The Emergent Reversal of Coagulopathies Encountered in Neurosurgery and Neurology: A Technical Note

Joshua Eric Medow, MD, MS; Matthew R. Dierks, PharmD; Eliot Williams, MD, PhD;
and J. Christopher Zacko, MD, MS

It is imperative for neurologists, neurosurgeons, and neurointensivists to know how to stop life-threatening hemorrhage in both surgical and non-surgical patients. However, knowing how to medically correct a coagulopathy has become increasingly challenging as more contemporary and sophisticated anticoagulation agents are developed and prescribed. In a time-sensitive and life-threatening situation, where there is little margin for error, the neurosurgeon may not have ready access to information about the drug or condition that caused the coagulopathy or the information on how to treat it. This thorough review of the literature provides a comprehensive overview of the medications and conditions that can lead to persistent and/or life-threatening intracranial hemorrhage.

Keywords: Anticoagulants; Coagulopathy; Intracerebral hemorrhage; Neurosurgery; Reversal

Recognizing the vital anatomy inherent to the central nervous system, one could argue that neurologists and neurosurgeons, above any other medical subspecialists, need to understand how to effectively stop life-threatening hemorrhage. That said, knowing how to medically correct a coagulopathy has become increasingly challenging as more contemporary and sophisticated anticoagulation agents are developed and prescribed. These newer agents not only broaden the store of knowledge required to treat these patients, but they also make it more difficult to achieve an effective reversal with each new generation of drugs that arrive on the market. When faced with a life-threatening coagulopathy, neurosurgeons and neurologists may not have ready access to information about the drug or condition that caused the coagulopathy or the information on how to treat it.

This technical note is a comprehensive overview of the medications and conditions that can lead to persistent (or initiation of) life-threatening intracranial hemorrhage. It is

compiled into nine tables that are organized by the mechanism of coagulopathy. It documents: (a) the duration of action of the offending agent or condition; (b) the treatment; (c) the half-life of the treatment; and (d) the laboratory tests needed (if available) to follow the reversal of the coagulopathy. By design, the text has been kept to a minimum, and the tables made succinct to most practically present the relevant information.

Methods

A comprehensive review of the literature including a PubMed search from 1966 to April 2014 and a Google scholar search was performed, and pertinent articles were reviewed and cited. Additional information from online medical sources were reviewed and cited as well.

Results

The tables provided in this article review key information about the medical conditions and drugs used to cause various coagulopathies. Reversal agent options are specifically

Corresponding Author: Joshua Medow MD, MS; Assistant Professor of Neurosurgery and Biomedical Engineering; Department of Neurosurgery; University of Wisconsin Hospital and Clinics; Room K4/822; 600 Highland Avenue; Madison, WI 53792-0001; Phone: (608) 263-0485; Fax: (608) 263-1728; Email: medow@neurosurgery.wisc.edu

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named and their half-lives are reported (for patients presumed to be without end-stage organ failure). The tables provide:

- Doses of reversal agents for adult patients
- The agents listed in order of preference
- Pediatric patient data was not compiled in these tables
- Associated laboratory tests that may be useful
- The levels of evidence offered are based on the University of Wisconsin Health Care (UWHC) Guidelines that follow criteria used by the American College of Cardiology and the American Heart Association (ACC/AHA).

Table 1 reviews those agents that *indirectly* affect thrombin (generally through antithrombin) and include drugs such as the heparinoids and their reversal agents.^{1,2} Heparin will potentiate the action of antithrombin III and thereby inactivates thrombin (as well as activated coagulation factors IX, X, XI, XII, and plasmin) and prevents the conversion of fibrinogen to fibrin. Therefore, thrombosis is blocked through the inactivation of activated Factor X and inhibition of prothrombin's conversion to thrombin. Unfractionated heparin binds to antithrombin III (ATIII) at the site of the native pentasaccharide sequence, changing its conformation and converting it from a slow to a rapid inactivator of several coagulation factors, particularly factor Xa. However, in order to inactivate thrombin, heparin must bind to thrombin and AT simultaneously, an effect that occurs only when the molecule exceeds 18 monosaccharide units (greater than 6000 daltons). Low molecular weight heparins (LMWHs) have a similar mechanism of action of heparin and retain the ability to inactivate factor Xa. However, because they are smaller molecules, they cannot simultaneously bind to thrombin and AT and, therefore, have a lesser effect on thrombin. Fondaparinux causes an antithrombin III-mediated selective inhibition of only factor Xa, but cannot inactivate thrombin because of its extremely short length. It contains only a sulfated pentasaccharide unit with higher antithrombin affinity than the native pentasaccharide seen with unfractionated heparin.

