REVERSAL OF ANTICOAGULANT-INDUCED HEMORRHAGE

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No Conflicts of Interest to Disclose
Objectives

1. Describe treatment options for emergent anticoagulant reversal.

2. Appropriately select patients for factor product administration.

3. Navigate the anticoagulant/antiplatelet reversal orderset at Sanford-Fargo.
Approvals - Collaboration

Trauma/
Acute Care Surgery

Pharmacy

Hematology
Abbreviations

- PCC = Prothrombin Complex Concentrate
- FFP = Fresh Frozen Plasma
- 3F-PCC = 3-Factor Prothrombin Complex Concentrate
- 4F-PCC = 4-Factor Prothrombin Complex Concentrate
- FVIIa = Activated factor seven
- VKA = Vitamin K Antagonist (warfarin)
- FIX = Factor IX (nine)
Anticoagulant Reversal - Warfarin

1. Vitamin K
2. FFP
3. 3-Factor PCC (Profilnine)
4. 4-Factor PCC (Kcentra)
5. Activated Factor VII (NovoSeven)
6. Activated 4-Factor PCC (FEIBA)
Anticoagulant Reversal

Rebound

INR

Time

Vit K IV

FFP

rFVIIa

PCC

PCC or rFVIIa + Vit K

Vit K PO

INR limitations

- Measure of coagulability
- Coagulability $\neq$ Hemostasis
- Highly sensitive to factor VII
- FFP and INR relationship

What’s in it? PCCs versus FFP

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Factor IX</th>
<th>Factor II</th>
<th>Factor VII</th>
<th>Factor X</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bebulin VH</td>
<td>100</td>
<td>120</td>
<td>(13)</td>
<td>100</td>
<td>Heparin</td>
</tr>
<tr>
<td>Profilnine SD</td>
<td>100</td>
<td>148</td>
<td>(11)</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td>Kcentra</td>
<td>100</td>
<td>128</td>
<td>68</td>
<td>152</td>
<td>Heparin, Protein C + S, Albumin</td>
</tr>
<tr>
<td>FFP</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>Large volume (1 IU/ml) Protein C + S, Antithrombin</td>
</tr>
</tbody>
</table>

International Units of all factors relative to Factor IX

Adapted from Sorensen et al. Critical Care, 2011.
## Anticoagulant Reversal

<table>
<thead>
<tr>
<th>FFP Advantages</th>
<th>FFP Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inexpensive</td>
<td>• Volume overload</td>
</tr>
<tr>
<td>• Decrease thrombotic complications</td>
<td>• Transfusion-related lung injury</td>
</tr>
<tr>
<td></td>
<td>• Delayed time to administration</td>
</tr>
<tr>
<td></td>
<td>• Variable amounts of factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCC Advantages</th>
<th>PCC Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No thawing necessary</td>
<td>• Venous thromboembolism</td>
</tr>
<tr>
<td>• No blood-typing necessary</td>
<td>• Myocardial infarction</td>
</tr>
<tr>
<td>• Reduced volume</td>
<td>• Disseminated intravascular coagulation (DIC)</td>
</tr>
</tbody>
</table>

Pandey et al. Transfusion. 2012.
3F-PCC vs 4F-PCC

- No comparative trials.

- CHEST 2012 = “...we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma”
  - Grade IIC recommendation
Systematic Review:

- **4F-PCC **MORE effective than 3F-PCC in decreasing INR to \( \leq 1.5 \) within 60 minutes of administration
- **VARIABLE** efficacy with increasing baseline INRs
- INR-based dosing more effective than fixed dosing

Voils *et al.* Thromb Res 2012
3F-PCC vs 4F-PCC

- Systematic Review Limitations:
  - Heterogeneity of trials
  - No trials after 2012 included
  - No direct 3F-PCC and 4F-PCC comparisons

