

Diagnosis and Treatment of Hemorrhagic Stroke

Robert E. Replogle M.D.
Rochester Neurosurgical Partners
Stroke Treatment Alliance of
Rochester

Stroke in the U.S.

- Stroke is the #1 cause of disability
- Stroke is the #3 cause of death
- 700,000 strokes annually
 - Approximately 80% ischemic
 - Up to 40% due to large vessel occlusions

Every 45 seconds someone in the U.S. has a stroke

Stroke survivors have a 10X greater risk of having a repeat stroke than the general population

Etiology of Stroke

- Ischemic- 80%
 - Occlusive
 - Intracerebral- large vessel vs small vessel
 - Embolic
 - Cervical carotid
 - Cardiac, arterial
- Hemorrhagic- 20%
 - Aneurysm- subarachnoid hemorrhage (SAH)
 - Arterial-venous malformation (AVM)- intracerebral hemorrhage (ICH)

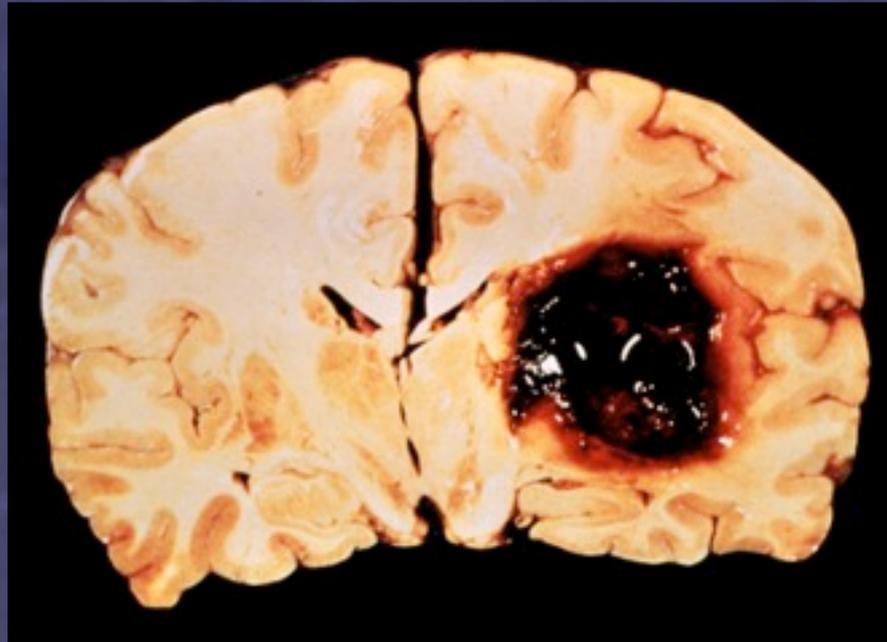
Classification

- Primary (78% ~ 88%)
 - Spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy
- Secondary
 - Vascular abnormalities (AVM, aneurysm, vasculitis, dural sinus thrombosis)
 - Tumor
 - Coagulopathy, underlying disorder, anticoagulants, antiplatelets, lytics
 - Drug abuse-cocaine

Guideline for the management of spontaneous intracranial hemorrhage

1. Intracerebral hemorrhage is more than **twice** as common as subarachnoid hemorrhage (SAH) and is much more likely to result in death or major disability than cerebral infarction or SAH.
2. Advancing age and **hypertension** are the most important risk factor for ICH.

Intracerebral Hemorrhage (ICH)



Gross specimen, coronal section of brain, large subcortical hypertensive ICH

© 2010 American Heart Association, Inc. All rights reserved. Unauthorized use prohibited.

Epidemiologic features

- Incidence
 - 10~20 cases per 100,000
 - Increases with age
 - Men, especially older than 55 years old
 - Blacks and Japanese
- Risk factor
 - Hypertension → the most important !
 - Excessive alcohol use

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.

Pathophysiological features

- Common site
 - A. Cerebral lobe
 - B. Basal ganglia
 - C. Thalamus
 - D. Brain stem (pons predominantly)
 - E. Cerebellum