The recommended laboratory tests to assess efficacy of each of these agents is as follows: activated partial thromboplastin time (aPTT) and/or activated clotting time (ACT) to measure heparin activity and anti-factor Xa +/- ACT to assess LMWH and fondaparinux activity. Protamine is the most commonly recommended reversal agent for heparin and LMWH. That said, protamine has not been shown to be successful in reversing fondaparinux. In severe cases, one could consider also giving Factor VIIa in an attempt to reverse severe bleeding after administration of fondaparinux.³

Table 2 lists the newest class of anticoagulants, the direct Factor Xa inhibitors.^{1,4} They differ from the agents in table 1 in that they do not require a cofactor (eg. ATIII) for activity and are considered direct Factor Xa inhibitors. While some practitioners will estimate drug activity with anti-factor Xa levels, it is important to emphasize that no therapeutic laboratory monitoring has been established. In mild to moderate cases of hemorrhage, it is advised to give 20–30

units/kg of prothrombin complex concentrate (PCC), while 40–50 units/kg should be given if bleeding is severe. While availability of PCCs varies among institutions, the authors advocate for the use of 4-factor PCCs over 3-factor PCC, if given the choice. There are ongoing efforts to develop reversal agents and effective treatment strategies for this class of anticoagulant.⁵

Table 3 reviews those agents that *directly* impact thrombin and includes some of the newer drugs such as dabigatran.^{1,4,6,7} There are no antidotes to these drugs at this time, but some are under development. There is also no reliable laboratory test to directly measure the extent of anticoagulation. Until such antidotes become available, 4-factor PCCs and 3-factor PCCs are recommended as an effective treatment strategy (although admittedly, the literature has some variation depending on the specific direct thrombin inhibitor used^{4,8}). Some have advocated for the use of activated charcoal if the patient recently took a dose of the medication.⁹ Another agent, factor eight inhibitor bypassing activity (FEIBA), has been shown to be effective in human plasma *ex vivo*.^{10,11} Factor VII has been shown to be less effective as a management option.^{12,13} In addition, as the agents are partially protein bound, one could consider dialysis in patients with renal impairment.

Table 4 demonstrates those agents/clinical situations that impact clotting through thrombolysis.^{1,14} Both alteplase and desmoteplase can typically be effectively reversed with either aminocaproic acid or tranexamic acid (depending on which is available in a hospital formulary). Also included in this table are clinical conditions where plasminogen activation and fibrinolysis are hallmarks of the condition (as the tPA-like agents work through plasminogen activation). With acute disseminated intravascular coagulation (DIC) (such as with infection) there is an underlying hypercoagulable state that exists and results in a consumptive coagulopathy. This can then promote bleeding in other areas due to low amount of clotting factors. Primary treatment is reliant upon treating the underlying condition with concurrent supportive care and broad replacement of coagulation factors via fresh frozen plasma (FFP), cryoprecipitate, and platelets. Using fibrinolysis inhibitors in these situations can cause massive thrombosis, because the areas where clotting is occurring can propagate clot if fibrinolysis is not allowed to occur, resulting in ischemia to affected tissues/organs.⁴ For this reason, fibrinolysis inhibitors for reversal of acute DIC are not recommended.

Table 5 demonstrates those coagulopathies that are measured by international normalized ratio (INR).^{1,6,14} They typically relate to the vitamin K factors or to the synthetic function of the liver if it is substantially impaired. It is recommended to always give vitamin K for 3 to 5 days when reversing warfarin, as acute reversal strategies can be short lived. At this point in time, PCCs are effective and preferable acute reversal agents for warfarin-associated coagulopathy as opposed to Factor VII.³ As with other cases where PCCs are

Table 1. Factor II (thrombin) and Factor X inhibition by antithrombin II activation with reversal agents.