Kcentra

- Only 4-factor PCC available in USA
- Only PCC with FDA-approved indication for VKA reversal
Summary:
- PCC is at least as effective as FFP in INR reversal.
- PCC has an acceptable safety profile compared to FFP.
- INR-based dosing of PCCs more reliably decreases INR to $\leq 1.5$ within one hour of administration.
- 4F-PCC more effectively decreases INR to $\leq 1.5$ within one hour of administration than 3F-PCC.
# Evidence: 3 Factor PCC

## Emergency Anticoagulation Reversal with 3F-PCC

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, prospective cohort trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>46 patients with acute symptomatic intracranial hemorrhage and INR&gt;= 2.</td>
</tr>
</tbody>
</table>
| Intervention      | • 10 mg Vitamin K IV -AND-  
• 3F-PCC dose relative to baseline INR |
| Endpoints         | 1°) INR values <= 1.5 30 minutes after PCC infusion  
2°) INR values <= 1.5 at 6, 24, 48, 72, and 96 hours after PCC infusion |
| Results           | • 34/46 (75%) patients had INR <= 1.5 at 30 minutes  
• Median INR remained <= 1.5 in 96% of all time points post-infusion  
• 0 early and 2 late thrombotic events occurred. |
| Summary           | 3F-PCC is a safe and effective treatment for urgent anticoagulant reversal in the setting of major bleeding. |

Evidence: 4 Factor PCC

<table>
<thead>
<tr>
<th>4F-PCC for VKA Patients with Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results</strong></td>
</tr>
<tr>
<td>Hemostasis</td>
</tr>
<tr>
<td>• Achieved in 68/98 (65.4%) patients</td>
</tr>
<tr>
<td>FFP</td>
</tr>
<tr>
<td>• Achieved in 71/104 (72.4%) patients</td>
</tr>
<tr>
<td>INR Correction</td>
</tr>
<tr>
<td>• Achieved in 61/98 (62.2%) patients</td>
</tr>
<tr>
<td>• 95% CI = 52.6 to 71.8</td>
</tr>
<tr>
<td>• Achieved in 10/104 (9.6%) patients</td>
</tr>
<tr>
<td>• 95% CI = 3.9 to 15.3</td>
</tr>
<tr>
<td>Safety</td>
</tr>
<tr>
<td>• Related: 10 (9.7%)</td>
</tr>
<tr>
<td>• Serious Related: 2 (1.9%)</td>
</tr>
<tr>
<td>FFP</td>
</tr>
<tr>
<td>• Related: 23 (21.1%)</td>
</tr>
<tr>
<td>• Serious Related: 4 (3.7%)</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
</tr>
<tr>
<td>4F-PCC is noninferior to FFP for providing hemostasis in VKA-related bleeding. 4F-PCC provides greater INR reversal at 30 minutes than FFP.</td>
</tr>
</tbody>
</table>

Orderset

- Restricted ordering
  - Trauma, neurosurgery, intensive care, anesthesiology, and hematology
  - Orderset-only unless by hematologist

Order Sets

- SMF ED EMERGENT ANTICOAGULANT/ANTIPLATELET REVERSAL IN SEVERE HEMORRHAGE
  These orders are to be used in patients with acute, refractory and massive bleeding or emergent invasive surgery.

  If all reversible factors have been addressed then the use of PCC may be indicated. Notify pharmacy STAT when PCC use is being considered.

  ORDER OF PCC RESTRICTED TO; ACUTE TRAUMA SERVICES, NEUROSURGERY, INTENSIVE CARE MEDICINE, ANESTHESIOLOGY AND HEMATOLOGY.
Profilnine / Kcentra Guideline

- Strict Inclusion Criteria (must meet all 3):
  - Patient on warfarin, dabigatran, or Xa inhibitor
  - Life-threatening hemorrhage and/or requires emergent surgery
    - CNS bleed or requiring surgery within 2 hours to sustain life
  - If on warfarin, elevated INR (>2)

