Intracerebral Hemorrhage (ICH)
s. spontaneous ICH (sICH), intraparenchymal hematoma (IPH)

Last updated: August 8, 2020

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- spontaneous ICH - no immediately preceding trauma.
- spontaneous ICH - most common type of nontraumatic intracranial hemorrhage.

Commonest sites of ICH:
- Putamen (40-44%)
- Thalamic (10-15%)
- Cerebellum (5-10%)
- Pons (15-15%)
- Caudate (4-7%)
- Lobar subcortical (10-25%)

i.e. 60% basal nuclei, 20% posterior fossa, 20% thalamus & subcortical white matter

- in *whites*, most of the initial and recurrent ICHs tend to be *lobar*, whereas *deep* hemorrhages (both initial and recurrent) are more common in *Asians*.

ICH - blood clot in brain parenchyma (usually from rupture of small penetrating artery)

- spontaneous ICH - no immediately preceding trauma.
- spontaneous ICH - most common type of nontraumatic intracranial hemorrhage.

[Diagram of ICH sites]

ETIOLOGY

Multiple microbleeds:
- Elderly – chronic hypertension or amyloid angiopathy.
- Children – cavernomas or hematologic abnormalities.

Any age - acute disseminated encephalomyelitis (s. acute hemorrhagic leukencephalopathy, Weston-Hurst disease).

1. Arterial hypertension – most common cause of ICH (called hypertensive ICH).
- acute hypertension can be caused by sympathomimetic drugs.
- chronic hypertension causes amyloid arteriolosclerosis (lipohyalinosis) in and CHARGE-BOUCHARD microaneries.
- mostly affected are deep penetrating arteries (of circle of Willis and of basilar artery) – feed directly off medium-sized arteries and are not protected by the usual step-down in vessel size that protects more distal end arteries of cortical vessels from high intraluminal pressure; subcortical arteries are less frequently affected.
- exclusion of these arteries causes lacunar infarctions.

commonest sites for hypertensive ICH (in order of frequency):
1) putamen / external capsule – classic!
2) thalamus
3) cerebellum
4) pons
5) caudate

N.B. lobar subcortical white matter is not usual site for hypertensive ICH! (because of improved hypertension control, percentage of lobar ICH has increased)

Hematoma centered in striatocapsular region - external capsule/putamen - classic for hypertensive hemorrhage:

Source of picture: Anne G. Osborn “Osborn’s Brain - Imaging, Pathology, and Anatomy” (2012); Publisher: Lippincott Williams & Wilkins; ISBN 13: 978-1931884211

2. Cerebral amyloid angiopathy (s. congophilic angiopathy)
- appears in Alzheimer’s disease (rare in patients < 55, except in Down syndrome) – look for dementia when collecting PMH / ROS.
- amyloid deposits (chemically related to Alzheimer plaques) in media of smaller cerebral arteries (but not elsewhere in body – no systemic amyloidosis!).
- probably amyloid potentiates PLASMINOGEN.
- multiple small nonhypertensive lobar hemorrhages.
- diagnosed only postmortem by Congo red staining (“congophilic angiopathy”).
- clinical diagnosis - modified Boston criteria (sensitivity 94.7%, specificity 81.2%).

Signs of moderate / severe CAA (vs. absent / mild CAA) in patients with lobar ICH:
1) SAH (89% vs 42%; P=0.014)
2) intracerebral hemorrhage with finger-like projections (39% vs 0%; P=0.043)
3) presence of APOE ε4 (genotyping from peripheral blood samples) (50% vs 8%; P=0.002).

SAH + either APOE ε4 or finger-like projections is 96% sensitive to rule in CAA-associated lobar ICH.

prognosis – see below >>
3. Structural lesions - most common etiology in lobar hemorrhages (vs. only rarely affect basal ganglia, thalamus, pons).

   Child with ICH - AVM until proven otherwise!

1) ruptured vascular malformations & aneurysms - second most common cause of ICH!
   e.g. young normotensive patient with lobar and intraventricular hemorrhages
   *aneurysms rarely bleed only into brain, causing local hematoma near brain surface (e.g. when surrounding subarachnoid space has been ‘sealed off’ by preceding SAH)

2) hemorrhages within tumors (esp. glioblastoma multiforme, metastases of melanoma, renal carcinoma, choriocarcinoma).


5. Hyperperfusion after carotid stenting / endarterectomy.

6. Venous sinus thrombosis.

7. Hollinger’s Spätapoplexie - delayed ICH post TBI.

ETIOLOGY ACCORDING TO PATIENT’S AGE

YOUNG PERSONS – vascular disorders (AVM, aneurysm, vasculitis), drug abuse (amphetamine, cocaine); hematologic abnormalities

ELDERLY PERSONS – hypertension, amyloid angioptathy, tumors, coagulopathies (incl. anticoagulants).

PRECIPITATING CONDITIONS

1. Pregnancy (esp. with eclampsia)
   - eclampsia causes > 40% ICHs in pregnancy.
   - ICH is common cause of death from eclampsia.

2. Acute BP elses (can cause ICH even in absence of preexisting severe hypertension?), e.g. sympatheticetimetic drugs (esp. cocaine, amphetamine).

3. Bleeding diathesis (esp. iatrogenic anticoagulation and thrombolyis, liver dysfunction) - hemorrhages can occur at any site, tend to evolve slowly and be multiple.

