EMERGENCY HEMOSTASIS!

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Laboratory Testing

Common Causes of Abnormal Laboratory Tests

**Elevated PT/INR, Normal aPTT**
- Direct oral anticoagulants (DOACs)
- Factor VII deficiency
- Sepsis
- Vitamin K deficiency
- Warfarin

**Normal PT/INR, Elevated aPTT**
- Isolated factor deficiency (VIII, IX, XI, XII, Contact Pathway proteins)
- DOAC
- Heparin
- High Hematocrit (>60% - spurious)
- Lupus Inhibitor
- Specific Factor Inhibitor

**Elevated PT/INR, Elevated aPTT**
- Multiple Coagulation Factor Deficiencies
  - Liver Disease
  - Disseminated Intravascular Coagulation
- Dilutional
- DOACS
- Dysfibrinogemia
- Factor V inhibitors
- High heparin levels
- Isolated Factor X, V or II deficiency
- Low Fibrinogen (< 50 mg/dL)
- Warfarin excess

IMMEDIATE THERAPY - TRANSFUSION THERAPY

The Five Basic Tests:
1. Hematocrit
2. Platelet count
3. Prothrombin time
4. Activated partial thromboplastin time
5. Fibrinogen level

Management of Coagulation Defects

A. Platelets <50-75,000/ul in a bleeding patient or <10,000/ul in a stable patient: Give Platelet Concentrates or 6 Pack of Single Donor Platelets.
B. Fibrinogen <150mg/dl: Give 10 Units of Cryoprecipitate
C. Hematocrit below 21% in a bleeding patient: Give Red Cells
D. Protime >INR 2.0 and aPTT >1.3x control: Give 2-4 Units of FFP.
Massive Transfusions
Massively transfusion is defined as one who receives greater transfused blood than one blood volume in 24 hours or more practically defined as receiving one blood volume in two hours or less. Coagulation defects are common in the massively transfused patients due to dilution or underlying medical or surgical conditions.
* Give RBC and FFP in 1:1 ratio with platelets for every 6 units of RBC
* Consider Tranexamic acid 1 gram load and 1 gram continuous infusions over 8 hours – especially in trauma and post-partum hemorrhage
* Five basic labs to “tune-up” coagulation defects

Two common problems in massive transfusions:
1) Isolated elevations of the PT/INR
   * Factor VII labile
   * If aPTT normal should not effect coagulation
2) Greatly prolonged INR
   * Low fibrinogen
   * Heparin contamination

Thromboelastography (TEG) based therapy

<table>
<thead>
<tr>
<th>TEG parameter</th>
<th>Interpretation</th>
<th>Direction - Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Time</td>
<td>Reaction time – time to fibrin formation</td>
<td>Increased - FFP</td>
</tr>
<tr>
<td>K time</td>
<td>Kinetics – time 2 to 20 mm of amplitude</td>
<td>Increased – cryoprecipitate</td>
</tr>
<tr>
<td>Alpha angle</td>
<td>r/k slope of tracing– increase in</td>
<td>Decreased – cryoprecipitate</td>
</tr>
<tr>
<td></td>
<td>thrombus strength, fibrinogen concentration</td>
<td></td>
</tr>
<tr>
<td>Maximal Amplitude</td>
<td>Strength and stability of the thrombus</td>
<td>Decreased – platelets</td>
</tr>
<tr>
<td>Whole Blood Lysis Index</td>
<td>Fibrinolysis</td>
<td>Increased - antifibrinolytic</td>
</tr>
</tbody>
</table>

TEG Based Management
If r time prolonged -> FFP  
If MA low -> plt/cryoprecipitate (if fibrinogen < 150)  
If fibrinogen < 150 -> cryoprecipitate  
If platelets < 50 - > platelet transfusions  
If LY30 increased -> 1000mg tranexamic acid

Correcting Coagulation Defects before Procedures
Risk correlated more with skill of operator than coag defects
Elective procedures:
   Platelets 20-30,000/ul  
   aPTT < 1.5 times normal  
Emergency: most skilled person to do procedures

Thrombocytopenia

Differential Diagnosis of Thrombocytopenia
Disseminated Intravascular Coagulation
Drug induce thrombocytopenia
HELLP Syndrome
Hemophagocytic Syndrome
Heparin Induced thrombocytopenia
Immune Thrombocytopenia
Liver Disease
Post-Transfusion Purpura
Pseudothrombocytopenia
Thrombotic Thrombocytopenia Purpura

