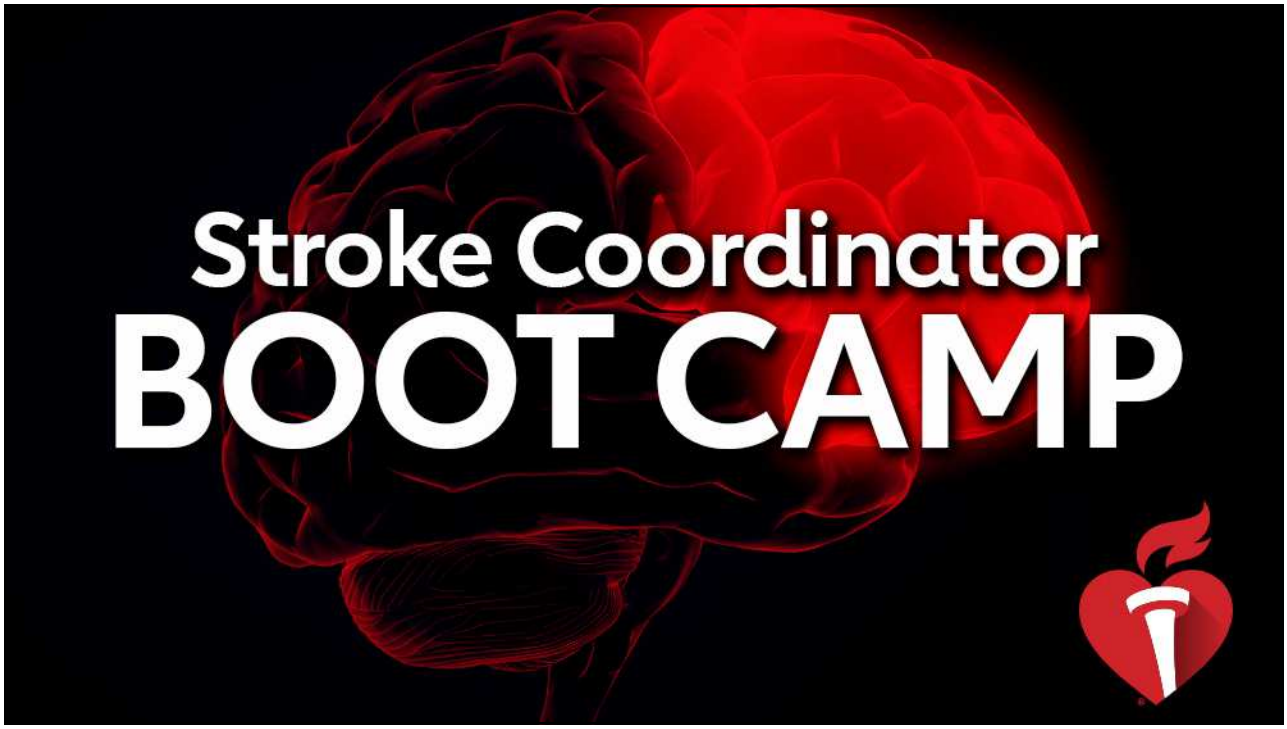


1

Stroke Coordinator BOOT CAMP

HEMORRHAGIC STROKE: THE GOLDEN HOUR

MICHELLE HILL, MS, RN, AGCNS-BC, CNRN, CCRN, SCRN

COMPREHENSIVE STROKE PROGRAM MANAGER: RIVERSIDE METHODIST HOSPITAL

DISCLOSURES: NONE

WENDY SMITH, BS, MA, RES, RCEP, RN, MBA, SCRN, FAHA

ENTERPRISE STROKE PROGRAM MANAGER: CLEVELAND CLINIC HEALTH SYSTEM

DISCLOSURES: NONE

2

American Stroke Association. A division of the American Heart Association.

2

HEMORRHAGIC STROKE: OBJECTIVES

OBJECTIVES

- Discuss the 2 types of hemorrhagic stroke: intracerebral and subarachnoid
- Review cerebral anatomy
- Discuss acute treatment of hemorrhagic stroke
- Discuss transfers considerations

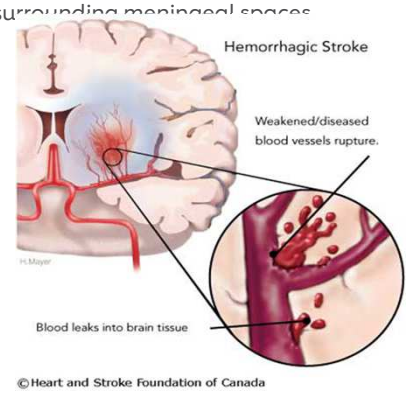
3

3

HEMORRHAGIC STROKE: TYPES

PATHOLOGICAL ACCUMULATION OF BLOOD WITHIN THE CRANIAL VAULT

- Intracranial hemorrhage
  - May occur within brain parenchyma or surrounding meningeal spaces
  - May extend into the ventricles (IVH)
- Subarachnoid hemorrhage
  - Aneurysmal rupture
  - AVM rupture



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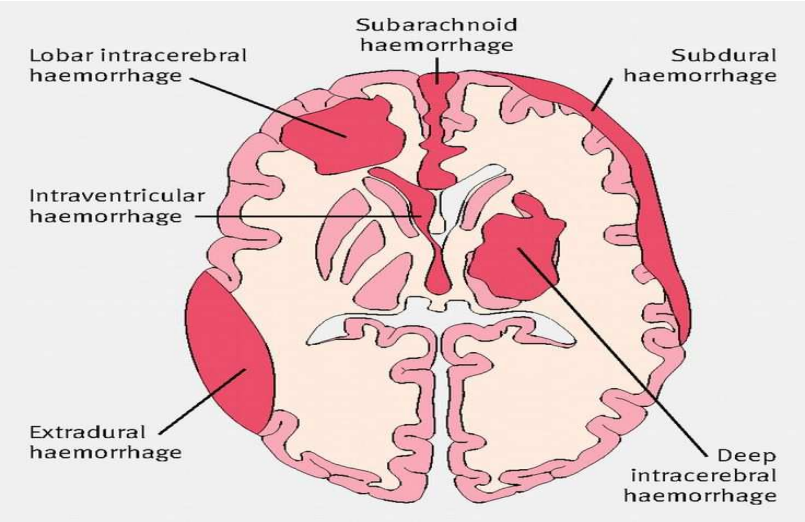
HEMORRHAGIC STROKE: LOCATIONS



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INTRACEREBRAL HEMORRHAGE

MOST COMMON CAUSE: BLOOD VESSEL WALL DAMAGE DUE TO HYPERTENSION- 60% OF CASES

OTHER CAUSES:

- Autoregulatory dysfunction (re-perfusion injury, hemorrhagic transformation)
- Arteriopathy (amyloid angiopathy, moya-moya)
- Altered hemostasis (thrombolysis, anticoagulation)
- Hemorrhagic necrosis (tumor, infection)
- Venous outflow obstruction (cerebral venous thrombosis)
- Sympathomimetic drugs (cocaine, methamphetamine)

6

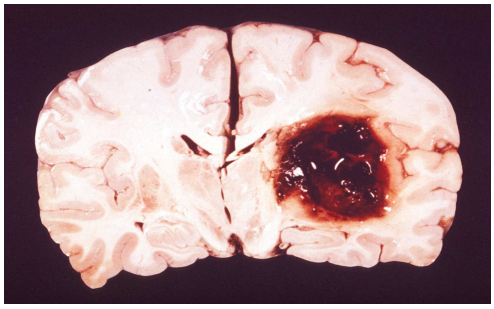
6

ICH: MORBIDITY/MORTALITY

20,000 DEATH ANNUALLY IN US

30 DAY OVERALL MORTALITY RATE OF 44%

- 75% at 24 hours with pontine/brainstem hemorrhages



Coronal section of the brain with a hypertensive putaminal hemorrhage associated with mass effect

Photographs courtesy of Jose Biller, MD

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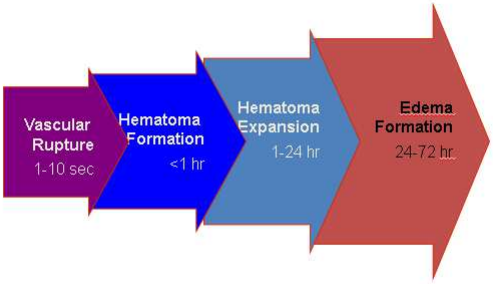
ICH: PATHOPHYSIOLOGY

ICH is a dynamic and complex process



Rincon F et al. *Curr Opin Crit Care.* 2004;10:94-100.

8

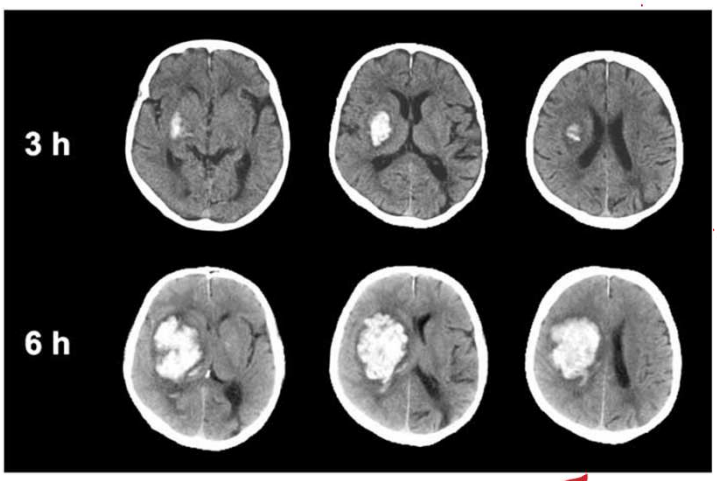
8

ICH: EARLY DETERIORATION

EARLY DETERIORATION IS COMMON

GREATER THAN 20% WILL EXPERIENCE DECREASE IN GCS OF 2 OR MORE POINTS BETWEEN EMS ASSESSMENT AND ED INITIAL EVALUATION

15%-23% DEMONSTRATE CONTINUED DETERIORATION WITHIN THE 1ST FEW HOURS AFTER HOSPITAL ARRIVAL



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Hemphill, J.C., et al (2015). Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke; 46:* 2032-2060.

9

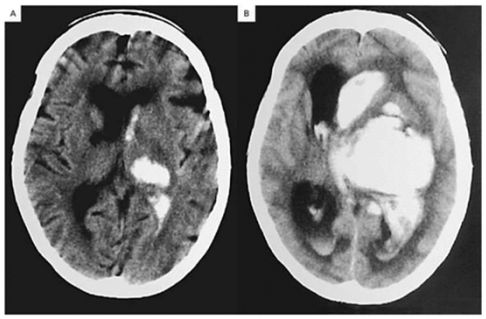
ICH: HEMATOMA EXPANSION

RELATED TO ACTIVE BLEEDING THAT MAY PROCEED FOR HOURS AFTER SYMPTOM ONSET

TENDS TO OCCUR EARLY

INCREASES RISK OF POOR FUNCTIONAL OUTCOME AND DEATH

28%-38% HAVE HEMATOMA EXPANSION OF GREATER THAN 1/3 OF THE INITIAL HEMATOMA VOLUME ON FOLLOW UP CT



10

Hemphill, J.C., et al (2015). Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke; 46:* 2032-2060.

10

PATIENT PRESENTATION: HEMORRHAGIC STROKE

- SUDDEN FOCAL NEUROLOGICAL DEFICIT
- HEADACHE – 40%
- NAUSEA AND VOMITING – 40%-50%
  - Common with posterior fossa stroke
- DECREASED LEVEL OF CONSCIOUSNESS – 50%
  - Not as common with ischemic stroke
- ELEVATED BLOOD PRESSURE – 90%
- SEIZURES – 6-7%

11

Liebeskind, D.S. (2017). Intracranial Hemorrhage. https://emedicine.medscae.com/article/1163977

11

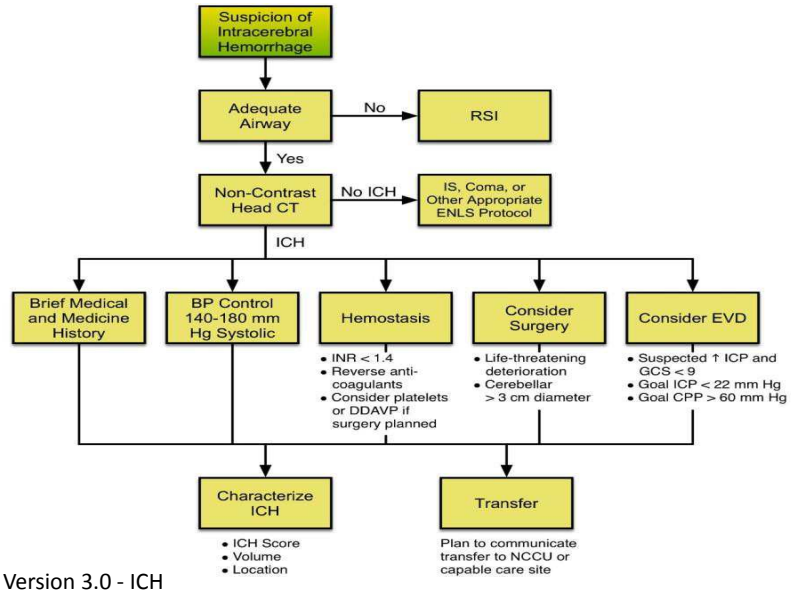
ED MANAGEMENT: THE GOLDEN HOUR

- PERFORM A RAPID NEUROLOGICAL EX
- ABC'S/STABILIZE
- DIAGNOSE
  - Calculate the ICH score if possible
- CLASSIFY
- CORRECT COAGULAPATHY
- MANAGE BP
- COMMUNICATE WITH TEAM
- GET PATIENT TO THE RIGHT PLACE