4. Trauma (4-23% head injury cases) – multifocal inhomogeneous hemorrhages (most common in frontal and temporal lobes).

5. Heavy alcohol consumption (acute or chronic).

6. Drug abuse (amphetamine, cocaine)

RISK FACTORS

1. Age > 70 (increases ICH risk 7x) – amyloid angiopathy, use of anticoagulants

2. Male sex

3. Non-Caucasian race

4. Previous CVA (23x)

5. NSAID use – only cyclopedic and meldeicin (RR 1.27; 95% CI, 1.02–1.59 and RR 1.27; 95% CI, 1.08–1.50, respectively).

6. Statin use; however, the ischemic stroke benefit greatly outweighs the risk.

PATHOLOGY, PATHOPHYSIOLOGY

- hematomas are at first soft and dissect along white matter fiber tracts (rather than destroying brain tissue locally).

- hematoma may spread (lobar and cerebellar hemorrhages tend to remain confined within parenchyma:
  a) intraparenchymal extensions
  b) intraventricular extension (primary intraventricular hemorrhage is rare!) → acute hydrocephalus
  c) SAH

- bleeding is spontaneously limited by resistance of surrounding tissue pressure (usually within 30 minutes);
  - once bleeding stops, it generally does not start again.
  - in severe cases, bleeding continues until death.

- large hematoma causes mass effect → distorts structures (with ischemic pressure damage), increases ICP → herniation.

- if patient survives initial ICP changes, blood is absorbed over weeks > months → cavity or cleft (lined by glial scar and hemosiderin-containing macrophages) that may disconnect brain pathways.
  - less frequently, blood clot is treated as FOREIGN BODY - calcified and is surrounded by thick glial membrane.

Pathemorrhatic basal ganglia hemorrhage:

Source of picture: “WebPath – The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD) >>

Hypertensive basal ganglia hemorrhage:
INTRACRANIAL HEMORRHAGE (ICH)

EPIDEMIOLOGY

- ≈ 10-15% of all strokes (up to 30% in blacks and Asians).
- men ≥ women.
- peak incidence (for spontaneous ICH) = 60 yrs (incidence in individuals > 55 yrs doubles with each decade until age 80 years).
CLINICAL FEATURES

Most clinically destructive ICH are located near basal ganglia, internal capsule, thalamus, cerebellum, or brain stem!

- often history of arterial hypertenison.
- usually no prodromal attacks.
- most hemorrhages occur during activity (e.g. sexual intercourse, Valsalva's maneuvers, parturition labor).
- presentation
  a) MAXIMUM AT ONSET (33%)
  b) SMOOTH PROGRESSION over several hours (66%) - because hemorrhages arise from tiny vessels; further clinical evolution is due to brain swelling.
  - 20% of patients experience a decrease in the GCS of ≥ 2 points between the prehospital EMS assessment and the initial evaluation in the ED.
  - another 15-23% of patients demonstrate continued deterioration within the first hours after hospital arrival.

Abrupt & increasing focal signs → mass effect (ICP↑) → herniation → death

1. Focal signs - depend on site of hemorrhage (as hematoma enlarges, focal symptoms increase);
   - if hematoma remains small, the only symptoms relate to focal blood collection. see below

2. Signs of mass effect (develop after hematoma becomes large enough to raise ICP):
   1) headache (40-50%).
   2) nausea & vomiting (40-50%).
   3) normal - decreased level of consciousness (50%); may progress to coma in 24-48 hrs (consciousness is sometimes impaired at start - esp. pontine or thalamic hemorrhage).

3. Seizures (clinical 6-16%, electrographic 28-31%, status 0.4% within first 7 days*).
   *much more common with lobar hemorrhage (≈ 25% patients) - cortical irritation by blood.

CVAE score for severe risk:
1. Cortical involvement
2. Age > 65 y
3. Volume > 10 mL
4. Early seizures
   ≥ 2 present – epilepsy risk?

4. Meningeal irritation – if bleeding extends to subarachnoid space.

<table>
<thead>
<tr>
<th>CLINICAL</th>
<th>SITE OF HEMORRHAGE</th>
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<tbody>
<tr>
<td>Unconsciousness</td>
<td>Later</td>
</tr>
<tr>
<td>Hemiaparesis</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensory change</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemianopia</td>
<td>Yes</td>
</tr>
<tr>
<td>Pupils (Size / Reaction)</td>
<td>Normal / sh</td>
</tr>
<tr>
<td>Gaze paresis</td>
<td>Contralateral (eyes look to ICH)</td>
</tr>
<tr>
<td>Response to caloric</td>
<td>Yes</td>
</tr>
<tr>
<td>Ocular bobbing</td>
<td>–</td>
</tr>
<tr>
<td>Gait lost</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Occasional</td>
</tr>
</tbody>
</table>

Ocular signs are rapid method of localizing hemorrhages!

DIAGNOSIS

- Lambur puncture is contraindicated! – may cause herniation; CSF does not provide definitive diagnostic information
- CSF is usually bloody several hours after hemorrhage, but sometimes it is normal initially.

Either CT or MRI may be used for initial neuroimaging (but MRI may be more difficult to perform because of impaired consciousness, vomiting, or agitation)

BLOOD
- CBC, chemistries, coagulation studies (prothrombin time, PTT, bleeding time, platelet count), arterial blood gas analysis (in patients with reduced alertness), toxicology screen.

EEG
- polymorphic slow waves over region.

IMAGING

Noninvasive CT
- very reliable! - accurately documents hematoma, mass effect, intraventricular hemorrhage, hydrocephalus.
- performed immediately in suspected acute ICH.
- follow-up CT is frequently requested changes in lesion size, ventricular system).
- 1/3 of patients have ICH size growth on repeat imaging!
- fresh hematoma - homogeneous rounded area of increased density (≥ 30-80 HU) + mass effect (vs. hemorrhagic infarctions - areas of increased density [blood] interspersed with areas of decreased density [infarction]).
  - acute hematoma volume ≥ 80 cm³ is usually fatal.
  - no edema around fresh clot (!!!!), but clot retraction → fine rim of low density.
  - in severely anemic patients (Hct < 20%), hematomas can be isointense to surrounding brain.
  - multifocal hemorrhages at poles (frontal, temporal, or occipital) suggest TRAUMATIC etiology.
  - TUMORS can acquire similar density in contrast CT!

