ANTICOAGULATION REVERSAL IN THE HEMORRHAGING PATIENT
WE 302496
58 year old male
PMH: HTN, squamous cell carcinoma, Afib on Coumadin, gout
PSH: LRRT ’88
Medications: Prednisone, Cyclosporine, Lasix, Atenolol, Minoxidil, Nexium, Coumadin 6 qHS
NKDA
1/27 PM
CC: worsening SOB x 1 week; subjective fever x 1 day
Also with complaints of right flank pain of acute onset but denied any recent trauma
Vital signs: T 99.8  BP 155/82  HR 65
Physical exam: tenderness to palpation of the right flank; no external findings
Labs: INR of 2.6; WBC 6.7, Hct 35.3; Cr 1.48
Admitted to transplant service
- HOD#1
- Labs: INR 3.2; Coumadin order was suspended
- He received another dose of Coumadin both that night and the following morning
- CT C/A/P obtained
HOD#2
- Small area of ecchymosis overlying the area of reported right flank pain
- Serial Hct 32.8 → 31.5 → 28.7 and INR was 4.9.
- 2 FFP and Vitamin K x 1 dose given
- Repeat INR 3.4; another FFP was given
HOD#3
Area of ecchymosis had expanded with accompanied worsening right flank pain

Labs: INR 3 and Hct 27.6

2 u FFP given in preparation for the OR

OR: Evacuation of approximately 700 cc retroperitoneal hematoma

Post-op Hct 23.6; 2 u FFP, 1u pRBC given
- HOD#4
  - Labs: Hct 21.6
  - 2 u pRBC given with post-transfusion Hct 26.3

- HOD#5
  - CT C/A/P obtained
- **HOD#6**
  - Hct 21.9 and 2 units PRBC were transfused with response to 25.3

- **HOD#7**
  - Hct 25.6; hemodynamically stable
  - **OR:** Evacuation of approximately 800 cc hematoma with washout and packing with plan for return next day

- **HOD #8**
  - Re-exploration with hemostasis
  - Post-op Hct stable
  - Daily physical therapy
  - Discharged home HOD#11
OVERVIEW

- Coagulation cascade
- Indications for use
- Agents of reversal
- Treatment/Guidelines for reversal
- The decision to continue anticoagulation
COAGULATION CASCADE

TF/FVIIa

Then a miracle occurs

Hemostasis

"I think you should be more explicit here in step two."

S. Harris
The diagram illustrates the coagulation cascade, showing the intrinsic and extrinsic pathways converging at the common pathway. Antithrombin III, an inhibitor of thrombin, is shown at the end of the cascade, preventing the formation of fibrin clot.
INDICATIONS FOR USE

- DVT prophylaxis
- DVT/PE
- CVA prophylaxis
- Afib
- NSTEMI
- STEMI
### AVAILABLE REVERSAL AGENTS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>$10</td>
</tr>
<tr>
<td>Protamine Sulfate</td>
<td>$147</td>
</tr>
<tr>
<td>Fresh Frozen Plasma (FFP)</td>
<td>$178</td>
</tr>
<tr>
<td>Prothrombin complex concentrate (PCC)</td>
<td>$1645</td>
</tr>
<tr>
<td>Recombinant Factor VIIa (rFVIIa)</td>
<td>$4500</td>
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</table>
30 million prescriptions in the US annually

Estimated 3-7% per year of patients on Coumadin require rapid reversal for major bleeding, need for urgent surgery, other invasive procedures

50-60% of patients are within therapeutic range

Risk of major hemorrhage 1%

FFP most widely used antidote for VKA reversal
- **Vitamin K reductase inhibitor (VKA)**
  - Inhibits II, VII, IX, X, protein C, S
- **Indication:**
  - DVT/PE (INR 2.5)
  - Non-valvular Afib (INR 2.5)
  - Mechanical and Bioprosthetic heart valves (INR 3.0)
- **Clearance:** Hepatic
- **Reversal:** ??
VITAMIN K AND INR 6-10
VITAMIN K AND INR >10
# FFP VS. PCC