**Typical Platelet Counts in Various Disease States**

**Moderate Thrombocytopenia (50,000-100,000/ul)**
Disseminated Intravascular Coagulation
Hemophagocytic Syndrome
Heparin induce thrombocytopenia
Liver disease
Sepsis
Thrombotic Thrombocytopenic Purpura

**Severe Thrombocytopenia (<20,000/ul)**
Drug induced Thrombocytopenia
Immune Thrombocytopenia
Post-Transfusion Purpura
Severe Sepsis

**Two key questions for thrombocytopenia:**
1) How low is the platelet count (low vs really low [<10,000])
2) Is the patient sick?

Very low but not sick
   Immune thrombocytopenia (ITP)
   Drug induced thrombocytopenia

Very low and sick
   Thrombotic thrombocytopenic purpura (TTP)
   Overwhelming sepsis

Low and sick
   TTP
   Liver disease and other problem
   Sepsis
   Disseminated intravascular coagulation

Addition features
ITP/Drug ITP: other blood counts normal, usual rapid onset
TTP: schistocytes, organ dysfunction, high LDH
DIC: very high D-dimers, low fibrinogen, usually 2nd to other illness

**Diagnostic Clues to Thrombocytopenia**

<table>
<thead>
<tr>
<th>CLINICAL SETTING</th>
<th>DIFFERENTIAL DIAGNOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Surgery</td>
<td>Cardiopulmonary bypass, HIT, dilutional thrombocytopenia</td>
</tr>
<tr>
<td>Interventional Cardiac Procedure</td>
<td>Glycoprotein IIb/IIIa blockers, HIT</td>
</tr>
<tr>
<td>Sepsis Syndrome</td>
<td>DIC, Ehrlichiosis, Sepsis hemophagocytosis syndrome, drug-induced, misdiagnosed TTP,</td>
</tr>
<tr>
<td>Diagnostic Clues to Coagulation Defects</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>

**Cardiac Surgery**
- Factor V inhibitor, heparin excess or rebound, protamine excess, fibrinolysis

**Sepsis Syndrome**
- Isolated factor VII deficiency, DIC, vitamin K deficiency

**Recent use of Quinine, Second or Third generation cephalosporin**
- Drug induced Hemolysis/DIC syndrome

**Post-surgery**
- Dilutional, DIC, thrombin inhibitors

**Pregnancy**
- HELLP syndrome, fatty liver of pregnancy, vitamin K deficiency

**Acute Liver failure**
- Consumption, DIC, fibrinolysis, vitamin K deficiency (biliary obstruction)

**DIC** = disseminated intravascular coagulation, **HELLP** = Hemolysis, Elevated Liver function tests, and Low Platelets

**ITP**

Counts can be < 10,000
Otherwise healthy
Normal CBC except for low platelets (can see anemia due to bleeding)

Therapy: Dexamethasone 40 mg/d x 4 days
If very low (< 5,000) or older (> 65) or severe bleeding:
- IVIG 1 gram/kg
- Refractory ITP “Platelet Boilermaker”
  - IVIG 1 gram/kg over 24 hours with one unit of platelets every 6 hours all continuous infused
Do NOT transfuse platelets unless life-threatening bleeding.
Response to platelet transfusion is NOT a diagnostic test for ITP

**Drug Induced Thrombocytopenia**

Counts can be < 10,000
Otherwise healthy
Normal CBC except for low platelets (can see anemia due to bleeding)
Recent exposure (two weeks) to suspect drug

Therapy: stop offending drug

**Drug Induced Hemolytic-DIC Syndromes**

Patients with severe hemolytic anemia and thrombotic DIC
* One form seen with 2nd and 3rd generation cephalosporins (cefotetan, ceftriaxone most common).
Starts 7-10 days after getting ATB. Patient present with severe Coombs positive hemolytic anemia, hypotension and DIC.