CT is always performed without contrast medium if hemorrhage is possible!

- layering in clot (as if fluid-blood layer) or mixed iso-hyperdense picture:
  a) hyperacute / ongoing bleeding
  b) coagulopathic patient
INTRACEREBRAL HEMORRHAGE (ICH)

Vas20 (6)

- **blend sign** - blending regions of high and low density with clear boundary within the hematoma - predicts hematoma expansion:

  (a) blend sign (+); (b) blend sign (−)

- **blood may leak into ventricle:**
  - a) adheres to ependyma or choroid plexus;
  - b) sinks to most dependent part of ventricular system (usually occipital horns) → fluid level within ventricular fluid

- **after several days,** hematoma becomes less radiodense (density decreases by ≈ 2 HU/d) from periphery towards centre (therefore appears smaller); vasogenic edema develops in surrounding white matter (IV contrast → ring enhancement*).

  *vs. gyral enhancement typical of infarction

- **after 2 weeks,** CT density becomes similar to that of brain or CSF (i.e. isointense); surrounding rim of contrast enhancement may persist for months.

- **in chronic stage,** lesion becomes hypodense slit-like cavity (many disappear into isodense tissue) - resembles infarct; H: MRI

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- **in chronic stage,** lesion becomes hypodense slit-like cavity (many disappear into isodense tissue) - resembles infarct; H: MRI

- **hypertensive ICH (CT):** hematoma (high density signal) in thalamus (left arrow) with extension into 3rd ventricle (top arrow) and occipital horns of ipsilateral (bottom arrow) and contralateral (right arrow) lateral ventricles.

- **Dual-energy CT (DECT)** allows differentiation between blood and calcium and other hyperdense etiologies:
  
  DECT showing calcification of the posterior left thalamus.
There is hyperdensity on noncontrast CT, with a differential of calcium vs ICH. Hyperdensity persists on CT with calcium overlay B, but not on virtual noncalcium image C, confirming that this represents calcium and not ICH.

DECT images showing lymphoma of the left thalamus.

On the initial contrast-enhanced images, there is a hyperdense lesion within the left thalamus A, with a differential of an enhancing mass vs ICH. There is persistent hyperdensity on the iodine overlay image B and only mild hyperdensity on the virtual noncontrast image C indicating that this represents a hypercellular, enhancing tumor (lymphoma) and not ICH.

MRI - picture depends on precise sequence used and age of hemorrhage (hemoglobin degradation products [different paramagnetic properties] play important role) – further see p. D51 >

- not highly sensitive in first few hours?
- MRI is not necessary in most instances.
- one advantage of MRI – ability to detect small hemorrhages in brain stem (CT may not detect small pontine hemorrhages?)
- T2* (either GRE or SWI) is most sensitive sequence; SWI is more sensitive:

VASCULAR IMAGING (angiography / CTA / MRA):
Common causes
- Hypertensive encephalopathy
- Trauma
- Aneurysm
- Mycotic aneurysm
- Hyperviscosity syndrome
- Anticoagulant therapy
- Cerebrovascular disease
- Intracerebral hemorrhage

Clinical presentation
- Headache
- Nausea and vomiting
- Seizure
- Loss of consciousness
- Motor weakness
- Cranial nerve palsy

CTA – CTA is the first choice.
- if CTA is negative, DSA is considered (esp. patient < 45 yo without history of hypertension – diagnostic yield of DSA > 22%)
- timing of angiography – delay* until hematoma has resolved (vascular lesions can be compressed by acute hematoma – not apparent angiographically)

*if hematoma needs surgical evacuation → immediate angiography.

spot sign – CTA marker of contrast extravasation (> 120 HU contrast spot) within nonenhancing hematoma and is not continuous with vessel - highly predictive of hematoma expansion and poor outcome – such patients could be selected for hemostatic therapies.

**speculative**

### SPECIFIC ANATOMIC LOCATIONS

**Basal ganglia / thalamus**
- 1. Hypertensive
- 2. Drug abuse (in young person)
- 3. Ruptured aneurysm – rare
- 4. Tumor – very rare

**Putaminal Hemorrhage**
- Most common form of ICH (putamen is most common site of hypertensive ICH) – 33-50% of all ICHs.

**Classic presentation** of large hemorrhage (involves internal capsule, corona radiata, centrum semiovale, temporal lobe / insula, lateral ventricles):
1) rapidly progressing contralateral hemiplegia (incl. face) with less severe hemisensory loss (with small hematoma, there can be pure motor hemiparesis):
- arm and leg gradually weaken until become flaccid or extend rigidly
- Bálint sign
- Allesthesia (with nondominant putaminal hemorrhage) – noxious stimulus on side of hemisensory disturbance is perceived on opposite normal side in corresponding area.
2) homonymous hemianopia
3) conjugate horizontal gaze palsy (eyes “look toward hematoma and away from hemisensory”)
4) global aphasia (dominant hemisphere) / hemineglect (nondominant hemisphere)

**massive** putaminal hemorrhage → upper brainstem compression → lethargic / comatose (within minutes to hours) with deep, irregular respirations.

**Thalamic Hemorrhage**
- ≤10-20% of all ICHs.
- usual case is hypertensive.
- ICH may extend laterally to internal capsule, inferomedially to subthalamus and midbrain, or medially to 3rd ventricle.

