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CONSULTATIVE HEMATOLOGY FOR INPATIENTS

How I approach bleeding in hospitalized patients

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Excessive bleeding is relatively common in adult inpatients, whether as the primary reason for admission or as a development during the hospital stay. Common causes include structural issues, medication effects, and systemic illnesses; occasionally, unexpected bleeding can develop as a result of an undiagnosed or newly acquired bleeding disorder. The first step in caring for the inpatient who is bleeding is to determine whether the bleeding symptom is truly new or whether the patient has a history of abnormal bleeding. Patients with a history of abnormal bleeding may warrant evaluation for inherited bleeding disorders, such as platelet function disorders, von Willebrand disease, hemophilia, or rare factor deficiencies. Patients with no history of bleeding, for whom other causes, such as liver dysfunction, medication effect, disseminated intravascular coagulation, or certain vitamin deficiencies have been ruled out may require evaluation for acquired coagulopathies, such as acquired hemophilia or acquired von Willebrand disease. Here, we present 3 cases to discuss the diagnosis and management of the 2 most common acquired bleeding disorders as well as a patient with a congenital bleeding disorder with a historical diagnosis.

Introduction

Unexpected and excessive bleeding in adults who are hospitalized is common and may be due to both common and uncommon factors. Common factors include structural issues, medication effects, and systemic illnesses (Table 1). Bleeding due to structural issues (eg, bleeding varices, trauma, and surgical bleeding) are best managed with local control and supportive care, including transfusion support. Medication effects, such as those related to antiplatelet and/or anticoagulant therapy also require local/supportive care, in some cases with specific additional therapies, such as reversal agents (direct oral anticoagulants), factor support (vitamin K antagonists), or platelet transfusions (certain types of bleeding in patients receiving antiplatelet agents). Bleeding due to systemic illness, in addition to the aforementioned treatment, also includes treatment of the underlying cause (eg, treatment of sepsis causing disseminated intravascular anticoagulation or malignancy causing thrombocytopenia). Uncommon factors include congenital or acquired bleeding disorders. Because the diagnosis of inherited bleeding disorders, particularly in women, is frequently delayed, diagnosis may be made initially in an inpatient or postoperative setting.[1] In addition, acquired bleeding disorders may be presented quite dramatically in the emergency or inpatient setting. These disorders require specific management and therapies.

Relatively common inherited bleeding disorders, which may present with trauma-induced or spontaneous bleeding, include von Willebrand disease (VWD), factor VIII (FVIII) deficiency or hemophilia A, FIX deficiency or hemophilia B, and FXI deficiency. However, rarer disorders such as inherited deficiencies of FV, FVIII, FX, or FXIII can also present with bleeding, requiring hospitalization, even as an adult.[2,3] Adult patients with FXIII deficiency rarely present with a spontaneous intracranial hemorrhage.[4,5] Qualitative platelet disorders commonly present with mucocutaneous bleeding; however, given the diagnostic challenges and need for specialized testing, a diagnosis may go undetected until a patient presents with severe postsurgical or posttraumatic bleeding.[6] Patients with dysfibrinogenemia can present with either bleeding or thrombosis.[7]

Acquired bleeding disorders, although rare, can have remarkably severe presentations necessitating hospitalization. Acquired VWD can be associated with lymphoproliferative disorders, severe cardiac/valvular disease, and the use of supportive devices such as a left ventricular assist device and can present with severe bleeding.[8] The incidence of acquired hemophilia increases with age, and although an underlying cause is not determined in approximately half of the patients, it can be associated with autoimmune disorders, malignancy, infection, or pregnancy (usually post partum) and can present with substantial soft tissue or gastrointestinal bleeding.[9]

When assessing a patient who is bleeding, in either the inpatient or outpatient setting, the single most important tool is having a comprehensive bleeding history, which may be best accomplished via a standardized tool, such as the ISTH-Bleeding Assessment Tool. Important factors include any prior history of bleeding, any family history of bleeding, and the type and location of bleeding. Distinguishing between lifelong symptoms, which may have previously gone unrecognized, and truly new symptoms is paramount. Attention to other

Table 1. Common and uncommon causes of bleeding in adults who are hospitalized

Common
Anatomic/traumatic causes (ulcers, surgery, trauma, and so on)
Medication effect (anticoagulants, antiplatelets, NSAIDs, and so on)
Thrombocytopenia
Liver disease (coagulopathy, variceal bleeding, and so on)
Renal failure/uremia
Consumptive coagulopathy
Vitamin K deficiency (with dietary restriction/antibiotics)
Rare
Inherited bleeding disorders (hemophilia, VWD, platelet disorders, and so on)
Acquired bleeding disorders (FVIII inhibitors, acquired VWD, and so on)
Connective tissue disorders
Vitamin C deficiency

NSAIDs, nonsteroidal anti-inflammatory drugs.

diagnoses, which may predispose or increase a patient's risk for acquired disorders is also critical.

