Hematologic Emergencies

CSIM Workshop
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University of Alberta
Division of Clinical Hematology
Disclosures

- No conflict of interest to disclose
- Off label use of products will be discussed in this presentation
Acknowledgements

Thanks to
Dr. Susan Nahirniak
Dr. Bruce Ritchie
Dr. Art Szkotak
Dr. Gwen Clarke
for their collaboration in preparing this presentation
Learning Objectives

1) Participants will be able to specify the appropriate management for a patient with anticoagulant associated bleeding.

And if time permits...

2) Participants will be able to identify a patient with microangiopathic hemolytic anemia and initiate the appropriate diagnostic evaluation and stabilization.
Format

• Background
• Questions with answer via Poll Everywhere
• Small group discussion of cases
  – All cases derived from real life cases from TM call in Edmonton
• Share answers with the group and large group discussion
Background

• A side effect common to all anticoagulants is bleeding
• Increased options for anticoagulants has complicated the management of the bleeding patient
• As internists often called upon to provide management advice to our colleagues
Coagulation Testing

• Basic Tests of Coagulation include
  – Platelet count
  – Activated Partial Thromboplastin Time (PTT)
    • Kaolin is added to activate FXII and HMWK to generate thrombin through the activation of XI, IX, VIII, X, V and II
  – Prothrombin Time (PT)
    • Excess of thromboplastin (aka tissue factor) is added to plasma resulting in the generation of thrombin through activity of FVII, X, V and II.
    • Is not the same as the thrombin time
  – Fibrinogen
Esoteric Coagulation Tests

- **Thrombin Time**
  - Excess thrombin is added to citrated plasma
  - Prolonged in dysfibrinogenemia, thrombin inhibitors (*heparin*, lepirudin, dabigatran, argatroban, etc.)

- **Anti-Xa levels**
Case one:

- 57 y/o M with prior history of remote DVT, DMT2, CKD, and atrial fib, presents to the ER with 2 day history of melena. Medications include adalat XL, metformin and warfarin.

- Vitals on presentation HR 130, BP 90/60, RR 16, O2 98% RA. Wt 80 kg

- DRE confirms melena.
<table>
<thead>
<tr>
<th>Lab</th>
<th>Baseline June 2014</th>
<th>In ER on presentation</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L)</td>
<td>132</td>
<td>68</td>
<td>135-175</td>
</tr>
<tr>
<td>Plt (10^9/L)</td>
<td>283</td>
<td>511</td>
<td>140-450</td>
</tr>
<tr>
<td>Cr (umol/L)</td>
<td>141</td>
<td>147</td>
<td>50-115</td>
</tr>
<tr>
<td>INR</td>
<td>2.5</td>
<td>4.3</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>-</td>
<td>55</td>
<td>28-39</td>
</tr>
</tbody>
</table>

The ER physician has ordered cross-match and 3 units of RBC. The physician who is going to do the diagnostic/therapeutic endoscopy wants your advice on correcting the coagulopathy.

1) What would you recommend? Specify the medication/product, and dose.

2) What follow up testing should be done and when?
1) What would you recommend? Specify the medication(s)/product(s), and dose.

- Vitamin K 10 mg IV
- Octaplex 80 ml (2000 IU)

2) What follow up testing should be done and when?

- Stat repeat INR 10-30 min post octaplex administration. If still bleeding and INR still > 1.5 can administer additional 40 ml octaplex.
- Max total dose is 120 ml (for warfarin reversal)

- Ongoing CBC, PTT, INR, +/- fibrinogen as clinically indicated. Recall that octaplex effect ~6h.

