EB MEDICINE

EM Critical Care

UNDERSTANDING AND CARING FOR CRITICAL ILLNESS IN EMERGENCY MEDICINE

Emergency Management Of Coagulopathy In Acute Intracranial Hemorrhage

Volume 2, Number 2

Abstract

In the setting of an acute intracranial hemorrhage, very small amounts of additional bleeding may result in catastrophic consequences to the patient. When a coagulopathic patient with an intracranial hemorrhage presents to the emergency department, rapid reversal of coagulopathy is the most urgent medical intervention. Treatment of coagulopathy is necessary to both prevent hematoma expansion and facilitate neurosurgical interventions. In some cases, coagulopathy may be obvious and easily monitored, such as in a patient receiving warfarin. Other situations may be more complex, such as in a patient who is intermittently compliant with antiplatelet therapy. Many pharmacologic agents and blood products are available to modulate these clotting derangements, but they have varying efficacy and side-effect profiles. Furthermore, patients requiring anticoagulation have high rates of underlying thrombophilia and vascular disease. In these patients, tipping the coagulation system toward clotting may be necessary to stop bleeding but may also result in stroke, myocardial infarction, or other adverse thromboembolic events. This article reviews existing data and recommendations and suggests an approach to managing coagulopathy in patients with various forms of acute intracranial bleeding.

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CME Objectives

Upon completion of this article, you should be able to:

1. Describe the complications associated with anticoagulation in the setting of intracranial hemorrhage.
2. Describe the reversal options for VKAs, antiplatelet agents, and heparins.
3. Tailor a patient-specific reversal strategy based on the risks and benefits of available agents and patient-specific variables.
4. Describe novel anticoagulants and the challenges they pose.

Prior to beginning this activity, see “CME Information” on the back page.

Case Presentations

The first patient of your shift is a 63-year-old male complaining of sudden-onset severe headache and left-sided weakness that started 45 minutes prior to arrival. Pertinent past medical history includes long-standing hypertension, atrial fibrillation, and congestive heart failure. Current medications include hydrochlorothiazide, lisinopril, furosemide, and warfarin. He is lethargic on evaluation, with left hemiparesis. Emergent CT imaging demonstrates a right basal ganglia hemorrhage with intraventricular extension casting the third and fourth ventricles and dilatation of the temporal horns, suggesting obstructive hydrocephalus. The patient's INR is 2.8. Knowing that your next phone call is to the covering neurosurgeon to advocate for ventriculostomy placement, you begin to review your options for coagulopathy reversal to both limit hematoma expansion and facilitate potential neurosurgical intervention.

Your second patient is a pleasant 58-year-old female who tripped on the curb yesterday and now has mild right hemiparesis, expressive aphasia, and dysarthria. CT imaging demonstrates a left occipitoparietal acute-on-chronic subdural hematoma with 0.3 cm of subfalcine (midline) shift and a small contra-coup frontal contusion. The patient's daughter tells you that her medications include a cholesterol-lowering drug and both aspirin and clopidogrel for remote TIAs.

How should you approach the medical management of coagulopathy in these patients?

Abbreviations

COX-1: Cyclo-oxygenase-1
DDAVP: Desmopressin
DTI: Direct thrombin inhibitor
ED: Emergency department
FFP: Fresh frozen plasma
INR: International normalized ratio
IV: Intravenous
LMWH: Low-molecular-weight heparin
PCC: Prothrombin complex concentrate
PT: Prothrombin time
PTT: Partial thromboplastin time
rFVIIa: Recombinant activated factor VII
TBI: Traumatic brain injury
TT: Thrombin time
UFH: Unfractionated heparin
VKA: Vitamin K antagonists
VTE: Venous thromboembolism

Introduction

Intracranial hemorrhage is one of the most feared complications of oral anticoagulant therapy with vitamin K antagonists (VKA), such as warfarin. Intracerebral hemorrhage occurs 10 times more frequently in patients receiving VKAs than in the general population and up to 100 times as often in certain subpopulations.[1] Further, 10% to 25% of intracerebral hemorrhage cases admitted to academic centers are warfarin associated.[2] Controlled trials have reported an increasing incidence of intracranial hemorrhage of 0.2% per year, while observational studies report increases of 0.4% to 0.6% per year, which more likely reflect real-life scenarios.[3-6] This variability in incidence of anticoagulant-associated intracranial hemorrhage is attributable to different patient comorbidities, indication for anticoagulation, age, concomitant use of antiplatelet therapy, and the intensity of anticoagulant effect as measured by the international normalized ratio (INR).[7] Anticoagulation intensity is thought to be the most important determinant of intracranial hemorrhage. Several trials demonstrated higher bleeding rates when targeting therapeutic INRs > 3.0 when compared to targets of 2.0 to 3.0.[8,9] The mortality associated with spontaneous intracerebral hemorrhage is 30% to 55% and may spike to as high as 67% in the setting of oral anticoagulant therapy.[2,10,11] This higher mortality has been linked to greater hematoma expansion shortly after admission in the setting of incomplete warfarin reversal.[12] Similarly, observational studies describe worse outcomes of anticoagulated patients following traumatic brain injury (TBI).[13-17] More worrisome is the increasing number of patients being prescribed anticoagulants, which contributes to the growing numbers of patients requiring emergent reversal in the emergency department (ED).[18] With prompt anticoagulation reversal, hemorrhage extension and resultant mortality can be mitigated, as demonstrated in the TBI population.[19]

Similar trends are seen in patients on various antiplatelet therapies. More than 50 million adults in the United States take aspirin regularly for primary and secondary prevention of cardiovascular disease, making it the most widely used antithrombotic agent.[20] Many others receive thienopyridine derivatives, such as clopidogrel or prasugrel, alone or in combination with aspirin, for prevention of atherothrombotic events. While dual antiplatelet therapy has been demonstrated to have greater efficacy in several clinical situations, this combination is associated with higher bleeding risk (including intracranial hemorrhage) than monotherapy.[21-23] The true impact of antiplatelet therapy on outcomes in the setting of intracranial hemorrhage is uncertain. Nonetheless, in light of the life-threatening nature of intracranial hemorrhage, the majority of published expert opinions remain in favor of some reversal strategy for patients receiving antiplatelet agents with either spontaneous intracerebral hemorrhage or TBI. As with VKA reversal, the optimal reversal strategy among many options remains unclear.

Another patient cohort that may present to the ED is that taking low-molecular-weight heparin

(LMWH), often for treatment of venous thromboembolism (VTE). While rates of severe hemorrhage have been shown to be significantly lower with LMWH than with warfarin therapy,[24,25] it behooves the emergency clinician to be familiar with LMWH-reversal strategies.

Clinicians may also face intracerebral hemorrhage following thrombolytic therapy for ischemic stroke, myocardial infarction, or pulmonary embolism. Depending on the timing of thrombolysis, these patients may require emergent reversal.

Finally, newer oral anticoagulants (including factor Xa inhibitors and direct thrombin inhibitors [DTIs]) are being increasingly used in clinical practice. While the risks of severe hemorrhage associated with these agents appear no worse than with more conventional therapies, strategies for reversal agents are lacking.

This issue of *EMCC* focuses on strategies for reversing the effects of anticoagulants and antithrombotics. We will focus on the more common VKA and antiplatelet agents, while also addressing heparins, thrombolytic agents, and the more novel oral anticoagulants. As there is little consensus in many of these situations, one must understand the pharmacologic rationale for using various agents, their limitations, and their potential adverse effects. The details of the appropriate reversal agents are shown in **Table 1 (page 4)**, which summarizes reversal guidelines from the lead author's institution.

