Acquired Hemophilia A

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KEYWORDS

• Hemophilia • Inhibitor • Bleeding disorder • aPTT • Acquired hemophilia A

KEY POINTS

- Acquired hemophilia A is a potentially severe bleeding disorder caused by antibodies against the patient's own factor VIII.
- Bleeding in acquired hemophilia A can be spontaneous and severe.
- The clinical and laboratory presentation of acquired hemophilia A can be confused with other coagulopathies.
- The 1:1 mix can be a useful way of differentiating factor deficiency from inhibitors when faced with an isolated elevation of the activated partial thromboplastin time. However in acquired hemophilia A, inhibitor activity is time and temperature dependent, so the effect on the 1:1 mix is most evident when samples are intubated.
- Treatment involves control of bleeding and eradication of the inhibitor. Clinicians should be alert for side effects of eradicating therapies.

INTRODUCTION

Acquired hemophilia A is a bleeding disorder caused by antibodies to factor VIII (FVIII). These antibodies—called *inhibitors*—interfere with normal hemostasis, leading to potentially catastrophic bleeding. Acquired hemophilia A is a rare disease, and there is a paucity of randomized trial data to guide its treatment. However, understanding the pathogenesis and presentation of acquired hemophilia A can help clinicians to detect this severe bleeding disorder early and manage it in an evidence-based fashion.

NATURE OF THE PROBLEM

Acquired inhibitors have been reported for all coagulation factors, but by far the most common acquired inhibitor is the FVIII antibody—the inhibitor that causes acquired hemophilia A.[1,2]

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FVIII is synthesized as a 330-kDa precursor protein composed of a heavy chain and a light chain[3] (**Fig. 1**). After proteolytic cleavage, FVIII binds to the phospholipid components of platelets and endothelial cells, and to other clotting factors. The antibodies that cause acquired hemophilia A tend to be IgG antibodies that interfere with FVIII binding to factor X and factor IXa, or that interfere with FVIII binding to phospholipid and von Willebrand factor.[3–6]

Acquired FVIII inhibitors show type II or second-order kinetics, inactivating FVIII in a nonlinear fashion[7–9] (**Fig. 2**). Initially, inactivation is rapid, but it then slows to an equilibrium. The time- and temperature-dependent nature of acquired FVIII inhibitors has important implications for the laboratory detection of acquired hemophilia A (see Approach).

EPIDEMIOLOGY

With an incidence estimated to be between 1 and 2 cases per million population per year, acquired hemophilia A is rare disease.[10] The 2012 prospective EACH2 study captured the clinical and demographic characteristics of 501 European patients with acquired hemophilia A, who presented between 2003 and 2008.[11] It showed that the median age at presentation was 73.9 years (range, 61.4–80.4 years), with an even split between males and females. There have been rare reports of acquired hemophilia A in children as young as age 8, and also in the extreme elderly ($\geq$ 85 years).[12,13]

Acquired hemophilia A seems to be caused by a combination of genetic and environmental factors, leading to a breakdown of immune tolerance.[14,15] At this time, it is not possible to predict whether a particular individual will develop a FVIII inhibitor. However, acquired hemophilia A is associated with several underlying conditions.[2] Approximately 10% of acquired hemophilia A is associated with malignancy, with both solid tumors and hematologic malignancies reported. Case series suggest that there is a close temporal relationship between the appearance of the inhibitor and a tumor diagnosis, and that less advanced cancer is associated with inhibitors that