Laboratory assessments are essential (Figure 1) but must be driven by the use of the bleeding history data. Notably, useful and important assays, such as platelet aggregation studies, may not be available locally and may not be valid in a patient who is ill and hospitalized and receiving multiple medications, adding to the challenge of making a diagnosis. Such testing must be done off medications known to interfere with platelet function and, typically, must be scheduled in the outpatient setting. Often, a patient who is first noted to have bleeding in the inpatient setting ultimately requires finalization of the workup in the outpatient setting, after the initial bleed is controlled.

Evaluation and management of bleeding in a patient who is critically ill or perioperative

Case 1

A 37-year-old woman admitted with hepatic failure due to autoimmune hepatitis develops severe epistaxis and melena, accompanied by an acute worsening of anemia (hemoglobin dropped to 5.8 g/dL from 8.4 g/dL). A physical examination is remarkable for jaundice, scleral icterus with conjunctival pallor, ascites, and extensive ecchymoses at venipuncture sites. A laboratory workup reveals a severely prolonged prothrombin time (PT) at 32 seconds, a mildly prolonged activated partial thromboplastin time (aPTT) at 42 seconds, marked thrombocytopenia (platelet count of 18 × 10^3/μL), and decreased fibrinogen at 126 mg/dL. Transfusion of red blood cells and platelets is prescribed. The hepatology team plans to perform a transjugular intrahepatic portosystemic shunt procedure but is concerned about the bleeding risk because of the International Normalized Ratio (INR) being reported as 5.0 and states that it should be <2.0 in order to perform the procedure. She is eligible for a liver transplant but is not anticipated to get an organ for several months.

Discussion of case 1

Liver disease, whether chronic or acute, is a common and complex cause of coagulation abnormalities. Many changes, including decreases in fibrinogen, platelet count, and multiple clotting factors (demonstrated as prolonged PT and, occasionally, aPTT) predispose to bleeding. Because these changes are most apparent in laboratory evaluation, there is a tendency to think of the coagulopathy of liver failure as predisposing primarily to bleeding. However, other changes, less easily measured with standard coagulation tests, including the reduction in anticoagulant factors such as protein C, protein S, and antithrombin and increased von Willebrand factor (VWF) levels predispose to thrombosis as well. The availability of new data over the last few decades has resulted in a new understanding of the changes in coagulation in liver disease to be a state of rebalanced hemostasis, rather than a primarily hemostatic defect.[10]

Based on this understanding as well as the awareness of the potential harms of transfusion, including the risk of transfusion-associated circulatory overload, allergic or hemolytic transfusion reactions, and alloantibody development, the current model of care is in transition. Importantly, recent data have demonstrated a lack of correlation between INR and the risk of bleeding in liver disease. Although there is a direct correlation between the risk of bleeding and supratherapeutic INRs in patients receiving vitamin K antagonists (hazard ratio, 4.70; INR >3.5), this does not hold true for patients with liver disease. In such patients, although the risk of bleeding does increase with an INR >1.5 compared with an INR in the normal range (hazard ratio, 2.25), it does not progressively increase with levels >1.5.[11] This new evidence argues against the old standard practice of transfusing the product to reach a goal INR of ≤2.0 in patients with liver disease. Other studies have also failed to demonstrate a benefit with this approach and have demonstrated harms with transfusion of fresh frozen plasma (volume overload) or the use of prothrombin complex concentrate (PCC) (increased risk of thromboembolic events) targeted toward normalizing INR. Furthermore, fresh frozen plasma fails to correct an INR >1.5,[12] and correction of the INR with PCCs is only partial, at best.[13]

Thrombocytopenia is common in patients with liver disease, primarily because of splenic sequestration in patients with portal hypertension but also because of reduced thrombopoietin in those with cirrhosis.[14] Thrombocytopenia may be further exacerbated by marrow suppression because of an infection, acute illness, ongoing alcohol use, or nutritional deficiencies such as inadequate folate intake. Although standard transfusion goals, including platelet counts of ≥50 × 10^3/μL in noncentral nervous system bleeds and platelet counts ≥100 × 10^3/μL for central nervous system bleeds are often used, it is unclear whether this is truly necessary because platelet adhesion to the subendothelium appears to be restored in some patients with liver disease.[15] This is believed to be partially due to decreased ADAMTS-13 and increased VWF levels.[16] Thrombin generation appears to be preserved at platelet counts as low as 60 × 10^3/μL in patients with cirrhosis.[17] In addition to the standard approach of platelet transfusion to a specific goal, which may be difficult to