- Monitor for VTE as complication (both at 24h and 30 days)
Guidelines on Warfarin Reversal

• CHEST
  – PCC or rFVIIa for **serious or life threatening** bleeding at any INR elevation
  – rFVIIa has Health Canada warning for use outside of Hemophilia pts with inhibitors

• BJH – UK guidelines on Oral Anticoagulation
  – (50 IU/kg) PCC for **major** bleeding (included in guideline since 1998)

• Australian Consensus Guidelines on Warfarin Reversal
  – PCCs for **clinically significant** bleeding or PCCs for INR > 9 without bleeding

• Italian Federation of Anticoagulation Clinics
  – PCCs for **serious** bleeding
Prothrombin Complex Concentrates

- Many “prothrombin complex concentrates” or PCCs available
- octaplex licensed in Canada in 2008; beriplex licensed in 2010
- Licensed PCC have been available in EU and in Australia for years
Prothrombin Complex Concentrates – or PCC

• Lyophilized **pooled plasma concentrates**
  – Contain FII, *FVII*, FIX, FX, Protein C and Protein S
  – Vitamin K dependent clotting factors
  – FXI removed; some remove antithrombin
  – Solvent detergent treated along with nanofiltration
  – Heparin added to limit the activation of clotting factors during production and purification

• **Activated PCCs are different** products
  – characterized by the presence of activated prothrombin complex factors (especially VIIa) and used in treatment of patients with coagulation factor inhibitors.
  – **FEIBA** is licensed and in use in Canada
  – Highly thrombogenic – in the 1970’s post operative thrombotic complications occurred in 46% of Hemophilia B patients receiving perioperative PCC

PCC Dosing

DOSE:

- Dosing of prothrombin complex concentrate should be based on the National Advisory Committee recommendations as found in the table below. Dosing is based on INR. If the INR is unknown or major bleeding is present, 80 mL should be administered.

<table>
<thead>
<tr>
<th>Dose of octaplex ®</th>
<th>INR 1.5 – 2.9</th>
<th>INR 3.0 – 5.0</th>
<th>INR &gt; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mL (1000 IU)</td>
<td>80 mL (2000 IU)</td>
<td>120 mL (3000 IU)</td>
<td></td>
</tr>
<tr>
<td>Vitamin K1</td>
<td>10 (mg IV) co-administration strongly recommended if reversal is required for longer than 6 hours.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- If time permits reassessment of INR at 10 - 30 minutes post dose is recommended, with additional PCC provided if the INR remains greater than 1.5 and bleeding continues. In the event sufficient product is not available to meet the above recommendations, the maximum dose available should be given with consideration for transferring the patient to another facility for additional treatment.

- Maximum total dose = 120 mL

Contraindicated in heparin induced thrombocytopenia

http://www.albertahealthservices.ca/3319.asp
http://www.nacblood.ca/resources/guidelines/PCC.html
# Blood Components & Products Information

- Blood Components & Products Information
- CMV Negative and Irradiated Blood Component Use
- Consent to Blood and Blood Product FAQs
- Informed Consent to Transfusion
- Transfusion Medicine Forms
- Transfusion Reactions
- Transfusion Sample Labeling
- Other Transfusion Medicine Zone Resources
- Back to Transfusion Medicine

## Blood Components

- Red Blood Cells
- Platelets
- Plasma
- Cryosupernatant Plasma
- Cryoprecipitate

## Blood Products

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Factor VII, recombinant</td>
<td>Niasate RT®</td>
</tr>
<tr>
<td>Albumin, human</td>
<td>Albumin 5% (Plasbumin®, Alburex®)</td>
</tr>
<tr>
<td></td>
<td>Albumin 25% (Plasbumin®, Alburex®)</td>
</tr>
<tr>
<td>Anti-hemophilic Factor, recombinant</td>
<td>Advate®, HeliHate® FS, Kogenate® FS</td>
</tr>
<tr>
<td>Anti-inhibitor Coagulant Complex</td>
<td>FEIBA™ NF</td>
</tr>
<tr>
<td>Antithrombin III (ATIII)</td>
<td>Antithrombin III Immuno</td>
</tr>
<tr>
<td>C1 Esterase Inhibitor</td>
<td>Berinert®, CINRYZE™</td>
</tr>
<tr>
<td>Cytomegalovirus Immune Globulin (CMVIG)</td>
<td>Cytogam®</td>
</tr>
<tr>
<td>eptacog alfa</td>
<td>Niasate RT®</td>
</tr>
<tr>
<td>Factor V</td>
<td></td>
</tr>
</tbody>
</table>
Incidence of thromboembolic complications