## PRO

<table>
<thead>
<tr>
<th>Fresh frozen Plasma</th>
<th>Prothrombin complex concentrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability</td>
<td>Not blood-type specific</td>
</tr>
<tr>
<td>Less cost</td>
<td>High clotting factor concentration</td>
</tr>
<tr>
<td></td>
<td>Faster reversal</td>
</tr>
<tr>
<td></td>
<td>Small volume</td>
</tr>
</tbody>
</table>

## CON

<table>
<thead>
<tr>
<th>Fresh frozen Plasma</th>
<th>Prothrombin complex concentrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thawing time</td>
<td>Safety profile unclear</td>
</tr>
<tr>
<td>Transmission infectious agents</td>
<td>High cost</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td></td>
</tr>
<tr>
<td>Fluid overload</td>
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</table>
INR VS. % COAGULATION FACTORS

Fig. 4. General relationship between the INR test or PT and the percentage of clotting factors in blood. The dotted line at 30% factors is a general threshold for adequate hemostasis. The hatched horizontal bar represents INR values that correspond to the zone of adequate factor levels. The dark horizontal bar represents INR values of anticoagulation. Arrows depict the effect of 1 to 2 units of FFP.
27 studies (1992-2010)
- PCC used for rapid reversal due to major bleeding, need for surgery, invasive procedure
- Number of thromboembolic events recorded

Results:
- 1.4% of patients had thromboembolic complications
- 1.9% incidence in major bleeding vs 0.8% in those treated before urgent surgery or invasive procedure
- 1.8% 4-factor PCC vs 0.7% 3-factor PCC
Availability of PCC our institutions

- Kings County Hospital
- Downstate
- Richmond University Medical Center
- Brooklyn VA
<table>
<thead>
<tr>
<th>INR</th>
<th>CLINICAL SCENARIO</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.5</td>
<td>No bleeding</td>
<td>• Hold warfarin until INR in therapeutic range</td>
</tr>
<tr>
<td></td>
<td>Rapid reversal required</td>
<td>• Hold warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider vitamin K 2.5mg oral</td>
</tr>
<tr>
<td>4.5-10</td>
<td>No bleeding</td>
<td>• Hold warfarin until INR in therapeutic range</td>
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<td>Rapid reversal required</td>
<td>• Hold warfarin</td>
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<tr>
<td></td>
<td></td>
<td>• Give vitamin K 2.5mg oral or 1mg IV infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(IV administration of vitamin K has faster onset of action)</em></td>
</tr>
<tr>
<td>&gt;10</td>
<td>No bleeding</td>
<td>• Hold warfarin until INR in therapeutic range</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give vitamin K 2.5mg oral or 1-2mg IV infusion over 30 minutes,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and repeat q24h as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(IV administration of vitamin K has faster onset of action)</em></td>
</tr>
<tr>
<td></td>
<td>Rapid reversal required</td>
<td>• Hold warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give vitamin K 1-2mg IV infusion over 30 minutes, and repeat q6-24h as needed</td>
</tr>
</tbody>
</table>
# Bleeding on Coumadin

## Any INR
- Serious or life-threatening bleeding

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Hold warfarin</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Give vitamin K 10mg IV infusion over 30 minutes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Give 4 units FFP/plasma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>OR consider 4-factor PCC (Kcentra)</strong></td>
<td>(preferred for life-threatening bleeding)</td>
</tr>
</tbody>
</table>
  - *INR 1.5 – 3.9*: 25 units/kg (maximum 2500 units) |
  - *INR 4.0 – 6.0*: 35 units/kg (maximum 3500 units) |
  - *INR > 6.0*: 50 units/kg (maximum 5000 units) |
- Binds antithrombin III
- Half-life: 30-90 minutes
- Clearance: Hepatic
- Reversal: Protamine (100% neutralization)

