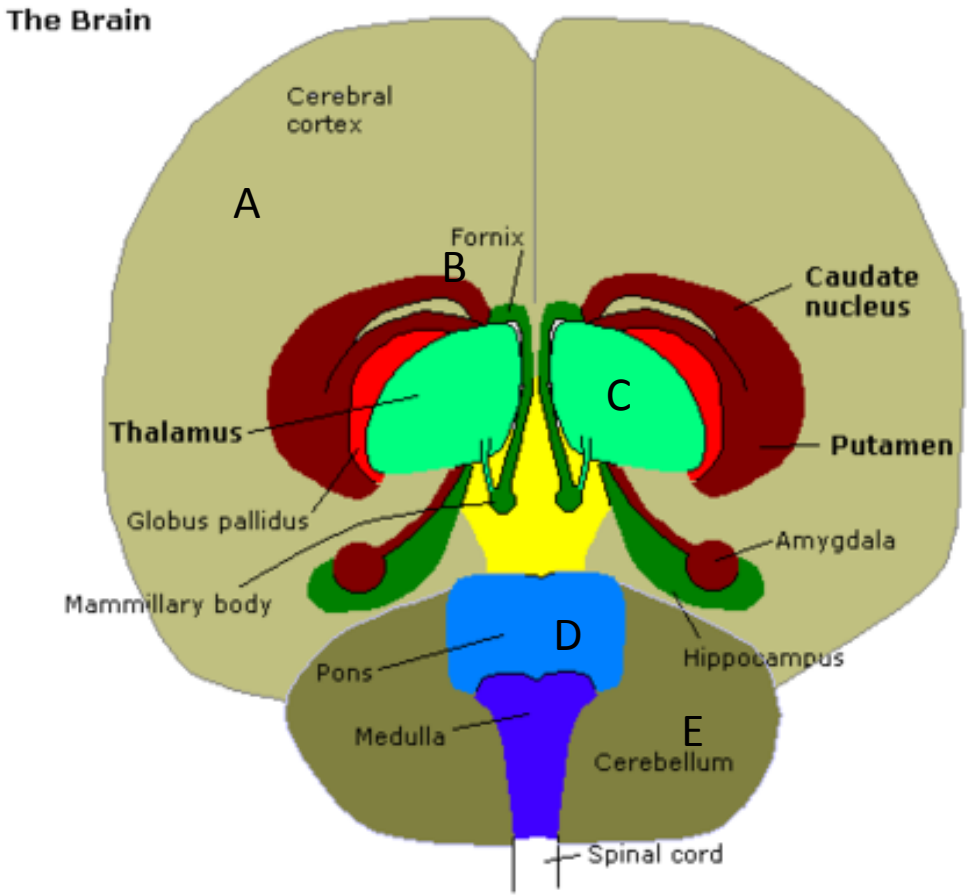
A. Lobar

B. Basal ganglia

C. Thalamus

D. Brain stem (pons predominantly)

E. Cerebellum



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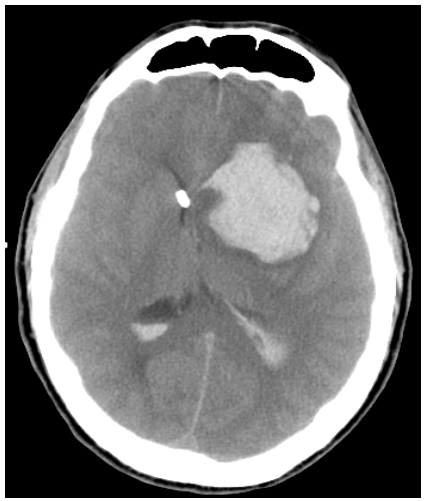
Predictors of Outcome

- Hematoma volume
- GCS
- Intraventricular hemorrhage
- Age
- ICH location
- Increased cerebral edema



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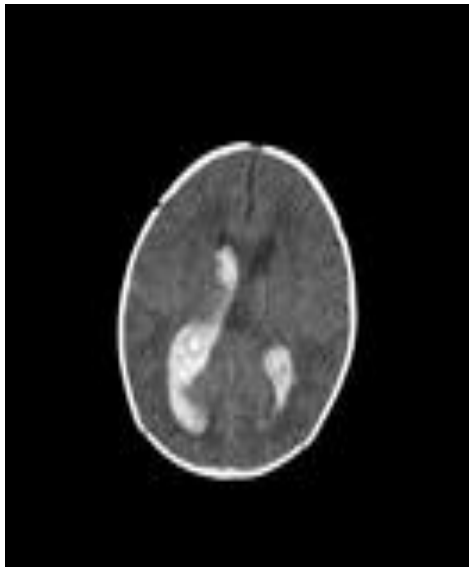