* Second form seen with quinine. 24-96 hours after ingesting present with DIC, anemia, and renal failure. Can also have immune neutropenia. Therapy is uncertain and process has high mortality - consider plasma exchange

**Disseminated Intravascular Coagulation**
DIC is the clinical manifestation of inappropriate thrombin activation
Patients with DIC can present in one of four ways:
1) Asymptomatic
2) Bleeding
3) Thrombosis
4) Purpura fulminans

Tests - routine coag tests may be normal. D-dimer has the highest predictive value for DIC. Low fibrinogen most specific

**Therapy**
* Treat primary cause
* Replace coagulation factors guided by the 5 basic tests
* Heparin only if patient having thrombosis - will need to use heparin levels to guide therapy

**Purpura Fulminans** is DIC association with symmetrical limb ecchymosis and necrosis of the skin.
1) Primary purpura fulminans
   * Often after viral infections
   * Often with acquire protein S antibodies
   * Therapy is with plasma to keep protein S > 25%, heparin, and IVIG
2) Secondary purpura fulminans
   * Overwhelming infections esp meningococcemia
   * Therapy: transfusion therapy guided by 5 basic tests.

**Thrombotic Thrombocytopenic Purpura**
TTP should be suspected when any patient presents with any combination of renal insufficiency, thrombocytopenia, and end organ damage.

There is currently no rapid diagnostic test for TTP - diagnosis is based on the clinical presentation. TTP should be consider in any patients who presents with multi-system illness and thrombocytopenia.

* Microangiopathic hemolytic anemia - schistocytes on the blood smear
* Thrombocytopenia - usually 20-60,000/ul range
* Renal insufficiency - often mild, frank renal failure rare. UA usually abnormal with red cells and proteinuria
* Fevers - seen in less than half of TTP
* Mental status changes - can range from confusion to coma. Seizures can also be seen.
* Pulmonary - patients can infiltrates and hypoxia
* Cardiac - coronary microthrombi common - can lead to ischemia and dysrhythmias
* GI - pancreatitis is a common complication.

One helpful clue is the presence of a raised LDH. LDH levels are often over 2 times normal in TTP and on fractionation is from all isoenzymes representing widespread tissue damage

Although inhibitors to ADAMTS13 are responsible for many if not most cases of TTP, rapid assays are not widely available so the diagnosis remains clinical. Activity < 10% specific but not sensitive for TTP. Levels above 10% can be seen in any ill patient.

**Therapy:**
Untreated TTP is rapidly fatal. Mortality in the pre-plasma exchange era ranged from 95-100%.
Today plasma exchange therapy is the cornerstone of TTP treatment and has reduced mortality to less than 30%.

** Plasma exchange (1.5 plasma volumes) is essential and has been shown to be superior to simple plasma infusion. Patients should get 5 days of therapy and then exchange is tapered based on LDH and platelet counts. If there is delay in plasma exchange plasma (units/4-6 hours) should be given.

* Glucocorticosteroid therapy, equivalent to 60-120 mg of prednisone is often used.
* Platelet transfusions are contraindicated in most patients with TTP and in most patients there is little justification for platelet transfusion.

* For patients not responding rapidly to therapy vincristine 1 mg/meter squared days 1, 4, 7, 10 can be tried.  
* For patients with anti-ADAMTS13 antibodies rituximab 375mg/m2 weekly x 4 should be started to reduce relapses and speed resolution  
* Caplacizumab may be indicted in severe or refractory cases: 11mg IV before plasmaexchange then 11mg sub-q daily for at least 30 days after last exchange and if ADAMTS13 is > 10% - if not then therapy needs to be extended until > 10%

Three patterns for ADAMTS13 will be found:  
* Very low levels (<10%), positive inhibitor: classic TTP, autoimmune; consider adding rituximab  
* Very low levels (<10%), no inhibitor: congenital TTP, will need long term plasma infusions to prevent relapses – can get genetic testing to confirm  
* Not low levels (>10%), positive inhibitor: can be TTP, consider other diagnosis or atypical HUS

** Hemolytic Uremic Syndrome**  
Consider: rapid onset renal insufficiency with thrombocytopenia, high LDH, and hypertension. If there is severe renal disease smear may not show schistocytes

Typical: post infection (Shiga toxin producing e coli) – preceded by bloody diarrhea, no role for plasmaexchange