12

12

ED MANAGEMENT: THE GOLDEN HOUR



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13

ED MANAGEMENT: THE GOLDEN HOUR

Checklist for the 1st hour
☐ Complete blood count with platelet count, PT, PTT, INR
☐ Head imaging results: hematoma size, location, presence of intraventricular hemorrhage
☐ Glasgow Coma Scale (GCS) score
☐ Calculate ICH Score
Interventions
☐ Coagulopathy reversal (goal INR < 1.4)
☐ Blood pressure lowering (goal SBP 140-180
☐ Surgical hematoma evacuation (if indicated)
☐ Airway/ventilation management

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14

ED MANAGEMENT: THE GOLDEN HOUR

INITIAL FOCUS ON ARRIVAL:

- Life support (A-B-C)
- Make sure patient is safe to go to CT
  - Can they protect their airway?
  - Hypoxia?
  - Avoid hyperventilation

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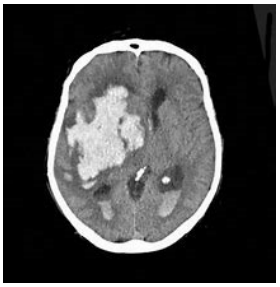
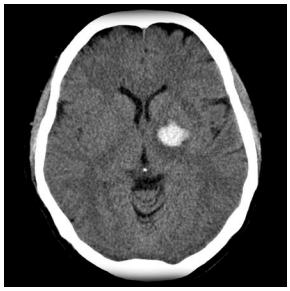
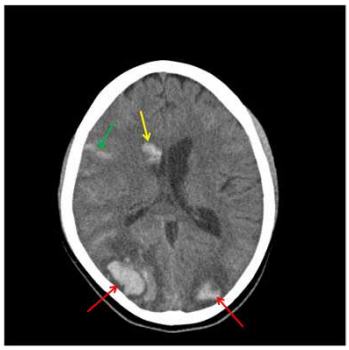
GOLD STANDARD FOR DIAGNOSIS OF ICH:
NON-CONTRAST HEAD CT







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16

ICH: SPOT SIGN

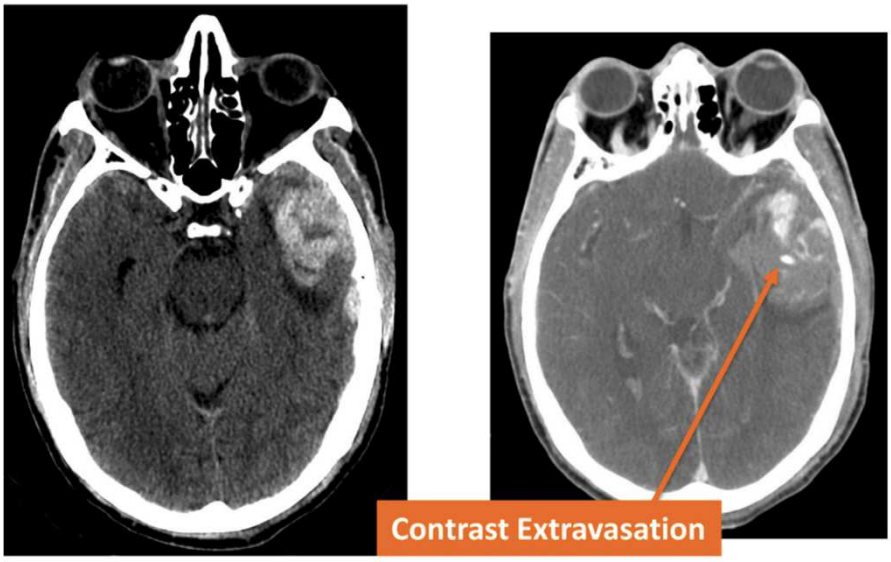

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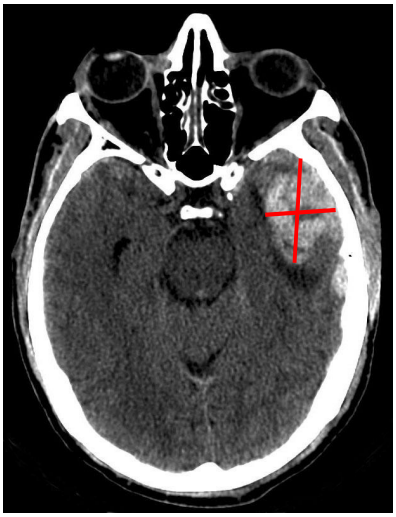
Photo Courtesy: ENLS Version 3.0 - ICH

17

CALCULATING ICH SCORE-



Characterize ICH

- ICH Score
- Volume
- Location

SUPRATENTORIAL
ORIGIN L TEMPORAL
LOBE MILD IVH

Volume = ABC/2

A = largest diameter = 4.2 cm
B = perpendicular = 2.8 cm

C = clot thickness= 2.5 cm
[0.25 cm slices x 10 slices (9 full and 2 half)]

ABC/2 =
(4.2 x 2.8 x 2.5)/2 = **14.7 cc**

ICH score is required for CSCs-
Not required for PSC/TSC or ASR

18

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18

CALCULATING ICH SCORE

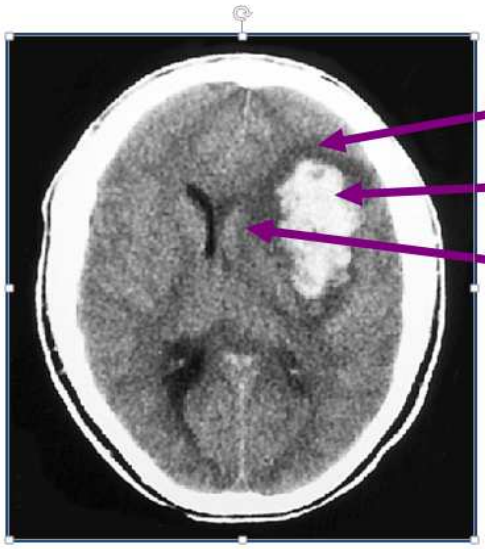
Component		ICH Score Points
GCS Score	3-4	2
	5-12	1
	13-15	**0**
ICH Volume (cc)	≥ 30	1
	< 30	**0**
Intraventricular Hemorrhage	Yes	**1**
	No	0
Infratentorial Origin	Yes	1
	No	**0**
Age (years)	≥ 80	1
	< 80	**0**
Total ICH Score		**1**

ICH SCORE- WHY?

- Each point increase in the ICH Score is associated with an increased risk of mortality and a decreased likelihood of good functional outcome.
- It should not be used for prognosis; use it as a method for communicating disease severity.

GCS	
3-4	2 pts
5-12	1 pt
13-15	0 pts
ICH volume	
≥ 30cm³	1 pt
< 30 cm³	0 pts
IVH	
Yes	1 pt
No	0 pts
Location	
Infratentorial	1 pt
Supratentorial	0 pts
Age	
≥ 80 yrs	1 pt
< 80 yrs	0 pts

ICH



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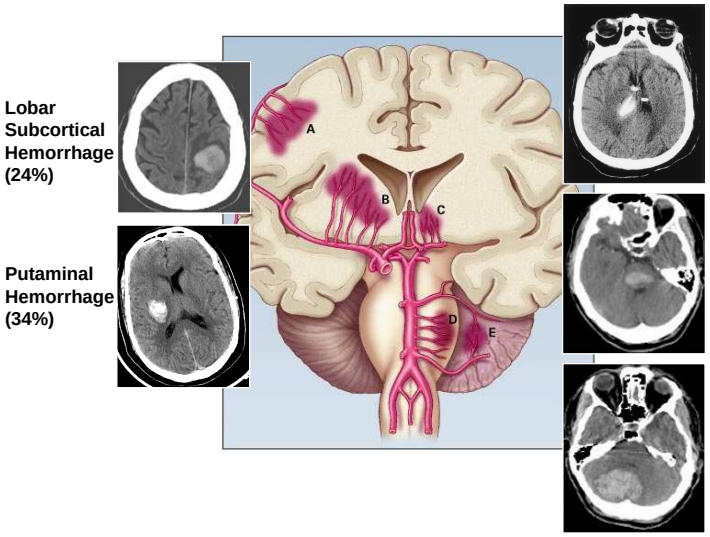
21

SITES OF SPONTANEOUS ICH



Lobar Subcortical Hemorrhage (24%)

Putaminal Hemorrhage (34%)

Thalamic Hemorrhage (20%)

Pontine Hemorrhage (6%)

Cerebellar Hemorrhage (7%)

A=cortical branches of anterior, middle, or posterior cerebral arteries;
B=basal ganglia from middle cerebral artery;
C=thalamus;
D=pons;
E=cerebellum.

22

Mayer SA, Rincon F. *Lancet Neurol*. 2005;4:662-672.
Kase CS et al. In: *Stroke: Pathophysiology, Diagnosis, and Management*. 1998:649-700.
Drawing reproduced with permission of Qureshi AI et al. *N Engl J Med.* 2001;344:1453.

22

CASE STUDY: PT PRESENTATION

45 YR OLD MALE

PRESENTS TO ED VIA AMBULANCE AT 2153 WITH C/O:

- Disorientation, slurred speech, facial droop, right sided weakness

STROKE TRIAGE

- Last normal/Onset time: 1830-1900
- Exam: drowsy, follows commands, weak on right, speech slurred, right facial droop, confused, GCS 14
- Finger stick glucose: 109

23

23

CASE STUDY: ICH PRESENTATION

VS: BP 198/100; HR 83; RR 18; SAO2 98%

IV START

LAB DRAW

- CBC, PT, INR, aPTT, BMP, type & screen

BEGIN COLLECTING FOCUSED HISTORY

- HTN, hyperlipidemia, obesity, sleep apnea, recently started on coumadin for AF; no trauma, surgeries, stroke, ICH

CT SCAN

EKG AT SOME POINT

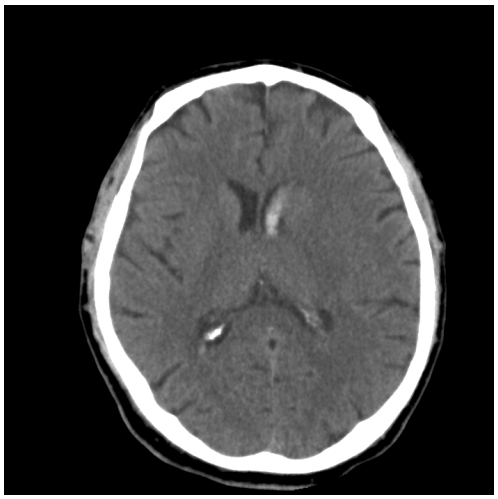
CHEST XRAY IF INDICATED

Don't delay CT for EKG/Chest X-ray; Hold off on labs if difficult stick

24

24

CASE STUDY: ICH- DIAGNOSE AND CLASSIFY



LG ACUTE INTRAPARENCHYMAL HEMORRHAGE

LEFT BASAL GANGLIA

3.2 X 1.5 CM'S

RUPTURED INTO LEFT LATERAL VENTRICLE

SMALL AMOUNT OF BLOOD IN RIGHT LATERAL VENTRICLE AND 3RD VENTRICLE

25

25

CASE STUDY: ICH- LABS

WBC	4.31
HGB	12.4
HCT	35.7
PLAT	198
INR	***2.1***
APTT	35
GLU	109
BUN	11
CR	.96
NA	141
K	3.3
CL	119
CO2	17
CA	8.3
ALB	2.1
ALT	40
AST	38
ALK PHOS	92
T BILI	0.2

26

26

ICH: THE GOLDEN HOUR: WHAT CAN GO WRONG???

- What Can Go Wrong (or Is Going Wrong)?
  - Herniation and brain(stem) compression
  - Airway compromise
  - Hematoma expansion
  - Elevated intracranial pressure
  - Secondary brain injury
    - » Seizures
    - » Fever
    - » Hyperglycemia

27

27

ICH: THE GOLDEN HOUR: FOCUS

1. Stabilization and reassessment of the patient's airway, breathing, circulation
2. Rapid and accurate diagnosis using neuroimaging
3. Concise clinical assessment regarding ICH characteristics and patient condition
4. Targeted assessment for potential early interventions:
   Control of elevated blood pressure
   Correction of coagulopathy
   Need for early surgical intervention
5. Anticipation of specific patient care needs such as:
   Specific treatment related to underlying ICH cause
   Risk for early clinical deterioration and hematoma expansion
   Need for intracranial pressure (ICP) or other monitoring Patient disposition from the emergency department

28

28

CASE STUDY: ICH- BP MANAGEMENT

- FOR ICH PATIENTS PRESENTING WITH SBP BETWEEN 150 AND 220 MM HG AND W/O CONTRAINDICATIONS TO ACUTE BP TREATMENT, ACUTE LOWERING OF SBP TO 140 MMHG IS SAFE (CLASS 1, LEVEL A) AND CAN BE EFFECTIVE FOR IMPROVING FUNCTIONAL OUTCOME (CLASS IIA; LEVEL B)

- FOR ICH PATIENTS PRESENTING WITH SBP >220 MMHG, IT MAY BE REASONABLE TO CONSIDER AGGRESSIVE REDUCTION OF BP WITH A CONTINUOUS IV INFUSION AND FREQUENT BP MONITORING (CLASS ILB, LEVEL C)

29

Hemphill, J.C., et al (2015). Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke; 46*: 2032-2060.