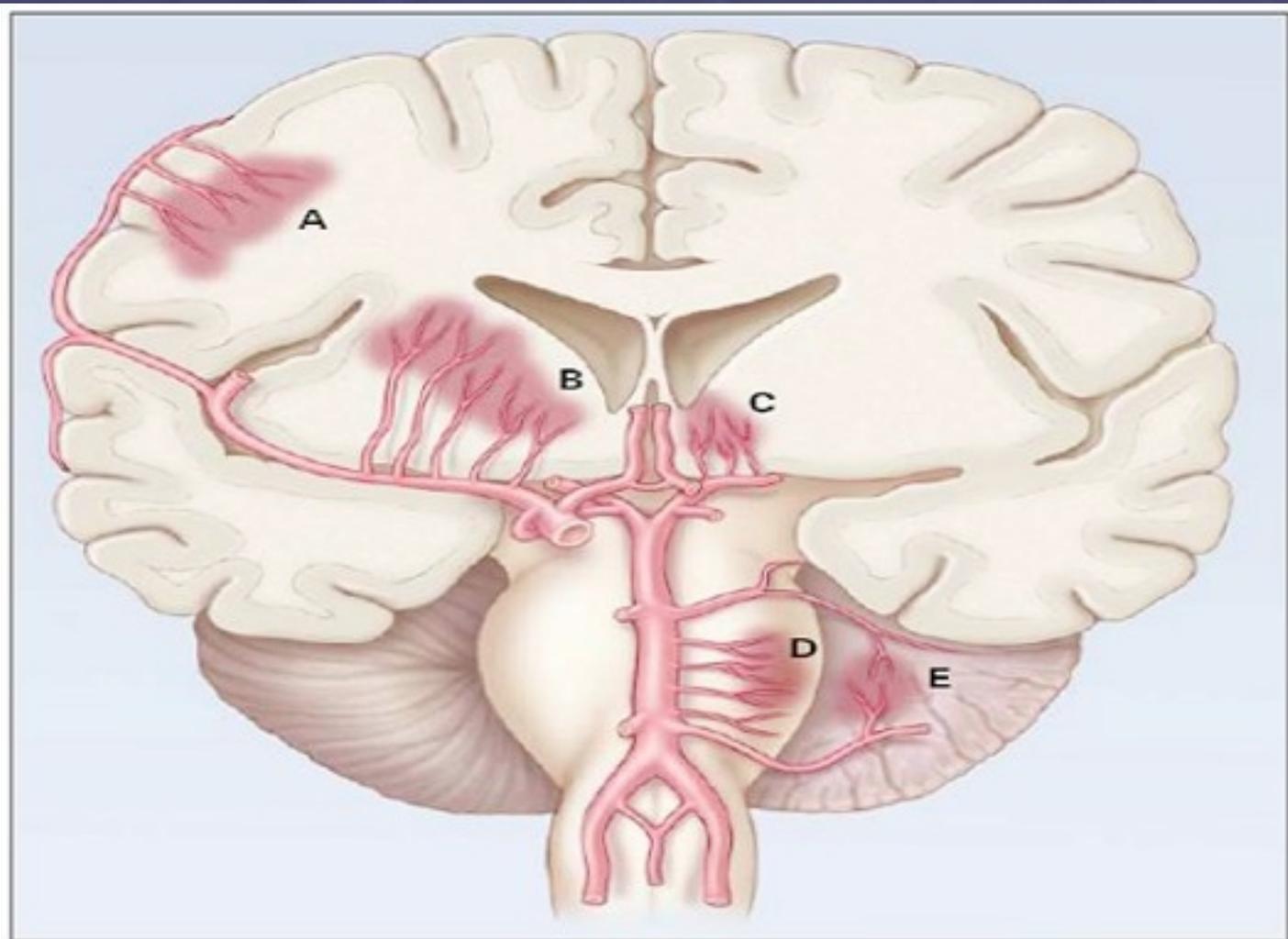


Figure 2. Most Common Sites and Sources of Intracerebral Hemorrhage.

Intracerebral hemorrhages most commonly involve cerebral lobes, originating from penetrating cortical branches of the anterior, middle, or posterior cerebral arteries (A); basal ganglia, originating from ascending lenticulostriate branches of the middle cerebral artery (B); the thalamus, originating from ascending thalamogeniculate branches of the posterior cerebral artery (C); the pons, originating from paramedian branches of the basilar artery (D); and the cerebellum, originating from penetrating branches of the posterior inferior, anterior inferior, or superior cerebellar arteries (E).

HISTORY

COMMENTS

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 &

PHYSICAL EXAMINATION	COMMENTS
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

COMMENTS

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 &

OTHER ROUTINE TESTS

COMMENTS

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

Clinical features

- Neurologic status at presentation
 - Decreased level of consciousness
 - Increased ICP, compression of the thalamic and brain-stem reticular activating system.
 - Supratentorial ICH
 - Contralateral sensory-motor deficits → involving putamen, caudate, thalamus.
 - Aphasia, neglect, gaze deviation, hemianopia → subcortical white matter or cortex

Clinical features

- Infratentorial ICH
 - Abnormal gaze, cranial nerve , contralateral motor deficits → brain stem
 - Ataxia, nystagmus, dysmetria → cerebellum
- Others
 - Headache, vomiting → increased ICP
 - Meningismus → blood in the ventricles

Pathophysiological features

- Progression of hematoma
 - CT scan showed hematomas expand over time.
 - Brott et al:
 - 103 pts → 26% within 1 hours, 38% within 20 hours
 - Acute hypertension, local coagulation deficit may be associated.

Pathophysiological features

- Secondary Neuronal injury
 - Hematoma initiates edema and neuronal damage in surrounding parenchyma.
 - Edema → 5 days ~ 2 weeks
 - Osmotically active serum proteins from clot, vasogenic edema, cytogenic edema (disruption of BBB, Na pump failure, cell death..)

Clinical features

- Secondary Deterioration
 - 25% pts → deterioration in the level of consciousness within the first 24 hrs
 - Expansion of the hematoma : first 3 hrs
 - Worsening cerebral edema : 24 ~ 48 hrs
 - Late progression of edema: 2 ~ 3 weeks

Clinical features

- Outcome
 - Mortality rate : 23% ~ 58% in 6 months
 - (1) Low GCS score
 - (2) Large volume of the hematoma
 - (3) Presence of ventricular blood on CT

Clinical features

- Outcome
 - Broderick et al: mortality rate at one month was best predicted by initial
(1) GCS (2) hematoma volume
 - GCS < 9 , volume > 60 ml \rightarrow 90%
 - GCS ≥ 9 , volume < 30 ml \rightarrow 17%

Diagnosis

- CT scan → infarction or hemorrhage
 - Location and size of the hematoma
 - Presence of ventricular blood
 - Hydrocephalus

Neuroimaging of ICH

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



Large left intraparenchymal hematoma (ICH)

Image courtesy the UTHSCSA

TABLE 1. Calculation of the SICH Score^{ab}

Parameter	Points
NCCT categorization^c	
High-probability	2
Indeterminate	1
Low-probability	0
Age, y	
18-45	2
46-70	1
≥71	0
Sex	
Female	1
Male	0
Neither known hypertension nor impaired coagulation^d	
Yes	1
No	0

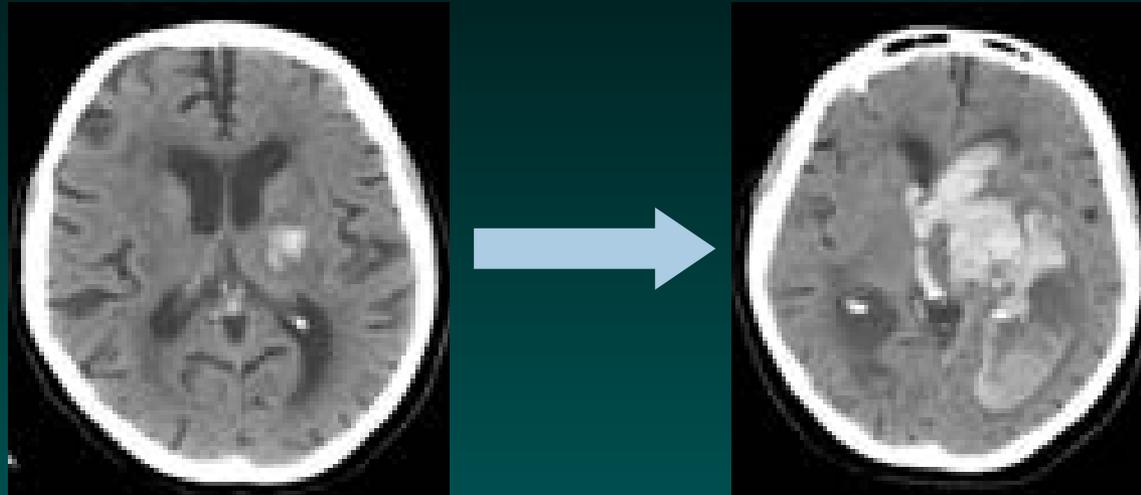
TABLE 4. Diagnostic Performance of the Secondary Intracerebral Hemorrhage Score in the Patient Populations^a