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Mechanisms of Injury

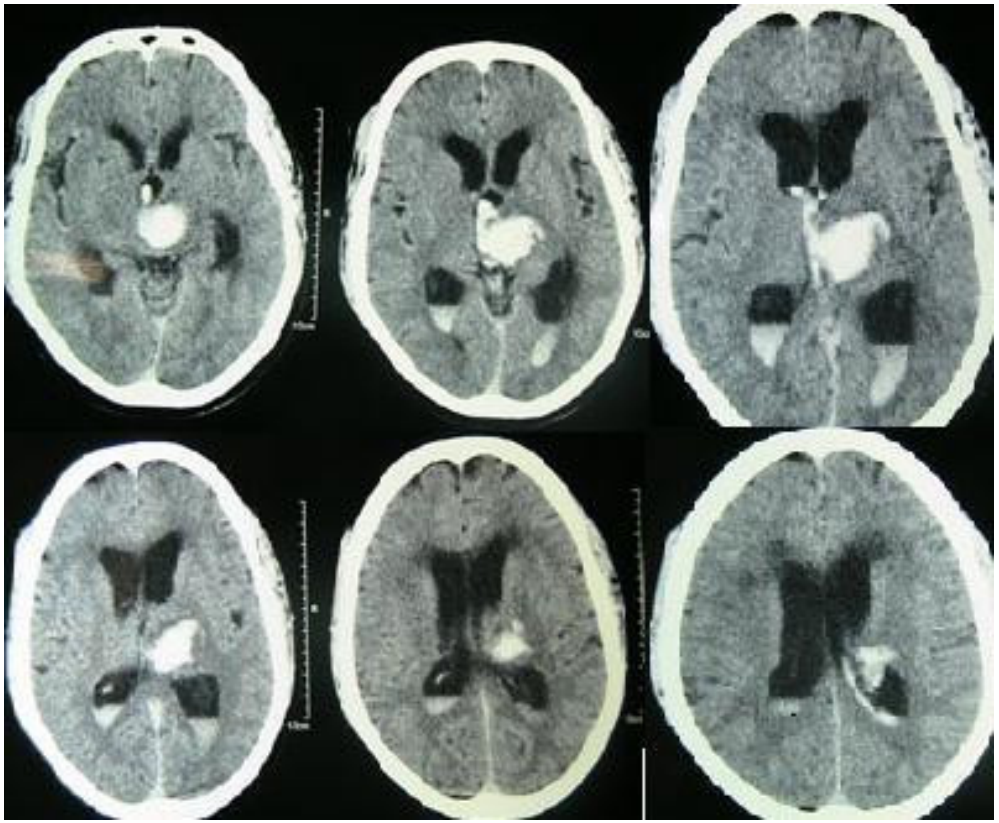
- **Early hematoma growth**
  - Hematoma enlargement
  - Increase in ICP, tissue disruption, shear forces
- **Edema and toxic effects of blood products**
  - Osmotically active serum products
  - Thrombin
- **Inflammatory response**

Hematoma Expansion

72% have some hematoma expansion over the first 24 hours

38% have significant (>33%) expansion over 24 hours

In 26% of these cases, the enlargement is within 1 hour



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Definition of Classes and Levels of Evidence Used in AHA Stroke Council Recommendations

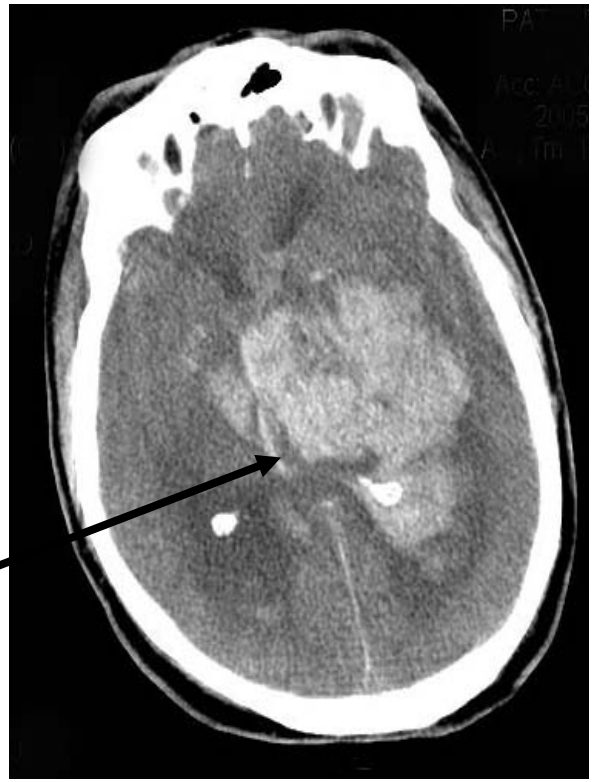
- **Class I** — **Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.**
- **Class II** — **Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.**
- **Class IIa** — **The weight of evidence or opinion is in favor of the procedure or treatment.**
- **Class IIb** — **Usefulness/efficacy is less well established by evidence or opinion.**
- **Class III** — **Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.**
- **Therapeutic recommendations**
- **Level of Evidence A** — Data derived from multiple randomized clinical trials or metaanalyses
- **Level of Evidence B** — Data derived from a single randomized trial or nonrandomized studies
- **Level of Evidence C** — Consensus opinion of experts, case studies, or standard of care
- **Diagnostic recommendations**
- **Level of Evidence A** — Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
- **Level of Evidence B** — Data derived from a single grade A study, or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
- **Level of Evidence C** — Consensus opinion of experts

Presentation Content Areas

- Neuroimaging of ICH
- Hemostasis
- Blood pressure management
- Inpatient management and prevention of secondary injury
- Intracranial pressure (ICP)/glucose/seizures/ hydrocephalus
- Surgical treatment of ICH
- Intraventricular hemorrhage
- Withdrawal of technological support
- Prevention of recurrent ICH
- Rehabilitation and recovery

