How to manage bleeding disorders in aging patients needing surgery

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With improvements in medical care, the life expectancy of patients with bleeding disorders is approaching that of the general population. A growing population of older adult patients with bleeding disorders is at risk of age-related comorbidities and in need of various elective and emergent age-related procedures. The increased risk of thrombosis and volume overload in older adults complicates perioperative hemostatic management. Furthermore, antithrombotic treatment such as antiplatelet or anticoagulant therapy, which is frequently required for various cardiovascular interventions, requires a meticulous individualized approach. Evidence-based guidelines for the management of aging patients with bleeding disorders are lacking, largely due to the underrepresentation of older adult patients in clinical trials as well as the rarity of many such bleeding disorders. We discuss the current guidelines and recommendations in the perioperative hemostatic management of older adult patients with hemophilia and von Willebrand disease as well as other rare bleeding disorders. The optimal management of these patients is often complex and requires a thorough multidisciplinary and individualized approach involving hematologists, surgeons, anesthesiologists, and the specialists treating the underlying disorder.

LEARNING OBJECTIVES

- Recognize the challenges unique to the aging patient, such as age-related risks for thrombosis and volume overload
- Review the guidelines for the peri-operative hemostatic management of various bleeding disorders
- Apply an optimal approach in complex management scenarios, utilizing an individualized treatment plan and multi-disciplinary approach

Introduction

With improvements in medical care, the life expectancy of patients with bleeding disorders, such as hemophilia, is approaching that of the general population.[1] As a result, there is a growing population of older adult patients with bleeding disorders in need of various elective and emergent age-related procedures.[1-3] These commonly include orthopedic procedures such as joint arthroplasties and spinal surgery as well as cardiac interventions such as percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and heart valve replacement, all of which are increasingly prevalent with age. In addition to the significant bleeding and thrombotic risks that many of these procedures carry, several challenges may further complicate perioperative management in older adult patients in comparison to children and young adults.

One such major challenge is the increased risk of thrombosis that occurs with age. Several age-related physiological changes, such as vessel wall remodeling, endothelial dysfunction, venous stasis, and an increase in procoagulant proteins, have been suggested as mechanisms for the increased thrombotic risk seen in older adults (Figure 1).[4-9] Chronic cardiovascular comorbidities, such as hypertension, diabetes, and hypercholesterolemia, further exacerbate this risk. Despite having bleeding tendencies, older adult patients with bleeding disorders are prone to these age-related changes that contribute to thrombosis and are not considered protected from these complications. While the incidence of cardiovascular disease in hemophilia patients, for example, has been reported to be less than that of the general population (15% vs 25.8%),[10] events such as myocardial infarction and stroke still occur and should be prevented.[2,3,10-13] Particular attention should be given to older adults with bleeding disorders undergoing surgery in order to prevent perioperative thrombotic complications as well as bleeding. This necessitates the judicious use of hemostatic agents, such as coagulation factors or hemostatic bypass agents, that may subject patients to a higher risk of thrombosis.[14] In addition, another considerable age-related risk is that of volume overload, which may occur as a complication of receiving the

