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GUIDELINES FOR REVERSAL OF ANTICOAGULATION

Anticoagulation is a high risk treatment which requires careful monitoring and follow-up due to the severity of adverse drug events associated with its use, the complexity of dosing these medications, and significant patient compliance issues.¹ Anticoagulants have been identified as one of the top five drug types associated with patient safety incidents in the United States.^{2,3} National data from 2003 and 2004 reported that anticoagulants ranked 1st in the number of deaths for drugs causing "adverse effects in therapeutic use".⁴ In addition, there were 29,000 emergency room visits in the United States for bleeding complications from warfarin between 1999 and 2003.⁴ Furthermore, reports from University of Iowa Hospitals and Clinics parallel the national data.

In accordance with **The Joint Commission's National Patient Safety Goal 03.05.01** (formally NPSG 3E): "reduce the likelihood of patient harm associated with the use of anticoagulation therapy,"¹ and recent **Sentinel Event Alert: Preventing Errors Relating to Commonly Used Anticoagulants**,⁵ several risk reduction strategies have been undertaken at UIHC. Evidence-based guidelines have been developed for prevention and treatment of venous thromboembolism, management of warfarin therapy, management of heparin-induced thrombocytopenia, baseline and ongoing laboratory tests needed for anticoagulant therapy, and reversal of anticoagulation. Standardized patient education materials have been developed and staff education is underway. The following Guidelines for Reversal of Anticoagulation have been developed by the Anticoagulation Task Force to aid in this process of promoting the safe use of anticoagulants; they are also available on *The Point* (through the Clinical Applications Web Links, UIHC Clinical Practice Reference/Anticoagulation Management) and through the online version of the *Formulary* (Anticoagulation Management link).

BACKGROUND

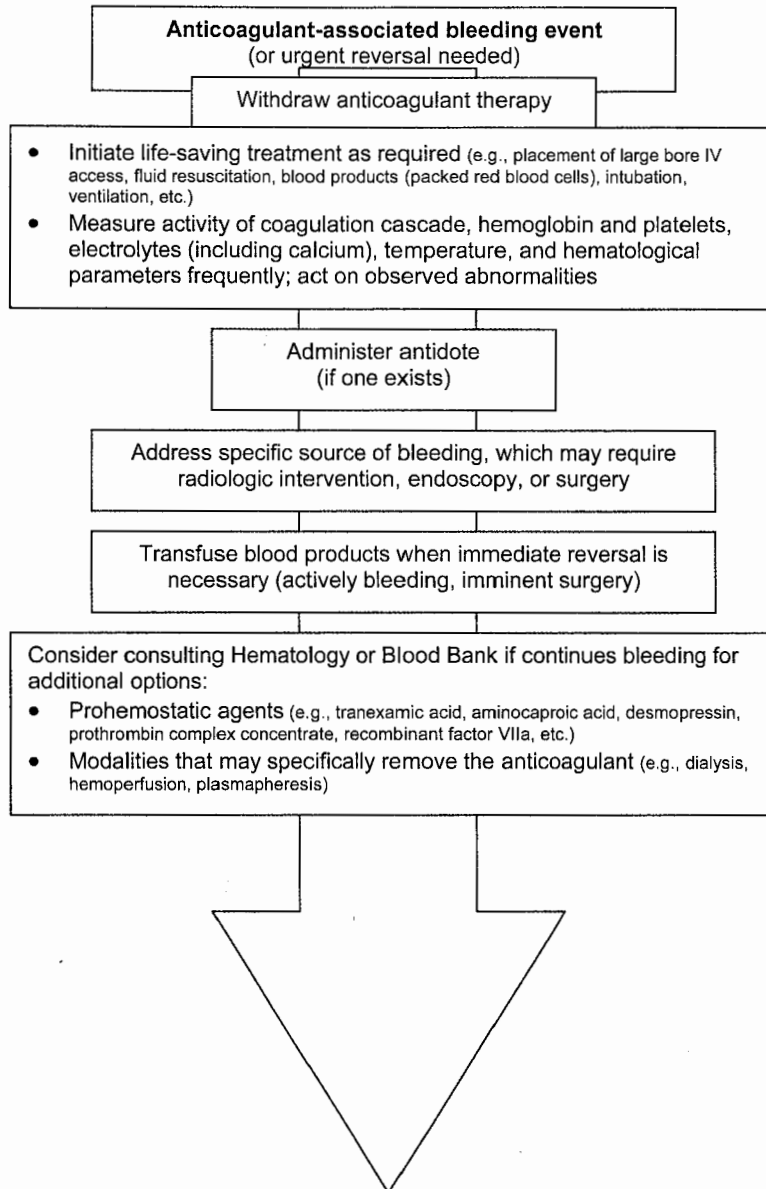
Bleeding is the primary complication of anticoagulant therapy, and is a risk of all anticoagulants, even when maintained within usual therapeutic ranges.⁶ Unfortunately, there is little evidence to guide the management of the anticoagulated and bleeding patient.⁶ If rapid reversal of the anticoagulant effect is required for heparin, low-molecular-weight heparin (LMWH) or warfarin, as a result of bleeding or need for an invasive procedure, the following reversal agents can be used: protamine sulfate (heparin and LMWH); vitamin K (warfarin). Specific antidotes for the newer anticoagulants, (i.e., fondaparinux, argatroban, bivalirudin, lepirudin) do not currently exist.⁶

