GUIDELINES FOR REVERSAL OF ANTICOAGULANTS – 9:17

Department of Pharmacy Policies & Procedures – Inpatient Clinical Policy

Number: 9:17

Approved By: Pharmacy & Therapeutics Committee

Date Approved: 6/15

Last Reviewed: 6/15

Revisions:

Subject: GUIDELINES FOR REVERSAL OF ANTICOAGULANTS

I. POLICY

The following policy will outline the procedures that clinical staff should follow when needing to reverse the effects of anticoagulants. In all cases of substantial bleeding, supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition, maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. **Pharmacy should be notified ASAP if reversal products will be needed – 686-6221**

II. GUIDELINES

Anticoagulant	Elimination Half-life	Reversal agent/bleeding treatment	Lab
Factor Xa Inhibitors			
PO: Apixaban (Eliquis®) Rivaroxaban (Xarelto®) Edoxaban (Savaysa®) SubQ: Fondaparinux (Arixtra®)	8-15h (longer in renal impairment) 5-9h (longer in elderly and renal impairment) 10-14h (longer in renal impairment) 17-21h (longer in renal impairment)	• Hold the Factor Xa inhibitor • There is no specific reversal agent or pharmacologic antidote, so management is primarily supportive • If ingested within 2-3 hours, administer activated charcoal 50 g for oral agents • **Consider 4-factor PCC (Kcentra®) 50 units/kg (max 5000 units)** • **Call pharmacy at 686-6221. Kcentra has to come to room temp before it can be reconstituted. Doses of Kcentra will be rounded to the nearest vial size**	Anti-factor Xa activity, PT
Direct Thrombin Inhibitors			
PO: Dabigatran (Pradaxa®)	14-17h up to 34h in severe renal impairment	• Hold the dabigatran • There is no specific reversal agent or pharmacologic antidote, so management is primarily supportive • If ingested within 2-3 hours, administer activated charcoal 50 g • **Consider 4-factor PCC (Kcentra®) 50 units/kg (max 5000 units)** • Hemodialysis removes~ 60% of the drug within 2h, consider for bleeding patients, especially those with renal impairment	aPTT TT

In all cases of substantial bleeding, supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition, maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. **Pharmacy should be notified ASAP if reversal products will be needed – 686-6221**

IV: Argatroban Bivalirudin	40-50 minutes 25 minutes (up to 1h in severe renal impairment)	• Turn off the infusion • There is no specific reversal agent or pharmacologic antidote • Due to the short half-life of these agents, management is primarily supportive	aPTT

Unfractionated Heparin (UFH)

Heparin	60-90 minutes (dose dependent)	• D/c heparin • **Protamine: 1mg neutralizes ~ 100 units of heparin** • Calculate dose based on UFH administered within the last 2 hours • Maximum single dose 50mg	aPTT, Anti-factor Xa activity

Time since last dose of heparin	Dose of protamine for each 100 units of heparin administered
Immediate	1mg (or 25mg fixed dose)
30 minutes to 2 hours	0.5mg (or 10mg fixed dose)
2 hours	0.25mg (or 10mg fixed dose)

Low-Molecular Weight Heparin

Enoxaparin (Lovenox®) Dalteparin (Fragmin®)	3-5 hours (longer in renal impairment)	• D/C LMWH • Partial reversal of effects with **protamine**: neutralizes ~ 60% of LMWH's anti-factor Xa activity • Calculate dose based on LMWH administered within the last 8-12h • Maximum single dose 50mg	Anti-factor Xa activity

Time since last dose of LMWH	Dose of protamine for each 1mg of enoxaparin or 100 units of dalteparin administered
< 8 hours	1mg (or 50mg fixed dose)
8-12 hours	0.5mg (or 25mg fixed dose)
12 hours	Not likely to be useful (or 25mg fixed dose)

Vitamin K Antagonist	INR	Clinical Scenario	Management
Warfarin (Coumadin®) T1/2 ~ 36-48 hours, 3-7 days for INR to	< 4.5	No or minor bleeding	• Hold warfarin until INR in therapeutic range
		Rapid reversal required	• Hold warfarin • Consider vitamin K 2.5mg oral • If reversal is required in < 2h, consider FFP 10-15mL/Kg (2 units)
	4.5-10	No or minor bleeding	• Hold warfarin until INR in therapeutic range • Consider vitamin K 2.5mg oral
		Rapid reversal required	• Hold warfarin • Consider vitamin K 2.5mg-10mg PO or *IV infusion** over 20 minutes • If reversal is required in < 2h, consider FFP 10-15mL/Kg (2 units)
	>10	No or minor bleeding	• Hold warfarin • Give vitamin K 2.5mg -10mg PO or *IV infusion** over 20 minutes, repeat q24h as needed
		Rapid reversal required	• Hold warfarin • Give vitamin K 5-10mg *IV infusion** over 20 minutes and repeat q6-24h as needed

