ICU Management of Malignant Ischemic Stroke, ICH and SAH

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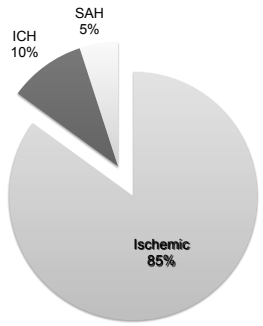
Stroke Statistics

- WHO estimates 15 million / year
- 5 million permanently disabled
- 2 million ICH / year worldwide
- ~ 50,000 / year United States
- ICH mortality 42-48% at 30 days
- $6 billion annually United States
- Cost $125,000 / patient / year



CL Sudlow and CP Warlow, *Stroke* **28** (1997), pp. 491–499.
http://www.americanheart.org
ML Flaherty, M Haverbusch and P Sekar *et al. Neurology* **66** (2006), pp. 1182–1186

Admission Requirements

- Initial monitoring and management should take place in an intensive care unit with physician and nursing expertise in neuroscience critical care
- Emergent neurosurgical evaluation and treatment available 24 hours a day
- Neurological assessments q1h for first 24 hours and then q2h if stable
- Low threshold for repeat head CT with increasing somnolence, changes in mental status, new focal findings
- Strict NPO and SLP evaluation prior to any intake

Acute Management

Prevent Secondary Brain Injury

Malignant MCA Ischemic Stroke

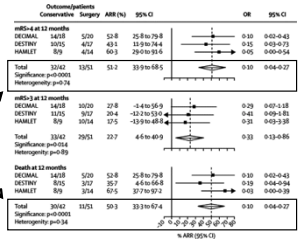
- Clinical signs of a severe unilateral MCA infarction
- Decreased level of consciousness: either from the beginning or progressively deteriorating over the first 48 h (a score of ≥1 as assessed in item 1a of the National Institutes of Health Stroke Scale [NIHSS], or a score of <14 in the Glasgow Coma Scale)
- Infarction of the MCA territory of ≥50%

Decompressive Hemicraniectomy for Malignant MCA Stroke Trials

- Prospective randomized study evaluating the efficacy of decompressive hemicraniectomy vs medical management in improving functional outcome in patients with malignant MCA stroke

- Enrolled 93 patients age 18 – 60
- CT with > 50% MCA territory affected
- Surgery within first 48 hours if neurological deterioration
- mRS or death at 12 months

**Improved outcome: 75% vs 24%
**Reduced mortality: 22% vs 71%



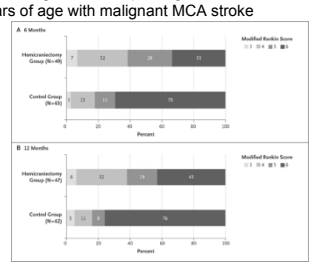
The Lancet Neurology, Volume 6, Issue 3, 2007, 215 - 222

Decompressive Hemicraniectomy for Malignant MCA Stroke for Patients > 60

- Prospective randomized study evaluating the efficacy of decompressive hemicraniectomy vs medical management in improving functional outcome in patients > 60 years of age with malignant MCA stroke

- Enrolled 112 patients
- CT with infarct > 2/3 MCA territory including basal ganglia
- Surgery within first 48 hours if neurological deterioration
- mRS or death at 12 months

**Improved outcome: 39% vs 18%
**Reduced mortality: 43% vs 76%



N Engl J Med 2014;370:1091-1100

Effect of tPA or ASA prior to DC surgery

Table 2 Perioperative hemostatic therapy in patients without and with thrombolysis treatment prior to DC

	DC without prior thrombolysis ($n = 63$)	DC after thrombolysis ($n = 52$)
RBC transfusion	18 (29)	17 (33)
Platelet infusion	7 (11)	8 (15)
FFP	4 (6)	3 (6)
Preoperative ASA medication	23 (37)	21 (40)
Preoperative laboratory values		
INR	1.16 ± 0.16	1.16 ± 0.14
PTT (s)	36 ± 6	35 ± 6
Platelet count (/nl)	210 ± 67	214 ± 53
Fibrinogen (mg/dl)	406 ± 109	353 ± 176
Hemoglobin (g/dl)	12.2 ± 2.2	12.5 ± 1.6
Postoperative laboratory values		
INR	1.31 ± 0.19	1.28 ± 0.16
PTT (sec)	40 ± 13	37 ± 6
Platelet count (/nl)	184 ± 63	186 ± 41
Fibrinogen (mg/dl)	332 ± 127	296 ± 122
Hemoglobin (g/dl)	9.7 ± 1.7	9.7 ± 1.8
Postoperative complications	23 (37)[†]	30 (58)[†]
Favourable outcome (3 mo, mRS 0–3)	12 (19)	10 (19)

Values represent number of patients unless otherwise indicated (%). Means are given with SDs
DC decompressive craniectomy, *RBC* red blood cells, *FFP* fresh frozen plasma, *ASA* acetylsalicylic acid, *INR* international normalized ratio, *PTT* partial thromboplastin time, *s* seconds
[†] $p = 0.03$, OR 2.4, 95 % CI 1.1–5

