Factor Products

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LEARNING OBJECTIVES

1. Distinguish between different clotting factor deficiencies and the available clotting factors.
2. Devise a dosing and monitoring plan for acute bleeding in the patient with a clotting factor deficiency.
3. Distinguish among reversal strategies for different anticoagulant agents.
4. Delineate the role of individual reversal agents in coagulopathy normalization, together with the risk profile and monitoring values for each agent.

ABBREVIATIONS IN THIS CHAPTER

aPCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
DOAC	Direct-acting oral anticoagulant
FFP	Fresh frozen plasma
FIX	Factor IX
FVIII	Factor VIII
FXa	Activated factor X
IVR	In vivo recovery
MASAC	Medical and Scientific Advisory Committee (National Hemophilia Foundation)
PCC	Prothrombin complex concentrate
PT	Prothrombin time
rFVIIa	Recombinant activated factor VII (VIIa)
VKA	Vitamin K antagonist
VWD	von Willebrand disease
VWF	von Willebrand factor
VWF:Ag	von Willebrand factor antigen
VWF:RCo	von Willebrand ristocetin cofactor activity

Table of other common abbreviations.

INTRODUCTION

The clotting factor cascade maintains a balance between thrombosis and bleeding. Patients with inherited or acquired deficiencies in the various clotting factors are at increased risk of bleeding. Congenital factor deficiencies usually involve von Willebrand factor (VWF), factor VIII (FVIII), and factor IX (FIX). Bleeding risk is based on residual factor quantity and function. Inhibitor development, alloantibodies that neutralize the hemostatic effects of exogenous or endogenous factors, is one of the main complications in the treatment of hemophilia. Anticoagulation with vitamin K antagonists (VKAs) and direct-acting oral anticoagulants (DOACs) places a significant percentage of the population at an increased risk of bleeding. Factor replacement therapy is essential in treating or preventing bleeding in patients with clotting factor deficiencies, whether from genetic causes such as hemophilia or iatrogenic causes such as anticoagulation therapy (Table 1). Treatment of these disorders has evolved from administering blood products to administering the targeted factor products. Advances in purifying and treating human plasma and the advent of recombinant technology have greatly increased the availability and variety of factor products. Development of specific reversal agents for DOACs has greatly changed the treatment of bleeding in those situations. The potential life-threatening nature of bleeding caused by the clotting factor deficiency makes a baseline knowledge of factor replacement strategies and available products imperative.

VON WILLEBRAND DISEASE

Von Willebrand disease (VWD) is the most common congenital clotting factor disorder. Von Willebrand disease is caused by a qualitative or quantitative defect in VWF. Von Willebrand factor is a multimeric glycoprotein that binds collagen at the site of vascular injury and is involved in platelet adhesion and aggregation. Von Willebrand factor also binds circulating FVIII, protecting it from degradation and prolonging its half-life. A deficiency in functional VWF contributes to bleeding tendency

by both platelet function and coagulation because of the resultant reduction in FVIII plasma concentrations (Leebeek 2016). Von Willebrand disease is more often identified in women than in men, given that menorrhagia is common in increased bleeding. Von Willebrand disease has a prevalence of 0.6%–1.3% according to population studies but has a wide spectrum of manifestation, with about 1 in 10,000 seeking referral at specialized centers for bleeding (Nichols 2008).

Diagnosis of VWD is based on a personal and/or family history of bleeding and laboratory values indicating reduced VWF concentrations or function (Box 1). Bleeding score or questionnaires can identify patients with a bleeding disorder who may benefit from an additional diagnostic workup (Nichols 2008). Initial laboratory workup includes activated PTT (aPTT), PT, and Plt. Findings consistent with VWD include a prolonged or normal aPTT, a normal or low Plt, and a normal PT. If the aPTT is prolonged, a 1:1 mixing study should be done to determine the deficiency of clotting factor or presence of an inhibitor. Laboratory diagnosis includes quantitative and qualitative measurement of VWF and FVIII concentrations. Values are expressed as international units per deciliter on the basis of the WHO plasma standard and can be thought of as the percentage of normal. von Willebrand factor antigen (VWF:Ag) is an immunoassay that provides quantitative measurement of plasma VWF. von Willebrand ristocetin cofactor activity (VWF:RCo) is a functional assay of VWF-dependent platelet aggregation. Factor VIII testing measures functional cofactor activity in the plasma. Depending on initial VWD laboratory testing, specialized VWD testing may be considered to further define, diagnose, or specify the VWD subset (Nichols 2008).

Clinical presentation of VWD ranges from asymptomatic to severe, depending on the concentration of functional VWF. Most patients have mild to moderate forms of the disease, and the most common manifestations are easy bruising, mucocutaneous bleeding (gum bleeding, epistaxis, menorrhagia), and the potential for postoperative bleeding. Von Willebrand disease is classified into three genotypic subgroups on the basis of quantitative and qualitative deficiencies in VWF. Type 1 VWD is the most common form, accounting for 70%–80% of patients with VWD, and is associated with mild to moderate quantitative reductions in VWF. Type 2, which is characterized by a qualitative defect in VWF, accounts for 20%–30% of patients. Bleeding is usually more severe than in type 1. Type 2 VWD is divided into four subgroups depending on the type of defect (Table 2). Type 2B is unique with the presence

Box 1. Diagnosis of VWD

Patient history
- Personal bleeding history
- Family bleeding history
- Consider bleeding assessment tool

Initial laboratory tests
- CBC and Plt
- aPTT
- PT
- 1:1 mixing study if aPTT prolonged

Initial VWD tests
- VWF:Ag
- VWF:RCo
- FVIII

Specialized VWD tests
- Repeat initial VWD studies
- Ratio of VWF:RCo to VWF:Ag
- Multimer distribution
- Collagen binding
- RIPA or platelet binding
- FVIII binding
- Platelet VWF studies
- DNA sequencing of *VWF* gene

FVIII = factor eight; RIPA = ristocetin-induced platelet aggregation; VWD = von Willebrand disease; VWF = von Willebrand factor.

Information from: Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) expert panel report (USA). Haemophilia 2008;14:171-232.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the coagulation cascade and clotting pathways
- General knowledge of pathophysiology of von Willebrand disease and hemophilia
- Mechanism of action of common anticoagulants such as warfarin, heparin, low-molecular-weight heparin, and factor Xa inhibitors

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- World Federation of Hemophilia (WFH). Guidelines for the Management of Hemophilia.
- National Heart, Lung, and Blood Institute (NHLBI). von Willebrand Disease (VWD): Evidence Based Diagnosis and Management Guidelines.
- Leebeek FWG, Eikenboom JCJ. Von Willebrand's disease. N Engl J Med 2016;375:2057-80.
- 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation.
- American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed.

Table 1. Incidence of Clotting Factor Disorders Associated with Bleeding Disorders

Clotting Factor	Prevalence	Treatment	Plasma Half-Life
Fibrinogen	1 in 1,000,000	Cryoprecipitate Fibrinogen concentrates	2–4 days
Prothrombin	1 in 2,000,000	FFP/PCC	3–4 days
Factor V	1 in 1,000,000	FFP	36 hours
Factor VII	1 in 500,000	FFP/PCC rFVIIa	4–6 hours
FVIII	1 in 5000	DDAVP FVIII concentrates	8–12 hours
Factor IX	1 in 30,000	Factor IX concentrates	18–24 hours
Factor X	1 in 1,000,000	FFP/PCC factor X concentrate	40–60 hours
Factor XI	1 in 1,000,000	FFP	40–70 hours
Factor XIII	1 in 2,000,000	Cryoprecipitate FXIII concentrates	11–14 days
VWF	1 in 100	DDAVP VWF concentrates	8–12 hours

DDAVP = desmopressin; FFP = fresh frozen plasma; FVIII = factor XIII; PCC = prothrombin complex concentrate; rFVIIa = recombinant activated factor VII; VWF = von Willebrand factor.

Information from: Arruda VR, High KA. Coagulation disorders. In: Kasper D, Fauci A, Hauser S, et al, eds. Harrison's Principles of Internal Medicine, 19th ed. New York: McGraw-Hill, 2014; and Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) expert panel report (USA). Haemophilia 2008;14:171-232.

Table 2. VWD Classification

VWD Type	Description	VWF:RCo (units/dL)	VWF:Ag (units/dL)	VWF:RCo/ VWF:Ag Ratio	FVIII (units/dL)
	Normal population	50–200	50–200	> 0.5–0.7	Normal (> 40)
Low VWF	Partial quantitative deficiency	30–50	30–50	> 0.5–0.7	Normal
Type 1	Partial quantitative deficiency	< 30	< 30	> 0.5–0.7	↓ or normal
Type 2A	Decreased platelet adhesion because of deficiency of large VWF multimers	< 30	< 30–200	< 0.5–0.7	↓ or normal
Type 2B	Increase affinity for platelet glycoprotein Ib, decreased Plt	< 30	< 30–200	< 0.5–0.7	↓ or normal
Type 2M	Decreased platelet adhesion without deficiency of large VWF multimers	< 30	< 30–200	< 0.5–0.7	↓ or normal
Type 2N	Decreased VWF binding affinity for FVIII	30–200	30–200	> 0.5–0.7	↓↓
Type 3	Complete deficiency of VWF	< 3	< 3	N/A	↓↓↓ (< 10 IU/dL)

N/A = not applicable; VWD = von Willebrand disease.