Anticoagulant	Half-life	Duration of action	Reversible	Reversal agent	Reversal dose	Reversal agent half-life	Lab tests
Heparin IV*	1.5 hrs	2.5–4 hrs	Yes	Protamine (Class I, Level B)	1 mg protamine / 100 units heparin given in the past 2 hours (max = 50 mg) infused over 10 minutes. ** If heparin off for 30–120 minutes use ½ the calculated protamine dose. *** If heparin off >120 minutes and PTT is abnormal then use ¼ the calculated protamine dose.	7.4 mins	aPTT ACT
Heparin SQ*	6 hrs	8–12 hrs	Yes	Protamine (Class I, Level B)	For 5000 units given < 120 minutes use 25 mg. For 5000 units given > 120 minutes use 12.5 mg. Probably no need to treat > 12 hours. (may need multiple divided doses because of depot effect)	7.4 mins	aPTT ACT
Fragmin* (Dalteparin) / Normiflo* (Ardeparin) - LMWH	3–5 hrs	8–12 hrs, depending on renal function	Partially	Protamine (Class I, Level B)	60% reversal: 1 mg Protamine / 100 units of dalteparin / ardeparin given in the past 2 hours (max = 50 mg) infused over 10 minutes if received within the past 8 hours. ** If enoxaparin given > 8 hours before then give ½ the calculated protamine dose. Probably no need to treat > 12 hours.	7.4 mins	Anti-Factor Xa +/- ACT
				Factor VIIa (Class IIb, Level C)	For life-threatening bleeding: Factor VIIa dosing is 70-90 mcg/kg IV with repeat dose of 70–90 mcg/kg after 2 hours if needed.	2.3 hrs	
Lovenox* (Enoxaparin) - LMWH	7 hrs	8–12 hrs depending on renal function	Partially	Protamine (Class I, Level B)	60% - 80% reversal: 1 mg protamine / 1 mg of enoxaparin given in the past 2 hours (max = 50 mg) infused over 10 minutes if received within the past 8 hours. ** If enoxaparin given >8 hours before then give ½ the calculated protamine dose. Probably no need to treat >12 hours.	7.4 mins	Anti-Factor Xa +/- ACT
				Factor VIIa (Class IIb, Level C)	For life-threatening bleeding: Factor VIIa dosing is 70-90 mcg/kg IV with repeat dose of 70–90 mcg / kg after 2 hours if needed.	2.3 hrs	
Arixtra** (Fondaparinux)	17-21 hrs	2–4 days depending on renal function	Limited Evidence	Factor VIIa (Class IIb, Level C) Note: Protamine NOT effective	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70 – 90 mcg / kg after 2 hours if needed.	2.3 hrs	Anti-Factor Xa

*Heparin and Low Molecular Weight Heparin have effects on both Factor Xa and Factor II; **Fondaparinux selectively inhibits Factor Xa
 IV=intravenous; SQ=subcutaneous, LMWH=low molecular weight heparin, PTT=partial thromboplastin time; aPTT=activated partial thromboplastin time; ACT=activated clotting time;

Table 2. Direct Factor Xa inhibitors.

Anticoagulant	Half-life	Duration of action	Reversible	Treatment strategy	Treatment dose	Treatment agent half-life	Laboratory tests
Eliquis (Apixaban)	8-15 hrs	>24 hrs	Not currently reversible	Prothrombin complex concentrate (Class IIb, Level C) (No human studies)	25-50 units/kg IV with repeat dose if needed after 4 hours. Use lower dose in non-emergent or minor hemorrhage and higher dosage in moderate to severe bleeding.	Each factor ranges from 4.2-60 hours	Anti-Factor Xa
Xarelto (Rivaroxaban)	7–11 hrs	8–12 hrs but Xa levels affected for 24 hrs	Not currently reversible	Prothrombin complex concentrate (Class IIb, Level C)	25-50 units/kg IV with repeat dose if needed after 4 hours. *Use lower dose in non-emergent or minor hemorrhage and higher dosage in moderate to severe bleeding.	Each factor ranges from 4.2-60 hours	Anti-Factor Xa
				Factor VIIa (Animal Studies Only)	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70 – 90 mcg / kg after 2 hours if needed.	2.3 hours	
Lixiana (Edoxaban)	9-10 hrs	>24 hrs	Not currently reversible	Prothrombin complex concentrate (Class IIb, Level C) (No human studies)	25-50 units/kg IV with repeat dose if needed after 4 hours. *Use lower dose in non-emergent or minor hemorrhage and higher dosage in moderate to severe bleeding.	Each factor ranges from 4.2-60 hours	Anti-Factor Xa

IV=intravenous

utilized, the dose can vary between 20 units/kg for minor bleeding to 50 units/kg for severe bleeding. Once the initial dose of PCC has been given, one can usually verify correction of INR and then administer FFP as needed to maintain correction.¹⁵