29

CASE STUDY: ICH – BP CONTROL

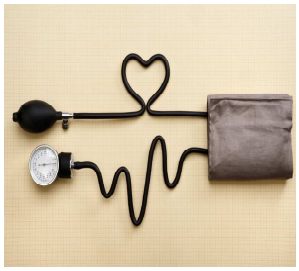
COMMON MEDICATIONS

LABETALOL (NORMODYNE)

- Labetalol 10-20 mg IV over 1-2 mins, may repeat or double every 10 mins for max of 300mg

NICARDIPENE (CARDENE)

- Nicardipine 5mg/hr IV infusion as initial dose; titrate to desired effect by increasing 2.5mg/hr every 5 mins to max of 15mg/hr



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CORRECTION OF COAGS: BASED ON MEDICATION

Stroke Coordinator BOOT CAMP

WARFARIN (COUMADIN) ASSOCIATED

- K Centra: 4 factor Prothrombin complex concentrate (PCC)
- Profil 9: 3 factor PCC – use instead of K Centra if heparin allergy
- Vitamin K 5-1-mg IV

PRADAXA (DABIGATRAN)

- Reversal agent – Praxbind (Idarucizumab)
  - Dose = 5 grams
    - 2 vials, 2.5 grams/50 mls each
    - Draw up and administer IV push, one after the other (no more than 15 mins apart)

FACTOR XA INHIBITORS (HOT OFF THE PRESS…)

- Andexanet alfa (Andexxa)
- Only approved for Rivaroxiban and Apixaban

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31

31

JOINT COMMISSION UPDATE ON ANTICOAGULANT NATIONAL PATIENT SAFETY GOAL (NPSG)

DID YOU KNOW THAT ALL TJC –ACCREDITED HOSPITALS, CRITICAL ACCESS HOSPITALS, NURSING CARE CENTERS AND MEDICAL CENTERS ARE REQUIRED TO HAVE ANTICOAGULANT REVERSAL PROTOCOLS???

STARTING JULY 1, 2019: NPSG 03.05.01 HAS 8 NEW/REVISED ELEMENTS OF PERFORMANCE (EPS).

- EP 1- PROTOCOLS FOR STARTING AND CONTINUING ANTICOAGULANT TREATMENT MUST BE EVIDENCE BASED.
- EP 2- ANTICOAGULATION REVERSAL AND BLEEDING MANAGEMENT PROTOCOLS MUST BE EVIDENCE-BASED.
- EP 3- PERIOPERATIVE MANAGEMENT PROTOCOLS FOR ORAL ANTICOAGULANTS MUST BE EVIDENCE BASED.
- EP 4- HAVE A WRITTEN POLICY ON THE NEED FOR LABORATORY TESTS TO ADJUST AND MONITOR ANTICOAGULANT THERAPY
- EP 5- ESTABLISH A PROCESS TO RESPOND TO ADVERSE DRUG EVENTS AND EVALUATE AND IMPROVE ANTICOAGULATION SAFETY PRACTICES
- EP 6- PROVIDE EDUCATION TO PATIENT AND FAMILIES ON THEIR ANTICOAGULANT TREATMENT
- EP 7- IF AVAILABLE, FACILITIES SHOULD ONLY USIE PRE-FILLED SYRINGES, PREMIXED INFUSION BAGS, OR ORAL UNIT-DOSE PRODUCTS
- EP 8- USE PROGRAMMABLE PUMPS WHEN ADMINISTRATING HEPARIN INTRAVENOUSLY AND CONTINUOUSLY

- HTTPS://WWW.PSQH.COM/NEWS/JOINT-COMMISSION-UPDATES-ANTICOAGULANT-NPSG/

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32

32

DIRECT ORAL ANTICOAGULANTS: AKA NOACS

Direct thrombin inhibitor

- Pradaxa (Dabigatran)

FACTOR XA INHIBITORS

- Xarelto (Rivaroxiban)
- Eliquis (Apixaban)
- Savaysa (Edoxaban)

33

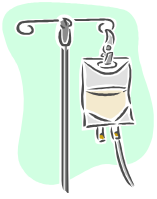
33

CORRECTION OF COAGULOPATHY

USEFULNESS OF PLATELET TRANSFUSIONS ICH PATIENTS WITH HISTORY OF ANTIPLATELET USE IS UNCERTAIN (CLASS IIB, LEVEL C)

2018 SYSTEMATIC REVIEW:

- No benefit, may be harmful



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Cusack, T.J., et al (2018). Update on the Treatment of Spontaneous Intraparenchymal Hemorrhage: Medical and Interventional Management. *Curr Treat Options Neurol 20:1.* Published online: 3 February 2018; DOI 10.1007/s11940-018-0486-5.

34

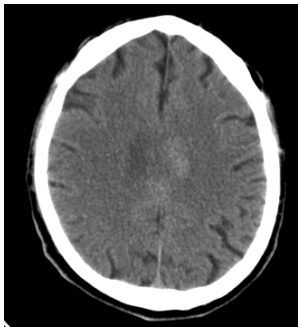
34

CASE STUDY: ICH- WHAT NEXT

22:17 – CHANGE IN NEURO STATUS IS NOTED: SPEECH INCOMPREHENSIBLE, INCREASED DROWSINESS

22:33 – RAPID SEQUENCE INTUBATION TO PROTECT AIRWAY

23:00 – REPEAT CT



GROWN CONSIDERABLY IN SIZE OVER 1 HOUR

3.2 X 1.5 → 4.5 X 3.6 CM'S

- *Hematoma volume = ~45 cc's*

BLOOD IN ALL VENTRICLES

VENTRICLES ALREADY ENLARGING

8MM MIDLINE SHIFT

VASOGENIC EDEMA

35

35

CASE STUDY: ICH- CONSIDER SURGERY

Location	Surgery urgently:
Cerebellum	• Declining neuro exam • Size > 3 cm, or • Compressive effects brainstem, or • Hydrocephalus
Lobar	ICH causing mass effect/herniation in severely affected but salvageable patient and as a life-saving measure

36

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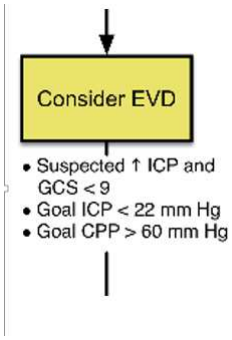
36

CASE STUDY: ICH- CONSIDER EVD



ICP MAY BE ELEVATED

PATIENTS WITH IVH ARE AT RISK FOR HYDROCEPHALUS AND ELEVATED ICP

~~EVD RECOMMENDED IN:~~

GCS < 9

LARGE MASS EFFECT

HYDROCEPHALUS

37

OTHER CONSIDERATIONS: SEIZURES

CLINICAL SEIZURES SHOULD BE TREATED WITH AED'S

DEPRESSED MENTAL STATUS OUT OF PROPORTION TO DEGREE BRAIN INJURY IS AN INDICATION FOR EEG MONITORING

ELECTROGRAPHIC SEIZURES ON EEG SHOULD BE TREATED WITH AED'S

PROPHYLACTIC ANTICONVULSANT MEDICATION SHOULD NOT BE USED (CLASS III)

38

SEIZURE TREATMENT: ANTICONVULSANTS

LEVITERACITAM (KEPPRA)

FOSPHENYTOIN (CEREBYX)

PHENYTOIN (DILANTIN)

Ativan is usually given IV for emergency treatment – followed by loading dose of any of the above AED's

39

OTHER CONSIDERATIONS: NAUSEA

ZOFRAN

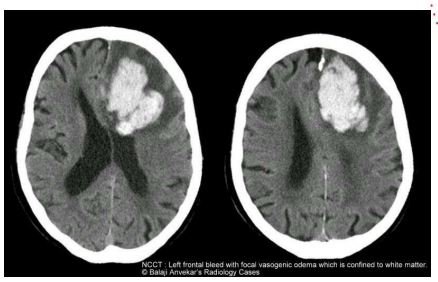
PHENERGAN

- Not a preferred agent
- Causes drowsiness or confusion – compromises neuro exam

40

OTHER CONSIDERATIONS: CEREBRAL EDEMA

- MANNITOL – OSMOTIC DIURETIC
  - Typically, Mannitol 20% IV 0.25g/kg to 1g/kg over 2-10 minutes
  - Calculation:
    - # grams ordered X pt's wt in kg's = desired dose
    - $\frac{\text{Desired dose}}{20}$ X 100 = #cc's to give
  - Increases intravascular osmotic pressure by drawing water from the extracellular space, thus decreasing brain mass
  - Hypertonic Saline – Osmotic Diuretic
    - Given as small bolus or continuous infusion
    - Watch sodium levels!



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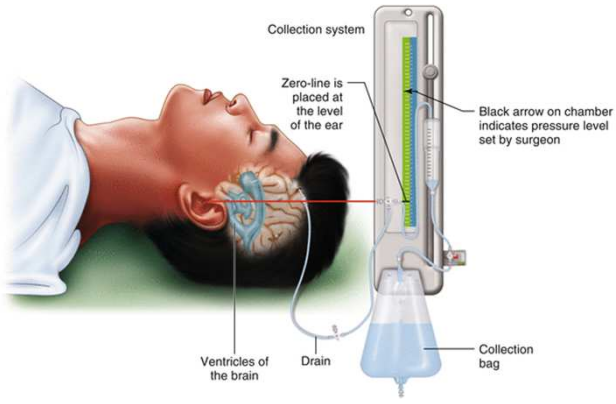
41

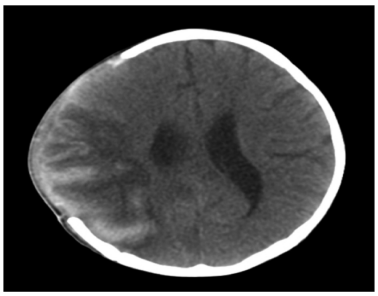
TREATMENT

INCLUDES MOSTLY MEDICAL MANAGEMENT/SUPPORTIVE CARE

NEURO-ICU

SURGERY INDICATED ONLY FOR PLACEMENT OF EVD, CEREBELLAR HEMORRHAGE OR RELIEF OF ICP WITH HEMICRANIECTOMY





42

42

RESEARCH

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MISTIE III

- Minimally invasive surgery plus Rt-PA for ICH Evacuation Phase III
- Missed primary endpoint- but there were encouraging results
- For those that had their hematoma reduced to a volume of 15mL or less, there was a 10.5% difference in the likelihood of achieving a good functional outcome.

ENRICH

- Early Minimally-invasive Removal of IntraCerebral Hemorrhage
- No preliminary data, however, they have started excluding anterior basal ganglia hemorrhages

43

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ANEURYSMAL SUBARACHNOID HEMORRHAGE

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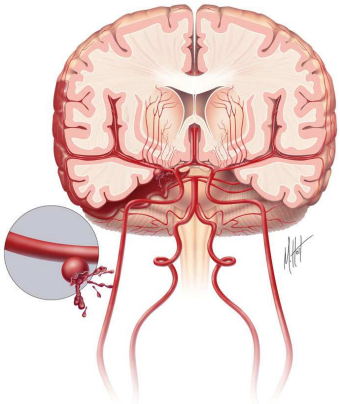
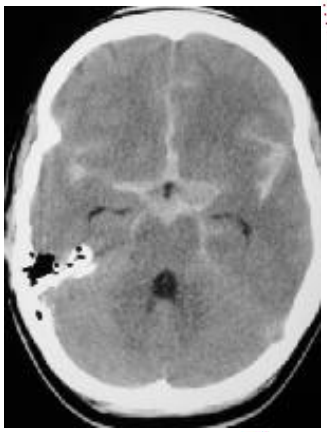
BLEEDING INTO THE SPACE BETWEEN THE ARACHNOID MEMBRANE AND THE PIA MATER

ACCOUNTS FOR 6%-8% OF AL STROKES

ASAH





44

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SAH: MORBIDITY AND MORTALITY

LOW INCIDENCE: 10/100,000 PEOPLE PER YEAR

- 11% DIE BEFORE REACHING MEDICAL ATTENTION
- 40% DIE WITHIN 4 WEEKS AFTER ADMISSION TO HOSPITAL
- 30% OF SURVIVORS HAVE SIGNIFICANT MORBIDITY AND ARE DEPENDENT FOR ADLS
- NEARLY 50% OF SURVIVORS DEVELOP COGNITIVE DYSFUNCTIONS

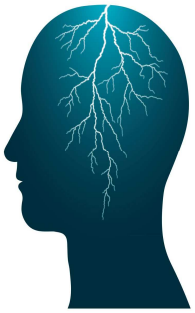
45

Ciurea, AV, et al: *Subarachnoid hemorrhage and cerebral vasospasm- Literature review,* Journal of Medicince and Life, June 2013

45

PRESENTATION: SAH

- SUDDEN, SEVERE, GENERALIZED HEADACHE
  - "Thunder-clap headache"
  - "The worst headache of my life" 97%
- 30-60%- SENTINEL HEMORRHAGE OR WARNING HEADACHES IN THE WEEKS BEFORE SAH
- TRANSIENT LOSS OF CONSCIOUSNESS
- NAUSEA/VOMITING, BLURRED VISION
- PHOTOPHOBIA
- SEIZURES



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46

PRESENTATION: SAH

Clinical Features

CLASSIC	NOT-SO-CLASSIC
Abrupt onset of severe headache (HA), i.e. thunderclap	HA is not reported as abrupt (patient may not remember event well)
NEW, QUALITATIVELY DIFFERENT HA	HA responds well to non-narcotic analgesics
May have nausea, vomiting and neck pain	HA resolves on its own in few hours
May transiently lose consciousness, present in coma, or have focal deficits	40% patients with aneurysmal SAH will have normal neuro exam without meningismus
Nature of HA onset distinguishes from other forms of stroke	Do not necessarily appear acutely ill