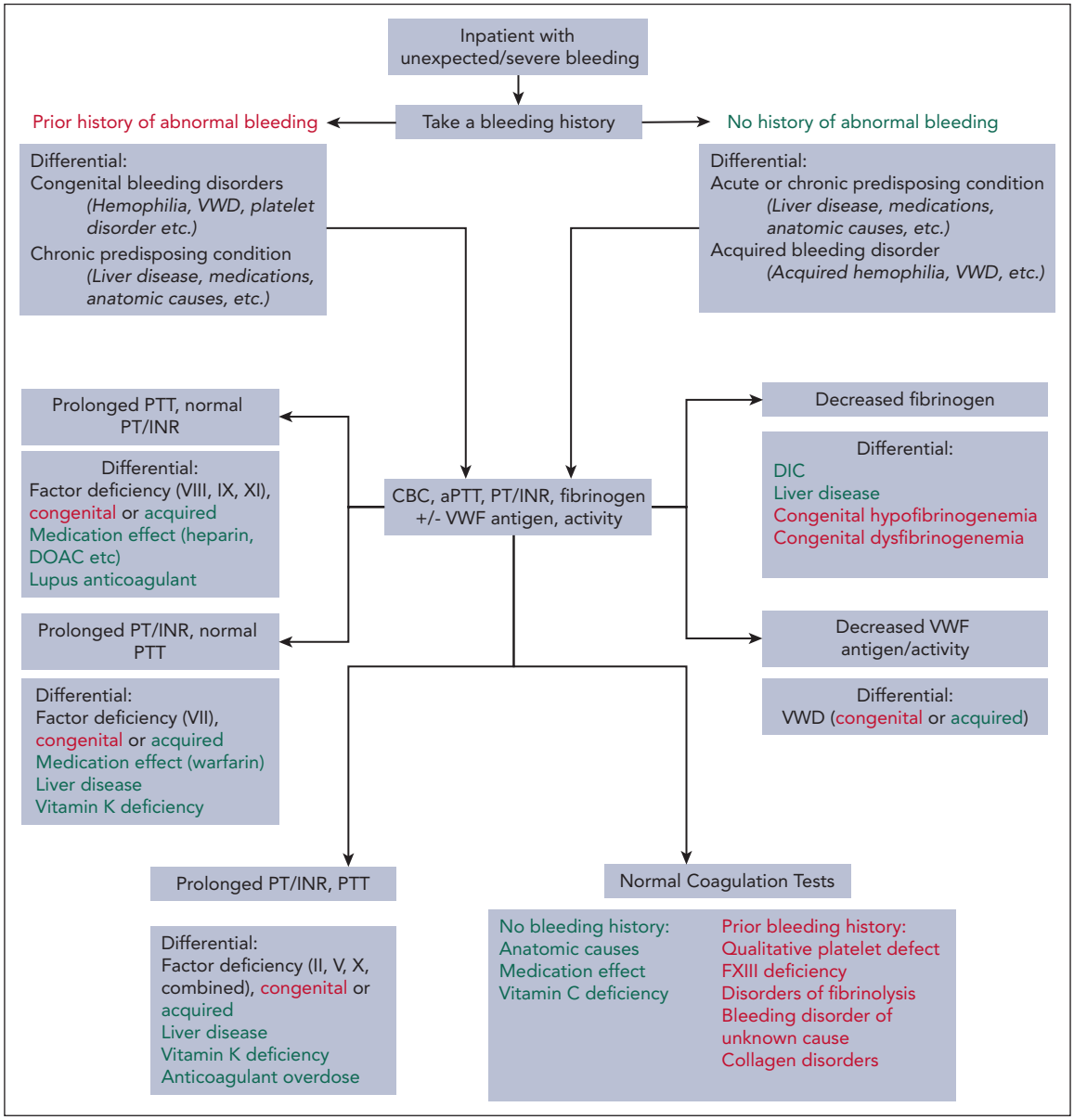

Figure 1. Algorithm for evaluation of an adult inpatient with excessive or unexpected bleeding. The first step in evaluation is determining whether bleeding symptoms are new developments. The differential diagnosis is further narrowed, and diagnosis is ultimately made based upon the results of laboratory testing. Congenital disorders are designated in red, and acquired disorders in green. DOAC, direct oral anticoagulant; CBC, complete blood count.

achieve because of splenic sequestration and/or shortages of blood products, thrombopoietin receptor agonists may be used to increase platelet levels before procedures. Because it can take up to 2 weeks to achieve optimal effect, this is not an adequate solution for acute bleeding.[18] Of note, decreased hemoglobin has also been shown to inversely correlate with an increased bleeding time, supporting improved platelet function; although the impact of this on clinical outcomes has not been studied.[19,20] Nonetheless, appropriately resuscitating with red blood cells is an important component of managing acute bleeding.