Table 6 shows those coagulopathies that are related to platelet dysfunction due to medications.^{1,16-18} Note that the laboratory tests listed may be of limited value due to the inherent differences in results between individual patients. Also note that fish oil is not listed, because the exact mechanism of action is not entirely known. It is generally thought to have weak anticoagulant properties. Fish oil affects cell membranes, and its effects are likely permanent with respect to the affected platelets. This means its duration of action could reside in the 5 to 10 day range until new platelets are made, but anticoagulation would also be based on the clearance of fish oil from the body, which is not known.¹⁴ A commonly employed and supported treatment strategy used with several antiplatelet agents is platelet transfusion.¹⁹ This is certainly the case for non-steroidal anti-inflammatory drugs, aspirin, and clopidogrel, prasugal, abciximab, cilostazol, and aggrenox. Admittedly, this is an area of active investigation for two reasons: (1) lab work to measure the extent of

antiplatelet activity is notoriously inaccurate, and (2) the need for reversal for minor cases has not been validated (nor has the efficacy). However, it is typically agreed that in severe cases of bleeding it is prudent to administer platelet transfusion. In addition, many practitioners will give DDAVP (desmopressin acetate) in addition to platelet transfusion if a procedure is imminent. Antiplatelet agents that may respond to reversal strategies other than platelet transfusion include ticlopidine (can use methylprednisolone) and dipyridamole (where aminophylline may work).

Table 7 shows those coagulopathies that are related to platelet dysfunction from maldevelopment or acquired deficiencies on platelet function.^{1,14,20} The majority of these conditions respond to platelet transfusion with the exception of uremia/renal failure, which may require dialysis, cryoprecipitate, or desmopressin. It is also worth noting that there is no standardization when it comes to terminology surrounding platelet transfusion and dosage administered. In this paper, a “dose” is typically six random donor platelets (aka, a “six pack”).

Table 8 shows the occasional scenario where an immune-related factor inhibitor is present in the blood.^{1,14} This type of

Table 3. Direct factor II (thrombin) inhibition with reversal agents.

Table 3. Direct factor II (thrombin) inhibition with reversible agents.									
Anticoagulant	Half-life	Duration of action	Reversible	Treatment strategy	Treatment dose	Treatment agent half-life	Laboratory tests		
Argatroban (Argatroban)	45 minutes	51 mins	Not currently reversible	Factor VIIa (Theoretical only; limited experience has not shown benefit)	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70–90 mcg / kg after 2 hrs if needed.	2.3 hrs	aPTT INR TEG ACT* Thrombin time		
Pradaxa (Dabigatran)	Multiple doses 12–17 hrs			Prothrombin Complex Concentrate	Prothrombin Complex Concentrate dosing is 50 units/kg IV with repeat dose if needed after 4 hrs.	4–12 hrs	TEG ACT Thrombin time ECT*		
				FEIBA	100 U/kg	Has Factor II with half-life of ~72 hrs			
	Single dose 8 hrs			Hemodialysis (Class IIb, Level B)	Not applicable	Not applicable			
				Factor VIIa (Animal studies only) and has questionable efficacy	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70–90 mcg / kg after 2 hrs if needed.	2.3 hrs			

*Laboratory tests minimally useful since values (except possibly ACT, TEG, and antifactor IIa) do not necessarily correlate with level of coagulopathy (INR and PTT are often only elevated in supratherapeutic doses, thrombin time is elevated if the drug is present). ECT may be useful for dabigatran (if available). IV=intravenous; aPTT=activated partial thromboplastin time; INR=international normalized ratio; TEG=thromboelastography; ACT=activated clotting time; ECT=ecarin clotting time.

coagulopathy is often associated with an elevated aPTT. In such clinical cases, it is unlikely that a specific inhibitor will be identified in a timely matter. In addition, it is unlikely that a specific antidote will be available. Therefore, reversal strategies are broad in scope in hopes of controlling acute bleeding. At this point in time, PCCs are the favored agent. One could also consider Factor VII, aminocaproic acid, or tranexamic acid. Reversal strategies for inhibitor related coagulopathies can be augmented with steroids, intravenous immunoglobulin or plasmapheresis if severe. That said, if a particular factor specific inhibitor can be identified, it may be possible to give that specific factor when developing a reversal strategy.