Critical Appraisal Of The Literature

A review of the literature from 1961 to the present using the databases Ovid MEDLINE®, PubMed, the Cochrane Database of Systematic Reviews, the National Guideline Clearinghouse, and Web of Knowledge was performed. Topics and search terms included: *bleeding complication; coagulopathy reversal (vitamin K antagonist reversal, coumadin, warfarin, antiplatelet agent reversal, aspirin reversal, clopidogrel reversal, heparin reversal, DTI, pentasaccharide reversal); intracranial hemorrhage (intraparenchymal hemorrhage, traumatic brain injury, hemorrhagic stroke);* and *coagulant (plasma, factor VIIa, prothrombin complex concentrate, DDAVP).* Over 350 articles were retrieved and reviewed for relevance. References from pertinent articles were also reviewed and included, if appropriate.

Antithrombotic Mechanisms And Monitoring Of Effect

Vitamin K Antagonists

Warfarin represents the most frequently used oral anticoagulant to treat and prevent a host of thrombotic cardiovascular disorders. It works by inhibiting hepatic synthesis of vitamin K-dependent coagulation proteins. It does so via inhibition of vitamin K epoxide reductase, the enzyme responsible for converting vitamin K into its active form. As a result, coagulation factors II, VII, IX, and X production is rendered ineffective. The reduced activity of these coagulation factors, and the degree of anticoagulation, occurs at a rate proportional to their various half-lives. The half-life of warfarin is 36 to 42 hours, accounting for patients' daily or every-other-day dosing to maintain therapeutic anticoagulation.[23] The prothrombin time (PT) and INR are the mainstays of VKA-anticoagulation monitoring. The PT responds to reduced activity of factors II, VII, and X and is reported as the more standardized INR (derived by calibrating the PT to a local reference value).

Antiplatelet Agents

Aspirin therapy affects both primary and secondary hemostasis via irreversible acetylation of cyclooxygenase-1 (COX-1) and fibrinogen, respectively. By acetylating COX-1, aspirin prevents the formation of thromboxane A2, which activates platelets and augments their aggregation.[27] Acetylation of fibrinogen makes clots more susceptible to fibrinolysis. A single dose of aspirin irreversibly suppresses thromboxane production for 1 week. With cessation of aspirin therapy, new platelet production recovers by approximately 10% per day; thus, it may take up to 10 days for full restoration of a functional supply of platelets.[28] Importantly, however, patients may manifest normal hemostasis with as few as 20% of platelets maintaining normal COX-1 activity.[29] This may explain why most invasive procedures (not including neurosurgical interventions) can often be safely performed without aspirin cessation.[30]

Thienopyridine derivatives (clopidogrel and prasugrel) act by blocking the platelet ADP (adenosine diphosphate) receptor required for platelet activation. Similar to aspirin, clopidogrel-induced platelet inhibition is irreversible, and after drug cessation, platelet function gradually recovers as the 10% daily platelet production accumulates. Platelet function is fully restored to baseline 7 days after thienopyridine cessation, but patients may manifest normal hemostasis earlier.[31] Prasugrel is more potent than clopidogrel, and it demonstrated a significantly increased profile of major bleeding compared to clopidogrel in a recent large randomized trial.[32]

In the setting of hemorrhage related to antiplatelet therapy, determining the degree of platelet inhibition would be helpful; however, platelet counts do not reflect function, and a functional test like the Bleeding Time test is exceptionally crude and poorly reproducible. Several more sophisticated platelet function tests may be used (typically by cardiologists) to identify patients with antiplatelet-therapy resistance and resultant high-residual platelet reactivity or, conversely, low-residual platelet reactivity.

Table 1. Intracranial Hemorrhage Anticoagulant/Antithrombotic Reversal Guideline

Antithrombotic Agent	Half-life	Reversal Agents	Dose	Rate of Administration	Time to Effect	Risks/ Cautions	Comments
VITAMIN K ANTAGONISTS							
Warfarin	36 h (5 d for INR normalization)	Vitamin K (phytonadione) **PLUS** FFP **OR** PPC and FFP **OR** rfVIIa and FFP	Hold warfarin & give vitamin K 5-10 mg IV (may repeat q12h) FFP: 10-30 mL/kg PCC: 25-50 U/kg* + 2 U FFP rFVIIa: 1-2 mg (10-40 mcg/kg)* + 2 U FFP	Vitamin K: administer IV; dilute in 50 mL NS and give over 30 min FFP: at least 10 mL/min PCC:* do not exceed 2 mL/min. Give 1-2 U FFP for factor VII replacement rFVIIa: IV bolus over 3-5 min (use within 3 h of reconstitution)	Vitamin K: PO: 24 h IV: 12 h FFP: 2-6 h PCC: < 30 min rFVIIa: < 30 min	IV formulation is associated with a very low risk of anaphylaxis FFP carries risk of infection and transfusion-related acute lung injury, must be thawed, and requires a large volume (often > 1 liter) PCC is associated with risk of thrombosis rFVIIa is associated with risk of thrombosis	**Off-label use of rFVIIa and PCC: REQUIRES ATTENDING APPROVAL** **ROUND DOSE TO NEAREST WHOLE VIAL**
ANTIPLATELET AGENTS							
Aspirin	15-30 min BUT 5-10 d for platelet recovery	DDAVP. Consider platelet transfusion.	DDAVP: 0.3 mcg/kg IV x 1 Platelets: 1-2 U	DDAVP: over 15 min	DDAVP: immediate Platelets: immediate	Serial DDAVP doses are associated with tachyphylaxis, hyponatremia, and seizures.	Patient may need transfusion of functioning platelets to attenuate bleeding.
Clopidogrel	8 h (approximately 5 d for platelet recovery)						
Prasugrel	7 h (< 7 d for platelet recovery)						
HEPARINS							
UFH	1-2 h	Protamine 1 mg reverses 100 U of UFH	See chart at the bottom of page 5	Administer SIVP. Do not exceed 5 mg/min. **Do not exceed 50 mg in a single dose, as high doses of protamine can have a paradoxical anticoagulant effect.**	5-15 min	Rapid administration can cause severe hypotension and anaphylaxis.	Prophylactic SQ doses of UFH do not lead to increased risk of hemorrhage. Look for other causes of hemorrhage.
LMWHs (enoxaparin)	2-8 h	Protamine (not as effective at reversing LMWH as UFH)	1 mg for each 1 mg of enoxaparin in last 8 h **If > 12 h have elapsed since LMWH administration, protamine may not be necessary.**				For LMWH, if PTT remains prolonged, may give second dose of 0.5 mg protamine per 1 mg LMWH. Consider FFP and other blood product support.