In severe liver disease, fibrinogen may be low because of decreased synthesis in the setting of compromised liver function. Levels may also be decreased in the setting of ongoing consumption because of bleeding or disseminated intravascular coagulation (DIC). In addition, plasma hyperfibrinolysis may be observed.[21] Fibrinogen levels may be raised with cryoprecipitate or fibrinogen concentrate but an optimal goal level is not defined in liver disease. In the setting of DIC or acute bleeding, management may be dictated by guidelines for these disorders (goal typically ≥100 mg/dL). Tranexamic acid (TXA) is contraindicated in the setting of DIC. In patients with acute bleeding and without DIC, TXA may be considered, although a randomized, controlled trial of a high-dose 24-hour infusion of TXA failed to demonstrate a reduction in death due to bleeding among patients with acute gastrointestinal bleeding. The trial also demonstrated a slight increase in venous thromboembolic risk, although overall risk was low (0.8% vs 0.4%; relative risk, 1.85; 95% confidence interval, 1.15-2.98).[22] Of note, in general, TXA

has not been associated with an increased risk of thrombosis in any study with a typical dosing (1000 mg intravenously every 8 hours or 1300 mg orally every 8 hours).

Management of acute bleeding or around procedures in patients with coagulopathy associated with liver disease must be driven by patient presentation, given only few data based on laboratory analyses provide other guidance. However, the use of thromboelastography (TEG) to guide factor repletion in liver transplant surgery has been shown to reduce red blood cell and plasma transfusion volumes.[23] TEG has also effectively demonstrated, what is believed to be, the rebalanced hemostatic picture in compensated cirrhosis and thus may be the best available assessment of overall hemostatic balance in liver disease.[24]Although TEG is not universally available in all hospitals, it is available in virtually all transplant centers, which may be the ideal setting for patients such as the one described in case 1, where it may serve to provide reassurance of rebalanced hemostasis and prevent circulatory overload and/or increased risk of thromboembolism from traditional, INR-based transfusion strategies.

Evaluation of a patient presenting with acute bleeding

Case 2

A 64-year-old man presents in a grave situation to the emergency department with shortness of breath, pallor, and presyncope. He is markedly anemic (6.8 g/dL), but his white blood cell and platelet counts are within normal limits. A physical exam shows that the patient has extensive ecchymoses of arms, legs, and trunk, without bruising of inner surfaces. His stool is found to be heme positive. The patient reports a history of multiple surgeries, including total hip replacement, cholecystectomy, and spine surgery without abnormal bleeding. He denies a family history of abnormal bleeding. He was previously healthy, except for hypertension and a 50–pack-a-year smoking history. He notes shortness of breath, a productive cough, and an unintentional weight loss of 4.5 kg over the last few months.

In addition to severe anemia, his initial laboratory workup reveals a prolonged aPTT at 73 seconds. An aPTT mixing study shows correction upon immediate mixing but prolongation of the aPTT with incubation at 37°C for 30 minutes. His FVIII activity level is <1%, with an FVIII inhibitor of 35 Bethesda units. He receives recombinant porcine FVIII (rpFVIII) at a dose of 200 units per kilogram, with FVIII levels monitored for response, and undergoes endoscopy and colonoscopy in which it is noted that he has a small but actively bleeding ulcer, which was treated endoscopically. He is transfused with 1 unit of red blood cells.

Discussion of case 2

This is a relatively common presentation of acquired hemophilia A (AHA). Subcutaneous and muscle bleeding are the most common sites of bleeding in AHA, affecting >80% and >40%, respectively.[7] The next most common site of bleeding is the gastrointestinal tract (>20%). Genitourinary, retroperitoneal, and other site bleeding are less common (<10%), and intracranial hemorrhage is reported but is rare. Joint bleeds are also quite rare, unlike in patients with congenital hemophilia. Most patients (77%) present with spontaneous bleeding, and 70% experience serious bleeding (hemoglobin <8 g/dL or a decrease >2 g/dL).[9] AHA is associated with a high mortality rate (21%) and when accompanied by serious bleeding, is a hematologic emergency that requires rapid recognition and treatment.[25]

AHA occurs as a result of the spontaneous development of autoantibodies against FVIII. Although these autoantibodies share specificity against FVIII and neutralizing effects with the inhibitors that develop in congenital hemophilia, key differentiators are that patients have no significant bleeding history or pathogenic genetic variants in the *F8* gene and, if tested, normal FVIII levels previously. AHA usually occurs in older individuals, and thus bleeding challenges in the patient's history are common.

Laboratory evaluation of the patient who is bleeding and hospitalized begins with the aPTT and PT. Prolongation of the aPTT in a patient with AHA may be mild or moderate; similarly, FVIII activity may be absent or merely low (typically ≤30%), which may appear out of proportion to the severity of bleeding. Inhibitor titers, as measured by the Bethesda assay or with its Nijmegen modification, may seem low in comparison with the severity of bleeding. This is because, in large part, of the type 2 kinetics of inhibitors in AHA, which may result in significant discordance between factor activity, inhibitor titer, and clinical bleeding symptoms.[26]

Although suspicion for AHA should be high in this patient, based on an initial presentation of isolated, prolonged aPTT, and spontaneous, largely subcutaneous bleeding, it is important to keep the differential broad until a specific diagnosis is confirmed. In a patient such as this one, it is important to measure all factors that could potentially contribute to an isolated prolonged aPTT, including FVIII, FIX, and FXI. Also important, particularly in settings in which specific factor level measurements are not readily available, is the use of a mixing study, in which an aPTT is performed using patient plasma mixed with normal plasma. Although the aPTT may decrease slightly or even correct immediately after mixing, when a FVIII inhibitor is present, it will prolong after incubation at 37°C. It is important to notify the laboratory that the patient has new bleeding symptoms and request that the incubation step be performed.