In all cases of substantial bleeding, supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition, maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. **Pharmacy should be notified ASAP if reversal products will be needed – 686-6221**

<table>
<tr><td>normalize</td><td></td><td></td><td>• If reversal is required in < 2h, consider FFP – may require > 2 units</td></tr>
<tr><td></td><td>Any INR</td><td>Serious or life threatening bleeding</td><td>• Hold warfarin
• Give vitamin K 10mg IV infusion* over 20 minutes
• Give 4 units FFP/plasma <u>OR</u>
• 4-factor PCC (Kcentra®) ** <u>(preferred for life-threatening bleeding)</u>**
<table><tr><th>Pre-treatment INR</th><th>Dose of PCC</th></tr><tr><td>2.0-3.9</td><td>25 units/kg (max 2500 units)</td></tr><tr><td>4-6</td><td>35 units/kg (max 3500 units)</td></tr><tr><td>> 6</td><td>50 units/kg (max 5000 units)</td></tr></table></td></tr>
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**IV infusion administration has faster onset of action. IVPB vitamin K (phytonadione) comes in 50ml of NS and infuses over 20 minutes. The default button is 10mg, but you should type in the dose you want.*

Antiplatelet Agents			
Aspirin Clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), dipyridamole, NSAIDS	2-4.5 h 7-10 h variable	• If appropriate, discontinue antiplatelet agent 5-10 days prior to procedure (risk vs. benefit of stopping has to be weighed) • Consider platelet transfusion prior to high risk bleeding procedures • **Platelet transfusion for urgent bleeding** • ASA, clopidogrel and prasugrel irreversibly inhibit platelet function for the lifetime of the platelets • Ticagrelor and NSAIDS are reversible inhibitors, platelet function normalizes after drug clearance • DDAVP may be considered as a last resort for refractory bleeding ○ **DDAVP 0.3mcg/kg in 50ml NS IVPB over 15-30 minutes**	

In all cases of substantial bleeding, supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition, maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. **Pharmacy should be notified ASAP if reversal products will be needed – 686-6221**

Oral Agent Review and Coagulation Evaluation

Dabigatran –A normal aPTT in a patient receiving dabigatran is sufficient evidence to eliminate a **significant** dabigatran effect. A normal TT (thrombin time) in a patient receiving dabigatran is sufficient evidence to **exclude** dabigatran as a potential cause of bleeding. The TT is extremely sensitive to the effects of dabigatran and can be prolonged even by trivial amounts of the drug.

Rivaroxaban, apixaban, edoxaban – **Specific assays for anti-factor Xa activity of these drugs are not currently available at UAMS**. The absence of anti-factor Xa activity, regardless of how an assay has been calibrated, indicates that no clinically relevant anti-factor Xa drug effect is present. Increased anti-factor Xa activity may reflect the presence of continued anti-factor Xa anticoagulant effect; however, unless the assay used has been calibrated for the specific anticoagulant the patient is taking, the amount of anticoagulant effect present cannot be reliably determined.

General Measures for Management of Sustained Bleeding:

1. Identify the source and cause of bleed.
2. Management of hemorrhage includes maintenance of hemodynamic and respiratory stability.

Drug	PT/INR	aPTT/TT	Anti-factor Xa activity
Factor Xa Inhibitors • Rivaroxaban • Apixaban • Edoxaban	↑ indicates presence but not degree of anticoagulation ↓↔ implies no bleeding due to factor Xa inhibitors	No significant effect	↑ indicates presence but not degree of anticoagulation ↓↔ implies no bleeding due to factor Xa inhibitors
Direct thrombin inhibitors • Dabigatran	↔ at therapeutic levels (May be moderately elevated at supra-therapeutic levels)	↑ indicates presence but not degree of anticoagulation ↓↔ implies no bleeding due to direct thrombin inhibitors	No significant effect
Vitamin K antagonist • warfarin	↑ in relation to dose	No significant effect	No significant effect

When necessary provide mechanical ventilation, fluid resuscitation, hemodynamic support and therapeutic procedures to stabilize the patient and promote coagulation.

3. Maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation.
    a. Maintaining adequate serum ionized calcium concentrations is vital since calcium is essential for vitamin K dependent coagulation factor bridging, fibrinogen stabilization and platelet function. Hypocalcemia is not uncommon with the transfusion of rapid administration of large amounts of blood products with major hemorrhages. Saline fluid resuscitation, hypovolemic shock and ischemia contribute to the development of acidosis and the extent of acidosis correlates with mortality. In the severely injured patient hypothermia, acidosis and hypotension are associated with coagulopathy.
4. If applicable, apply packing or dressing, use local hemostatic measures or surgical intervention to control bleeding.

In all cases of substantial bleeding, supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition, maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. **Pharmacy should be notified ASAP if reversal products will be needed – 686-6221**

5. Consider the risk versus benefit of continuation of anticoagulation therapy. Discontinue anticoagulant and/or concomitant antiplatelet therapy in patients with life threatening or massive trauma hemorrhage. If possible discontinue interacting medications that potentiate or prolong the pharmacodynamics of an anticoagulant (e.g., ciprofloxacin and warfarin).
6. If an overdose of oral anticoagulant is suspected, administer activated charcoal in patients with low risk for aspiration if the patient does not have a gastric bleed.
7. After control of major bleeding and stabilization of the patient, reassess for risk of thromboembolism and initiate a short acting agent if anticoagulation is required.
8. If reversal products are going to be utilized, pharmacy should be notified as soon as possible to expedite the process. 686-6221

Anticoagulant Bleeding Recommendations and Therapeutic Options:

A. Factor Xa Inhibitors: Apixaban, Rivaroxaban, Edoxaban, Fondaparinux

There is no specific reversal agent or pharmacologic antidote, thus management of hemorrhagic complications is primarily supportive. Rivaroxaban and apixaban are highly protein bound and are not dialyzable. Management of Factor Xa inhibitor-related bleeding events is summarized below:

Consider any of the following based on bleeding severity:

- Symptomatic treatment
- Mechanical compression
- Surgical intervention
- Fluid replacement and hemodynamic support
- Blood product transfusion – RBCs for severe or symptomatic anemia, platelets if thrombocytopenia
- Antifibrinolytic agents can be considered (aminocaproic acid, tranexamic acid)
- Oral activated charcoal for apixaban, rivaroxaban and edoxaban (if previous dose ingested within 2 hours)
    - Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose

If hemostasis is not achieved with the strategies outlined above, proceed to the steps below:

For severe, life-threatening bleeding

No agent currently available in the US has been shown to successfully reverse the anticoagulant effects of Factor Xa inhibitor-related bleeding events. However, the strategy below may be considered based on the currently available evidence. Therefore, the pharmacologic interventions below may be considered, but are not required in the management of Factor Xa inhibitor-related bleeding.

1. **Administer Kcentra® (4-factor PCC)**
    a. **50 units/kg IV x 1 (max dose 5000 units)**
    b. **STOCKED IN PHARMACY – call with STAT order 686-6221**
2. **For persistent refractory bleeding, consider pursuing formal Hematology consult.**
3. **To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, anti-Xa activity, CBC (platelets).**
4. **If PT prolonged, administer vitamin K 10mg IVPB x one dose (as there may be vitamin K deficiency present).**

B. Direct Thrombin Inhibitors (DTIs): IV: Argatroban, Bivalirudin

There is no specific reversal agent or pharmacologic antidote. Due to the short half-life of these agents (Argatroban 40-50 min; Bivalirudin 25 min), management of hemorrhagic complications is primarily supportive and interruption of treatment will be sufficient to reverse the anticoagulant effect.

Consider any of the following based on bleeding severity:

- Symptomatic treatment
- Mechanical compression
- Surgical intervention
- Fluid replacement and hemodynamic support
- Blood product transfusion – RBCs for severe or symptomatic anemia, platelets if thrombocytopenia

If hemostasis is not achieved with the strategies outlined above, consider the administration of 2-4 units of fresh frozen plasma (FFP).

In all cases of substantial bleeding, supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition, maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. **Pharmacy should be notified ASAP if reversal products will be needed – 686-6221**

For severe, life-threatening bleeding

No agent has been shown to successfully reverse the anticoagulant effects of intravenous DTIs or treat DTI-related bleeding events. However, the interventions below may be considered.