47

47

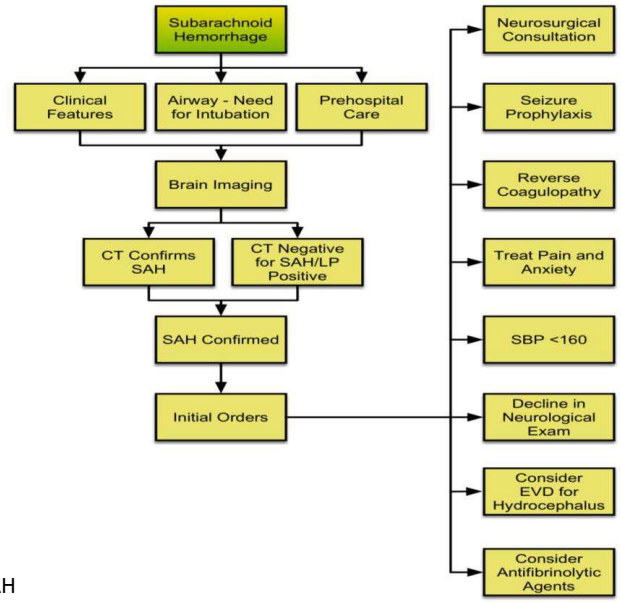
ED MANAGEMENT: SAH THE GOLDEN HOUR

- ABC'S/STABILIZE
- DIAGNOSE
- CLASSIFY
- CORRECT COAGULAPATHY
- MANAGE BP
- COMMUNICATE WITH TEAM
- GET PATIENT TO THE RIGHT PLACE

48

48

ED MANAGEMENT: SAH THE GOLDEN HOUR



49

SAH CHECKLIST

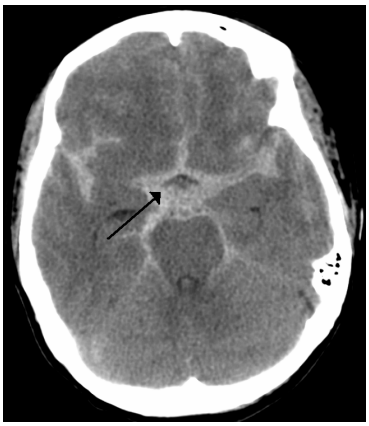
Checklist
☐ Brain Imaging
☐ Labs: PT/PTT, CBC, electrolytes, BUN, Cr, troponin, toxicology screen
☐ 12 lead ECG
☐ Blood pressure goal established
☐ Consult neurosurgery
☐ Address hydrocephalus

50

ED MANAGEMENT: THE GOLDEN HOUR

INITIAL FOCUS ON ARRIVAL:

- Life support (A-B-C)
- Make sure patient is safe to go to CT
  - Can they protect their airway?
  - Hypoxia?
  - Avoid hyperventilation



51

51

CLINICAL SEVERITY OF SAH

Hunt & Hess Clinical Grading Scale

Grade	Criteria
1	Asymptomatic, mild headache, slight nuchal rigidity
2	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3	Drowsiness / confusion, mild focal neurologic deficit
4	Stupor, moderate-severe hemiparesis
5	Coma, decerebrate posturing

World Federation Neurological Scale

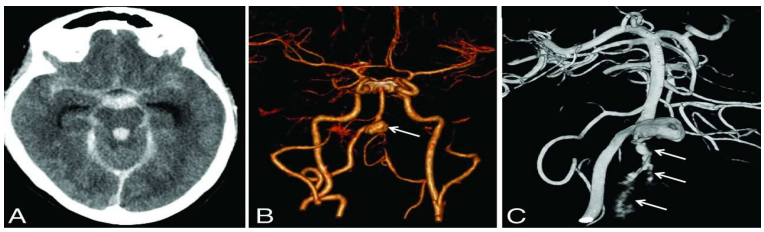
Grade	Criteria
1	GCS 15
2	GCS 13-14, without neurological deficit
3	GCS 13-14, with neurological deficit
4	GCS 7-12
5	GCS 3-6

52

52

DIAGNOSIS OF SAH

- HISTORY AND NEURO EXAM RESULTS
- CT SCAN W/O CONTRAST
  - Within 48 hrs blood appears white
  - Will detect in 95% or more of cases
- NEGATIVE CT → LUMBAR PUNCTURE USED IN SELECTED CASES (*CONTRAINDICATED IF INCREASED ICP IS SUSPECTED)*
  - *Need cell count on all tubes sent to lab*
- CEREBRAL ANGIOGRAPHY – GOLD STANDARD
  - Prepare for trip to OR



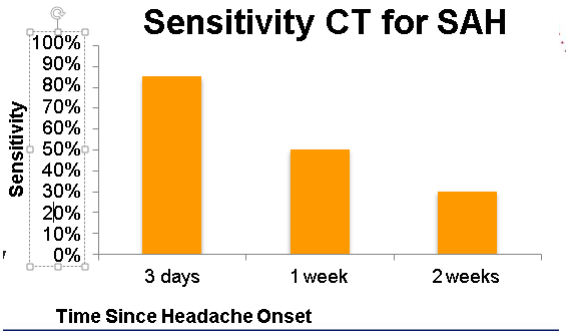
53

Connolly, E.S., et al (2012). Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke 43*

53

ED MANAGEMENT: THE GOLDEN HOUR- IMAGING

- Non-contrast CT imaging of the brain is the gold-standard for identifying SAH with sensitivity of 95-100% if:
  - Classic presentation with thunderclap HA
  - CT completed within six hours of HAonset
  - The patient is completely neurologically intact
  - The CT is read by an attending radiologist
- Sensitivity of CT decreases with time
- Falsely negative CT: time, anemia (HCT <30) low volume SAH, and a technically poor scan



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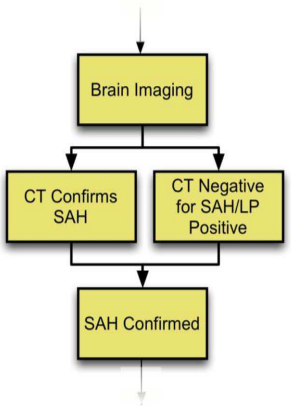
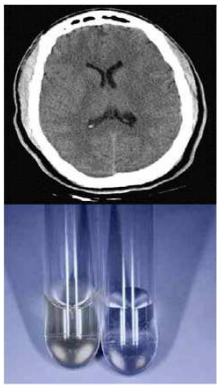
ED MANAGEMENT: THE GOLDEN HOUR- LUMBAR PUNCTURE



- Must perform LP if CT is negative and history suggests SAH
- Rationale for LP is to confirm xanthochromia- staining of CSF by heme breakdown products
- Presence of xanthochromia is time dependent- takes several hours to develop

(-) Head CT

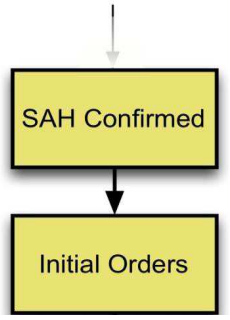


ENLS Version 3.0 - SAH

SAH- GOLDEN HOUR- LUMBAR PUNCTURE

Typical LP Findings	Atypical or Inconclusive	Not suggestive of SAH
↑ RBCs, No clearing from tube 1→4	Clearing of RBCs from tube 1→4	CSF clear of RBCs
< 5 WBC, WBC:RBC ratio 1:700	↑ WBC:RBC ratio suggest another process, meningitis or encephalitis	Occasionally, rapidly expanding unruptured aneurysm may present with HA, recommend urgent consultation
Xanthochromia present (However if CSF Protein >100mg/dL may be false positive)	Xanthochromia absent (Assuming LP is done more than 12 hours following headache onset).	Xanthochromia absent
Opening pressure elevated (~2/3 patients)	OP normal	OP normal

SAH: INITIAL MANAGEMENT



Once SAH is diagnosed, take these first steps:

- Bed rest
- Obtain pre-intervention labs: CBC, Platelets, PT/PTT, INR, electrolytes, BUN, Cr, cardiac enzymes
- 12-lead ECG
- Cardiac telemetry
- Nimodipine 60 mg po/ng (watch for hypotension)
- AED until aneurysm secured
- Consult Neurosurgery

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BP MANAGEMENT: ACUTE SAH

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BETWEEN SYMPTOM ONSET AND ANEURYSM OBLITERATION BP SHOULD BE CONTROLLED WITH A TITRATABLE AGENT TO BALANCE RISK OF STROKE, HTN RELATED REBLEEDING AND MAINTENANCE OF CPP (CLASS I; LEVEL B).

MAGNITUDE OF BP CONTROL NOT ESTABLISHED, BUT DECREASE IN SBP TO <160 MMHG IS REASONABLE (CLASS LLA; LEVEL C).

- Precise guidelines for BP management in SAH unfortunately do not exist
- Retrospective data suggest higher rates of re-bleeding with SBP > 160 mmHg
- Over treatment of BP can potentially lead to brain ischemia - especially if hydrocephalus or vasospasm is present.
- Pre-morbid BP should be taken into considerations
- **Experts recommend to aim for SBP < 160 mmHg, or MAP < 110 mmHg,** keeping principles above in mind
- Use short acting, titratable intravenous medications such as beta blockers or nicardipine.
- Avoid long-term nitroprusside due to concern of raising ICP

Stroke 2009 40:994, Diringer et al Neurocrit Care (2011) 15:211–240, Connolly ES, et al. Stroke 2012; 43:1711-1737

Connolly, E.S., et al (2012). Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke 43*

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EARLY COMPLICATIONS: HYDROCEPHALUS

COMMUNICATING

- Problem with absorption of CSF; blood in CSF plugs the arachnoid villi

DIAGNOSED BY CT – DILATED VENTRICLES

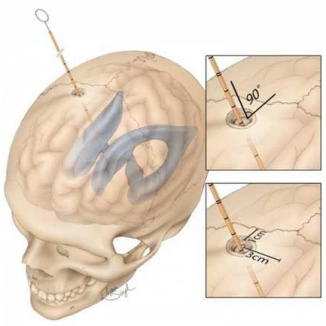
SEVERITY RELATED TO SIZE OF BLEED

- Arachnoid villi unable to reabsorb CSF, laden with byproducts of blood breakdown

MAY REQUIRE EMERGENT INSERTION OF EXTRA-VENTRICULAR DRAIN

ASTUTE NEUROLOGICAL ASSESSMENTS

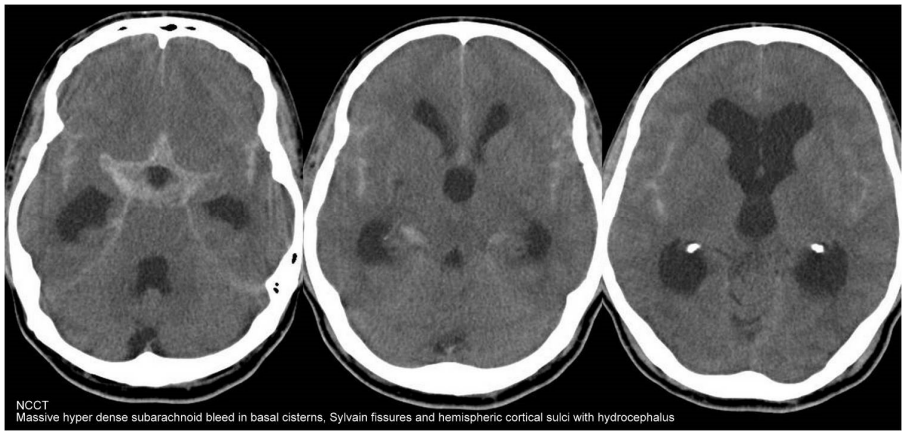
- WILL BECOME SLEEPIER…SLOWER TO RESPOND
- OVERALL DECREASE IN LOC



59

59

EARLY COMPLICATIONS: HYDROCEPHALUS



NCCT
Massive hyper dense subarachnoid bleed in basal cisterns, Sylvain fissures and hemispheric cortical sulci with hydrocephalus

The following CT scan shows hydrocephalus. Note the enlargement of the ventricles with CSF, as denoted in black.

60

http://www.neuroradiologycases.com/2011/11/imaging-in-sub-arachnoid-hemorrhage.html

60

OTHER CONSIDERATIONS: SEIZURES

- DIFFERENCE FOR ASAH:
- ROUTINE USE OF PHENYTOIN NOT RECOMMENDED (LOW QUALITY EVIDENCE; STRONG RECOMMENDATION)
- ROUTINE USE OF OTHER ANTICONVULSANTS FOR PROPHYLAXIS MAY BE CONSIDERED (VERY LOW QUALITY EVIDENCE; WEAK RECOMMENDATION)
- IF ANTICONVULSANT PROPHYLAXIS USED, A SHORT COURSE IS RECOMMENDED (3-7-DAYS) (LOW QUALITY EVIDENCE; WEAK RECOMMENDATION

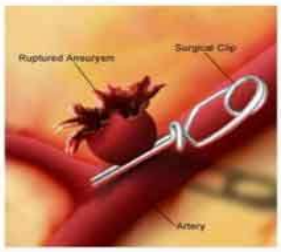
61

Diringer, M.N., et al. (2011). Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care 15:* 211-240.

