Guidelines for Reversing Coagulopathies in Patients with Symptomatic Spontaneous Intraparenchymal Hemorrhage

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Future updates are anticipated as new evidence accumulates. The most recent version of these guidelines will be posted on the Stroke web site (www.stroke.washington.edu). This document can be downloaded in its entirety as a PDF document from the Stroke web site by following the links to the Acute Stroke Algorithm and to intraparenchymal hemorrhage. For bleeding on tissue plasminogen activator (tPA), see online Stroke Algorithm* at the end of the document for IV tPA “inclusion/exclusion criteria”. *Online Stroke Algorithm can be found under www.stroke.washington.edu, then click on the “Referrals and TeleStroke Service” link on the left bar and find the “Stroke Algorithm” link. Or go directly to http://uwmedicine.washington.edu/Patient-Care/Our-Services/Medical-Services/Stroke-Center/Documents/HMC_Rx_Algorithm.pdf

Any questions or comments about these guidelines can be addressed to any of the people indicated above or can be sent to Claire Creutzfeldt at clairejc@uw.edu.

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For each patient, go through all 17 items below.

1. **STAT** bloods for:
   - Emergency Stroke Panel (includes PT/INR, a modified PT (mPT), thrombin time (TT), fibrinogen, platelets, and hematocrit) and PTT
   - Type and Screen – EMERGENCY
   - If crash craniotomy is considered, request 2 Units emergent uncrossmatched Group O (universal donor) packed red blood cells.
2. Obtain history about use of antithrombotic treatments (antiplatelet agents, warfarin, DTIs (e.g. dabigatran), Xa inhibitors (e.g. rivaroxaban, apixaban), unfractionated heparin, low-molecular-weight heparin, and others). If on LMWH, rivaroxaban or apixaban, send an anti-Xa assay specific for the anticoagulant in use (LMWXA, RIVAR1, or APIXN1); if on an injectable Direct Thrombin Inhibitor send a DTI assay (DTIPAT); if on dabigatran, send a dabigatran assay (DABIG). These tests will not be available emergently. The emergency stroke panel should be used to guide emergent reversal of life threatening hemorrhage in the presence of an unknown anticoagulant.

3. If on warfarin:
   - Give vitamin K 10 mg IV
   - If INR 1.6-1.9, may consider 4-factor prothrombin concentrate complex (4-factor PCC/Kcentra®) as described below. 4-factor PCC/Kcentra is approved for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in patients with acute major bleeding or a need for an urgent surgery/invasive procedure. Given the scarce evidence and the possible thrombotic risk of 4-factor PCC, FFP may be considered as an alternative (see FFP pathway below).
   - If INR ≥ 2.0, determine eligibility for 4-factor PCC (preferred) vs FFP.

Relative contraindications to 4-factor PCC use include:
   1) History of thrombotic or thromboembolic event in past 6 weeks (DVT, PE, ischemic stroke, acute coronary syndrome, acute venous/arterial ischemia etc.);
   2) Known prothrombotic condition (malignancy, DIC, hypercoagulable condition, hepatic disease, polytrauma, HIT, etc.);
   3) Major surgery in the past 6 weeks;
   4) Intraparenchymal hemorrhage thought not survivable.

IF ANY OF THESE RELATIVE CONTRAINDICATIONS ARE PRESENT, please discuss with stroke attending the possibility of giving 4-factor PCC regardless, or instead giving thawed plasma/FFP (as outlined below).

A. 4-factor PCC/Kcentra Pathway:
   - Infuse 2000 units of 4-factor PCC immediately upon arrival from Pharmacy.
     - Dosing is based on factor IX content (in units) and a 1000 unit vial contains a minimum of 1000 units, but frequently contains slightly more (20-40 units) but NEVER less. Pharmacy will prepare the dose with the contents of 2 vials which will ALWAYS be at least 2000 units.
   - Check PT/INR at 15-30 minutes, 6 hours and 24 hours after completion of above PCC infusion
   - If PT/INR is still >1.5 after infusion of 4-factor PCC, consider other possible causes such as a low fibrinogen or the presence of an inhibitor. Page the Hematology ATTENDING for consult. While awaiting hematology ATTENDING response, may consider administering another 500 units of 4-factor PCC or 2-4 units of thawed FFP/plasma (see B below).
   - If INR remains > 1.5 at 6 hours, repeat dose of Vitamin K 10 mg IV
B. Alternative Thawed FFP/Plasma Pathway:
When above cautionary/contraindications for 4-factor PCC are met (or if PT/INR is still >1.5 after infusion of 4-factor PCC)