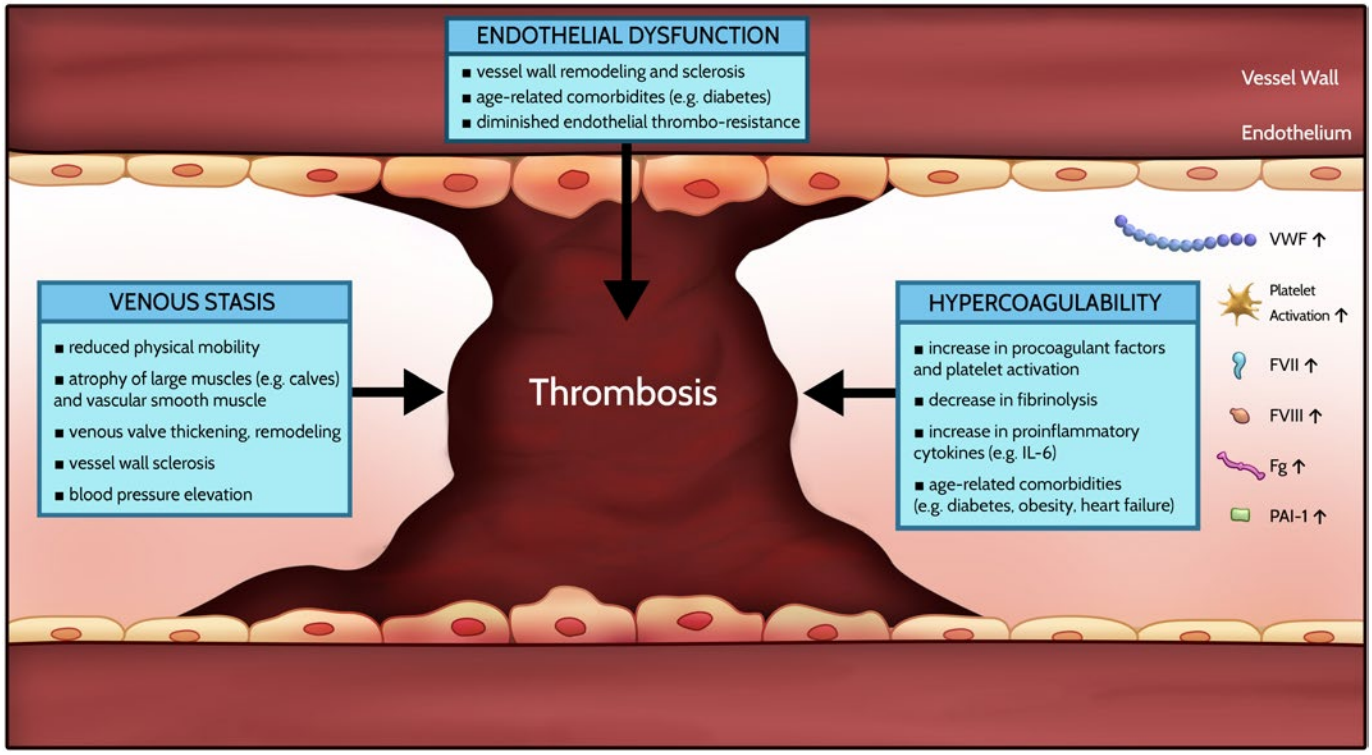

Figure 1. Proposed age-related mechanisms contributing to increased risk of thrombosis with age, based on Virchow's triad. FVII, factor VII; FVIII, factor VIII; Fg, fibrinogen; PAI-1, plasminogen activator inhibitor 1; VWF, von Willebrand factor.

large volumes of fresh frozen plasma (FFP) and platelet transfusions required in managing certain bleeding disorders.

Evidence-based guidelines for the management of aging patients with bleeding disorders are lacking, largely due to the underrepresentation of older adult patients in clinical trials as well as the rarity of many bleeding disorders. The optimal perioperative management of these patients is often complex and requires a thorough multidisciplinary approach that involves hematologists, surgeons, anesthesiologists, and the specialists treating the underlying disorder.[15]

CLINICAL CASE 1

An 88-year-old man with severe hemophilia A (HA; baseline factor VIII [FVIII] activity level <1%, without inhibitors) has severe, debilitating left hip arthropathy. He is otherwise healthy and does not have any other medical comorbidities. He self-administers prophylactic factor replacement 3 times a week and receives his care within a hemophilia treatment center (HTC). He is evaluated by an orthopedic surgeon and deemed a fit candidate for elective left total hip arthroplasty. The hematologist is consulted to assist with perioperative management to prevent bleeding complications. The patient is treated with 50U/kg of antihemophilic factor (Advate) before surgery and achieves a peak FVIII level of 108% and good postoperative hemostasis. He is then maintained on daily factor replacement for the rest of the week and begins physical rehabilitation. He is not placed on prophylactic anticoagulation.

Intraoperative and postoperative hemostasis

In the above scenario, meticulous hemostatic support is crucial for the success of the surgical procedure. The overall hemostatic management and available agents vary significantly among different bleeding disorders, and we discuss each separately below. However, regardless of the type of bleeding disorder, the management concepts are similar: to provide effective and sufficient hemostatic support to prevent surgical-related bleeding, to support wound healing, and to avoid side effects and complications related to the therapy used. The World Federation of Hemophilia (WFH) 2020 guidelines recommend that patients with hemophilia requiring surgery should always be managed at or in consultation with recognized HTCs with appropriate hematologic support, reliable laboratory monitoring, and available and sufficient clotting factor concentrates.[16] This concept applies to patients with any bleeding disorder. The HTC should be supported by a multidisciplinary team that includes nurses, social workers, and physical therapists familiar with the needs of hemophilia patients undergoing surgery.[17] As in the case above, procedures should be performed electively when possible, early in the week, and early in the day by experienced surgeons and anesthesiologists.[15] Preoperative in vivo recovery studies are used to evaluate the pharmacokinetic properties of coagulation factors, which may differ based on the product and the patient. In hemophilia patients this allows for a more precise estimation of peak FVIII and factor IX (FIX) levels and can help tailor the dosing and frequency of factor replacement according to the need of the individual patient, especially before major surgery. The presence of inhibitors should also be assessed prior to surgery.