Neuroimaging of ICH

Computed tomography (CT) scan showing Left hemisphere intracerebral hemorrhage (ICH) with intraventricular extravasation



Large left intraparenchymal hematoma (ICH)

Recommendations for Neuroimaging in ICH

- **Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH**

  Class I, Level of Evidence A *(Unchanged from the previous guideline).*

- **CT angiography and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion**

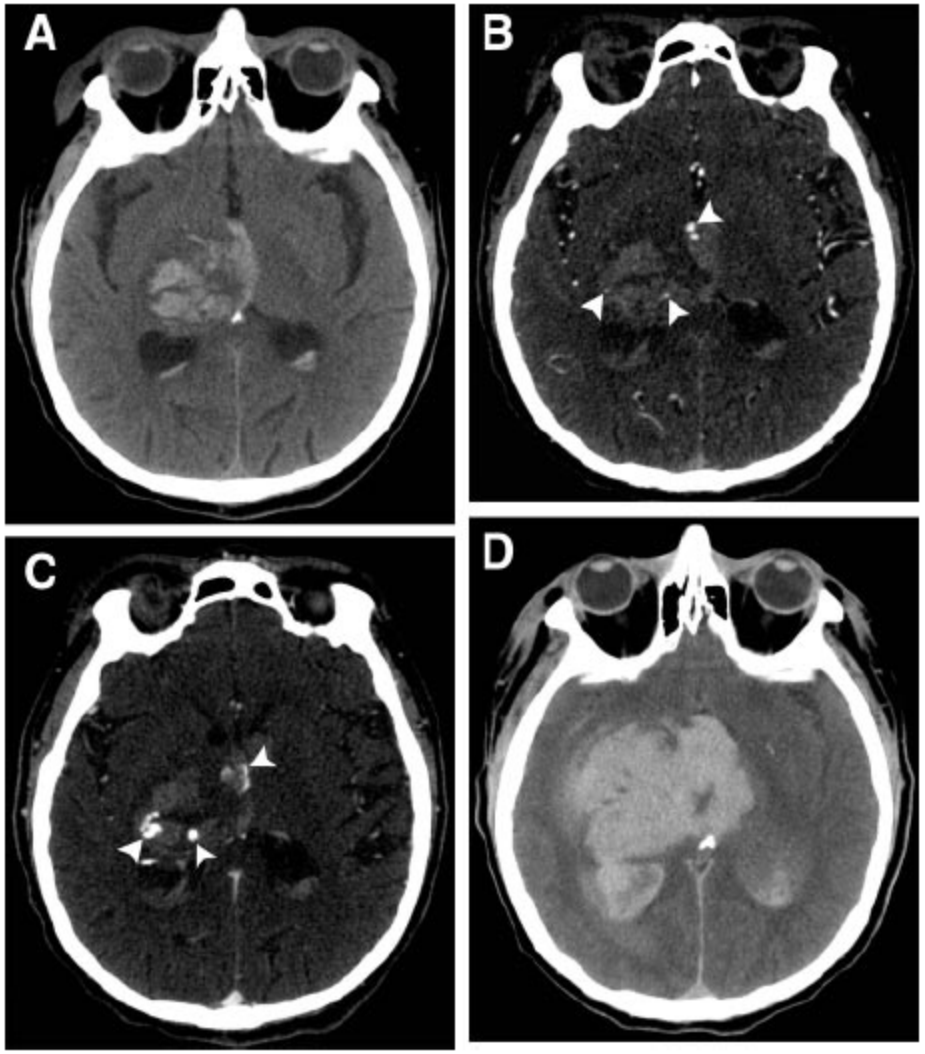
  Class IIb, Level of Evidence B

- **CT angiography, CT venography, contrast-enhanced CT, contrast-enhanced MRI, MRA and MRV can be useful to evaluate for underlying structural lesions including vascular malformations and tumors when there is clinical or radiologic suspicion**

  Class IIa, Level of Evidence B (*New recommendation).*

CTA and ICH: SPOT sign

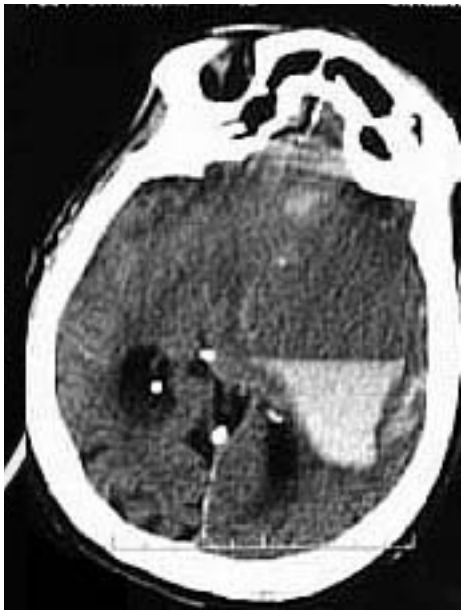
- CT contrast extravasates into hematoma
  - Spot sign, white arrows
- May predict hematoma expansion



Imaging of Underlying Structural Lesions?