Treatment of AHA in a patient who is bleeding is 2-pronged. Firstly, hemostasis must be achieved (Table 2). Although patients with lower titer inhibitors (<5 Bethesda units) may respond to a higher dose FVIII replacement, this can only be given in a setting in which FVIII levels can be actively monitored because the response is not predictable. Ongoing monitoring is important, both to ensure adequate hemostasis without risk of elevated FVIII in this usually elderly population and to improve cost effectiveness of treatment. One option is the use of rpFVIII. rpFVIII is approved for treatment of AHA-associated bleeding in the United States, Canada, and Europe. Cross-reactivity of the inhibitor against rpFVIII is variable, and, therefore, close monitoring of FVIII levels and dose adjustment is necessary, but responses are generally superior to those expected with human FVIII.[27] In settings in which rpFVIII is unavailable and/or ineffective, or in which real-time monitoring is unavailable, bypassing agents, such as recombinant FVIIa (rFVIIa) and/or activated PCC (aPCC) can be used, keeping in mind the

Table 2. Hemostatic treatment options for AHA

	Pros	Cons
rpFVIII	More specific than bypassing agents More effective than human FVIII	Requires ongoing FVIII monitoring Some inhibitors may have cross-reactivity
rFVIII	More specific than bypassing agents	Likely requires very large doses and will not be able to achieve goal levels with high titer inhibitors Requires ongoing FVIII monitoring
aPCC	2-3 times daily Laboratory monitoring not required	Nonspecific and potentially ineffective in some patients No laboratory measure of efficacy
rFVIIa	May be effective in patients who do not respond to aPCC or rFVIII, or when rpFVIII is not available Laboratory monitoring not required	Nonspecific and potentially ineffective in some patients. Very frequent dosing (daily, every 2-3 hours) required No laboratory measure of efficacy
Tranexamic acid	Has some efficacy, especially for mucosal bleeding Oral and IV routes. Efficacy not reduced by inhibitor presence	Likely to be inadequate as a single-agent therapy Should not be administered with aPCC because of DIC risk
Emicizumab	May reduce/eliminate risk of bleeding with infrequent subcutaneous dosing	Not effective or adequate for acute bleeding Studies ongoing, thus, data limited Interferes with inhibitor monitoring May not ameliorate need for additional/more specific therapies Is contraindicated in conjunction with aPCC

bleeding symptoms.[28] rFVIIa, 90 μg/kg every 2 to 3 hours with a later switch to an aPCC, if needed or desired, may be used to treat severe bleeding, with gradual tapering over subsequent days if bleeding is controlled. In patients with nonsevere bleeding who require hemostatic treatment, aPCC given in a dosage of ~50 to 100 units per kg every 8 to 12 hours (not exceeding 200 units per kg per day) may control bleeding and require fewer health care resources for short-term treatment. Patients with mucocutaneous bleeding may benefit from TXA or other antifibrinolytic agents alone or in conjunction with factor replacement although use with aPCC should be avoided. If FVIII activity levels are not immediately available, temporizing management of moderate to severe bleeding with rFVIIa or aPCC is reasonable after a newly prolonged aPTT has been confirmed and shown not to correct on mixing study with incubation. Transfer to a center where a definitive diagnosis can be promptly established and FVIII activity monitoring is available is recommended.

Although not yet approved for this indication in the United States, there are several case reports and small studies on the use of emicizumab, a bispecific FVIII-mimetic antibody approved for the prevention of bleeding in patients with congenital hemophilia A, for AHA.[29] Notably emicizumab has been approved for the treatment of AHA in 1 country (Japan), and clinical trials are ongoing in the United States (NCT05345197) and Germany (NCT04188639). Emicizumab interferes with the standard, 1-stage FVIII activity assay, and a chromogenic FVIII assay using bovine reagents must be used for monitoring FVIII levels.[30] Thus, if the chromogenic FVIII assay is not available, emicizumab would interfere with the ability to provide accurate, real-time monitoring of rFVIII and rpFVIII therapy and responses to inhibitor eradication. Importantly, the use of aPCC is contraindicated in patients receiving emicizumab because of the risk of thrombosis/thrombotic microangiopathy, and although rVIIa is typically considered safe in this setting, a case of stroke was noted in a patient with AHA treated with emicizumab.[31] Because AHA frequently occurs in the elderly, it is a challenge to balance bleeding control with the risk of thrombosis.