Table 1. Suggested factor replacement schedule for older adult persons with hemophilia A or B without inhibitors based on WFH guidelines

	Hemophilia A		Hemophilia B	
Indication	**Target peak levels (%)**	**Duration**	**Target peak levels (%)**	**Duration**
Minor surgery	50–80	Day of surgery	50–80	Day of surgery
	30–80	Days 1–5	30–80	Days 1–5
Major surgery	80–100	Day of surgery	60–80	Day of surgery
	60–80	Days 1–3	40–60	Days 1–3
	40–60	Days 4–6	30–50	Days 4–6
	30–50	Days 7–14	20–40	Days 7–14

Adapted with permission from Srivastava et al.[16]

Hemophilia A

The hemostatic agents available for HA include desmopressin and FVIII replacement. Desmopressin may be considered in patients with mild HA undergoing minor surgery in whom a response to desmopressin has been demonstrated, particularly when the cost or development of inhibitors due to exposure to FVIII products is of concern. Issues with the use of desmopressin include free water retention, hyponatremia, fluid shifts, and exacerbation of cardiovascular disease. For those reasons it should be used with considerable caution in older adult patients prone to volume overload and cardiovascular morbidity and is contraindicated in patients with active cardiovascular disease or seizure disorder.[16,18]

FVIII replacement therapy is the treatment of choice for all other patients without high-titer inhibitors, such as the patient in our case above. Suggested plasma FVIII target levels are provided in Table 1, adapted from WFH guidelines.[16] However, high-quality data guiding this practice are lacking.[19] Additionally, patients undergoing cardiac procedures indicated for antithrombotic treatment may require an extended duration of factor replacement to allow for safe administration of the former. This is discussed separately below.

Hemophilia B

While the overall clinical manifestations and management approaches in hemophilia B (HB) are similar to those in HA, a few differences should be noted. In contrast to HA, the bleeding phenotype in HB may be milder,[19-25] and the recommended target levels in the WFH 2020 guidelines are lower for major surgery (Table 1).[16] The dosing frequency should also consider the longer half-life of FIX. Patients with HB do not have desmopressin as an available option, and FIX replacement is the treatment of choice for major procedures. While the incidence of inhibitors is much rarer in HB than in HA,[26] their presence should also be assessed prior to surgery.

Patients with inhibitors

Hemophilia patients with high-titer inhibitors to FVIII, FIX, or factor XI (FXI) require the use of bypass agents, mainly recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC), which pose an additional risk for thrombosis, especially in older adults. Several studies note that the risk of thrombosis due to these agents increases with age, and arterial thrombosis is a particular concern.[27-29] While the overall incidence of these events remains low and both rFVIIa and aPCC are generally considered safe in older adults,[27,30-32] patients should be very cautiously monitored for thrombosis. The lack of reliable therapeutic monitoring parameters for bypass agents further complicates their optimal dosing strategy, and meticulous clinical evaluation of bleeding and thrombosis is crucial. Data from the European Acquired Hemophilia Registry suggests a similar safety and efficacy profile for both rFVIIa and aPCC[27]; however, parallel use of different bypass agents should be avoided because it may confer a higher risk for thrombosis.[33] Suggested dosing of bypass agents is summarized in Table 2.

A similar approach applies to acquired HA, an autoimmune disorder caused by antibodies against FVIII that is more common in older adults.[34] In addition to bypass agents, these patients also have the option of recombinant porcine FVIII as a hemostatic agent.[34,35] While the recommended initial dose of recombinant porcine FVIII is 200U/kg, it has been suggested that an initial dose of 100U/kg may be sufficient for most patients and can be considered for those at risk of thrombosis.

Perioperative thromboprophylaxis

The WFH recommends against the routine use of pharmacologic thromboprophylaxis in patients with HA or HB undergoing major noncardiac surgery.[16] For orthopedic procedures, such as the case above, the American Academy of Orthopaedic Surgeons and the American College of Chest Physicians also suggest forgoing the routine use of antithrombotic agents in patients with bleeding disorders, as does the WFH, with the exception of high plasma levels of coagulation factors.[36] As previously mentioned, however, older adult patients with bleeding disorders are not necessarily protected from thrombotic outcomes, including venous or arterial thrombosis, and this risk may increase with age due to age-related prothrombotic physiological changes (Figure 1). In older patients, an individualized risk/benefit assessment is necessary when additional thrombotic risk factors are present, especially in patients with corrected factor levels after orthopedic surgery.