Information from: Leebeek FWG, Eikenboom JCJ. von Willebrand's disease. N Engl J Med 2016;375:2057-80; and Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) expert panel report (USA). Haemophilia 2008;14:171-232.

of thrombocytopenia that may be exacerbated during surgery or another stress state because of the increased affinity of platelet glycoprotein IB. Type 2N is the least common but most severe type and is characterized by a greatly reduced affinity of VWF for FVIII, resulting in reduced FVIII concentrations because of increased clearance. Accounting for only 1%–3% of cases, type 3 is the rarest but most severe form of VWD. In essence, the quantitative deficiency results in almost undetectable VWF concentrations, which, commensurately, results in severely reduced FVIII concentrations because of enhanced clearance. Similar to patients with hemophilia A, patients with type 2N and type 3 VWD are at a greater risk of spontaneous or joint bleeds, depending on reduced FVIII concentrations.

Treatment varies depending on the type and severity of VWD as well as the site and severity of bleeding, with the goal of correcting platelet aggregation and coagulation defects. Strategies for hemostatic management include stimulating the release of endogenous VWF (i.e., desmopressin), administering exogenous VWF and FVIII concentrates, using a combination of the aforementioned options, and using agents that promote hemostasis.

Desmopressin, which stimulates the release of VWF and FVIII from endothelial cells, may prevent and treat acute bleeding in patients with adequate endogenous stores. Patients with low VWF, patients with type 1 VWD, and some patients with type 2 VWD may respond to DDAVP with a predicted rise of 2–5 times baseline concentrations of plasma VWF and FVIII (Nichols 2008). Intrapatient variability is significant, primarily depending on VWD subtype, with type 2 less likely to have an adequate response than type 1. Treatment with desmopressin should be preceded by a test dose with VWF:RCo and FVIII concentrations obtained at baseline and within 1 hour to measure response. Additional concentrations should be obtained at 2–4 hours to assess for increased clearance. Use desmopressin with caution in patients with type 2B, given the potential for pseudothrombocytopenia. In addition, children younger than 2 years may have a reduced response to desmopressin, and patients with type 3 VWD are not expected to have a clinical response (Nichols 2008).

Intravenous administration is preferred when desmopressin is used for prophylaxis of surgical bleeding and major hemorrhage in patients whose response to a test dose is adequate (Nichols 2008). Standard dosing is 0.3 mcg/kg diluted in 30–50 mL of normal saline and infused over 30 minutes. If given preoperatively, desmopressin should be administered 30 minutes before the scheduled procedure. Repeat dosing may be considered in 12–24 hours. Therapy is limited to 3–4 days because of the development of tachyphylaxis caused by the depletion of endogenous stores of VWF. Major adverse effects include hyponatremia and myocardial infarction. Patients should be screened for cardiovascular disease before administration, and fluid restriction should be considered with repeat dosing. Intranasal desmopressin may be considered for mild to moderate bleeding. Dosing is 1 puff for patients weighing less than 50 kg and 2 puffs for patients weighing more than 50 kg using the 150 mcg/puff (1.5 mg/mL) concentration (Stimate). A different concentration (0.1 mg/mL) of intranasal desmopressin is available for use in diabetes insipidus and nocturia, which is not appropriate for substitution in VWD because of the lower dose administered.

Von Willebrand factor replacement therapy is indicated for the prophylaxis and treatment of bleeding events in patients with VWD when desmopressin is known to be inadequate or contraindicated. Von Willebrand factor concentrates are the treatment of choice for type 3 VWD, many patients with type 2 VWD who have an inadequate response to desmopressin, and patients with type 1 VWD who are unresponsive to desmopressin or require a protracted treatment (Nichols 2008). Although cryoprecipitate does contain VWF, its use is not recommended because of the possibility of viral transmission, except when life and limb are threatened and VWF concentrates are not available (MASAC Document 250 2017). The goal of therapy for VWF replacement is to normalize VWF and FVIII concentrations in order to provide adequate hemostasis according to the type of procedure or severity of bleed (Table 3).

Von Willebrand factor concentrates are dosed on the basis of VWF:RCo units and secondarily on basis of FVIII units. Predicted in vivo recovery (IVR) is about 1.5–2 units/dL for each unit/kg of VWF:RCo infused and 2 units/dL for each unit/kg of FVIII infused (Leebeek 2016). However, individual patient pharmacokinetics vary, and monitoring of VWF:RCo and FVIII is recommended (Nichols 2008). In vivo recovery may be calculated by the following formula:

$$IVR = [\text{peak VWF:RCo} - \text{baseline VWF:RCo}]/\text{dose (units/kg)}$$

An individual patient's IVR may be used to calculate future and subsequent doses. Therapy duration and frequency of monitoring are based on the severity of the bleeding event or type of procedure. When a single dose of VWF concentrate is used for uncomplicated procedures, concentrations need not be monitored.

In emergencies and when a patient's baseline VWF:RCo is unknown, initial dosing is empiric on the basis of target concentrations and predicted IVR (Table 4). For planned procedures when baseline VWF/RCo concentrations are known, the loading dose may be calculated by the following formula:

$$\text{loading dose} = [(\text{target peak} - \text{baseline VWF:RCo}) \times \text{weight}]/IVR$$

If the patient-specific IVR is unknown, the predicted value of 2 units/dL per unit/kg may be used. The maintenance dosing is usually initiated at 50% of the loading dose at an 8- to

Table 3. VWF Replacement Therapeutic Goals and Therapy Duration

Indication	Target VWF:RCo and FVIII Concentrations	Therapy Duration
Major bleeding Major surgery *Examples:* *Cardiothoracic* *Neurosurgical* *Cesarean delivery* *Abdominal* *Orthopedic*	Peak: > 100 units/dL Trough: > 50 units/dL	7–14 days
Minor bleeding Minor surgery *Examples:* *Biopsy* *Complicated dental or laparoscopic* *Vaginal delivery*	Peak: > 50–80 units/dL Trough: > 50 units/dL	3–5 days
Uncomplicated procedures *Examples:* *Cardiac catheterization* *Endoscopy* *Lacerations* *Simple dental*	Often managed with a single preoperative dose without subsequent monitoring of concentrations	1 day

Information from: Leebeek FWG, Eikenboom JCJ. von Willebrand's disease. N Engl J Med 2016;375:2057-80; and Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) expert panel report (USA). Haemophilia 2008;14:171-232.

Table 4. Empiric Dosing for VWF Replacement[a]

	Major Surgery/Bleeding	Minor Surgery/Bleeding
Loading dose	40–60 units/kg	30–60 units/kg
Maintenance dose	20–40 units/kg every 8–24 hr	20–40 units/kg every 12–48 hr
Monitoring	VWF:RCo and FVIII trough and peak daily	VWF:RCo and FVIII trough at least once
Safety parameter	Do not exceed VWF:RCo 200 units/dL and/or FVIII 250–300 units/dL	

[a]Dosing units based on VWF:RCo activity.

Information from: Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) expert panel report (USA). Haemophilia 2008;14:171-232.

12-hour interval. Intrapatient variability in IVR and half-life may be significant. Monitoring of VWF:RCo and FVIII concentrations for subsequent dose adjustments is recommended.

There are currently three human plasma–derived and one recombinant VWF concentrate products in the United States for the treatment of VWD (Table 5). The products differ in the specific activity (units VWF/mg of total protein) and in the ratio of VWF/FVIII and are not interchangeable. Human plasma–derived products contain both VWF and FVIII and are approved for use in VWD and, in some cases, hemophilia A. Dosing for VWD is based on labeled VWF:RCo units, and hemophilia A dosing is based on FVIII units. Increased thrombotic risk is associated with elevated FVIII concentrations, and products with a higher VWF/FVIII ratio may be preferred

Table 5. VWF Replacement Products

Product Name	Source	Half-Life (hr)	Specific Activity (units of VWF/mg of protein)	VWF/FVIII Ratio
Alphanate	Human plasma derived	4–16	9–28	1.3:1
Humate-P	Human plasma derived	3–34	3.6–11.2	2.4:1
Vonvendi	Recombinant third generation	19–22	99–147	N/A[a]
Wilate	Human plasma derived	6–49	> 60	1:1

[a]Contains VWF only, FVIII is administered separately

Information from: National Hemophilia Foundation; Medical and Scientific Advisory Council. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. MASAC Document 250.

in patients with a history of thrombosis or when FVIII concentrations exceed 250 units/dL during treatment. The human plasma–derived products undergo many steps of viral screening and inactivation but have a risk of possible infectious transmission.

Recombinant VWF concentrate (Vonvendi) was FDA approved in 2015 for on-demand treatment and control of bleeding episodes in adults with VWD. Recombinant VWF concentrate is a third-generation recombinant product that does not contain FVIII. To achieve adequate hemostasis, FVIII coagulation activity must be greater than 40 units/dL. If the baseline FVIII concentration is less than 40 units/dL or unknown, an initial dose of recombinant FVIII concentrate should be administered together with the recombinant VWF concentrate. This combination is usually given empirically in a 1.3:1 ratio of VWF to FVIII concentrates, respectively, to achieve a goal VWF:RCo greater than 60 units/dL and FVIII greater than 40 units/dL. The ratio may be adjusted if baseline concentrations are known. The FVIII concentrate product should not contain additional VWF, and recombinant products are recommended. Timing is important, with the infusion of FVIII to follow within 10 minutes of VWF replacement. This allows for stabilization of FVIII by VWF. According to the package insert, patients who do not require an immediate rise in FVIII or who have baseline concentrations greater than 40 units/dL do not require an initial FVIII dose because concentrations show a sustained increase by 6 hours after single infusion. Maintenance dosing is an 8- to 24-hour interval guided by subsequent VWF:RCo monitoring, and additional FVIII is only required if concentrations decrease below 40 units/dL.