Clinical presentation (represents putaminal ICH):
1) contralateral hemisensory deficit of all modalities with later* & lesser degree hemiparesis (hemianesthesia precedes hemiparesis! – vs. putaminal ICH)
- arm & leg weakness
- Bálint sign
- Allesthesia (with nondominant putaminal hemorrhage) – noxious stimulus on side of hemisensory disturbance is perceived on opposite normal side in corresponding area.
2) homonymous hemianopia
3) conjugate horizontal gaze palsy
4) global aphasia (dominant hemisphere) / hemineglect (nondominant hemisphere)

**massive** putaminal hemorrhage → upper brainstem compression → lethargic / comatose (within minutes to hours) with deep, irregular respirations.

**Lobar Hemorrhage**
- bleeding within subcortical white matter (i.e. cerebral lobes outside basal ganglia).
- most patients are elderly!

Common causes:
1) amyloid angiopathy - most common cause in elderly
2) tumor
3) vascular malformation, hematologic malignancy – young person
4) trauma
5) extension of deep hemorrhage
6) hemorrhagic transformation of ischemic infarct
7) venous (sinus or cortical vein) thrombosis

N.B. if clinical syndrome and CT findings are typical of hypertensive hemorrhage in basal ganglia, pons, or cerebellum, angiography is not necessary.

American Stroke Association (ASA) guidelines do not specify which patients may benefit from vascular imaging for evaluation of secondary causes.

- CTA is the first choice.
- if CTA is negative, DSA is considered (esp. patient < 45 yo without history of hypertension – diagnostic yield of DSA > 22%)
- timing of angiography – delay* until hematoma has resolved (vascular lesions can be compressed by acute hematoma – not apparent angiographically)

*if hematoma needs surgical evacuation → immediate angiography.

spot sign – CTA marker of contrast extravasation (> 120 HU contrast spot) within nonenhancing hematoma and is not continuous with vessel - highly predictive of hematoma expansion and poor outcome – such patients could be selected for hemostatic therapies.

**speculative**
Uncommon - acute disseminated encephalomyelitis (s. acute hemorrhagic leukoencephalopathy, Westen-Hust disease).

Hemorrhages at gray-white matter interface – embolic phenomena: metastases, septic embol, fungal infection.

Clinical presentation (resembles thromboembolic infarction):
- **FRONTAL lobe** - abulia, contralateral hemiparesis, conjugate gaze palsy toward side of hemorrhage.
- **PAretal lobe** - contralateral hemisensory loss & mild hemiparesis, neglect of contralateral visual field, occasional hemianopia or anosognosia.
- **TEMPORAL lobe** - visual field deficit, agitated delirium. Wernicke aphasia (extension into DHV to 35% dominant parietal lobe → conductus or global aphasia).
- **OCCIPITAL lobe** - contralateral homonymous hemianopia, ipsilateral orbital pain.
- **normal pupils.**
- **headache, nausea & vomiting** occur with same frequency but less intensity (as in deep, hypertensive hemorrhages).
- **coma is less common** (bulk of hemorrhage is comparatively small and located in subcortical white matter).
- **seizures are common** (frontal, temporal, or parietal lobes).

**Pontine Hemorrhage**
- □ 10-15% of all ICHs.
- □ usually placed symmetrically at junction of basis and tegmentum (paramedian vessels from basal artery).
- □ hematoma can extend rostrally into midbrain or rupture into 4th ventricle.

**Clinical presentation** (large pontine ICH):
- 1) abrupt coma, vomiting often occurs at onset
- 2) quadriparesis, cerebellar ataxia
- 3) pinpoint (1 mm) reactive pupils (check with magnifying glass)
- 4) grossly disconjugate centrally positioned eyes (gaze paresis) with absent oculocephalic & oculovestibular reflexes
- 5) ocular bobbing
- 6) ataxic Cheyne-Stokes respiration
- **Death occurs within few hours** (> 75%), but there are exceptional survivors!
- □ **lateral basis pontis** - pure motor hemiparesis.
- □ **lateral pontine tegmentum** - ipsilateral conjugate gaze paresis, ipsilateral intercerebellar ophthalmoplegia, "one-and-a-half" syndrome, ipsilateral missus, ocular bobbing, ipsilateral hemiataxia with crossed hemisensory deficits.

**Caudate Hemorrhage**
- □ 8-10% of all ICHs.
- □ most common cause is long-standing hypertension.
- □ most common locations: dentate nucleus → vermis.
- □ **clinical presentation**: abrupt occipital headache, nausea & vomiting (may be severe and repetitive), severe **ataxia** (ataxia-abasia, vertigo, dysarthria, dystagmus.
- □ *gait (truncal) ataxia may be only neurologic sign – test gait in all patients!* 
- □ N.B. consciousness is preserved!
- □ N.B. consciousness is predictably unresponsive (may deteriorate quickly – check patient very often) - may cause brain stem compression:
  1) **ocular findings**: colorless-resistant ipsilateral gaze palsy → eye deviation toward opposite side; small reactive pupils, skew deviation (Magendie-Hertwig sign), gaze-parietic nystagmus, ocular bobbing
  2) **cranial nerve findings** (ipsilateral facial weakness, ipsilateral absence of corneal reflex)
  3) **contralateral hemiparesis** (late sign?)
  4) **loss of consciousness** (coma = too late for surgical evacuation!)
  - **Neurosurgeon consultation is indicated for all patients!**
  - More lateral (hemispheric) hemorrhage and smaller hematoma, more likely brainstem structures are spared (better prognosis)
  - **may obstruct CSF flow into or out of 4th ventricle → HYDROCEPHALUS** (may cause reversible loss of consciousness; H: prompt ventricular drainage).
  - **further brain stem compression, cerebellar herniation → death** (H: prompt clot evacuation!)