Table 3 Patients without and with previous ASA medication

	Without ASA medication prior to DC ($n = 71$)	With ASA medication prior to DC ($n = 44$)
RBC transfusion	17 (24)	18 (41)
Platelet infusion	3 (4)[‡]	12 (27)[‡]
FFP	1 (1)[‡]	6 (14)[‡]
Preoperative thrombolysis	31 (44)	21 (48)
Preoperative laboratory values		
INR	1.16 ± 0.16	1.17 ± 0.13
PTT (s)	35 ± 7	35 ± 5
Platelet count (/nl)	217 ± 63	204 ± 57
Fibrinogen (mg/dl)	393 ± 143	370 ± 142
Hemoglobin (g/dl)	12.5 ± 1.9	12.1 ± 2
Postoperative laboratory values		
INR	1.29 ± 0.18	1.30 ± 0.18
PTT (s)	39 ± 7	39 ± 15
Platelet count (/nl)	183 ± 58	186 ± 51
Fibrinogen (mg/dl)	309 ± 125	330 ± 127
Hemoglobin (g/dl)	9.8 ± 1.7	9.6 ± 1.7
Postoperative complications	25 (35)[§]	28 (64)[§]
Favourable outcome (3 mo, mRS 0–3)	19 (27)[¶]	3 (7)[¶]

Values represent number of patients unless otherwise indicated (%). Means are given with SDs
DC decompressive craniectomy, *ASA* acetylsalicylic acid, *RBC* red blood cells, *FFP* fresh frozen plasma, *INR* international normalized ratio, *PTT* partial thromboplastin time, *mo* months, *mRS* modified Rankin scale
[‡] $p = 0.009$, OR 8.5, 95 % CI 2.2–32.2
[†] $p = 0.01$, OR 11.1, 95 % CI 1.3–95.3
[§] $p = 0.004$, OR 3.2, 95 % CI 1.5–7.1
[¶] $p = 0.008$, OR 4.9, 95 % CI 1.4–18

NJ Neurol 2013;260:2149-2155

Surgical Management of Cerebellar Infarct

- Prospective observational multicenter study
- 84 patients with cerebellar infarct and mass effect
- Treatment decision at discretion of provider
- Medical (36) vs ventriculostomy (14) vs decompression (34)

Table 3 Outcome at follow-up 90 days after infarction by treatment

	Medical treatment ($n = 36$)		Ventricular drainage ($n = 14$)		Craniotomy ($n = 34$)	
	n	%	*n*	%	*n*	%
Outcome						
Good (Rankin ≤ 2)	30	83	10	71	22	65
Poor (Rankin > 2)	6	17	4	29	12	35
Subgroup analysis of Rankin score (day 90)						
Good outcome (Rankin ≤ 2)	23	85	3	100	5	83
Poor outcome (Rankin > 2)	4	15	0	0	1	17
Somnolent/stupor ($n = 29$)						
Good outcome (Rankin ≤ 2)	7	32	6	27	9	41
Poor outcome (Rankin > 2)	2	22	2	25	3	25
Coma ($n = 19$)						
Good outcome (Rankin ≤ 2)	–	–	1	33	8	50
Poor outcome (Rankin > 2)	–	–	2	67	8	50

J Neurol 1999;246:257-264

Surgical Management of Cerebellar Infarct

- Prospective observational multicenter study
- 84 patients with cerebellar infarct and mass effect
- Treatment decision at discretion of provider
- Medical (36) vs ventriculostomy (14) vs decompression (34)

Neurosurgical Options: Recommendations

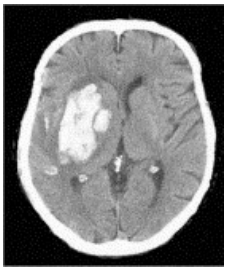
4. Suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarctions who deteriorate neurologically despite maximal medical therapy (*Class I; Level of Evidence B*).

J Neurol 1999;246:257-264

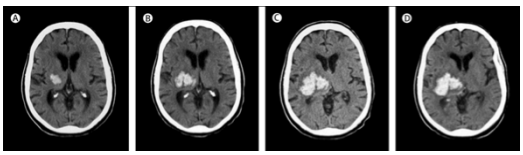
Intracerebral Hemorrhage

Etiology of Non-Traumatic ICH

- **Hypertension (70%)**
- **Arteriopathy**
  - Cerebral amyloid angiopathy (15%)
  - Moyamoya
- **Altered hemostasis**
  - Anticoagulation
  - Thrombolysis
  - Bleeding diathesis
- Venous sinus thrombosis
- Infection
- Brain tumors
  - Primary = GBM, pilocytic astrocytoma
  - Metastatic = thyroid, renal cell, melanoma, choriocarcinoma, lung
- Vascular Malformations
  - Arteriovenous malformation
  - Cavernoma
  - Aneurysm
- Vasculitis
- Sympathomimetics
- Eclampsia / post-partum vasculopathy
- Reperfusion injury / hemorrhagic transformation



Hematoma Expansion



t = 0 t = 2.5 hr t = 4 hr t = 24 hr

- 35% of patients will have clinically prominent enlargement of hematoma at 3 hr
- Most hematoma enlargement occurs within the first 3 hours although expansion up to 24 hours can occur

Qureshi AI, Mendelow AD, Hanley DF. Lancet. 2009 May 9;373(9675):1632-44
SM Davis, J Broderick and M Hennerici *et al. Neurology* **66** (2006), pp. 1175–1181