- CTA/CTV, MRI with gadolinium, MRA/MRV can all be useful to evaluate for underlying structural lesions, including vascular malformations and/or tumors
  - When there is clinical or radiologic suspicion

Anticoagulation and ICH



- Anticoagulation leads to more hematoma growth and higher mortality
  - Reverse warfarin promptly and aggressively
  - FFP or prothrombin complex concentrates (PCCs)
  - IV vitamin K
    - Faster than SQ/PO but a small risk of anaphylactoid reaction

Reversal of Anticoagulation in ICH patients

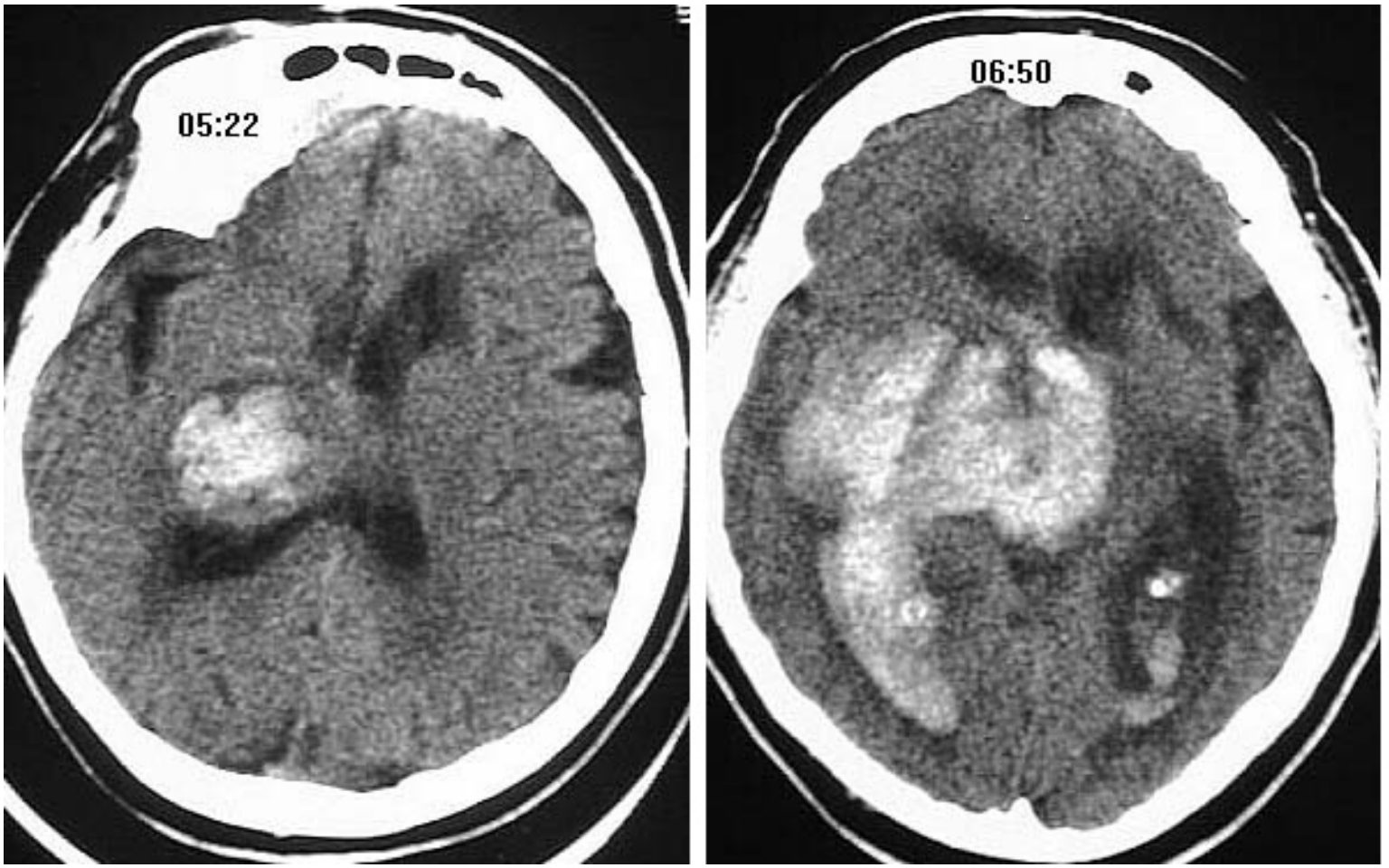
- Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively (Class I, C)

- Patients with ICH whose INR is elevated due to OAC's should have their warfarin withheld, receive therapy to replace vitamin K-dependent factors and correct the INR, and receive intravenous vitamin K (Class I, C)

- PCCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP (Class IIa, B)

- The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and is considered investigational (Class IIb, B)