Serious adverse drug reactions to VWF concentrates include hypersensitivity or anaphylactoid reactions, thrombosis, transmission of infectious agents, and development of inhibitors. Hypersensitivity may develop to proteins or components. Increased thrombotic risk has been associated with VWF:RCo concentrations greater than 200 units/dL and/or FVIII greater than 250 units/dL, and concentrations should be monitored with prolonged administration to avoid this. Inhibitor development is less common in patients with VWD than in patients with hemophilia but is a potential risk in patients with type 3 VWD. Management of acute bleeding would require the use of bypassing agents and is covered later in the chapter. Although low, the risk of infectious transmission is higher with human plasma–derived products than with recombinant products.

Adjunctive treatments should be considered alone or in combination with specific VWF therapies to reduce or control bleeding. Hormonal contraceptives are the first-line therapy for menorrhagia in women who do not desire pregnancy. Antifibrinolytics are an important additional treatment for mucocutaneous bleeding and prevention of procedural and postoperative bleeding. Oral tranexamic acid is approved for use in menorrhagia at a dose of 1300 mg three times daily. Intravenous tranexamic acid or aminocaproic acid may be considered perioperatively. Tranexamic acid is dosed at 10 mg/kg every 8 hours. Aminocaproic acid may be given as an intravenous loading dose of 4–5 g, followed by an infusion of 1 g/hour or orally 4–6 g every 4–6 hours, until bleeding is controlled. The total daily dose of aminocaproic acid should be limited to 24 g to minimize potential adverse effects. Antifibrinolytics may also be locally administered in the oral cavity (swish and swallow) or genitourinary tract (continuous bladder irrigation). A variety of topical treatments may be used, including thrombin, fibrin sealants, and glues.

HEMOPHILIA A AND B

Hemophilia is an X-linked recessive congenital bleeding disorder most commonly caused by FVIII deficiency (hemophilia A) or FIX deficiency (hemophilia B). Other clotting factor deficiencies have been reported but at much lower incidence (see Table 1). Factor VIII is a glycoprotein that functions as a cofactor to amplify the rate of factor X activation by activated FIX. The absence or reduced function of FVIII or FIX

Table 6. Severity of Hemophilia

Severity	Clotting Factor Concentration	Bleeding Episodes
Severe	< 1 unit/dL or < 1% of normal	Spontaneous bleeding in absence of insult; severe/prolonged bleeding with minor surgery or trauma
Moderate	1–5 units/dL or 1%–5% of normal	Occasional spontaneous bleeding; severe/prolonged bleeding with minor surgery or trauma
Mild	5–40 units/dL or 5%–40% of normal	Rare spontaneous bleeding; severe/prolonged with major surgery or trauma

Information from: Srivastava A, Brewer AK, Mauser-Bunchoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013;19:e1-e47; Blanchett VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost 2014;12:1935-9.

results in impaired thrombin generation and resultant clot formation. Over 4000 genotypic variants of *FVIII* and *FIX* genes have been identified, leading to the absence or reduced function of the resultant coagulation cascade proteins. Hemophilia affects around 20,000 patients in the United States and 400,000 patients worldwide (Srivastava 2013). Factor VIII deficiency is more common than FIX deficiency, representing 80%–85% of the overall hemophilia population. Severe hemophilia is almost exclusively manifested in males, though female carriers may have reduced factor concentrations (Mannucci 2001).

Accurate diagnosis of hemophilia is essential for appropriate treatment. Hemophilia should be suspected in male patients with spontaneous bleeding or unexplained bruising early in childhood or excessive bleeding after surgery or trauma. Most patients with hemophilia have a family history of bleeding disorders, though up to 30% of hemophilias may result from spontaneous mutation of the factor genes (Srivastava 2013). Initial laboratory workup includes aPTT, PT, and Plt. Laboratory findings include a prolonged aPTT (severe and moderate) with a normal Plt and PT. A mixing study is indicated when the aPTT is prolonged in the absence of heparin therapy. Patient plasma is mixed with normal plasma, the mixture is incubated, and the aPTT is repeated. If the mixture's aPTT result corrects to normal range, the patient may have a coagulation factor deficiency. If the mixture's aPTT result does not correct, the patient may have an inhibitor. There are specific inhibitors such as FVIII inhibitor, which is associated with bleeding, and antiphospholipid antibodies, which is associated with thrombosis. Results of the mixing study are used to direct further studies. Definitive diagnosis of hemophilia depends on a factor assay showing deficiency of FVIII or FIX with values less than 40% compared with controls (Blanchett 2014). The factor activity concentrations are usually expressed as international units per deciliter on the basis of WHO plasma standard and can be thought of as percentage of normal (i.e., 20 units/dL is 20% of normal). Patients with reduced FVIII concentrations should also be tested for VWD because some forms of VWD have concurrent reductions in FVIII. Genetic testing is indicated in patients with hemophilia and in potential carriers (Srivastava 2013).

The clinical manifestation of hemophilia is an increased propensity for bleeding. Disease severity is primarily related to the decreased circulating factor concentrations (Table 6), which are then used to classify bleeding risk as mild, moderate, or severe. Severe hemophilia often presents early in life with spontaneous bleeding. However, mild hemophilia may not be diagnosed until later in life when manifested as excessive bleeding in the setting of major surgery or trauma. Spontaneous bleeding is rare when factor concentrations are 1% or greater (Srivastava 2013).

Hemarthrosis (joint bleed) is the most common site of spontaneous bleeding in severe hemophilia, followed by muscular and mucocutaneous. Hemarthrosis is most common in weight-bearing hinged joints such as the knees, ankles, and elbows and represents 70%–80% of spontaneous bleeding in patients with hemophilia (Srivastava 2013). Hemarthrosis is diagnosed clinically and is associated with pain, reduced mobility, and swelling. Inflammation may increase the susceptibility of the joint to recurrent bleeding. Development of a target joint is defined as three or more bleeding events within a 6-month period in the same joint and may lead to permanent joint damage, disability, and chronic pain (Hanley 2017).

The primary goal of care in patients with hemophilia is to treat and prevent bleeding by exogenously replacing the deficient clotting factor. Factor replacement can be given as routine prophylaxis to prevent bleeding events or as on-demand therapy in response to a bleeding event. The goal of prophylaxis is to maintain factor concentrations greater than 1% because this factor concentration can reduce spontaneous bleeding and the associated long-term complications in patients with severe factor deficiency. Primary prophylaxis is regular administration of factor concentrate initiated before age 3 years and before a large joint bleeding event. Patients

with severe hemophilia are recommended to receive primary prophylaxis, given the efficacy of preventing spontaneous bleeding and subsequent complications (joint damage). Secondary prophylaxis is regular administration initiated after more than two bleeding episodes but before the onset of joint damage. Patients with severe hemophilia and two or more bleeds are recommended to receive secondary prophylaxis. Tertiary prophylaxis is regular administration of factor products initiated after the onset of joint disease. Intermittent prophylaxis is administered for weeks to months for patients with mild to moderate hemophilia in the setting of an acute joint bleed, high-impact physical activity that predisposes to joint bleeding, or a planned surgical procedure. On-demand therapy refers to administration of factor products only in the setting of bleeding (Blanchett 2014; Srivastava 2013).

The World Federation of Hemophilia (WFH) guidelines and the Medical and Scientific Advisory Committee (MASAC) of the National Hemophilia Foundation recommend that patients with severe hemophilia A and B receive prophylactic factor at a young age, given the proven benefit and cost-effectiveness (MASAC Document 241 2016; Srivastava 2013). A 2007 study randomized boys 6–30 months of age with severe hemophilia A to receive primary prophylaxis or on-demand treatment with FVIII concentrate. When assessed at age 6 years, 93% of patients receiving prophylactic therapy had no evidence of joint damage, as assessed by MRI, compared with 55% in the on-demand treatment group (p=0.006). Joint and total bleeding events were also significantly lower in patients receiving prophylaxis compared with on-demand treatment (p<0.001 for both measures) (Manco-Johnson 2007). These results were confirmed with the ESPRIT trial in which prophylaxis significantly reduced joint damage and bleeding events and improved quality of life compared with on-demand treatment in pediatric patients with hemophilia (Gringeri 2011).

Many different prophylactic protocols are in use, and the optimal regimen is not defined. The two primary prophylactic dosing protocols referenced in the hemophilia guidelines are listed in Table 7. The two aforementioned trials both used a dose of FVIII concentrate 25 units/kg given three times weekly (Gringeri 2011; Manco-Johnson 2007). Hemophilia A requires more frequent dosing than hemophilia B because of the shorter half-life of FVIII (8–12 hours) compared with FIX (18–24 hours) (Fischer 2016). The guidelines emphasize that the prophylactic regimen should be individualized on the basis of patient response, factor availability, specific factor product, vascular access, and patient preference. The newer extended half-life products may offer the benefit of less frequent dosing and are discussed later in this chapter. Data analyses suggest that lower doses or less frequent administration are also effective in resource-limited situations. Despite apparent benefits, many patients do not use prophylactic dosing because of resource limitations, the burden of frequent injections, and the need for vascular access (Fischer 2016).