1. **Administer Kcentra® (4-factor PCC)**
    a. **50 units/kg IV (max dose 5000 units) x 1**
    b. **STOCKED IN PHARMACY – call with STAT order 686-6221**
2. **For persistent refractory bleeding, consider pursuing formal Hematology consult**
3. **To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, TT, CBC (platelets).**

PO: Dabigatran

There is no specific reversal agent or pharmacologic antidote, thus management of hemorrhagic complications is primarily supportive. Hemodialysis is effective at removing approximately 60% of dabigatran in a 2 hr session.
Consider any of the following based on bleeding severity:

- Symptomatic treatment
- Mechanical compression
- Surgical intervention
- Fluid replacement and hemodynamic support
- Blood product transfusion – RBCs for severe or symptomatic anemia, platelets if thrombocytopenia
- Antifibrinolytic agents can be considered (aminocaproic acid, tranexamic acid)
- Oral activated charcoal (if previous dose ingested within 2 hours)
    - Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose

If hemostasis is not achieved with the strategies outlined above, consider the administration of 2-4 units of fresh frozen plasma (FFP).

For severe, life-threatening bleeding

In the setting of acute renal failure, initiation of hemodialysis may be considered for the purpose of facilitating drug elimination. No agent has been shown to successfully reverse the anticoagulant effects of dabigatran or treat dabigatran-related bleeding events. However, the interventions below may be considered.

1. **Administer Kcentra® (4-factor PCC)**
    a. **50 units/kg IV x 1 (max dose 5000 units)**
    b. **STOCKED IN PHARMACY – call with STAT order 686-6221**
2. **For persistent refractory bleeding, consider pursuing formal Hematology consult**
3. **To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, TT, CBC (platelets).**

C. Correction of Supratherapeutic Anticoagulation with Warfarin

Management of warfarin reversal and bleeding events is summarized below:

1. Management of life-threatening bleeds in patients on warfarin
    1. Vitamin K 10mg IVPB + Kcentra® (4-factor PCC) is first line unless otherwise contraindicated
    2. Each dose of Kcentra® (4-factor PCC) will be rounded to the nearest vial size

Pre-treatment INR	Dose of PCC
2.0-3.9	25 units/kg (max 2500 units)
4-6	35 units/kg (max 3500 units)
> 6	50 units/kg (max 5000 units)

    3. The responsibility of the clinical provider (MD, PA, NPP)
        i. Ensure patient is on warfarin/anticoagulant
        ii. Ensure INR is obtained
        iii. Administration of Kcentra® should not be delayed for INR results

In all cases of substantial bleeding, supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition, maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. **Pharmacy should be notified ASAP if reversal products will be needed – 686-6221**

iv. Call the pharmacy at 686-6221 to facilitate order verification and delivery
v. Kcentra is kept refrigerated and must come to room temp before reconstitution.
vi. Kcentra cannot be sent through the tube system.

4. Recheck INR 10-30 minutes after 4-factor PCC administration. Due to short half-life of PCC, check INR q6hrs for 24 hours
5. Redosing of Kcentra® is not recommended

2. Additional Information about Warfarin Reversal
   1. Oral vitamin K is preferred for patients without severe bleeding.
   2. IVPB vitamin K should be ordered only if patient has life threatening bleeding, or needs an emergent procedure, where a shorter onset of anticoagulation reversal may be required.
   3. Subcutaneous or intramuscular doses are not recommended as routine care.
   4. Full effect of vitamin K on warfarin reversal occurs approximately 24 hours after administration. Partial effects may be seen in 6-12 hours.
   5. Doses of vitamin K greater than 10 mg are excessive and do not reverse anticoagulation more quickly.

D. Unfractionated Heparin (UFH)

1. Protamine sulfate is used to reverse the anticoagulant effect of heparin.
   a. Increased risk of hypersensitivity reaction, including anaphylaxis, in patients with a fish allergy or prior exposure to protamine.
   b. Pre-medicate with corticosteroids and antihistamines if at risk for protamine allergy.
      i. Hydrocortisone 50-100 mg IV x 1 over 15 minutes
      ii. Diphenhydramine 50 mg IV/PO x1
2. Dose calculation
   a. 1 mg of protamine neutralizes approximately 100 units of UFH
   b. Use only the last 2 hours prior to reversal when considering the total amount of heparin administered to patient, due to the short half-life of UFH.
      i. If the patient is on a continuous infusion, calculate the total amount administered over the past two hours prior to reversal.
      ii. If the patient is receiving SQ heparin, calculate the total amount administered with the last subQ injection.
   c. Maximum single protamine dose is 50 mg
3. Administration
   a. IV heparin reversal
      i. Administer protamine IV with maximum infusion rate of 5 mg/min to prevent hypotension and bradycardia.
   b. SC heparin reversal
      i. Administer bolus dose of protamine 25 mg and infuse remaining dose via intravenous infusion over 8 hours.
3. Monitor aPTT starting 5-15 minutes after protamine infusion.
   a. Onset of reversal effect is seen 5 minutes after administration
   b. Duration of reversal activity is approximately 2 hours.
   c. Multiple protamine doses may be required if bleeding or elevation of aPTT level persists.