Potential Treatments for ICH: The Problem of Hematoma Expansion



Source Undetermined

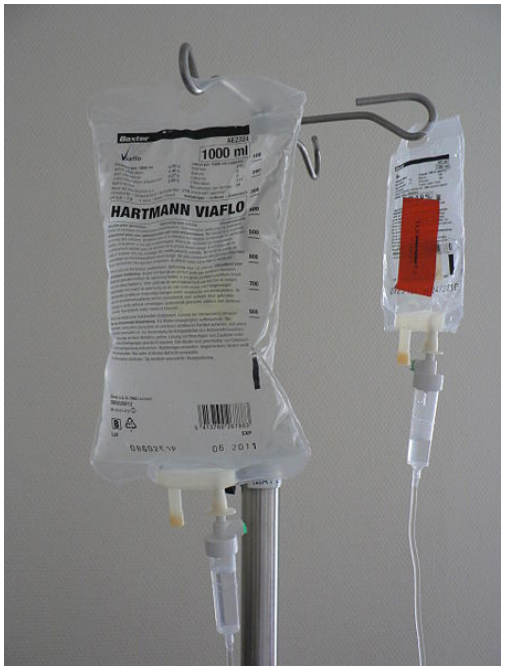
Hematoma Expansion is Common

- Brott, et al., 1997
  - 103 pts., prospective observational study with serial CT scanning (baseline, 1 hr and 20 hrs following ICH)
  - 26% showed >33% enlargement on 1 hr CT
  - 38% showed >33% enlargement on 20 hr CT
  - Neurologic deterioration correlated with hematoma expansion

- Brott T et al, Stroke. 1997 Jan;28(1):1-5.

Recombinant Activated Factor VII*

- rFVIIa, NovoSeven©
- Used for hemophilia
- Induces local hemostasis when it binds to tissue factor
  - The complex can activate Factors IX and X
  - Factor Xa helps convert prothrombin to thrombin



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*Not FDA approved for ICH

“FAST” Trials

- A phase II randomized trial showed that treatment with rFVIIa within four hours after ICH onset
  - limited hematoma growth
  - improved clinical outcomes relative to placebo
  - increased frequency of thromboembolic events (7% vs. 2%)

- A subsequent phase III study comparing placebo to 20 µg/kg and 80 µg/kg of rFVIIa:
  - both doses diminished hematoma enlargement
  - failed to show differences in clinical outcome
  - Overall serious thromboembolic adverse event rates were similar, the higher rFVIIa (80 µg/kg) group had significantly more arterial events than placebo.

- The authors noted imbalances in treatment groups, particularly intraventricular hemorrhage in the higher dose rFVIIa group

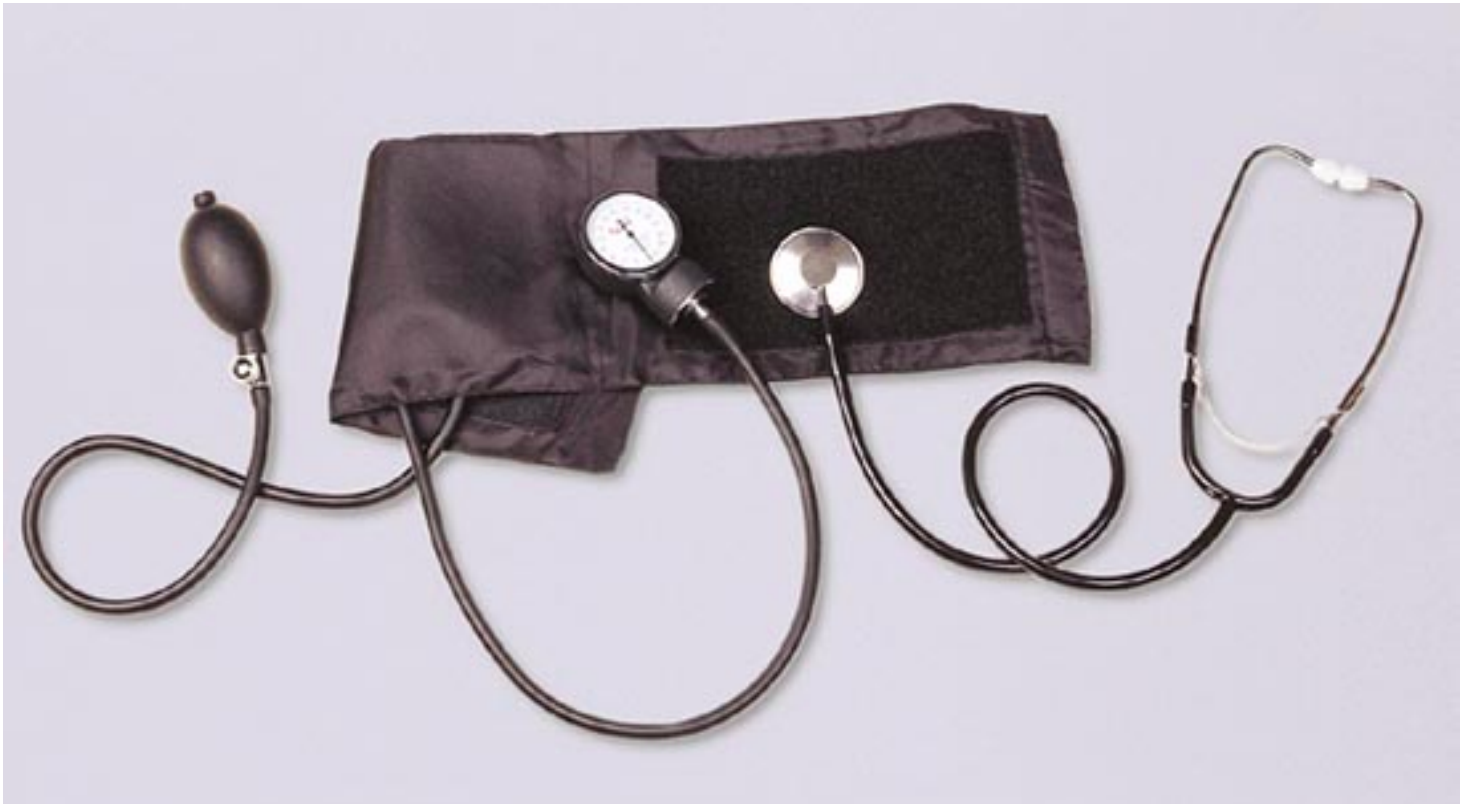
Mayer SA, et al for the FAST Trial Investigators., N Engl J Med. 2008 May 15;358(20):2127-37.
Mayer SA for the FAST Trial Investigators. N Engl J Med. 2005 Feb 24;352(8):777-85.