- In analysis of 14 studies (prospective and retrospective) including 460 patients:
  - No DIC
  - 7 thrombotic complications (7/460 = 1.5%)
    - 1 Thrombotic stroke;
    - 2 DVT
    - 2 MI*
    - 2 non hemorrhagic stroke**

Why not Frozen Plasma

➢ All major guidelines recommend PCC over plasma
➢ 15-30 minutes required for thawing
➢ INR of frozen plasma =1.2-1.6
  • **Risks include:**
    – Infectious disease transmission
    – Volume overload (TACO)
    – TRALI
    – hemolysis
  • slow correction owing to infusion time
  • **Overall PCC is more cost effective than plasma for warfarin reversal**
Cost Effectiveness of PCCs

- PCC is $0.62/unit = 80 ml dose (2000 IU) = $1240
- FP $200-400/unit = equivalent 80 ml octaplex is 6 unit FP = $1200
- Does not include tech time (plasma thaw vs octaplex no prep time in lab) and nursing time (octaplex 15-30 min administration time, vs plasma 2-4h)
- If we continue to use the FP cannot be sent for fractation products, therefore we have to buy more frac products (albumin, IVIg etc) from US sourcing, therefore more expensive. If we use less FP the cost albumin and IVIg will decrease

- There is also more transfusion reactions with FP, therefore more cost to investigating reactions (tech time, TM MD time, specimens, nursing).
If you need a procedure...
Case Two

- 88 y/o F with a fib, HTN, CKD presented to the ER with massive lower GI bleeding. Her medications include dabigitran 75 mg BID, bisoprolol 5 mg, digoxin 0.0625 mg. Estimated weight 65 kg

- Vitals : BP 60/42, HR 88, RR 22, O2 78%, GCS 14/15

<table>
<thead>
<tr>
<th>Lab</th>
<th>Baseline 3 months prior</th>
<th>In ER on presentation</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L)</td>
<td>111</td>
<td>43</td>
<td>120-160</td>
</tr>
<tr>
<td>Plt (10**9/L)</td>
<td>197</td>
<td>140</td>
<td>140-450</td>
</tr>
<tr>
<td>Cr (umol/L)</td>
<td>233</td>
<td>242</td>
<td>50-115</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>4.1</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>-</td>
<td>75</td>
<td>28-39</td>
</tr>
</tbody>
</table>
After resuscitation with IVF and 4 units uncross-matched blood HR 122, BP 90/60. The ER physician calls you for advice on how to “reverse” the dabigatran.

1) What would you recommend? Specify the medication(s)/product(s), and dose.

2) What other supportive care measures could you consider?

3) If the patient was also on ASA would your recommendations change? If the patient was on Plavix would your recommendations change?

4) Is there a way to determine if the dabigatran effect is gone?
1) What would you recommend? Specify the medication(s)/product(s), and dose.

FEIBA 25-50 IU/kg – an attempt to provide hemostatic support, NOT a true reversal. = 1600 to 3250 IU

Ongoing transfusion of RBC,
Tranexamic acid 10/kg IV q 8h (usually 1g upfront then next 1g as slow infusion over next 8h)
Monitor fibrinogen levels, if low (1.0-1.5 g/L) give cryoprecipitate as fibrinogen replacement

2) What other supportive care measures could you consider?
Consider activated charcoal if last dose of dabigatran was < 2 – 4 h ago
Consider dialysis for drug removal if significant renal impairment
3) If the patient was also on ASA would your recommendations change? If the patient was on Plavix would your recommendations change?
   • If on Plavix could consider plt transfusion to reverse the effect of anti-plts
   • Can take up to two doses of plt to reverse plavix effect, but recommended to start with one dose and clinically reassess.