- Relative Contraindications to PCC use:
  1. Known thrombotic tendency.
  2. Mechanical prosthetic heart valve in situ.
  3. Recent coronary angioplasty and/or stent insertion.
  4. History of recent thrombotic event (e.g. MI, PE, Embolic CVA)
  5. Evidence of DIC or systemic sepsis.
  6. Severe peripheral vascular disease.
Orderset

“ED EMERGENT ANTICOAGULANT/ANTIPLATELET REVERSAL IN SEVERE HEMORRHAGE”
Orderset

- Select agent being reversed

**Medications**

- **Emergent Anticoagulant/Antiplatelet Reversal In Severe Hemorrhage**
  - warfarin (COUMADIN) reversal
  - Second PCC dose
    - 25 Units/kg (Ideal), IV, One time prn, other (Specify), If 20 minutes after initial dose the INR is greater than 1.5
  - Direct Thrombin Inhibitors/Factor Xa Inhibitors Reversal
  - aspirin reversal
    - STAT, Now, 1 unit of single donor platelets
  - ADP Inhibitor reversal - clopidogrel (PLAVIX), prasugrel (EFFIENT), ticagrelor (BRILINTA) and ticloidine (TICLID)
Orderset

- Inclusion criteria = hard stops
Anticoagulant Reversal - Warfarin

- Preselected recommendations:
  - 10 mg Vitamin K IV
  - 3F-PCC 25 units/kg IBW IV for INR <4
    - 50 units/kg IBW IV for INR >4
  - 2 Units FFP IV

- Second 3F-PCC dose 25 units/kg
  - If INR >1.5 20 minutes after 1st dose
Orderset

- Products automatically selected

- phytonadione (Vitamin K, AQUAMEPHYTON) 10 mg in dextrose 5% 50 mL
  - 10 mg, IV, Now, 1 dose Today at 1715, 50 mL

- factor IX complex (PROFILNINE SD) IV solution 1,253 Units
  - 25 Units/kg x 50.1 kg (ideal weight) = 1,253 Units, IV, One time, 1 dose Today at 1815, 0 mL

- TRANSFUSE FRESH FROZEN PLASMA
  - Routine, ONCE First occurrence Today at 1715
  - Indication for transfusion: Other (specify in comments)
  - Product required: FFP
  - Amount to transfuse: Other (specify in comments)
Flow of duties

1. Verify information from the orderset (Inclusion criteria, relative exclusions)
2. Calculate dose
   - 25 – 50 units/kg factor IX per INR
   - Consider IDEAL BODY WEIGHT
   - Max dose of 5000 units
3. Find array of vials that “fit” the dose
   - Sanford policy allows rounding to nearest vial as long as the dose is within 10% of prescribed dose
4. Reconstitute per package insert
   - Infuse at 2ml/min
**Novel anticoagulants**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Emergent Anticoagulant/Antiplatelet Reversal In Severe Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>warfarin (COUMADIN) reversal</td>
</tr>
<tr>
<td></td>
<td>Second PCC dose</td>
</tr>
<tr>
<td></td>
<td>Direct Thrombin Inhibitors/Factor Xa Inhibitors Reversal</td>
</tr>
<tr>
<td></td>
<td>aspirin reversal</td>
</tr>
<tr>
<td></td>
<td>ADP Inhibitor reversal - clopidogrel (PLAVIX), prasugrel (EFFIENT), ticagrelor (BRILINTA) and ticloidine (TICLID)</td>
</tr>
</tbody>
</table>

DEFAULTS KCENTRA 50 units/kg actual body weight
## Approximate Cost

<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>Profilnine</th>
<th>Kcentra</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost / Unit FIX</strong></td>
<td>N/A</td>
<td>$1 per unit</td>
<td>1.25 per unit</td>
</tr>
<tr>
<td><strong>Cost / Avg. Dose</strong></td>
<td>$150 (2 units FFP)</td>
<td>$3,200 (50 IU FIX/kg)</td>
<td>$4,500 (50 IU FIX/kg)</td>
</tr>
</tbody>
</table>
What if the request for Profilnine or Kcentra falls outside of recommendations?

Hematologist Consult
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