CLINICAL CASE 2

A 79-year-old woman with hypertension, diabetes, and type 2A von Willebrand disease (VWD; VWF [von Willebrand factor]:Ag=35, VWF:RCo=15, FVIII:C=110) is scheduled for elective

Table 2. Suggested dosing regimens of bypass agents in hemophilia patients with inhibitors

Agent	Dosing for minor surgery	Dosing for major surgery	Comments
rFVIIa	90μg/kg/dose immediately before surgery and every 2 hours for 2 days and then every 2–6 hours until healed.	90μg/kg/dose immediately before surgery and every 2 hours for 2 days. Then every 2–3 hours for 5 days, then every 4 hours until days 7–10, then every 6 hours until days 14–21	• Preferred agent for patients with HB and high-titer inhibitors per WFH guidelines since aPCC contains FIX and may cause or worsen an allergic reaction. • For patients with FIX deficiency, low dose (15–30μg/kg) in combination with TXA has been shown to be effective for major surgery in limited studies and can be considered for those at risk of thrombosis.[33]
Activated prothrombin concentrate complex	50–100U/kg immediately before surgery and then every 6–12 hours	50–100U/kg immediately before surgery, then every 6–12 hours	• Maximum: 100 units/kg/dose; 200 units/kg/d). • Less preferred for HB patients with high-titer inhibitors per WFH guidelines.

cholecystectomy. She is admitted and receives 60U/kg of VWF concentrate prior to surgery, achieving VWF:RCo=104, and FVIII:C=225. Her surgical course is uncomplicated, but the next morning she complains of substernal chest pain. She is found to have non-ST elevation myocardial infarction. With her VWF activity levels still normal, she undergoes PCI and is found to have severe triple vessel disease. She is recommended for elective CABG. The patient's management is discussed in a multidisciplinary approach involving cardiology, cardiothoracic surgery, and hematology.

Von Willebrand disease

The 2021 guidelines by the American Society of Hematology, International Society of Thrombosis and Hemostasis, National Hemophilia Foundation, and WFH recommend a goal VWF activity and FVIII level of >50% for at least 3 days for major surgeries using VWF/FVIII concentrates.[18] This is often extended to a duration of 7 to 14 days based on the individual type of surgery. In older adults, special precaution must be taken to avoid overdosing of factor replacement, as prolonged supraphysiologic FVIII levels may lead to thrombotic complications. Available options include plasma-derived formulations of VWF/FVIII as well as recombinant VWF when available. Older adult patients may have normal or elevated baseline FVIII levels, and this should be taken into consideration when choosing the appropriate VWF replacement product. This includes plasma-derived products with a higher VWF to FVIII ratio, such as Humate-P, or dose adjustment of concomitant FVIII replacement given with recombinant VWF.

Patients with type 1 VWD responsive to desmopressin without active cardiovascular disease may be considered for desmopressin for minor surgery, with a goal VWF level >50 per the 2021 guidelines.[18] The same risks and precautions for desmopressin described under HA above apply for VWD. Close monitoring for thrombotic complications is necessary for older adult patients, especially if concomitant tranexamic acid (TXA) is given. Patients with mild type 1 VWD undergoing minor mucosal procedures may be considered for TXA alone in some cases,[18] which would minimize the risks associated with factor replacement or desmopressin.

Several studies on patients with type 1 VWD have demonstrated that VWF levels may normalize with age due to physiological increases in VWF.[37-42] The 2021 guidelines suggest reconsidering the diagnosis in these patients, as opposed to removing it.[43] Whether the normalization of VWF levels in older patients results in an amelioration of bleeding symptoms has not been established. While that may be possible in some patients, it has been suggested that supranormal VWF levels may be required in others.[44] Those with normalized VWF levels in whom bleeding symptoms have resolved may be harmed by the unnecessary administration of VWF concentrates, especially if they have cardiovascular risk factors.[44] There are currently insufficient data to guide optimal management in these cases. An individualized risk/benefit assessment is crucial in patients with normalized VWF levels, with careful clinical evaluation of bleeding and thrombotic risk factors.