4) Is there a way to determine if the dabigatran effect is gone?
   • A TT<35 sec in a patient on Dabigatran with normal fibrinogen levels indicates very low levels of drug that are unlikely to cause bleeding.
   • This will indicate the renal clearance of the drug, not the “reversal” effect of the FEIBA
Dabigatran

- **Direct thrombin inhibitor**
- **Renal excretion**
  - In a single-center study, 50 mg of dabigatran etexilate was given orally to six patients with end-stage renal disease before dialysis, and the mean fraction of the drug removed by the dialyzer was 62% at 2 hours and 68% at 4 hours

- **Testing:**
  - PTT prolonged but not correlative, INR not typically affected;
  - Thrombin time significant prolongation (normal 10.3 -16.6 s)

<table>
<thead>
<tr>
<th>Dabigatran ng/ml</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT(s)</td>
<td>11.9</td>
<td>16.8</td>
<td>26.0</td>
<td>38.1</td>
<td>52.3</td>
<td>66.2</td>
<td>81.5</td>
<td>94.8</td>
<td>136.8</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

- **NO ANTIDOTE**
  - Some suggestion that 25-50 IU/kg of FEIBA may be of benefit
  - Alberta NOAC bleeding guideline recommends FEIBA only for lifethreatening bleeding

Fawole, A., Cleveland Clinic Journal of Medicine July 2013 vol. 80 443-451

Eerenberg et al. Circulation Sept 2011
http://circ.ahajournal.org/content/early/2011/09/06/CIRCULATIONAHA.111.02901
When to consider use of FEIBA in Dabigatran anticoagulated patients

- TT prolonged *or*
- Known history of dabigatran anticoagulation
- Life threatening hemorrhage *and/or*
- Intracranial hemorrhage
- Decreased creatinine clearance/GFR
- *And* recommendation by RAAPIID or consultant

- *Not* if bleeding can be managed with standard blood product support
- *Not* in patients with known DIC
- *Not* with a recent history of thrombosis, coronary artery disease or thromboembolism

Note that FEIBA will not necessarily reverse the prolonged TT seen following Dabigatran treatment;

TT cannot be used to monitor “reversal” or therapy with FEIBA
Case Three

65 y/o F one week post total hip replacement. Was discharged home on rivaroxaban as VTE prophylaxis, and arthrotec as pain control. She presents to ER after 1 episodes of melena, was brought by EMS to ER.

Vitals: HR 90, BP 82/40, RR 16, O2 sat 92% RA, afebrile weight 96kg
<table>
<thead>
<tr>
<th>Lab</th>
<th>Baseline 6 months prior</th>
<th>In ER on presentation</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L)</td>
<td>136</td>
<td>48</td>
<td>120-160</td>
</tr>
<tr>
<td>Plt (10**9/L)</td>
<td>272</td>
<td>283</td>
<td>140-450</td>
</tr>
<tr>
<td>Cr (umol/L)</td>
<td>55</td>
<td>35</td>
<td>50-115</td>
</tr>
<tr>
<td>INR</td>
<td>-</td>
<td>1.8</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>-</td>
<td>30</td>
<td>28-39</td>
</tr>
</tbody>
</table>

The ER physician orders 4 units RBC and calls you for advice on how to “reverse” the rivaroxaban.

1) What would you recommend? Specify the medication(s)/product(s), and dose.

2) Is there a way to determine if the rivaroxaban effect is gone?
1) **What would you recommend?** Specify the medication(s)/product(s), and dose.

- Octaplex/Beriplex 50 IU/kg as one time dose = 50 IU(96kg) = 4800 IU
- Vial = 40ml = 1000 IU
- Would dispense 200 ml = 5000 IU
- Tranexamic acid 10/kg IV q 8h (usually 1g upfront then next 1g as slow infusion over next 8h)

2) Is there a way to determine if the rivaroxaban effect is gone?