Table 9 differs from table 8 in that the factor is inherently absent or inadequate in function rather than being blocked by an inhibitor.^{1,14,21} In Von Willebrand's disease, the best treatment options include desmopressin (not in acute hemorrhage), PCC, or Factor VII. In pseudo-Von Willebrand's, platelet transfusion is recommended. In cases of low fibrinogen or Factor XIII, cryoprecipitate is the recommended reversal agent. Lastly, Factor VII was specifically created for use in hemophilia A, while Factor IX concentrate can be given in hemophilia B (or PCC if not available).

Discussion

The included tables propose succinct and pertinent information intended to allow physicians a quick reference to develop a

reversal strategy for a given coagulopathy. Each table lists potential reversal agents in order of preference. For refractory or complicated cases (involving more than one category of coagulopathy), a practitioner may opt to use a combination of agents felt necessary to treat the coagulopathy. It is important to stress that the doses listed for Factor VIIa and PCC are high doses intended for the treatment of severe, life-threatening bleeding. In cases of less severe bleeding, or simple prophylactic reversal, lower doses would be effective.²² A crucial caveat to the reversal strategies presented in the tables is that there may be variations regarding the availability of certain agents among institutions. It is advisable that every practitioner who may treat a life-threatening intracranial hemorrhage be acutely aware of the reversal agents available within a given institution. Additionally, being aware of (or establishing) coagulopathy reversal protocols (including dosing) for particular clinical scenarios is imperative. This is especially true of PCCs, as they are not all the same. PCCs are diverse reversal agents comprised of varying concentrations of either three or four of the vitamin K-dependent cofactors (II, VII, IX, and X). Each PCC formulation has slightly different concentrations of each of the cofactors: 4-factor concentrates have adequate concentrations of all four of these cofactors, while 3-factor concentrates have much less factor VII. In addition, each PCC can have subtle variations in the relative concentrations of each cofactor present in the drug. It should now be clear that understanding exactly which PCC is available within a particular institution is vital to optimize

Table 4. Plasminogen activation/fibrinolysis with reversal agents and laboratory tests.*

Anticoagulant / Disease process	Half-life	Duration of action	Reversible	Reversal agent	Reversal dose	Reversal agent half-life	Laboratory tests
Activase / Cathflo (Alteplase/tPA)	26.5–46 mins	72 mins	Yes	Amicar (aminocaproic acid)	4–5 g load followed by 1 g/hr infusion.	4 hrs	D-Dimer Fibrin split products
				or Tranexamic acid	10 mg/kg IV hrs	2 hrs	
Desmoteplase	4 hrs	6–8 hrs	Yes	Amicar (aminocaproic acid) or	4–5 g load followed by 1 g/hr infusion.	4 hrs	D-Dimer Fibrin split products
				Tranexamic acid	10 mg/kg IV	2 hrs	
Sepsis-related or Acute DIC	n/a	n/a	No	Treatment of underlying cause	n/a but might include antibiotics and steroids	n/a	
				Platelets	1–2 units / 10 kg per day if platelets <50 K/microL	1–2 days	
				FFP	Variable to keep INR < 1.5.	variable 4–12 hrs	
				Cryoprecipitate	10 bags of American-Red-Cross-prepared cryoprecipitate (roughly 100–150 mL) to keep goal fibrinogen level 100–150.	3–5 days	
Non-septic, non-thrombotic chronic DIC (promyelocytic leukemia etc.) Note use of fibrinolysis inhibitors for reversal in acute DIC can be fatal and is not recommended.	n/a	n/a	Maybe	Amicar (aminocaproic acid) or	4–5 g load followed by 1 g/hr infusion.	4 hrs	aPTT INR ACT D-Dimer Fibrin split products
				Tranexamic acid	10 mg/kg IV every 6 hrs (adjust for renal insufficiency).	2 hrs	

*Labs minimally useful with tPA and chronic DIC since values do not necessarily correlate with level of coagulopathy.

DIC=disseminate intravascular coagulation; IV=intravenous; FFP= fresh frozen plasma; aPTT-activated partial thromboplastin time; ACT=activated clotting time; INR=international normalized ratio;

Table 5. Factor II, VII, IX, X (or all except VIII in liver failure) with reversal agents and labs.