Score	Massachusetts General Hospital Cohort (n = 845)		Washington University Cohort (n = 341)	
	Patients, n (%)	% Positive CTAs	Patients, n (%)	% Positive Cases
0	52 (6.1)	0	4 (1.2)	0
1	212 (25.1)	1.4	63 (18.5)	1.6
2	277 (32.8)	5.1	129 (37.8)	7.8
3	178 (21.1)	18.5	80 (23.5)	18.8
4	82 (9.7)	39.0	41 (12.0)	39.0
5	38 (4.5)	84.2	24 (7.0)	79.2
6	6 (0.7)	100	0	n/a
AUC (95% CI)	0.87 (0.84-0.89)		0.82 (0.78-0.86)	
MOP	>2		>2	
Sensitivity	85.8		82.0	
Specificity	72.3		66.1	
P	<.001		<.001	

Diagnosis

- Conventional angiography → for secondary cause of ICH (AVM, aneurysm..)
 - Patient with lobar or primary intraventricular hemorrhage
 - Patient with putaminal, thalamic or cerebellar hemorrhage → normal BP, 45 years younger
 - AHA guideline → all Pts with no clear cause of hemorrhage who are candidates for surgery.
- MRI, MRA → sensitivity ?

Hematoma Expansion



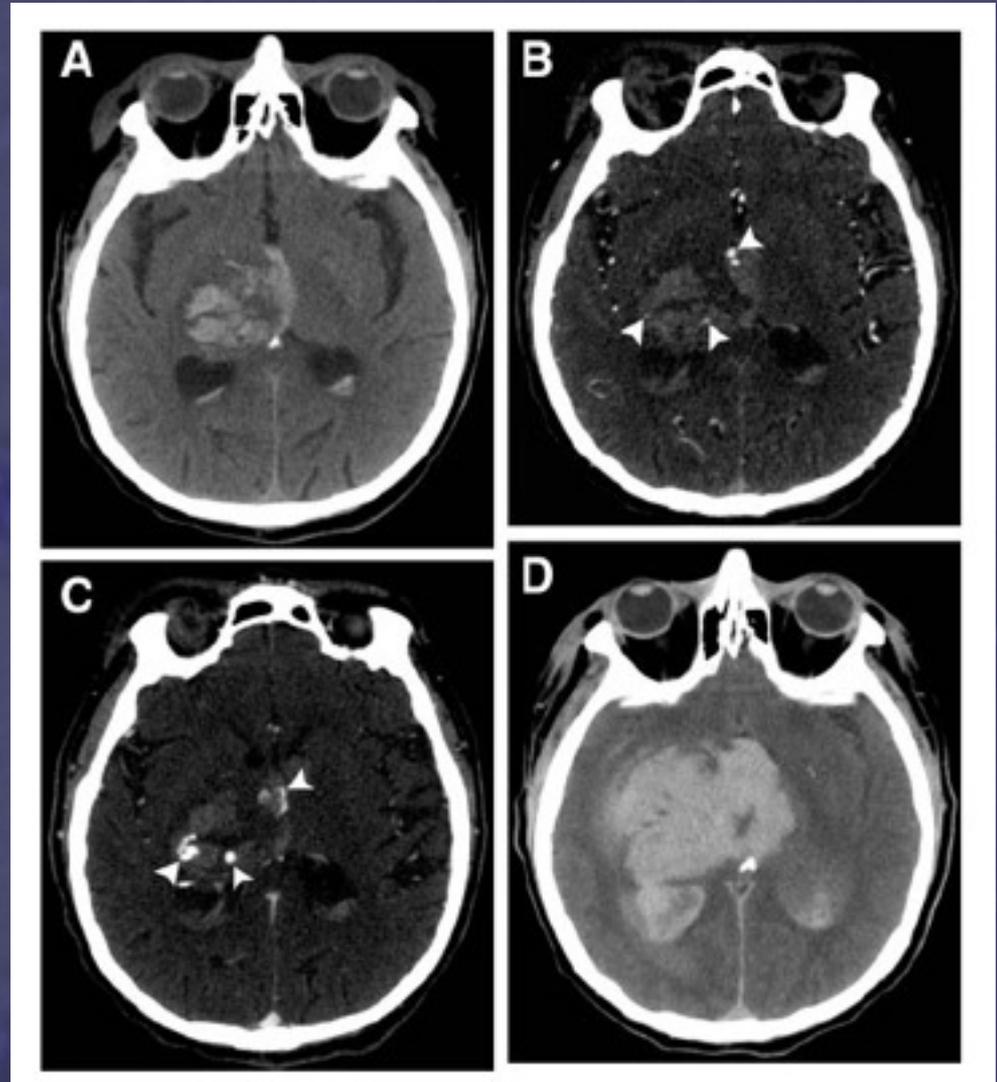
- **Within 3 hours from onset:**
 - 26% with 33% or greater growth in next hour
 - 12% with 33% or greater growth 1-20 hours
- **72% experience some hematoma expansion over the first 24 hours**

Davis SM, et al. *Neurology*. 2006;66:1175-1181;

Brott T, et al. *Stroke*. 1997;28:1-5.

