



Editorial

Volume 29 Issue 3 - July 2025
DOI: 10.19080/CTOIJ.2025.29.556265

Cancer Ther Oncol Int J

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Update in Acquired Hemophilia A (AHA)



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Submission: July 05, 2025; **Published:** July 31, 2025

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Abstract

Acquired hemophilia A (AHA) is a rare serious autoimmune bleeding disorder caused by the development of autoantibodies that neutralize coagulation factor VIII. AHA typically affects older adults or women in the postpartum period without any personal or family history of bleeding. Patients often present with spontaneous, severe bleeding into the skin, muscles, or mucous membranes, while joint bleeding is uncommon.

Keywords: Acquired Hemophilia; Spontaneous Bleeding; Autoantibodies; Solid Tumor; Emicizumab

Abbreviations: IST: Immunosuppressive Therapy; BPA: Bypassing Agents; APCC: Activated Prothrombin Complex Concentrate; RF: Recombinant FVIII; RPVIII: Recombinant Porcine FVIII; PT : Prothrombin Time; TT: Thrombin Time; IST: Immunosuppressive Treatment.

Introduction

Acquired hemophilia A (AHA), is also termed acquired factor VIII inhibitor disorder. It is a rare autoimmune bleeding condition [1] caused by the presence of neutralizing autoantibodies (inhibitors) that attack coagulation factors VIII (FVIII) [2]. Patients usually present with spontaneous bleeding in the absence of known bleeding disorders or risk factors such as trauma, recent surgery, or anticoagulant use. It is largely undiagnosed, in elderly people in whom other bleeding conditions may coexist [1].

Epidemiology

AHA has an estimated incidence of 1 to 6 cases per million per year. The median age at diagnosis is 65 years old with no gender difference. Two peaks are observed in AHA incidence. The first peak affects young women in the postpartum period or having autoimmune diseases. The second peak occurs in patients over 60 years old. Incidence in pediatric cases is extremely rare (0.045 per million per year) [3].

Etiology

Idiopathic cause

More than 50% of AHA cases are idiopathic [3]. The exact trigger for spontaneous production of neutralizing IgG antibodies against FVIII in these patients is currently unknown [4].

Associated conditions

AHA can be secondary to other medical conditions such as:

- Postpartum.
- Autoimmune disorders (e.g., rheumatoid arthritis, SLE, dermatomyositis, Sjögren's syndrome, Goodpasture's syndrome).
- Graft-versus-host disease in allogeneic liver or hematopoietic progenitor transplantation.
- Certain cancers especially solid tumors.
- Infectious diseases.
- Reactions to medications like penicillin, sulfonamides, interferon, phenytoin and fludarabine [3].

Acquired Hemophilia A (AHA) Secondary to Neoplasia

AHA is more frequent among solid organ neoplasms. There is no predominant oncological entity. It may precede tumor diagnosis by months, so it can be labeled as a paraneoplastic syndrome. Sometimes, it is detected after the start of treatment of the specific neoplasm. There is a possibility of non-causal association between neoplasms and AHA, since both pathologies could coexist in advanced age [3].

Pathophysiology

All IgG subclass antibodies and IgA (46%) or IgM (9%) antibodies were detected in AHA though the most common subtypes with the highest titers and affinities were IgG1 and IgG4. The IgA antibodies correlate with outcome. The IgG antibodies correlate with titers of inhibitor. IgG antibodies could be proteolytic to-

wards FVIII. Some studies demonstrate that the IgG antibodies are generally polyclonal and largely bind to the A2 and C2 domains of FVIII and impair its function [4].

There is an association between AHA and CTLA4, non-hemophilic F8 gene variants, and certain human leukocyte antigen (HLA) types e.g., DRB1*16 and DQB1*0502 polymorphisms. Some studies suggested that FVIII-reactive CD4+ T cells may derive autoimmune response in AHA with inhibitors. There is a possibility that a trigger leads to a break in tolerance and allows CD4+ T cells to proliferate and lead to AHA in the right context [4].

Diagnosis

Typical clinical presentation of AHA is a new onset of mucocutaneous bleeding of variable intensity in the absence of previous personal or family history of bleeding [2]. It can lead also to soft tissues, recurrent gastrointestinal, intramuscular, or intracranial bleeding [1]. Hemarthrosis is rare. Infrequently, asymptomatic patients may be detected on abnormal routine screening tests of hemostasis [2]. Screening hemostatic assays show prolongation of APTT with a normal prothrombin time (PT) and thrombin time (TT).

Prolongation of APTT beyond 100 seconds is atypical in the presence of FVIII inhibitors. An alternative or co-existing causes should be suspected such as contamination of specimen by heparin or infrequently presence of a non-specific inhibitor (e.g. a lupus anticoagulant) or deficiency of a contact coagulation factor (e.g., homozygous factor XII deficiency). Mixing studies with an equal volume of normal plasma typically showed immediate inhibition of APTT.