Factor VIIa

- Factor VIIa can limit hematoma expansion in non-coagulopathic patients, but also increases thromboembolic risk.
  - *rFVIIa is not recommended in unselected patients*
- rFVIIa does NOT replace clotting factors, even though INR normalizes
  - *rFVIIa is not recommended as the only agent to reverse INR in ICH patients*

Mayer SA, et al for the FAST Trial Investigators., N Engl J Med. 2008 May 15;358(20):2127-37.
Mayer SA for the FAST Trial Investigators. N Engl J Med. 2005 Feb 24;352(8):777-85.

Blood Pressure and ICH: Is it safe to lower BP in the acute setting?



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INTERACT

- 404 ICH pts, randomized into:
  - Target SBP of 140mmHg within 1 hr OR
  - Target SBP of 180mmHg
- Trend towards lower hematoma growth
- No increase in adverse events related to BP-lowering
- No differences in clinical outcome/QOL
  - Not powered for clinical endpoints

Anderson CS, et al. *Lancet Neurol.* 2008;7(5):391-399

ATACH

- 80 ICH pts
- 4-tier, dose escalation of IV nicardipine-based lowering of BP
- Confirmed safety and feasibility of early rapid BP lowering

Qureshi AI, et al, for the ATACH Investigators Arch Neurol. 2010 May;67(5):570-6

Summary of New BP Lowering in ICH Trials

- These new studies have shown that intensive BP lowering is clinically feasible and potentially safe
- BP targets, duration of therapy is unknown
- No studies have shown clinical benefit so far

Blood Pressure Recommendations

- Until ongoing clinical trials of BP intervention for ICH are completed, physicians must manage BP on the basis of the present incomplete efficacy evidence (Class IIb, C)
- In patients presenting with a systolic BP of 150-220 mmHg, acute lowering of systolic BP to 140 mmHg is probably safe (*Class IIa, B*)

Recommended BP Treatment Targets

- If SBP is >200 mmHg or MAP is >150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.

- If SBP is >180 mmHg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure $\geq$ 60 mmHg

Recommended BP Treatment Targets

- If SBP is >180 mmHg or MAP is >130 mm Hg and there is not evidence of elevated ICP, then consider a modest reduction of blood pressure (eg, MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically reexamine the patient every 15 minutes.

Inpatient Management: Medical Considerations

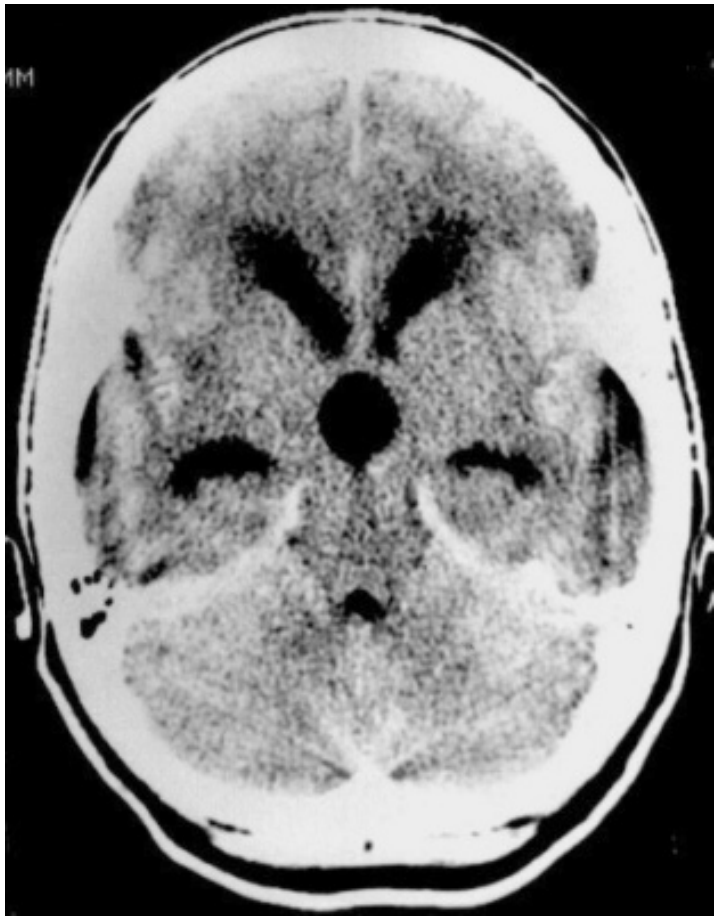
- Initial monitoring and management of ICH patients should take place in an intensive care unit with physician and nursing neuroscience intensive care expertise (Class I, B)
- Glucose should be monitored and normoglycemia is recommended *(Class I, C)*
- Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings (Class I, B)
- After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset *(Class IIb, B)*

