REVERSAL OF ANTICOAGULANT-INDUCED HEMORRHAGE

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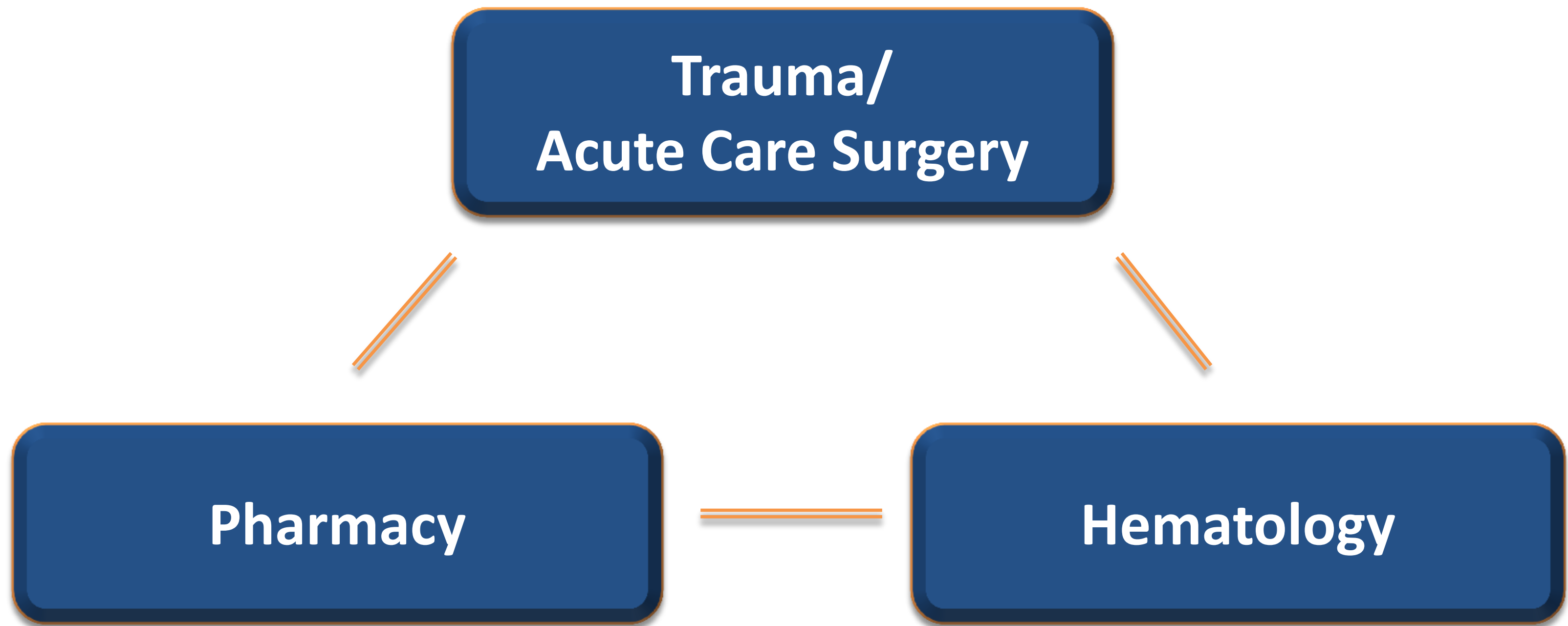
No Conflicts of Interest to Disclose

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.