The second key component of treating AHA is inhibitor eradication. This can be approached in a variety of ways, although first-line therapy includes corticosteroids alone or in combination with either oral cyclophosphamide or rituximab.[32] Combination therapy with corticosteroids and cytotoxic agents leads to an earlier remission compared with steroids alone, although it may result in higher rates of adverse effects, including infection.[33] Patients for whom corticosteroids are contraindicated may benefit from single-agent therapy with cyclophosphamide.[34] Remissions can be slow to achieve, taking a median of between 40 and 48 days, depending on the therapy used and the inhibitor titer.[33] Because of a paucity of data, there are no specific second- or third-line therapeutic recommendations; however, if no change in inhibitor titer and/or FVIII activity level is observed within 3 weeks, adding additional agents to single- or double-agent regimens may be appropriate, with the understanding that this increases toxicity and infection risk. Another important consideration is evaluation for an associated underlying condition, such as autoimmune disease, malignancy, infection, and/or medication. Treatment may affect the AHA and/or the approach to immunosuppression. Importantly, relapse/recurrence occurs in 20% of patients ongoing monitoring is necessary for most patients.[33] In case 2, the patient described had many risk factors and/or possible indicators of malignancy, including a smoking history, weight loss, shortness of breath, and a persistent cough and should undergo appropriate imaging.

Evaluation and management of a patient with peripartum bleeding

Case 3

A 27-year-old woman presents in a critical situation to the obstetrics service, with heavy vaginal bleeding 9 days after the delivery of a healthy infant. Her initial postpartum course, after

normal spontaneous vaginal delivery at 40 weeks and 1 day, was typical, with an estimated blood loss of <500 mL. She was discharged on postdelivery day 2 and had normal lochia. She noticed an increase in bleeding over 24 to 48 hours before presentation, and, at the time of presentation, was saturating a maxipad every 20 to 30 minutes. Initial laboratory analysis reveals anemia (hemoglobin dropped to 6.2 g/dL from 10.8 g/dL on postdelivery day 1) and a slightly prolonged aPTT at 37 seconds. Other coagulation assays, including PT and fibrinogen, are normal. Upon careful history taking, the patient reveals that she did in fact have excessive bleeding in the past, after childhood tonsillectomy, and thinks she might have been diagnosed with VWD. She also notes that her periods have always been heavy (saturating a pad or tampon every 1 to 2 hours on heavy days) and that she has a history of easy bruising and iron deficiency dating back to her teens. This was her first delivery. Her condition is managed with TXA, 1000 mg intravenously, thereafter 1300 mg orally every 8 hours and supportive care while laboratory analysis is performed. She is ultimately diagnosed with VWD per a VWF antigen level of 28%, VWF activity level of 26%, and FVIII level of 45%.

Discussion of case 3

This case is a fairly typical example of secondary postpartum hemorrhage due to an inherited bleeding disorder. In women with VWD or hemophilia A, VWF and FVIII increase significantly during pregnancy, peaking around the time of delivery. As a result, many pregnant individuals with type 1 VWD or mild hemophilia A have a sufficient increase in levels and may not have excessive bleeding at the time of delivery. The optimal levels needed peripartum to prevent hemorrhage are not defined but recent data support a goal of >100%, which is higher than that recommended in the past.[35] Levels begin to decline rapidly within the first day after delivery, approaching baseline by postpartum day 7, and reaching baseline around 3 weeks post partum.[36] As a result, secondary postpartum hemorrhage (blood loss of >1000 mL that occurs from 24 hours to 6 weeks after delivery) is relatively common among patients with these factor deficiencies.

As with case 1, further investigation of this mildly prolonged aPTT is important. Although some patients with type 1 VWD have FVIII levels low enough to prolong the aPTT, many patients have normal aPTTs. In a case such as this, it is important to consider and potentially measure the activity of factors and coagulation proteins known to increase in pregnancy and decrease in the postpartum setting. This includes primarily VWF, FVIII, and fibrinogen. FVII and FX also increase, although to a lesser degree.[37] FVII deficiency does not prolong the aPTT. Because deficiencies of FX are rare and levels low enough to be associated with bleeding would typically be expected to also affect the PT, it is most reasonable to begin a workup in this patient by measuring FVIII activity and VWF antigen and activity levels.

Other nonbleeding-disorder causes of secondary postpartum hemorrhage that require specific therapies include retained products of conception, endometritis, vascular abnormalities such as arteriovenous malformations, and uterine subinvolution. All of these should be considered in the evaluation and workup of this patient; however, the personal history of abnormal bleeding, and a report of historical VWD diagnosis, is highly suggestive of an inherited bleeding disorder. Primary postpartum hemorrhage can also be observed in bleeding disorders but is more commonly due to uterine atony, tissue trauma, or aberrant placental tissue/retained products of conception.[38,39]

TXA is generally efficacious in treating postpartum hemorrhage. Although it has been primarily studied in the setting of primary postpartum hemorrhage (blood loss of >1000 mL, which occurs within 24 hours of delivery),[40] it is effective for uterine bleeding in general, including heavy menstrual bleeding,[41] and would be an appropriate first-line therapy in this case. TXA can be administered intravenously (1000 mg every 8 hours) or orally (1300 mg every 8 hours) and, importantly, there is no evidence of increased risk of venous thromboembolism with its use in this setting. TXA is an excellent first-line hemostatic therapy to use for postpartum or other periprocedural bleeding when laboratory analysis, such as VWF levels, are not immediately available.