Inpatient Management of Prevention of Secondary Brain Injury: Medical Considerations *Seizures and Antiepileptic Drugs*

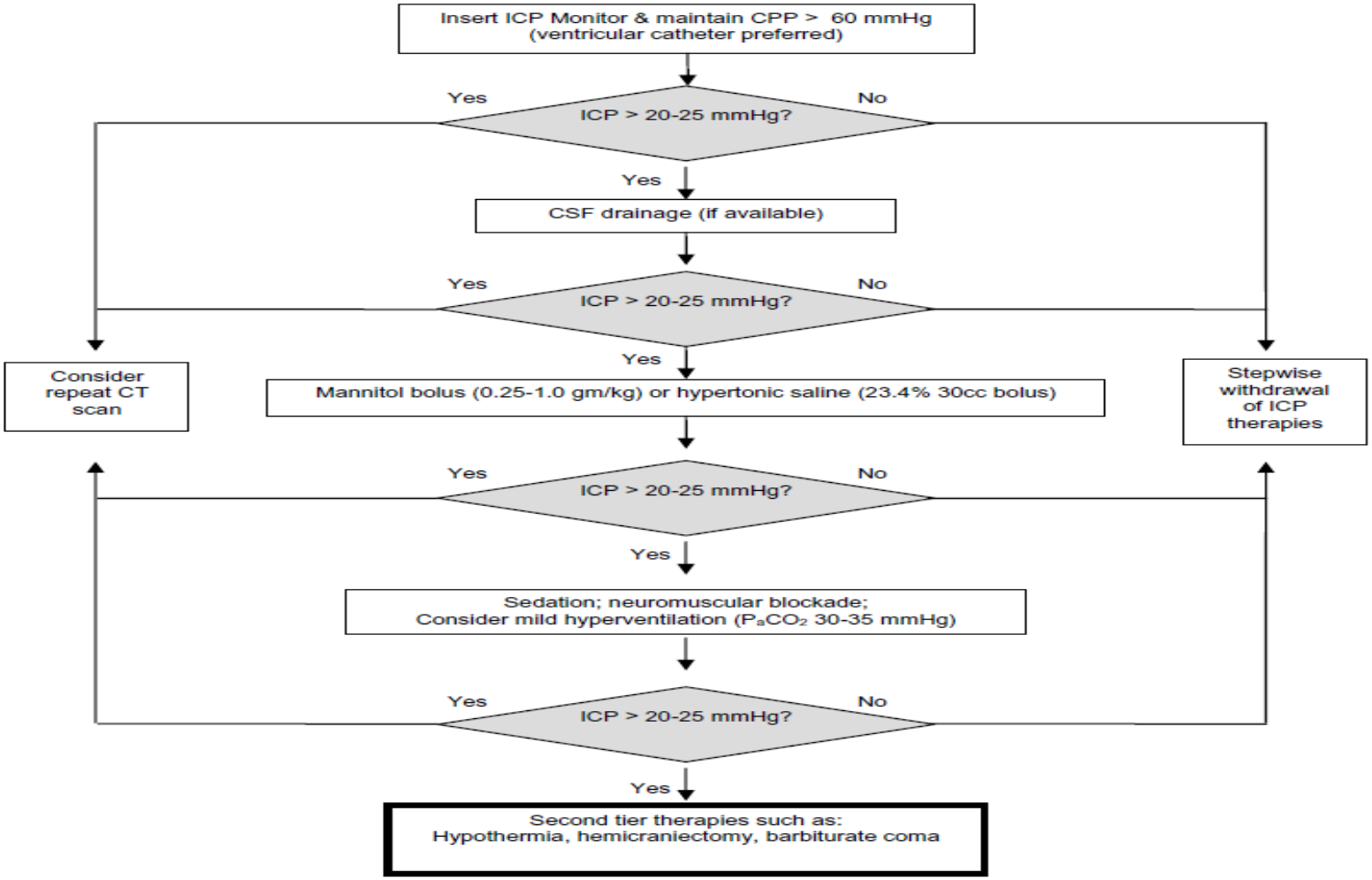
- Clinical seizures should be treated with anti-epileptic drugs *(Class I, A)*
- Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury (Class II, B)
- Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with anti-epileptic drugs (Class I, C)
- Prophylactic anticonvulsant medication should not be used *(Class III, B)*

Hydrocephalus

- Hydrocephalus can accompany ICH, especially intraventicular rupture (IVH)
- Elevates ICP
- Results in early or delayed neurologic deterioration



Intracranial Pressure Treatment Algorithm



CLEAR-IVH Trial

- 52 pts with IVH
- Open-label intra-ventricular rt-PA to accelerate blood clearance and lysis
- Adverse events
  - Symptomatic bleeding 4%
  - Bacterial ventriculitis 2%
  - 30 day mortality 17%
- Efficacy requires confirmation before use of intraventricular fibrinolysis can be recommended, Phase III trial in progress

