

## Diagnosing & Treating Emergency Department CNS Hemorrhage Patients

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## Global Objectives

- Improve pt outcome in CNS hemorrhage
- Know how to quickly evaluate stroke pts
- Know clinically how to use protocols
- Provide rationale ED use of therapies
- Facilitate useful disposition, documentation
- Improve Emergency Medicine practice

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## A Clinical Case

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## Clinical History

- 66 year old male presents with acute onset of aphasia and right sided weakness while eating at home
- Initially complained of a headache
- BP of 220/118 mm Hg
- Accucheck 316
- Initial GCS of 14

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## ED Presentation

- ED VS
  - BP 224/124, P 100, RR 16, T 98.8, pulse ox 99%
- Somnolent, but slowly responds to simple commands
- Snores a bit when not stimulated
- Clear lungs and a regular cardiac rate and rhythm
- Neuro screening exam
  - Pupils midpoint, equal and reactive
  - L sided gaze preference
  - R facial weakness
  - R upper > lower extremity weakness
  - Expressive aphasia

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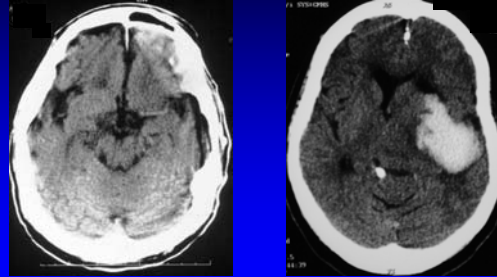


## Key Clinical Questions

- What are the key diagnostic issues?
- How can ED patient Rx be optimized?
- What guidelines direct our therapy?
- What drugs must be available for use?
- How can these drugs best be used?
- How should this ICH Rx be documented?

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## Which of these belong to this patient?



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## Ethnicity of ICH Risk

- Age and sex adjusted rate
  - U.S. 15 per 100,000
  - World wide 10-20 per 100,000
- Rates: 13.5 per 100,000 Caucasian  
 38 per 100,000 African Americans  
 55 per 100,000 Japanese

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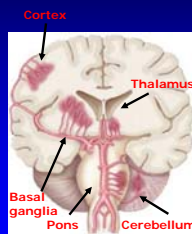
## Primary Risk Factors

- Age
- Hypertension
- Alcohol intake
- Gender (M > F)
- Race
- Smoking
- Diabetes
- Vascular malformations
  - Moyamoya / aneurysms
- Infections
  - Vasculitis
  - Mycotic aneurysms
- Cerebral venous thrombosis
- Genetic
  - Apolipoprotein E ε4

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## Location

- Lobar
  - Associated with amyloid angiopathy
- Nonlobar
  - Due to hypertension
- Cerebellar
- Brain stem



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## ICH is Dynamic



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### ICH Progression

- Symptoms often progress, associated with ICH growth
  - 2/3 with progression of symptoms
  - 1/3 maximal at onset
- Within hours from onset:
  - 26% with >33% growth in next 1°
  - 12% with >33% growth 1-20°

2.0 hours after onset      6.5 hours after onset

(Brott, Stroke 1997;28:1-5) E. Bradshaw Bunney, MD

### Size Matters

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(Image courtesy T. Brott, MD)

### Prognosis

- **Worse**
  - Volume > 60 cm<sup>3</sup> and GCS < 9
    - 91% dead at 30 days
  - Patients with > 30 cm<sup>3</sup>
    - 1 / 71 independent at 30 days
  - Other: age, seizures, intraventricular extension
- **Better**
  - Volume < 30 cm<sup>3</sup> and GCS 9 or higher
    - 19% dead at 30 days

(Broderick, Stroke 1993;24:987- 93) E. Bradshaw Bunney, MD

### Hematoma Volume

- Formula for volume of an ellipsoid
  - $\frac{4}{3}\pi (A/2)(B/2)(C/2)$
  - Simplified  $A*B*C / 2$

a 3.0cm  
b 2.5cm

(Kothari, Stroke 1996;27:1304-5) E. Bradshaw Bunney, MD


## Medical Management

### The Basics are Important

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## ICH Management

- Immediate stabilization (ABC's)
- Supportive medical care
  - Frequent comorbidities
- Neurologic specific care
- Hemorrhage specific interventions