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MANAGEMENT STRATEGIES FOR TREATING BLEEDING IN AN ANTICOAGULATED PATIENT

Although there are few high-quality data comparing different strategies for the management of bleeding associated with anticoagulation, the necessity for awareness of the basic principles of bleeding management, including rapid assessment of the source, cause, and severity of bleeding, and prompt appropriate action, both mechanical and systemic, to control the bleeding are imperative.⁶ The following algorithm for basic management principles can be applied:⁶



GUIDELINES FOR REVERSAL OF ANTICOAGULATION

While it is imperative that anticoagulation be reversed as quickly as possible in potentially life-threatening bleeding or emergency interventions, this population of patients (those on anticoagulants) is at high risk for thrombotic events, necessitating caution that the reversal be carefully controlled.¹³ Overcorrection of anticoagulation with reversal agents may lead to deleterious effects. In addition, for those requiring reversal in non-emergency situations, it is important to use a cautious approach to reversal if continuing anticoagulation is deemed necessary. The recommendations in Table 1 are intended to be used if reversal of the anticoagulant effect of these agents is required.

Table 1. Reversal of Anticoagulation⁶⁻⁸

Anticoagulant	Management	Assess	Special Considerations
<p><u>Management of supratherapeutic INRs into target range:</u></p> <p>Not bleeding with INR < 5.0: Omit or lower dose^{*,†}; Monitor INR more frequently</p> <p>Not bleeding with INR 5.0 to 9.0: Omit 1 to 2 doses of warfarin and adjust dose as necessary; Optional[#] oral vitamin K 1 to 2.5 mg; Monitor INR more frequently</p> <p>Not bleeding with INR ≥ 9.0: Hold warfarin; Give oral vitamin K 2.5 to 5 mg (may repeat); Monitor INR more frequently; Resume warfarin at a lower dose when INR therapeutic</p>	<p><u>Management of bleeding or emergent/urgent surgery or procedure:</u></p> <p>Not bleeding, surgery or procedure imminent: Hold warfarin; give vitamin K 1 to 5 mg PO[#]</p> <p>Serious of life threatening bleeding / emergent surgery / procedure: Hold warfarin; Give IV vitamin K 10 mg (may repeat); and / or FFP[‡]; 5 to 8 mL/Kg for therapeutic INR, 15 mL/Kg for supratherapeutic INR; and / or PCC[‡]; 20 to 100 units/Kg^ψ</p>	<p>INR, pt</p>	<p>➤ Subcutaneous and intramuscular vitamin K is not recommended due to unpredictable/delayed absorption and lack of trials evaluating efficacy. Furthermore, intramuscular injection in patients on anticoagulation therapy (particularly when over-anticoagulated) poses a significant risk of causing a hematoma in addition to the issue of intramuscular injections having depot characteristics that may interfere with recommencement of anticoagulation therapy.</p> <p>➤ IV route of vitamin K may produce an anaphylactic reaction. If given IV, dilute in 50 mL normal saline and infuse slowly over 20 min (rate not to exceed 1 mg/min). Low doses and slow infusion rates of are recommended, but may not avoid anaphylaxis.</p> <p>➤ Expect significant reduction of INR within 24 to 48 hr after vitamin K administration.</p> <p>➤ Repeat doses of vitamin K may be given, but do not give sooner than 12 hr after first dose.</p> <p>➤ High doses of vitamin K may lower INR more than necessary and lead to warfarin resistance for a week or more. If continuing warfarin therapy is indicated following high doses of vitamin K, heparin or LMWH can be given until the effects of vitamin K have been reversed and patient becomes responsive to warfarin.</p> <p>➤ The dose of FFP to reverse anticoagulation may require a large volume and could lead to fluid overload and pulmonary edema.⁹</p> <p>➤ Complete and rapid reversal of warfarin-induced bleeding can be achieved more successfully with PCC than with FFP. PCC is associated with a more rapid normalization of INR and better clinical outcome due to the balanced ratio of four vitamin-K-dependent clotting factors plus coagulation inhibitors protein C and Protein S.^{10,21}</p> <p>➤ PCC contains coagulant factors II, VII, IX, and X; expect a correction of INR within 10 min after of PCC administration¹¹; there is a risk for thrombotic events with the use of PCC.^{8,11-13}</p> <p>➤ If vitamin K, FFP, and PCC are unsuccessful, consult Hematology or Blood Bank for additional treatment options</p>
Warfarin			

aPTT = activated partial thromboplastin time; pt = prothrombin time; INR = international normalized ratio; FFP = fresh frozen plasma; PCC = prothrombin complex concentrate

[^] A dosage change may not be needed if only slightly above target INR range or transient cause

^{*} If need for surgical intervention or invasive procedure, give oral vitamin K ≤ 5 mg (if INR still elevated 24 hr after administration, an additional 1 to 2 mg oral vitamin K can be given)