- Anti-Xa is very sensitive to Rivaroxaban. The drug produces a significant elevation (>0.10 U/ml “LMWH Units”) when the concentration is >10-15 ng/ml. This is the test of choice for ruling out the presence of Direct Xa Inhibitors.

Eerenberg et al. Circulation Sept 2011
http://circ.ahajournal.org/content/early/2011/09/06/CIRCULATIONAHA.111.02901

AHS DOAC Practice Guideline, 2014
**Rivaroxaban measuring**

- In patients on stable anticoagulation (20mg/day)
  - Median peak 290 ng/ml Median trough 32 ng/ml
- PT and PTT are relatively insensitive to Rivaroxaban – requiring concentrations typically >100 ng/ml to become prolonged
- TT and Fibrinogen should not be affected by Rivaroxaban.
- Anti-Xa is very sensitive to Rivaroxaban. **This is the test of choice for ruling out the presence of Direct Xa Inhibitors.**
- Hepzyme does not remove Rivaroxaban. This can be used to distinguish DXIs from heparin.


Edmonton Zone Coag Lab data
## Local Data from Edmonton Zone

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>PCC</th>
<th>FEIBA</th>
<th>rVIIa</th>
<th>NO TX</th>
<th>OTHER</th>
<th>alive</th>
<th>deceased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>81</td>
<td>46</td>
<td>16</td>
<td>6</td>
<td>17</td>
<td>6</td>
<td>57</td>
<td>24</td>
</tr>
<tr>
<td>Apixa</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dabi</td>
<td>44</td>
<td>13</td>
<td>15</td>
<td>6</td>
<td>12</td>
<td>5</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>Riva</td>
<td>36</td>
<td>33</td>
<td>1</td>
<td></td>
<td>4</td>
<td>1</td>
<td>26</td>
<td>10</td>
</tr>
</tbody>
</table>

Local database, retrospective data, any patient requiring product for “reversal”,
Case fatality rate for severe NOAC bleeds = 24/81 = 30%

Unpublished data supplied by Dr. Susan Nahirniak
Summary Bleeding on NOAC

- Stop the drug
- Continue other supportive care with RBC, cryo etc
- Fix structural defects (ie: clip it, cautery etc)
- Tranexamic acid
- For severe/lifethreatening bleeds
  - PCC 50 IU/kg for DXI
  - FEIBA 25-50 IU/kg for DTI
- Consider charcoal and dialysis for dabi bleeds

Siegal et al, Blood, 2014
Table 1a: Management of patients with bleeding on Dabigatran

<table>
<thead>
<tr>
<th>Major Bleeding</th>
<th>Moderate Bleeding</th>
<th>Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, INRPTT, Creatinine</td>
<td>CBC, INRPTT, Creatinine</td>
<td>CBC, INRPTT, Creatinine</td>
</tr>
<tr>
<td>Local therapy</td>
<td>Local therapy</td>
<td>Local therapy</td>
</tr>
<tr>
<td>Surgery intervention</td>
<td>Surgery intervention</td>
<td>Surgery intervention</td>
</tr>
<tr>
<td>Consider platelet transfusion if anticoagulant agents are in use</td>
<td>Consider platelet transfusion if anticoagulant agents are in use</td>
<td>Consider platelet transfusion if anticoagulant agents are in use</td>
</tr>
</tbody>
</table>

Testing:
- CBC, INRPTT, Creatinine
- Local therapy
- Surgery intervention
- Consider platelet transfusion if anticoagulant agents are in use

Supportive Therapy:
- Local therapy
- Surgery intervention
- Consider platelet transfusion if anticoagulant agents are in use

Drug Dosing:
- Hold Dabigatran
- Hold anticoagulant agents

Reversal/Anatranoval:
- None

Procoagulant Agents:
- None

Table 1b: Management of patients with bleeding on Rivaroxaban/Apixaban

<table>
<thead>
<tr>
<th>Major Bleeding</th>
<th>Moderate Bleeding</th>
<th>Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, INRPTT, Fibrinogen, TAT</td>
<td>CBC, INRPTT, Fibrinogen, TAT</td>
<td>CBC, INRPTT, Fibrinogen, TAT</td>
</tr>
<tr>
<td>Local therapy</td>
<td>Local therapy</td>
<td>Local therapy</td>
</tr>
<tr>
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<td>Consider platelet transfusion if anticoagulant agents are in use</td>
</tr>
</tbody>
</table>