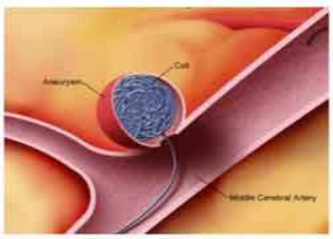
61

ANEURYSM TREATMENT

Clipping



Coiling



- Neuro ICU care
- Stay generally around 21 days depending on complications
- Specific management to treat complications (vasospasm, hydrocephalus, electrolyte imbalances

62

http://surgicalunits.com/aneurysm-clip-311.html

62

STROKE OUTPATIENT MEASURES

STK-OP-1 DOOR TO TRANSFER TO ANOTHER HOSPITAL

- Hemorrhagic stroke
  - Will need to track door in door out times when transferring all hemorrhagic stroke patients
  - No benchmark at this time

- Transfer consideration
  - Hospice- keep the patient locally if able

63

63

PACKAGING FOR TRANSFER

ADEQUATE AIRWAY PROTECTION?

- If not intubated – is this patient going to be able to manage their airway for transport?

BLOOD PRESSURE MANAGEMENT

- Is the blood pressure within recommended guideline or per MD recommendations from receiving center?

DISTANCE (CRITICAL CARE TRANSPORT)

- Air vs ground transport
- ACLS with paramedic

IMAGING RESULTS

- Do you have some kind of cloud service or sharing capability with receiving center?
- If not, will need a disc to go with patient

ANY NECESSARY CHART COPIES

64

64

PACKAGING FOR TRANSFER

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COMMUNICATION

- Obtain cell phone number for family
  - Provide them with information about transfer facility if available
- Obtain contact number to call report to receiving facility ICU
  - History, any treatments done at your ED/facility
    - BP meds, seizure meds, nausea meds, etc…
    - Imaging done
  - Last neuro exam at your facility (be specific – terms like obtunded, stuporous, or unresponsive are not helpful)

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65

QUESTIONS

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CONTACT INFORMATION

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WENDY SMITH: SMITHW@CCF.ORG

REVERSAL PROTOCOLS START ON THE NEXT SLIDE!!!!

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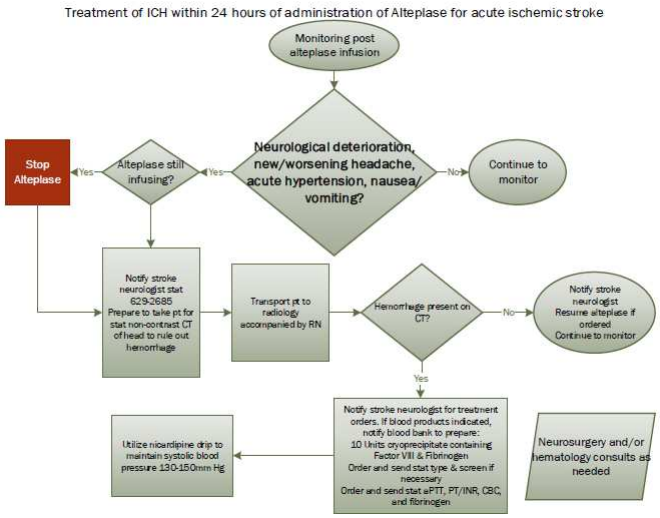
66

TPA REVERSAL- NORTON HEALTH PAGE 1



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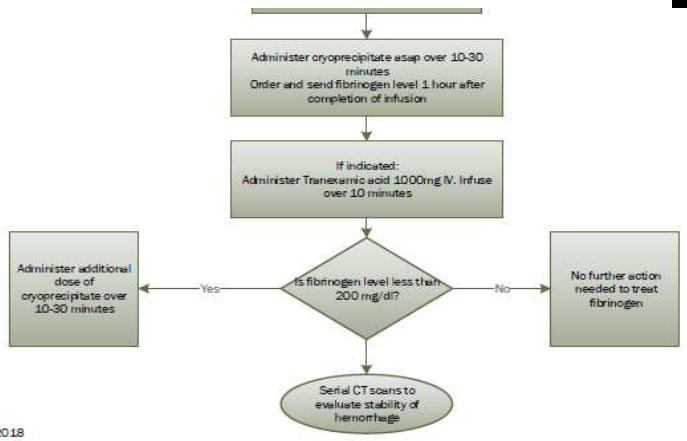
TPA REVERSAL – NORTON HEALTH PAGE 2



Update JLH/NT 6/2018
Powers, W.J., et al. 2018 Guidelines for the early management of patients with acute ischemic stroke

68

68

Norton Health

Factor Xa Inhibitor Reversal

Rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa)

- **General Principals for Management of Anticoagulation-Associated Bleeding**
  - **HASHTI** Acronym from the American Society of Hematology
    1. Hold further doses of anticoagulant
    2. Consider an Antidote
    3. Supportive treatment: volume resuscitation, inotrope as needed
    4. Local or surgical Hemostatic measures
    5. Transfusion (red cells, PLT, FFP as indicated)
    6. Investigate the bleeding source
- **2016 Neurocritical Care Guidelines for reversal of antithrombotics in ICH:**
  - Discontinue factor Xa inhibitor
  - Obtain information on the time elapsed since last dose and possible med interactions to assist in estimating the degree of anticoagulation exposure
  - Pharmacological reversal should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing
  - Activated charcoal (50g) may be given if present within 2 hours of ingestion of an oral direct factor Xa inhibitor (including intubated ICH patients with enteral access and/or those at low risk of aspiration)
  - Administration of 4-factor PCC (50 u/kg) if ICH occurred within 3-5 terminal half-lives of drug exposure or in the context of liver failure.
  - Administration of 4-factor PCC is suggested over rFVIIa because of the lower risk of adverse thrombotic events
- **Definitions Used for Reversal Situations**
  - Non-urgent: reversal is elective (procedure >7 days)
  - Urgent without bleeding: reversal needed within hours
  - Urgent with bleeding: emergency reversal

Non-Urgent	Urgent without bleeding	Urgent, life-threatening bleeding
Hold at least 24 hours Drug presence may be assessed by anti-Xa assay	If procedure can be delayed 24 hours, hold dosing	HASHTI and PCC if meets criteria

Agent	Elimination Half-life	Reversal Recommendation
Rivaroxaban (Xarelto)	5 to 9 hours (11 to 13 hours in elderly)	No specific antidote; for major bleeding May consider PCC
Apixaban (Eliquis)	8 to 15 hours	Not dialyzable Activated charcoal may be used if ingestion occurred within 2 hours of presentation
Edoxaban (Savaysa)	10 to 14 hours	

KCentra® - Four Factor Prothrombin Complex Concentrate

- **4 Factor PCC**
  - Contains vitamin K dependent factors II, VII, IX, and X as well as antithrombotic proteins C and S. Kcentra also contains a small amount of heparin.
  - Approved for reversal of acute major bleeding due to warfarin therapy
  - Black Box warning: Pts with underlying risk or diagnosed thromboembolic disease state, administration of PCC may predispose the patient to a thromboembolic event. Benefits of reversal should be weighed against potential clot risk.
- **Indication -** ALL of the following criteria must be present before reversal agents can be ordered:
  - Patient is currently taking rivaroxaban, apixaban, or edoxaban
  - Life threatening hemorrhage (defined as one of the following: symptomatic intracranial hemorrhage or hemoglobin decrease greater than 4 or transfusion greater than 4 or hypotension requiring vasopressors)
  - Patient does not have heparin induced thrombocytopenia (HIT) or heparin allergy
    - If present, use 3 factor PCC (Profilnine®)
  - Patient does not have disseminated intravascular coagulopathy (DIC)
    - If present, use 3 factor PCC (Profilnine®)
- **Dosing**
  - Consider administering 25 units/kg to max dose of 2500 units and with the option of giving an additional dose if deemed clinically necessary. Maximum dose of 50 units/kg up to 5000units.
    - Risk of thrombosis should be considered when selecting dose.
    - Dose using actual body weight. Round dose to nearest vial size.
- **Considerations prior to administration**
  - Time of last Xa inhibitor dose
  - pH, temperature, adequate circulating platelets, thromboembolic risks
- **Administration**
  - Infuse no faster than 200 units/min in dedicated line
    - If adverse infusion reaction occurs, slow rate or administer antihistamine
  - Flush line afterwards with 50mL NS to ensure line is cleared
- **Monitoring**
  - Signs/symptoms of bleeding or thromboembolic events or infusion reactions

**KCentra and Profilnine can be obtained using order sets:

- Four Factor Prothrombin Complex Concentrate (Kcentra) Protocol
- Three Factor Prothrombin Complex Concentrate (Profilnine) for Heparin Allergy Focused

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69

69

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Dabigatran (Pradaxa) Reversal

Non-Urgent Reversal

- Hold further doses. Consider longer times for major surgery, placement of spinal or epidural catheter or port.
  - CrCl > 50 ml/min: hold 1-2 days
  - CrCl < 50 ml/min: hold 3-5 days or longer
  - Drug presence may be assessed by thrombin time
  - Half life: 12-14 hours

Urgent/Emergent/Life-threatening Reversal

- Hold further doses of dabigatran
- Draw baseline coagulation tests
  - Normal aPTT – unlikely dabigatran is contributing to bleeding
  - Prolonged aPTT – dabigatran present and may be contributing to bleeding
- Activated charcoal if recent ingestion: less than 2 hours since last dabigatran dose
- **HASHTI**
  1. **H**old further doses of anticoagulant
  2. Consider **A**ntidote
  3. **S**upportive treatment
     a. Volume resuscitation (intravenous fluids)
     b. Hemodynamic support (inotropes, monitoring)
  4. Local or surgical **H**emostatic measures
     a. Anti-fibrinolytic agents can be considered (aminocaproic acid, tranexamic acid)
  5. **T**ransfusion
     a. Red blood cells for severe or symptomatic anemia
     b. Platelets if thrombocytopenia (<50 x 109/L) or patient on long-acting antiplatelet agents
  6. **I**nvestigate for bleeding source
- Idarucizumab may be considered for:
  - Life threatening hemorrhage (defined as one of the following: symptomatic intracranial hemorrhage or hemoglobin decrease greater than 4 or transfusion greater than 4 or hypotension requiring vasopressors)
  - **An anticoagulation reversal order set is being created for the management of reversal agents such as idarucizumab. In interim, call inpatient pharmacy to order idarucizumab.**

Idarucizumab (Praxbind)

Description and Indications

- Idarucizumab is a humanized monoclonal antibody fragment (Fab) providing immediate and specific reversal for dabigatran (Pradaxa). Idarucizumab binds specifically to dabigatran and its metabolites with an affinity for dabigatran that is ~350 times greater than that of thrombin, and neutralizes the anticoagulant effect.
- Idarucizumab is indicated in patients treated with dabigatran when reversal of the anticoagulant effects of dabigatran is needed:
  - For emergency surgery/urgent procedures
  - In life-threatening or uncontrolled bleeding

Dosing and Administration

DOSING

- The recommended dose of idarucizumab is 5 g, provided as two separate vials each containing 2.5 g/50 mL. idarucizumab
  - No dosage adjustment is necessary; renal impairment does not impact the reversal effect of idarucizumab.
  - There are no dosage adjustments provided in the manufacturer's labeling for hepatic impairment (this has not been studied).

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70

70

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ADMINISTRATION

- Each 2.5 g/50 mL vial can be drawn up in a 60 mL syringe and given via IV push, one after the other no more than 15 minutes apart.
- Administration should begin within 1 hour of removing the solution from the vial.
- Before administration, the line must be flushed with normal saline.
- No other infusions should be administered in parallel via the same intravenous access.

Storage/Dispensing

- Idarucizumab vials are to be stored in the refrigerator at 2°C to 8°C (36°F to 46°F). Prior to use, the unopened vial may be kept at room temperature 25°C (77°F) for up to 48 hours, if stored in the original package in order to protect from light, or up to 6 hours when exposed to light.
- Idarucizumab will be dispense in original packaging. RN will draw up and administer on the floor.

Additional Info

STUDY HIGHLIGHTS

- An interim analysis of the RE-VERSE AD trial, an ongoing single cohort case series trial, included data for 123 patients. Results of central laboratory evaluations were available for a subset of 90 patients (51 in Group A, 39 in Group B).
- Among the 90 patients with available data, the median maximum reversal of the pharmacodynamic anticoagulant effect of dabigatran as measured by ECT or dTT in the first 4 hours after administration of 5 g Idarucizumab was 100%, with most patients (>89%) achieving complete reversal. Reversal of the pharmacodynamics effects was evident immediately after administration. In a limited number of patients, between 12 and 24 hours after administration of 5 g Idarucizumab, elevated coagulation parameters (e.g., aPTT or ECT) have been observed.
- In the interim analysis of the RE-VERSE AD trial, 5 of 123 patients reported thrombotic events, 1 patient 2 days after treatment with idarucizumab and 4 patients 7 days or more after treatment with idarucizumab. None of these patients were on antithrombotic therapy at the time of the event, and in each of these cases, the thrombotic event could be attributed to the underlying medical condition of the patient.

ADVERSE EFFECTS

- Most frequently reported adverse events in ≥5% of healthy volunteers was headache and in ≥5% of patients were: hypokalemia, delirium, constipation, pyrexia, and pneumonia
- Low potential for immune reactions—4% of volunteers had low levels of possibly persisting treatment-emergent antibodies (low titers)

WARNINGS

- Thromboembolic Risk: Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Resume anticoagulant therapy as soon as medically appropriate.
- Hypersensitivity reactions: Discontinue administration and evaluate.
- Patients with hereditary fructose intolerance may be at risk of adverse reactions.

Formulary Status

- Norton Healthcare Pharmacy and Therapeutics Committee and Medical Executive Committee has designated idarucizumab formulary restricted to patients currently taking dabigatran AND experiencing a life threatening hemorrhage (defined as one of the following: symptomatic intracranial hemorrhage or hemoglobin decrease greater than 4 or transfusion greater than 4 or hypotension requiring vasopressors).