ICP Monitoring and Ventriculostomy

- Patients with a GCS score of 8 or less, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment. A CPP of 50-70 mmHg may be reasonable to maintain depending on the status of cerebral autoregulation *(Class IIb, C)*
- Ventricular drainage as treatment for hydrocephalus is reasonable in patients with decreased level of consciousness *(Class IIa, B)*
- Although intraventricular administration of rt-PA in IVH appears to have a fairly low complication rate, efficacy and safety of this treatment is uncertain and is considered investigational *(Class IIb, B)*

Surgical Management of ICH

STICH Trial

- 902 ICH pts randomized trial of early hematoma evacuation (<96 hrs) vs medical
  - Excluded cerebellar ICH
- If ICH >1 cm from cortical surface, OR

  GCS ≤ 8
  - Surgical patients tended to do worse than medical
- If ICH < 1cm from surface
  - Trended toward better outcomes with surgery, but not significant (OR 0.69, 95% CI 0.47-1.01)

Mendelow AD, et al for the STICH Investigators. *Lancet* 2005;365(9457):387-397

Surgical ICH Trials

- Timing of surgery: What is “early”?
  - Trials have been done using <24, 48, 72, and 96 hours
  - Regardless of definition, no clear benefit for surgery
- Minimally invasive techniques are being studied

Surgical Recommendations

- For most patients with ICH, the usefulness of surgery is uncertain *(Class IIb, C)*
- Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible *(Class I, B)*
- Initial treatment of these cerebellar hemorrhage patients with ventricular drainage alone rather than surgical evacuation is not recommended *(Class III,C)*

Surgical Recommendations

- For patients presenting with lobar clots >30 cc and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered *(Class IIb, B)*
- The effectiveness of minimally invasive clot evacuation utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain and is considered investigational *(Class IIb, B)*
- While theoretically attractive, no clear evidence at present indicates that ultra-early removal of supratentorial ICH improves functional outcome or mortality rate. Very early craniotomy may be harmful due to increased risk of recurrent bleeding (Class III, B)

Outcome Prediction and Withdrawal of Technological Support

- Aggressive full care early after ICH onset and postponement of new DNR orders until at least the second full day of hospitalization is probably recommended (Class IIa, B)
- Patients with pre-existing DNR orders are not included in this recommendation. Current methods of prognostication in individual patients early after ICH are likely biased by failure to account for the influence of withdrawal of support and early DNR orders. Patients who are given DNR status at any point should receive all other appropriate medical and surgical interventions unless otherwise explicitly indicated. *(revised from the previous guideline).*

Risk Factors for Recurrent ICH

- Lobar ICH
- Older age
- Anticoagulation
- Apo E e2 or e4 alleles
- Increased number of “microbleeds” on MRI

Integral components of the history, physical examination & work up of the ICH patient in the emergency department

- **History**

• Time of symptom onset (or time the patient was last normal)	
• Vascular risk factors	Hypertension, diabetes, hypercholesterolemia, and smoking
• Medications	Anticoagulants, antiplatelet agents, decongestants, antihypertensive medications, stimulants (including diet pills), sympathomimetics
• Recent trauma or surgery	Carotid endarterectomy or carotid stenting in particular, as ICH may be related to hyperperfusion after such procedures
• Dementia	Associated with amyloid angiopathy
• Alcohol or illicit drug use	Cocaine and other sympathomimetic drugs are associated with ICH, stimulants
• Seizures	
• Liver disease	May be associated with coagulopathy
• Cancer and hematologic disorders.	May be associated with coagulopathy

Integral components of the history, physical examination & work up of the ICH patient in the emergency department

- **Physical Examination**

- Vital signs

Fever is associated with early neurologic deterioration.[19]

Higher initial blood pressure is associated with early neurologic deterioration and increased mortality.[216]

- A general physical exam focusing on the head, heart, lungs, abdomen, and extremities.

- A thorough but time urgent neurologic exam

A structured exam such as the National Institutes of Health Stroke Scale (NIHSS) can be completed in minutes and provides a quantification that allows easy communication of the severity of the event to other caregivers. Glasgow Coma Score (GCS) is similarly well known, easily computed, and the initial GCS is a strong predictor of long term outcome. [167, 215] These can be supplemented as needed.

Integral components of the history, physical examination & work up of the ICH patient in the emergency department

- **Serum and Urine Tests**

• Complete blood count, electrolytes, blood urea nitrogen and creatinine, and Glucose	Higher creatinine is associated with hematoma expansion. Higher serum glucose is associated with hematoma expansion and worse outcome (although there are no data to suggest that normalization improves outcome).[216, 217]
• Prothrombin time (PT) or international normalized ratio (INR) and an activated partial thromboplastin time (aPTT)	Warfarin-related hemorrhages are associated with an increased hematoma volume, greater risk of expansion, and increased morbidity and mortality. [17, 197, 218]
• Toxicology screen in young or middle-aged patients to detect cocaine and other sympathomimetic drugs of abuse	Cocaine and other sympathomimetic drugs are associated with ICH
• Urinalysis and urine culture and a pregnancy test in a woman of childbearing age.	

Integral components of the history, physical examination & work up of the ICH patient in the emergency department

- **Other Routine Tests**

• EKG	To assess for active coronary ischemia or prior cardiac injury that may indicate poor cardiac function, and to obtain a baseline in the event of cardiopulmonary issues during hospitalization.
• Chest radiograph	
• Neuroimaging	As described in the text