Another potential consideration, if there is a preexisting diagnosis of either VWD or mild hemophilia A and the patient has been shown to respond, is the use of desmopressin, which increases plasma levels of VWF and FVIII by inducing a release of endogenous stores of these factors. However, it should be noted that desmopressin does not work for all patients with these disorders and is, in fact, contraindicated in VWD type 2B because it can decrease factor levels and induce thrombocytopenia. In addition, it can induce hyponatremia, thus, fluids should be restricted, which is a challenge in a hemorrhaging patient, and serum sodium levels monitored.

In this patient, both local control measures and TXA should be used while FVIII and VWF levels measurements are prioritized. Based on her VWF and FVIII levels, replacement VWF product would be appropriate for this patient, with an initial goal of ≥100%, given she is has severe hemorrhages.[42] This may be achieved via the use of plasma-derived products containing both VWF and FVIII, recombinant VWF or, on an emergency basis in settings in which these therapies are not available, blood-containing products with increased concentrations of VWF and FVIII (cryoprecipitate). If neither the rapid measurement of individual factors nor specific replacement therapies are available, then transfer of care to a location where these resources are available is recommended. Care for her VWD should be established post partum, and hemostatic coverage for future pregnancies planned based on laboratory levels before and during pregnancy, including during the third trimester.

Conclusions

Evaluation and management of bleeding in an adult who is hospitalized, although often urgent, still requires careful attention to the clinical history and prompt, thorough laboratory assessment. Although suspicion for an acquired coagulopathy should be high, it is important to also consider that diagnosis of congenital bleeding disorders may be delayed until the patient encounters a major bleeding challenge, such as injury, surgery, or childbirth. Although some fundamental principles of hemostasis are applicable across settings, such as the importance of local control, blood product support, and the use of antifibrinolytics, the best therapy is often a directed one, and, thus, a rapid and accurate diagnosis is essential. The optimal

therapies in many of these situations, such as AHA and aVWD, are not defined and more research is urgently needed.