**Caudate Hemorrhage**
- □ 45% of all ICHs.
- □ may dissect posteroilaterally into internal capsule and putamen (contralateral conjugate gaze paresis, contralateral hemiparesis).
- □ may dissect inferiorly into thalamus (upward gaze paresis, hemisensory deficits), hypothalamus (Horner’s syndrome)

**INTRACEREBRAL HEMORRHAGE (ICH)**

**a) primary** (confined to the ventricles)
- **secondary** (extension of ICH): most of IVHs - hypertensive hemorrhages involving the basal ganglia and thalamus.
- **occurs in** 45% of patients with spontaneous ICH
- **ICH is independent factor associated with poor outcome** (risk of death increased from 20% without ICH to 35% with ICH).
- □ **etiologies** - head trauma, vascular malformation, aneurysm, tumor, hypertension, and clotting disorders.
- □ **clinical features**: meningesm, headache, vomiting, mental status changes with few motor or sensory signs, "hormone" (periodic tonic spasms of limbs & atonic pauses).
- □ **complications** - obstructive hydrocephalus, delayed communicating hydrocephalus, thrombocytopenia and inflammation in reaction to ventricular blood.
- **treatment** → see below >>

**TREATMENT**

ICH is the least treatable form of stroke!

The two most pressing ICH investigational goals are: 1) early BP control and 2) hematoma volume reduction.

**hematoma expansion occurs in 16-40% patients (typically within first few hours); each 10% increase in hematoma size from baseline → 5% increase in mortality and 16% increase in chance of worse functional outcome.
Conservative Measures

General Measures

- bedrest during first 24 hours; clinically stable patients → progressive increase in activity (avoid strenuous exertion).
- N.B. all ICH patients with limited mobility need prophylaxis against DVT (intermittent pneumatic compression stockings same day, low-molecular-weight heparin next day following bleeding cessation)
- treatment of fever may be reasonable (Class Ib, Level of Evidence C)
- maintain normoglycemia (< 180 mg/dl), both hyperglycemia and hypoglycemia should be avoided (Class I, Level of Evidence C); target glucose level remains to be clarified.
- diaphyseal screening for all ICH patients before they start oral intake - to reduce risk of pneumonia (Class I, Level of Evidence C) - most common medical sequelae seen in this patient population; if failed → early enteral feeding.
- systematic screening for myocardial ischemia or infarction (with ECG and cardiac enzymes) is reasonable (Class IIa, Level of Evidence C).

BP Control

(wide BP swings are common in initial period): intra-arterial pressure monitoring + continuous ECG
- patients presenting with SBP 150-220 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 Ib, Level of Evidence B) - (INTERACT 2 N: 48 for patients presenting with SBP > 220 mm Hg, it may be reasonable to consider reduction of BP (Class Ib, Level of Evidence C).
- hypertension (systolic > 180, MAP > 150) increases bleeding and rises ICP.
- hypertension (MAP > 100) is contraindicated.
- drugs: IV nicardipine or labetalol or sodium nitroprusside or trimetaphan camlylate.

INTERACT 2

(Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial)
- rapid blood pressure reduction to SBP < 140 was found to be safe and caused reduced hematoma expansion (14% vs. 36%), but these results were not statistically significant.
- INTERACT 2 – patients with small-moderate ICH and presenting with SBP 150-220 → intensive treatment to SBP < 140 vs. standard treatment to SBP < 180 for 7 days:
  - intensive treatment is safe.
  - intensive treatment has no significant effect on hematoma growth.
  - intensive treatment has favorable trend to reduce poor outcome (mRS ≥ 3): 52% vs. 55.6% with standard treatment (p = 0.06).
  - intensive treatment led to modestly better functional recovery (OR for greater disability, 0.87; 95% CI, 0.77 to 1.00; P=0.04) and quality of Life (mean health utility scores, intensive group 0.65 ± 0.39 vs. standard group 0.63 ± 0.30; P=0.002).
- N.B. study did not include patients with very high SBP on presentation (soon > 220 mm Hg), large and more severe ICH, and those requiring surgical decompression.
- Ongoing trial in phase III - Antihypertensive Treatment of Cerebral Hemorrhage (ATACH 2 trial) - randomizing ICH patients to goal SBP of < 140 mmHg vs. < 180 mmHg within 3.5 hours of symptom onset. BP targets are to be maintained for 24 hours after randomization using nicardipine (labetalol may also be used if maximum amounts of nicardipine are used).
- Perindopril Protection Against Recurrent Stroke Study (PROGRESS) - risk of ICH recurrence was lowest among patients with lower blood pressure levels on follow-up (median, 112 mmHg systolic and 72 mmHg diastolic) - Class I, Level of Evidence A.

ICP Control

- elevating head of bed, analgesia, mild sedation, mannitol, etc. see p. 850

Small hematomas and limited IVIH usually do not need ICP treatment!

Causes of elevated ICP in ICH: 1) hydrocephalus from IVH 2) mass effect from the hematoma (or surrounding edema)

Aggressive 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, Level of Evidence B). Patients with preexisting DNR orders are not included in this recommendation. Current prognostic models for individual patients early after ICH are biased by failure to account for the influence of withdrawal of support and early DNR orders. DNR status should not limit appropriate medical and surgical interventions unless otherwise explicitly indicated (Class II, Level of Evidence C)
Preop CTA is a must! and volume control are critical

Modern thinking

Traditionally

• patient on warfarin → factor (II, VII, IX, X) prothrombin complex concentrate PCC (Kcentra) is first line treatment; then try. K [PRACYLONE Add 20-40 mg IV], FFP.