CTA and ICH:

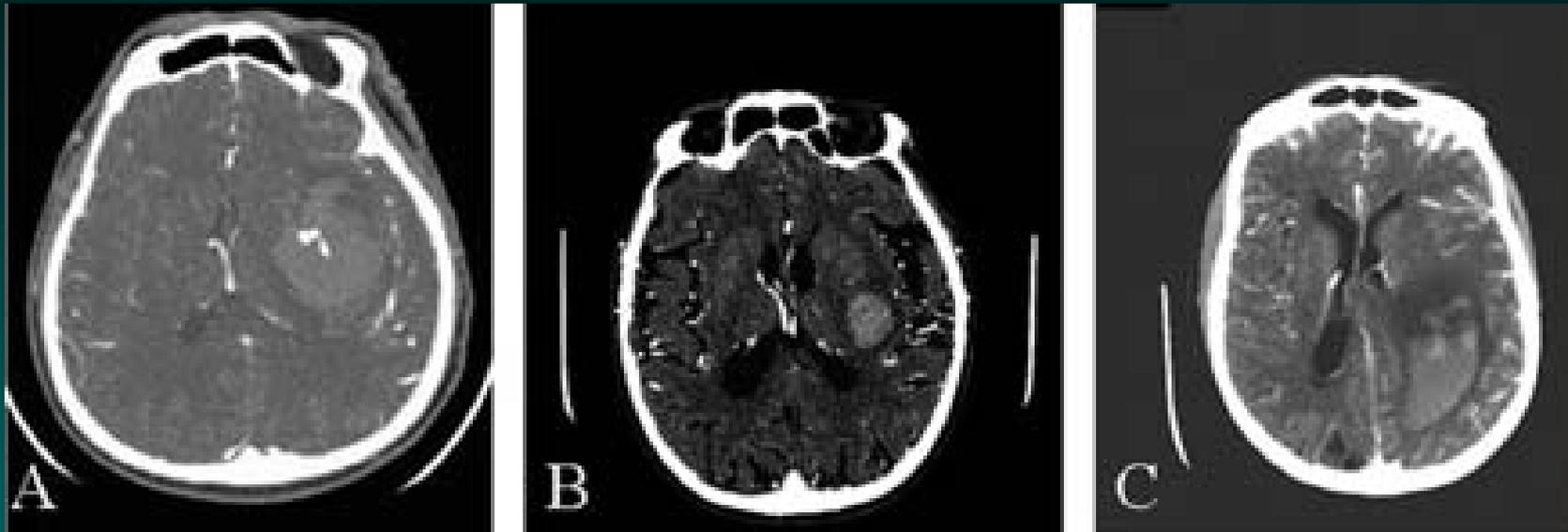
- CT contrast extravasates into hematoma
 - Spot sign, white arrows
- May predict hematoma expansion



Delgado Almandoz et al. Stroke, 40 (9): 2994. 2009

© 2010 American Heart Association, Inc. All rights reserved. Unauthorized use prohibited.

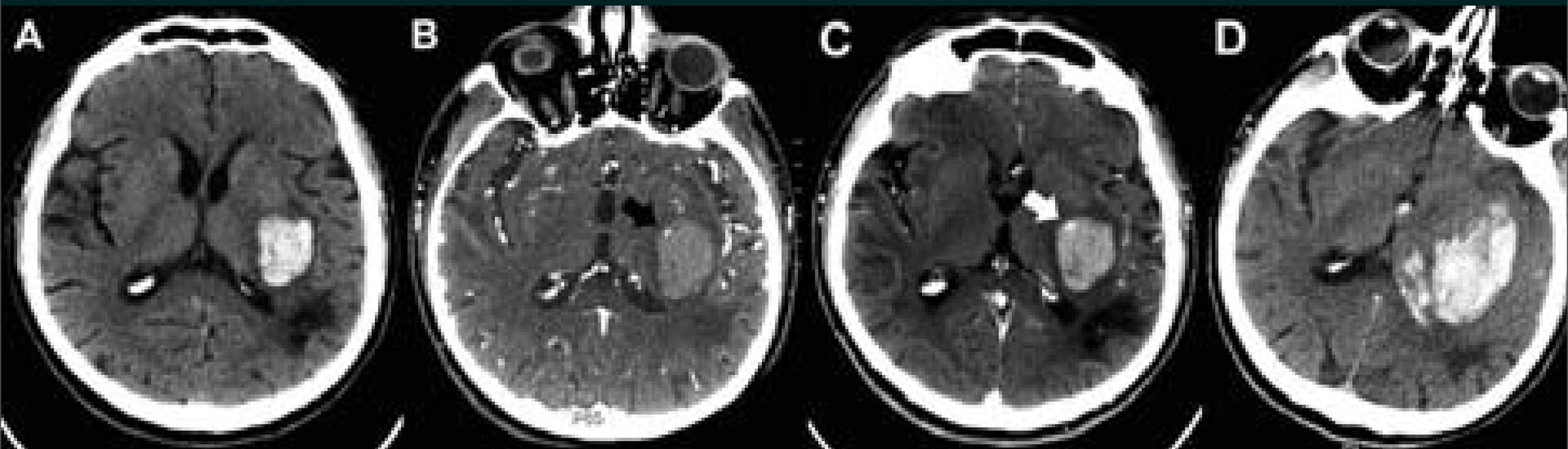
Contrast Extravasation as a Marker for Hematoma Expansion



- Contrast extravasation an independent predictor of hematoma expansion (OR 18, 95% CI 2.1 to 162)
 - Sensitivity 93%
 - Specificity 50%
 - PPV 24%
 - NPV 98%