Testing:
- CBC, INRPTT, Fibrinogen, TAT |
- Local therapy
- Surgery intervention
- Consider platelet transfusion if anticoagulant agents are in use

Supportive Therapy:
- Local therapy
- Surgery intervention
- Consider platelet transfusion if anticoagulant agents are in use

Drug Dosing:
- Hold Rivaroxaban/Apixaban
- Hold anticoagulant agents

Reversal:
- None

Procoagulant Agents:
- None

Note: *Urineal blood loss is a relative contraindication for Tranexamic acid, which can cause Gouty colic.*
**Major upper GI bleeding is a relative contraindication for activated charcoal**

If you have any questions or comments regarding the information in this guideline, please contact Policy at policy@peteranet-services.ca
Case Four

45 y/o F with breast cancer presents to the ER with uncontrollable epistaxis that been ongoing for over 60 minutes. She is Day 10 post chemo, and had significant nausea and vomiting with this cycle of treatment. She was diagnosed with a DVT 2 months ago and is treated with Dalteparin 14000 units SC daily. Her last dose was 4 hours ago.

• Vitals HR 110, BP 90/60, RR 14, O2 sat 94% RA
<table>
<thead>
<tr>
<th>Lab</th>
<th>Baseline 6 months prior</th>
<th>In ER on presentation</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L)</td>
<td>140</td>
<td>62</td>
<td>120-160</td>
</tr>
<tr>
<td>Plt (10**9/L)</td>
<td>230</td>
<td>57</td>
<td>140-450</td>
</tr>
<tr>
<td>Cr (umol/L)</td>
<td>55</td>
<td>130</td>
<td>50-115</td>
</tr>
<tr>
<td>INR</td>
<td>-</td>
<td>1.3</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>-</td>
<td>38</td>
<td>28-39</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>-</td>
<td>1.9</td>
<td>1.9-4.1</td>
</tr>
</tbody>
</table>

After the patient bleeds through nasal packing done by ENT within 15 min, the ER physician calls you for advice managing the coagulopathy.

1) What would you recommend? Specify the medication(s)/product(s), and dose
After the patient bleeds through nasal packing done by ENT within 15 min, the ER physician calls you for advice managing the coagulopathy.

1) What would you recommend? Specify the medication(s)/product(s), and dose.

- Stop dalteparin
- Protamine 1 mg per 100 units Dalteparin in previous 8 hours to a max dose of 50 mg
- $14000/100 = 140$
- administer max dose of 50 mg protamine.
- Repeat coags including fibrinogen in 1h if still bleeding. If fibrinogen $<1.5$ consider 10 units of cryo, if fibrinogen $< 1.0$ transfuse 10 units cryo
- Consider plt transfusion if bleeding persists.
Protamine for LMWH

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Half-Life</th>
<th>Protamine Sulfate Dosing for Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td>Maximum dose is 50 mg</td>
</tr>
</tbody>
</table>
| Heparin      | 1-2 hours | • 1 mg per 90-100 units heparin given in previous 2-3 hours  
  e.g., 25-35 mg if 1000-1250 units/hour heparin infusion |
| Enoxaparin   | 4.5 hours | • 1 mg per 1 mg Enoxaparin in previous 8 hours |
| Dalteparin   | 2.2 hours | • 1 mg per 100 units Dalteparin in previous 8 hours |
| Tinzaparin   | 3.9 hours | • 1 mg per 100 units Tinzaparin in previous 8 hours |

*Half-life is longer with subcutaneous administration for all agents so may require monitoring with PTT (heparin) or anti-Xa level (LMWH) every 3 hours with repeat protamine (0.5 mg per indicated amount of LMWH or heparin) if bleeding continues.