Anticoagulant / disease process	Half- life	Duration of action	Reversible	Reversal agent	Reversal dose	Reversal agent half-life	Laboratory tests
Coumadin (warfarin, jantoven)	40 hrs	2–5 days	Yes	Vitamin K infusion and (Class I, Level B)	10 mg IV infusion (may repeat PO/IV daily over 3 days).	2 hrs	INR
				Prothrombin complex concentrate or (Class IIa, Level B)	Prothrombin complex concentrate dosing is 20-30 for mild coagulopathy and 40-50 units/kg IV for more severe bleeding. ¹⁷ Repeat dose if needed after 4 hrs.	Variable 4–12 hrs	
				Factor VIIa (Class IIa, Level B)	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70–90 mcg / kg after 2 hrs if needed.	2.3 hrs	
				FFP (Class I, Level B)	As needed.	variable 4–12 hrs	
Liver Failure	n/a	n/a	No	FFP / Plasmapheresis and	As needed (with plasmapheresis performed daily when liver has limited synthetic function).	Variable 4–12 hrs	INR
				Amicar (aminocaproic acid) or	4–5 g load followed by 1 g/hr infusion.	4 hrs	
				Tranexamic acid	10 mg/kg IV every 6 hours (adjust for renal insufficiency).	2 hrs	
				Prothrombin complex concentrate or	Prothrombin complex concentrate dosing is 50 units/kg IV with repeat dose if needed after 4 hrs.	Variable 4–12 hrs	
				Factor VIIa	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70–90 mcg / kg after 2 hrs if needed.	2.3 hrs	

IV=intravenous; PO=orally; FFP=fresh frozen plasma; INR=international normalized ratio

Table 6. Platelet inhibition with reversal agents and laboratory tests*

Antiplatelet	Half-life	Duration of action	Reversible	Reversal agent	Reversal dose	Reversal agent half-life	Laboratory tests
NSAIDs	Varies based on drug	< 1 day	Competitive cyclooxygenase binding	Generally not needed but can use platelets, desmopressin, or cryoprecipitate	Not well documented	Varies based on agent used	PFA 100
Aspirin	2–4.5 hrs	5–7 days	Partially	Platelets	1000 ml–1300 ml	1–2 days	PFA 100 CDP Collagen/ Epi
Plavix (clopidogrel)	6 hrs	5–7 days	Partially	Platelets	1000 ml–1300 ml	1–2 days	Aggregometry Mapping with TEG / ADP Verify Now System
Effient (prasugrel)	7 hrs (range 2–15 hrs)	5–9 days	Partially	Platelets	1000 ml–1300 ml	1–2 days	Aggregometry Mapping with TEG / ADP Verify Now System
Ticlid (ticlopidine)	12 hrs	4–10 days	Yes	Methylprednisolone	20 mg IV x 1	18–26 hrs	Bleeding time
Brilinta, Brilique, Possia (ticagrelor)	7–8.5 hrs	24–48 hrs	Yes	Time (platelet inhibition subsides competitively) Platelets?	1000 ml–1300 ml	1–2 days	Aggregometry Mapping with TEG / ADP Verify Now System
Integrilin (eptifibatide)	2.5 hrs	2–4 hrs	Bleeding time normal within 15-30 min Platelet function (60% of baseline) returns after 2 hours	Platelets maybe useful after 1–2 hrs (before this the amount of drug greatly outnumbers receptors)	1000 ml–1300 ml	1–2 days	PFA 100
Aggrastat (tirofiban)	2 hrs	4–8 hrs	Bleeding time normal within 3 hours Platelet function (>50% of baseline) returns after 4 hours	Platelets maybe useful after 1–2 hrs (before this the amount of drug greatly outnumbers receptors)	1000 ml–1300 ml	1–2 days	PFA 100 ACT
Reopro (abciximab)	10 days in the circulation bound to platelets	48 hrs	Platelet inhibition of 50% at 24 hours;	Platelets (since plasma half-life is short)	2000 ml–2600 ml	1–2 days	PFA 100 ACT
Pletal (cilostazol)	11–13 hrs	48 hrs	Yes	Platelets	1000 ml–1300 ml	1–2 days	CDP Collagen/ Epi
Persantine (dipyridamole)	Alpha (40 mins) Beta (10 hrs)	About 24 hrs	Yes but of limited value	Aminophylline?	50–100 mg IV	7–9 hrs	No labs
Aggrenox (dipyridamole + aspirin)	2–4.5 hrs based on aspirin	5–7 days based on aspirin	Partially	Platelets	1000 ml–1300 ml	1–2 days	PFA 100 CDP Collagen/Epi

*Labs arguably minimally useful at determining extent of antiplatelet effect

NSAIDs=non-steroidal anti-inflammatory drugs; PFA=platelet function testing; CDP= β -cyclodextrin-containing polycation; ACT=activated clotting time

Table 7. Platelet maldevelopment /dysfunction syndromes with reversal agents and laboratory tests.