Table 1. Intracranial Hemorrhage Anticoagulant/Antithrombotic Reversal Guideline (continued)

Antithrombotic Agent	Half-life	Reversal Agents	Dose	Rate of Administration	Time to Effect	Risks/ Cautions	Comments
PENTASACCHARIDES/FACTOR Xa INHIBITORS							
Fondaparinux/ rivaroxaban	17-21 h in normal renal function	rFVIIa **OR** PCC	rFVIIa: 2 mg (40 mcg/ kg).* May repeat in 2 h if continued bleeding PCC: 25-50 U/kg.* Give 1-2 U FFP for factor VIIa component	rFVIIa: IV bolus over 3-5 min (use within 3 h of reconstitution) PCC: do not exceed 2 mL/min	rFVIIa: < 30 min PCC: < 30 min	rFVIIa is associated with risk of thrombosis PCC is associated with risk of thrombosis	Do not give rFVIIa and PCC together due to high risk of thrombosis.
DIRECT THROMBIN INHIBITORS							
Dabigatran	14-17 h	rFVIIa **OR** PCC. Consider DDAVP.	rFVIIa: 100 mcg/kg.* May repeat in 2 h if continued bleeding PCC: 25-50 U/kg.* Give 1-2 U FFP for factor VIIa component DDAVP: 0.3 mcg/kg IV x 1	rFVIIa: IV bolus over 3-5 min (use within 3 h of reconstitution) PCC: do not exceed 2 mL/min DDAVP: over 15 min	rFVIIa: < 30 min PCC: < 30 min DDAVP: Immediate	rFVIIa is associated with risk of thrombosis PCC is associated with risk of thrombosis Serial DDAVP doses associated with tachyphylaxis, hyponatremia, and seizures as well as isolated cases of thrombosis	Short half-life and discontinuation of DTIs are the primary means of attenuating bleed; provide support with crystalloid and blood products to facilitate rapid renal clearance. May also consider activated charcoal in the event of dabigatran overdose if it can be administered within 1-2 hours of ingestion. Hemodialysis may be considered as a last resort. Do not give rFVIIa and PCC together due to high risk of thrombosis. **There is no strong evidence for rVIIa or PCC dosing for reversal of DTIs.**

*Denotes doses that are NOT based on high-quality evidence.

Abbreviations: DDAVP, desmopressin; DTI, direct thrombin inhibitor; FFP, fresh frozen plasma; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NS, normal saline; PCC, prothrombin complex concentrate; PTT, partial thromboplastin time; rFVIIa, recombinant activated factor VII; SIVP,

Time elapsed since UFH administration	Dose of protamine per 100 U UFH over last 3 h
< 30 min	1 mg
30-120 min	0.5 mg
> 120 min	0.25 mg

These patients may have increased risks of ischemic and bleeding complications, respectively. Examples of potentially useful bedside tests are the platelet function assay 100 and the VerifyNow platelet aggregometry test, evaluating aspirin and clopidogrel inhibition, respectively. However, threshold values to predict bleeding complications are poorly validated outside of cardiac procedures, and it is unclear how (or if) these assays may guide therapy in the setting of urgent antiplatelet agent reversal.[33,34] At this time, use of these assays in EDs is primarily isolated to research protocols.

Heparins

Unfractionated heparin (UFH) exerts its anticoagulant effect primarily by inhibiting both thrombin and factor Xa. It has a short, dose-dependent half-life of 30 to 90 minutes. Bleeding risks are dose dependent and increase with concomitant use of other antithrombotics.[35] In the setting of UFH treatment, therapeutic effect is typically monitored via the partial thromboplastin time (PTT), which responds to heparin inhibition of both thrombin and factor Xa. Alternatively, some institutions monitor anti-factor Xa levels directly, typically in the inpatient setting.[36] Prophylactic heparin dosing does not typically confer an increased risk of major bleeding and, thus, is not monitored using laboratory parameters.

LMWHs also inactivate factor Xa but have a comparably reduced ability to inactivate thrombin (factor II). LMWHs have a more predictable dose-response curve as well as a longer half-life. As such, laboratory monitoring is not typically required or practiced. Monitoring anti-factor Xa levels may be useful when pharmacokinetics are uncertain, such as in renal insufficiency and obesity.[35] High anti-factor Xa levels (> 0.8 U/mL) have been associated with increased bleeding in some studies, but the utility of these measurements to guide reversal therapy is unclear. The 3 FDA-approved LMWHs are enoxaparin, dalteparin, and tinzaparin.

Pentasaccharides

The pentasaccharide, fondaparinux, is currently used at different doses for VTE prophylaxis and treatment. Pentasaccharides such as fondaparinux differ from other LMWHs in that they have no direct inhibitory effect on thrombin. They inhibit factor Xa by binding to and potentiating antithrombin III. This unique mechanism impacts the reversal strategy of this versus other heparin products. Similarly, changes in PT and PTT do not accurately reflect its anticoagulant effect, and anti-factor Xa levels may be helpful in monitoring the degree of anticoagulation. The elimination half-life of fondaparinux is approximately 17 hours, and it may be longer in the setting of renal insufficiency.[37] Thus, in the setting of acute intracranial hemorrhage, consider the use of reversal agents even 24 to 36 hours after dosing.

Antithrombotic Reversal Strategies

Reversing Vitamin K Antagonists

Treatment options for warfarin-associated intracranial hemorrhage include vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and recombinant activated factor VII (rFVIIa). There are no prospective comparative trials evaluating the efficacy of these various therapies in the setting of VKA-associated intracranial hemorrhage. These therapeutic options are summarized in **Table 1 (page 4)**. Aside from vitamin K administration, there is no clear consensus regarding which of

Table 2. Published Guidelines For Reversal Of Warfarin Anticoagulation In Patients With Intracerebral Hemorrhage

Society (year)	Vitamin K (mg)	Plasma (mL/kg)		PCC (U/kg)	rFVIIa
Australian (2004)	IV (5-10)	Yes (NS)	AND	Yes (NS)*	NS
British Standards (2005)	IV (5-10)	Yes (15)	OR	Preferred (50)	NS
EU Stroke (2006)	IV (5-10)	Yes (10-40)	OR	Yes (10-50)	NS
ACCP (2008)	IV (10)	Yes (NS)	OR	Preferred (NS)	Yes†
AHA (2010)	IV (NS)	Yes (10-15)	OR	Yes (NS)	No
French (2010)	Oral or IV (10)	Yes (NS)‡	OR	Preferred (25-50)	No

*If a 3-factor PCC is administered, fresh frozen plasma is also recommended as a source of factor VII.

†Use of PCCs or rFVIIa may vary, depending on availability.

‡Use plasma only when PCCs are not available.

Abbreviations: ACCP, American College of Chest Physicians; AHA, American Heart Association; EU, European Union; IV, intravenous; NS, not specified; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

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the other therapies should be used alone or in combination.[38] This is reflected in the various intracerebral hemorrhage coagulopathy reversal guidelines.[39] **(See Table 2.)** Furthermore, the target INR during reversal is also unclear, as specific INR values are designed to correlate with percentages of factor activity **(Figure 1)** and not clinical bleeding risks. Thus, in the absence of clear evidence, intensivist and neurosurgical groups use different target INRs, typically within a range of 1.2 to 1.5.

Vitamin K

Administration of supplemental vitamin K will replete intrahepatic stores and allow factor activation to resume. Vitamin K at a dose of 5 to 10 mg diluted in D5W or D5 saline infused at a rate of 1 mg/min is necessary to achieve a sustained reversal of the INR; however, given as a single agent, it is insufficient, with an onset of action of 2 to 6 hours and requiring up to 24 hours to achieve a complete response.[1,26] Intravenous (IV) administration is preferred, as both oral and subcutaneous vitamin K administration are less reliable and delay INR correction.[40-43] Though commonly cited, an anaphylactoid reaction is increasingly rare, with most cases occurring when large doses are administered rapidly with inadequate dilution.[44] The risk of an anaphylactoid reaction has been further decreased due to modern formulations lacking the causative castor oil diluents.[45]

In addition to restoring substrate for coagulation factor activation, emergent factor repletion is required for a more rapid coagulopathy reversal.