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## Emergent Evaluation

- Baseline labs
  - CBC, coagulation parameters, electrolytes
- Neuroimaging
  - CT remains gold standard
    - Identify ICH and complications (hydrocephalus, herniation)
  - MRI / MRA
    - For structural abnormalities (AVM, aneurysms)
  - Angiography
    - Rarely emergently indicated, identifies vascular issues

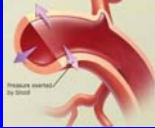
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## Medical Management

- ABC's
  - Maintain oxygen saturation  $\geq 92\%$
  - Rapid sequence intubation
- Medical management
  - Prevention of hyperthermia ( $< 37.5^\circ\text{C}$ )
  - Glycemic control
  - Coagulopathy correction (FFP, vitamin K)
  - No glycerol, corticosteroids, hemodilution
  - Secondary complication prevention

(EUSI, *Cerebrovasc Dis* 2003;16:311-318) E. Bradshaw Bunney, MD 


## Medical Management is Important Blood Pressure



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## Blood Pressure Management

- Hypertension very common
  - MAP  $> 140$  in 34%,  $> 120$  in 78%
  - Many 'normalize' over first 24 hours
- General goals
  - Maintain MAP  $< 130$  mmHg with history of hypertension
  - Prevent hypotension (SBP  $< 90$  mmHg)
  - Maintain:
    - Cerebral perfusion pressure (CPP=MAP-ICP) CPP  $> 70$  mmHg
    - Central venous pressure from 5-12 mmHg
- Optimal blood pressure still to be determined

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## Blood Pressure Management

**Common agents**

- Labetalol
- Nicardipine
- Nitroprusside (theoretical risk of increasing ICP)


**New data suggest SBP  $\leq 150$  mm Hg**

Elevated blood pressure (some suggested medications)

Labetalol	5-100 mg/h by intermittent bolus doses of 10-40 mg or continuous drip (2-8 mg/min)
Esmolol	500 µg/kg as a load, maintenance use, 50-200 µg · kg <sup>-1</sup> · min <sup>-1</sup>
Nitroprusside	0.5-10 µg · kg <sup>-1</sup> · min <sup>-1</sup>
Hydralazine	10-20 mg Q 4-6 h
Ertaprilol	0.625-1.2 mg Q 6 h as needed

The following algorithm adapted from guidelines for antihypertensive therapy<sup>16</sup> in patients with acute stroke may be used in the first few hours of ICH (level of evidence V, grade C recommendation):

1. If systolic BP is  $\geq 230$  mm Hg or diastolic BP  $\geq 140$  mm Hg on 2 readings 5 minutes apart, initiate nitroprusside.
2. If systolic BP is 180 to 230 mm Hg, diastolic BP 105 to 140 mm Hg, or mean arterial BP  $\geq 130$  mm Hg on 2 readings 20 minutes apart, initiate intravenous labetalol, esmolol, enalapril, or other smaller doses of easily titratable intravenous medications such as diltiazem, lisinopril, or verapamil.
3. If systolic BP is  $\geq 160$  mm Hg and diastolic BP  $\geq 105$  mm Hg, defer antihypertensive therapy. Choice of medication depends on other medical contraindications (eg, avoid labetalol in patients with asthma).
4. If ICP monitoring is available, cerebral perfusion pressure should be kept at  $\geq 70$  mm Hg.