<table>
<thead>
<tr>
<th>Time since last dose of heparin</th>
<th>Dose of protamine for each 100 units of heparin administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>1mg (or 25mg fixed dose)</td>
</tr>
<tr>
<td>30 minutes – 2 hrs</td>
<td>0.5mg (or 10mg fixed dose)</td>
</tr>
<tr>
<td>&gt;2 hrs</td>
<td>0.25mg (or 10mg fixed dose)</td>
</tr>
</tbody>
</table>

- Degree of reversal assessment: PTT, antifactor Xa activity
ENOXAPARIN (Lovenox)

- Factor Xa > IIa inhibitor
- Indications:
  - DVT prophylaxis (30 or 40 mg SC daily)
  - DVT/PE (1.5 mg/kg SC daily, or 1mg/kg SC q12H)
  - NSTEMI (30mg IV bolus + 1mg/kg SC + 1mg/kg SC q12H)
- Clearance: Renal (decrease if CrCl <30)
- Reversal: Protamine (60% neutralization)
  - Response to dialysis: 20%
- Monitoring: Anti-Xa activity

<table>
<thead>
<tr>
<th>Time since last dose of LMWH</th>
<th>Dose of protamine for each 100 units of dalteparin or 1mg of enoxaparin administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8 hrs</td>
<td>1mg (or 50mg fixed dose)</td>
</tr>
<tr>
<td>8-12 hrs</td>
<td>0.5mg (or 25mg fixed dose)</td>
</tr>
<tr>
<td>&gt; 12 hrs</td>
<td>Not likely to be useful (or 25mg fixed dose)</td>
</tr>
</tbody>
</table>
Indirect Factor Xa inhibitor (SubQ)

**Indications:**
- DVT prophylaxis in orthopedic surgery (2.5mg subQ daily)
- DVT/PE (7.5mg subQ daily)

**Clearance:** renal (contraindicated if CrCl <30)

**Monitoring:** anti-Xa activity

**Reversal:** no specific antidote
- Level reduced by 20% via dialysis
- Consider giving PCC
- **Direct thrombin inhibitor (PO)**
- **Indications:**
  - Prevention of DVT/PE after orthopedic surgery
  - Prevention of stroke in patients with non-valvular Afib (150 mg BID)
- **Reversal:** no specific antidote
  - Activated charcoal if ingestion <2 hours prior
  - HD for 60% clearance 2-3 hours
  - Neutralizing monoclonal antibody (in development)
- **Monitoring:** Thrombin test (TCT)
- **Periop management:** stop 24-48 hours prior; restart same evening 6 hrs postop
Direct thrombin inhibitor (IV)

Indications: Prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia

Clearance: Hepatic

Monitor: PTT (1.5-2.5x baseline)

Reversal: no specific antidote

- 20% plasma concentration can be cleared via dialysis
A new risk scheme to predict Warfarin-associated hemorrhage

- Population: 9,186 patients with Afib
- 461 hemorrhage events (median 3.5 years)
- 5-variable risk score
Urgent Coumadin reversal issues are complex
Recommendation to give PCC-4 and Vitamin K; if not then give FFP
Large volumes quickly, risk of overload
3 and 4-component PCC are prothrombotic, use with caution in elderly, vasculopathes
New oral anticoagulant alternatives have limited use as reversal of agents is difficult
REFERENCES


- Should Patient Characteristics Influence Target Anticoagulation Intensity for Stroke Prevention in Nonvalvular Atrial Fibrillation? The ATRIA Study; Daniel E. Singer; Circulation: Cardiovascular Quality and Outcomes. 2009; 2: 297-304 Published online before print June 9, 2009.


- Update on Antithrombotic Therapy: New Anticoagulants; John W. Eikelboom, MBBS; Circulation. 2010; 121: 1523-1532.


- Lubetsky et al; Comparison of Oral vs IV Vitamin K in Patients with Excessive Anticoagulation; Arch Intern Med 2003;163:2469-2473.