Authorship

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Footnote

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REFERENCES

1. Kirtava A, Crudder S, Dilley A, Lally C, Evatt B. Trends in clinical management of women with von Willebrand disease: a survey of 75 women enrolled in haemophilia treatment centres in the United States. *Haemophilia*. 2004;10(2):158-161.
2. Kadir RA, Sharief LA, Lee CA. Inherited bleeding disorders in older women. *Maturitas*. 2012;72(1):35-41.
3. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. 196: Thromboembolism in pregnancy. *Obstet Gynecol*. 2018;132(1):e1-e17.
4. Hsieh L, Nugent D. Factor XIII deficiency. *Haemophilia*. 2008;14(6):1190-1200.
5. Pelcovits A, Schiffman F, Niroula R. Factor XIII deficiency: a review of clinical presentation and management. *Hematol Oncol Clin North Am*. 2021;35(6):1171-1180.
6. Dorgalaleh A, Tabibian S, Shamsizadeh M. Inherited platelet function disorders (IPFDs). *Clin Lab*. 2017;63(1):1-13.
7. Casini A, de Moerloose P. How I treat dysfibrinogenemia. *Blood*. 2021;138(21):2021-2030.
8. Franchini M, Mannucci PM. Acquired von Willebrand syndrome: focused for hematologists. *Haematologica*. 2020;105(8):2032-2037.
9. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: updated review of evidence and treatment guidance. *Am J Hematol*. 2017;92(7):695-705.
10. Ballantine A, Martin D, Thakrar SV. The coagulopathy of liver disease: a shift in thinking. *Br J Hosp Med (Lond)*. 2021;82(6):1-9.
11. Afzal A, Gage BF, Suhong L, Schoen MW, Korenblat K, Sanfilippo KM. Different risks of hemorrhage in patients with elevated international normalized ratio from chronic liver disease versus warfarin therapy, a population-based retrospective cohort study. *J Thromb Haemost*. 2022;20(7):1610-1617.
12. Evans CR, Cuker A, Crowther M, Pishko AM. Prophylactic fresh frozen plasma versus prothrombin complex concentrate for preprocedural management of the coagulopathy of liver disease: a systematic review. *Res Pract Thromb Haemost*. 2022;6(4):e12724.
13. Huang WT, Cang WC, Derry KL, Lane JR, von Drygalski A. Four-factor prothrombin complex concentrate for coagulopathy reversal in patients with liver disease. *Clin Appl Thromb Hemost*. 2017;23(8):1028-1035.
14. Koruk M, Onuk MD, Akcay F, Savas MC. Serum thrombopoietin levels in patients with chronic hepatitis and liver cirrhosis, and its relationship with circulating thrombocyte counts. *Hepatogastroenterology*. 2002;49(48):1645-1648.
15. Lisman T, Bongers TN, Adelmeijer J, et al. Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology*. 2006;44(1):53-61.
16. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med*. 2011;365(2):147-156.
17. Tripodi A, Primignani M, Chantarangkul V, et al. Thrombin generation in patients with cirrhosis: the role of platelets. *Hepatology*. 2006;44(2):440-445.
18. Terrault N, Chen YC, Izumi N, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. *Gastroenterology*. 2018;155(3):705-718.
19. Gerrard JM, Docherty JC, Israels SJ, et al. A reassessment of the bleeding time: association of age, hematocrit, platelet function, von Willebrand factor, and bleeding time thromboxane B2 with the length of the bleeding time. *Clin Invest Med*. 1989;12(3):165-171.
20. Valeri CR, Cassidy G, Pivacek LE, et al. Anemia-induced increase in the bleeding time: implications for treatment of nonsurgical blood loss. *Transfusion*. 2001;41(8):977-983.
21. Caldwell SH, Hoffman M, Lisman T, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. *Hepatology*. 2006;44(4):1039-1046.
22. HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. *Lancet*. 2020;395(10241):1927-1936.
23. Kang YG, Martin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. *Anesth Analg*. 1985;64(9):888-896.
24. Thalheimer U, Triantos CK, Samonakis DN, et al. A comparison of kaolin-activated versus nonkaolin-activated thromboelastography in native and citrated blood. *Blood Coagul Fibrinolysis*. 2008;19(6):495-501.
25. Bitting RL, Bent S, Li Y, Kohlwes J. The prognosis and treatment of acquired hemophilia: a systematic review and meta-analysis. *Blood Coagul Fibrinolysis*. 2009;20(7):517-523.
26. Tiede A, Werwitzke S, Scharf RE. Laboratory diagnosis of acquired hemophilia A: limitations, consequences, and challenges. *Semin Thromb Hemost*. 2014;40(7):803-811.
27. Kruse-Jarres R, St-Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. *Haemophilia*. 2015;21(2):162-170.
28. Holmstrom M, Tran HTT, Holme PA. Combined treatment with APCC (FEIBA®) and tranexamic acid in patients with haemophilia A with inhibitors and in patients with acquired haemophilia A–a two-centre experience. *Haemophilia*. 2012;18(4):544-549.
29. Thomas VM, Abou-Ismail MY, Lim MY. Off-label use of emicizumab in persons with acquired haemophilia A and von Willebrand disease: a scoping review of the literature. *Haemophilia*. 2022;28(1):4-17.
30. Peyvandi F, Kenet G, Pekrul I, Pruthi RK, Ramge P, Spannagl M. Laboratory testing in hemophilia: impact of factor and non-factor replacement therapy on coagulation assays. *J Thromb Haemost*. 2020;18(6):1242-1255.
31. Knoebl P, Thaler J, Jilma P, Quehenberger P, Gleixner K, Sperr WR. Emicizumab for the treatment of acquired hemophilia A. *Blood*. 2021;137(3):410-419.
32. Collins P, Baudo F, Knoebl P, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *Blood*. 2012;120(1):47-55.

33. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. 2007;109(5):1870-1877.

34. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol*. 2003;121(1):21-35.

35. Leebeek FWG, Duvekot J, Kruip MJHA. How I manage pregnancy in carriers of hemophilia and patients with von Willebrand disease. *Blood*. 2020;136(19):2143-2150.

36. James AH, Konkle BA, Kouides P, et al. Postpartum von Willebrand factor levels in women with and without von Willebrand disease and implications for prophylaxis. *Haemophilia*. 2015;21(1):81-87.

37. Bremme KA. Haemostatic changes in pregnancy. *Best Pract Res Clin Haematol*. 2003;16(2):153-168.

38. Kazi S, Arusi I, McLeod A, Malinowski AK, Shehata N. Postpartum hemorrhage in women with von Willebrand disease: consider other etiologies. *J Obstet Gynaecol Can*. 2022;44(9):972-977.

39. Reale SC, Easter SR, Xu X, Bateman BT, Farber MK. Trends in postpartum hemorrhage in the United States from 2010 to 2014. *Anesth Analg*. 2020;130(5):e119-e122.

40. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389(10084):2105-2116.

41. Naoulou B, Tsai MC. Efficacy of tranexamic acid in the treatment of idiopathic and non-functional heavy menstrual bleeding: a systematic review. *Acta Obstet Gynecol Scand*. 2012;91(5):529-537.

42. Bannow BS, Konkle BA. Inherited bleeding disorders in the obstetric patient. *Transfus Med Rev*. 2018;32(4):237-243.