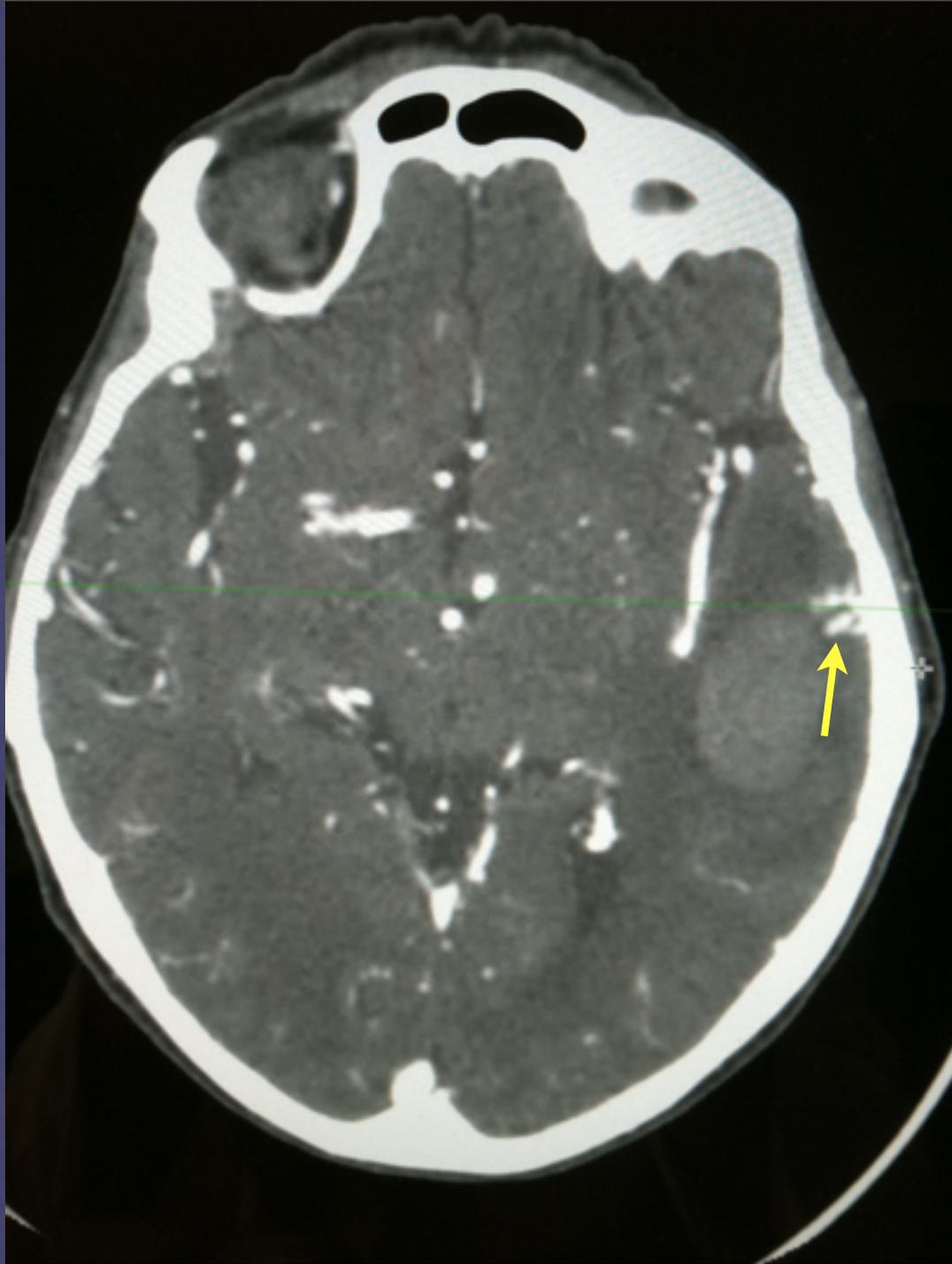
Goldstein J et al. *Neurology* 2007; 68(12):889-894.

“Spot Sign” as a Marker for Hematoma Expansion



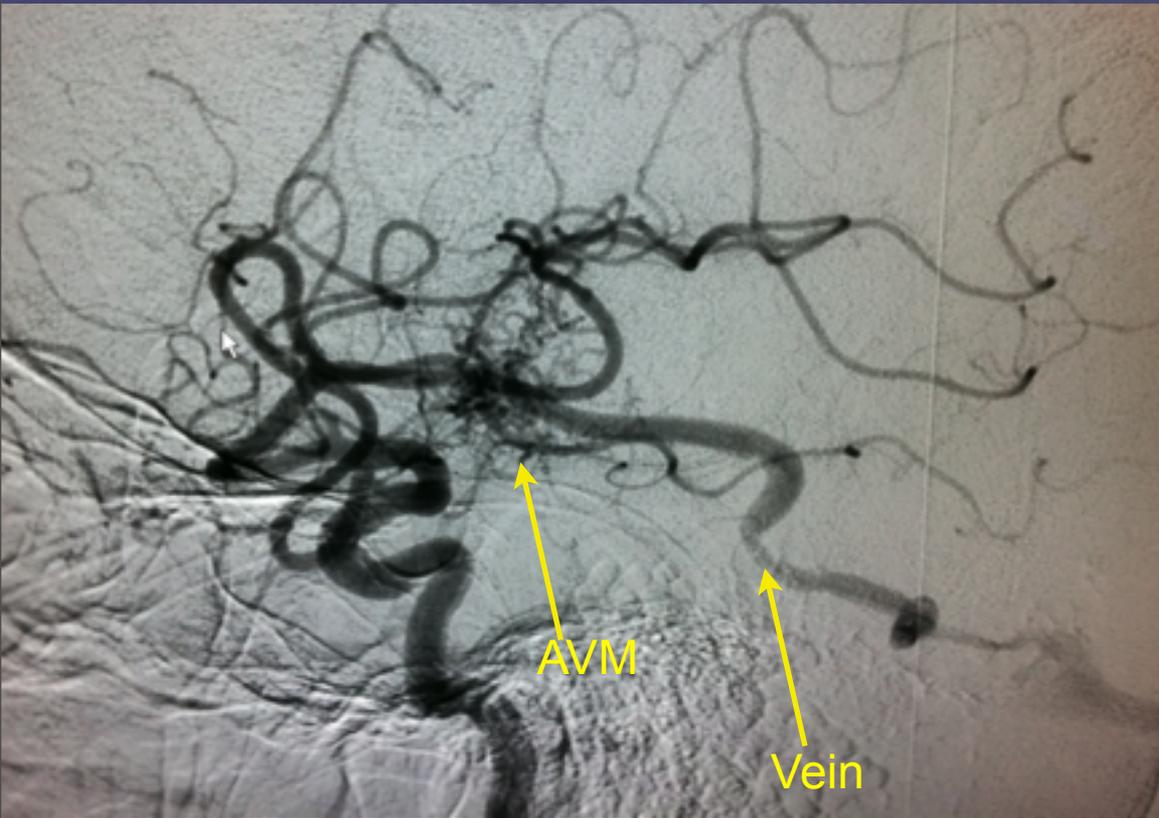
- 39 patients presenting < 3 hours from ictus
- 28% with hematoma growth
- “Spot Sign”
 - Sensitivity 91%
 - Specificity 89%
 - PPV 77%
 - NPV 96%

Wada R et al. *Stroke* 2007; 38(4):1257-1262.