Table 7. Hemophilia Primary Prophylactic Protocols

Protocol	Dose	Frequency
Malmo	25–40 units/kg/dose	Hemophilia A: Three doses per week Hemophilia B: Two doses per week
Utrecht	15–30 units/kg/dose	Hemophilia A: Three doses per week Hemophilia B: Two doses per week

Information from: Srivastava A, Brewer AK, Mauser-Bunchoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013;19:e1-e47; Fischer K, Collins PW, Ozelo MC, et al. When and how to start prophylaxis in boys with severe hemophilia without inhibitors: communication from the SSC of the ISTH. J Thromb Haemost 2016;14:1105-9.

Patients with hemophilia A or B who have acute bleeding or need surgical intervention require adequate factor replacement to achieve hemostasis. The targeted factor concentration and duration depend on the severity and site of bleeding or on the site of planned intervention (Table 8). Surgery or invasive procedures for a patient with hemophilia require additional planning and assessment. These patients are best treated at, or in consultation with, a comprehensive hemophilia treatment center. Adequate laboratory support should be available for the monitoring of clotting factor concentrations and inhibitor testing. A supply of blood product and clotting factor concentrates should be available for both the surgery and the postoperative coverage. The dose and duration of clotting factor concentrate depend on the type of surgery.

Serious or life-threatening bleeding in a patient with hemophilia should be considered a medical emergency, and factor replacement should be initiated immediately. Treatment should be initiated on the basis of suspicion of bleeding without waiting for imaging confirmation or laboratory test results (MASAC Document 252 2017). Target factor concentrations should be a peak of 80–100 units/dL, and deficient factor concentrations should be maintained at greater than 50 units/dL during the recovery or at-risk period (i.e., trough). Maintenance doses should be timed when a factor concentration of 50 units/dL will occur. Alternatively, a factor replacement plan, including an initial bolus dose targeting a peak concentration of 80–100 units/dL followed by a continuous infusion titrated to maintain concentrations greater than 50 units/dL, could be used (Srivastava 2013).

The WFH guidelines recommend plasma-derived factor concentrates or recombinant factor concentrates in preference to cryoprecipitate or fresh frozen plasma (FFP) to treat bleeding disorders because of the lower risk of infectious transmission.

Table 8. Target Factor Concentrations and Therapy Duration According to Site and Severity of Bleeding or Procedure

	Hemophilia A		Hemophilia B	
Site	Goal Concentration (units/dL)	Therapy Duration (days)	Goal Concentration (units/dL)	Therapy Duration (days)
Joint	40–60	1–2, may be longer depending on response	40–60	1–2, may be longer depending on response
Superficial muscle	40–60	2–3, may be longer depending on response	40–60	2–3, may be longer depending on response
Deep muscle, iliopsoas, neurovascular injury, or significant blood loss	Initial: 80–100	1–2	60–80	1–2
	Maintenance: 30–60	3–5	30–60	3–5
CNS/head	Initial: 80–100	1–7	60–80	1–7
	Maintenance: 50	8–21	30	8–21
Throat/neck	Initial: 80–100	1–7	60–80	1–7
	Maintenance: 50	8–14	30	8–14
GI	Initial: 80–100	7–14	60–80	7–14
	Maintenance: 50		30	
Renal	50	3–5	40	3–5
Deep laceration	50	5–7	40	5–7
Surgery (major)	Preoperation: 80–100		60–80	
	Postoperation: 60–80 40–60 30–50	1–3 4–6 7–14	40–60 30–50 20–40	1–3 4–6 7–14
Surgery (minor)	Preoperation: 50–80		50–80	
	Postoperation: 30–80	1–5, depending on type of procedure	30–80	1–5, depending on type of procedure

Information from: Srivastava A, Brewer AK, Mauser-Bunchoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013;19:e1-e47.

The WFH guidelines do not prefer plasma-derived to recombinant products; however, the MASAC recommends recombinant factor concentrate products as the treatment of choice because of the lower risk of infectious transmission (MASAC Document 250 2017; MASAC Document 226 2014; Srivastava 2013). The choice of clotting factor is based on local preference, availability, and patient response.

Plasma-derived clotting factor concentrates differ in purity or type of viral inactivation. Purity refers to the final percentage of desired factor relative to other proteins present. Higher-purity products usually have lower production yield and are costlier. Lower-purity products may have a higher incidence of allergic reactions. Patients who react to a specific product may benefit from antihistamine administration before use or

may require a change to a higher-purity or recombinant product. Improved donor screening and viral depleting processes have greatly improved the safety of plasma-derived factor concentrates, with no cases of HIV, hepatitis C, or hepatitis B viral transmission from the currently available products. However, plasma-derived products can potentially transmit prions, the agents causing Creutzfeldt-Jakob disease, or nonenveloped viruses such as parvovirus B19, which are not eliminated by current viral inactivation and product purification techniques (MASAC Document 226 2014).

Recombinant factor products are produced in either animal or human cell lines and are classified on the basis of their generation. First-generation products are produced from transfected animal cell lines and use human or animal proteins in the production process, with albumin added as a final stabilizer. Second-generation products are produced from transfected animal cell lines and use human or animal proteins during the production process but use sucrose as the final stabilizer. Third-generation products are produced from animal cell lines but contain no added human or animal protein. Fourth-generation products are produced from human cell lines and contain no added human or animal protein. First- and second-generation recombinant products are considered much safer with respect to infectious transmission; however, because human and animal proteins are used in the production process, a theoretical risk remains. Third- and fourth-generation products have no exposure to human or animal proteins and thus have no risk of infectious transmission. The MASAC recommends that manufacturers phase out recombinant products that use human or animal proteins in the production process because of the theoretical increased risk of infectious transmission (MASAC Document 250 2017).

Newer recombinant products may also have additional modifications of the factor gene to enhance manufacturing production or improve pharmacokinetics by increasing half-life (Table 9; Table 10). The *FVIII* gene encodes a mature protein consisting of a single chain with six distinct domains. During secretion, the single-chain form is cleaved into a heavy chain and a light chain held together by metal ions. The FVIII is converted into activated FVIII by cleavage at three sites, resulting in a three-chain molecule without the B-domain. Deletion or truncation of the B-domain improves production yield but does not affect the factor activity or half-life (MASAC Document 250 2017).

Several modifications have been made to extend the half-life of recombinant factor products, including Fc-fusion, single-chain fusion, pegylation, and albumin fusion. Fc-fusion domain products contain the factor FVIII fused with Fc fragment of human immunoglobulin G subclass 1 (IgG-1). The Fc-FVIII binds the neonatal Fc receptor and is recycled back into circulation rather than undergoing lysosomal degradation, resulting in an increased half-life of 1.5- to 1.7-fold. Another modified FVIII product consists of an FVIII molecule with covalent linkage between heavy and light chains, resulting in a single-chain form with increased stability and

Table 9. FVIII Concentrates

Product Name	Source	Bioengineering	Half-Life (hr)
Advate	Recombinant third generation	None	9–12
Adynovate	Recombinant third generation	Pegylation	13–16
Afstyla	Recombinant third generation	Single-chain rFVIII	10–14
Eloctate	Recombinant third generation	B-domain deleted, IgG-1 Fc domain fusion protein	13–20
Hemophil M	Human plasma derived immunoaffinity purified	None	15
Kogenate FS Helixate FS	Recombinant second generation	None	11–16
Kovaltry	Recombinant third generation	None	12–14
Monoclate-P	Human plasma derived immunoaffinity purified	None	18
Novoeight	Recombinant third generation	B-domain truncated	11–12
Nuwiq	Recombinant third generation	B-domain deleted	18
Recombinate	Recombinant first generation	None	15
Xyntha	Recombinant third generation	B-domain deleted	8–11

Information from: National Hemophilia Foundation; Medical and Scientific Advisory Council. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. MASAC Document 250.

Table 10. Factor IX Concentrates

Product Name	Source	Bioengineering	Half-Life (hr)
AlphaNine SD	Human plasma derived	None	18
Alprolix	Recombinant third generation	IgG-1 Fc domain fusion protein	54–90
BeneFIX	Recombinant third generation	None	16–19
Idelvion	Recombinant third generation	Albumin fusion protein	104
Ixinity	Recombinant third generation	None	24
Mononine	Human plasma derived	None	23
Rebinyn	Recombinant third generation	Pegylation	114.9
Rixubis	Recombinant third generation	None	23–26

Information from: National Hemophilia Foundation; Medical and Scientific Advisory Council. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. MASAC Document 250.

increased VWF affinity and a resulting increase in half-life. Pegylated recombinant products are composed of the factor component covalently fused to a polyethylene glycol molecule. Pegylation protects the bound factor from degradation, increasing the product's half-life. The most recent modified recombinant factor product is FIX-albumin fusion protein. The half-life is extended because of the high molecular weight and interaction with the neonatal Fc receptor, preventing intracellular degradation (MASAC Document 250 2017; Hartman 2016). The goal of extending the half-life is to allow for less-frequent dosing of the factor product. The FVIII products have a relatively moderate increase in half-life of about 1.5-fold. The FIX products have a more significant increase, with half-life increased to greater than 100 hours in the FIX-albumin fusion protein, allowing for the administration of prophylaxis at a 7- to 14-day interval according to the package insert.

Factor VIII concentrates are the treatment of choice for hemophilia A. Each unit per kilogram of FVIII administered is predicted to increase plasma FVIII concentrations by 2 units/dL. The following formula may be used for initial dose calculations (Srivastava 2013).

dose = desired rise in factor concentration (units/dL)
x *weight (kg)* x *0.5*

Package insert and guideline recommendations are for the use of actual body weight in dosing calculations. Goal concentrations are determined by the site of bleeding or procedure. Factor VIII concentrations should be measured 15 minutes after completing the infusion to assess the patient-specific calculated dose. Subsequent doses should be based on the FVIII concentrate's half-life and factor concentrations. Alternatively, continuous infusions have been used for FVIII administration. An initial bolus dose may be administered on the basis of factor concentration goals, followed by a continuous infusion. An initial rate of 2–4 units/kg/hour may be used, with frequent factor monitoring and adjustment depending on factor concentration goal. Continuous infusions may lead to more stable factor concentrations and may reduce the total factor quantity used. Desmopressin may be considered for mild bleeding or minor procedures in patients with mild hemophilia A and documented response (Srivastava 2013).