Atypical HUS  
Primary: presents like HUS but no infection or other provoking factors  
Secondary: drugs: gemcitabine, tyrosine kinase inhibitors, VEGF inhibitors; stem cell and solid organ transplant  
Therapy: Eculizumab 900mg IV weekly then 1200mg every other week. Hematological response is rapid but can take months to see renal response especial if severe renal disease/failure is present. Duration is controversial – can stop once drug induced resolves but in other situation unclear when to stop

**Hemophagocytic syndrome**  
Multisystem disease with fevers, organomegaly, and cytopenias. Can be primary or complication infections and hematological malignancies

Diagnosis:  HLH-94 criteria need 5/8 criteria  
• Fevers  
• Splenomegaly  
• Cytopenia  
  • Hgb < 9.0  
  • Platelets < 100  
  • ANC < 1  
• Hypertriglycerideremia or hypofibrinogenemia  
  • Fasting triglycerides > 265  
  • Fibrinogen < 150  
• Ferritin > 500 (3000)
• sCD25 > 2400
• Decrease NK cell activity
• Hemophagocytosis on biopsy

Therapy: HLH-94 with dexamethasone/etoposide still standard, for EBV related add rituximab.

**Heparin Induced Thrombocytopenia (HIT)**

**Natural History:** Occurs at least 4 days after starting heparin in any form. Thrombocytopenia is modest - 60,000/ul is average - rare for counts to be under 20,000/ul. 20-50% of patients will have thrombosis. Can occur rapidly if patient has had heparin in past 100 days. Some patients can present with HIT up to 2 weeks after heparin exposure.

**Pathogenesis:** Formation of antibodies directed against the complex of heparin that bind to platelet factor 4 (PF4)
Frequency of HIT: Standard heparin 1-5% (bovine > porcine), LMWH <1%.

**Diagnosis:** Suspect if any of these occur:
* Platelet counts drops by 50% - most sensitive
* Platelet counts fall under 100,000/ul
* New thrombosis on heparin

**Laboratory testing:**
* Platelet activation assays - sensitive and specific but technically difficult and not always available
* Anti-PF4 ELISA - Very sensitive but not specific especially in cardiac surgery patients
Testing most useful for patients with multiple causes for their thrombocytopenia and low to moderate pretest probability for HIT

**Therapy**
The first step in therapy of HIT consists of stopping all heparin. Given high rate of thrombosis all patients with HIT should receive antithrombotic therapy. LMWH CANNOT be used due to cross-reactivity. Of agents available best choice for ICU patients is argatroban.

**Argatroban:** Direct thrombin inhibitor. Hepatically cleared. Dose at 2 ug/kg/min infusion with dose adjustments to keep aPTT 1.5 - 3 times normal. No dose adjustment for renal disease but for severe liver disease dose is 0.5 ug/kg/min. Also for patients with MOSF use 1ug/kg/min. Will also raise INR to 2-4.

**Other agents:**
Fondaparinux: Appears not to react with HIT antibodies. Long half-life and renal clearance makes ICU difficult - useful later in course
Direct oral anticoagulants – Increasing use in HIT but most expert prefer to start with argatroban in severe cases
Bivalirudin: Limited data - most useful in HIT patients needing cardiac procedures

**Suggested HIT Protocol**

<table>
<thead>
<tr>
<th>Points</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>&gt;50% fall or nadir 20-100,000/ul</td>
<td>30-50% fall or nadir 10-19,000/ul</td>
<td>Fall &lt; 30% or nadir &lt;10,000/ul</td>
</tr>
<tr>
<td>Timing of platelet fall</td>
<td>Onset day 5-10 of heparin or &lt; 1 day if patient recently exposed</td>
<td>Consistent but not clear records or count falls after day</td>
<td>Platelets falls &lt; 5 days and no recent (100)</td>
</tr>
</tbody>
</table>
Thrombosis

<table>
<thead>
<tr>
<th></th>
<th>to heparin</th>
<th>10 days) heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>New thrombosis or skin necrosis or systemic reaction with heparin</td>
<td>Progressive or recurrent thrombosis or suspected but not proven thrombosis</td>
</tr>
<tr>
<td>oTher cause for thrombocytopenia</td>
<td>No</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Pretest Score 6-8=high, 4-5 intermediate, 0-3 low

Warkentin, Heddle Current Hematology Reports 2:148 2003

If HIT score is >6 or
Patient has documented new thrombosis on heparin or
Platelets fall by over 50% for no other reason than heparin exposure
Then stop heparin and substitute argatroban

If HIT score is 4-5 than obtain HIT test. If test positive then stop heparin and substitute argatroban
If HIT score is 0-3 no need to obtain HIT test

Thrombocytopenia and Pregnancy

Three syndromes in the critically ill pregnant woman who presents with coagulation defects.