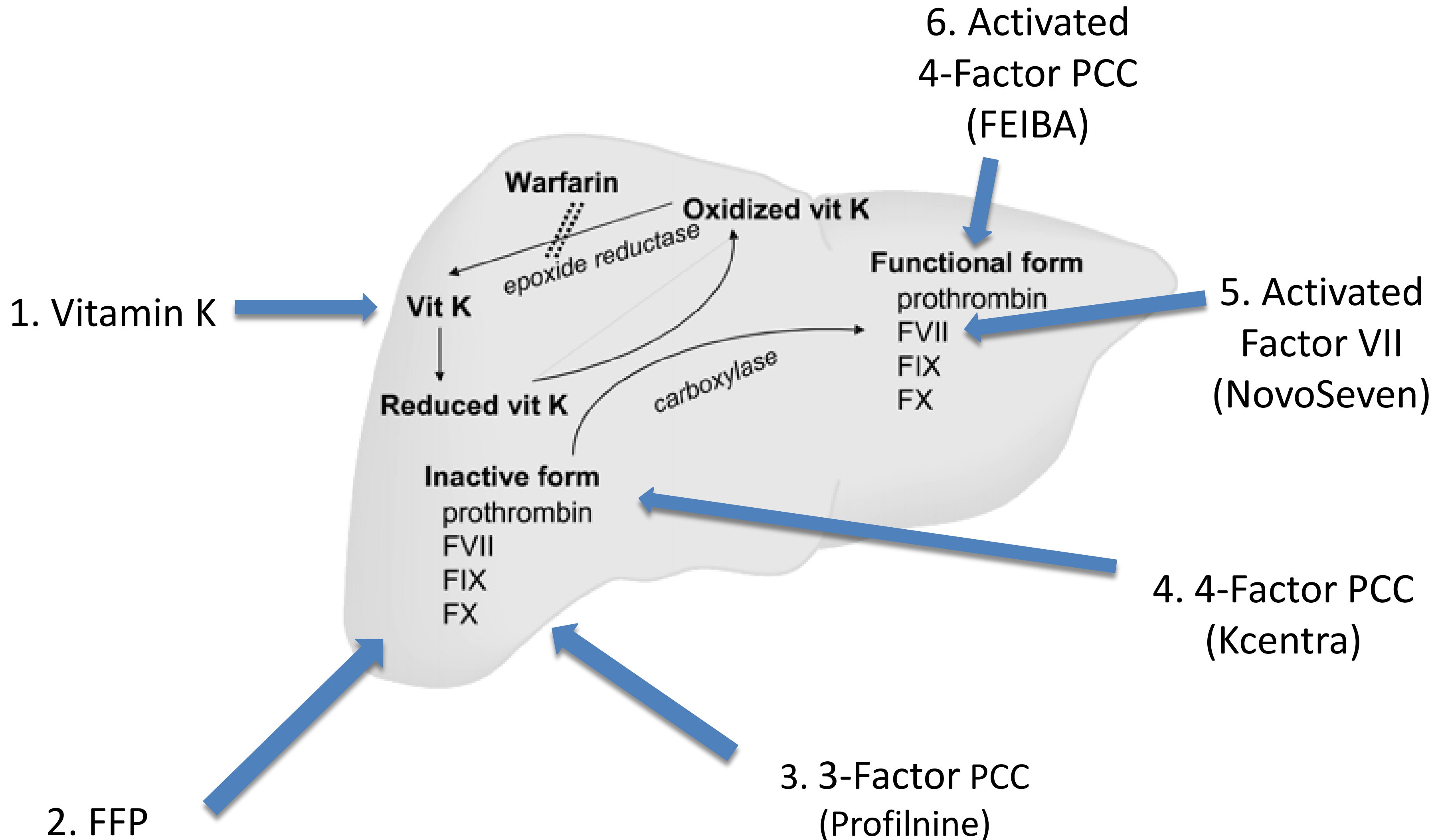
Approvals - Collaboration



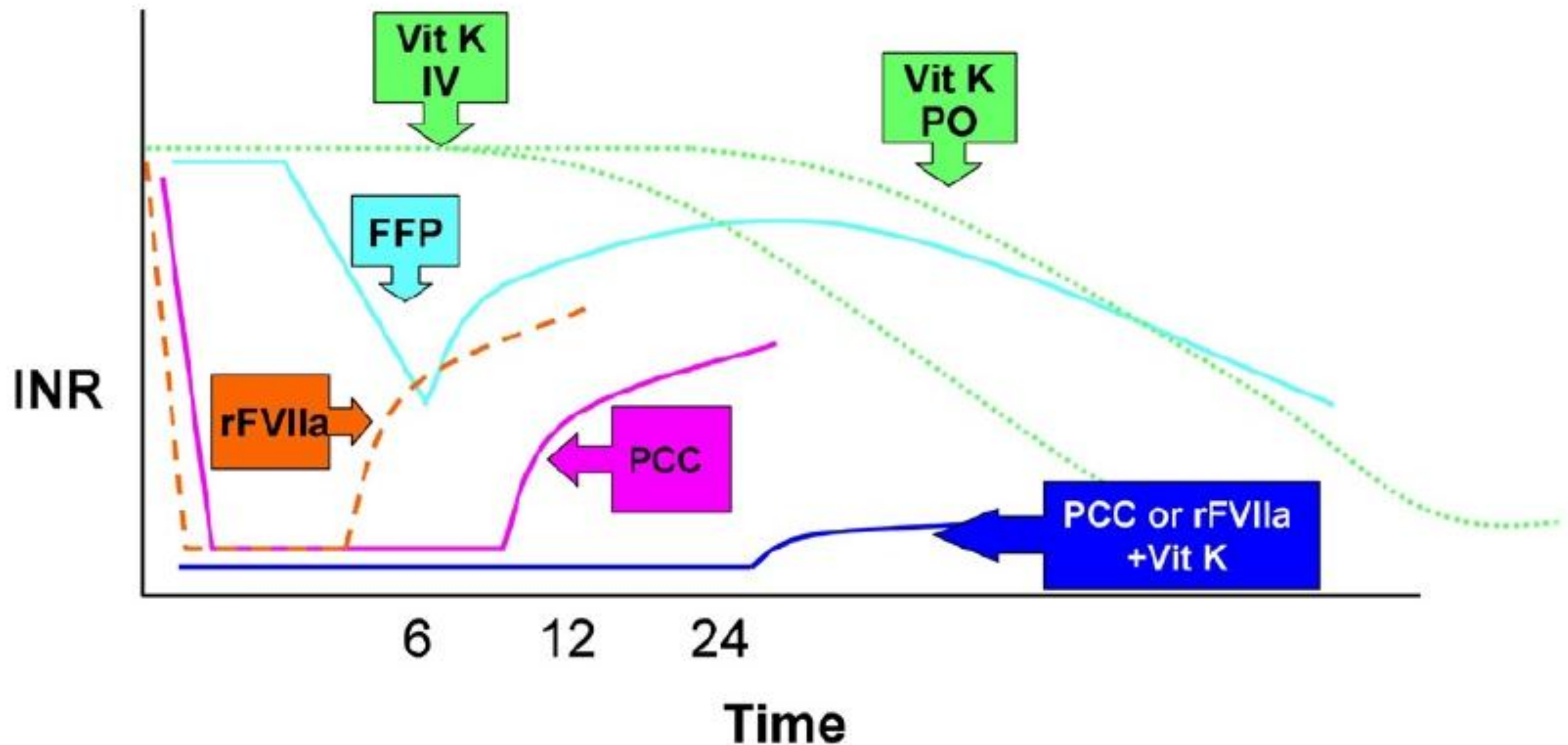
Abbreviations

- 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



Anticoagulant Reversal



Aguilar et al. Mayo Clin Proc, 2007.

INR limitations

- Measure of coagulability
- Coagulability ≠ Hemostasis
- Highly sensitive to factor VII
- FFP and INR relationship

Awad et al. P&T, 2013.

What's in it? PCCs versus FFP

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

International Units of all factors relative to Factor IX

Adapted from Sorensen *et al. Critical Care,* 2011.