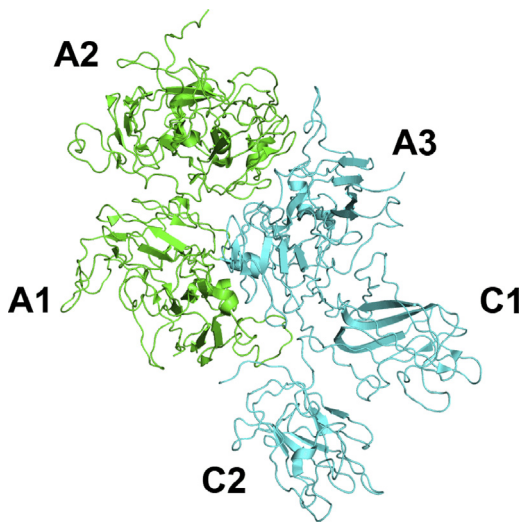

Fig. 1. Tertiary structure of B-domainless FVIII with A1, A2, A3, C1, and C2 domains labeled. By Mattkosloski (21 January 2013), distributed under a CC-BY 3.0 license. Available at: https://en.wikipedia.org/wiki/Factor_VIII#/media/File:Fviii_2R7E.png.

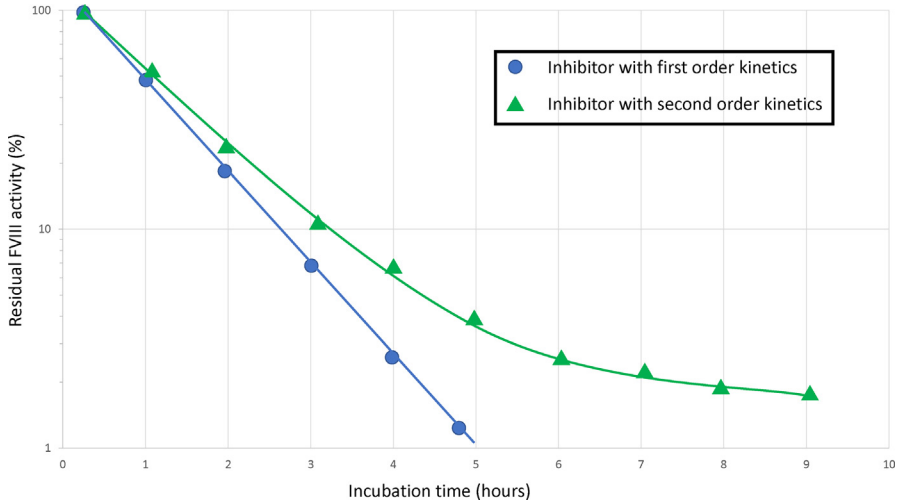

Fig. 2. Kinetics of FVIII inhibitors. Type 1 inhibitors are alloantibodies that develop in patients with congenital hemophilia A, and typically demonstrate first-order (linear) kinetics. Type 2 inhibitors are alloantibodies that develop in patients with acquired hemophilia A, and typically demonstrate second-order (nonlinear) kinetics. These acquired inhibitors rapids neutralize FVIII. However an equilibrium is soon reached, and residual FVIII can be detected in vitro. This residual FVIII activity is not, however, associated with a decreased risk of bleeding in vivo.

are more responsive to treatment.[16] Autoimmune disease underlies approximately another 10% of acquired hemophilia A, with the most common conditions reported to be rheumatoid arthritis and systemic lupus erythematosus.[1,17,18] Pregnancy is an important association in women with acquired hemophilia A, with most inhibitors diagnosed in the puerperium. Women with pregnancy-associated FVIII inhibitors tend to have good clinical outcomes; this is likely due to their young age, generally good health, and the transient nature of their underlying condition.[19] FVIII inhibitors have also been associated with drugs, including antibiotics (penicillin, sulfonamides), immunomodulatory agents (interferon, fludarabine), and antiepileptic drugs (phenytoin).[2] Approximately 50% of cases of acquired hemophilia A are idiopathic, with no underlying cause found.[2]

APPROACH

General Approach to Evaluation

Acquired hemophilia A should be suspected in any bleeding patient with an isolated elevation of the activated partial thromboplastin time (aPTT). Cooperation between the clinician and the laboratory is essential to evaluating the patient and confirming the diagnosis.