Platelet Maldevelopment / Dysfunction	Mechanism	Reversible	Reversal Agent	Reversal Dose	Reversal Agent Half-Life	Laboratory tests
Bernard–Soulier Syndrome	GpIb glycoprotein deficiency with giant platelets	Yes	Platelets	Dose as needed to keep platelet count > 100k	1–2 days for transfused platelets	CBC PFA 100 ACT
Glanzmann's Thrombasthenia	GpIIb/IIIa integrin failure	Yes	Platelets	Dose as needed to keep platelet count > 100k	1–2 days for transfused platelets	CBC PFA 100 ACT
Thrombocytopenia	Bone marrow failure, dilution, or consumption. (In liver failure only additional platelets may have a role besides replacing factors.)	Yes	Platelets	Dose as needed to keep platelet count > 100k	1–2 days for transfused platelets	CBC ACT
			Steroids	Prednisone 1mg/kg/day	1 hr	
			Splenectomy	n/a	n/a	
Uremia / Renal Failure	Decreased thromboxane A2 function and increased platelet-inhibitory prostaglandin excess nitric oxide synthesis	Maybe	Dialysis	Dialysis is the preferred method of treatment	n/a	PFA 100 ACT
			Cryoprecipitate	10 bags of American-Red-Cross-prepared cryoprecipitate (roughly 100–150 mL)	3–5 days	
			Desmopressin	.3 mg/kg IV or SC or 300 mg intranasal. Repeat in 9–24 hours as needed.	1.5–2.5 hrs	
			Conjugated Estrogen	0.6 mg/kg IV daily infusion for 5 days maximum	About 13 hrs	

Clarification of terminology regarding platelet transfusions:

- Platelet preparations vary from hospital to hospital, making it difficult to suggest a standardized “dose”. For the purposes of this paper, it is noted platelets are supplied primarily in two ways: 1) Single donor apheresis concentrates (SDP) and 2) Platelets derived from whole blood, aka random donor platelets (RDP's). RDP's are the most common preparation used in neurosurgery (SDP's are harder and more expensive)
- One pooled concentrate (from one person) = 1 RDP, which is typically suspended in 40-70mL of plasma and contains $0.55\text{--}0.8 \times 10^{11}$ platelets and typically raises the platelet count by 5-10K

CBC=complete blood count; ; PFA=platelet function testing; ACT=activated clotting time

Table 8. Inhibitor related coagulopathies with reversal agents and laboratory tests.

Factor inhibitor	Mechanism	Reversible	Reversal agent	Reversal dose	Reversal agent half-life	Laboratory tests
Immune-related blood inhibitor	Factor is either bound or receptor is bound preventing the factor from functioning effectively	No / Maybe If an inhibitor is the source of the coagulopathy, specific factor concentrate may need to be augmented with steroids, IVIG, and / or plasmapheresis.	Factor VIIa	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70–90 mcg / kg after 2 hrs if needed.	2.3 hrs	Often a PTT, but can be factor specific.
			or			
			Prothrombin complex concentrate	Prothrombin complex concentrate dosing is 50 units/kg IV with repeat dose if needed after 4 hrs.	4–12 hrs	
			Amicar (aminocaproic acid)	4–5 g load followed by 1 g/hr infusion.	4 hrs	
			or			
			Tranexamic acid	10 mg/kg IV every 6 hrs (adjust for renal insufficiency).	2 hrs	
			Factor specific	Factor specific	Factor specific	

IVIG=intravenous immunoglobulin; aPTT-activated partial thromboplastin time

Table 9. Factor deficiency related coagulopathies with reversal agents and laboratory tests.