Anticoagulant Reversal

FFP Advantages	FFP Risks
• Inexpensive • Decrease thrombotic complications	• Volume overload • Transfusion-related lung injury • Delayed time to administration • Variable amounts of factors

PCC Advantages	PCC Risks
• No thawing necessary • No blood-typing necessary • Reduced volume	• Venous thromboembolism • Myocardial infarction • Disseminated intravascular coagulation (DIC)

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

Holbook *et al.* Chest 2012

3F-PCC vs 4F-PCC

- Systematic Review:
  - 4F-PCC **MORE** effective than 3F-PCC in decreasing INR to </= 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

Voils *et al.* Thromb Res 2012

- Only 4-factor PCC available in USA
- Only PCC with FDA-approved indication for VKA reversal

Kcentra Prescribing Information. CSL Behring. 2014.

Kcentra

- Summary:
  - PCC is at least as effective as FFP in INR reversal
  - PCC has acceptable safety profile compared to FFP
  - INR-based dosing of PCCs more reliably decreases INR to </= 1.5 within one hour of administration
  - 4F-PCC more effectively decreases INR to </= 1.5 within one hour of administration than 3F-PCC

Evidence: 3 Factor PCC

Emergency Anticoagulation Reversal with 3F-PCC	
Design	Multicenter, prospective cohort trial.
Population	46 patients with acute symptomatic intracranial hemorrhage and INR>/= 2.
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.

Imberti *et al*. Blood Transfus, 2011.

Evidence: 4 Factor PCC

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

Sarode et al. Circulation, 2013.

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 — Add Order

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"

Order Set

SnapShot
Patient Summary
Chart Review
Results Review
Flowsheets
Problem List
History
Notes
Demographics
Medications
Allergies

Order Set
Order Sets
Orders

Order Sets
ED
Add
Advanced
Right click on an Order Set to add to favorites.

Record Select
Search: ED REVERSAL

%	Protocol Name	Protocol ID
	SMF ED EMERGENT ANTICOAGULANT/ANTIPLATELET REVERSAL ...	41061

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 ticolidine (TICLID)

Orderset

Inclusion criteria = hard stops

Administer via slow IV push at 2 mL/min

☑ Inclusion Criteria - All criteria must be met to proceed with PCC

Routine, ONCE First occurrence Today at 1715

Accept | Cancel

Priority: Routine | Routine | ASAP | STAT

Frequency: ONCE | Once

Starting: 9/23/2014 | Today | Tomorrow | At: 1715

First Occurrence: **Today 1715**

Scheduled Times: Hide Schedule

9/23/14 | 1715

Questions:

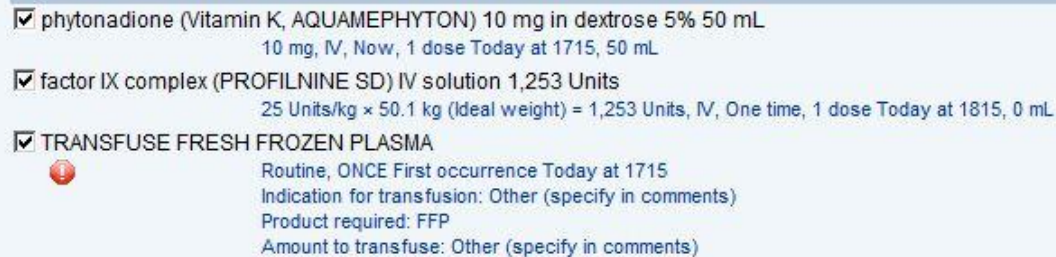
Prompt	Answer	Comments
1. Patient taking Warfarin, Dabigatran, or Xa-inhibitor	yes / no	
2. Life-threatening hemorrhage and/or requires emergent surgery	yes / no	
3. If warfarin-related bleed, INR is elevated (most clinical trials of PCC limited use to patients with INR >2)	yes / no / NA	

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



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

Medications

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DEFAULTS KCENTRA 50 units/kg actual body weight

Approximate Cost

	FFP	Profilnine	Kcentra
Cost / Unit FIX	N/A	$1 per unit	1.25 per unit
Cost / Avg. Dose	$150 (2 units FFP)	$3,200 (50 IU FIX/kg)	$4,500 (50 IU FIX/kg)

What if the request for Profilnine or Kcentra falls outside of recommendations?

Hematologist Consult

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