Clinical Evaluation

The clinical presentation of acquired hemophilia A is not identical to congenital hemophilia A.[11] Although the latter often manifests as joint bleeding, the former manifests as soft tissue, mucosal, or muscle bleeding. Bleeding in acquired hemophilia A occurs spontaneously, with minimal trauma. Severe bleeding, including gastrointestinal and intracranial bleeds, can also be seen in acquired hemophilia A. Bleeding can be highly

morbid in acquired hemophilia A; the 2012 EACH2 survey identified that 87% of patients experienced major bleeding, and 22% died from complications of their inhibitor.[11] Bleeding remains a risk until the FVIII inhibitor has been eliminated.[20] Males and females are also equally affected with acquired hemophilia A, unlike in congenital hemophilia A, where males tend to have more severe bleeding symptoms. And although congenital hemophilia A tends to present in childhood, especially in its moderate and severe forms, acquired hemophilia A tends to manifest in older people.[2]

The clinical evaluation of the patient should focus on establishing the degree and time course of bleeding, as well as the presence of any possible underlying conditions. Clinicians should examine the patient for hematomas; inquire about severe, sustained, or unusual blood loss; and educate the patient about the risk of life- and limb-threatening bleeding. It is vital that clinicians (and patients) note even mild bleeding, so it can be monitored for progression.

Nearly all patients with acquired hemophilia A present with bleeding, and more than 80% of patients with acquired hemophilia A experience hemorrhage or bleeding significant enough to merit transfusion.[1,11,21] Patients with soft tissue bleeding can present with pain, color change, and swelling of the limbs; this condition can easily be confused with deep vein thrombosis and can rapidly progress to compartment syndrome if not managed with hemostatic treatment. The regular monitoring of pain, pulses, sensory function, and motor function is important to ensure soft tissue bleeding does not progress to limb loss. Patients can also develop rapidly evolving intracranial hemorrhages in acquired hemophilia A, so any change in neurologic status should prompt clinical and radiographic assessment. And even minor interventions, such as arterial line placement or venipuncture, can provoke severe bleeding; these procedures should be minimized.

Laboratory Evaluation

Acquired hemophilia A presents a diagnostic challenge, and can easily be confused with other coagulopathies. It should be suspected in any patient with an abnormal aPTT and a normal prothrombin time, international normalized ratio, thrombin time, fibrinogen, and platelet count; however, the differential diagnosis of this finding can also include congenital factor deficiencies, nonspecific inhibitors, and anticoagulants like heparin (**Fig. 3**).

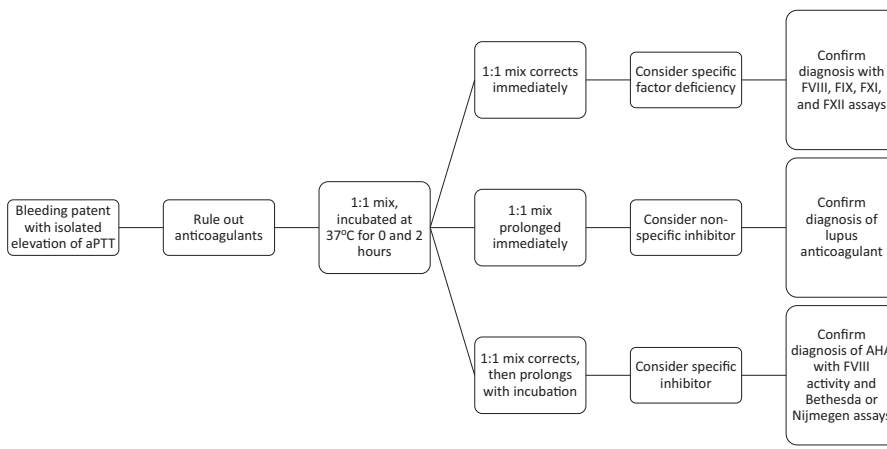

Fig. 3. Laboratory workup of an isolated elevation of aPTT.

The first step in working up an isolated prolongation of the aPTT is determining if the patient is bleeding. Acquired hemophilia A nearly always comes to clinicians' attention because of bleeding (see Clinical Evaluation). Next, heparin contamination of the sample should be ruled out, either by redrawing a blood sample from an uncontaminated peripheral vein, by performing a thrombin time and a reptilase time, or by attempting to neutralize any heparin in the sample with protamine or heparinase. The presence of FXa inhibitors (including low molecular-weight-heparin, fondaparinux, apixaban, rivaroxaban, and edoxaban) can be ruled out with an anti-Xa assay. Once anticoagulants have been ruled out, it is prudent to look back at previous laboratory results for the patient, if available; unlike a congenital factor deficiency (of factors VIII, IX, or XI, or of the so-called intrinsic factors), previous aPTTs should be normal in a patient with acquired hemophilia A.

The use of a 1:1 mix in the diagnostic assessment of acquired coagulation factor inhibitors is controversial. Classical teaching is that when patient plasma is mixed with normal pooled plasma, complete correction of the aPTT suggests a factor deficiency. Conversely, partial or no correction suggests an inhibitor, either specific (eg, FVIII inhibitors) or nonspecific (ie, lupus anticoagulant). Mixing studies are straightforward to perform, even in lower resource settings. They can provide valuable clues to the presence of an underlying inhibitor. However, caution should be exercised when interpreting mixing studies, because they are not standardized and different procedures can lead to different results.[22] The appropriate mixing study to investigate an acquired inhibitor is the 2-step mixing study, which looks at aPTT correction immediately after mixing and then at 1 and 2 hours while the sample is incubated at 37 °C. Samples from patients with acquired hemophilia A may "correct" immediately after mixing. However, the time- and temperature-dependent nature of the acquired FVIII inhibitor is demonstrated by partial or no correction with warming and incubation. A weak inhibitor tends to require a longer incubation ($\geq$2 hours) to demonstrate partial or no correction of the 1:1 mix.[23] It is important for the treating clinician to communicate with their coagulation laboratory when ordering mixing studies, to understand how the assay is performed and reported.

The presence of a lupus anticoagulant can confound or confuse the diagnosis of acquired hemophilia A. A lupus anticoagulant does cause an isolated prolonged aPTT, similar to an acquired FVIII inhibitor[24]; however, it does not cause a bleeding phenotype. Because a lupus anticoagulant causes immediate and sustained inhibition, a 1:1 mixing study will immediately fail to correct—and this result will be sustained despite warming and incubation.[23]

The definitive laboratory tests to diagnose acquired hemophilia A are the FVIII activity and the FVIII inhibitor (Bethesda) assay.[25] FVIII activity is reduced in acquired hemophilia A, but affected individuals often have some detectable FVIII activity in vitro. This occurs because of the inhibitor's second-order kinetics; after a rapid phase, inactivation of FVIII slows to an equilibrium. Yet this residual in vitro activity does not translate into a decreased bleeding risk in vivo.[11,23] The Bethesda assay is used to detect and determine the strength of the FVIII inhibitor. In this assay, serial dilutions of patient plasma are incubated with normal pooled plasma for 2 hours at 37 °C. FVIII activity is then measured at each dilution. The incubated control is considered to be 100% FVIII activity, and the reciprocal dilution of patient plasma that yields 50% FVIII activity is defined as a Bethesda unit (BU).[23,26] For example, if the residual FVIII activity is 50% with a dilution of 1:10, then the actual inhibitor titer within the plasma sample is 10 BU. A stronger inhibitor requires additional dilution to allow FVIII activity to break through, and is thus assigned a higher BU. We consider low-titer inhibitors to be less than 5 BU and high titer inhibitors to be 5 BU or greater.

The classical Bethesda assay can underestimate inhibitor titers at very low titers (<1 BU). This is because changes in pH and protein concentration affect the stability of FVIII inactivation, and these changes can have a large impact on weaker inhibitors. To account for this, some laboratories use a Nijmegen-modified Bethesda assay when the inhibitor titer is low or suspected to be low, buffering the normal plasma and using immunodepleted FVIII deficient plasma to make the serial dilutions.[27–30] Heat treatment of the sample may also improve test sensitivity with low titer inhibitors.[23,28]

THERAPEUTIC OPTIONS

The management of acquired hemophilia A involves 2 parallel strategies: the treatment of bleeding and eradication of the inhibitor.

Treat Bleeding

Clinicians have 2 options for immediate treatment of bleeding in acquired hemophilia A: increasing FVIII levels to overwhelm the inhibitor and bypassing FVIII to activate coagulation despite the presence of the inhibitor. If the bleeding is not severe and the inhibitor titer is less than 5 BU, it is reasonable to attempt local control and focus on increasing plasma FVIII levels. A target of 30% to 50% is generally adequate to achieve hemostasis.[31] Hemostasis can sometimes be achieved with 1-deamino-8-D-arginine vasopressin (DDAVP). DDAVP is a synthetic analogue of the antidiuretic hormone vasopressin, and it increases circulating levels of FVIII.[32] Doses of 0.3 μg/kg subcutaneously daily for 3 to 5 days are typically used in acquired hemophilia A. However, unless the inhibitor titer is very low (<3 BU), DDAVP is often insufficient to manage bleeding.[33]

Severe bleeding with a low titer inhibitor (<5 BU) may be managed with local control and FVIII concentrate, again aiming for a plasma FVIII level of 30% to 50%.[34] Human FVIII replacement is generally not effective, because it is quickly overcome by all but the lowest titer inhibitor. It should be used as a first-line therapy only if no other alternatives are available. Conversely, porcine (pig) FVIII has in vivo activity in humans, but its protein sequence is different enough from human FVIII that it is less affected by acquired FVIII inhibitors. A recombinant porcine FVIII product (OB-1, Obizur) has been shown to control bleeding in acquired hemophilia A, particularly when given as a primary therapy.[35] (All patients in this prospective study also received immunosuppression, and some patients developed inhibitors to Obizur.) The usual starting dose of Obizur is 50 to 100 U/kg. Because incremental recovery is often inadequate, FVIII activity should be checked every 2 to 3 hours, with repeat dosing as needed. It is important to note that patients can develop antiporcine FVIII antibodies in response to the administration of recombinant porcine FVIII; this point limits the effectiveness of subsequent doses, and patients may require a higher initial dose (eg, 200 U/kg) for severe bleeding.

Factor bypassing agents are a more effective way to treat bleeding in acquired hemophilia A, particularly if it is severe and associated with a high titer inhibitor. Both activated prothrombin complex concentrate (aPCC) or recombinant factor VIIa (rFVIIa) have been successfully used in acquired hemophilia A. The EACH2 registry (which was reported before the approval of recombinant porcine FVIII) demonstrated that bleeding was most successfully controlled with bypassing agents with (>90% achieving control), when compared with human FVIII and DDAVP.[33] There was no appreciable difference between rfVIIa and aPCC.

Recombinant FVIIa acts by binding to the surface of activated platelets and promoting thrombin generation directly, independent of FVIII.[36] Studies using rFVIIa as a

second-line agent for the treatment of acquired hemophilia A showed a response rate of more than 90% and a complete response rate of 75%.[37] The starting dose of rFVIIa is 70 to 90 μg/kg, repeated every 2 to 3 hours until bleeding stops. The dosing interval can then be lengthened. There is no accurate way to monitor response to rFVIIa treatment with laboratory assays, so clinical monitoring is essential. The most important side effect of rFVIIa is thrombosis—both arterial and venous.[38,39] This complication is most common in older patients, patients with a history of thrombosis, and patients with an underlying prothrombotic condition (eg, cancer).[33]

Activated PCC is a plasma-derived concentrates containing clotting factors II, VII, IX, and X (in both activated and inactivated forms). A retrospective study of aPCC in acquired hemophilia A showed a complete response rate of more than 80% with a dosing regimen of 75 U/kg every 8 to 12 hours until bleeding stopped.[40] (A median number of 10 doses was required to control severe bleeding.) The EACH2 registry demonstrated that 93.3% of bleeds were controlled successfully when aPCC was given.[33] Like rFVIIa, the response to aPCC treatment cannot be monitored accurately with standard laboratory assays, so clinical monitoring is required. In addition, aPCCs carries a risk of thrombosis; daily doses should be limited to less than 200 U/kg to minimize this risk. Because aPCCs contain small amounts of FVIII, they can also trigger an anamnestic increase in inhibitor titer.[26]

Because registry data suggest that both rFVIIa and aPCC are similarly effective, clinicians should use the product that is most available at their center and with which they are most comfortable.

Eradicate the Inhibitor

Surveys of patients with acquired hemophilia A who do not receive immunosuppression suggest that in about one-third of patients, the inhibitor will disappear spontaneously.[41] These spontaneously remitting inhibitors tend to be associated with the postpartum state or with drugs.[1] However, it is not possible to predict at the outset if or when an inhibitor will remit spontaneously. And as long as an acquired FVIII inhibitor persists, there is a risk of serious bleeding. For this reason, most patients undergo immunosuppressive therapy to eradicate their inhibitor.

There are no randomized trial data demonstrating the superiority of any one immunosuppressive regimen, although registry data suggest that combining steroids with additional agents may increase the likelihood of remission.[42] Rituximab-based regimens seem to take longer to effect complete remission. And regardless of the choice of first-line therapy, second-line therapy, if required, can still be successful in approximately 60% of patients.[43]

Corticosteroids are often the first choice for immunosuppression in patients with acquired hemophilia A. Most clinicians are familiar with these drugs, and the risk of serious side effects associated with their short-term use is low. Prednisolone at a dose of 1 mg/kg/d, or prednisone 1 mg/kg/d, eradicates inhibitors in approximately 30% of patients, generally within 3 weeks.[43,44] Adding cyclophosphamide to nonresponding patients at a dose of 2 mg/kg/d can increase the response rate to nearly 70%. It can take up to 6 weeks to demonstrate a response to steroids and cyclophosphamide, and there is a risk of relapse when they are stopped.[43,44]

Second-line therapy for acquired hemophilia A includes inhibitor removal with plasmapheresis or immunoadsorption, azathioprine, vincristine, mycophenolate mofetil, intravenous immunoglobulin, or combined protocols.[45] Because the majority of patients respond to corticosteroids and cyclophosphamide, these agents are not recommended as initial therapy.[45]

Rituximab, an anti-CD20 monoclonal antibody, can be effective in patients who have failed or who cannot tolerate first-line therapy. It seems to confer durable remission in patients with acquired hemophilia A, and most responses occur within the first 2 weeks of therapy.[46–49] Its use in acquired hemophilia A remains off-label in many jurisdictions at this time, but the most commonly used dosing regimen is 375 mg/m^2 weekly for 4 weeks.

Patients receiving immunosuppressive treatment should have FVIII activity levels and inhibitor titers monitored weekly, until the inhibitor becomes undetectable and FVIIII activity goes back to normal.[45]

Focus on Pregnancy

Pregnant women with acquired hemophilia A are managed very similarly to nonpregnant patients. Steroids are the safest and most effective option to eradicate inhibitors.[50] Pregnancy-associated FVIII inhibitors, although they have a lower relapse rate overall, can recur in subsequent pregnancies. Because FVIII inhibitors tend to be IgG antibodies, they can cross the placenta and result in life-threatening fetal and neonatal hemorrhage.[12] For this reason, it is essential to eradicate pregnancy-associated FVIII inhibitors in the first instance and closely monitor patients in subsequent pregnancies.[19]

CLINICAL OUTCOMES

Acquired hemophilia A is a highly morbid condition. Mortality is estimated to range between 15% and 50%, with older patients and those with underlying malignancy at greatest risk of death.[51] The direct cause of death is not always bleeding—patients can die from complications of bleeding, from their underlying disease, or from complications of treatment. The EACH2 registry found that immunosuppressive therapy accounted for 16% of all deaths.[11] This underscores the adverse effects associated with immunosuppression to eradicate inhibitors.

Modern studies suggest that more than 70% of patients achieve complete remission with immunosuppression, which makes it the treatment option of choice. Even when patients relapse after a first complete remission, more than 60% of them go on to achieve a second complete remission.[21,43] Patients with lower titer antibodies and higher residual FVIII activity tend to achieve remission more readily, as do pregnant patients.[52] Patients on immunosuppression generally experience a decrease in inhibitor titer or a risk in baseline FVIII level after 3 to 5 weeks of therapy. If they do not, second-line therapy should be considered. Once remission has been achieved, patients should be monitored for relapse, initially with FVIII activity, and then clinically. EACH2 suggested that relapse occurs in 18% of patients who achieved remission on steroids alone and in 12% receiving corticosteroids and cyclophosphamide, whereas only 3% of patients achieving remission with rituximab-based regimens relapsed. The median time to relapse in this study was approximately 135 days.[43]

Patients receiving treatment should be monitored for adverse effects, including thrombosis from FVIII bypassing agents, and infectious complications of immunosuppression. A UK surveillance study demonstrated that 33% of patients developed sepsis and, in 12% of patients, sepsis contributed to death.[21] Of the patients in the EACH2 registry, 4.2% died from complications of immunosuppression.[43]

DISCUSSION

Further research is needed to improve outcomes for patients with acquired hemophilia A. Novel treatment strategies currently being explored include the use of

emicizumab—a recombinant bispecific monoclonal antibody that bridges FIXa and FX, functioning like FVIIIa.[53–56] However, on a more fundamental level, our understanding of which patients respond best to inhibitor eradication treatments and which patients are most likely to attain sustained remission remains incomplete. Future studies of this rare disease should help us to develop better treatment strategies, to help patients achieve durable responses with minimal side effects.

SUMMARY

Acquired hemophilia A is a bleeding disorder caused by antibody formation to FVIII. Acquired hemophilia A manifests as spontaneous, often severe bleeding in individuals with no previous bleeding history. Patients are often older and may have an underlying condition (eg, cancer, autoimmune disorder, pregnancy, drugs). The laboratory manifestations of acquired hemophilia A include an isolated prolongation of the aPTT, decreased FVIII activity, and an inhibitor detectable by the Bethesda assay (with Nijmegen modification for low titer antibodies). Treatment of acquired hemophilia A includes early detection, management of bleeding with hemostatic agents, and eradication of the inhibitor. Acquired hemophilia A is a highly morbid condition; patients suffer the grave effects of bleeding and also of their treatments. Although a majority of patients with acquired hemophilia A will achieve remission—with an undetectable inhibitor titer and cessation of bleeding symptoms—many will die from its complications. Prompt recognition of this bleeding disorder, coupled with evidence-based care, is vital.

CLINICS CARE POINTS

- Acquired hemophilia A should be suspected in any bleeding patient with an isolated elevation of the activated partial thromboplastin time (aPTT).
- Acquired hemophilia A often manifests as soft tissue, mucosal, or muscle bleeding, occurring spontaneously, with minimal trauma. Severe, life threatening bleeding can occur.
- Clinical evaluation should focus on establishing the degree and time course of bleeding, and exploring underlying conditions. 50% of acquired hemophilia A is due to underlying conditions, including pregnancy, autoimmune disease, drugs, or cancer.
- The definitive laboratory tests to diagnose acquired hemophilia A are the FVIII activity and the FVIII inhibitor (Bethesda) assay.
- The management of acquired hemophilia A involves 2 parallel strategies: the treatment of bleeding and eradication of the inhibitor.

DISCLOSURE

The authors have no commercial or financial conflicts of interest.

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