- Immediately give 4 Units emergency-release FFP/plasma and request that 4 Units of type-specific thawed FFP/plasma be sent as soon as possible (Send sample for STAT Type and screen).
  - At Harborview, call Transfusion Services (744-3088) to request 4 units of emergency-release thawed FFP/plasma.
  - At UWMC, the same protocol should be followed except that 4 U of emergency-release thawed FFP/plasma should be obtained from UWMC Transfusion Support Services (598-6240) and 4 U of type-specific thawed FFP/plasma need to be requested from the Puget Sound Blood Center (206-522-2462).

- Consider a diuretic such as furosemide if the patient has a history of congestive heart failure, because of the potential for volume overload.

- Upon completion of the infusion, immediately send STAT Emergency Hemorrhage Panel (includes PT/INR, fibrinogen, plt, HCT).
- If INR is still >1.5, give the 4 U of type-specific thawed FFP/plasma
- Upon completion of this infusion, immediately repeat the STAT Emergency Hemorrhage Panel (includes PT/INR, fibrinogen, plt, HCT)
- If INR is still >1.5, repeat vitamin K 10mg IV and consult hematology ATTENDING
- Once INR is ≤ 1.5, repeat INR every 6 hours for 24 hours to make sure it does not drift up above 1.5.
- If INR increases from below to > 1.5, repeat vitamin K 10mg IV and consult hematology ATTENDING

4. If on Dabigatran (direct thrombin inhibitor) and the TT is prolonged or not readily available: (Note: If the TT assay is normal (not elevated/prolonged), little or no dabigatran effect is present, and consider other factors that may be contributing to hemorrhage. The TT assay usually takes <10 minutes and is part of the Emergency Stroke Panel).

- IF ingestion within 2 hrs, give one dose activated charcoal orally.
- Give idarucizumab (Praxbind) 5gm IV, administered as two 2.5gm doses no more than 15 minutes apart, each infused over 5-10 minutes
- If idarucizumab is not available or if the hemorrhage is associated with a direct thrombin inhibitor other than dabigatran, consider reversal with PCC:
  - infuse 2000 units of 4-factor PCC as above
    - Note: There is very limited data on the efficacy of PCC, but it may be beneficial. Please note that PCC carries a potential pro-thrombotic risk – for more information on PCC and for cautionary criteria, please see above under # 3 warfarin reversal.
- Emergent dialysis has not been studied but may be considered in certain circumstances (renal failure, overdose); 65% of dabigatran is not protein-bound,
  - Note: With a creatinine clearance of >80 ml/min, dabigatran's half-life is approximately 12 hours. This rises with worsening renal function, up to 34 hours if creatinine clearance <30ml/min.
5a. If on Rivaroxaban or Apixaban (Factor Xa inhibitors) and modified PT is prolonged or the anti-Xa assay for the specific anticoagulant confirms the presence of the anticoagulant (RIVAR1 or APIXN1): (Note: If mPT/anti Xa level is normal, no meaningful amount of Rivaroxaban/Apixaban is present, and consider other factors that may be contributing to hemorrhage.

- If ingestion within 2 hrs, give one dose activated charcoal orally.
- If reversal with 4-factorPCC will be attempted, infuse 2000 units
  - Note: There are very limited data on the efficacy of 4-factorPCC in this setting, but it may be beneficial. 4-factor PCC carries a potential pro-thrombotic risk – for more information on relative contraindications see #3 (warfarin reversal) above.
  - Note: Rivaroxaban and Apixaban are not removed by dialysis
  - Rivaroxaban’s half-life is approx. 9 hours (longer in renal impairment).
  - Apixaban’s half-life is approx. 12 hours (longer in renal impairment)

5b. If on Edoxaban: no calibrated assay exists at this time. A normal mPT may or may not exclude the presence of clinically relevant amounts of Edoxaban, and clinical judgement based on patient history is required. If high suspicion that patient is on Edoxaban, proceed with protocol as in 5a.