References:

1. Praxbind® Prescribing Information and Patient Information Leaflet. 2015. http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Praxbind/Praxbind.pdf
2. Pollack et al. Idarucizumab for Dabigatran Reversal. N Engl J Med. 2015 Aug 6;373(6):511-20.
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71

71

Norton Health

Vitamin K Antagonist (VKA) Reversal

- **General Principals for Management of Anticoagulation-Associated Bleeding**
  - **HASHTI** Acronym from the American Society of Hematology
    1. Hold further doses of anticoagulant
    2. Consider an Antidote
    3. Supportive treatment: volume resuscitation, inotrope as needed
    4. Local or surgical Hemostatic measures
    5. Transfusion (red cells, PLT, FFP as indicated)
    6. Investigate the bleeding source
- **Chest 2012 Recommendation:** "For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma. We suggest the additional use of vitamin K 5 to 10mg administered by slow IV injection rather than reversal with coagulation factors alone."
- **Definitions Used for Reversal Situations**
  - Non-urgent: reversal is elective (procedure >7 days)
  - Urgent without bleeding: reversal needed within hours
  - Urgent with bleeding: emergency reversal

Non-Urgent	Urgent without bleeding	Urgent with bleeding
Stop warfarin 5 days prior to procedure AND	If procedure can be delayed 6-24 hours, vitamin K 5-10mg PO/IV; OR	HASHTI and Vitamin K 5-10mg IV
Check INR 1-2 days prior and give vitamin K 1-2mg PO if INR >1.5	FFP prior to procedure. Repeat in 6-12 hours if INR high AND Vitamin K 5-10mg PO/IV	PCC if meet criteria or FFP
No procedure and w/o bleeding • INR <5, omit warfarin dose or continue with lower dose • INR 5-9, omit doses and consider reversal with vitamin K • INR > 9, omit doses and give vitamin K		

Agent	Contents	Advantages	Disadvantages
Vitamin K	Vitamin K	Long duration of reversal (good in combo with factor products)	IV*: onset 1-2h, peak effect: 12-14 h PO: onset 6-10h, peak effect 24-48h
Fresh Frozen Plasma (FFP)	All clotting factors	Contains all clotting factors	Large volume; administration 30-60 min or longer; requires thawing (45min); requires blood type
Kcentra®**	Factor II, VII, IX, X, proteins C, S, heparin	Small volume; reversal within 10 minutes	Cost; thromboembolic risk
Profilnine®**	Factor II, IX, X	Small volume; reversal within 15-20 minutes	Cost; thromboembolic risk

*Vitamin K is IV or PO only. SubQ/IM should not be used due to erratic absorption and risk of hematoma.
**KCentra and Profilnine can be obtained using order sets:

- Four Factor Prothrombin Complex Concentrate (Kcentra) Protocol
- Three Factor Prothrombin Complex Concentrate (Profilnine) for Heparin Allergy Focused

KCentra® - Four Factor Prothrombin Complex Concentrate

- **4 Factor PCC**
  - Contains vitamin K dependent factors II, VII, IX, and X as well as antithrombotic proteins C and S. Kcentra also contains a small amount of heparin.
  - Approved for reversal of acute major bleeding due to warfarin therapy
  - Black Box warning: Pts with underlying risk or diagnosed thromboembolic disease state, administration of PCC may predispose the patient to a thromboembolic event. Benefits of reversal should be weighed against potential clot risk.
- **Indication - One** of the following criteria must be present before reversal agents can be ordered:
  - INR greater than 2 -and- a life threatening hemorrhage (defined as one of the following: symptomatic intracranial hemorrhage or hemoglobin decrease greater than 4 or transfusion greater than 4 or hypotension requiring vasopressors)
  - INR greater than 1 –and- symptomatic intracranial hemorrhage (Use lowest recommended dose of the appropriate PCC.)
  - AND -
  - Patient does not have heparin induced thrombocytopenia (HIT) or heparin allergy
    - If present, use 3 factor PCC (Profilnine®)
  - Patient does not have disseminated intravascular coagulopathy (DIC)
- **Dosing**
  - Administer vitamin K 10mg IV once
  - KCentra® dose is based on pretreatment INR
    - INR 2 to <4: Administer 25 units/kg (max dose: 2,500 units)
    - INR 4 to 6:Administer 35 units/kg (max dose: 3,500 units)
    - INR >6: Administer 50 units/kg (max dose: 5,000 units)
    - Round dose to nearest vial size. One time dose only.
- **Considerations prior to administration**
  - pH, temperature, adequate circulating platelets, thromboembolic risks
- **Administration**
  - Infuse no faster than 200 units/min in dedicated line
    - If adverse infusion reaction occurs, slow rate or administer antihistamine
  - Flush line afterwards with 50mL NS to ensure line is cleared
- **Monitoring**
  - Repeat INR 30 minutes after infusion complete
  - Signs/symptoms of thromboembolic events or infusion reactions

Profilnine® Three Factor Prothrombin Complex Concentrate

- **3 Factor PCC**
  - Contains vitamin K dependent factors II, IX, X
  - Should only be used when the above KCentra® criteria are met AND the patient has a heparin allergy or HIT
- **Dosing:** Initial and follow-up dosing. Always administer with Vitamin K 10mg IV once.
  - Initial IV Push dosing
    - INR 1.5 – 3.9: 25 IU/kg
    - INR 4 – 5.9: 35 IU/kg
    - INR > 5.9: 50 IU/kg
  - Repeat INR after 20 mins >1.5, 2nd dose:
    - INR 1.5-3.9: 25 IU/kg
    - INR 4-5.9: 15 IU/kg
    - INR > 5.9: No further PCC.
  - Max Cumulative dose: 50 IU/kg

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72

72

OhioHealth

OhioHealth Emergent Anticoagulant Reversal Guidelines for Patients with Spontaneous Intracranial Hemorrhage/Subarachnoid Hemorrhage

	Reversal Agents	Redosing schedule	Comments
dabigatran (**Pradaxa**),	Idarucizumab (Praxbind) 5 grams administered undiluted as two separate 2.5gram/50ml IV push over 2 minutes each (no more than 15 minutes apart)		Kcentra and Vitamin K are not appropriate reversal agent
rivaroxaban (**Xarelto**) apixaban (**Eliquis**) fondaparinux (**Arixtra**) edoxaben (**Savaysa**)	Prothrombin Complex Concentrate (Kcentra) 50units/kg IVPB given over 25 minutes	**	Vitamin K is not an appropriate reversal agent
warfarin (**Coumadin**)	1. Vitamin K 10 mg IV Piggyback x1 2. Prothrombin complex concentrate (Kcentra) IVPB Weight (kg)-_____ INR-_____ a. If INR 1.5-3.9 give 25 units/kg (max 2,500 units) over 12 minutes b. If INR 4.0-6.0 give 35 units/kg (max 3,500 units) over 17 minutes c. If INR > 6.0 give 50 units/kg (max 5,000 units) over 25 minutes	Recheck INR in 30 minutes. If INR ≥ 1.5 **	Goal is to achieve INR ≤ 1.4 If giving Kcentra recheck INR 30 minutes after infusion and then every 4 hours X3.
IV Heparin enoxaparin (**Lovenox**)	Protamine IVP at rate of 10 mg (1 ml) over 2 minutes. Maximum dose = 50 mg IVP over 10 minutes Time since last Heparin dose administration: • < 30 minutes: 1 mg Protamine for each 100 units Heparin • 30-120 minutes: 0.5 mg Protamine for each 100 units Heparin • 2 hours: 0.25 mg Protamine for each 100 units Heparin Time since last Enoxaparin administration: • < 8 hours: 1 mg per Protamine per 1 mg Enoxaparin • 8-12 hours: 0.5 mg Protamine per 1 mg Enoxaparin • 12 hours: do not administer Protamine		1 mg Protamine neutralizes 100 units of Heparin remaining 1 mg Protamine neutralizes 1 mg of Enoxaparin
Vorapaxar (**Zontivity**)	No recommended reversal strategy		
aspirin	Consider 5 units (1 dose pooled) platelets if patient going emergently to OR.		Transfusion of platelets may be withheld at the discretion of the treating physician
clopidogrel (**Plavix**) ticlopidine (**Ticlid**) ticagrelor (**Brilinta**) prasugrel (**Effient**)	Consider 10 units (2 doses pooled) platelets if patient going emergently to OR.		Transfusion of platelets may be withheld at the discretion of the treating physician
Tissue Plasminogen Activator (**tPA**)	Stop thrombolytic infusion • Draw CBC, INR, PTT, Thrombin Time, Fibrinogen before and after treatment • Rapidly give 2 doses of Cryoprecipitate IV (equivalent to 10 units) • Give 1 dose of pooled platelets (equivalent to 5 units)		Give within 4 hour of completion of tPA administration

(Blood bank has 4 units of AB type Fresh Frozen Plasma thawed for emergent cases)

University Hospitals

WARFARIN OR DIRECT ORAL ACTING ANTICOAGULANT (DABIGATRAN, APIXABAN, AND RIVAROXABAN) ASSOCIATED LIFE THREATENING INTRACEREBRAL/SPINAL CORD HEMORRHAGE OR LIFE THREATENING TRAUMA RELATED HEMORRHAGE GUIDELINE

Definitions

Life-threatening bleeding

1. Intracerebral/spinal cord hemorrhage
2. Decrease of Hgb ≥ 5 g/dL
3. Hemodynamically unstable patients requiring inotropic support
4. Bleeding requiring emergent surgery (per Neurosurgeon, Trauma Surgeon's, or UH Community Hospital authorized personnel approval)
5. Bleeding into a critical site (intracranial, intraspinal, intraocular, pericardial, intra- articular, intramuscular with compartment syndrome, retroperitoneal)

General Recommendations:

Hold all oral anticoagulants

If above criteria met for warfarin or dabigatran and the prescriber is from Neurosurgery, Trauma or the Emergency Department, proceed as described below. Other providers should consult Hematology for further guidance.

Warfarin Reversal[1]

1. Administer vitamin K as 10 mg phytonadione/50 mL 0.9% sodium chloride IVPB[2] over 10-15 minutes
   - May repeat dose every 12 hours until INR corrects to <1.4
2. Administer prothrombin complex concentrate/**4-factor** (PCC; KCentra™) as a single dose:
   a. Dosing:
      i. If INR 1.4-1.6 give PCC[3] 10 international units (IU)/kg (Max dose 1,000 units) IVPB once
      ii. If INR 1.7-1.9 give PCC[3] 15 international units (IU)/kg (Max dose 1,500 units) IVPB once
      iii. If INR 2.0 – 3.9 give PCC[3] 25 international units (IU)/kg (Max dose 2,500 units) IVPB once
      iv. If INR 4.0 – 6.0 give PCC[3] 35 international units (IU)/kg (Max dose 3,500 units) IVPB once
      v. If INR >6 give PCC[3] 50 international units (IU)/kg (Max dose 5,000 units) IVPB once
      vi. 4-factor PCC is administered as an IV infusion. Pharmacy will calculate the infusion time based on dose (typical is 15-20 minutes).
   b. If documented heparin allergy use **3-factor** PCC (Profilnine®), dosing based on INR:
      i. If INR 2.0 to 4.0 give PCC[3] 50 international units (IU)/kg once
      ii. If INR >4.0 give PCC[3] 65 international units (IU)/kg once
      iii. Administer 2 Units of FFP along with PCC if not already given
   c. Repeat INR 3 hours following administration of PCC, if:
      i. INR < 1.4 monitor patient, repeat INR every 6 hours x 24 hours
      ii. If INR at 3 h > 1.4, consider cautious use of following:
         - 5-10 ml/kg FFP or
         - 10-30 mcg/kg rVIIa[4]—one time

Factor Xa Inhibitor Reversal

1. For **Apixaban (Eliquis®) or Rivaroxaban (Xarelto®)** reversal administer Coagulation Factor Xa (recombinant), inactivated-zhzo (FXa) (Andexxa®)
   ***NOTE:** Restricted to Neurosurgery, Hematology, and Vascular Medicine for Intracranial Bleeding; if used for other types of bleeding, perioperative hemostasis, or other factor Xa inhibitors consult Hematology (pager #31251).
   a) Note: If the patient has already received a dose of PCC for reversal, then Coagulation Factor Xa (recombinant), inactivated-zhzo may not be appropriate. **Consult UHCMC Hematology** (pager #31251) for recommendations.
   b) **Dosing:** Determine if Low Dose or High Dose regimen of Coagulation Factor Xa is required based on the following table:

Factor Xa Inhibitor	Factor Xa Inhibitor Last Dose	Timing of Factor Xa Inhibitor Last Dose	
		< 8 Hours or Unknown	≥ 8 Hours, but less than 18 h*
Apixaban	≤ 5 mg	Low Dose	Low Dose
	> 5 mg or Unknown	High Dose	
Rivaroxaban	≤ 10 mg	Low Dose	
	> 10 mg or Unknown	High Dose	

   - Low Dose
     - Initial IV Bolus: 400 mg at rate of 30 mg/minute immediately followed by continuous infusion of 480 mg at rate of 4 mg/min for 120 minutes
   - High Dose
     - Initial IV Bolus: 800 mg at rate of 30 mg/minute immediately followed by continuous infusion of 960 mg at rate of 8 mg/min for 120 minutes
   - * If drug was taken > 18 hours prior, correction of anticoagulant effect probably not needed if the patient has normal renal and liver function. Patient support should be sufficient.
2. For **Edoxaban (Savaysa®), Betrixaban (Bevyxxa®), enoxaparin (Lovenox®), or fondaparinux (Arixtra®)** reversal: Consult Hematology for recommendations