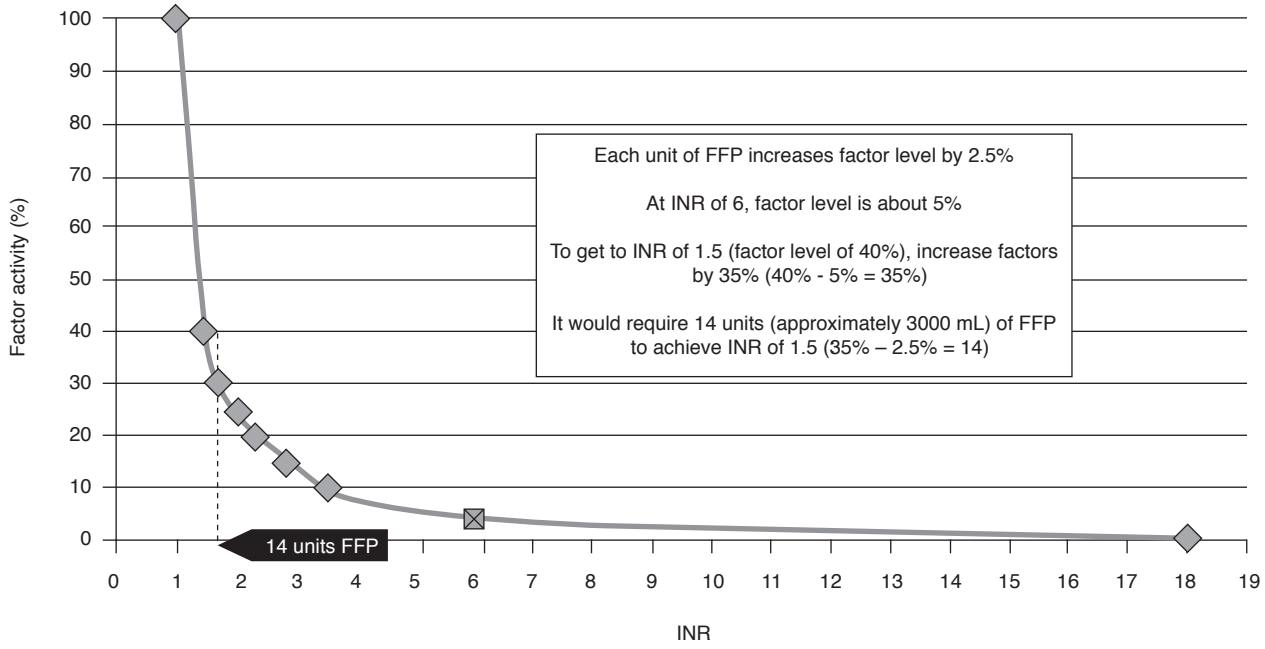
Plasma Transfusion

FFP contains all coagulation factors, including the vitamin K-dependent factors II, VII, IX, and X. While this may be the most widely used strategy of coagulation factor replacement in the United States,[44] limitations include the unpredictable rate and extent of INR correction as well as complications such as volume overload and acute lung injury.

The actual levels of vitamin K-dependent factors in FFP vary, making INR normalization unpredictable. **Figure 1** shows the estimated percentages of vitamin K-dependent clotting factors present at various INR values. One milliliter of FFP per kg generally increases the levels of coagulation factors by 1 to 2 IU/dL, or about 2.5% per unit of FFP.[1] Using this estimation and the example of a 70-kg patient with an INR of 6.0, 14 units (3000 mL) would be needed to replete factor levels to 35% of normal, corresponding to an INR of 1.5. Another strategy to estimate the volume (in milliliters) of FFP required to normalize the INR is:

(Target percentage of factor - actual percentage of factor) x body weight (kg)

Figure 1. Factor Activity Correlating With INR, And The Relative Impact Of FFP Transfusion



Abbreviations: FFP, fresh frozen plasma; INR, international normalized ratio.

Abstracted from: Burnett A, Cohen J, Garcia DA. Hemorrhagic complications of anticoagulants in hospitalized patients. In: Fang MC, ed. *Inpatient Anticoagulation.* Wiley-Blackwell; 2011. Reproduced with permission of John Wiley & Sons, Inc.

Commonly, upwards of 2 to 4 units of FFP are required for INR correction of a warfarin recipient in the therapeutic range (INR 2.0–3.0). The rapid rate of infusion of the large volume of colloid required to increase plasma protein levels makes circulatory overload a concern in patients with underlying chronic renal, cardiovascular, or hepatic disease. Another systemic complication of plasma transfusion is transfusion-related acute lung injury, which has an estimated incidence of 1 in 2000 to 1 in 8000 units transfused.[46,47] Strategies to limit this complication by using donor plasma without human leukocyte antigen antibodies (using predominantly male donors) are being developed and studied.[48,49] Other adverse events include infection transmission and a spectrum of allergic reactions ranging from mild urticaria to overt anaphylaxis.[47]

As this is a blood product containing ABO antigens, compatibility testing must be performed by the blood bank prior to administration, which routinely requires 20 to 30 minutes. FFP requires an additional 20 minutes to thaw once compatibility is established. The unavoidable delays to plasma transfusion are not without consequence. One study of 69 warfarinized patients with intracerebral hemorrhage found that each 30-minute delay in FFP transfusion decreased the incidence of full INR reversal at 24 hours by 20%.[51] Another recent retrospective analysis showed similar delays to reversal using FFP as well as increased 30-day mortality in intracerebral hemorrhage patients with uncorrected INR at 24 hours.[52]

The delays and other drawbacks inherent in FFP administration have led to a search for faster means of INR reversal.

Coagulation Factor Concentrates (PCC And rFVIIa)

Concentrated clotting factor preparations, known as PCCs, can be rapidly reconstituted and injected and are often effective at normalizing the INR within 30 minutes of administration. Initially developed and currently FDA approved for the management of hemophilia B (factor IX deficiency), PCCs are derived from large donor plasma pools and contain variable concentrations of factors II, VII, IX, X, protein C, and protein S. PCC formulations also include small amounts of heparin, which may help prevent thromboembolic complications. In the United States, approved nonactivated PCC formulations contain only 3 factors (II, IX, and X), while in Europe nonactivated 4-factor concentrates that additionally include factor VII are available.[53] An activated 4-factor concentrate (FEIBA) is FDA approved; however, whether or not the activated components make it too thrombogenic to be safe remains controversial. Studies evaluating 4-factor PCCs have consistently shown them to reverse the INR to less than 1.5 and increase circulating vitamin K-dependent factor levels within 10 to 30 minutes.[54,55] The 3-factor PCCs may be somewhat less effective, unless a small amount of FFP is given concurrently.[56] This is the supporting rationale for guidelines recommending FFP transfusion in addition to the 3-factor PCC.[57] All existing guidelines recommend concomitant vitamin K administration, as the INR correction with PCC alone may be transient.[58] The half-lives of the factor components II, VII, IX, and X are 60, 4, 17-24, and 31 hours, respectively, dictating the overall half-life of the particular PCC preparation.[59] The collectively longer half-life as compared to rFVIIa administration alone is one advantage in the setting of VKA reversal. While optimal PCC dosing is uncertain, weight-based dosing between 25 and 50 U/kg is typical, reserving the higher dose of 50 U/kg for INR values ≥ 5.0.[41,50,60-62] Several observational and retrospective studies demonstrated more rapid coagulopathy reversal using PCC as compared to FFP in the setting of intracerebral hemorrhage.[50,63-65] Of these, one trial of 55 patients demonstrated reduced hematoma growth in addition to faster INR correction.[65] Additionally, a recent analysis suggested that PCC may be more cost effective than FFP for warfarin reversal after life-threatening hemorrhage.[66] While PCCs are promising enough to have generated expert recommendations for their use in patients with intracranial bleeding receiving VKAs,[26,150-152] rigorous studies and those evaluating neurologic outcomes or mortality end points are lacking. Currently, PCCs are the preferred VKA reversal agents at the authors' institutions.