1) HELLP (Hemolysis, Elevated Liver tests, Low Platelets)
   * Variant of pre-eclampsia
   * High LDH, schistocytes, DIC
   * Responds to delivery of child
   * Severe cases may require plasma exchange

2) Fatty liver of pregnancy
   * Severe coagulation defects and liver failure
   * Responds to delivery of child

3) TTP
   * Occurs most often in 2nd trimester
   * Can support mother through pregnancy with plasma exchange

Pregnancy Related Diseases -TTP/HUS, HELLP Syndrome, and Acute Fatty Liver of Pregnancy (FLP)

<table>
<thead>
<tr>
<th></th>
<th>HELLP</th>
<th>TTP/HUS</th>
<th>AFLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Always present</td>
<td>Sometimes present</td>
<td>Sometimes present</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Always present</td>
<td>Sometimes present</td>
<td>Sometimes present</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Always</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>LDH Elevation</td>
<td>Present</td>
<td>Marked</td>
<td>Present</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Normal to Low</td>
<td>Normal</td>
<td>Normal to Very Low</td>
</tr>
<tr>
<td>Schistocytes</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Liver Tests</td>
<td>Elevated</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Glucose</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
</tr>
</tbody>
</table>

HELLP = Hemolysis, Elevated Liver tests, and Low Platelets
TTP/HUS = Thrombotic Thrombocytopenic Purpura/Hemolytic Uremia Syndrome
AFLP = Acute Fatty Liver of Pregnancy

Very Quick Guide to Reversing Antithrombotic Therapy
<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-life</th>
<th>Renal Disease</th>
<th>Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>15-30 minutes</td>
<td>No change</td>
<td>DDAVP, Platelet Transfusions (?)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>8 hours</td>
<td>Metabolites renally cleared</td>
<td>DDAVP(?), 2 units of platelet transfusions</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>7 hours</td>
<td>Metabolites renally cleared</td>
<td>DDAVP(?), 2 units of platelet transfusions</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>7 hours</td>
<td>No change</td>
<td>DDAVP(?), 2 units of platelet transfusions (may be ineffective)</td>
</tr>
<tr>
<td>Abciximab</td>
<td>30 minutes</td>
<td>No change</td>
<td>Platelet Transfusion</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>2 hours</td>
<td>Decrease dose by 50% if ClCr &lt; 30 ml/min</td>
<td>Platelet transfusions, DDAVP, cryoprecipitate, dialysis</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>2-3 hours</td>
<td>Decrease dose by 50% if ClCr &lt; 30 ml/min</td>
<td>Platelet transfusions, DDAVP, cryoprecipitate, dialysis</td>
</tr>
<tr>
<td>Unfractionated Heparin</td>
<td>30-150 minutes</td>
<td>45-225</td>
<td>Protamine - see table</td>
</tr>
<tr>
<td>Low Molecular Weight Heparin</td>
<td>2-8 hours</td>
<td>4-16 hours</td>
<td>Protamine - see table</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>17-21 hours</td>
<td>Clearance decreased by 50% if ClCr &lt; 30 ml/min</td>
<td>PCC 50 units/kg</td>
</tr>
<tr>
<td>Argatroban</td>
<td>40 minutes</td>
<td>No change</td>
<td>PCC 50 units/kg</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>25 minutes</td>
<td>60% dose reduction if ClCr &lt; 30 ml/min</td>
<td>PCC 50 units/kg</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>12-14 hours</td>
<td>Avoid if ClCr &lt; 30 ml/min</td>
<td>Idarucizumab 5grams</td>
</tr>
<tr>
<td>Apixaban</td>
<td>12-14 hours</td>
<td>Can be used in dialysis patients</td>
<td>PCC 50 units/kg or Andexanet</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>19-27 hours</td>
<td>50% reduction if CrCl 15-30 ml/min, Avoid if ClCr &lt; 15 ml/min</td>
<td>PCC 50 units/kg</td>
</tr>
<tr>
<td>Drug</td>
<td>Elimination Time</td>
<td>Elimination Mechanism</td>
<td>Reversal Options</td>
</tr>
<tr>
<td>------------</td>
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<td>-----------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>10-14 hours</td>
<td>50% reduction if CrCl 30-60 ml/min, Avoid if ClCr &lt; 30 ml/min</td>
<td>PCC 50 units/kg</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>4-9 hours</td>
<td>Avoid if ClCr &lt; 15 ml/min</td>
<td>PCC 50 units/kg or Andexanet</td>
</tr>
<tr>
<td>Warfarin</td>
<td>36 hours</td>
<td>50% reduction in CYP C2P9</td>
<td>vitamin K, FFP, PCC, rVIIa - see table</td>
</tr>
<tr>
<td>Streptokinase</td>
<td></td>
<td>Hepatically cleared</td>
<td>Plasma, platelet, cryoprecipitate</td>
</tr>
<tr>
<td>tPA</td>
<td>3 minutes</td>
<td>Hepatically cleared</td>
<td>Plasma, platelet, cryoprecipitate</td>
</tr>
<tr>
<td>Reteplase</td>
<td>13-16 minutes</td>
<td>Hepatically cleared</td>
<td>Plasma, platelet, cryoprecipitate</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>15-20 minutes</td>
<td>Hepatically cleared</td>
<td>Plasma, platelet, cryoprecipitate</td>
</tr>
</tbody>
</table>

