



Prevention and Management of Bleeding Episodes in Patients with Acquired Hemophilia A

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Abstract

Acquired hemophilia A (AHA) is a rare autoimmune disease caused by autoantibodies inhibiting the function of coagulation factor VIII. It is characterized by spontaneous bleeding in patients with no previous family or personal history of bleeding. Although several large registries have collected clinical data on AHA, limited information is available on the optimal management of AHA because controlled clinical trials are lacking. AHA can easily be diagnosed if the problem (prolonged activated partial thromboplastin time in a bleeding patient) is recognized. After the effects of anticoagulants are excluded, low factor VIII activity and the detection of circulating inhibitors confirms the diagnosis. However, lack of familiarity with this rare condition may delay diagnosis and adequate therapy. Treatment of AHA is based on measures for prompt hemostatic control to stop (and prevent) bleeding, immunosuppression to eradicate the autoantibodies, and supportive care for the adverse effects of that treatment and patients' often complex comorbidities. This article gives a comprehensive overview of the current knowledge about the pathophysiology, diagnosis, and treatment of AHA.

Key Points

Acquired hemophilia A is a rare autoimmune disease that causes severe bleeding.

Hemostatic therapy is complex and expensive, and should be guided by experienced specialists.

The ultimate therapeutic goal is the long-term eradication of the autoantibodies.

1 Introduction

Acquired hemophilia A (AHA) is a rare autoimmune disorder characterized by the development of inhibiting autoantibodies to coagulation factor VIII [1, 2]. The disease is characterized by either spontaneous or induced hemorrhage in patients with no previous family or personal history of bleeding [3, 4]. With the exception of younger women with

postpartum inhibitors, affected patients are often older and therefore have several other comorbidities that must be considered when caring for such a patient [5]. Although the condition is rare, registry data and large case series on hundreds of patients have been published, all showing a rather consistent pattern of demographical and clinical parameters (Table 1). However, treatment strategies have changed considerably over time, mainly because of the development of a variety of new hemostatic compounds but also because of improved immunosuppressive strategies [6, 7]. Finally, prognostic parameters predicting response to therapy have been developed, allowing individualized therapy [8, 9]. However, to date, no controlled trials have assessed the efficacy of therapeutic strategies. This article gives a comprehensive overview of the current knowledge about the pathophysiology, diagnosis, and treatment of AHA.

2 Pathophysiology of Acquired Hemophilia A (AHA)

AHA is caused by an autoimmune process during which autoantibodies directed against functional epitopes of coagulation factor VIII are formed. The immune response is oligo- or polyclonal rather than monoclonal, and the autoantibodies can be of various classes and subclasses of immunoglobulins

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Table 1 Publications on large acquired hemophilia A collectives [5, 7]

	Green and Lechner [15]	Delgado et al. [16]	Collins et al. [14]	Knoeb1 et al. (EACH2) [5]	Borg et al. (SACHA) [29]	Kessler et al. (HTRS) [20]	Tiede et al. (GTH) [9]
Collection period	Before 1981	1985–2002	2001–2003	2003–2009	2001–2006	2000–2011	2010–2013
Study design	Retrospective survey	Meta-analysis	Prospective surveillance, predefined population	Multicentre registry	Prospective follow-up	Retrospective	Prospective, predefined immunosuppression
Region	World	World	UK	Europe	France	USA	Germany, Austria
Patients (<i>N</i>)	215	234	172	501	82	166	124
Age, years	57 (<10–90)	64 (8–93)	78 (2–98)	74 (13–102)	77 (25–103)	70 (13–92)	74 (26–97)
% Male	53	45	45	53	61	48	58
Factor VIII activity (%)	NR	2 (0–30)	3 (<1–25)	2 (<1–40)	2 (0–30)	NR	1.4 (<1–31)
Inhibitor titer (BU/mL)	NR	10 (0.9–32,000)	7 (40.8–717)	12.8 (0.1–28,000)	16 (1–2800)	50 (1–2969)	19 (1–1449)
Underlying disorders (%)							
None (idiopathic)	46.1	57.7	63.3	51.9	55	44.1	44.1
Malignancy (any type)	6.7	18.4	14.7	11.8	19.5	14.5	14.5
Autoimmune disorder	18.0	9.4	16.7	11.6	15	18.6	28.3
Postpartum	7.3	14.5	2.0	8.4	7.3	3.4	3.4
Infections	NR	NR	NR	3.8	NR	NR	NR
Dermatological conditions	4.5	NR	3.3	1.4	NR	NR	NR
Drug induced	5.6	NR	NR	3.4	NR	NR	NR
Other	11.8	NR	NR	11.6	NR	38.6	4.8

