

## HAEMOSTASIS AND THROMBOSIS

# Acquired hemophilia A

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### Abstract

Acquired hemophilia A is a rare but severe autoimmune bleeding disorder, resulting from the presence of autoantibodies directed against clotting factor VIII. The etiology of the disorder remains obscure, although approximately half of all cases are associated with other underlying conditions. A prompt diagnosis and appropriate management enable effective control of this acquired hemorrhagic disorder: the aims of therapy are to terminate the acute bleeding episode and eliminate or reduce the inhibitor. The recent availability of bypassing agents, first activated prothrombin complex concentrates and then recombinant activated factor VII, has significantly reduced mortality during the acute phase of the disease in patients with high titer inhibitors. On another front, immunosuppressive therapy (corticosteroids and cytotoxic agents, alone or in various combinations) has resulted in long-term inhibitor suppression in up to 70% of the cases. Moreover, new therapeutic strategies (anti-CD20 monoclonal antibody and immune tolerance protocols) are very promising and may further improve the prognosis of acquired hemophilia A.

**Keywords:** *Acquired, hemophilia, factor VIII, bleeding, treatment*

### Introduction

Acquired hemophilia A is an uncommon but potentially life-threatening hemorrhagic disorder caused by the development of autoantibodies (mostly IgG) directed against the coagulation factor VIII (FVIII) [1–7]. The incidence of acquired hemophilia A has been estimated to be 0.2–1.0 case per 1 million persons per year, but this figure may be an underestimate given the difficulty in making the diagnosis. The clinical picture is dominated by severe hemorrhage in the majority of patients, with an inhibitor-related mortality rate of up to 22% [8–13]; most of these deaths occur within the first few weeks after presentation. However, the reduction in mortality rate observed in the most recent studies may reflect therapeutic improvements in the management of acute bleeding during the last few years (first porcine factor VIII and prothrombin complex concentrates [PCC] and then recombinant

activated factor VII [rFVIIa]) [14,15]. Nevertheless, the morbidity and mortality rates may be underestimated due to the high median age at the time of diagnosis (60–70 years old).

The age distribution of autoantibodies is typically biphasic with a small peak between 20 and 30 years (postpartum inhibitors) and a major peak in patients aged 68–80 years [1,3]. Factor VIII inhibitors are distributed equally by sex, although females predominate in the younger age group because of the association with pregnancy while males constitute the majority of patients over the age of 60 [16]. However, it is difficult to draw any firm conclusions as regards epidemiology, clinical aspects and therapy of this disease from literature data, since most of the reports are anecdotal and describe only a few cases.

In this review, we briefly report present knowledge about acquired hemophilia A, analyzing its epidemiology, pathogenesis, diagnostic and clinical features. We

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also describe the main characteristics of the disorder according to its association with different conditions and the most important advances in the treatment of bleeding episodes and eradication of the autoantibody.

### Source of materials

This review presents information from studies so far published in the medical literature on acquired hemophilia A. MedLine reports were searched via PubMed using the following terms without time limits: “acquired hemophilia A”, “acquired hemophilia and factor VIII”, “acquired hemophilia and coagulation factors”, “acquired inhibitors”, “acquired factor VIII inhibitors”, “acquired inhibitors and coagulation factors”, “autoantibodies and coagulation factors”, “anti-factor VIII antibodies”, “factor VIII autoantibodies”, “autoimmune factor VIII inhibitors”, “hemophilia and inhibitors”, “hemophilia and autoantibodies”, “spontaneous inhibitors and factor VIII”. All these terms were searched for alone and in combination with “idiopathic”, “elderly”, “postpartum”, “pregnancy”, “autoimmune diseases”, “collagen disorders”, “rheumatologic diseases”, “systemic lupus erythematosus”, “rheumatoid arthritis”, “thyroid”, “malignant disease”, “cancer”, “carcinoma”, “neoplasm”, “solid tumor”, “hematologic diseases”, “lymphoproliferative disorders”, “lymphoma”, “myeloma”, “drugs”, “allergy”, “vaccine”, “dermatologic diseases”, “neurologic diseases”, “infection”, “hepatitis”, “surgery”, “therapy”, “treatment”, “desmopressin”, “porcine factor VIII”, “prothrombin complex concentrates”, “plasmapheresis”, “extracorporeal immunoadsorption”, “recombinant activated factor VII”, “corticosteroids”, “immunosuppression”, “cyclophosphamide”, “immunoglobulins”, “azathioprine”, “cyclosporin”, “rituximab”, and “immune tolerance induction”.