N.B. according to AHA/ASA guidelines:

- SURGICAL TREATMENT

INDICATIONS

EUROPROTECTIVE STRAT

Outcome of prophylaxis is not recommended.

Some studies suggest anticonvulsants may be lin AEDs make no outcome difference.

ICH has much higher seizure risk than primary ICH but still routine primary seizure prophylaxis is not recommended.

N.B. anticoagulants (if indicated for other comorbid conditions, eg. mechanical cardiac valves) can be restarted within 2-3 weeks after ICH (within 3-30 days if risk for thromboembolism is very high)

AED

N.B. according to AHA/ASA guidelines: prophylactic antiarbitration medication is not recommended (Class II; Level of Evidence B).

• AEDs make no outcome difference.

- candidates:

  - INOCYCLINE

  - PLATELET TRANSFUSION:

  - thrombolytic-associated bleeding → CYPREDEXTAPE 10 units IV, replacement of clotting factors®, AMINOCAPRIC ACID (5 g over 30-60 minutes → 1 g IV for continued bleeding).

  - Replacement of clotting factors:

    a) FRESH-FROZEN PLASMA 20 mL/kg – fluid overload!

    b) PCC (prothrombin complex concentrate), FACTOR IX COMPLEX concentrate, and RECOMBINANT ACTIVATED FACTOR VII – act very rapidly and with lower fluid volumes than fresh frozen plasma, but greater potential of thromboembolism.

• N.B. anticoagulants (if indicated for other comorbid conditions, eg. mechanical cardiac valves) can be restarted within 2-3 weeks after ICH (within 3-30 days if risk for thromboembolism is very high)

- MELD®PROTECT TTV STRATEGIES

  Candidates:

  1. MISOXICLINE

  2. DIREDOXAMINE

  3. Hyperthermia, more effective in combination with magnesium.

• PENCAMBOLIN (phosphine-1-phosphate receptor modulator approved for MS) may improve outcomes of ICH.


  Oral fingolimod 0.5 mg for 3 consecutive days for patients with primary supratentorial ICH and hematoma volume of 5-30 mL → safe and effective in reducing perihematomal edema and neurologic deficits, with enhanced recovery.

SURGICAL TREATMENT

Pathophysiological cues for surgical evacuation – see p. ThH1 >>

Traditionally ICH was considered a monophasic disease with little demonstrated benefit from support care or craniotomy and with medical management as the standard of care.

Modern thinking: ICH is a biphasic disease, with the second phase of injury from perihematoma inflammation and edema accounting for the delayed neurological deterioration - time of intervention and volume control are critical

Proph CTA is a must!

INDICATIONS

1. Cerebellar hematomas compressing vital structures in medulla (suggested by declining level of consciousness, posturing, altered respiration, shifted or obliterated 4th ventricle, hydrocephalus).

   Patients with cerebellar hematoma who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hematoma as soon as possible (Class I; Level of Evidence B).

   Cerebellar hematoma > 2.5-3 cm require surgical evacuation within hours.

   • Surgery is not indicated - GCS score ≥ 14 (some investigators say ≥ 9) with small hematoma (<3-4 cm) without hydrocephalus.

   • contusion (poor surgery results) - large midline hematoma with loss of midline function and fluctuating coma.

   Small time margin between alert state (surgery still not indicated) and irreversible coma (surgery is too late)

   • consider preoperative MANNITOL 1 g/kg.

   • EVD has risk of upward herniation of cerebellum and does not relieve brainstem compression.

   Initial treatment with ventricular drainage rather than surgical evacuation is not recommended (Class III; Level of Evidence C).
2. Supratentorial hemorrhages with signs of herniation, declining sensorium (esp. if clot is on nondominant side and ≤ 1 cm from cortical surface).

For most supratentorial ICH, the usefulness of surgery is not well established (Class Ib; Level of Evidence A).

Routine evacuation of supratentorial ICH by standard craniotomy within 96 hours of ictus is not recommended!

Supratentorial hematoma evacuation in deteriorating patients might be considered as a life-saving measure (Class Ib; Level of Evidence C).

Early hematoma evacuation is not clearly beneficial compared with hematoma evacuation when patients deteriorate (Class Ib; Level of Evidence A).

**SURGICAL APPROACHES & TECHNIQUES**

A. Ultrasound-guided evacuation via craniotomy (ultrasonography can confirm clot localization) – esp. for lobar clots within 1 cm of surface.

- Surgery between 24-48 h is the best time - vessel has stopped leaking (either spontaneously, or after hemostatic therapy); if earlier - increased risk of rebleeding.
- Aspirate, irrigate; most authors recommend leaving small bits of clot on vessels in order to avoid new hemorrhage.
- Hemostasis - bipolar coagulation, cotton balls with peroxide, SurgiFoam / FloSeal; may finish by Surgicel on hematoma walls.

**International Surgical Trial in Intracerebral Hemorrhage (STICH)**

cf. STITCH trial – traumatic ICH – see p. THI >


**STICH I** – (within 24 hrs of randomization) surgery (craniotomy or CT-guided aspiration) vs. best medical management.

- Class I evidence (1033 patients, 83 centers in 27 countries).
- Craniotherapy is as safe as medical therapy.
- No overall benefit from early surgery versus initial conservative treatment.