rFVIIa is an FDA-approved treatment for congenital factor VII deficiency and hemophiliacs with inhibitors to factor VIII, but it has been used with increasing frequency to reverse VKA-associated coagulopathy.[67] Its dual mechanism of action involves both initiating coagulation via the tissue factor VIIa pathway and direct platelet activation with a resultant thrombin burst.[68,69] Given its 4-hour half-life, INR reversal after factor VIIa dosing is transient, and vitamin K and FFP should be used concomitantly. The appropriate dose is unknown, with heterogeneous regimens described in the literature. Studies have shown similar efficacy with fewer thrombotic complications using lower doses (10-40 mcg/kg) for VKA-associated intracranial hemorrhage.[70-72] At the lead author's institution, if one chooses to use rFVIIa over PCC for VKA reversal, the 1- or 2-mg vials (14-28 mcg/kg in a 70-kg patient) are administered, depending on the degree of INR derangement. Many case series and observational studies of coagulopathic patients with intracranial hemorrhage report more rapid and consistent INR correction as compared to FFP, typically within 10 to 30 minutes.[70,71,73-79] However, the INR correction may simply reflect the ex-vivo effect of VIIa on the PT assay and may not always correlate with clinical hemostasis.[80-82] Several studies using rFVIIa for VKA-associated intracranial hemorrhage have demonstrated shorter times to neurosurgical intervention as well as cost savings as compared to plasma, owing to decreased

blood product transfusion and shorter hospitalizations.[72,73,83] Nonetheless, as in the PCC literature, there are no prospective randomized trials demonstrating outcome benefits.

The feared complication of both PCC and rFVIIa administration is primarily that of inadvertent thrombosis, either venous or arterial. Complications of cerebral infarction, myocardial infarction, deep vein thrombosis, pulmonary embolism, and peripheral arterial thrombosis have all been reported after PCC or rFVIIa therapy. Higher doses, repeat dosing, and traumatic vascular injury have been associated with these events.[84-86] Theoretically, PCC may have a lower risk of inadvertent thrombosis given its more balanced replacement of clotting factors, including anticoagulant protein C, protein S, antithrombin III, and heparin; however, this has not been evaluated in head-to-head trials. Administration of rFVIIa has been implicated in thromboembolic complications in the setting of off-label use.[87] The often-cited rFVIIa trial for acute intracerebral hemorrhage and a more recent meta-analysis of similar trials reported increased rates of thromboembolic complications.[88,89] Importantly, however, these trials excluded coagulopathic patients. Other large reviews were unable to substantiate increased incidence of inadvertent thrombosis after rFVIIa treatment.[90,91] Patients requiring warfarin therapy often have an inherently higher thrombotic risk profile, so VKA reversal using any modality may subject them to such complications.[92] Only prospective randomized trials will help settle this debate.

Variables such as the timeliness of reversal, the patient's tolerance for volume expansion, and the risks of inadvertent thrombosis are important considerations when choosing between factor concentrates and plasma as the primary reversal agent. Other considerations, such as the size and exact intracranial location of bleeding, should probably not affect these decisions. Even small hemorrhages in "noneloquent" areas of the brain may expand to catastrophic proportions without rapid coagulopathy management. Further, the authors believe that pharmaceutical cost should not deter administration of factor concentrates given the critical nature of intracranial bleeding and the cost analyses mentioned previously.

Reversing Antiplatelet Agents

While it may seem intuitive that antiplatelet therapy worsens both extension of hemorrhage and outcome, data are conflicting. In the setting of spontaneous intraparenchymal hemorrhage, several observational studies report increased hematoma expansion and mortality in those using single or dual antiplatelet therapy.[93-97] Other studies showed no such differences between patients on antiplatelet therapy versus controls.[98-100] Similarly, there is a lack of consensus in the TBI literature, with some literature implicating antiplatelet therapy as a predictor of poor outcomes[17,101,102] and some refuting that correlation.[103-107] Antiplatelet agent users may present with worse hemorrhage, but expansion is not clearly linked to these agents, and poor outcomes may instead be related to medical comorbidities.[19] Observational data are confounded by heterogeneity of patient populations, differing antiplatelet regimens, unreliable patient history of antiplatelet agent use, and variable patient response to antiplatelet therapy. Further confounding the dilemma, platelet dysfunction has been shown to be present in many intracerebral hemorrhage patients not reporting antiplatelet use.[108] These problematic findings and the life-threatening nature of intracranial hemorrhage have led opinion leaders to advocate for active reversal strategies while calling for future randomized trials to guide best practice in this setting.[109]