Factor IX concentrates are the treatment of choice for hemophilia B. Use of pure FIX concentrates is preferable to use of 3- or 4-factor prothrombin complex concentrates (PCCs) containing FIX. Because hemophilia B results from a deficiency of FIX alone, administering PCCs containing additional clotting factors results in supraphysiologic concentrations of the additional factors and increased thrombotic risk. Administration of 1 unit/kg is predicted to increase FIX plasma concentrations by 1 unit/dL. The following formula may be used for initial dose calculations (Srivastava 2013).

dose = desired rise in factor concentration (units/dL)
x *weight (kg)*

Recombinant FIX concentrates have a lower recovery than those that are plasma derived and are predicted to increase FIX concentrations by 0.8 international units/dL in adults and 0.7 international units/dL in children. Goal concentrations are determined by the site of bleeding or procedure. Factor IX concentrations should be measured 30 minutes after completing the infusion to assess the patient-specific calculated dose. Subsequent doses should be based on the FIX concentrate's half-life and factor concentrations. Similar to FVIII, FIX concentrates may be administered as a continuous infusion (Srivastava 2013).

The most severe sequela of treatment with factor concentrates is the development of inhibitors. These alloantibodies neutralize the hemostatic effects of exogenous factors in severe hemophilia, making the treatment with all standard factor concentrates ineffective. Inhibitors develop in about 30% of patients with severe FVIII deficiency, but only in 3%–4% of patients with severe FIX deficiency. Development of an inhibitor leads to increased morbidity and mortality, decreased quality of life, and increased health care resource use compared with inhibitor-free patients with hemophilia (Rocino 2017). Risk factors for developing inhibitors include type of variant, family history of inhibitors, type of factor concentrate infused, intensity and early exposure to factor concentrates, and polymorphisms in immune response genes. Inhibitors usually develop within the first 50 exposure-days. Development of inhibitors in patients with mild/moderate hemophilia A is less common than in patients with severe forms of the disease. Inhibitor development tends to occur later in life and is usually associated with a period of intense factor administration, often in surgery. Patients often have a dramatic change in bleeding phenotype, which may resemble severe hemophilia A (spontaneous bleeds) or acquired hemophilia A (mucocutaneous) (Peerlinck 2006).

Data are conflicting if the choice of factor concentrate product influences inhibitor development. Recombinant factor concentrates may be more immunogenic than plasma-derived factor. The RODIN cohort study evaluated previously untreated patients for up to 75 exposure-days. This study found no difference in the rate of inhibitor development between patients receiving recombinant factor concentrates and those receiving plasma-derived factor concentrates. However, inhibitor development rates in patients receiving second-generation recombinant products were 60% higher than in patients receiving third-generation products (Guow 2013). The SIPPETT trial randomized previously untreated patients to plasma-derived or recombinant FVIII to assess the incidence of inhibitor development. The SIPPETT trial found that patients receiving plasma-derived FVIII had a lower incidence of inhibitor development than did patients receiving recombinant FVIII. The SIPPETT trial was terminated early based on the results of the RODIN study. Early termination of SIPPETT was due to the treatment option of a second-generation recombinant product (Kogenate) found to have increased incidence of inhibitor development in RODIN. When that recombinant product was removed from analysis, plasma-derived products still had lower rates of inhibitor development (Peyvandi 2016). In addition to early termination, the SIPPETT trial had several limitations that may limit the generalizability of its results, including low use of third-generation recombinant products. According to MASAC, previously untreated patients should balance the potential risks of infectious transmission with plasma-derived products with the potential for an increased risk of inhibitor development with recombinant products (MASAC Document 243 2016).

Development of an inhibitor should be assessed before surgery or in a patient who stops responding clinically to clotting factors. Development of an inhibitor is confirmed with the modified Bethesda assay. This test measures residual factor concentrations after mixing test plasma with normal plasma and comparing it with a control. Residual factor is converted into inhibitor units using a semi-log plot, with the assumption that 100% residual factor equals 0 Bethesda unit (BU)/mL. A low-responding inhibitor is considered less than 5 BU/mL, and a high-responding inhibitor is greater than 5 BU/mL. Patients with a low-responding inhibitor may be treated with specific factor replacement but require higher doses to mitigate the effects of the inhibitor. Patients with a high-responding inhibitor are unlikely to respond to specific factor replacement. Consequently, patients with a high-responding inhibitor will require bypassing agents for acute bleeds (Srivastava 2013). These factor products bypass the inhibitor of FVIII or FIX by providing an activated factor downstream in the clotting cascade, restoring hemostatic function. Bypassing agents include NovoSeven (recombinant activated factor II [rFVIIa]) and FEIBA (activated prothrombin complex concentrate [aPCC]). Bypassing agents have a higher thrombotic risk and require more frequent administration than standard FVIII and FIX concentrates, resulting in significantly higher costs. Because of the higher potential for thrombosis, bypassing agents are usually used on demand for acute bleeding and less commonly as prophylaxis. Eradication of inhibitors in patients with severe hemophilia A may be possible with immune tolerance induction (ITI). Immune tolerance induction involves avoiding specific factor replacement to allow inhibitor titers to decrease as low as possible before a high-dose regimen of FVIII replacement. Use of ITI in patients with hemophilia B is less well established, and inhibitor development is commonly associated with allergic reactions to the administration of FIX products (Rocino 2017).

Acquired hemophilia refers to the development of inhibitors in patients without a history of hemophilia, usually to FVIII (Table 11). Acquired hemophilia is a rare disease that is most common in older adults and is associated with more morbidity and mortality than congenital hemophilia. Diagnoses associated with developing inhibitors include pregnancy or postpartum, malignancy, rheumatoid arthritis, systemic lupus erythematosus, and drug reactions, though up to 50% of patients have no associated history. Bleeding is the most common complication, with more than 70% of patients presenting with serious bleeding. Bleeding can occur at any site, but joint bleeding is much less common than congenital hemophilia (Kruse-Jarres 2016). Acquired inhibitors may be suspected in a patient with an unexplained severity of bleeding, a prolonged aPTT that does not correct in a mixing study, and negative lupus anticoagulant. Presence of an inhibitor is confirmed with the modified Bethesda assay, as described earlier. Patients with acquired inhibitors are unlikely to respond to standard FVIII or FIX products and require bypassing

Table 11. Factor Concentrate Products for Use in Patients with Inhibitors

Product	Source	Factor	Initial Dosinga
NovoSeven	Recombinant	VIIa	• 90 mcg/kg every 2–3 hr
FEIBA	Human plasma derived	II IX X VIIa	• 50–100 units/kg every 6–12 hr • Not to exceed 200 units/kg/day
Obizur	Recombinant Porcine	VIII	• 200 units/kg; then titrate on the basis of FVIII concentrations • Usual interval = every 4–12 hr

[a]WHF guideline and package insert use actual body weight.

Information from: National Hemophilia Foundation; Medical and Scientific Advisory Council. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. MASAC Document 250.

agents to manage acute bleeding. In addition to rFVIIa and aPCC, recombinant porcine FVIII concentrate (Obizur) has been approved for use in acquired hemophilia A. Porcine FVIII restores hemostasis due to decreased cross-reactivity with the autoantibodies to endogenous human FVIII. Allergic reactions and the development of antibodies to porcine FVIII have been reported. Long-term inhibitor eradication with immunosuppressive therapy is recommended for definitive treatment. Treatment with cyclophosphamide and corticosteroids after resolution of acute bleeding is the most common eradication treatment, but intravenous immunoglobulin and rituximab have also been used (Kruse-Jarres 2016).

FUTURE THERAPIES

Improving the care of patients with factor deficiencies is an area of active research and innovation. Current research is focused on improving factor replacement products, nonfactor replacement strategies, and gene therapy. Increased half-life and subcutaneous delivery methods of replacement factor products would greatly ease administration in the home setting and decrease the need for vascular access. Nonfactor replacement strategies are investigating replacing the cofactor function of FVIII or altering the balance of pro- and anticoagulant proteins. Emicizumab is a monoclonal antibody designed to bind activated FIX and factor X, bypassing the cofactor activity function of FVIII. A recent phase III trial of emicizumab administered as prophylaxis in patients with hemophilia A and FVIII inhibitors decreased bleeding events by 87% compared with placebo ($p<0.001$). Emicizumab can also be a once-weekly subcutaneous injection, reducing the number of administrations and need for vascular access compared with current prophylactic treatment options (Oldenburg 2017). The FDA has granted priority review, and an approval decision is expected in early 2018. Reduced antithrombin concentrations may improve thrombin generation and mitigate the hemostatic effects of hemophilia. A recent phase I dose escalation trial of RNA interference therapy directed against antithrombin decreased antithrombin generation and increased thrombin activity when administered as a monthly subcutaneous injection (Pasi 2017). Several gene therapy programs are investigating phase I trials. The greatest focus is on adeno-associated virus vectors, but cell-based therapy and gene editing are also being investigated (Hartman 2016).