Protamine will reverse 60-80% of the LMWH activity, and is often not considered in LMWH/heparin bleeds

Cushman et al, ASH clinical practice guide, 2014
Edmonton Zone >50kg Massive Hemorrhage\(^1\) Protocol

### Appropriate Initial Interventions
- Intravenous access: 2 large bore IVs + CVC
- Crystalloid: as per attending physician
- Labs: Crossmatch, CBC, INR, PTT, Fibrinogen, electrolytes, Mg, lactate, creatinine, ABGs and ionized Ca
- Continuous Monitoring
- Aggressive rewarming
  - Blood warmer if rate >50 ml/kg/h
- Prevent/reverse acidosis
- Correct hypocalcemia: Ca gluconate 3 gm IV slowly
- Transfuse with unmatched RBCs on hand
- Tertiary Trauma Survey

### Other considerations
- Heparin reversal
  - Protamine 1 mg IV / 100 U of heparin
- Warfarin reversal
  - Vitamin K 10 mg IV
  - Prothrombin Complex – dose as per INR based protocol
- Consider antifibrinolytics
  - Tranexamic Acid 1 g IV bolus
    - (if not already administered)
    - followed by 1g over 8 hours
- Cell Salvage

### General Guidelines for Blood Product Replacement in Adults
- **RBCs**
  - No threshold
  - Dose: MD discretion
- **FFP**
  - If INR>1.5
  - Dose: 10-15 mL/kg
- **Platelets**
  - If Plt <50 x 10^9/L or <100 x 10^9/L if CNS injury
  - Dose: 1 platelet pool
- **Cryoprecipitate/Fibrinogen**
  - Dose: 1 Unit /10kg

---

**Identify & Manage Surgical Bleeding**
- **Surgery**
- **Angiographic Embolization**
- **Endoscopy**

**Transfusion Medicine Sends MHP “Pack”**
- 6 units RBCs + 4 units FFP + 1 Pool of Platelets*
- Allow ~30 min for pack and FFP preparation
- * Platelets may be withheld depending on clinical situation, lab parameters and type of bleed

**Stop MHP**
- Notify Blood Bank
- Return any unused products ASAP
- Resume standard ordering practices

**Clinical designate contacts TM for additional products**
- Attending MD or TMMD can adjust pack based on labs as needed

**Hemostasis & resolution of coagulopathy?**
- **No**
  - Consider activating MHP
- **Yes**
  - Repeat CBC, INR, PTT & fibrinogen
  - Q1h consider repeat ionized Ca and K+

---

\(^1\) Massive Hemorrhagae is defined as blood loss > 150 mL/min or replacement of 50% of blood volume in 3 h or greater than one blood volume in < 24 h.
To re-anticoagulate??

<table>
<thead>
<tr>
<th>Would you restart A/C acute episode over?</th>
<th>If you would restart A/C what drug?</th>
<th>How would you monitor?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1: GI bleed on warfarin, CKD, Afib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 2: GI bleed on dabi, afib, CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 3: GI bleed on riva, VTE proph post THA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 4: epistaxis on LMWH, DVT in cancer pt</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Polleverywhere
Table 4. Timing of interruption of dabigatran or rivaroxaban before surgery or invasive procedures

<table>
<thead>
<tr>
<th>Calculated creatinine clearance, mL/min</th>
<th>Half-life, hours</th>
<th>Timing of last dose before surgery</th>
<th>Standard risk of bleeding</th>
<th>High risk of bleeding†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 80</td>
<td>13 (11-22)</td>
<td>24 h</td>
<td>24 h</td>
<td>2 d</td>
</tr>
<tr>
<td>&gt; 50- ≤ 80</td>
<td>15 (12-34)</td>
<td>24 h</td>
<td>24 h</td>
<td>2 d</td>
</tr>
<tr>
<td>&gt; 30- ≤ 50</td>
<td>18 (13-23)</td>
<td>2 d</td>
<td>2 d</td>
<td>4 d</td>
</tr>
<tr>
<td>≤ 30</td>
<td>27 (22-35)</td>
<td>4 d</td>
<td>4 d</td>
<td>6 d</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>12 (11-13)</td>
<td>24 h</td>
<td>24 h</td>
<td>2 d</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Unknown</td>
<td>2 d</td>
<td>2 d</td>
<td>4 d</td>
</tr>
</tbody>
</table>

*Examples are cardiac catheterization, ablation therapy, colonoscopy without removal of large polyps, and uncomplicated laparoscopic procedures, such as cholecystectomy.