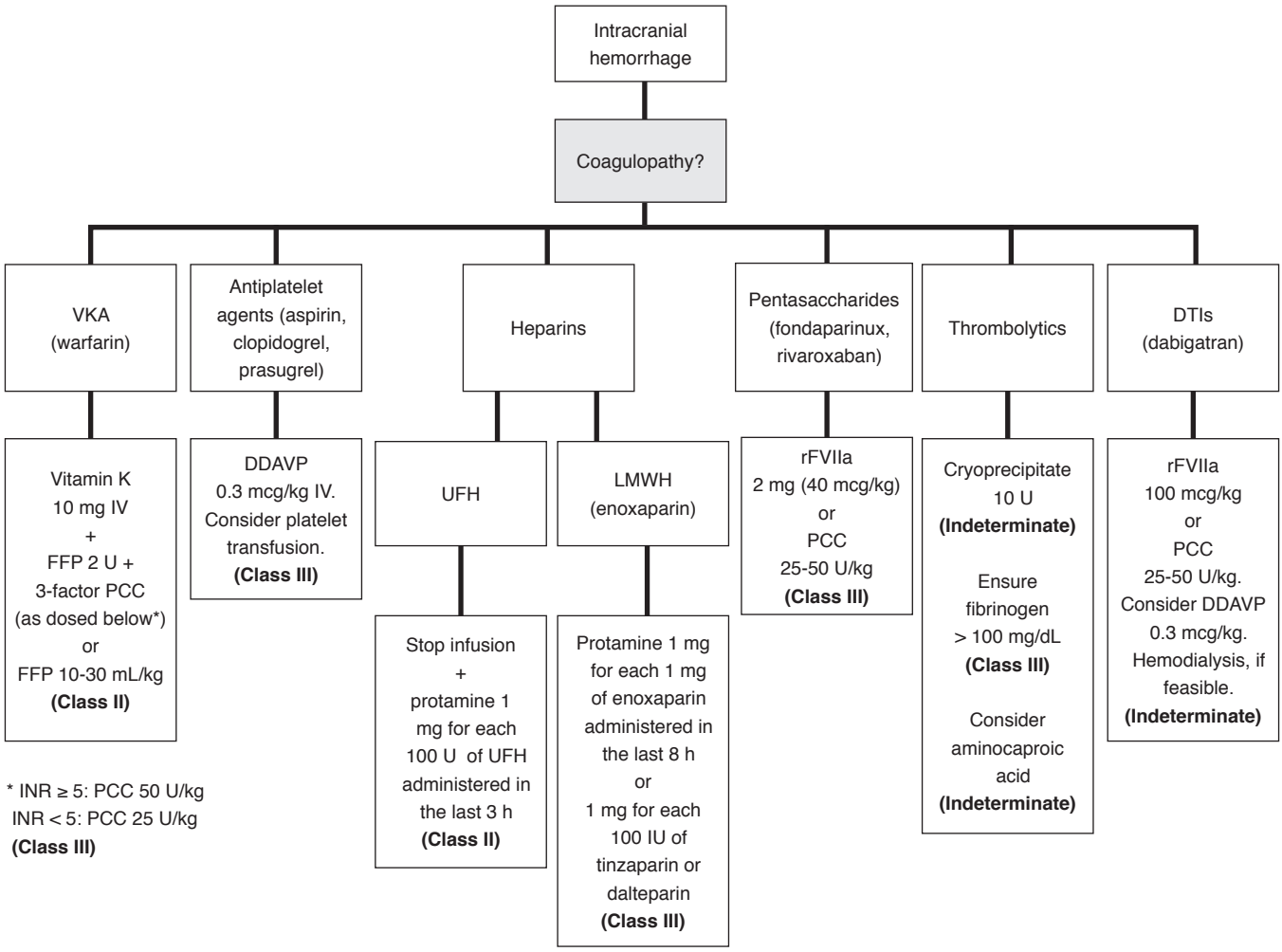
Platelet Transfusion

Even if it were clear that antiplatelet therapy worsened outcomes in intracranial hemorrhage, it doesn't necessarily follow that aggressive reversal can improve outcome. None of the observational trials comparing patients on aspirin or clopidogrel who received platelet transfusions to those who did not could demonstrate a favorable impact.[102,107,110-113] There are no controlled trials evaluating platelet transfusion therapy, so the negative results of these small observational trials represent the best available evidence, albeit with significant limitations. Thus, some authors make the case for withholding platelet transfusion after intracranial hemorrhage[111,114] or advocate the use of platelet function assays to guide transfusion therapy.[115] One study successfully used aspirin response testing to identify TBI patients with and without platelet dysfunction and guide platelet transfusion therapy,[115] but here too, there were no outcome differences between groups. Disadvantages of platelet transfusion may include infection transmission, transfusion-related acute lung injury, and allergic reactions.[116] Future trials may clarify both the utility of platelet function assays and platelet transfusion in the treatment of platelet-inhibited TBI patients.[117,118] Until then, for reasons discussed earlier in this issue, the authors believe that these platelet function assays are not ready for these applications. Further, extrapolating futility of platelet transfusion from observational studies is problematic primarily because patients felt to be sicker with worse hemorrhages were likely to receive platelet transfusions. At present, the authors' institutions often transfuse platelets to patients with intracranial hemorrhage who are on dual therapy but less routinely to those on single antiplatelet therapy.

DDAVP And rFVIIa

Other treatment options for patients with intra-

Clinical Pathway For Reversal Of Coagulopathy In Acute Intracranial Hemorrhage



Abbreviations: DDAVP, desmopressin; DTI, direct thrombin inhibitor; FFP, fresh frozen plasma; IV, intravenous; LMWH, low-molecular-weight heparin; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII; UFH, unfractionated heparin; VKA, vitamin K antagonists

Class Of Evidence Definitions

Each action in the clinical pathways section of *EM Critical Care* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA.* 1992;268(16):2289-2295.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

cranial hemorrhage on antiplatelet agents include desmopressin (DDAVP) and rFVIIa administration. DDAVP induces the release of von Willebrand factor and factor VIII, augmenting hemostasis. DDAVP, which is effective for reversing uremic platelet dysfunction, also corrects aspirin- and clopidogrel-induced platelet dysfunction[119-121]; however, there are no clinical outcome data supporting this intervention. DDAVP at a dose of 0.3 mcg/kg administered IV is relatively benign but may cause diuresis, hyponatremia, and seizures, all of which may be problematic for patients with intracranial hemorrhage. DDAVP probably carries less risk than platelet transfusion, is the first-line therapy at the authors' institutions, and is given routinely in cases where platelet transfusion is felt to be indicated. Lastly, rFVIIa has been reported to reverse aspirin- and clopidogrel-induced platelet dysfunction by augmenting thrombin generation in healthy volunteers.[122] As rFVIIa has shown utility in other forms of platelet dysfunction, it may prove to be another option.[123]

Reversing Heparins

Protamine

If an intracranial hemorrhage is suspected or confirmed in a patient receiving an infusion of UFH, the infusion should be stopped and residual drug reversed using IV protamine sulfate at a ratio of 1 mg protamine per 100 units of UFH infused over the last 3 hours. In practice, a recent heparin bolus can be reversed with 50 mg of protamine. After stopping an infusion of 1000 U/hr, reversal may be achieved using 20 to 30 mg of protamine.[35] The PTT should be followed to monitor heparin neutralization. Protamine administration may cause hypotension, bradycardia, and anaphylactoid reactions, and even a paradoxical anticoagulant effect, which can be minimized by giving a slow infusion over 3 minutes and avoiding doses greater than 50 mg at any one time.

Protamine is less effective at neutralizing LMWH, as it only partially reverses its anti-factor Xa effect.[124] Also problematic is the longer half-life of subcutaneously administered LMWH. There are no evidence-based guidelines on LMWH reversal; thus, the authors advise following the manufacturer's recommendations to administer 1 mg protamine per 1 mg of enoxaparin or 1 mg of protamine for every 100 U of dalteparin or tinzaparin administered within the previous 8 hours. If bleeding persists, an additional half-dose of protamine is recommended.[35]

Reversing Pentasaccharides

rFVIIa

Both monitoring and reversing the anticoagulant effect of pentasaccharides (such as fondaparinux) is based on quite limited data. Only rFVIIa has been studied as a potential pentasaccharide reversal agent. Two studies have demonstrated efficacy of rFVIIa in correcting markers of anticoagulation (including PT, PTT, thrombin generation time, and endogenous thrombin potential) in healthy volunteers after pentasaccharide administration.[80,125] However, there are no studies evaluating clinical efficacy in bleeding patients. Based on these studies, rFVIIa at 40 mcg/kg represents the most reasonable therapy to reverse pentasaccharide effect in the setting of intracranial bleeding.

Reversing Thrombolytic Agents

The incidence of symptomatic intracranial hemorrhage after thrombolysis for acute ischemic stroke is between 2% and 7%.[126-129] A recent study reported that 40% of thrombolysis-associated intracranial hemorrhages demonstrated hematoma expansion on repeat CT imaging.[125] This observational report also noted that no reversal of thrombolytic therapy was attempted in most patients. The various thrombolytic agents have extremely short half-lives (5-20 minutes); thus, by the time intracranial hemorrhage is diagnosed, these agents may no longer be active. If caught early, there are theoretical benefits to administering various agents. The use of the antifibrinolytic agent, aminocaproic acid, may be supported by the rationale that thrombolytic agents augment degradation of fibrin.[130] As thrombolytics induce fibrinogenolysis, some experts advocate fibrinogen repletion using FFP or cryoprecipitate.[131] Finally, clot lysis releases D-dimers exerting antiplatelet effects, providing a rationale for platelet transfusion. There are no clinical data comparing these approaches. These treatments were suggested in the 2007 American Heart Association guidelines but have been removed in the subsequent updated version due to lack of supporting evidence.[132,133] In the absence of any evidence-based strategy, the authors recommend treating thrombolytic-associated intracerebral hemorrhage empirically with fibrinogen repletion using 10 units of cryoprecipitate. Then, check the fibrinogen to assure a value > 100 mg/dL. Given aminocaproic acid's prothrombotic activity in the setting of a recent ischemic stroke, the decision to administer it should be made along with the patient's treating neurologist and hematology consultant.