Approved by UH Medication and Safety Therapeutics Committee May 2016

University Hospitals

Dabigatran (Pradaxa®) Reversal	Administer Idarucizumab (Praxbind®) 5 Gm a) Administer as two separate 2.5 Gm doses IVPB over 5-10 minutes, dosed no more than 15 minutes apart b) Use vented tubing when administering
Antiplatelet Medications	If patient taking aspirin, $P2Y_{12}$ antagonists (clopidogrel, prasugrel, ticagrelor), IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), or SSRI: consider 2 pack platelet infusion, since platelet function abnormality contributing to bleeding as well.
Special Notes:	a) Guideline is Restricted to Divisions of Neurological Surgery, Trauma Surgery, Cleveland Medical Center Emergency Department, and UH Community Hospital authorized personnel as determined by each site b) IV administration is the preferred route of administration in life threatening bleeding (Chest 2010) due to erratic absorption rates when given IM and Subcutaneously c) PCC (KCentra®) vials have a nominal potency of 500 IU/vial or 1,000 IU/vial a. Exact dosage is expressed on each vial which will vary from 20-31 factor IX units/mL, pharmacy will adjust dose based on actual potency and round to nearest 5% of ordered dose. d) PCC (Profilnine®) vials are sized as follows: ~500 IU, ~1000, IU, or ~1500 IU; pharmacy will round to nearest vial size within 5% of ordered dose a. Exact dosage is expressed on each vial e) Usual dosage range when used with 3-factor PCC (Profilnine®): 1 to 2 mg, case reports have dosed up to 3 mg f) **NOTE**: Coagulation Factor Xa (recombinant), inactivated-FXa (FXai) (Andexxa®) is only stocked at UH Cleveland Medical Center

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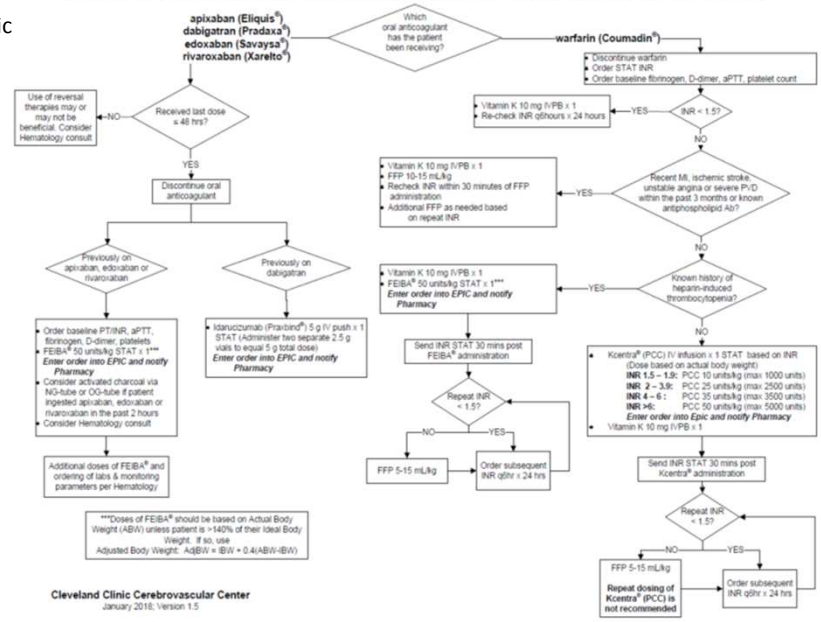
75

Cleveland Clinic

CC MAIN CAMPUS GUIDELINE for Reversal of Oral Anticoagulant Induced Coagulopathy With Intracranial Hemorrhage



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January 2018; Version 1.5

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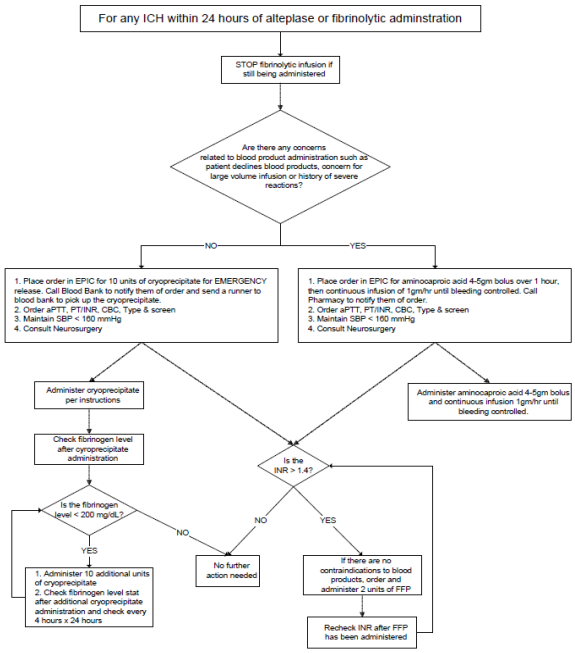
76

CLEVELAND CLINIC ICH-RELATED FIBRINOLYTIC COAGULOPATHY REVERSAL



77

Anticoagulation Reversal: Unfractionated Heparin (UFH) and Low Molecular Weight Heparin (LMWH)

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- Patient with life-threatening or major bleeding while on UFH/LMWH
  - Life-threatening or major bleeding may include:
    - Intracranial hemorrhage
    - GI hemorrhage requiring intervention
    - Retropharyngeal or retroperitoneal bleeding
    - Emergent surgery
    - Ruptured hollow viscus
    - Intraocular bleed compromising vision
    - Cardiac tamponade
- Discontinue UFH/LMWH
- Consider indication for anticoagulation when considering interventions for bleeding
- Fluid replacement and hemodynamic support
  - Consider PRBC

UFH

- If UFH was given as:
  - **IV bolus within:**
    - **< 30 mins:** 1 mg protamine*/ 100 units UFH
    - **30-60 mins:** 0.5 mg protamine*/ 100 units UFH
    - **1-3 hrs:** 0.25 mg protamine*/ 100 units UFH
  - **Continuous infusion:** 1 mg protamine* /100 units UFH infused over the last 3 hrs
  - **Subcutaneous:** 1 mg protamine*/100 units UFH given in the last 12 hrs
    - Give 25 mg as a bolus over at least 5 mins followed by an infusion of the remainder of the dose over 8 hrs
- **Maximum protamine dose: 50mg**

- Check aPTT and/or activated clotting time (ACT) 5–15 mins after protamine administration.
- If aPTT/ACT remains elevated with active bleeding, consider additional, lower dose of protamine.

LMWH

- If LMWH given:
  - **≤ 8 hrs ago:** 1 mg protamine* per 1 mg enoxaparin (or 100 anti-Xa Units of other LMWH e.g. dalteparin)
  - **8-12 hrs ago:** 0.5 mg protamine* per 1 mg enoxaparin
  - **≥ 12 hrs ago:** protamine administration may not be advised; factors such as dose and renal function should be considered. A reduced dose of protamine may also be considered.
- **Maximum protamine dose: 50mg**

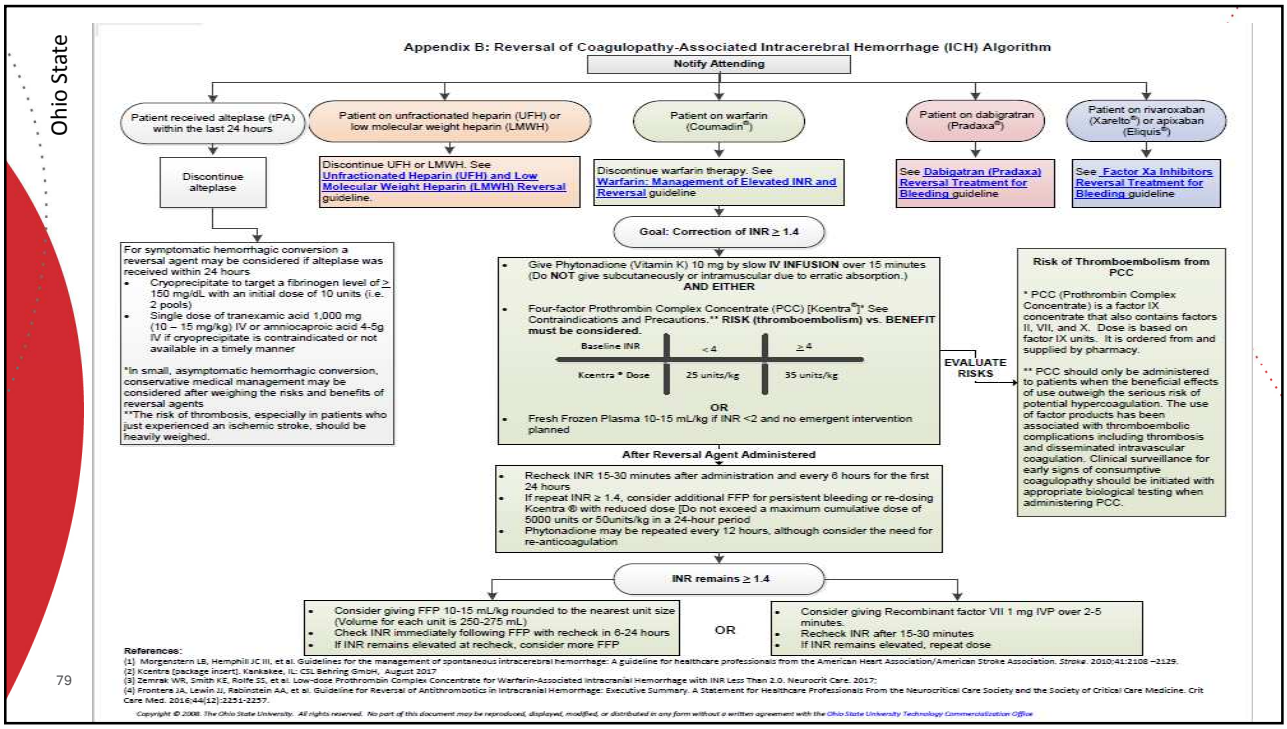
- Check aPTT level 2–4 hrs after first protamine dose
- For normal treatment doses of LMWH, it is unlikely that aPTT will be elevated
- If bleeding continues, may repeat with reduced dose 0.25-0.5 mg protamine* per 1 mg enoxaparin (or 100 anti-Xa units of other LMWH).
- Since LMWHs are not fully reversed by protamine, some case reports have used Recombinant Factor VIIa (FVIIa) in life-threatening bleeding.
  - Safety for this indication is unknown and there is concern for the risk of thrombotic events. FVIIa is generally not recommended in cases of intracerebral hemorrhage
  - Hematology consultation should be considered prior to using FVIIa
  - There is no established dose of FVIIa but low doses (1–2 mg) are advised

Protamine Sulfate:

- Protamine neutralizes anti-factor IIa activity of LMWH but not anti-factor Xa activity
- Protamine does not reverse fondaparinux
- Increased risk of hypersensitivity reaction amoung (may consider premedication with corticosteroid/antihistamine if time permits):
  - Vasectomized or sterile males
  - Patients with fish (not shellfish) allergy
  - Patients who use protamine-containing insulin (NPH or NPH-containing combinations)
- Protamine test dose: protamine prescribing information does not include a recommendation for a test dose, nor do standard references. Some authors recommend that a small intravenous dose of protamine (5–10 mg) be given to test the sensitivity in potentially allergic patients.

*Slow administration (max 5 mg/min) to minimize adverse reactions. **Max single dose= 50 mg in any 10 min period.** Doses ≤ 25 mg may be given as IV push over at least 5 mins. Doses > 25 mg should be given as IV piggyback over at least 10 mins.

78



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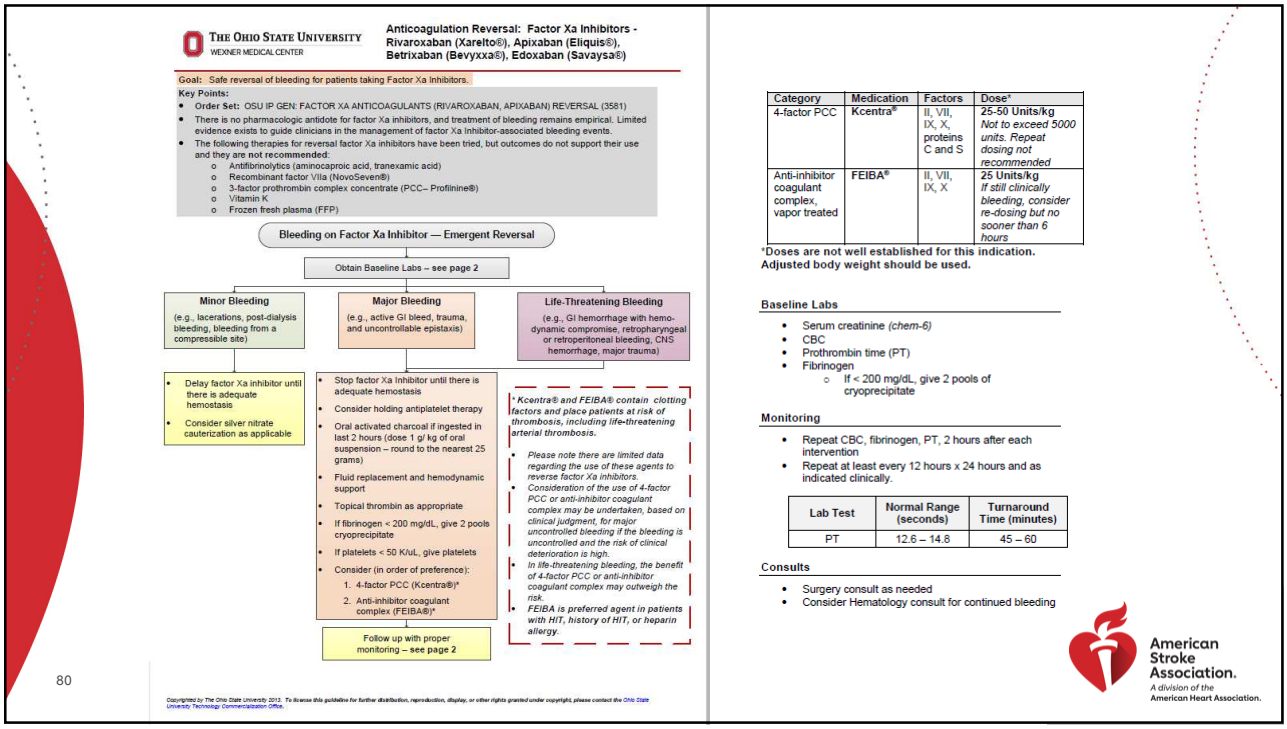

Category	Medication	Factors	Dose*
4-factor PCC	Kcentra®	II, VII, IX, X, proteins C and S	25-50 Units/kg *Not to exceed 5000 units. Repeat dosing not recommended*
Anti-inhibitor coagulant complex, vapor treated	FEIBA®	II, VII, IX, X	25 Units/kg *If still clinically bleeding, consider re-dosing but no sooner than 6 hours*

*Doses are not well established for this indication. Adjusted body weight should be used.