[#] If patient is at high risk of bleeding or imminent, but non-emergent surgery or invasive procedure planned, give oral vitamin K as listed. Lower doses of IV vitamin K (0.5 to 1 mg) have also been used for imminent, non-emergent surgery or invasive procedures.^{22,23}

[‡] If serious bleeding, FFP and PCC are optional

^ψ A single study administered a total of 20 units/Kg of PCC as two rapid (1 minute each) IV infusions separated by a 1 minute interval.¹⁴

Table 1. Reversal of Anticoagulation⁶⁻⁸ (continued)

Anticoagulant	Management	Assess	Special Considerations
Heparin	<p>Protamine[^]: 1 mg IV per 100 units of heparin given over the previous 4 hr (max dose 50 mg)</p>	aPTT	<p>➢ Because the half-life of IV heparin is 60 to 90 minutes, only the heparin given over the preceding 4 to 6 hr should be considered when calculating the dose of protamine</p> <p>➢ If protamine is unsuccessful, consult Hematology or Blood Bank for additional treatment options</p>
Enoxaparin	<p>Protamine[^]: 1 mg IV per 1 mg of enoxaparin given within the previous 8 hr (although smaller doses of protamine can be given if the time since enoxaparin administration is longer than 8 hr); a second dose of 0.5 mg protamine per 1 mg may be given if continued bleeding</p>	aPTT, pt	<p>➢ Approximately 60% of the anticoagulant effect of enoxaparin is neutralized by protamine</p> <p>➢ Smaller doses of protamine can be given if time since enoxaparin administration is > 8 hr</p> <p>➢ If protamine is unsuccessful, consult Hematology or Blood Bank for additional treatment options</p>
Fondaparinux	<p>There is no known antidote for fondaparinux. Consult Hematology or Blood Bank for fondaparinux-related anticoagulation reversal management.</p> <p>Case reports and anecdotal information suggest that the following may be considered:</p> <p>Recombinant factor VIIa^{17,18}: 22.5 to 90 mcg/Kg</p> <p>Tranexamic acid¹⁸: 15 mg/Kg IV q 8 hr until bleeding subsides</p>	aPTT, pt/INR, thrombin-generation time	<p>➢ Immediate effect of rFVIIa should be seen; duration of effect is 2 to 6 hours;¹⁷ in vitro data suggest that rFVIIa might not fully reverse the anticoagulant effects of fondaparinux^{19,20}</p>

aPTT = activated partial thromboplastin time; pt = prothrombin time; INR = international normalized ratio; FFP = fresh frozen plasma; PCC = prothrombin complex concentrate

[^] Slow administration (≤ 5 mg/min) is advised to reduce the risk of hypotension and bradycardia¹⁵; protamine dose should be maintained < 100 mg over 2 hr; 50% of dose can be administered initially with subsequent doses titrated according to bleeding response¹⁶ patients who have previously received protamine sulfate-containing insulin, have undergone vasectomy, or have known sensitivity to fish are at increased risk of having preformed antibodies against protamine sulfate and to suffer from allergic reactions, including anaphylaxis (pretreat with corticosteroids and antihistamines)

Table 1. Reversal of Anticoagulation⁶⁻⁸ (continued)

Anticoagulant	Management	Assess	Special Considerations
<p>Direct Thrombin Inhibitors (e.g., argatroban, lepirudin, bivalirudin)</p>	<p>There are no known antidotes for the direct thrombin inhibitors. Consult Hematology or Blood Bank for direct thrombin inhibitor-related anticoagulation reversal management.</p> <p><u>Case reports and anecdotal information suggest that the following may be considered:</u></p> <p>Desmopressin acetate (DDAVP): 0.3 mcg/Kg IV</p> <p>Cryoprecipitate: At least 10 units</p> <p><u>Antifibrinolytic therapy</u></p> <p>Aminocaproic acid: 0.1 to 0.15 g/Kg IV over 30 min followed by IV infusion at 0.5 to 1 g/hr until bleeding subsides</p> <p>-OR-</p> <p>Tranexamic acid: 10 mg/Kg IV q 6 to 8 hr until bleeding subsides</p> <p>FFP: initial dose 2 units</p> <p>Hemodialysis or hemoperfusion can remove bivalirudin or argatroban (however, given their short half-lives, this is rarely necessary)</p>	<p>aPTT, INR, thrombin times, clottable fibrinogen</p>	<p>> Desmopressin acetate should be given over 15 minutes; and immediate effect should be seen; doses can be repeated at 8 to 12 hour intervals; serial doses are associated with tachyphylaxis, hyponatremia, and seizures (particularly in children < 2 yrs)</p> <p>> Cryoprecipitate contains fibrinogen, factor VIII/von Willebrand factor, and factor XIII; 10 units will raise the fibrinogen by approximately 0.7 g/L in the average-sized adult</p>

aPTT = activated partial thromboplastin time; pt = prothrombin time; INR = international normalized ratio; FFP = fresh frozen plasma; PCC = prothrombin complex concentrate

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