Special Circumstances: Patients At High Risk For Thrombotic Disorders

Throughout this review, we have proposed treatments based on the life-threatening nature of coagulopathy-associated intracranial hemorrhage, implying that reversal of coagulopathy is required independent of the underlying indication for VKA or antiplatelet therapy. However, patients may incur serious risks with such reversal. Cases include patients with significant VTE clot burden, mechanical prosthetic valves, and recently placed drug- eluting

coronary artery stents requiring antiplatelet therapy. In such cases, if the intracranial hemorrhage is seemingly minor, one might intuitively question the need for reversal. The risk-benefit ratio in patients who are anticoagulated must be regularly re-evaluated. While initial resuscitation warrants normalization of coagulation parameters in nearly all circumstances, re-anticoagulation should be undertaken as soon as hematoma expansion is felt to be unlikely.[54,92] Hematoma expansion is most common within the first 24 hours after hemorrhage, but restarting anticoagulation may precipitate bleeding beyond that time frame, and a delay of several days or weeks may be deemed necessary. Guidance on restarting anticoagulation will often be directed on a case-by-case basis between the subspecialty services caring for the patient.

In the setting of antiplatelet therapy shortly after coronary stent placement, the risk-benefit analysis and correct management is less clear. As reviewed previously, the current evidence has not demonstrated clear clinical benefits to antiplatelet reversal despite it being a common practice. On the other hand, cessation of antiplatelet therapy in the setting of a recently deployed coronary artery stent that has yet to epithelialize is clearly linked to stent thrombosis and subsequent cardiac events.[134] Most clinicians would be hard pressed to actively continue antiplatelet therapy in the setting of acute intracranial hemorrhage (even minor hemorrhage). However, a reasonable strategy would be to withhold platelet transfusion or DDAVP administration in the setting of minor intracranial hemorrhage and recent stent placement. Risk of stent thrombosis increases with time abstaining from antiplatelet therapy and when treatment is stopped within 1 month of stent placement.[135] In the absence of data to drive management in these situations, such decisions should be made with collaboration between the neurosurgical, cardiology, emergency, and intensive care clinicians.

Cutting Edge: New Oral Anticoagulants And Challenges

A rapidly emerging oral anticoagulant is the DTI, dabigatran etexilate. Dabigatran is as effective as warfarin for acute VTE treatment and thromboembolism prevention in patients with atrial fibrillation.[136,137] A recent trial reported lower rates of intracranial hemorrhage in the dabigatran arm and has since led to FDA approval of its use for nonvalvular atrial fibrillation.[137] The incidence of bleeding outside of these monitored trials may be higher, however, because patients with comorbidities that increased their risk of bleeding and those requiring concomitant antiplatelet therapy were excluded from the aforementioned studies. As the risk of major bleeding (including intracranial hemorrhage) remains, we should expect to see increasing numbers of patients requiring emergent DTI anticoagulation reversal.

Typically administered twice daily, the onset of anticoagulation begins shortly after ingestion, with peak plasma concentration and maximum effect at 2 hours. Dabigatran's half-life is between 14 and 17 hours. In healthy individuals with normal renal function, the anticoagulant activity is reduced to 50% after 12 hours and is absent at 24 hours.[138] Anticoagulant activity may be prolonged in those with impaired renal disease. The reliable pharmacokinetics eliminates the need for continued monitoring of anticoagulant activity, which may contribute to its growing popularity over warfarin.

Unfortunately, there is no accepted monitoring strategy or reversal agent.[139] While the PT and PTT may be prolonged, they provide only rough qualitative assessments of anticoagulant activity and cannot be used to guide therapy. The thrombin time (TT) provides the most precise quantification of DTI anticoagulation and, in the future, may be useful to monitor upon admission and during attempts at reversal. This test is available at many hospitals and can be added to coagulation panels using existing coagulation laboratory instrumentation, if desired. Currently, however, no universal TT value can be used to guide treatment other than to detect anticoagulant effect, as the test's reagent is not standardized among labs.[140]

FFP transfusion does not reverse thrombin inhibition and is unlikely to reverse this coagulopathy despite dabigatran-induced PT/INR prolongation. A recent study failed to demonstrate any reversal of DTI anticoagulation using a standard dose of PCC.[141] rFVIIa administration has appeal since it activates thrombin on the platelet surface. Ex-vivo studies in healthy patients and animals suggest that this strategy may work,[142,143] but the therapy has not been tested in bleeding patients and is of uncertain benefit. DTIs can also be removed using hemodialysis, although the drug's half-life and delays to hemodialysis may make this approach impractical.

Until further data are available or an antidote is developed, clinicians should consider rFVIIa administration or hemodialysis while awaiting urinary drug clearance and should use the TT as guidance of anticoagulation effect in the setting of life-threatening intracranial hemorrhage. In this setting, a normal TT would suggest that little anticoagulant effect is present; however, elevated values cannot accurately quantify the degree of anticoagulant effect present to drive management strategies. DDAVP at a dose of 0.3 mcg/kg IV has shown some promise with an older DTI (hirudin) and, therefore, may be used to offset dabigatran-induced coagulopathy with little risk.[144,145]

Another new anticoagulant is the Xa inhibitor,

rivaroxaban. Instead of direct thrombin inhibition, this drug inhibits its precursor: factor Xa. Unlike LMWH (which also inhibits factor Xa), it does not concomitantly activate antithrombin. After several clinical trials assessing safety and efficacy,[146-148] this drug was recently approved by the FDA for stroke prevention in patients with atrial fibrillation and for VTE prevention after joint replacement. Rivaroxaban has a half-life of 3 to 9 hours and is prescribed at a fixed dose without laboratory monitoring. Similar to trials of dabigatran, rivaroxaban studies demonstrated an improved bleeding profile compared to warfarin. Administration results in concentration-dependent prolongation of the PT; however, assay variability renders PT/INR monitoring unreliable in clinical practice. Assays of anti-factor Xa activity are better indicators of plasma concentration, but it is unclear how these are to be used in the setting of emergent reversal.[149] Similar to dabigatran, there is no clear reversal agent in the event of hemorrhagic complications. Theoretically, rFVIIa or PCC might be successful reversal agents by counteracting Xa inhibition by directly activating thrombin on the platelets' surface. One laboratory study of healthy human subjects given rivaroxaban reported normalization of the PT and the endogenous thrombin potential using 4-factor PCC.[141] Doses of 50 U/kg were used, but the study authors acknowledge that this may be a larger dose than is necessary. There are no trials of bleeding patients thus far.