Baseline Labs

- Serum creatinine *(chem-6)*
- CBC
- Prothrombin time (PT)
- Fibrinogen
  - If < 200 mg/dL, give 2 pools of cryoprecipitate

Monitoring

- Repeat CBC, fibrinogen, PT, 2 hours after each intervention
- Repeat at least every 12 hours x 24 hours and as indicated clinically.

Lab Test	Normal Range (seconds)	Turnaround Time (minutes)
PT	12.6 – 14.8	45 – 60

Consults

- Surgery consult as needed
- Consider Hematology consult for continued bleeding

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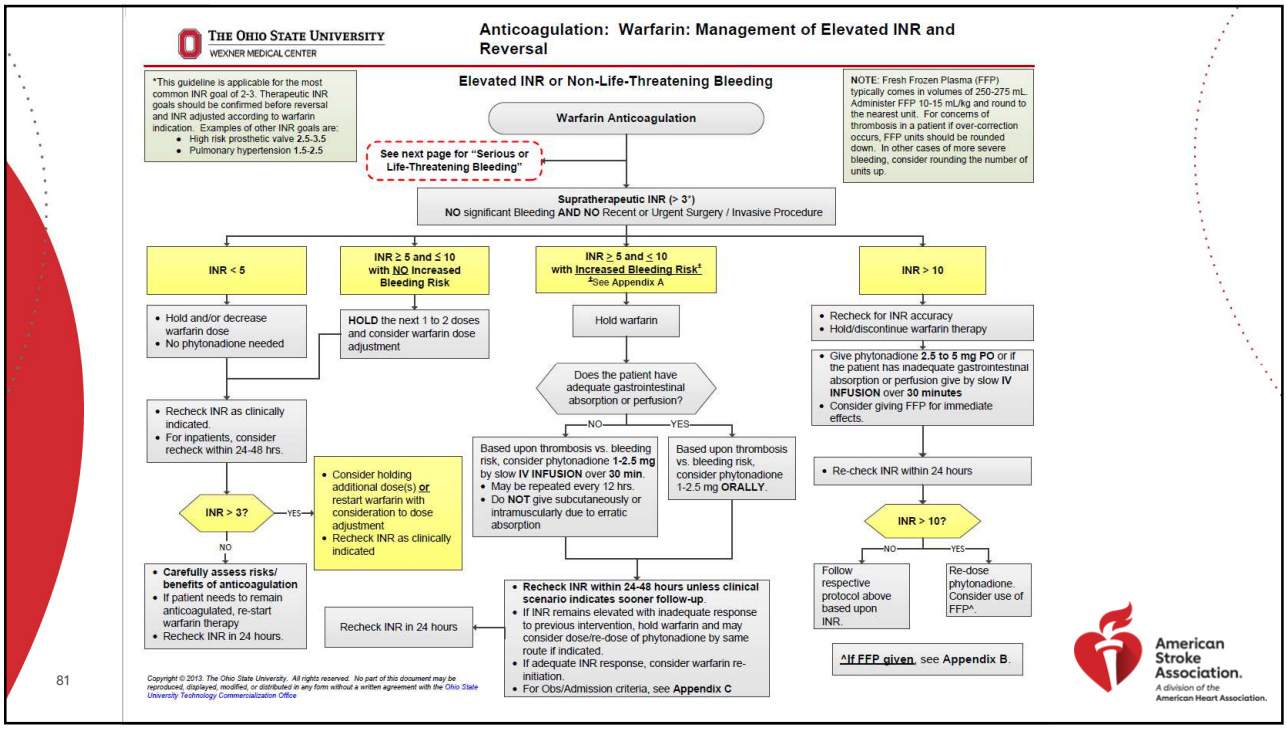
80


THE OHIO STATE UNIVERSITY
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Anticoagulation: Warfarin: Management of Elevated INR and Reversal
*This guideline is applicable for the most common INR goal of 2-3. Therapeutic INR goals should be confirmed before reversal and INR adjusted according to warfarin indication. Examples of other INR goals are:
High risk prosthetic valve 2.5-3.5
Pulmonary hypertension 1.5-2.5
Elevated INR or Non-Life-Threatening Bleeding
NOTE: Fresh Frozen Plasma (FFP) typically comes in volumes of 250-275 mL. Administer FFP 10-15 mL/kg and round to the nearest unit. For concerns of thrombosis in a patient if over-correction occurs, FFP units should be rounded down. In other cases of more severe bleeding, consider rounding the number of units up.
Warfarin Anticoagulation
See next page for "Serious or Life-Threatening Bleeding"
Supratherapeutic INR (> 3*)
NO significant Bleeding AND NO Recent or Urgent Surgery / Invasive Procedure
INR < 5
INR ≥ 5 and ≤ 10 with NO Increased Bleeding Risk
INR ≥ 5 and ≤ 10 with Increased Bleeding Risk‡
‡See Appendix A
INR > 10
Hold and/or decrease warfarin dose
No phytonadione needed
HOLD the next 1 to 2 doses and consider warfarin dose adjustment
Hold warfarin
Recheck for INR accuracy
Hold/discontinue warfarin therapy
Give phytonadione 2.5 to 5 mg PO or if the patient has inadequate gastrointestinal absorption or perfusion give by slow IV INFUSION over 30 minutes
Consider giving FFP for immediate effects.
Does the patient have adequate gastrointestinal absorption or perfusion?
NO
YES
Recheck INR as clinically indicated.
For inpatients, consider recheck within 24-48 hrs.
Based upon thrombosis vs. bleeding risk, consider phytonadione 1-2.5 mg by slow IV INFUSION over 30 min.
May be repeated every 12 hrs.
Do NOT give subcutaneously or intramuscularly due to erratic absorption
Based upon thrombosis vs. bleeding risk, consider phytonadione 1-2.5 mg ORALLY.
Re-check INR within 24 hours
INR > 3?
YES
NO
Consider holding additional dose(s) or restart warfarin with consideration to dose adjustment
Recheck INR as clinically indicated
INR > 10?
NO
YES
Carefully assess risks/ benefits of anticoagulation
If patient needs to remain anticoagulated, re-start warfarin therapy
Recheck INR in 24 hours.
Recheck INR in 24 hours
Recheck INR within 24-48 hours unless clinical scenario indicates sooner follow-up.
If INR remains elevated with inadequate response to previous intervention, hold warfarin and may consider dose/re-dose of phytonadione by same route if indicated.
If adequate INR response, consider warfarin re-initiation.
For Obs/Admission criteria, see Appendix C
Follow respective protocol above based upon INR.
Re-dose phytonadione. Consider use of FFP^.
^If FFP given, see Appendix B.
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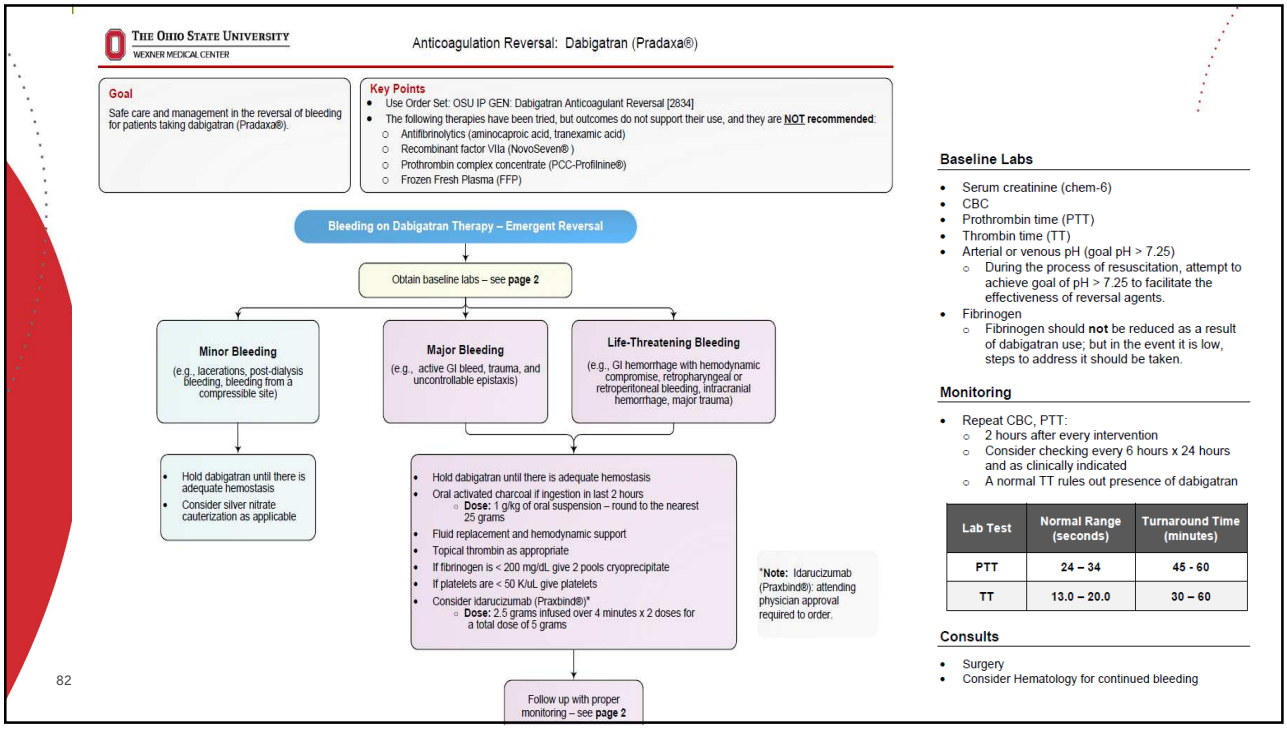
American Stroke Association.
A division of the American Heart Association.

81

81


THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
Anticoagulation Reversal: Dabigatran (Pradaxa®)
Goal
Safe care and management in the reversal of bleeding for patients taking dabigatran (Pradaxa®).
Key Points
Use Order Set: OSU IP GEN: Dabigatran Anticoagulant Reversal [2834]
The following therapies have been tried, but outcomes do not support their use, and they are NOT recommended:
Antifibrinolytics (aminocaproic acid, tranexamic acid)
Recombinant factor VIIa (NovoSeven®)
Prothrombin complex concentrate (PCC-Profilnine®)
Frozen Fresh Plasma (FFP)
Bleeding on Dabigatran Therapy – Emergent Reversal
Obtain baseline labs – see page 2
Minor Bleeding
(e.g., lacerations, post-dialysis bleeding, bleeding from a compressible site)
Major Bleeding
(e.g., active GI bleed, trauma, and uncontrollable epistaxis)
Life-Threatening Bleeding
(e.g., GI hemorrhage with hemodynamic compromise, retropharyngeal or retroperitoneal bleeding, intracranial hemorrhage, major trauma)
Hold dabigatran until there is adequate hemostasis
Consider silver nitrate cauterization as applicable
Hold dabigatran until there is adequate hemostasis
Oral activated charcoal if ingestion in last 2 hours
Dose: 1 g/kg of oral suspension – round to the nearest 25 grams
Fluid replacement and hemodynamic support
Topical thrombin as appropriate
If fibrinogen is < 200 mg/dL give 2 pools cryoprecipitate
If platelets are < 50 K/uL give platelets
Consider idarucizumab (Praxbind®)*
Dose: 2.5 grams infused over 4 minutes x 2 doses for a total dose of 5 grams
*Note: Idarucizumab (Praxbind®): attending physician approval required to order.
Follow up with proper monitoring – see page 2
Baseline Labs
Serum creatinine (chem-6)
CBC
Prothrombin time (PTT)
Thrombin time (TT)
Arterial or venous pH (goal pH > 7.25)
During the process of resuscitation, attempt to achieve goal of pH > 7.25 to facilitate the effectiveness of reversal agents.
Fibrinogen
Fibrinogen should not be reduced as a result of dabigatran use; but in the event it is low, steps to address it should be taken.
Monitoring
Repeat CBC, PTT:
2 hours after every intervention
Consider checking every 6 hours x 24 hours and as clinically indicated
A normal TT rules out presence of dabigatran
Lab Test | Normal Range (seconds) | Turnaround Time (minutes)
PTT | 24 – 34 | 45 - 60
TT | 13.0 – 20.0 | 30 – 60
Consults
Surgery
Consider Hematology for continued bleeding

82

82