PCC = prothrombin complex concentrates, FFP = Fresh Frozen Plasma

Standard Heparin Reversal: Protamine:

<table>
<thead>
<tr>
<th>Time since last heparin dose</th>
<th>Dose of Protamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 minutes</td>
<td>1 unit/100 units of heparin</td>
</tr>
<tr>
<td>30-60 minutes</td>
<td>0.5 - 0.75 units/100 units of heparin</td>
</tr>
<tr>
<td>60-120 minutes</td>
<td>0.375 - 0.5 units/100 units of heparin</td>
</tr>
<tr>
<td>&gt; 120 minutes</td>
<td>0.25 - 0.375 units/100 units of heparin</td>
</tr>
</tbody>
</table>

Infusion rate should not exceed 5 mg/min. Maximum dose is 50 mg

Low Molecular Weight Heparin
Reversal of Bleeding: Protamine (works just as well with LMWH as heparin) - it with-in 4 hours of dose 1mg of protamine for each 1mg of enoxaparin or 100 units of dalteparin and tinzaparin. Should repeat one-half dose in 4 hours. If 4-8 hours after dose give 0.5 mg for each 1 mg of enoxaparin or 100 units of dalteparin and tinzaparin.

Therapy of the Bleeding Patient on Warfarin
Key point about vitamin K
● sub-Q erratic and should NOT be used
● PO effective in most patients
● IV should be given slowly (over one hour)
● A little goes a long way - the RDA is 80 ug/day

Not Bleeding: Goal is INR in 2-3 range
<table>
<thead>
<tr>
<th>INR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-3.45</td>
<td>Hold dose until INR decreased</td>
</tr>
<tr>
<td>4.5-10</td>
<td>1.25 mg Vitamin K PO</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>2.5 -5 mg Vitamin K PO</td>
</tr>
</tbody>
</table>

Should see INR back in therapeutic range in 24-48 hours

**Bleeding: Goal is INR under 2**

<table>
<thead>
<tr>
<th>INR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4.5</td>
<td>2.5 mg Vitamin K ± FFP (15ml/kg)</td>
</tr>
<tr>
<td>4.5-10</td>
<td>5 mg Vitamin K ± FFP (15ml/kg)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>5-10 mg Vitamin K ± FFP (15ml/kg)</td>
</tr>
</tbody>
</table>

Consider Intravenous route for Vitamin K if faster effect desired

Use Prothrombin Complex Concentrates for life-threatening bleeding such as intracranial hemorrhage - dosing:
- If INR 2-4: 25 units/kg (not to exceed 2500 units)
- If INR 4-6: 35 units/kg (not to exceed 3500 units)
- If INR > 6: 50 units/kg (not to exceed 5000 units)