Disposition

According to the Brain Trauma Foundation, American Heart Association, and Neurocritical Care Society guidelines, patients with acute intracranial bleeding should be treated at neurosurgical centers with available expertise to perform intracranial pressure monitoring, cerebrovascular interventions, and surgical decompression of mass lesions.[133,151-152] It may occasionally be appropriate to admit a stable patient with a small intracranial bleed, without an underlying anatomical lesion, and with minimal risk of progression to a non-neurosurgical center for observation. However, the presence of coagulopathy is always associated with increased risk of hematoma expansion and warrants transfer to a higher level of care. Prior to transfer, patients should receive urgent infusions of reversal agents that can be rapidly prepared. Vitamin K, PCC, rFVIIa, DDAVP, and protamine are examples of agents that can be rapidly employed. When patients require products that require ABO compatibility testing, thawing, and slow infusion, and the transfer time is short, it may be preferable to transfer the patient prior to complete reversal of the coagulopathy.

Summary

Treatment of coagulopathy is the most important medical intervention for patients with acute intracranial hemorrhage and is necessary for surgical intervention. While consensus opinion does not exist, this review summarizes approaches and treatment options based on the available evidence and expert guidance. The emergency clinician should be familiar with the pros and cons of various strategies, as each patient with intracranial hemorrhage warrants a patient-specific risk-to-benefit analysis to arrive at the optimal treatment strategy. VKA reversal options include vitamin K repletion, plasma transfusion, rFVIIa, and PCC. When treating intracranial hemorrhage in the setting of antiplatelet therapy, many physicians recommend aggressive reversal despite conflicting data. Options include platelet transfusion, DDAVP, or rFVIIa.

Faced with new drug therapies with complex pharmacology, clinicians must master a basic understanding of the various mechanisms and pharmacodynamics of anticoagulants and their reversal agents and must understand how pathophysiology informs the choice of treatment options. Survival with optimal neurological function for patients with coagulopathy-associated intracranial bleeding relies upon multidisciplinary collaboration between emergency, intensive care, neurosurgical, hematology, pharmacy, and transfusion specialists. The best outcomes may result from protocolization and standardization within one's institution and across healthcare systems.

Must-Do Markers Of Quality ED Critical Care

- Immediate and comprehensive assessment of coagulopathy in all patients presenting with intracranial bleeding, to include pertinent lab work, evaluation of medications, and a comprehensive medical history.
- When warfarin is involved: complete reversal of the INR as soon as possible and always within 6 hours of ED presentation.
- When other forms of coagulopathy are present: documented administration of appropriate reversal agents within 1 hour of ED presentation.
- Urgent neurosurgical or neurocritical care consultation within 1 hour of ED presentation or rapid triage and transfer to a neurosurgical center.
- Development of institutional and system-wide protocols for managing coagulopathy in patients with intracranial bleeding.

Case Conclusions

The 63-year-old patient with intracerebral hemorrhage received 10 mg vitamin K by IV infusion. Next, you considered options for more rapid INR correction than can be achieved with vitamin K repletion alone. The patient's last echocardiogram documented an ejection fraction of 20%. You estimated that VKA reversal using FFP might require between 4 and 6 units and worried that the patient couldn't tolerate this colloid load. Further, you were concerned about the delays to reversal using FFP in a setting where the patient required insertion of a ventriculostomy catheter. You reviewed your hospital's guideline and decided to administer 25 U/kg of your 3-factor PCC and transfused 1-2 units of FFP as a source of factor VII. (Once 4-factor PCC is available in the United States, this might be your preferred single therapy.) Twenty minutes later, the INR was repeated and returned at 1.2. The consulting neurosurgeon placed an external ventricular drain for this increasingly lethargic patient, whose mental status rapidly improved, obviating the need for intubation. His coagulation profile was repeated at 6 and 24 hours and did not drift back up. (Alternatively, you might have administered 1-2 mg [14-28 mcg/kg] rFVIIa.)

For the second patient on antiplatelet therapy, you ordered a transfusion of 1 unit of apheresis platelets (equivalent to a "6-pack") despite a normal absolute platelet count. In your risk-benefit analysis, aggressive reversal in the setting of TBI took priority over continuing antithrombotic therapy, which in this case was for secondary prevention of cardiovascular disease. Additionally, you administered 0.3 mcg/kg of DDAVP. Repeat CT imaging in 12 hours demonstrated minimal expansion of contusions, but the patient's neurologic exam remained unchanged.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. **A patient presents to your community ED after a mechanical fall. The patient's medical history is significant for atrial fibrillation, for which he takes warfarin. A head CT reveals a 1 cm subdural and punctate intraparenchymal hemorrhage. The patient is alert and oriented, without any neurologic deficits. The INR is 3.2. Your facility does not provide neurosurgical services. What is the best plan of management?**
   a. Administer vitamin K and admit the patient to the surgical ICU at your facility.
   b. Call an outside facility to arrange for transfer. In the meantime, draw lab work including coagulation profile and administer vitamin K and PCC.
   c. Arrange for transfer to an outside facility, deferring reversal of anticoagulation to the accepting hospital.

2. **Which of the following regarding the use of protamine for reversal of UFH is FALSE?**
   a. Protamine 1 mg reverses 100 units of UFH.
   b. The time to effect of protamine is 5 to 15 minutes.
   c. Rapid administration of protamine can cause severe hypotension.
   d. Up to 75 mg of protamine can be given in a single dose.

3. **Which component of a warfarin reversal strategy acts most rapidly?**
   a. Vitamin K
   b. FFP
   c. PCC
   d. DDAVP

4. **The most aggressive strategy to manage aspirin- and clopidogrel-associated coagulopathy in acute intracranial hemorrhage would be:**
   a. Platelet transfusion only
   b. DDAVP only
   c. PCC
   d. Platelet transfusion and DDAVP

5. **All of the following are limitations to using FFP for reversal of warfarin-induced coagulopathy EXCEPT:**
   a. FFP interacts with vitamin K.
   b. FFP administration requires thawing prior to administration.
   c. FFP administration can result in transfusion-related acute lung injury.
   d. A large volume of FFP is typically required for complete INR reversal.

6. **Which of the following statements regarding factor concentrate use is TRUE?**
   a. 3-factor PCCs typically include a significant amount of factor VII.
   b. Using factor concentrates for warfarin reversal is not a cost-effective strategy.
   c. Warfarin reversal using factor concentrates has been proven to improve neurologic outcomes after intracerebral hemorrhage.
   d. IV vitamin K should be administered concomitantly with factor concentrates for warfarin-associated intracerebral hemorrhage.
   e. Factor concentrate administration poses no risks to those with an elevated INR.

7. **Anticoagulation with DTIs such as dabigatran is:**
   a. Monitored using the PTT
   b. Easily reversed using FFP
   c. Typically fully metabolized at 24 hours in patients with normal renal function
   d. Prolonged in the setting of renal insufficiency
   e. Both C and D

8. **Choose the most appropriately matched anticoagulant and reversal agent.**
   a. DTI reversal using FFP
   b. Thrombolytic reversal using PCC
   c. Fondaparinux reversal using rFVIIa
   d. Warfarin reversal using protamine sulfate
   e. LMWH reversal using PCC

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Date of Original Release: April 1, 2012. Date of most recent review: March 1, 2012. Termination date: April 1, 2015.

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Goals: Upon completion of this article, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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EM Critical Care (EMCC) (ISSN Print: 2162-3031, ISSN Online: 2162-3074, ACID-FREE) is published 6 times per year by EB Medicine (5550 Triangle Parkway, Suite 150, Norcross, GA 30092).