Factor deficiency	Mechanism	Reversible	Reversal agent	Reversal dose	Reversal agent half life	Laboratory tests
Von Willebrand's Disease (vWD)	Type 1 – low production of vWF / heterozygous	vWD Type 1	Desmopressin (not recommended for acute hemorrhage)	.3 mg/kg IV or SC or 300 mg intranasal. Repeat in 9–24 hrs as needed.	1.5–2.5 hrs	aPTT Ristocetin
	Type 2 – normal vWF levels but abnormal structure	vWD Types 1 – 3	Factor VIII vWF Concentrate (Haemosolve)	50 units/kg IV. Repeat every 8–24 hrs as needed.	10–11.5 hrs	Keep factor VIII levels above 100 IU/dL with trough levels above 50 IU/dL for the next 7 – 10 days. Do not exceed 200 IU / dL because of thrombosis risk.
	Type 2A – decreased function small structure		Factor VIIa	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70–90 mcg / kg after 2 hrs if needed.	2.3 hrs	
	Type 2B – functional gain due to excessive platelet binding and thus vWF consumption		Prothrombin Complex Concentrate	Prothrombin complex concentrate dosing is 50 units/kg IV with repeat dose if needed after 4 hrs.	4–12 hrs	
	Type 2M – decreased function large structure		Amicar (aminocaproic acid) or	4–5 g load followed by 1 g/hr infusion.	4 hrs	
	Type 2N – failure of vWF to bind factor VIII		Tranexamic Acid	10 mg/kg IV every 6 hrs (adjust for renal insufficiency).	2 hrs	
Type 3 – severe with vWF absence / homozygous						
Pseudo - vWD Platelet Type	vWF is normal but binding site on platelets is abnormal	Maybe	Platelets	? 40 pack multidonor (2000 ml–2600 ml).	1–2 days	aPTT Ristocetin
Low Fibrinogen or Factor XIII	Dilution, Consumption, failure to synthesize	Yes	Cryoprecipitate	10 bags of American-Red-Cross-prepared cryoprecipitate (roughly 100–150 mL)	3–5 days	aPTT Fibrinogen level Keep fibrinogen > 100 mg / dL
Hemophilia A	Low production / absence	Yes	Factor VIII vWF Concentrate (Haemosolve)	50 units/kg IV. Repeat every 8–24 hrs as needed.	10–11.5 hrs	aPTT Factor VIII level
			Factor VIIa or	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70–90 mcg / kg after 2 hrs if needed.	2.3 hrs	Keep factor VIII levels above 100 IU/dL with trough levels above 50 IU/dL for the next 7–10 days. Do not exceed 200 IU/dL because of thrombosis risk.
			Amicar (aminocaproic acid) or	4–5 g load followed by 1 g/hr infusion.	4 hrs	
			Tranexamic Acid	10 mg/kg IV every 6 hours (adjust for renal insufficiency).	2 hrs	
Hemophilia B	Low production / absence	Yes	Factor IX Concentrate (Haemosolve) also contains Factors II, VII, and X	60–90 units/kg IV. Repeat 12–24 hrs as needed.	16–30 hrs	aPTT Factor IX level
			Prothrombin Complex Concentrate	Prothrombin complex concentrate dosing is 50 units/kg IV with repeat dose if needed after 4 hrs.	4–12 hrs	
			Factor VIIa	Factor VIIa dosing is 90 mcg/kg IV with repeat dose of 70–90 mcg / kg after 2 hrs if needed.	2.3 hrs	

IV=intravenous; aPTT-activated partial thromboplastin time

treatment strategies. Lastly, the clinician should be aware that many of the reversal agents, such as Factor VIIa and PCC can cause thrombosis and other adverse reactions (eg, in the case of protamine, it is actually an anticoagulant at higher doses).

Conclusion

A series of nine tables are presented to help neurologists, neurosurgeons, and neurointensivists rapidly determine the best course of action to reverse coagulopathies. This paper intentionally does not comment on which patients qualify for reversal, as there is limited data supporting the use of some reversal agents in specific situations (eg, hemorrhage location, size, clinical status). The tables specifically address the laboratory tests that can assist in quantifying the degree of coagulopathy or treatment progress, the common causes of coagulopathies, the agents used to reverse them, and the duration of action of the offending agents, as well as their effective antidotes. To this point, this technical note should provide a succinct reference for the treatment of critically ill neurosurgical patients with life-threatening bleeding disorders.

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Author Affiliations

Joshua Eric Medow, MD, MS*; Matthew R. Dierks, PharmD†; Eliot Williams, MD, PhD‡; J. Christopher Zacko, MD, MS§

*Department of Neurosurgery University of Wisconsin Hospital and Clinics, Madison, Wisconsin

†Department of Pharmacy, University of Wisconsin Hospital and Clinics, Madison, Wisconsin

‡Department of Hematology, University of Wisconsin Hospital and Clinics, Madison, Wisconsin

§Department of Neurosurgery, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania