Background

Acquired hemophilia (AH) is a rare disorder characterized by the sudden onset of typically severe subcutaneous, muscle, or gastrointestinal bleeding, but bleeding and significant bruising can occur anywhere.¹ The condition occurs with an estimated incidence of between 1.34 and 1.48 per 1,000,000 per year in the general population and predominantly affects older people.²,³ It is due to the production of autoantibodies, which inhibit the activity of coagulation factor VIII (FVIII). In approximately 50% of cases, AH is associated with the obvious or occult presence of other autoimmune disorders, malignancies, the peripartum, and certain medications (Table 1).¹²³

Table 1. Disease States Associated With Acquired Hemophilia¹

<table>
<thead>
<tr>
<th>Disease States</th>
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<tbody>
<tr>
<td>• Collagen, vascular, and other autoimmune diseases, eg, rheumatoid arthritis,</td>
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<td>systemic lupus erythematosis, and polymyalgia rheumatica</td>
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<td>• Malignancy, eg, leukemia, lymphoma, and solid tumors⁵</td>
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<td>• Skin diseases, eg, pemphigus, psoriasis vulgaris, and exfoliative dermaîtis¹⁵</td>
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<td>• Possible reaction to drugs, eg, penicillin, ampicillin, phenytoin, chloramphenicol, and ciprofloxacin⁴⁵</td>
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<tr>
<td>• Pregnancy</td>
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<td>• Idiopathic</td>
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Pathogenesis

The pathogenesis of FVIII autoantibody formation remains largely unknown, but FVIII inhibitors are usually polyclonal, high-affinity immunoglobulin G (IgG) molecules. The synthesis of these molecules requires the activation of CD4+ T helper cells. In both congenital and acquired hemophilia, inhibitor antibodies are predominantly of the IgG4 subclass and, to a lesser extent, IgG1. In the case of acquired hemophilia, immunoglobulin M (IgM) and immunoglobulin A (IgA) inhibitors have also been described. The majority of FVIII inhibitors are directed against one of the following areas: the carboxyl end of the C2 domain, which contains phospholipids and von Willebrand factor binding sites; the amino end of the A2 domain, which forms part of the intrinsic pathway factor X (FX) activation complex; or the amino end of the A3 domain, which contains a factor IX (FIX) binding site.

Mechanisms by which inhibitor antibodies neutralize the procoagulant function of FVIII have been enhanced by the characterization of the epitopes to which these antibodies bind. Which epitope is recognized by T cells that help in the synthesis of FVIII inhibitors remains unclear.

Clinical Presentation

Acquired hemophilia presents with bleeding, ranging from life- and limb-threatening to mild in patients with no personal or family history of bleeding, and has a high mortality, estimated at between 9% and 22%. Patients may suddenly experience spontaneous bleeding (mainly involving the skin or mucosa) or trauma- (ie, intramuscular injections) or surgery-induced bleeding. Bleeding can
involve any site, with the site, extent, and intensity defining the bleeding as major or minor (Figure 1). Compartmental and retroperitoneal bleeding are often misdiagnosed and life threatening. Hemarthrosis occurs less frequently in AH than in congenital hemophilia. Post-bleeding anemia often arises; its severity is related to the severity of bleeding.

![Figure 1](image)

Patients with AH usually present to physicians who are not hematologists or experienced in the recognition and diagnosis of this condition and who have not previously managed a case, such as geriatricians, obstetricians, rheumatologists, oncologists, emergency physicians, or surgeons. Lack of familiarity with the disorder may lead to delayed diagnosis and suboptimal treatment. Thus, immediate consultation with a hematologist at a hemophilia treatment center who is experienced in the management of FVIII inhibitors is necessary for optimal patient outcomes.¹

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**Diagnosis**

In the proper clinical setting, diagnosis should be suspected when an activated prothrombin time (aPTT) is prolonged in association with a normal prothrombin time.¹ A mixing test should then be performed. In this test, the patient's plasma is mixed with normal plasma (1:1 and additional increasing dilutions) and incubated for 2 hours at 37°C (the interaction between inhibitor and factor
VIII coagulant [FVIII:C] is time and temperature dependent). If the aPTT remains abnormally high after incubating the mixture for 2 hours, then this defines the presence of an inhibitor. If there is correction of the prolonged aPTT after 2 hours, then the presence of an anti-FVIII neutralizing antibody is presumably absent. On the other hand, a unique situation exists with anti-FVIII antibodies in that occasionally the baseline aPTT is corrected immediately after mixing patient with normal plasma sources. This illustrates the time dependency of the antibody to neutralize FVIII activity. FVIII:C and inhibitor titers can also be determined, but they are not reliable predictors of bleeding risk or response to treatment. Figure 2 presents a useful algorithm for the diagnosis of AH.

Differential Diagnosis

Lupus anticoagulant (LAC) and antiphospholipid antibodies syndromes are associated with prolonged aPTT. In contrast to the anti-FVIII antibody inhibitor, the LAC prolongs the aPTT at time 0 after mixing patient with normal plasma and does not produce further prolongation of the aPTT in the mixture after 2 hours of incubation at 37°C. The presence of heparin (unfractionated or
low-molecular-weight heparin) either used as a flushing agent in an indwelling catheter through which a coagulation blood sample is drawn or used for treatment should also be ruled out since coagulation testing will identify the anticoagulant as a circulating inhibitor.

In your practice, which disease states have been most frequently associated with AH?

- Pregnancy/postpartum
- Autoimmune disorders (eg, rheumatoid arthritis)
- Malignancies (solid or hematologic)
- Drug reaction
- Other/idiopathic

Case 1: Maria G.

Maria G. is a 25-year-old woman who was admitted to San Salvatore Hospital, University of L’Aquila-Italy, after presenting to the emergency room (ER) for treatment of bilateral hematomata of the elbows associated with prolonged aPTT values. Her past clinical history was negative for any underlying medical condition, and her family history was negative for bleeding diatheses.

Recent clinical history included a vacuum extraction vaginal delivery 45 days before the current ER visit, and heavy postpartum bleeding, which did not require transfusions of packed red blood cells. Laboratory evaluations of PT and aPTT were normal during pregnancy and immediately after delivery. The newborn was healthy and had no evidence of bruising or bleeding. The patient was discharged 3 days after delivery with no specific treatment except for oral iron supplementation for iron deficiency anemia.

At the time of Maria G.’s current hospital admission, laboratory test results were as follows: PT, 12.5 s; aPTT, 65.2 s; factor VIII activity, 4%; antibodies to FVIII, 2.7 BU; and FIX coagulant (FIX:C) activity, 92%. These findings resulted in a diagnosis of postpartum acquired hemophilia A.
Case 2: Peter S.

Peter S. is a 56-year-old Caucasian male who returned to his dermatologist for treatment of persistent bleeding from a right thigh skin biopsy site. The skin biopsy was performed 48 hours earlier to evaluate a suspicious-appearing nevus. The biopsy incision continued to ooze despite suturing and a local pressure dressing. Concurrently, the patient experienced the onset of acute lumbar and right groin pain without hematuria and went to the ER thinking that he had a renal calculus. The plain kidney, ureter, and bladder x-ray showed no significant abnormality, and he was discharged with pain medications and instructions to undergo a follow-up intravenous pyelogram.

The patient returned to the ER the next day for increasingly intense right flank pain. A computed tomographic (CT) scan revealed the presence of a large retroperitoneal bleed with no evidence of lymphadenopathy, solid organ lesions, or other pathology. His complete blood count (CBC) showed a low hemoglobin (10 g/dL) and hematocrit (28%) but was otherwise normal. Differential count and cell morphology on the peripheral smear were also unremarkable. The patient's prior medical history was pertinent for Binet stage B (Rai stage IIA) chronic lymphocytic leukemia (CLL) that had been successfully treated with fludarabine and cyclophosphamide (CTX) 4 years earlier. Recent flow cytometry of his peripheral blood was consistent with continued complete response, and the patient was otherwise healthy.

Following admission, his laboratory data confirmed the diagnosis of AH with an inhibitor titer of 325 BU and a FVIII:C activity level of 9%.

What is the typical age of your patients with AH?

- 16-45 years
- 46-60 years
- 61-75 years
- >75 years

[View Results]
Treatment of AH

Treatment of AH aims to control acute bleeding and to eradicate the neutralizing anti-FVIII inhibitor (the latter should begin as soon as possible to reduce the risk of bleeding). Acute bleeding control is mandatory because of the high early mortality rate associated with major bleeding. The target level of FVIII:C needed to control most bleeding events is 30% to 50% of normal. Choice of treatment depends on the severity of the bleeding, the clinical setting, and the initial and historical peak titers of antihuman FVIII inhibitors.

Recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC; FEIBA) are the most commonly used first-line therapies to reverse or prevent bleeding complications when the inhibitor titer is high (>5 BU). The dosing of these products is derived from clinical trial experience and mirrors the dosing regimens used in the treatment of alloantibody inhibitors of FVIII in congenital hemophilia A.11,12 aPCC treatment (50-100 U/kg bw) should be repeated every 6 to 12 hours, while rFVIIa is administered as a bolus injection of 90 mcg/kg every 2 to 3 hours.13,14 Continuous infusion of rFVIIa (8-50 mcg/kg/h) and aPCC have been reported anecdotally but have not been studied in AH.15

The duration of treatment with either agent is based on clinical scenario, clinical response to treatment, and the critical nature of the bleed. For acute bleeding situations in AH, it is typical to administer a “consolidating” dose of either product after a minimum of 1 dose of aPCC or 2 doses of rFVIIa concentrate controls the bleeding. Both drugs are well tolerated, with few adverse events. Thrombogenic complications have been reported in AH patients but are considerably less common than in off-label uses of the medications. There is also a small, but theoretical, risk of viral or prion transmission related to aPCC. Local adjunctive hemostatic measures, such as antifibrinolytic agents or topical fibrin glues and recombinant topical thrombin, may also help in controlling bleeding in AH but the former may enhance thrombogenic potential if not used sparingly. The use of FVIII concentrates to reverse or prevent bleeding events in AH is recommended only with documented low titer anti-FVIII inhibitors (<5 BU). The ability to predict adequate dosing of these agents to overcome the inhibitory response and achieve adequate hemostasis is tenuous at best. One algorithm recommends an FVIII dose of 20 IU/kg body weight for each BU of inhibitor plus 40 additional IU/kg administered as a bolus.16 There are also anecdotal reports of desmopressin use in this setting of low-titer antibodies (<5 BU).1

Immune tolerance induction (ITI) protocols have not been systematically studied for the eradication of the autoantibody inhibitor directed against FVIII in AH, in contrast to their use for the elimination of the alloantibody inhibitor in congenital hemophilia A, where there is over 50%
success. Nevertheless, modified ITI protocols may be considered in selected patients with AH.\textsuperscript{17} It should be noted that spontaneous remissions of the autoantibody do occur in up to 38\% of the patients, predominantly in postpartum and drug-related cases; however, these responses are unpredictable, and the risk of severe bleeding is high if the inhibitor persists.\textsuperscript{4} If an autoantibody inhibitor spontaneously remits in the postpartum period, the likelihood of recurrence during subsequent pregnancies is low, but such recurrences have been reported.

Therapy for the eradication of the autoantibody inhibitor in AH typically requires immunosuppression, which should be initiated as soon as possible after the diagnosis of AH is confirmed and the acute bleeding episode is controlled. Prednisone as monotherapy or in combination with CTX and azathioprine represents the standard first-line intervention. The response rate with prednisone alone (at a dose of 1 mg/kg) is high, but a sustained remission after prednisone discontinuation is rare, and the adverse effects of corticosteroids often limit their usefulness.\textsuperscript{16}

Other immunosuppressive medications have been employed for eradication of particularly refractory autoantibody inhibitors; these include azathioprine, cyclosporine, tacrolimus, mycophenolate, mofetil, sirolimus, and 2-chlorodeoxyadenosine. Combination treatment with FVIII concentrate, CTX, and methylprednisolone, or other similar immunomodulation protocols, has been successful in inhibitor eradication with low recurrence rates.\textsuperscript{18} At this time, in the absence of prospective, randomized, controlled trials, which may be difficult to achieve in this very low incidence disorder, rituximab, an anti-CD20 monoclonal antibody, should be considered salvage therapy and should be administered after failure of first- or second-line therapy.\textsuperscript{18} There is suggestive evidence from anecdotal reports that rituximab works better for lower-titer autoantibody inhibitors. Several additional new potential treatment modalities are currently being developed or in clinical trials, including new rFVIIa constructs, recombinant combined factor II (FII)-FX complex, and recombinant porcine FVIII concentrate.
What hemostatic treatments have you used most often to reverse or prevent bleeding events in your patients with acquired hemophilia A?

- FEIBA (activated prothrombin complex concentrate) (0%)
- rFVIIa (60%)
- Human FVIII (20%)
- Desmopressin (0%)
- Other (20%)

Case 1: Maria G.’s Treatment Plan

The patient was breast-feeding when she received her diagnosis of postpartum acquired hemophilia A. First-line treatment with prednisone at a daily dose of 1.5 mg/kg (total dose, 90 mg) was started immediately. FVIII:C and inhibitor levels were determined weekly for the following 8 weeks. The inhibitor disappeared, and the resulting FVIII:C levels were >80% after the fourth week of treatment. Steroid tapering was attempted after 12 weeks; however, at a daily prednisone dose of <50 mg, FVIII:C levels decreased to 3.2% and the autoantibody inhibitor against FVIII reappeared (3.2 BU).

Although the patient did not experience major bleeding, she did develop extensive ecchymoses over the lower extremities. She opted to continue treatment with increased doses of single-agent prednisone at 75 mg daily until the end of her breast-feeding period (6 months after delivery). At that time, CTX was added to the regimen. All potential adverse effects of CTX were explained to the patient, including potential risks of embryo and fetal toxicity should she become pregnant. A second course of treatment with prednisone 75 mg and CTX 100 mg daily was administered for 4 weeks, at which time the FVIII:C activity was 66% and the autoantibody inhibitor was undetectable.

Over the following 3 months, prednisone dosage was tapered to 5 mg daily with continuous CTX (100 mg/d). FVIII:C activity eventually increased to 83% with undetectable inhibitor.

Prednisone was then discontinued and, in the following 2 months, CTX was administered as a single agent; FVIII:C activity remained normal.
CTX was then tapered to 100 mg daily for 5 days per week over the next month. While on this treatment regimen, the patient developed multidermatomal herpes zoster; CTX 100 mg was discontinued for 3 days and then resumed at a less intense dosing regimen of 3 days per week. Concurrent treatment with valacyclovir (500 mg tid) was instituted for 1 week and resulted in resolution of the herpes zoster infection. In the following 2 months, CTX was progressively reduced to 100 mg once weekly. FVIII:C activity remained in the normal range, and the patient experienced no bleeding episodes. The patient became pregnant while taking CTX 100 mg once per week.

The drug was discontinued immediately after the positive pregnancy test. Prenatal screening for chromosomal abnormalities was recommended; the patient refused elective termination of her pregnancy.

**Case 2: Peter S.' Treatment Plan**

Immediately following his diagnosis of AH, the patient was treated with intravenous boluses of rFVIIa (90 mcg/kg q3h) until the bleeding from his right thigh biopsy site and the flank pain were controlled. At that point, the decision was made to initiate an ITI regimen intended to eradicate the autoantibody inhibitor and to determine if the precipitating etiology of the FVIII antibody inhibitor was related to a recurrence of his CLL or to a previously unappreciated malignant process. Because of the patient’s bleeding propensity, major invasive diagnostic procedures were deferred. Interim therapy consisted of oral prednisone 1 mg/kg/d, and a bone marrow aspirate and biopsy and a total body CT scan were performed to evaluate for lymphadenopathy and any indication of recurrent CLL.

Immunophenotypic and immunohistochemical analysis of the bone marrow aspirate revealed 12% clonal lymphocytes, consistent with relapsed or minimal residual CLL. Rituximab 375 mg/m²/wk intravenously for 4 weeks was added to the high-dose corticosteroids, with the goals of eradicating the small clone of CLL and the FVIII autoantibody inhibitor. At the end of this treatment regimen, FVIII:C activity levels remained around 9% and the inhibitor persisted in the 250-BU range.

Within a week, the patient experienced another spontaneous life-threatening bleed into the retroperitoneal space and required emergency admission to the intensive care unit for fluid resuscitation, blood transfusions, and treatment with rFVIIa to control bleeding. When the patient was stabilized, the decision was made to initiate a second-line approach to inhibitor eradication, employing a modified ITI protocol (human rFVIII concentrate [100 IU/kg/d], CTX, vincristine, and
prednisone). This regimen was administered for 4 months, with excellent results after the first month. Currently, FVIII:C activity is 92% and FVIII:C autoantibody inhibitor is undetectable.

**Conclusions**

Acquired hemophilia A is a rare autoimmune disease characterized by the presence of neutralizing autoantibodies directed against FVIII:C. The disease state is associated with high morbidity and mortality secondary to bleeding, underlying diseases, and the toxic effects of immunosuppression. Successful management of the disease relies on rapid diagnosis and immediate control of bleeding, followed by prompt treatment with immunosuppressants to eradicate the autoantibody. Education of specialty physicians, including obstetricians, ER and trauma physicians, and physicians who care for the elderly, about AHA is critical for optimal patient outcomes.

**References**