77 YOF with no
history of
hypertension
Acute onset
dysphasia

Left Temporal AVM



Stroke. 2009 Jul;40(7):2393-7. Epub 2009 May 21.

CT angiography for intracerebral hemorrhage does not increase risk of acute nephropathy.

Oleinik A, Romero JM, Schwab K, Lev MH, Jhawar N, Delgado Almandoz JE, Smith EE, Greenberg SM, Rosand J, Goldstein JN.

Source

Department of Neurology, Massachusetts General Hospital, Boston, MA 02114, USA.

Abstract

BACKGROUND AND PURPOSE:

CT angiography (CTA) is receiving increased attention in intracerebral hemorrhage (ICH) for its role in ruling out vascular abnormalities and potentially predicting ongoing bleeding. Its use is limited by the concern for contrast induced nephropathy (CIN); however, the magnitude of this risk is not known.

METHODS:

We performed a retrospective analysis of a prospectively collected cohort of consecutive patients with ICH presenting to a single tertiary care hospital from 2002 to 2007. Demographic, clinical, and radiographic data were prospectively collected for all patients. Laboratory data and clinical course over the first 48 hours were retrospectively reviewed. Acute nephropathy was defined as any rise in creatinine of >25% or >0.5 mg/dL, such that the highest creatinine value was above 1.5 mg/dL.

RESULTS:

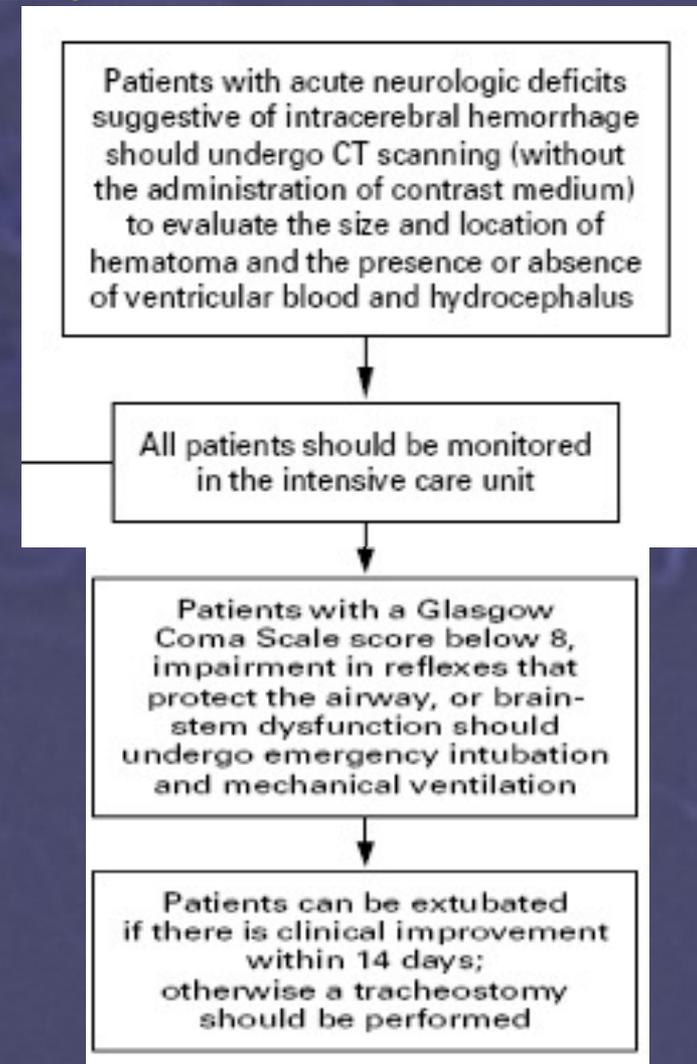
539 patients presented during the study period and had at least 2 creatinine measurements. 348 (65%) received a CTA. Acute nephropathy developed in 6% of patients who received a CTA and in 10% of those who did not (P=0.1). Risk of nephropathy was 14% in those receiving no contrast (130 patients), 5% in those receiving 1 contrast study (124 patients), and 6% in those receiving >1 contrast study (244 patients). Neither CTA nor any use of contrast predicted nephropathy in univariate or multivariate analysis.

CONCLUSIONS:

The risk of acute nephropathy after ICH was not increased by use of CTA. Studies of CIN that do not include a control group may overestimate the influence of contrast. Patients with ICH appear to have an 8% risk of developing "Hospital-Acquired Nephropathy."

Management

- Evaluation & management in the ER
 - Decreased level of consciousness or impairment of reflexes the protect airway → Intubation !
 - Urgent CT scan, NS consultation
 - Hyperventilation, intravenous mannitol and intraventricular catheter for drainage.



**Need to control BP and
coagulation issues ASAP!**

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.

© 2010 American Heart Association, Inc.