(Broderick, *Stroke* 1999;30(4):905-15)  
 (Ohwaki, *Stroke* 2004;35:1364-1367) E. Bradshaw Bunney, MD 

## Medical Management is Important Intracranial Pressure



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## Management of ICP

- Definition
  - ICP > 20 mm Hg for > 5 minutes
- Treatment goal
  - ICP < 20 mm Hg and CPP > 70 mm Hg
- Recommendations
  - ICP monitoring with GCS < 9
- Management
  - Patient positioning
  - Osmotherapy
  - Hyperventilation
  - Ventricular drainage

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## Management of ICP

- Head of bed at 45 degrees
- Osmotherapy
  - Mannitol 0.25-0.5 g/kg every 6 hours up to 5 days
  - Target mOsm  $\leq$  310 mmol/L
- Hyperventilation
  - Tidal volume of 12-15 ml/kg
  - Target pCO<sub>2</sub> 30-35 mm Hg
- Neuromuscular paralysis
  - Nondepolarizing agents

(Broderick, *Stroke* 1999;30(4):905-15)

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## Medical Management is Important Coagulation Correction



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## Coagulation Correction

- Warfarin
  - FFP 10 ml/kg
  - Vit K 10 mg IV over 10 mins
- Heparin (and some LMWH)
  - Correct with protamine 10 – 50 mg IVP over 1 – 3 mins
- Direct thrombin inhibitors
  - No antidote, consult hematology
- Platelet disorders
  - Correct with platelets (>100,000)
  - DDAVP 0.3  $\mu$ g/kg IV over 30 mins

(MGH Stroke Service, 2005)

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## Warfarin Related ICH

- Use increases ICH risk 7-10 times
  - >10 fold risk if over 50 years of age
  - Increased risk dramatic if INR >4.0
    - 50-90% OAC-related ICHs occur while INR in the target range
  - ICH risk greatest at the start of treatment

Punthakee X et al. *Thrombosis Research* 2003;108:31-36.  
Butler AC, Tate RC. *Blood Reviews* 1998;12:35-44.  
Winzen AR et al. *Ann Neurol* 1984;16:553-8.  
Frankle CL et al. *Stroke* 1990;21:726-30.  
Hyiek EM, Singer DE. *Ann Int Med* 1994;120(11):897-902.

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### Risk Factors for Warfarin Related ICH

- Advanced Age
- Hypertension
- Intensity of Anticoagulation
- Cerebral amyloid angiopathy

Hart RG. *Neurology* 2000;55:907-908.

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### Warfarin ICH Rx: Driving Principles

- Measure INR
- Establish the extent of INR elevation (< 5, 5-9, >9) and presence of bleeding
- Determine if an immediate neurosurgical intervention is needed
- Administer Vitamin K IV
- Order Coagulation Factor Replacement

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### Elevated INR Therapy: *The Procedure*

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### Elevated INR Rx Procedure

- Vitamin K 10 mg by slow IV infusion

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### Vitamin K

- Necessary to achieve more than a temporary reversal of anticoagulation
- Adequate response requires at least 2-6 and up to 24 hours
- Anaphylactic or anaphylactoid reactions rarely associated with IV administration
- Safest and most rapidly acting route of administration unclear

Wjasow C, McNamara R. *J Emerg Med* 2003;24(2):169-72.  
Fiore LD et al. *J Thrombosis & Thrombolysis* 2001;11(2):175-83.

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### Coagulation Factor Replacement

- Options include
  - FFP
  - Prothrombin Complex Concentrates (PCC)
  - Recombinant Factor VIIa
- Normal coagulation achieved more rapidly with PCC and rFVIIa than with FFP

Fredriksson K et al. *Stroke* 1992;23:972-977.  
Makris M et al. *Thromb Haemostasis* 1997;77:477-480.

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### Bedside Realities:

Can you answer these questions?

- Is thawed FFP immediately available from your blood bank?
- How long will it take your blood bank to get it to you?
- Does your hospital blood bank or inpatient pharmacy store PCC and rFVIIa?
- What is the relative rapidity of response of each of these agents?