### Conditions associated with acquired hemophilia A

Table I lists several conditions and diseases associated with the development of factor VIII inhibitors. In approximately 50% of cases FVIII autoantibodies occur in patients, usually elderly, lacking relevant concomitant diseases [4], whereas in nearly 10% of cases the autoantibody against FVIII appears during the postpartum period, usually in primiparas within 3 months of delivery [17–24]. Autoimmune diseases associated with the development of factor VIII inhibitors include systemic lupus erythematosus [25,26], rheumatoid arthritis [27,28], Sjögren’s syndrome [29,30], autoimmune hemolytic anemia [31], myasthenia gravis [8], Graves’ disease [32] and autoimmune hypothyroidism [31]. However, many other conditions associated with acquired hemophilia A are characterized by immune dysregulation such as inflammatory bowel diseases (ulcerative colitis) [8], dermatologic disorders (psoriasis, pemphigus) [8], respiratory diseases (asthma, chronic obstructive pulmonary disease) [8], diabetes [8], acute hepatitis C infection [33], and allergic reactions to medications (penicillin and its derivatives, sulfa antibiotics, phenytoin, chloramphenicol, and methyl dopa) [1,3,34]. Acquired hemophilia A is also seen after treatment with drugs interfering with the immune system, such as interferon-alpha and fludarabine [35–38]. Nearly 10% of patients with acquired hemophilia A have an underlying malignancy, either solid or hematologic [39–48]. The solid tumors most frequently involved are prostate and lung cancer, though a wide variety of cancers have been described (colon, pancreas, stomach, bile duct, head and neck, cervix, breast, melanoma and kidney) [39–46]. The relationship between factor VIII inhibitor and altered immune status is further confirmed by the fact that lymphoproliferative disorders (chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, multiple myeloma and Waldenström’s macroglobulinemia) are the most frequent hematologic malignancies

Table I. Conditions associated with acquired hemophilia A.

Idiopathic	
Pregnancy	
Autoimmune disorders	Systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, autoimmune hemolytic anemia, myasthenia gravis, Graves’ disease, autoimmune hypothyroidism
Inflammatory bowel disease	Ulcerative colitis
Dermatologic disorders	Psoriasis, pemphigus
Respiratory diseases	Asthma, chronic obstructive pulmonary disease
Allergic drug reactions	Penicillin and its derivatives, sulfamides, phenytoin, chloramphenicol, methyl dopa, interferon-alpha, fludarabine
Solid cancers	Prostate, lung, colon, pancreas, stomach, bile duct, head, neck, cervix, breast, melanoma, kidney
Hematologic cancers	Chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, multiple myeloma, Waldenström’s macroglobulinemia, myelodysplastic syndrome, myelofibrosis, erythroleukemia
Diabetes	
Acute hepatitis C infection	

associated with the development of inhibitors [47,48]. Other hematologic diseases include myelodysplastic syndrome, myelofibrosis and erythroleukemia [47].

### Diagnosis of acquired hemophilia A

The diagnosis of acquired hemophilia A is often difficult, since the patient does not have a personal or family history of bleeding episodes. Thus, the patient may be seen by several specialists and subjected to dangerous invasive investigations and interventions before the correct diagnosis is made. To complicate the diagnosis further, the clinical picture of acquired hemophilia A differs from that of "classical" hereditary hemophilia A. In fact, more than 80% of patients with FVIII autoantibodies hemorrhage into the skin, muscles or soft tissues and mucous membranes (e.g. epistaxis, gastrointestinal and urological bleeds and retroperitoneal hematomas), whereas joint bleeds, typical of congenital factor VIII deficiency, are unusual. Not rarely the hemorrhages in acquired hemophilia A are serious or life-threatening, such as in the case of rapidly progressive retroperitoneal hematomas, compartment syndrome due to intramuscular bleeds or cerebral hemorrhage [1]. Other manifestations include prolonged postpartum bleeding and excessive bleeding following trauma or surgery. However, some patients with low titer inhibitors remain clinically asymptomatic and are diagnosed during routine blood examinations (e.g. prior to surgery).

The diagnosis of acquired hemophilia A is based on the demonstration of an isolated prolongation of the activated partial thromboplastin time (APTT), not corrected by incubating the patient's plasma with equal volumes of normal plasma (mixing study), associated with a normal prothrombin time (PT), reduced factor VIII levels and formal evidence of a factor VIII inhibitor in a patient with no previous personal or family history of bleeding [1]. The APTT of the mixture of the patient's plasma with normal plasma must be measured before and after incubation at 37°C for 2 h, because inactivation of FVIII is related to both time and temperature. Furthermore, the presence of heparin and lupus anticoagulant must be excluded. The presence of heparin is suggested by a prolonged thrombin time in association with a normal reptilase time. APTT values of the mixing test (patient's plasma/normal plasma) that are similar at time 0 and after incubation are indicative of lupus anticoagulant (the diagnosis is then confirmed by specific tests: dilute Russell's viper venom time, kaolin clotting time) [49,50]. The diagnosis of an inhibitor is confirmed by specific assays of the factor and the inhibitor using the Nijmegen modification of the Bethesda assay [51]. Since porcine FVIII concentrate is not currently available, the search for inhibitors of porcine FVIII is not recommended.

The IgG autoantibodies directed against clotting factor VIII that develop in patients with acquired hemophilia A are predominantly of IgG<sub>1</sub> and IgG<sub>4</sub> subclasses [1]. The FVIII autoantibody epitope specificity is shown for the A2 and C2 domains of the FVIII protein [52]. Inhibitor antibodies may exert the effect by interfering with thrombin cleavage of FVIII or with the interaction of FVIII with activated factor IX, factor X or phospholipid and von Willibrand factor (VWF). The inactivation of FVIII resulting from this interaction is, however, very different between autoantibodies and alloantibodies. In fact, whereas alloantibodies inactivate FVIII activity completely (type I kinetics), autoantibodies usually have more complex, exponential kinetics (type II kinetics) undergoing an initial rapid inactivation, followed by a slower inactivation or a period of equilibrium in which some residual FVIII can still be assayed in the patient's plasma [53]. Thus, the Bethesda assay, which quantifies the *in vitro* inhibitor titer, may underestimate the *in vivo* inhibitor potency due to the complex, non-linear reaction kinetics and complicate therapeutic choices and monitoring.

### Treatment of acquired hemophilia A

The basic therapeutic strategy in patients with acquired hemophilia A is to treat any bleeding episodes and eradicate the autoantibody [54–58]. The treatment of bleeding episodes depends on the level of inhibitor. Patients with a low titer of inhibitor (<5 Bethesda Units [BU]/ml) can be treated with concentrates of human FVIII, administered at large enough doses to overwhelm the inhibitor so that hemostatic levels of FVIII can be achieved [57]. Desmopressin, alone for the treatment of minor bleeding episodes or in association with FVIII concentrates, may also be effective in patients with a low titer of inhibitor [59,60]. However, when the inhibitor titer is high (>5 BU/ml) the above mentioned drugs are ineffective. In the past heterologous porcine factor VIII, which has a reduced cross-reactivity with anti-human factor VIII antibodies [61–63], was successfully used in such patients. However, more recently, porcine factor has been substituted by bypassing agents, which circumvent the site of activity of inhibitors. Prothrombin complex concentrates derived from plasma and containing activated vitamin K-dependent coagulation factors are able to promote hemostasis in the absence of factor VIII [64–66]. A major step towards the control of bleeding in acquired hemophilia has been recently achieved with the introduction of a new hemostatic agent, recombinant activated factor VII (rFVIIa), which has been shown to be clinically safe and effective as both first and second line treatment for acute bleeding [67–75]. In a multicenter retrospective study, Hay and colleagues [71] described the results of rFVIIa

treatment of hemorrhages in 38 patients with acquired hemophilia. A good response was noted in all 14 bleeds for which rFVIIa was used as first-line therapy. In the 60 bleeding episodes in which rFVIIa was administered as salvage therapy, the response was good in 75%, partial in 17% and poor in 8% of cases. The conclusion of the analysis was that rFVIIa is a safe, useful and effective treatment for bleeding in patients with acquired hemophilia. Recently, Baudo and colleagues [75] reported the data collected in the Italian Registry of Acquired Hemophilia: bleeding was controlled in 90% of the 20 cases in which rFVIIa was used (in 19 cases as first-line therapy and in 1 case as salvage treatment), thus suggesting the drug's efficacy in this condition.