Acquired von Willebrand syndrome may result from the shearing of VWF (eg, across a stenotic cardiac valve or through mechanical circulatory support devices) or less commonly may arise as an autoimmune disorder with antibodies directed against VWF, often seen in patients with lymphoproliferative disorders and plasma cell dyscrasias. When due to an autoantibody, acquired von Willebrand syndrome can be effectively managed with intravenous immune globulin in addition to factor replacement for major surgery, as well as the use of continuous-infusion factor replacement.[45,46,47] In older adult patients with a risk of thrombosis or renal dysfunction, approaches such as therapeutic plasma exchange, rFVIIa, and TXA have been utilized, although data are lacking.[45]

Cardiovascular interventions

Percutaneous coronary intervention

PCI is a common procedure among older adult patients, and its challenges include the need for intraoperative heparinization as well as postoperative antiplatelet therapy. In patients with bleeding disorders, a best effort should be made to minimize the duration of dual antiplatelet therapy (DAPT). Earlier recommendations favored the use of bare metal stents over drug-eluting stents to limit the duration of DAPT to 1 month.[48,49] However, more recent data suggest that 1 month of DAPT may be considered with newer-generation drug-eluting stents with bioresorbable polymers,[50-52] which was the approach reported in a recent case series of hemophilia patients undergoing PCI.[53] The individual coronary anatomy, risks of restenosis, and bleeding propensity should all be factored into a multidisciplinary deci-

sion-making process. Due to the bleeding risk of DAPT, patients with bleeding disorders may require prophylactic hemostatic therapy throughout the duration of DAPT, even if they had not been receiving it before. For hemophilia patients, the WFH guidelines recommend trough levels of 15% to 30% of the deficient factor during the duration of DAPT and levels of 1% to 5% during single antiplatelet agent therapy.[16] Similarly, the 2021 VWD guidelines recommend prophylaxis with VWF concentrate during DAPT in patients with VWD and a severe bleeding phenotype.[18] In the patient above undergoing PCI, VWF:RCo levels >30 may be considered throughout the duration of DAPT.

Cardiac surgery

Data on cardiovascular procedures such as CABG, valve replacement, or device implantation in patients with bleeding disorders are limited. Management is more complex than other procedures due to the frequent need for postoperative antithrombotic therapy or the need for cardiopulmonary bypass in certain cases. Procedures that may require cardiopulmonary bypass, such as CABG, constitute several high risks for patients with bleeding disorders, including the need for systemic anticoagulation as well as the possible occurrence of consumptive coagulopathies.[54] Continuous replacement of the deficient factor may better maintain steady levels compared to IV boluses, and additional hemostatic products such as FFP or platelets may be necessary in cases of acquired coagulopathy. In high-risk patients, off-pump variations of such procedures should be considered, or less invasive alternatives such as multivessel PCI in lieu of CABG. As with PCI, an effort should be made to minimize the duration of DAPT when possible by weighing the risks and benefits of shorter durations.

In patients requiring valve replacement, bioprosthetic valves should be used instead of mechanical valves that require indefinite anticoagulation. An approach utilizing low-molecular-weight heparin for 10 days postoperatively followed by 3 months of vitamin K antagonist, with concomitant coagulation factor correction throughout that duration, has been suggested for hemophilia patients.[54,55] A similar approach can be implemented in patients with other bleeding disorders, with correction of the hemostatic defect applied throughout the duration of anticoagulation. An additional consideration in HB patients is the heightened severity of the disease that can occur as a result of vitamin K antagonist therapy leading to decreased FIX levels, as well as the interference with international normalized ratio monitoring caused by FIX replacement.[2]

The literature suggests that despite the major hemostatic challenges of various cardiac interventions, careful, multidisciplinary planning can help achieve optimal outcomes with minimal morbidity and mortality in patients with bleeding disorders.[53,54,56-60] However, these data may be subject to potential publication bias, and older adult patients are underrepresented.

Table 3. Hemostatic management of rare bleeding disorders and precautions in older adult patients