E. Low-Molecular Weight Heparin (LMWH)

1. Protamine sulfate may be used as a partial reversal agent (neutralizes approximately 60% of LMWH's anti-factor Xa activity).
2. Increased risk of hypersensitivity reaction, including anaphylaxis, in patients with a fish allergy or prior exposure to protamine.
   a. Premedicate with corticosteroids and antihistamines if at risk for protamine allergy.
3. Dose Calculation
   a. If last dose of LMWH was given in previous 8 hours, give 1 mg protamine for every 1 mg (or 100 units) of LMWH. Maximum total dose of protamine is 50 mg.
   b. If the last dose of LMWH was given in the previous 8-12 hours, give 0.5 mg protamine for every 1 mg (or 100 units) of LMWH. Max single dose of protamine is 50 mg.

In all cases of substantial bleeding, supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition, maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. **Pharmacy should be notified ASAP if reversal products will be needed – 686-6221**

c. If the last dose of LMWH was given more than 12 hours earlier, protamine is not recommended and an alternative agent may be needed to obtain hemostasis. If the patient requires other pharmacologic therapy to manage hemorrhagic complications, a Hematology/Coagulation consult is recommended.

4. Administration

   a. Maximum protamine sulfate IV infusion rate is 5 mg/min to prevent hypotension and bradycardia.

   b. Repeat dose 0.5 mg protamine for every 1 mg (or 100 units) of LMWH if bleeding continues or elevated anti-factor Xa activity level after 2-4 hours.

F. Antiplatelet agents that IRREVERSIBLY inhibit platelet function: aspirin, clopidrogel, prasugrel Antiplatelet agents that REVERSIBLY inhibit platelet function: dipyridamole, NSAIDs, ticagrelor

Duration of platelet inhibition by antiplatelet agents that irreversibly inhibit platelet function is not dependent on the agents' half-life, but may persist for 5-7 days.

1. Management of antiplatelet induced bleeding:

a. There are no specific reversal agents for antiplatelet agents.
b. Treatment of bleeding involves general hemostatic measures.
c. Discontinuation of antiplatelet agents due to a bleeding event must be weighed against the patient's risk of arterial thrombosis. The risk of thrombosis is particularly high within 1 month of receiving a bare metal coronary stent and within 3 months of receiving a drug eluting coronary stent. Premature cessation of dual anti-platelet therapy in these situations can lead to stent thrombosis which can potentially be fatal.
d. Antiplatelet agents should be reinstated as soon as hemostasis is obtained
e. **Platelet infusion may be considered as additional measure for severe critical bleeds, or prevention of bleeds before emergency surgery, but it may confer a risk of arterial thrombosis**.
f. DDAVP is another option that may be considered as a last resort for refractory bleeding
   a. DDAVP 0.3mcg/kg in 50ml NS IVPB over 15-30 minutes

In all cases of substantial bleeding, supportive strategies by means of discontinuation of anticoagulant, mechanical compression and administration of blood products, fluid resuscitation, hemodynamic and respiratory support are required. In addition, maintain normal body temperature, blood pH and electrolyte balance to facilitate coagulation. **Pharmacy should be notified ASAP if reversal products will be needed – 686-6221**

Appendix A:

Reversal Agents Mentioned In This Protocol

Agent	Dose	Comments
Vitamin K	1-10 mg IVPB/PO, not SQ or IM	• Infusion reactions rare; administer over 20-30 min • Takes 4-12h (IV) to 12-24h (PO) to reverse warfarin • The IV form can be administered orally for doses < 2.5mg • Large doses can cause warfarin resistance on resumption (10-15 mg) • SubQ or IM administration not recommended • Adding FFP to vitamin K gives minimal additional effect on the INR measured > 12 hours later
Protamine sulfate	10-50 mg IV	• Full reversal of unfractionated heparin • 60%-80% reversal of LMWH • No reversal of fondaparinux • Onset ~ 5 minutes • Hypotension, flash pulmonary edema and allergic reactions can occur with rapid administration
Platelets	1 apheresis unit	• Used in pts receiving antiplatelet therapy • Raise platelet count by 30 x 10^9/L • Goal platelet count 50 - 100 x 10^9/L (indication dependent)
Frozen plasma (FFP)	10-30 mL/kg (1 unit = ~250ml)	• Does not reverse anticoagulants, but replaces all coagulation factors - cannot fully correct ○ Hemostasis usually requires factor levels~30%, Factor IX may only reach 20% • Onset ~ 1-4 hours • May need repeat dose after 6 hours, short t1/2 • Large volume • Blood bank keeps a supply thawed for massive traumas and has a plasma thawer that can thaw frozen plasma in 12 minutes • Adverse events include volume overload, transfusion-related acute lung injury (TRALI), acute hemolytic transfusion reaction and urticaria
Prothrombin complex concentrates (Kcentra® - 4 factor PCC)	25-50 units/kg IV Use actual body weight (up to 100kg) Kept refrigerated in pharmacy. **Call pharmacy when placing order to facilitate more rapid delivery. 686-6221**	• Pooled human plasma, contains factors II, VII, IX, and X and antithrombotic proteins C and S and small amounts of heparin • Dosing based on factor IX component, pretreatment INR • Doses will be rounded to the nearest vial size • Rate 3units/kg/min, max of 200mg/min (e.g., 2500 units over 13 minutes) • Rapid, complete INR correction in warfarin patients • Small volume infusion over 10-30 minutes • Onset~ 5-15 minutes • Risk of thrombosis ~ 1.4% • Contraindicated with HIT, DIC (h/o HIT > 3mo ago, can still use Kcentra)

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Aminocaproic acid	4-5 g IV/po over 1 hr, then 1 g/hr x 8 hrs (max dose 30 g/24 hrs)	• May increase risk of thrombosis • May accumulate in patients with renal impairment, reduce loading dose or infusion rate • Caution or avoid use in hematuria due to upper urinary tract origin
Tranexamic acid	1g IV over 10 minutes followed by 1 g IV over 8h	• Non–cerebral trauma dose • Associated with cerebral infarction in studies of patients with subarachnoid hemorrhage • Thromboembolism rare • Order panel in Epic for tranxemic acid (trauma) • Currently off label use

Appendix B:

Administration Instructions for Kcentra®®:

Please refer to the package insert instructions for specific details on reconstitution and administration of Kcentra®® (4-factor PCC).

1. Ensure that the Kcentra® vial and diluent vial are at room temperature. Prepare and administer using aseptic technique.

2. Place the Kcentra® vial, diluent vial, and Mix2Vial transfer set on a flat surface.

3. Remove the Kcentra® and diluent vial flip caps. Wipe the stoppers with the alcohol swab provided and allow drying prior to opening the Mix2Vial transfer set in the clear package.

4. Open the Mix2Vial transfer set by peeling away the lid. Leave the Mix2Vial set in the clear package.

5. Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial set together with the clear package and push the plastic spike at the BLUE end of the transfer set firmly through the center stopper of the diluent vial.

6. Carefully remove ONLY the clear package from the Mix2Vial transfer set.

7. With the Kcentra® vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center stopper of the Kcentra® vial. The diluent will automatically transfer into the Kcentra® vial.

8. With the diluent and Kcentra® vials still attached to the Mix2Vial transfer set, gently swirl the Kcentra® vial to ensure that it is fully dissolved. DO NOT SHAKE THE VIAL.

9. With one hand, grasp the Kcentra® side of the Mix2Vial transfer set and with the other hand grasp the BLUE diluent side of the Mix2Vial set and unscrew the two pieces.

10. Draw air into an empty, sterile syringe. While the Kcentra® vial is upright, screw the syringe into the Mix2Vial transfer set. Inject air into the Kcentra® vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly.

11. Unscrew the syringe from the Mix2Vial transfer set and attach the syringe to a suitable IV administration set. Administer through a SEPARATE infusion line, DO NOT MIX WITH OTHER INFUSIONS.

12. After reconstitution, administration should begin promptly.

13. If the same patient is to receive more than one vial, you may pool the contents of multiple vials Use a separate, unused Mix2Vial transfer set for each product vial.