Treatment to eradicate the inhibitor is based on immunosuppression which is aimed at neutralizing the autoantibodies and inhibiting or eliminating the cell clone responsible for their synthesis. The drugs employed are prednisone, cyclophosphamide, azathioprine, 6-mercaptopurine, cyclosporin, vincristine and high-dose immunoglobulins, given alone or in various combinations [76–84]. Prospective, controlled clinical trials evaluating the efficacy of the different therapeutic strategies have not been performed, in part because of the spontaneous remissions that can occur (particularly in cases associated with pregnancy or drugs). Extracorporeal removal of the autoantibody by therapeutic plasmapheresis, or immunoabsorption of immunoglobulins to staphylococcal protein A has been employed in particular clinical situations such as prior to factor concentrate treatment in patients with a high titer of inhibitor and severe hemorrhage or before surgery [85–88]. Features that are prognostic of a better response to treatment are a low level of inhibitor and a short interval between the appearance of the inhibitor and the start of immunosuppressive therapy [81]. However, not all patients require immunosuppression in order to eradicate the autoantibody, since the inhibitor is cleared naturally in up to one third of patients. Thus, the appropriate treatment of patients with acquired inhibitors to factor VIII essentially depends on the natural history of any concomitant condition and the clinical presentation of the coagulopathy. Some patients, for instance those with postpartum or drug-induced inhibitors, may require nothing other than close observation (“watch and wait”), since these inhibitors tend to disappear spontaneously within a few months after delivery or drug discontinuation [1,3]. Idiopathic autoantibodies, especially those at a low titer, may also resolve spontaneously. Vice versa, the cases associated with an underlying autoimmune disease or a malignancy rarely resolve spontaneously and often require a combination of immunosuppressive therapy. However, given the risk of hemorrhage associated with the presence of inhibitors,

eradication therapy must be attempted when there are hemorrhagic symptoms or when the inhibitor remains present even if the bleeding symptoms are mild. Various prospective studies have shown that steroid therapy is the treatment of first choice [54,80]. In fact, a positive response is obtained within 3 weeks in one-third of the cases and the percentage of responses can increase to over 70% as the treatment is continued. The inhibitor may recur after withdrawal of prednisone. The dose used is 1–2 mg/kg/die for at least 3 weeks; thereafter the dose is adjusted according to the therapeutic response. Cyclophosphamide, in most cases associated with prednisone, has been evaluated in various studies and has been shown to produce a high rate of complete and sustained remissions (above 50–70%, on average), even in patients initially refractory to [76,79,80]. It could be a first-line treatment, in combination with corticosteroids, in selected cases, or a second-line treatment for those patients in whom initial treatment with corticosteroids fails to produce a response. The dose of cyclophosphamide used is 2 mg/kg/die per os, for 3–6 weeks or until complete remission, adjusting the dose according to hematologic tolerance. High dose immunoglobulins (HDIg), at a dose of 1 g/kg/day for 2 days or 0.4 g/kg/day for 5 days, have been shown to be effective in reducing inhibitor titer or eliminating the autoantibody in about 30% of cases [81,89,90] and could be considered in those patients who do not respond to standard immunosuppressive regimens. There are reports of promising results from the use of cyclosporin, 2-chloro-deoxyadenosine and interferon alpha [82,83,91–95], but the data are still insufficient. However, there is a growing body of evidence on the efficacy and good tolerability of anti-CD20 monoclonal antibody (rituximab), particularly in patients with low inhibitor titers [96–98]. That said, there are many aspects of this treatment that remain to be clarified, such as the optimal dose, its mechanism of action, and its long-term side effects. Finally, immune tolerance induction (ITI) protocols have been proposed for the eradication of autoantibodies against coagulation factors [99–101]. Their efficacy and safety were demonstrated by the Budapest protocol [99] (human FVIII 30 U/kg/die in the first week, 20 U/kg/die in the second week and 15 U/kg/die in the third week combined with i.v. cyclophosphamide 200 mg/die [total dose 2–3 g] and i.v. methylprednisolone [100 mg/die in the first week and then gradually tapered down over the subsequent 2 weeks]). It was reported that more than 90% of the patients achieved a sustained complete remission. Similar results were reported by Heidelberg's group using the modified Malmö protocol (immunoabsorption, high doses of FVIII, cyclophosphamide and corticosteroids) [102].

## Conclusions

A prompt diagnosis and appropriate management are essential for effective control of acquired hemophilia A. The therapeutic strategy for this clinically severe acquired hemorrhagic disorder is to treat the acute bleed and eliminate the inhibitor. While the new bypassing agent rFVIIa has been shown to be safe and effective in controlling acute bleeds in such patients, immunosuppressive therapy (corticosteroids and cytotoxic agents, alone or in various combinations) has resulted in long-term inhibitor suppression in up to 70% of the cases. Moreover, the preliminary results of the new therapeutic strategies (anti-CD20 monoclonal antibody and immune tolerance protocols) are very encouraging and may further improve the prognosis of patients with acquired hemophilia A.

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