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### Elevated INR Rx Procedure

- Vitamin K 10 mg by slow IV infusion
- Fresh frozen plasma (5-8 ml/kg, 1-2 units, 250-500 cc total)

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### Elevated INR Rx Procedure

- Vitamin K 10 mg by slow IV infusion
- Fresh frozen plasma (5-8 ml/kg, 1-2 units, 250-500 cc total)  
*OR*
- Prothrombin Complex Concentrate 25-50 IU/kg
  - Dose based on Factor IX units
  - Alternatively, 500 IU initially followed by second administration of 500 IU according to the INR value measured just after the first administration

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### Elevated INR Rx Procedure

- Vitamin K 10 mg subq or IVP
- Fresh frozen plasma (5-8 ml/kg) 1-2 units, 250-500 cc total  
*OR*
- Prothrombin Complex Concentrate 25-50 IU/kg  
*OR*
- Recombinant Factor VIIa (40-60 µgr/kg)
  - Usually 3-4 mg total

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### PCC

- Prepared from pooled plasma of thousands of blood donors
  - Less viral transmission risk than FFP
- Contains vitamin K-dependent procoagulant and factors
- Infused over 15 minutes
- Relative thromboembolic risk unclear
- Acquisition cost of usual adult dose ≈ \$450

Abe et al. *Rinsho to Kankyu* [in Japanese] 1987;64:1327-37.  
Sorensen B et al. *Blood Coagulation and Fibrinolysis* 2003;14:469-477.

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### Recombinant Factor VIIa

- Rapid onset of action
  - Almost immediate
    - Clinically apparent hemostasis within 10 minutes
- Short half life (2.3 hours)
- Relatively high acquisition cost
  - ≈ \$2,500-\$3,500 for 3-4 gm dose

Park p et al. *Neurosurgery* 2003;53:34-39.  
Sorensen B et al. *Blood Coagulation and Fibrinolysis* 2003;14:469-477.  
Novoseven [package insert], Princeton, NJ: Novo Nordisk Pharmaceuticals, Inc; 2003.

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## FVIIa in Warfarin-Related ICH

- Freeman: 2004 Mayo Clin Proc
- Key Concept: Warfarin-related ICH can be treated successfully with rec FVIIa
- Data: 62 micrograms/kg Factor VIIa
- Data: INR decreased from 2.7 to 1.1
- Implications: This therapy used today as an adjunct to blood therapies in ICH patients whose bleed is INR-related

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## FVIIa Safety, Efficacy in ICH

- Mayer: 2005 NEJM
- Key Concept: FVIIa is safe when given within 3 hours of presentation
- Data: 399 pts, 3 doses, ICH growth, 90-day
- Data: Less ICH growth, improved outcome
- Data: Thrombo-embolic events noted
- Implications: Larger study is critical in order to establish clear benefit, safety

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## FVIIa Adverse Events

- O'Connell JAMA 2006; 295:293-298
- Adverse events reported to the FDA
- 1999-2004
- 431 reported, 185 thromboembolic
- 39 CVA, 34 MI, 32 PE, 26 art. Thrombus
- 52% occur in the first 24 hours
- Thromboembolic AE's follow off label use

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## Surgery in ICH

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## STITCH ICH Surgical Trial

- Mendelow: 2005 Lancet
- Key Concept: Surgery within 24 hours does not affect 6 month outcome
- Data: 25% of pts had a good outcome
- Data: Surgery did not change this rate
- Data: Surgery occurred after many hours
- Implications: Need to consider timely and selective neurosurgical intervention in order to impact outcome

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## ED Treatment and Patient Outcome

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## **ED Patient Management**

- The BP treated with IV labetalol
- The INR was noted to be 5.6
- Vitamin K administered
- 2 units FFP administered
- The pt was admitted to the neurosurgical ICU

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## **Patient Outcome**

- The hemorrhage size increased slightly on CT with slight intraventricular extension
- The patient's clinical condition slightly improved gradually
- Discharged to rehab 10 days after admission

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## **Time Will Always Mean Brain!**

- ICH continue to expand
- Early medical management essential
- Early coagulation correction critical (drip and ship)
- Hemostatic therapy may work best early

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## **Questions??**

[www.ferne.org](http://www.ferne.org)  
[ferne@ferne.org](mailto:ferne@ferne.org)

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