Debate on Blood Pressure Goals in ICH

- To Treat
  - » Continued blood pressure elevation may lead to further bleeding
  - » Blood pressure elevation may worsen cerebral edema
- Not to treat
  - » Lowering blood pressure may lead to perihematomal cerebral ischemia
  - » Lowering blood pressure in the setting of elevated ICP may lead to reduced CPP with resultant ischemia

ICH Management: Blood Pressure

- ***Controversial***
- Single center studies have associated elevated blood pressure with clinical deterioration, death, and worse outcome

- Retrospective study of 76 patients with hypertensive ICH
- Maximum SBP was the strongest predictor of hematoma enlargement
- Target SBP <150 reduced likelihood of hematoma enlargement

TABLE 3. Differences in Target SBP Between Patients With and Without Hematoma Enlargement

Target SBP (mm Hg)	Patients Without Hematoma Enlargement n=60	Patients With Hematoma Enlargement n=16	Rate of Enlargement	P
140	16	2	3/33 (9%)	0.025
150	14	1		
160	22	8	13/43 (30%)	
170≤	8	5		

SBP indicates systolic blood pressure.

Ohwaki et al. Stroke (2004) 35: 1364-1367

What is the treatment threshold for BP?

- 404 patients with ICH and initiation of treatment within 6 hours
- IV antihypertensive
- SBP Target
  - » Guideline SBP 180
  - » Intensive SBP 140

Intensive lowering of BP is SAFE

	Guideline (n=201)	Intensive (n=203)	p*
Death or dependency†	95 (49%)	95 (48%)	0·81
Death	25 (13%)	21 (10%)	0·51
Dependency	70 (36%)	74 (37%)	0·98
Median mRS score‡	2 (1–4)	2 (1–4)	0·66
Median NIHSS score§	2 (1–5)	2 (1–5)	0·97
Median Barthel index score¶	95 (65–100)	95 (65–100)	0·77
Median MMSE score‖	28 (22–30)	27 (22–30)	0·97
Median EQ5D score**	0·78 (0·59–1·00)	0·75 (0·52–1·00)	0·97
Early neurological deterioration††	30 (15%)	31 (15%)	0·94
Patients with a serious adverse event	42 (21%)	42 (21%)	0·96
Numbers of serious adverse events	61 (30%)	54 (27%)	0·40
Recurrent stroke‡‡	3 (2%)	2 (1%)	..
Acute coronary event	0 (0%)	1 (0%)	..
Other vascular events	3 (1%)	2 (1%)	..
Neurological deterioration§§	28 (14%)	23 (11%)	..
Renal failure	2 (1%)	4 (2%)	..
Non-vascular events	21 (10%)	17 (8%)	..
Pneumonia	15 (7%)	11 (5%)	..
Sepsis	2 (1%)	1 (0%)	..
Fracture	1 (0%)	0 (0%)	..
Other non-vascular events	3 (1%)	5 (2%)	..
Hypotension	4 (2%)	5 (3%)	..
Mild hypotension¶¶	0 (0%)	2 (1%)	..
Severe hypotension‖‖	4 (2%)	3 (1%)	..

INTERACT. *Lancet Neurology* 2008;7:391-399.

How low is too low?

- 60 patients with ICH and initiation of treatment within 6 hours
- IV nicardipine
- SBP Goals
  - » Group I SBP 170 - 200
  - » Group II SBP 140 - 170
  - » Group III SBP 110-140

All treatment thresholds appear SAFE

Table 6. End points observed within subjects according to SBP target tier

Characteristics	First Tier, SBP 170–200 mm Hg, n = 18	Second Tier, SBP 140–170 mm Hg, n = 20	Third Tier, SBP 110–140 mm Hg, n = 22
Treatment failure	0	0	9 (41%)
N (%) with SAE within 72 hrs	0	1 (5%)	3 (14%)
N (%) with neurologic deterioration within 24 hrs	1 (6%)	2 (10%)	4 (18%)
N (%) with symptomatic hematoma expansion	0	1 (5%)	4 (18%)
N (%) with asymptomatic hematoma expansion	6 (33%)	2 (10%)	3 (14%)
N (%) with in-hospital mortality	2 (11%)	1 (5%)	1 (4 %)
N (%) with 3-mo mortality	3 (17%)	2 (10%)	5 (23%)
1-mo favorable outcome, mRS 0–2	4 (3 missing)	6 (3 missing)	4 (2 missing)
3-mo favorable outcome, mRS 0–2	8 (3 missing)	9 (4 missing)	7 (2 missing)

SBP, systolic blood pressue; SAE, serious adverse event; mRS, modified Rankin score.

ATTACH. *Critical Care Medicine* 2010;38:637-648

AHA Guidelines: Blood Pressure Targets

Table 6. Suggested Recommended Guidelines for Treating Elevated BP in Spontaneous ICH

1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 min.
2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure ≥60 mm Hg.
3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of elevated ICP, then consider a modest reduction of BP (eg, MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically reexamine the patient every 15 min.

Note that these recommendations are Class C. SBP indicates systolic blood pressure; MAP, mean arterial pressure.

Morgenstern et al. *Stroke*(2010) 41: 2108-2129

Reversal of Anticoagulation

Table 5. Products Commercially Available in the United States for Coagulation Factor Replacement

Product	Factor(s)	Dose (Consultation With a Hematologist Is Recommended for Specific Dosing)	Uses
Fresh-frozen plasma	I (fibrinogen), II, V, VII, IX, X, XI, XIII, antithrombin	10–15 mL/kg with ideal recovery would raise factor levels 15%–20%	OAC reversal Consumptive coagulopathy Hepatic dysfunction
Cryoprecipitate	I, VIII, XIII, vWF	1–2 U/10 kg	Hypo/a-fibrinogenemia Lack of factor-specific products for factor VIII deficiency or vWD Factor XIII deficiency
Prothrombin complex concentrates	II, IX, X (small amounts of VII)	Assayed in factor IX activity	Factor IX deficiency (hemophilia B)
Bebulin VH (Baxter), Profilnine SD (Grifols)		Both Bebulin and Profilnine are 3-factor PCCs that have approximately 1/10th the factor VII activity relative to factor IX activity. The amounts of factor II and X relative to IX is variable, but for Bebulin X>II>IX and for Profilnine II>X–IX Dosing for factor IX deficiency—1 U/kg raises activity by 1% Dosing for OAC reversal has not been well established	OAC reversal (not FDA-approved) 25-50 units/kg + Vitamin K 10mg IV

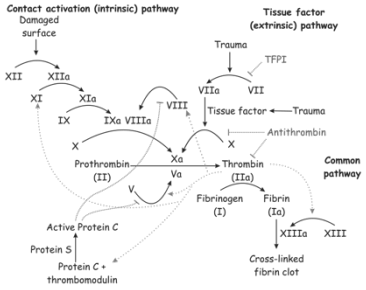
Morgenstern et al. *Stroke*(2010) 41: 2108-2129

Reversal of Anticoagulation

- Warfarin use increases risk of ICH 5-10 times
- Risk doubles for each 0.5 above 4.5
- ~15% of ICH associated with warfarin
- Warfarin use doubles risk of mortality
- Consider giving reversal agent without labs if rapid INR results not available
- All patients should get Intravenous Vitamin K at presentation

Morgenstern et al. *Stroke*(2010) 41: 2108-2129

What about direct thrombin or Xa inhibitors?

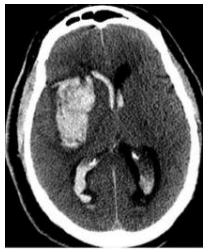


What about direct thrombin inhibitors?

- NO reversal agent or antidote available
- Not depleting clotting factors therefore blood products theoretically NOT effective
- Thrombin Time: Sensitive, if normal = no effective anticoagulation
- aPTT not a sensitive: mildly elevated = cont bleeding risk
- Renal cleared therefore if CRI half-life > 24 hours
- Dialysis is effective for removal (approx 60%) but not feasible in most centers
- Our approach for ICH: PCC plus aPCC or rFVIIa if hemostasis not achieved
- Recommendations:
  - Get your hematology colleagues involved
  - Develop a standardized protocol for patients with bleeding based on the acuity

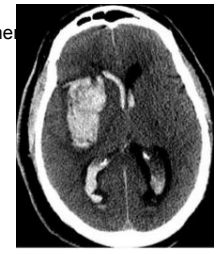
Intraventricular hemorrhage

- In the FAST trial 45% of patients had intraventricular hemorrhage after 24 hours
- Intraventricular hemorrhage and hydrocephalus are independent predictors of poor outcome
- If hydrocephalus occurs CSF drainage is indicated via an external ventricular drain



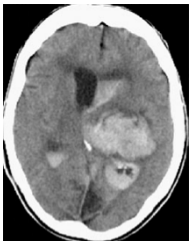
Surgical Management of ICH

- ➔ ICP pressure monitor placement
- ➔ External ventricular drain placement
- ➔ Surgical clot evacuation
- Endoscopic clot evacuation
- Decompressive Craniotomy
- ➔ Treatment of underlying lesion
  - » Vascular malformation
  - » Cavernoma
  - » Aneurysm



Which ICH patients need an ICP monitor?

- ICP monitor or external ventricular drain should be considered in all patients with an ICH and coma (GCS of 8 or less)
- External ventricular drain should be placed in patients with obstructive hydrocephalus preferably prior to exam deterioration
- Goal CPP > 60 mm Hg
- Goal ICP < 20 mm Hg



Surgical Management of Posterior Fossa Hemorrhage

- 22 Italian centers evaluated 205 posterior fossa hemorrhages (155 cerebellar)
- Brainstem hemorrhage mortality 57%
- "medical treatment appears to be the best policy for brainstem hematomas of limited size; for larger lesions, the outcome appears to be uniformly fatal, regardless of the treatment employed"
- Cerebellar hemorrhage – surgical evacuation if hydrocephalus and mass effect on 4th ventricle
- Cerebellar hemorrhage – timing of deterioration not predictable
- 50% comatose without surgery at 24 hours and 75% at 1 week
- Preoperative mental status predicted outcome
  - » Responsive 17% mortality
  - » Unresponsive 75% mortality

Table 3.—Surgical Mortality According to Preoperative Mental Status

	Cases			
	No.	Died	%	Comment*
Alert	2	0	0	...
Drowsy	10	2	20	Death 18th PO day, myocardial infarction; death 32nd PO day, reblied into metastatic cerebellar tumor
Stuporous	4	2	50	Death 1st PO day, reblied after reoperation; death after 9 hr, probably reblied
Coma	12	10	83	Two survivals, moderate disability and complete disability

Ott et. al. Arch Neurol. 1974 Sep;31(3):160-7
Da Pian et al. Neurol Res. 1984 Sep;6(3):145-51

International Surgical Trial for IntraCerebral Hemorrhage (STICH)

- Spontaneous supratentorial ICH
- Early surgery versus medical therapy
- Clinical equipoise therefore the patient must be deemed to not benefit from one treatment versus the comparison treatment
- If local investigator felt like patient would benefit from emergency surgery then they were not enrolled
- 1033 patients
- Primary endpoint "good recovery or moderate disability" on the Glascow Outcome Scale at 6 months by questionnaire

	Early surgery (n=468)	Initial conservative treatment (n=497)	Absolute benefit (95% CI)
Primary outcome			
Favourable	123 (26%)	118 (24%)	2·3 (-3·2 to 7·7)
Unfavourable	346 (74%)	378 (76%)	–
Not recorded		1	–
Secondary outcomes			
Mortality			
Alive*	304 (64%)	316 (63%)	1·2 (-4·9 to 7·2)
Dead	173 (36%)	180 (37%)	–
Prognosis-based modified Rankin index			
Favourable	152 (33%)	137 (28%)	4·7 (-1·2 to 10·5)
Unfavourable	312 (67%)	351 (72%)	–
Not recorded	4	9	–
Prognosis-based Barthel index			
Favourable	124 (27%)	110 (23%)	4·1 (-1·4 to 9·5)
Unfavourable	341 (73%)	377 (77%)	–
Not recorded	3	10	–

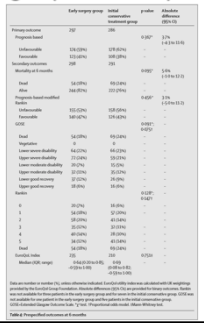
Data are number (%). *Includes 17 patients who were alive at 6 months but status was unknown.

Table 4: Outcomes at 6 months

Mendelow et al. Lancet. 2005 Jan 29-Feb 4;365(9457):387-97

International Surgical Trial for IntraCerebral Hemorrhage (STICH II)

- Spontaneous lobar supratentorial ICH without IVH
- Early surgery versus initial medical therapy
- Clinical equipoise therefore the patient must be deemed to not benefit from one treatment versus the comparison treatment
- 601 Patients
- Primary endpoint "good recovery or moderate disability" on the Glascow Outcome Scale at 6 months by questionnaire



Lancet 2013; 382: 397-408

AHA Guidelines for Surgical Treatment of ICH

For most patients with ICH, the usefulness of surgery is uncertain *(Class IIb; Level of Evidence: C)*.

→ **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 alone rather than surgical evacuation is not recommended *(Class III; Level of Evidence: C)*.

→ **For patients presenting with lobar clots >30 mL and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered *(Class IIb; Level of Evidence: 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; Level of Evidence: B)*.

Although 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; Level of Evidence: B)*.

Morgenstern et al. *Stroke*(2010) 41: 2108-2129

Seizures and ICH

- 30 day risk of clinically evident seizures is ~8%
- Convulsive status epilepticus seen in 2%
- Risk of epilepsy 5-20%
- Lobar location is an independent predictor of early seizures

- Seizures have been associated with:
  - » Neurological worsening
  - » Increased midline shift
  - » Poorer outcomes

Anticonvulsant Prophylaxis in ICH

Purpose: To characterize seizures after intracerebral hemorrhage (ICH), evaluating the risk of occurrence and relapse, predisposing factors, and prognostic significance, and to assess the utility of antiepileptic drug (AED) therapy as used in clinical practice.

Methods: The study sample consisted of 761 patients with spontaneous, nonaneurysmal, supratentorial ICH. Seizures were classified as immediate (within 24 h of ICH) and early (within 30 days of ICH). Baseline variables and clinical events were compared in the seizure and nonseizure group by using a multivariate regression model of failure time data.

Time after ICH (days)	Immediate and early seizures	Time after ICH (yr)	Recurrent seizures
1	4.4 (3.7–5.2)	1	5.3 (1.6–8.9)
5	7.2 (6.2–8.2)	2	5.3 (1.6–8.9)
10	7.6 (6.6–8.6)	3	19.3 (9.6–29.0)
15	8.0 (7.1–9.1)	4	27.0 (15.6–38.4)
30	8.1 (7.8–10.3)	5	27.0 (15.6–38.4)

Objective: To determine whether early seizures that occur frequently after intracerebral hemorrhage (ICH) lead to increased brain edema as manifested by increased midline shift.

Methods: A total of 109 patients with ischemic stroke (n = 46) and intraparenchymal hemorrhage (n = 63) prospectively underwent continuous EEG monitoring after admission. The incidence, timing, and factors associated with seizures were defined.

Characteristic	Intracerebral hemorrhage	Ischemic stroke
Age, y, mean ± SD	61.5 ± 15.3	62.7 ± 20.2
Male:female	36:27	24:23
NIHSS initial, mean ± SD	16.3 ± 8.1	14.7 ± 7.0
NIHSS final, mean ± SD	17.7 ± 7.5	16.0 ± 7.9
Lesion location, n		
Lobar	31	38
Subcortical	34	9
Mean initial lesion volume, cc*	23.5	32.7
Surgery, n	28	2
Ventriculostomy, n	26	1
Seizures, n (%)	18 (28.1)	3 (6)†
GOS, median	3	3

Passero et. al. Epilepsia. 2002 Oct;43(10):1175-80
Vespa et. al. *Neurology* 2003;60:1441-1446

When to treat?

ICH location	Untreated No.	Untreated With seizures	Treated No.	Treated With seizures	Crude risk (95% CI)	Adjusted risk (95% CI)
Deep (n = 382)	161	3 (1.9)	221	1 (0.5)	0.51 (0.16–1.58)	0.35 (0.13–1.10)
Lobar (n = 268)	66	9 (13.6)	202	12 (5.9)	0.59 (0.38–0.92)	0.62 (0.40–0.96)
Any lobar involvement (n = 362)	91	11 (12.1)	271	13 (4.8)	0.64 (0.43–0.95)	0.57 (0.38–0.86)
Any location (n = 650)	227	12 (5.3)	423	13 (3.1)	0.79 (0.53–1.17)	0.62 (0.41–0.94)

- AAN guidelines: only patients with electrographic or clinical seizures should be treated with anticonvulsants
- Prophylactic therapy should NOT be used for ICH
- Practical: Monitor all comatose patients for 48 hours to evaluate for convulsive or non-convulsive seizures and treat accordingly

Passero et. al. Epilepsia. 2002 Oct;43(10):1175-80
Broderick et al. *Stroke*(2007) 38(6): 2001-2023

Fever Control

- Fever after stroke is common
- Still must rule out an infectious or drug-related cause
- Sustained fever after ICH is independently associated with poor outcome
- Antipyretics and cooling measures should be used to maintain normothermia
  - » Not supported by data to suggest a better outcome
- While actively cooling a patient or using scheduled dose acetaminophen, one must be vigilant in monitoring for infection

Deep Venous Thrombosis Prophylaxis

- Deep venous thrombosis and pulmonary embolism are common causes of morbidity and mortality in patients with ICH
- Studies demonstrate 10-50% rate of DVT in stroke patients with hemoplegia
- 68 consecutive patients randomized to heparin 5,000 units tid to start on day 2, 4, or 10 after onset
  - » No difference in bleeding rates between groups
  - » Significant reduction in pulmonary embolism with initiation on day 2 or 4
- AHA Guidelines
  - » **Patients with acute primary ICH and hemiparesis/hemiplegia should have intermittent pneumatic compression for prevention of venous thromboembolism *(Class I, Level of Evidence B)***
  - » **After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered in patients with hemiplegia after 3 to 4 days from onset**

Start chemical DVT prophylaxis at 72 hours if no evidence for further bleeding

Boeer et al. *Journal of Neurology, Neurosurgery, and Psychiatry* 1991;**54**:466-467

When is it safe to restart anticoagulation?

- Retrospective
- 141 patients on warfarin for a high risk of thromboembolism
- Median time off warfarin 10 days (0 - 30 days)

Table 1. Baseline Demographic Characteristics

Table 2. Characteristics of the Patients With Ischemic Events After Discontinuation of Warfarin Therapy for Intracerebral Hematoma*

Patient Age, y	Hemorrhage	Indication for Anticoagulation	Carotid US or Angiographic Results	Echocardiographic Results	Time to Stroke Recurrence, d	Stroke Syndrome
75	SDH	Aortic metallic valve (BJ)	ND	ND	5	Occipital infarct
73	SDH	TIA	Normal	Normal	5	Lacunar infarct
75	SDH	TIA	High-grade stenosis of the BA	Normal	4	Vertebrobasilar TIA

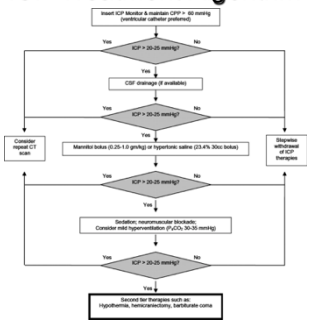
*All 3 patients were men. US indicates ultrasonographic; ICH, intracerebral hemorrhage; AF, atrial fibrillation; ND, not done; SAH, subarachnoid hemorrhage; BJ, Björk-Shiley; SDH, subdural hematoma; TIA, transient ischemic attack; and BA, basilar artery.

- Risk of recurrent stroke at 7 or 30 days 2.6 - 4.8%
- 35 patients resumed warfarin therapy with no subsequent ICH during hospitalization

Wait 7 days if feasible before restarting anticoagulation for patients with absolute indication (ex. mechanical heart valve)

Phan et. al. Arch Neurol. 2000 Dec;57(12):1710-3

ICP Treatment Algorithm



Morgenstern et al. *Stroke*(2010) 41: 2108-2129

Aneurysmal Subarachnoid Hemorrhage

Prevention of Early Rebleeding

- Prospective randomized trial
- 505 patients randomized to tranexamic acid vs control (no tranexamic acid)
- Primary outcome GOS at 6 months
- Secondary outcome included recurrent bleeding
- Instituted protocol = Aminocaproic acid for 72 hr from initial bleed
- Compared 73 patients treated with protocol to 175 prior patients
- Acute rebleeding rate evaluated before and after protocol initiated
- Increased risk of DVT but not PE with tx
- Avoid use in those with known thromboembolic disease

TABLE 5
Number of verified rebleeds and outcome in the control and AF groups

	Control Group (251 patients)				AF Group (254 patients)			
Hunt & Hess Grade Before Rebleed	No. W/ Rebleed	GOS Score 1	2–3	4–5	No. W/ Rebleed	GOS Score 1	2–3	4–5
I/II	20	10	3	7	4	1	1	2
III	3	0	1	2	1	0	0	1
IV	3	2	1	0	1	1	0	0
V	1	1	0	0	0	0	0	0
total	27	13	5	9	6	2	1	3

J Neurosurg 2002; 97: 771-778

Table 2. Outcomes in EACA- and Non-EACA-Treated Patients

	Non-EACA Group	EACA Group	Significance (*P* Value)
	n=175	n=73	
Acute rebleeding*	17 (9.7)	2 (2.7)	0.045

Stroke 2008; 39: 2617-2621

Cardiopulmonary Complications

- Cardiac complications are common in the acute phase of aneurysmal SAH
- Usually transient with resolution over weeks
- Recommend echocardiogram for all patients with SAH and abnormal cardiac enzymes or those at high risk for vasospasm
- Pulmonary complications are common in patients with aneurysmal SAH
- Retrospective analysis of 620 patients determined that 170 met criteria for Acute Lung Injury

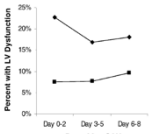


FIG. 2. Graph depicting the prevalence of an abnormally elevated (> 1) RWMS (*diamonds*) and an abnormally reduced (< 50%) LVEF (*squares*) for three time periods after the onset of symptoms of SAH.

J Neurosurg 2006; 105:15-20

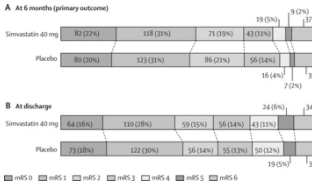
Table 2. Multivariate analysis for factors associated with development of acute lung injury (ALI) in patients with subarachnoid hemorrhage[a]

Variable	Adjusted OR	95% CI	*p* Value
SAPS II[b]	1.03	1.02–1.05	<.001
Hunt and Hess grade[c]	1.23	1.01–1.48	.035
Severe sepsis	2.96	1.22–7.17	.016
PRBC transfusions[d]	2.73	1.66–4.50	<.001

Crit Care Med 2006; 34: 196-202

Simvastatin in aneurysmal SAH (STASH)

- Prospective randomized double blind study
- Determine if simvastatin 40mg could improve long term outcome
- 803 patients randomized and 782 patients had outcome data included
- mRS score at 6 months as primary outcome



	Simvastatin 40 mg (n=391)	Placebo (n=412)	p value
Suspected delayed ischaemia			
Proven radiological infarct	61 (16%)	71 (17%)	0·5328
Clinical delayed ischaemic deficits	64 (16%)	67 (16%)	0·9675
Other causes of deterioration			
Sepsis	96 (25%)	99 (24%)	0·8628
Epilepsy	7 (2%)	12 (3%)	0·2956
Hypoxia	7 (2%)	5 (1%)	0·5008
Rebleed	8 (2%)	10 (2%)	0·7753
Hydrocephalus (requiring external ventricular drain)	69 (18%)	76 (18%)	0·7685
Other	35 (9%)	44 (11%)	0·4111

Lancet Neurol 2014; 13: 666-675

Vasospasm Monitoring with TCD

- Retrospective analysis
- 1877 TCD exams in 441 patients with confirmed aneurysmal
- Delayed cerebral ischemia occurred in 21% of patients
- Maximum sensitivity at day 8

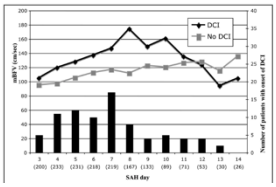


TABLE 2. Sensitivity, specificity, positive and negative predictive values, and adjusted odds ratios for delayed cerebral ischemia according to peak transcranial Doppler velocity*

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AOR	95% CI	*P* value
Peak mBFV (cm/s)							
>120	63	52	26	84	1.74	1.06–2.86	0.028
>140	51	65	28	84	1.96	1.21–3.18	0.006
>160	37	77	37	82	1.93	1.16–3.21	0.012
>180	30	85	34	82	2.08	1.20–3.59	0.009

* PPV, positive predictive value; NPV, negative predictive value; AOR, adjusted odds ratio; CI, confidence interval; mBFV, mean blood flow velocity. Odds ratios are adjusted for admission modified Fisher scale score, Hunt and Hess grade, and female sex.

Neurosurgery 2009; 65: 316-324

Vasospasm Monitoring with CTA

- Prospective study to compare the accuracy of CTA for the diagnosis of large-vessel vasospasm following SAH compared to DSA
- 33 patients enrolled
- All studies reviewed by neuroradiologists blinded to the results of studies
- Weighted kappa-coefficient for agreement was substantial overall
- **Consider using CTA for monitoring in patients in whom the exam may not be reliable**

Table 2. Weighted κ-coefficient for the degree of luminal narrowing

	Overall	Basilar	Vertebral artery	P1	P2	PCom	M1	M2	A1	A2	SICA
CTA-DSA comparison	0.638	0.732	0.401	0.535	0.520	0.577	0.603	0.550	0.674	0.562	0.772
Two observer agreement	0.712	0.755	0.718	0.703	0.701	0.726	0.767	0.678	0.780	0.706	0.684

Cerebrovas Dis 2008; 25: 144-150

Prevention of Vasospasm using Prophylactic Hypervolemia

- Prospective randomized study to determine the effectiveness of hypervolemic vs normovolemic fluid status on regional CBF and development of symptomatic vasospasm
- 82 patients enrolled
- Used isotonic crystalloid and albumin to maintain hypervolemic state beginning on the second day and continuing until day 14
- **No benefit to prophylactic hypervolemic therapy**

TABLE 5. Clinical Outcome

	14 d After SAH		3 mo After SAH	
	NV	HV	NV	HV
Independent, minimal deficit	27 (66)	27 (66)	29 (74)	30 (75)
Independent, moderate deficit	4 (10)	3 (7)	2 (5)	3 (7)
Dependent, severe deficit	9 (22)	10 (24)	5 (13)	5 (13)
Vegetative	0 (0)	0 (0)	0 (0)	0 (0)
Dead	1 (2)	1 (2)	3 (7)	2 (5)
Unknown	0	0	2	1

Values are n (%).

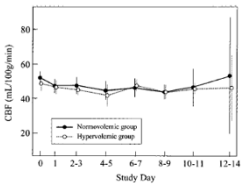


Figure 2. Mean global CBF (gCBF) in the hypervolemic and normovolemic treatment groups plotted over the 14-day study period. Error bars represent 95% CIs.

Stroke 2000; 31: 383-391

Treatment of Vasospasm – Hemodynamic Augmentation

- Quantitative CBF measurements using Xenon CT in patients with clinical signs of cerebral vasospasm
- 16 patients enrolled
- Direct CBF measurements obtained before and after treatment aimed to compare hypervolemia, increased MAP using vasopressors, or dobutamine to augment cardiac output
- **Increased MAP and augmentation of cardiac output led to increased CBF**

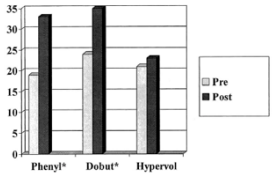


FIGURE 3. *CBF in ischemic regions before and after treatment. Changes in CBF after the different treatment regimens are charted. On the y axis, CBF is expressed in ml/100 g/min. Statistically significant changes are noted with phenylephrine and dobutamine but not with hypervolemia. *, P < 0.05.*

Neurosurgery 2003; 53: 1044-1052

Endovascular prevention and treatment of Vasospasm

- Prospective randomized study to determine if prophylactic transluminal balloon angioplasty prevents delayed ischemic neurological deficit and improves outcome at 2 months
- 170 patients enrolled, 85 intervention vs 85 control
- **No benefit to prophylactic angioplasty**

Table 3. Complications of pTBA of 483 Vessel Segments

Adverse Event	Outcome
Arterial perforation of left internal carotid artery	Good recovery
Arterial rupture of P1 segment	Death from procedure
Arterial perforation of left anterior cerebral artery	Death from procedure
Arterial rupture of basilar artery	Death from procedure

Table 7. Outcome by GOS at 3 Months After SAH

All Patients		Unfavorable		Favorable		Total
pTBA		43 (50.6%)		42 (49.4%)		85
	Died	Vegetative State	Severe Disability	Good Recovery	Moderate Disability	
	18 (21.1%)	0 (0%)	25 (26%)	14 (16.4%)	28 (32.9%)	
Control		48 (56.5%)		37 (43.5%)		85
	Died	Vegetative State	Severe Disability	Good Recovery	Moderate Disability	
	16 (18.8%)	3 (3.5%)	29 (34%)	10 (11.8%)	27 (31.8%)	
Total		91 (53.5%)		79 (46.5%)		170
Hunt-Hess grade I–II		Unfavorable		Favorable		
pTBA		8 (22.8%)		27 (77.2%)		35
Control		10 (32.3%)		21 (67.7%)		31
Total		18 (27.3%)		48 (72.7)		66

Neurosurgery 2003; 53: 1044-1052

Impact of Hospital-Related Factors on Outcome after SAH

- Retrospective analysis of all discharges in NY state from 1995-2000 with SAH or unruptured cerebral aneurysms
- 2200 admissions for unruptured cerebral aneurysm
- 3763 admissions for SAH
- **Hospital volume associated with fewer adverse outcomes and lower in-hospital mortality**

TABLE 4. Comparison of the Effect of Hospital Volume on Outcome After Clipping Versus Coiling of Cerebral Aneurysms

	Unruptured Aneurysms						Ruptured Aneurysms					
	Clipping			Embolization			Clipping			Embolization		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Adverse outcome	0.85	0.82–0.88	<0.0001	0.94	0.87–1.02	0.116	0.93	0.88–0.99	0.013	0.93	0.91–0.97	0.029
In-hospital death	0.94	0.90–0.98	0.004		NA		0.94	0.91–0.97	<0.001	0.97	0.92–1.02	0.207

NA indicates too few cases for algorithm to converge. Table shows effect of hospital volume on clipping and coiling of cerebral aneurysms separately. Expressed as OR for each additional 10 cases per year in total procedural volume.

Stroke 2003; 34: 2200-2207