In rare cases, such inhibition is detected only after a one- to two-hour incubation at 37°C when FVIII inhibitors titer is low [2]. The titer of factor VIII inhibitors can be measured using the Bethesda assay with Nijmegen modification and by chromogenic assays. The Bethesda assay provides the inhibitor titer in Bethesda units (BU). Alternative methods including qualitative enzyme linked immunoassays (ELISA), do not quantify the inhibitor titer [2].

Management

The cornerstone of treatment of AHA is immunosuppressive treatment (IST), together with hemostatic treatment. Hemostatic management include the use of bypassing agents (BPA) such as activated prothrombin complex concentrates [aPCC] or recombinant FVIIa [rFVIIa] or recombinant porcine FVIII (rpFVIII). There are no available data that suggest the superiority of one option over the other [2]. rpFVIII is effective in AHA due to the presence of differences in the A2 and C2 domains of the pFVIII and hFVIII molecule [2]. Anti-rpFVIII antibodies may be present at baseline in some patients while some will develop these antibodies after rpFVIII treatment.

Assessment of porcine FVIII inhibitor titer should be considered in patients treated with rpFVIII or if there is a change in

treatment response due to presence of cross-reacting anti-rpFVIII inhibitors to identify patients for whom rpFVIII may not be efficacious [2]. Human FVIII (hFVIII) is a reasonable initial therapy for those without access to BPA or rpFVIII and in patients with low-titer inhibitors (<5 BU). This results in an increase in inhibitor titer, rendering hFVIII ineffective. hFVIII is most likely ineffective in patients with high-titer inhibitors (>5 BU) [2].

Inhibitor Eradication with Immunosuppressive (IST) Therapy

The goal of IST therapy in AHA is to shorten the time to achieve remission and decrease bleeding [2]. Spontaneous remission is rare [2]. First-line monotherapy with glucocorticoids is sufficient for patients with favorable prognostic factors [2]. In general, cyclophosphamide or rituximab should be associated, if there is no response to steroids after 3 weeks, if they have not been used previously [3]. Combination therapy with glucocorticoid and either cyclophosphamide or rituximab is recommended as first-line option for those with FVIII:C less than 1 percent or inhibitor titer more than 20 BU [2]. Treatment of the underlying cancer does not replace IST; however, it will facilitate inhibitor elimination. IST should be individualized in cancer patients [3].

Complete remission (CR) is defined as normal FVIII level, without evidence of inhibitor or bleeding related to AHA in the absence of IST [3]. Partial remission (PR) is defined as factor VIII level more than 50% with no evidence of bleeding after 24 hours off hemostatic treatment [3].

Hemostatic Monitoring

Treatment response is assessed clinically (i.e., control of bleeding) and with laboratory assays for rpFVIII [3]. Evidence of inhibitor eradication is based on FVIII:C levels and Bethesda assays [2]. There are currently no routinely available assays assessing response to BPA [3]. Once complete remission is achieved, monitoring of FVIII:C should be performed monthly in the first 6 months, then every 2-3 months from 6 to 12 months, then every 6 months after 12 months [2].

AHA Relapse

Relapse occurs in about 7.1% to 20% after achieving remission with IST. FVIII levels are at the upper normal level, with a level higher than 100% during the first weeks after remission. Failure to reach this level in a patient may warrant closer monitoring for a possible higher relapse risk [3].

Prognostic Factors and Mortality

The main negative prognostic factors for AHA survival are very low FVIII activity (FVIII levels equal to or less than 1%), functional score of World Health Organization performance status (WHO-PS) greater than 2, presence of underlying malignancy, and failure to achieve CR. Additional unfavorable prognostic indicators include the presence of IgA isotype autoantibodies against FVIII, age more than 65 years, lack of response to eradica-

tion treatment, low hemoglobin level at diagnosis, high inhibitor titer and suboptimal IST scheme or inappropriate use of anticoagulant/ antiplatelet secondary prophylaxis before AHA diagnosis. The mortality rate associated with AHA ranges between 7% and 38%. The main causes of death are infection and life-threatening hemorrhagic events [3].

New Approaches to Treatment

Emicizumab, is a bispecific FVIII-mimetic antibody, that was recently used for management of newly diagnosed AHA patients and having contraindication to IST. Short-term use of emicizumab and reduced intensity IST led to hemostatic efficacy with BPA discontinuation after 1.5 (1-4) days of emicizumab initiation. A caution for FVIII:C monitoring while using emicizumab therapy. Emicizumab can falsely elevate one-stage FVIII:C assay. Chromogenic FVIII:C based on bovine reagents is the optimal assay in this condition [2].

Emerging Therapy

Several promising clinical trials therapies are advancing. Gene therapies like giroctocogene fitelparvovec (Pfizer) and BBM-H901 (Belief Biomed) are in development, aiming at providing long-term correction of coagulation defects [5].

Conclusion

There is a diverse range of therapeutic approaches for AHA from gene therapies and monoclonal antibodies to novel bypassing agents and immunomodulators. This diversity reflects the complex pathophysiology of the disease and the multiple potential intervention points. The potential introduction of gene therapies in the coming years could offer the possibility of long-term control of the condition with a single treatment.

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DOI: [10.19080/CTOIJ.2025.29.556265](https://doi.org/10.19080/CTOIJ.2025.29.556265)

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