N.B. trial only looked at ICH for which the surgeon was uncertain regarding the benefits of surgery versus conservative management – trial confirms that surgeons are correct to be uncertain for these patients but the results cannot be extrapolated to all ICHs.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early surgery group</th>
<th>Best medical management group</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable outcome</td>
<td>26%</td>
<td>24%</td>
<td>None</td>
</tr>
<tr>
<td>Unfavourable outcome</td>
<td>74%</td>
<td>76%</td>
<td>None</td>
</tr>
<tr>
<td>Mortality</td>
<td>36%</td>
<td>37%</td>
<td>None</td>
</tr>
</tbody>
</table>


**STICH II** – (within 12 hours of randomization) surgery for lobar ICH where the clot is within 1 cm of the cortical surface (STICH I subgroup analysis suggested that such patients might benefit from surgery).

- Inclusion: conscious patients with superficial lobar hematoma (10-100 mL) within 1 cm of the cortical surface and without IVH and who were admitted within 48 hours of ictus.
- Still no clear benefit from early surgery! (41% favorable outcome in surgery group vs. 38% in medical group, no statistical significance).

N.B. patients with deep ICH esp. with IVH do worse with surgery; but patients with poor prognosis (GCS 9-12) are better off with early surgery!

N.B. surgery is not beneficial for hematomas in putamen, thalamus, and pons. In general, surgical evacuation is seldom justified.

- Does not substantially improve mortality – considerably increases risk of severe, residual neurologic disability if patient survives.
- Best candidates are patients with increasing moderate to large hematomas who are still awake (GCS ≥ 9).

N.B. patients with massive hematoma who are in coma are not likely to benefit!

**B. Minimally invasive evacuation via transvenous approach using BrainPath.**

**ENRICH (Early Minimally-Invasive Removal of ICH) trial**

**Conflict of interest**
- All investigators participating in ENRICH trial were involved in BrainPath’s development, but were not involved in the surgical and data analysis of this study.

**Exclusion criteria**
- <10 mL
- <1 cm from the cortical surface
- Patients not stable enough to undergo surgery

**Inclusion criteria**
- >10 mL
- >1 cm from the cortical surface
C. Minimally invasive stereotactic aspiration via burr hole; clot mobilization methods: 
- mechanical rotors 
- fibrinolytic agent installation.

MISTIE (Minimally Invasive Surgery with Thrombolysis for ICH Evacuation) 
- Minimally invasive surgery aspiration ± rt-PA through intraocul catheter qths (up to 9 doses total) vs. medical therapy alone
- randomized, open-label, blinded endpoint, phase 3 trial done at 78 hospitals (USA, Canada, Europe, Australia, and Asia) – 499 patients.
- Including spontaneous supratentorial ICH ≥ 30 ml, with or without IVH not requiring EVD, with GCS ≤ 14 or NHSS ≥ 6; in 18-80 yo patient with symptom onset within 24 hours of diagnostic CT, initiation of treatment from 12 to 72 hours of diagnostic CT, with first dose given within 76 hours of the diagnostic CT.
- No no life-threatening mass effect requiring surgery.

Outcomes:
- Mean reduction in hematoma size: 69% in MISTIE group vs. 3% in standard group;
- death at 7 days: 1% in MISTIE group vs. 4% in standard group (p=0.02);
- death at 30 days: 9% in MISTIE group vs. 15% in standard group (p=0.07);
- serious adverse event at 30 days: 30% in MISTIE group vs. 33% in standard group (p=0.012);
- mRS score of 0-3 at 365 days: 45% in MISTIE group vs. 41% in standard group (adjusted risk difference 4% [95% CI –4 to 12], p=0.33).

MISTIE cannot be pragmatically recommended!

Proponents of MISTIE argue:
- reduction of mortality is good enough
- should not included basal ganglia ICH (very poor prognosis)
- time to complete treatment on average was 5.1 days – way too long
- only 56% of patients on MISTIE group achieved surgical success (due to catheter malfunction)

The effectiveness of minimally invasive clot evacuation with stereotactic or endoscopic aspiration ± thrombolytic usage is uncertain (Class IIb, Level of Evidence B).

Multicenter Study of Artemis, a Minimally Invasive Neuro Evacuation Device (MIND)

D. Hemiconanectomy (DC) - option for younger patients with rapidly declining conscious state and imminent herniation.

DC with or without hematoma evacuation might reduce mortality for patients with supratentorial ICH who are in a coma, have large hematomas with significant midline shift, or have elevated ICP refractory to medical management (Class IIb, Level of Evidence C).

E. Ventricular drainage for INTRAVENTRICULAR HEMORRHAGE with acute obstructive hydrocephalus (esp. in cerebellar hematomas, intraventricular hemorrhage), trapped ventricle:

- endoscopic neurosurgical techniques for IVH evacuation may be advantageous compared with EVD
- The efficacy of endoscopic treatment of IVH is uncertain (Class IIb, Level of Evidence B).

- EVD can be combined with low-dose intraventricular fibrinolytics (catheter-based clot lysis) to dissolve clot quicker (e.g. 1.0 mg uPA – 8-12 hrs) - dramatically reduced morbidity & mortality!!! (rationale: EVD alone is too slow in removal of intraventricular blood).
  - EVD must go into clot
  - clamp ventriculostomy for 30-60 minutes and monitor for increased ICP
  - monitor daily with CT
  - clots dissolve on average within 3-4 days.
Although intraventricular rtPA in ICH appears to have a fairly low complication rate, the efficacy and safety of this treatment are uncertain (Class IIb, Level of Evidence B).

**CLEAR (Clot Lysis Evaluating Accelerated Resolution of intraventricular hemorrhage) III trial** – intraventricular rtPA in patients with small ICH (< 30 mL) but with IVH (to test treatment for IVH and not to be obscured by large ICH):
- does not improve good functional outcome (mRS 0-3: 48% in alteplase group, 45% in saline group), but gives 10% reduction in mortality without increasing the number of patients left in a vegetative state or requiring nursing home care (best results in patients with > 20 mL or > 90% of blood removed; no benefit if IVH blood is < 20 mL to start).