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



*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

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

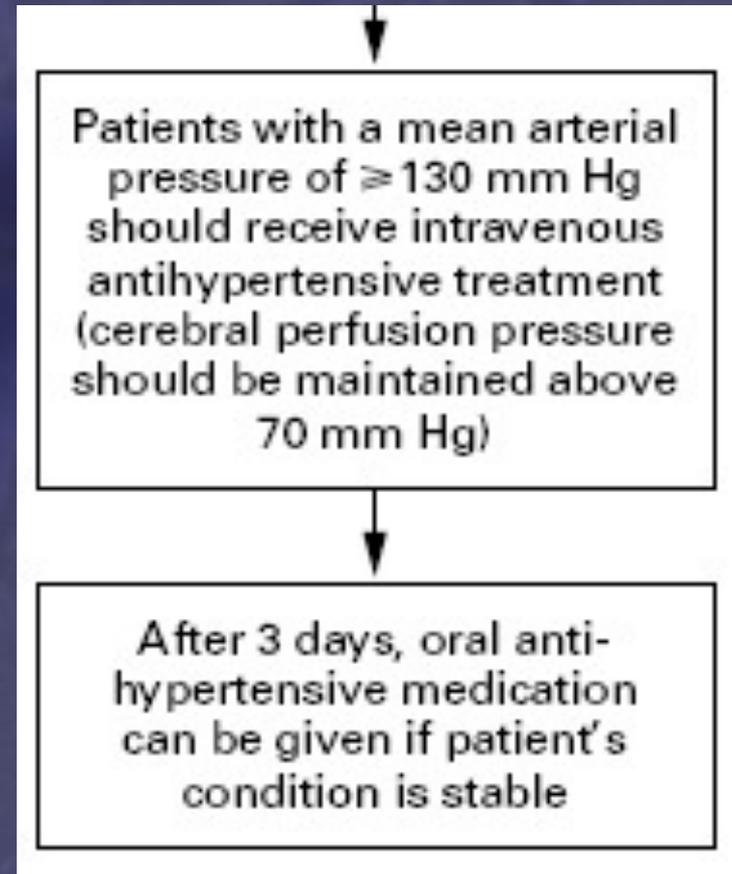
- Factor VIIa can limit hematoma expansion in non-coagulopathic patients, but also increases thromboembolic risk.
 - *rFVIIa is not recommended in unselected patients*
- rFVIIa does NOT replace clotting factors, even though INR normalizes
 - *rFVIIa is not recommended as the only agent to reverse INR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

Management

- Management of blood pressure
 - Elevation of blood pressure → expansion of hematoma → poor outcome !
 - AHA guideline



ICH: Secondary Effects

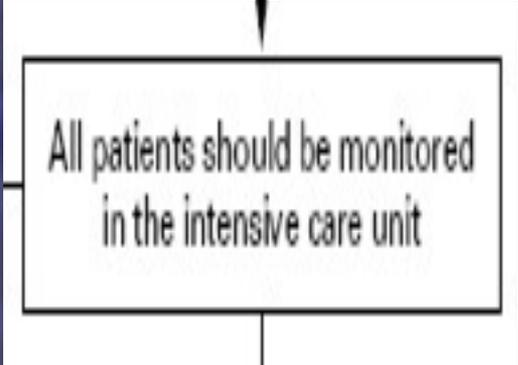
- Profound transitory elevation of BP
 - Secondary to increased ICP
- Cerebral autoregulation may be lost
- Goal is *controlled* reduction of hypertension
 - Low BP risks ischemia
 - High BP risks increased hemorrhage
 - Nitroprusside or nitroglycerin *not* first-line agents
 - Increase ICP
 - Impair cerebrovascular reactivity to changes in carbon dioxide partial pressure (PCO₂), critically problematic with elevated ICP
 - Exacerbate a decrease in CPP
 - Nicardipine

Minimal ICP effect

Rapid control of BP

Management

- Intensive monitoring of neurologic & cardiovascular status
 - Instability is highest during the first 24 hrs
 - GCS, hourly
 - BP

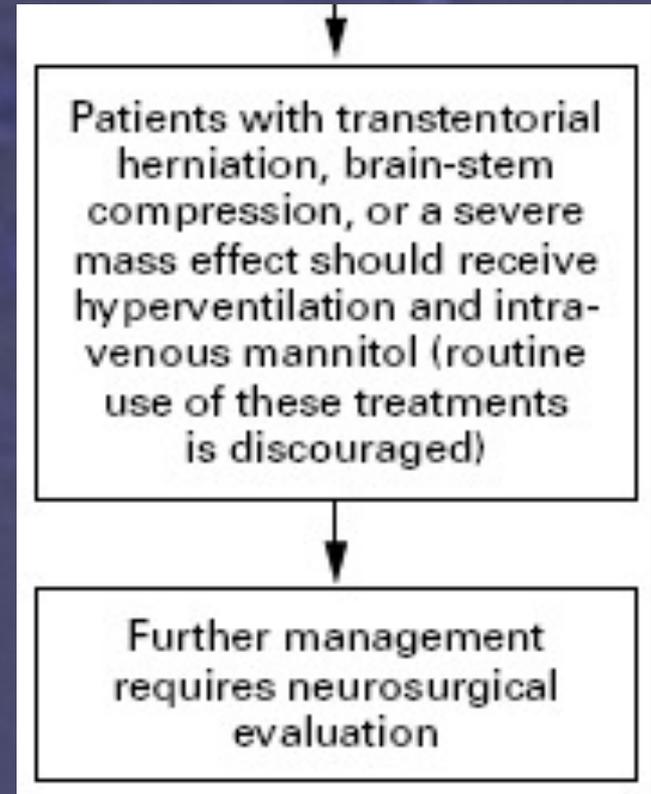


All patients should be monitored in the intensive care unit

A rectangular box with a black border, containing the text "All patients should be monitored in the intensive care unit". The box is part of a larger flowchart structure, with a vertical line extending upwards from the top center and a horizontal line extending to the left from the middle of the box.

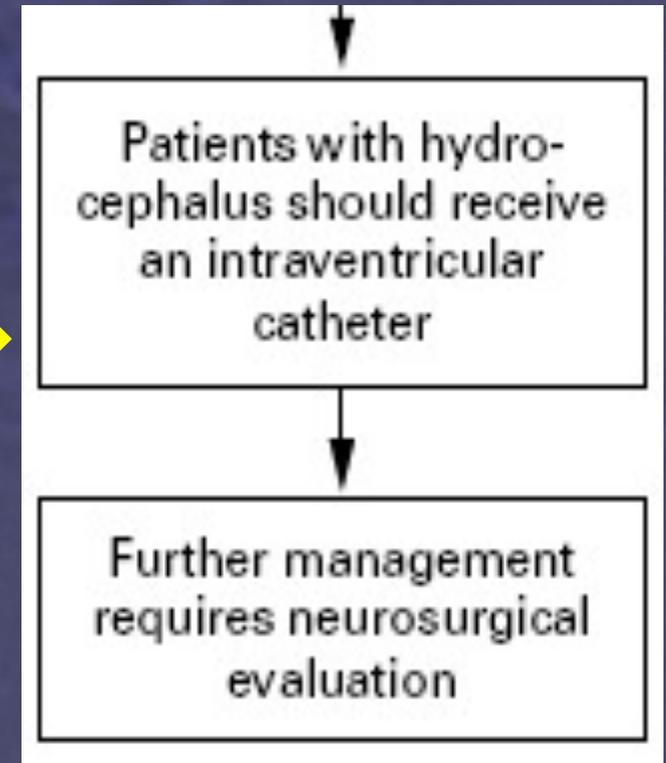
Management

- Mass effect & intracranial hypertension
 - Hematoma, edema tissue, obstructive hydrocephalus → herniation !
 - Use of hyperventilation and osmotic agent improved the long-term outcome
 - Corticosteroids should be avoided !



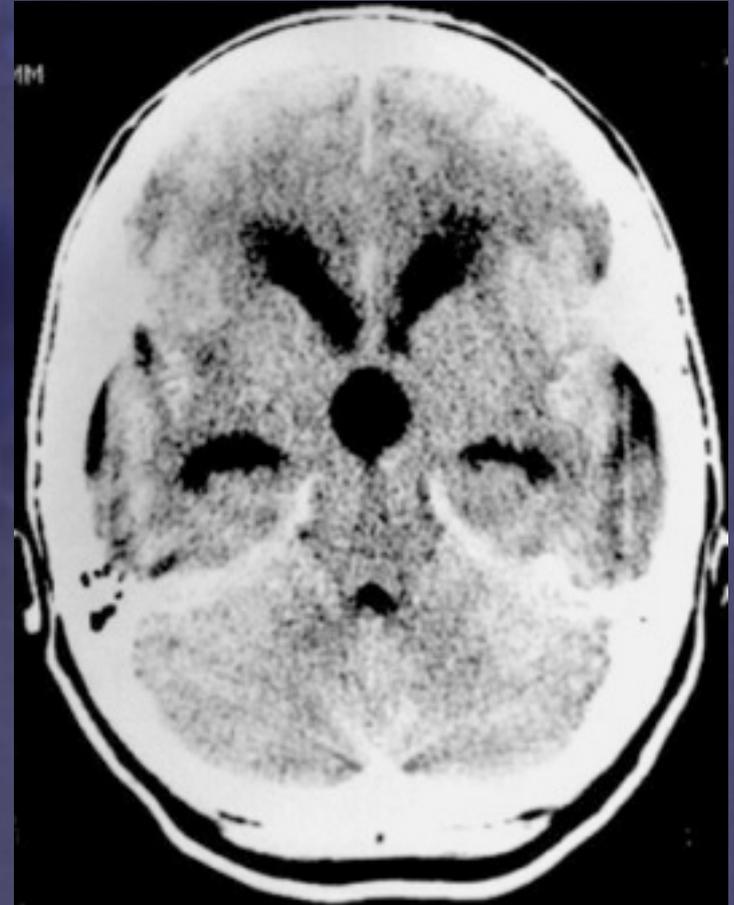
Management

- Ventricular blood and hydrocephalus
 - Blood in ventricles → obstructive hydrocephalus → high mortality rate !
 - External drainage
 - Clots in the catheter and infection



Hydrocephalus

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



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.

Management

- Surgical evacuation
 - Reduce mass effect, block the release of neurotoxic product from the hematoma
 - Surgery for supratentorial hemorrhage ?
 - Hankey et al:
 - 126 → not undergo surgery
 - 123 → surgical evacuation through an open craniotomy
 - surgery → higher rate of death (83% vs 70%) / 6m

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 \leq 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

© 2010 American Heart Association, Inc. All rights reserved. Unauthorized use prohibited.

Management

- Cerebellar hematoma
 - Can be approached with minor damage
 - Decompression of brain stem
 - Surgical → GCS < 14, volume > 40 ml
 - Conservative treatment

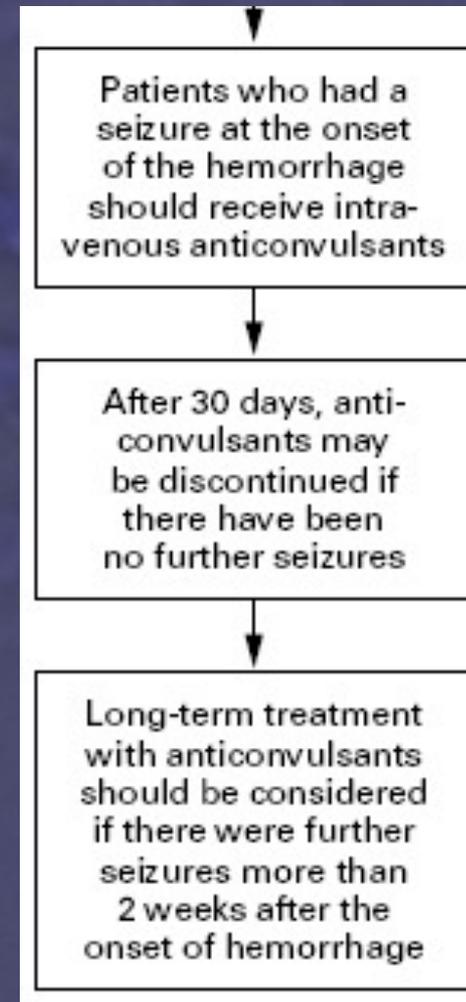
Selected patients should undergo surgical evacuation

Strongly recommended for patients with cerebellar hemorrhage if the diameter of the hematoma exceeds 3 cm, particularly if the Glasgow Coma Scale score is below 14

May be considered for young patients with moderate or large lobar hemorrhage and clinical deterioration or patients with basal ganglionic hemorrhage if volume of hematoma exceeds 30 ml, hematoma is expanding, or there is progressive neurologic deterioration

Management

- Seizures and recurrent hemorrhage
 - Most seizure → within 24 hrs
 - Anticonvulsants → discontinued after the first month if no seizure.
 - Seizures more than 2 weeks → at risk of further seizure → long-term treatment.
 - Arakawa et al. → recurrent hemorrhage : 2% per year.
 - Reduce by BP control !



Conclusions: ICH

- Get a CTA!
- Catheter angiography for CTA negative/ but suspicious
- Aggressive BP control/ICP management
- Possible factor VIIa for pts with CTA spot sign
- Surgery only in select patients: <1cm from cortex, cerebellar hematoma, large clot