†Examples are major cardiac surgery, insertion of pacemakers or defibrillators (resulting from the risk for pocket hematoma), neurosurgery, large hernia surgery, and major cancer/urologic/vascular surgery.
Summary: treating Bleeding on AC

For all bleeds
• Stop the drug
• Supportive treatment – RBC, cryo if fib low, tranexamic acid (unless GU bleeding)
• Fix the structural problem (clip it, cauterize etc)
• Consult TM on call

If life threatening/severe
• Warfarin – PCC + vit K
• LMWH/heparin – protamine
• DXI – PCC*
• DTI – FEIBA*
• *not true reversal
A quick word about MAHA

Case 5:

57 y/o male presents to the ER with fatigue, icterus, & petechial rash. HR 110, BP 150/62, T 37.7, O2 92% RA

<table>
<thead>
<tr>
<th>Lab</th>
<th>In ER at presentation</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L)</td>
<td>90</td>
<td>135-175</td>
</tr>
<tr>
<td>Plt (10**9/L)</td>
<td>14</td>
<td>140-450</td>
</tr>
<tr>
<td>Cr (umol/L)</td>
<td>140</td>
<td>50-115</td>
</tr>
</tbody>
</table>

Blood film: 4% schistos, thrombocytopenia, polychromasia

What tests to you order in prior to starting any treatment?
What tests do you order in prior to starting any treatment?

- LDH, bili, hapto, retic
- Viral serologies
- Blood cultures
- **ADAMTS13 activity and inhibitor**
  - Citrated samples required. Cannot use EDTA which is a strong inhibitor of ADAMTS13 function.*
- Consider autoimmune serologies (ANA, ANCA, LAC)

*Edmonton has local ADAMTS13 testing, previously was sent to Wisconsin Blood Center reference lab
Back to the DDx of MAHA

Nestor & Thomas, Hematology, 2012
TTP vs aHUS pathology

**TTP**

- TTP results from a deficiency of ADAMTS13
  - a serine metalloprotease
  - required for the cleavage of von Willebrand factor
- Majority of TTP cases:
  - Anti-ADAMTS13 autoantibodies results in low levels
  - Underlying disturbance in immune function

**aHUS**

- dysregulation of the complement system associated with gain- or loss-of-function mutations causing excessive complement activation

Scully & Goodship, BJH Review, 2014
aHUS pathology

Dysregulation of this pathway can lead to endothelial injury, platelet activation, and thrombosis

Factor H autoantibodies ~ 10% cases aHUS

Nestor & Thomas, Hematology, 2012
Dx of aHUS in the literature

Legendre et al., NEJM, 2014

GENETIC TESTING NOT REQUIRED FOR INITIATION OF ECULIZUMAB THERAPY

Legendre et al, NEJM, 2014
aHUS pts tend to have:
- Higher plt count
- Worse renal dysfxn
- Difficult to wean of PLEX
- Early eculizumab therapy renal protective
Summary TTP vs aHUS

• Plasma exchange should not be withheld while waiting for ADAMTS13 results
• ADAMTS13 levels
  – Low confirm diagnosis of TTP
  – Normal supports diagnosis of aHUS
• Differentiating TTP vs aHUS has important therapeutic and prognostic implications
• Important to draw ADAMTS13 levels when suspected TTP as cannot get accurate levels once PLEX initiated
• http://www.ncbi.nlm.nih.gov PMC2906185/