ANTICOAGULANT REVERSAL STRATEGIES

Anticoagulation is ubiquitous in the medical management of patients. Used to treat and prevent venous thromboembolism, stroke, acute coronary syndrome, and atrial fibrillation, anticoagulation and options for it are continually increasing. Because of guideline recommendations, ease of prescribing, and lack of required monitoring, DOACs account for most new anticoagulant prescriptions (Katz 2017; Desai 2014). Practitioners must therefore know how to approach both VKA- and DOAC-associated bleeding. Prothrombin complex concentrates in combination with vitamin K are the mainstay of VKA reversal. Drug- and class-specific antidotes for DOACs have been developed. Idarucizumab for reversing the direct thrombin inhibitor dabigatran is now commercially available, and andexanet alfa for activated factor Xa (FXa) inhibitors, fondaparinux, and low-molecular-weight heparin reversal is likely coming to market.

GENERAL TREATMENT AND ASSESSMENT TENETS

Prompt evaluation and history is required when confronted with the need to emergently reverse an anticoagulant. The site of bleeding and risk of complications should be assessed. Bleeding into confined or critical areas such as the brain or spinal cord can be just as devastating as large

blood losses resulting in hypovolemic shock. Assessing the level of anticoagulant effect should be part of the standard evaluation of all patients deemed to need emergency reversal. Laboratory testing varies depending on the anticoagulant agent and dosing used. The degree of anticoagulant reversal desired, whether partial or complete, should also be considered (Dager 2013). Partial reversal may be indicated with less severe bleeding concerns or in those for whom the risk of thromboembolic complications outweighs the bleeding concern. Complete reversal is often indicated when bleeding is life threatening or emergency surgery is indicated.

VKA-Associated Major Bleeding

Emergency VKA reversal consists of replacing depleted vitamin K–dependent coagulation factors and restoring their hepatic synthesis by phytonadione administration. Reversal is evaluated clinically and by the reduction in INR value. The INR is well established as an integral part of VKA management, having a direct and linear correlation to the level of anticoagulant activity; INR is readily obtainable in clinical settings. Therapeutic options for factor replacement include PCC, aPCC, FFP, and rFVIIa. These factor products provide rapid INR normalization, and phytonadione administration promotes sustained hepatic synthesis of the depleted factors II, VII, IX, and X.

Prothrombin Complex Concentrates

Prothrombin complex concentrates are used to describe a variety of products derived from pooled human plasma containing coagulation factors II, VII, IX, and X. Initially developed to prevent and control bleeding episodes in patients with hemophilia B, PCCs are now most commonly used for anticoagulation reversal and are now recommended as the VKA-associated bleeding reversal agent of choice over FFP (Holbrook 2012).

Prothrombin complex concentrate is stored as a powder vial and diluent to be reconstituted and administered within minutes. There is no requirement for ABO compatibility testing, and the total volume to be administered is usually less than 200 mL. Prothrombin complex concentrates are derived from donor pooled plasma; therefore, transmission of infectious agents is possible but considered rare.

Prothrombin complex concentrate products are categorized primarily by their content of factor VII. Profilnine SD (Grifols Biologicals, Los Angeles, CA) and Bebulin VH (Baxter Healthcare, Deerfield, IL) are considered 3-factor PCCs because of their therapeutic concentrations of inactivated factor II, IX, and X with minimal factor VII content. Of note, Bebulin VH also contains small amounts of heparin, which Profilnine does not. The FEIBA NH product (Baxter) is an aPCC containing factor VII in an activated form, with factors II, IX, and X contained in the inactivated form.

The 4-factor PCC available in the United States is Kcentra (CSL Behring, King of Prussia, PA). Many 4-factor PCCs are available outside the United States, including Beriplex P/N (CSL Behring Canada) and Octaplex (Octapharma PPmBH, Vienna, Austria), among others. These products contain all four vitamin K–dependent clotting factors in the inactivated form, protein C and S, and small amounts of heparin.

Dosing of all PCC products is based on weight, INR, and degree of anticoagulant reversal indicated. Dosing for VKA reversal is 25–50 international units/kg and is expressed as the FIX content within each vial. The FDA-approved dosing for Kcentra is 25 units/kg if the pretreatment INR is 2–3.9, maximum dose 2500 units; 35 units/kg for INR 4–6, maximum dose 3500 units; and 50 units/kg for INR greater than 6, maximum dose 5000 units.

Although 4-factor PCCs are preferred for VKA-associated bleeding, a niche for 3-factor PCCs remains for patients with a history of heparin-induced thrombocytopenia who are currently receiving anticoagulation with a VKA because Profilnine does not contain heparin; Kcentra does. In this scenario, to supply the sufficient FVII that 3-factor PCC lacks, 1–2 units of FFP should be administered to these patients in addition to Profilnine, but optimal dosing regimens are yet to be determined in this scenario.

With the commercial availability of a 4-factor PCC in the United States, off-label use of aPCCs for this indication has fallen out of favor because FDA approval for it is lacking and because of the potential for increased thromboembolic events (Wojcik 2009).

The INR must be repeated after administering PCCs to confirm reversal success and can be done within 15–30 minutes after dose administration. Re-dosing can be considered on the basis of the result and the patient's clinical appearance.

Recombinant Activated Factor VII

Recombinant activated factor VII contains only factor VII in its activated form. For VKA reversal, the doses required are much lower than those needed in patients with hemophilia. Although the optimal dosing of rFVIIa for anticoagulant reversal is unknown, doses as low as 1–2 mg can lower INR while minimizing the known thromboembolic risk associated with any rFVIIa use (Dager 2006).

Fresh Frozen Plasma

Fresh frozen plasma consists of plasma taken from whole blood containing all coagulation factors in homeostatic concentrations. Plasma is free of RBC, essentially free of leukocytes and platelets, and contains slightly lower concentrations of factor V and VIII. Because FFP contains ABO antibodies, blood group compatibility testing but not cross-matching is required. One unit of FFP contains 250–300 mL, and thawing is required before administration.

Fresh frozen plasma was once the mainstay of VKA reversal, but it has fallen out of favor because of large-volume requirements, delayed administration times owing to thawing and administration, inability to achieve complete reversal,

and potential for rebound increases in INR (Dager 2013; Holbrook 2012).

For VKA-associated bleeding, the minimum initial dose of FFP for reversal of anticoagulation is 15 mL/kg, with complete factor repletion requiring more than 30 mL/kg. Depending on the amount of available un–cross-matched, thawed FFP available, administration can be delayed by 12–48 hours, should demand outpace supply. The INR reduction with FFP often nadirs near 1.5. Further reduction targeting below 1.5 likely does not confer further hemostatic benefit and unnecessarily exposes the patient to risks of plasma transfusion. Transmission of infectious agents is possible with FFP because FFP is derived from human blood, but the risk is considered comparable with or lower than that with blood transfusion (Menzin 2012; Chapman 2011).

In large-volume, rapid, or massive transfusions, the content of citrate contained in both FFP and RBC transfusions should be considered. Calcium plays a critical role in coagulation, platelet adhesion, and the contractility of muscle cells. Calcium is also required by factors II, VII, IX, and X and protein C and S for activation at the endothelium and is involved in fibrinogen/platelet stabilization in developing clot. Each unit of RBC and FFP contains about 3 g of citrate as a preservative and anticoagulant. Normally, hepatic clearance of citrate occurs rapidly, but for rapid product transfusion and/or decreased hepatic clearance of citrate, plasma concentrations of citrate can increase and chelate calcium. Therefore, calcium replacement should be prioritized to maintain hemostasis (Dzik 1988).

Further complicating blood product administration is the risk of transfusion-related acute lung injury, acute respiratory distress syndrome (ARDS), and transfusion-associated circulatory overload. Transfusion-related acute lung injury is a relatively uncommon transfusion-associated adverse event occurring during or shortly after allogeneic blood transfusion (Goldman 2005). Transfusion-related acute lung injury is defined as acute lung injury characterized by hypoxia and bilateral pulmonary infiltrates and no evidence of left atrial hypertension. Transfusion-associated circulatory overload is hydrostatic pulmonary edema characterized by the acute onset of dyspnea, tachypnea, and tachycardia, paired with a significant increase in B-type natriuretic peptide above baseline. Management of these complications mirrors management of ARDS and fluid overload, respectively.

Phytonadione

Phytonadione administration promotes the hepatic production of clotting factors inhibited by warfarin and should be done in all patients for whom complete reversal is indicated. For acute or life-threatening bleeding episodes, intravenous administration is preferred (Holbrook 2012). Subcutaneous injection is not recommended because of unreliable absorption and unpredictable results. Although both intravenous and oral routes sufficiently result in similar reductions in INR at 24 hours, the intravenous effect is more rapid. To minimize the risk of anaphylactic reactions, administration over 60 minutes is suggested. Doses in excess of 10 mg should be limited because higher doses are not associated with increased efficacy, and the effect on coagulation may be prolonged (Dager 2013).

DOAC Reversal

The approach to bleeding patients receiving DOAC therapy differs significantly from the approach to those receiving VKA therapy. One of the main differences is that quantitative testing, which estimates the intensity or level of anticoagulation, is not currently clinically available. Qualitative testing for each class must be used instead, which gives information on the presence of effect but not the intensity. Another difference is that each DOAC class requires a different agent for reversal. Antidotes for the DOAC classes are increasingly available commercially. Idarucizumab (Boehringer Ingelheim) was FDA approved in 2015 for the reversal of the oral direct thrombin inhibitor dabigatran. Agents aimed at reversing the factor Xa inhibitors, low-molecular-weight heparin, and fondaparinux are in development and expected to be available soon.