- Notes: Edoxaban is not removed by dialysis
- Edoxaban’s half-life is approximately 10-14 hours (longer in renal impairment)

6. If on antiplatelet agents (aspirin, clopidogrel, ticlopidine, prasugrel, NSAIDS, glycoprotein IIb/IIIa antagonists [abciximab, eptifibatide, or tirofiban]):

- Discontinue antiplatelet agent(s)
- The only prospective randomized, controlled study of platelet transfusion in this clinical setting demonstrated no benefit but rather harm from platelet transfusion (Lancet 2016; 387:2605-13). Therefore, pending further evidence, we suggest not transfusing platelets routinely in patients with IPH in the setting of known use of antiplatelet medications

7. If on full-dose unfractionated heparin, stop it and give protamine 25 mg intravenously before blood results return. After infusion, repeat STAT PTT. If PTT > 43 sec, consider administering additional 10mg protamine doses until PTT < 43 sec, adequate hemostasis achieved, or a cumulative dose of 55 mg has been given. If platelets less than 100 THOU/µL, send for Heparin Induced Platelet Antibodies to screen for heparin induced thrombocytopenia (HIT). If positive, consult hematology through the paging operator.

8. If on low-molecular-weight heparin, [enoxaparin, dalteparin, or tinzaparin] within the last 8 hours, stop the agent and give protamine 50 mg intravenously before blood results return. If given within 8-24hrs (or not sure), give protamine 25 mg intravenously before blood results return. If last dose > 24 hours earlier, do not treat. If bleeding continues, a second dose of protamine 25mg intravenously can be given.
9. If having received IV tPA, see online Stroke Algorithm at the end of the document for IV tPA "inclusion/exclusion criteria", under “Algorithm for Treatment of Suspected Intracranial Hemorrhage after tPA” or go directly to:
https://depts.washington.edu/uwstroke/stroke_rx/IV_tPA_incl_excl.pdf

10. If on some other type of antithrombotic treatment, stop the agent and STAT consult hematology ATTENDING through the paging operator. Such agents would include pentasaccharides such as fondaparinux and direct thrombin inhibitors (DTIs) such as lepirudin, bivalirudin, or argatroban. There are no specific ‘antidotes’ for these parenteral DTIs or for fondaparinux. Lepirudin, bivalirudin, and argatroban have short-half lives. Repeat PTT at 60 minutes after stopping and if it is still prolonged consult hematology ATTENDING. Fondaparinux has a very long half-life, influenced by renal function - consult hematology ATTENDING.

11. Notify Neurosurgery and Stroke attending (206 744 6789) about the patient. If surgery is considered, call the Transfusion Service (744-3088) and request 2 Units crossmatched packed red blood cells (PRBC; takes approx. 5-50 minutes). If crash craniotomy is considered, request 2 Units emergent uncrossmatched emergency release PRBC (these are in house).

12. Review all blood results, which should be available within 30 minutes.

13. If prolonged PTT is the only abnormality identified on the STAT bloods (Step 1 of this protocol), immediately consult hematology ATTENDING through the paging operator.

14. Request additional products, as below, if not already requested as part of protocols above, based on the blood results and assuming an average-sized adult.
   - At HMC, contact Transfusion Services (744-3088), and at UWMC, contact the Puget Sound Blood Center (206-522-2462). Emergency FFP and cryoprecipitate at UWMC can be obtained from Transfusion support Services (206-598-6240).
   - If INR > 1.5, see above recommendations (#3) for use of FFP or 4-factor PCC.
   - If fibrinogen <125 mg/dL, request 2 pools of cryoprecipitate.
   - If platelets <50 THOU/µL, request 2 U universal-donor apheresis platelets (#4).
   - If platelets 50 to 100 THOU/µL, request 1 U of universal-donor apheresis platelets.

15. Repeat STAT Emergency Hemorrhage Panel after products have been given. If coagulopathy persists, consult hematology through the paging operator.

16. Notify the family and neurology attending about patient's condition.

17. Repeat CT head at 4 and 24 hours after initial scan or sooner if patient deteriorates.

18. Complete IPH order set.
Abbreviations:
CT = Computer Tomography
DIC = disseminated intravascular coagulation
DTI = Direct thrombin inhibitor
DVT = deep vein thrombosis
FFP = fresh frozen plasma
HMC = Harborview Medical Center
INR = international normalized ratio (of PT)
IPH = intraparenchymal hemorrhage
IU = international units
IV = intravenous
mPT = modified Prothrombin time
NSAIDs= non-steroidal anti-inflammatory drugs
PCC = prothrombin complex concentrate, for example Kcentra
PSBC = Puget Sound Blood Center
PT = prothrombin time (extrinsic coagulation)
PTT = partial thromboplastin time (intrinsic coagulation)
TT = thrombin time
UWMC = University of Washington Medical Center