**CLEAR IV trial** – patients with larger clots - awaiting a funding application.

**Future approaches**
- Hypertensive lipohyalinosis results in a Charcot–Bouchard aneurysm → vessel rupture → ICH (A-D) demonstrate inserting temporary stent to occlude origin of leaking vessel and maintaining dural perfusion - outcome is ischemic lacune rather than large hematoma with mass effect:

**Stereotactic extracranial cautery**: imaging (MRI or CT) identifies bleeding AVM or tumor; i.e. bleeding structural / vascular lesion is also indication for surgery.

**Ventriculoperitoneal shunt** for chronic hydrocephalus:
- predictors of development of shunt-dependent hydrocephalus after ICH: thalamic ICH, persistently elevated ICP.

**Prognosis**
- most patients who die of ICH do so during the initial acute hospitalization, and these deaths usually occur in the setting of withdrawal of support because of presumed poor prognosis.
- **30-day mortality** is 30% (30-52%) – higher than for ischemic stroke (10-30%).
- brainstem ICH (60%)
- deep ICH (44%)
- lobar ICH (49%)
- cerebellar ICH (34%)
- ICH is most deadly form of stroke!
- Half of deaths occur within the first 24 hours

**ICH score** (Hemphill et al.) - Class I, Level of Evidence B guidelines emphasize obtaining as baseline severity score:

| Feature     | Finding     | Points | Score | 30-day mortality%
|-------------|-------------|--------|-------|
| GCS         | 3-4         | 2      | 0     | 0%
|             | 5-12        | 2      | 1     | 13%
|             | 13-15       | 0      | 2     | 20%
| Age         | < 80        | 3      | 3     | 72%
|             | ≥ 80        | 0      | 4     | 97%
| Location    | supratentorial | 1     | 5     | 100%
|             | infratentorial | 0     | 6     | 100%
| ICH volume  | < 30 mL     | 1      | 0     | 0%
|             | ≥ 30 mL     | 0      | 0     | 0%

**Future approaches**

****Alteplase is associated with reduction in bacterial ventriculitis – 4% vs. 9% in placebo arm (P = 0.05).
Intracerebral Hemorrhage (ICH)

**Intraventricular blood**
- Yes
- No
<table>
<thead>
<tr>
<th>Total score</th>
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<tr>
<td>1</td>
</tr>
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- Poor prognostic factors:
  1) age
  2) large hemorrhage size (supratentorial > 5 cm, posterior fossa > 3 cm)
  3) brain stem hemorrhage (75% mortality at 24 hours)
  4) intraventricular extension (89-90% morbidity, 58-78% mortality)

**Functional recovery**
- There is no hard rule as to when recovery ends.
- Prognosis is surprisingly good in patients who survive acute illness (death occurs within first 2 days) - only 20% survivors require institutionalization (i.e. most survivors achieve good status or complete recovery).
- 10-25% patients with ICH can expect functional independence 6 months after ICH (≤ 10% when initial hematoma volumes are > 20-30 mL).
- Growing evidence that ICH patients make slightly greater and faster gains in recovery than patients with ischemic stroke.

**ICH recurrence**
- Risk of recurrent hemorrhage is relatively low (1-15% annually; AVMs can rebleed 2% annually)
- LVAD (risk of rebleed > 7 up to 5-fold)
- Risk of ICH recurrence is highest in the first year; the ongoing risk extends for years, particularly in patients with lobar ICH.
- Risk factors for ICH recurrence:
  1) hypertension - the lower BP, the lower is risk; no established bottom BP where risk reduction would plateau or reverse. ICH patients should have their BP lowered to or beyond the targets currently recommended in other high-risk groups, i.e. ≤130/80 mm Hg in the presence of diabetes mellitus, heart failure, or chronic kidney disease).
  2) older age - higher prevalence of cerebral amyloid angiopathy.
  3) location of the initial hemorrhage (1-year risk of ICH recurrence: 15% after lobar ICH vs. 2.1% for deep ICH).
  4) anticoagulant use* - anticoagulation should be avoided after lobar ICH but can be considered in patients with deep ICH if the risk of thromboembolism is particularly high.
  - Patients on antithrombotics should not be anticoagulated after ICH.

**Cerebral Amyloid Angiopathy**
- Higher risk for recurrent ICH than ICH resulting from arteriolesclerosis - prognostic and therapeutic decisions about use of antithrombotic drugs.
- 7% annual risk of recurrence (1.1% risk with non-CAA-related ICH).
- There is no way to control risk of bleeding from amyloid angiopathy!

### IVH
- No treatment - half die, 20% return home to live independently.
- EVD - 50% of patients live independently at home after 180 days; intracerebral hematoma improves this number by 10% (CLEAR III trial).
SPECIAL SITUATIONS

LVAD (LEFT VENTRICULAR ASSIST DEVICE)

Two types of LVADs:
1) pulsatile flow
2) nonpulsatile flow (more and more popular) – cannot use BP cuff; use A-line – see MAP

N.B. MAP > 90 mmHg is abnormal (risk of ICH)

- most important prognostic factor – GCS at presentation (no patients with GCS ≤ 11 did survive 30 days).
- patient is usually on Aspirin and warfarin; when to restart:
  - experts usually restart Aspirin in 7-14 days and warfarin in 14-21 days; no thrombotic complications reported from withholding so long;
  - once restarted, risk of rebleed ↑ 5-fold in one Italian study but no increased risk in one Canadian study.

BIBLIOGRAPHY

For ch. “Neurovascular Disorders”  follow this LINK