Dabigatran

Considerations in managing dabigatran-associated bleeding include renal function, timing from the last dose taken, and need for immediate reversal. Because of the shorter half-life of dabigatran compared with VKA therapy, the anticoagulant effect is likely diminished within 24–48 hours after withholding therapy. Because dabigatran is eliminated by the kidney, decreased renal function prolongs the elimination half-life.

When considering whether to pursue dabigatran reversal, coagulation testing is necessary. Common coagulation testing that is quantitative and linearly associated with dabigatran therapy is currently unavailable in the clinical setting. Because dabigatran is a direct thrombin inhibitor, thrombin time, or the plasma-diluted thrombin time, is an ideal assay. Ecarin clotting time, widely available in research laboratories, is also a quantitative test for dabigatran's effects. However, these are not currently widely available. The PT and aPTT can detect the presence of dabigatran; prolongation of these tests signals the presence of residual drug effect (Tripodi 2013).

Idarucizumab is a monoclonal antibody fragment that binds both free and thrombin-bound dabigatran to neutralize anticoagulant activity rapidly and completely (Pollack 2015; Schiele 2013; van Ryn 2010). Use of antibody fragments and fragment antigen binding (Fab) as antidotes to medications is uncommon but not novel. For example, digoxin immune Fab is widely used for digoxin toxicity (Schiele 2013). Idarucizumab has structural similarities to thrombin and potent binding to dabigatran with about a 350-fold greater affinity for dabigatran than thrombin (Schiele 2013). Idarucizumab lacks the catalytic area of thrombin and therefore has no active thrombin-like activity (Schiele 2013).

Patient Care Scenario

A 74-year-old man (height 68 inches, weight 89 kg) was admitted to the hospital 5 days ago for a chronic obstructive pulmonary disease (COPD) exacerbation and community-acquired pneumonia. He has been treated with prednisone, ceftriaxone, and azithromycin. In addition to COPD, his medical history includes hypertension, hyperlipidemia, and atrial fibrillation. His current medications include amlodipine 10 mg daily, apixaban 5 mg twice daily, atorvastatin 40 mg daily, cholecalciferol 1000 units daily, lisinopril 20 mg daily, fluticasone/salmeterol 500 mcg/50 mcg Diskus 1 inhalation twice daily, metoprolol succinate 100 mg daily, tiotropium 18 mcg once daily, and montelukast 10 mg daily. He tolerated all evening medications at 9:00 p.m. yesterday.

At 2:00 this morning, he had severe abdominal pain and bilious vomiting. His WBC was elevated to 20.6 x 10^3 cells/mm^3. Abdominal radiography revealed intraperitoneal gas, and chest radiography revealed free air under both hemidiaphragms. The medicine team immediately consulted the emergency surgical service, which wants to take this man to the operating room immediately for repair of a suspected bowel perforation. You are asked to guide the reversal of his apixaban therapy.

ANSWER

The clinical pharmacist should be prepared for this increasingly common clinical scenario. All further anticoagulant doses should be held. Depending on the urgency and timing of surgical intervention, obtaining an anti-factor Xa (anti-Xa) concentration to confirm the therapeutic effect of the medication is suggested. In this scenario, the patient took and tolerated apixaban less than 8 hours ago and is therefore expected to have a therapeutic anticoagulant effect at the time of his needed emergency surgery. It is reasonable to proceed with anticoagulation reversal without an anti-Xa concentration in this case.

Ideally, a specific antidote would be used for apixaban reversal, such as andexanet alfa or ciraparantag, but neither is currently commercially available. Until these agents come to market, patients requiring emergency reversal should receive PCC. The current American Heart Association recommendations prefer inactivated 4-factor PCCs (Kcentra) to aPCCs (FEIBA). A dose of 50 units/kg is recommended, with a dose cap of 5000 units. Obtaining anticoagulation values after PCC administration is not required.

1. **Raval AN, Cigarroa JE, Chung MK, et al. Management of patients on non-vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting: I scientific statement from the American Heart Association. Circulation 2017;135:e604-33.**
2. **Dager W. Developing a management plan for oral anticoagulant reversal. Am J Health Syst Pharm 2013;70(suppl 1):S21-31.**

The initial results from the RE-VERSE AD trial evaluating the ability of a 5-g dose of idarucizumab to reverse the anticoagulant effect of dabigatran in patients who had serious bleeding or who needed emergency reversal showed safe and rapid reversal (Pollack 2015). Reversal of anticoagulant effect was measured by dilute thrombin time and ecarin clotting time. Most patients had full reversal of anticoagulant effect after infusion of idarucizumab. Increases in drug concentration and correlating increases in clotting times were noted at the 12- and 24-hour intervals after administration, which potentially reflect the redistribution of extravascular dabigatran. Only 4.8% of patients had thrombotic events. Coexisting conditions or the inciting incidents leading to enrollment in the study were the cause of all deaths. Although the lack of reversal and recurrent elevation in clotting times 12–24 hours after administration led to few rebleeding events, subsequent doses may be indicated.

Hemodialysis is an option for clearing dabigatran because of low protein binding. Hemodialysis has successfully eliminated dabigatran in case reports, but logistical roadblocks often preclude its use. Placing a hemodialysis catheter in an anticoagulated, bleeding patient is associated with a bleeding risk itself, and the prolonged sessions needed for clearance may not be feasible in hemodynamically unstable patients. Further complicating this plan is the limited availability of emergency hemodialysis services.

FXa Inhibitors

Considerations for patients receiving oral FXa inhibitors include hepatic and renal function, timing of last dose taken, and need for reversal. Liver impairment can prolong the half-life of these agents because the hepatic clearance of FXa inhibitors is high, especially for apixaban (Tripodi 2013). Renal dysfunction can also prolong the half-life of these agents, but to a lesser degree. Because the clinical effect of these agents is typically no longer than 48 hours, care should be taken to determine the timing of the last dose received to avoid unnecessary reversal.

Currently available laboratory monitoring of the effect of FXa inhibitors is mainly qualitative. The anti-Xa assay is appropriate for these agents, given their mechanism of action, and in theory, an anti-Xa concentration can even provide quantitative results, as occurs with the monitoring of heparin and low-molecular-weight heparin. When anti-Xa assays are used to monitor heparin or low-molecular-weight heparin, the reagents used and the results obtained are relatively standardized. This is not true when using anti-Xa monitoring for oral FXa inhibitors; therefore, anti-Xa monitoring for

oral FXa inhibitors is currently considered qualitative. The PT, INR, and aPTT will likely be prolonged and signal the presence of anticoagulant effect.

No FXa antidote is currently available for anticoagulation reversal, and data are limited to guide reversal strategies (Dzik 2015). Four-factor PCCs and aPCCs, often given at high doses, have been widely accepted as a reversal strategy for FXa inhibitors. However, specific reversal antidotes are in development.

Andexanet alfa, also called r-Antidote, is a recombinant modified FXa protein that lacks enzymatic activity yet retains the ability to bind and reverse the anticoagulant activity of FXa inhibitors (Connolly 2016; Lu 2013). Initial studies indicate that andexanet alfa has a terminal half-life of 6 hours and has been well tolerated (Smythe 2016). Mild to moderate infusion reactions have been noted, but these are not usually dose limiting, nor do they require intervention (Smythe 2016).

Andexanet alfa does not interfere with normal FXa function and is also promising in reversing the effects of low-molecular-weight heparin and fondaparinux (Lu 2013). The anticoagulant effect of low-molecular-weight heparin and fondaparinux occurs through binding to antithrombin III (ATIII), which mediates the selective inhibition of FXa. Because andexanet alfa protein retains the FXa binding site, it can bind ATIII and displace low-molecular-weight heparin and fondaparinux, negating their systemic anticoagulant effects. This could offer a more effective reversal for these agents because protamine is only partly effective for low-molecular-weight heparin reversal and has no effect on fondaparinux (Lu 2013).

Preliminary data published from the ANNEXA-4 group evaluated the use of andexanet alfa in patients with acute major bleeding receiving an oral FXa inhibitor or enoxaparin (Connolly 2016). Dosing of the antidote was based on the timing from the last dose of anticoagulant taken. Doses taken more than 7 hours before the onset of bleeding were given a bolus of 400 mg, followed by a continuous infusion of 480 mg over 2 hours. If the timing of the dose last taken was unknown or within 7 hours, a bolus of 800 mg was followed by a continuous infusion of 960 mg intravenously over 2 hours. The infusion length was chosen to exceed the time needed for hemostasis to allow for clot formation. The most common types of bleeding were GI (49%) and intracranial (42%). In patients receiving oral FXa inhibitors, anti-Xa activity decreased by greater than 90% after administering the bolus dose and remained at about 90% at the end of the infusion. Four hours after the infusion ended, anti-Xa activity was about 30%–40% of baseline concentrations and remained at similar concentrations at 8 and 12 hours after the end of the infusion. Efficacy in decreasing anti-Xa activity in the patient receiving enoxaparin followed a similar trajectory, with initial substantial decreases with the bolus and continuous infusion, but with increases in anti-Xa activity 4 hours after the infusion. Clinical response was considered excellent or good in 79% of the patients after 12 hours. Thromboembolic adverse events were reported in 18% of the patients. Andexanet alfa is a promising reversal agent for oral FXa inhibitors and low-molecular-weight heparin.