Bleeding disorder	Recommended hemostatic treatment for minor surgery	Recommended hemostatic treatment for major surgery	Suggested target trough level of deficient factor
Rare factor deficiencies			
II	FFP (15–20mL/kg)	FFP (15–20mL/kg) PCC* (20–30U/kg)	>30%
V	FFP (15–20mL/kg)	FFP (15–20mL/kg)	>20%
V + VIII	FFP (15–20mL/kg)	FFP (15–20mL/kg)	Factor V: >20% FVIII: as in Table 1
VII	rFVIIa (15–30µg/kg every 4–6 hours)	rFVIIa (15–30µg/kg every 4–6 hours) PCC* (20–30mL/kg)	>20%
X	Factor X concentrate (10–20U/kg) FFP 15–20mL/kg	Factor X concentrate (10–20U/kg) FFP (15–20mL/kg) PCC* (20–30U/kg)	>20%
XIII	Plasma-derived factor XIII concentrate (40U/kg) Recombinant factor XIII concentrate (35U/kg) Cryoprecipitate (1 bag per 10kg)	Plasma-derived factor XIII concentrate (40U/kg) Recombinant factor XIII concentrate (35U/kg) Cryoprecipitate (1 bag per 10kg)	5%
Other rare bleeding disorders			
Platelet function defects	Intravenous or oral TXA (500–1000mg every 6–12 hours) Desmopressin	Platelet transfusions (4–6 units) Bypass agents†	
Hypo/dysfibrinogenemia†	Cryoprecipitate (1 bag per 10kg) Fibrinogen concentrate (20–30mg/kg) FFP (15–20mL/kg)	Cryoprecipitate (1 bag per 10kg) Fibrinogen concentrate (20–30mg/kg)	>100mg/dL
Disorders of fibrinolysis	Intravenous or oral TXA (500–1000mg every 6–12 hours)	Intravenous TXA (10–15mg/kg) every 6–12 hours	

*After PCC treatment, factors II, VI, IX, and X should not exceed 150%.

†Dysfibrinogenemia often presents with a thrombotic phenotype. Hypofibrinogenemia and afibrinogenemia usually present with bleeding, although both venous and arterial thrombosis can occur. Replacement recommendations apply to patients with a bleeding phenotype, and concomitant antithrombotic prophylaxis may be necessary in some, particularly older adults.

Adapted with permission from Mannucci et al.[67]

Management of such patients undergoing cardiac interventions requires a meticulous, individualized, and multidisciplinary approach, with careful monitoring of hemostatic parameters.

CLINICAL CASE 3

An 86-year-old man is evaluated by a urologist for consideration of transurethral resection of the prostate for a new diagnosis of early-stage prostate cancer. He has a history of congenital FXI deficiency, and his most recent tests show an FXI level of 24%. He has a history of hypertension, chronic kidney disease, aortic stenosis, and advanced heart failure with reduced ejection fraction. Because of his prior history of circulatory overload with FFP, the option of TXA in combination with single low-dose rFVIIa is discussed.

FXI deficiency

Compared to HA and HB, FXI deficiency has its own unique challenges in management. The poor correlation between FXI levels and bleeding phenotype limits the ability to predict bleeding outcomes.[61] In general, any FXI level <20% is considered severe.[61] The lack of FXI concentrates in the United States necessitates the use of FFP infusions (usually 10-20mL/kg) to replace FXI perioperatively or the use of bypass agents or antifibrinolytic agents.[59,61-63] In older adult patients, large volumes of FFP are a major risk factor for circulatory overload, especially in those with valve disease or congestive heart failure. In such patients, major surgery would require thorough factor replacement and large volumes of plasma, which may pose a substantial risk. Therapeutic plasma exchange has been utilized as a method to overcome this risk and should be considered as a potentially safer method of factor correction.[64,65] The optimal target FXI level is unknown; however, levels of >45% have been recommended for major surgery, with consideration of antifibrinolytic agents in areas of high fibrinolytic activity, such as the bladder, endometrium, and oropharynx.[61] For patients who cannot receive blood products or are at risk of circulatory overload, as in the patient above, the use of a single low-dose rFVIIa (Table 2) in combination with TXA has been shown to be effective in limited studies.[66]

Other rare bleeding disorders

Very limited data exist to guide the optimal perioperative management of older adults with rare bleeding disorders.[66] The availability of reliable laboratory testing and appropriate hemostatic products is necessary in the management of these patients as guided by a hemostasis expert. Table 3 summarizes some of the concerns that may arise in using specific hemostatic agents in each of these disorders in older adult patients, and necessary precautions should be implemented.

Conflict-of-interest disclosure

Mouhamed Yazan Abou-Ismail: no competing financial interests to declare.
Nathan T. Connell: no competing financial interests to declare.

Off-label drug use

Mouhamed Yazan Abou-Ismail: The use of bypass agents mentioned in this article, namely aPCC and rFVIIa, is considered off-label in various rare hematologic conditions due to paucity of data.
Nathan T. Connell: The use of bypass agents mentioned in this article, namely aPCC and rFVIIa, is considered off-label in various rare hematologic conditions due to paucity of data.

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