Questions remain about the optimal dosing strategy for andexanet alfa and whether a one-size-fits-all reversal strategy will be appropriate, or if anticoagulant specific regimens should be considered. Addressing the need for re-dosing or continuing the infusion in the setting of ongoing bleeding would be prudent. The ability to test for either drug concentration – or, more feasibly, quantitative testing such as dilute thrombin time and ecarin clotting time – will likely be available in the future. Both are commercially available and can be performed on most standard laboratory testing equipment, but they would first require regulatory approval (Tripodi 2017). The relatively high rate of thromboembolic adverse effects may affect use and, potentially, dosing and re-dosing considerations (Smythe 2016).

Also in development for oral FXa inhibitor reversal is ciraparantag. Ciraparantag is a small, positively charged, water-soluble molecule that binds dabigatran, rivaroxaban, apixaban, edoxaban, and heparin. Phase II trials show promising reversal of anticoagulant activity for the aforementioned anticoagulants. Such a universal agent is exciting, but further data on dosing, safety, and efficacy are needed.

CONCLUSION

Although factor-based reversal with PCCs is expected to remain the standard of care for VKA reversal, newer non–factor-based reversal strategies are likely to take over FXA inhibitor reversal. Knowledge of the application and limitations of current laboratory testing is essential in evaluating anticoagulant-induced coagulopathy. Ongoing education will be necessary to keep up to date with the new and emerging reversal agents as they become available.

Practice Points

When tasked with reversing oral factor Xa inhibitors, practitioners should consider the following:

- **The need for emergency reversal should be weighed with the risk of thrombosis. Should reversal not be emergent, holding therapy is preferred.**
- **Inactivated PCCs dosed at 50 units/kg is the suggested therapy of choice; the maximum dose is 5000 units.**
- **Once specific antidotes become available, they will likely preclude the use of PCCs in oral FXa inhibitor reversal.**

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Self-Assessment Questions

Questions 1–3 pertain to the following case.

J.R. is a 58-year-old woman admitted for an acute GI bleed. Her medical history is significant for coronary artery disease and hypertension. Her home drugs include aspirin 81 mg daily, metoprolol tartrate 50 mg twice daily, lisinopril 20 mg daily, and atorvastatin 20 mg daily. J.R. is hemodynamically stable but has required ongoing transfusion support to maintain Hgb greater than 7 g/dL. No source of bleeding was identified by imaging or endoscopy. Her Plt and PT were within normal limits; her aPTT was prolonged but corrected with a 1:1 mixing study. Additional laboratory test results for J.R. include FVIII 28 units/dL, VWF:Ag 16 units/dL, and VWF:RCo 18 units/dL.

1. Which one of the following best describes J.R.'s most likely clotting factor deficiency?

   A. Hemophilia A
   B. Type 1 von Willebrand disease (VWD)
   C. Type 2M VWD
   D. Acquired FVIII inhibitor

2. Which one of the following is best to recommend as the initial intervention to address J.R.'s clotting factor deficiency in the setting of ongoing bleeding?

   A. Advate 60 units/kg intravenously every 12 hours
   B. Vonvendi 30 units/kg intravenously every 72 hours
   C. Desmopressin 0.3 mcg/kg intravenously every 24 hours
   D. NovoSeven 90 mcg/kg intravenously every 2 hours

3. J.R. stabilizes after 3 days of this initial treatment. On the morning planned for discharge, she has large-volume hematemesis. Her Hgb decreases from 8.2 to 5.3 g/dL, and she has become hemodynamically unstable. Which one of the following is best to recommend regarding changes to J.R.'s clotting factor deficiency treatment?

   A. No change to initial therapy
   B. FEIBA 100 units/kg intravenously, followed by 50 units/kg every 6 hours
   C. BeneFIX 100 units/kg intravenously every 8 hours
   D. Humate-P 60 VWF:RCo units/kg intravenously, followed by 30 VWF:RCo units/kg every 12 hours

Questions 4–7 pertain to the following case.

A.W. is a 1-year-old boy with hemophilia A. He was given the diagnosis on the basis of factor testing at birth because of a family history of bleeding disorders, but he has not yet had a bleeding event. His FVIII concentration is less than 1%. A.W. is otherwise healthy and is about to start walking.

4. Which one of the following best describes the severity of A.W.'s hemophilia A?

   A. Mild
   B. Moderate
   C. Severe
   D. Does not meet the criteria for hemophilia A

5. Which one of the following strategies for factor replacement is best to recommend for A.W.?

   A. Give on demand only in the setting of bleeding.
   B. Give primary prophylaxis to prevent spontaneous bleeding without insult.
   C. Give secondary prophylaxis only starting after demonstrated history of bleeding.
   D. Given his severity of hemophilia, he is at low risk of bleeding.

6. Which one of the following is best to recommend for A.W.?

   A. Advate 30 units/kg intravenously three times a week
   B. Kogenate 50 units/kg intravenously every 12 hours
   C. Obizur 200 units/kg intravenously every 24 hours
   D. NovoSeven 90 mcg/kg intravenously every 4 hours

Questions 7-9 pertain to the following case.

M.K. is an 18-year-old man with a medical history of moderate hemophilia B complicated by the development of a high-activity inhibitor (10 BU/dL) and subsequent anaphylactoid reactions to FIX products. An avid skateboarder, he was found down in his driveway by his parents. On presentation, M.K. has a Glasgow Coma Scale score of 8 and obvious occipital hematoma.

7. Which one of the following is best to recommend as initial intervention for M.K.?

   A. Have him undergo head CT to determine need for factor concentrate before administration.
   B. Send laboratory values to assess FIX and inhibitor concentrations for dosage calculations before administration.
   C. Give NovoSeven 90 mcg/kg intravenously every 2 hours.
   D. Give Obizur 200 units/kg intravenously every 24 hours.

8. M.K. has an intracerebral hemorrhage on imaging. Which one of the following is best to recommend as total duration of clotting factor administration for M.K.?

   A. 12–24 hours
   B. 1–3 days
   C. 5–7 days
   D. 8–21 days

9. Which one of the following is the greatest concern with using bypassing agents for M.K.?

   A. Thrombosis
   B. Inhibitor development
   C. Infusion reactions
   D. Drug interactions

Questions 10 and 11 pertain to the following case.

R.F. is a 53-year-old man (weight 82 kg) who is brought to the ED by ambulance after a 10-ft fall from a ladder, landing on his right side. He is maintaining his airway but cannot give any medical history; no family members accompanied the patient. On review of his medical chart, R.F. has a medical history of atrial fibrillation, hypertension, and dyslipidemia. His home drugs include warfarin 5 mg/day, metoprolol succinate 50 mg/day, lisinopril 40 mg/day, and atorvastatin 20 mg/day. R.F.'s vital signs on presentation include blood pressure 140/92 mm Hg, heart rate 72 beats/minute, and respiratory rate 18 breath/minute. A point-of-care INR is 3.7. Initial CT head findings include a large subdural hematoma and scattered subarachnoid hemorrhages.

10. Which one of the following is best to recommend as the goal of INR reversal for R.F.?

    A. Do a complete reversal to normalized INR
    B. Do a partial reversal to INR in goal range for atrial fibrillation of 2–3
    C. No reversal is indicated at this time
    D. Reversal should be considered if he deteriorates clinically

11. After R.F. has been given reversal agents, which one of the following is best to recommend as timing of INR assessment for normalization?

    A. PCC provides complete reversal; therefore, INR need not be repeated.
    B. Recommend 15–30 minutes after completing factor administration.
    C. With routine laboratory testing, recommend the following morning or before any surgical intervention.
    D. Recommend every 6 hours until the INR is less than 1.5 for three separate checks.

12. A 62-year-old man is admitted to your service for pain control and monitoring after a motor vehicle collision. His injury burden includes four rib fractures and a sternal fracture. He is hemodynamically stable; his Hgb and Hct values have not changed over the past three blood tests within the past 12 hours and remain Hgb 13 g/dL and Hct 42%. The patient is anticoagulated with warfarin at baseline with a current INR of 2.8. The trauma team asks you whether this patient should receive warfarin reversal at this time. Which one of the following would be best to recommend?

    A. No, he is hemodynamically stable and does not appear to be actively bleeding.
    B. Yes, all trauma patients should receive prompt reversal of their INR.
    C. Yes, he has risk factors for bleeding.
    D. Yes, he could require a procedure during the hospital stay.

Questions 13 and 14 pertain to the following case.

K.K. is a 79-year-old man admitted to the medical ICU with diffuse GI bleeding. He is actively being resuscitated with the institution's massive transfusion protocol; in the past 20 minutes, he has received 14 units of RBCs, 15 units of FFP, and 2 units of platelets. K.K.'s most recent laboratory values include Hgb 7.0 g/dL, Hct 22%, Plt 64,000/mm^3, INR 1.51, and ionized calcium 0.6 mmol/L (normal range 1.14–1.28 mmol/L).

13. Which one of the following is the most likely source of K.K.'s hypocalcemia?

    A. Renal insufficiency
    B. Citrate chelation of calcium
    C. Dilution from large-volume resuscitation
    D. Thrombocytopenia

14. Which one of the following is best to recommend for calcium replacement in K.K.?

    A. Calcium citrate
    B. Calcium chloride
    C. Calcium gluconate
    D. No replacement indicated

15. A woman who is anticoagulated with warfarin for heparin-induced thrombocytopenia with thrombosis presents to the ED after a ground-level fall. A CT scan of the head reveals intraventricular blood, and the neurosurgeon would like you to reverse her anticoagulation so that she can place an extraventricular drain. Which one of the following is best to recommend for this patient?

    A. Kcentra
    B. Profilnine SD with FFP
    C. Bebulin VH
    D. FFP only