Data are presented as *n* (%) or median (range) unless otherwise indicated
NR not reported

and may have very different binding characteristics [8, 10, 11]. Whereas almost all patients (95%) have immunoglobulin G4 (IgG4) autoantibodies to factor VIII, up to 46% have also autoantibodies to other subclasses (Table 2). Moreover, the characteristics of the autoantibodies can change

and evolve during the autoimmune response and during immunosuppressive therapy [10]. The subclass pattern of the autoantibodies has a prognostic value: Patients with IgA anti-factor VIII antibodies have a lower probability of remission and higher mortality rates [8, 11]. The autoantibodies

Table 2 Autoantibody subclass pattern in patients with acquired hemophilia A [8]

Isotype or subclass	Positive screening	Titer in positive patients	Apparent affinity, <i>n</i> ; K_A [M^{-1}]
IgG1	71 (88)	1:640 (1:320–1:2560)	70; 1.4×10^{10} (0.8×10^{10} – 4.2×10^{10})
IgG2	62 (77)	1:80 (1:40–1:320)	40; 1.9×10^9 (1.0×10^9 – 3.2×10^9)
IgG3	33 (41)	1:80 (1:40–1:320)	19; 1.3×10^{10} (0.5×10^{10} – 1.8×10^{10})
IgG4	79 (98)	1:5120 (1:1280–1:20,480)	77; 5.8×10^{10} (2.4×10^{10} – 1.3×10^{11})
IgA	37 (46)	1:80 (1:40–1:160)	18; 1.7×10^9 (0.9×10^9 – 4.6×10^9)
IgM	7 (9)	1:80 (1:40–1:80)	ND

Data are presented as *n* (%) or median (interquartile range) unless otherwise indicated
Ig immunoglobulin, ND not determined

partially or completely neutralize the activation or function, or accelerate the clearance, of factor VIII.

This immune response is very different from congenital hemophilia A, wherein affected patients may also develop inhibitory antibodies against FVIII following exposure to exogenous FVIII during substitution therapy, but these alloantibodies have different laboratory and clinical properties. In congenital hemophilia A, alloantibodies typically inactivate FVIII completely with a linear (type 1) kinetics, dependent on both concentration and time. In contrast, in AHA, autoantibodies show a type 2 kinetics with a rapid initial inactivation phase followed by a slower equilibrium phase, dependent on temperature and time, and some residual FVIII activity can be detected *in vitro*, even with high-titer inhibitors. The Bethesda assay may therefore underestimate the *in vivo* inhibitor potency in AHA because of the complex nonlinear autoantibody kinetics [12, 13]. Consequently, FVIII activity or inhibitor titer cannot be used to predict the severity of bleeding events and identify patients with AHA who are at high risk of fatal bleeding episodes, but factor VIII levels are useful to predict the course of the disease, *i.e.*, rate of remission, time to remission, and overall survival [9, 11].

3 Demographics of AHA

AHA is a rare condition with an estimated incidence of approximately 1.5 per million population per year [14]. A series of reports (registry data and large case series) have been published since 1980 (Table 1) and provide deep insight into the demographic and clinical characteristics of patients with AHA. In 1981, Green and Lechner [15] published a retrospective survey on 215 patients with AHA referred to specialist centers. In 2003, Delgado *et al.* [16] performed a meta-analysis of all reports on AHA published between 1985 and 2002, comprising 249 patients from 21 case series. Later, the UK Haemophilia Centre Doctors Organisation (UKHCDO) performed a prospective surveillance study, collecting data on all 172 patients with AHA who presented in the UK between 2001 and 2003 [14]. This created a consecutive cohort of patients unaffected by referral and reporting bias, which enabled reliable calculations of incidence, characteristics, and outcomes of patients with AHA. In 2010, results from the EACH2 registry, which collected data on 501 patients with AHA from 13 European countries between 2003 and 2008, making it the largest prospective collection of patients with AHA to date, have provided deeper insight into the demographics and underlying disorders associated with AHA [5, 17–19]. The HTRS registry, conducted in the USA, comprised a more ethnically diverse population, as 24% of patients were Black [20]. This incidence appears overrepresented compared

with the percentage of Black people within the US population (13.6%) and suggests that Black individuals could be preferentially affected by AHA, as they are for allo-FVIII antibodies [20]. The GTH-AH 10/2010 study comprised 102 patients treated with a standardized escalating immunosuppressive protocol to identify factors predicting the course of the disease [9].

All these publications demonstrate a rather consistent demographical pattern: The median age of patients with AHA is about 70 years, with a small population of women of childbearing age who develop factor VIII inhibitors in association with pregnancy (postpartum inhibitors). Male patients have a slightly higher incidence than females. In half of the patients, no underlying or predisposing disease could be identified (“idiopathic AHA”). Malignancy, pregnancy, infections, certain medications, and other autoimmune diseases have been associated with AHA. At presentation, the factor VIII activity levels of patients may be severely suppressed (<1% of normal) but can also be in a higher and apparently safe range. Nevertheless, the characteristics of the antibodies mean that even those patients may develop severe bleeding. The typical median titer of the inhibitors is 20 BU/mL, with a broad range between barely detectable inhibitors and very high titers. However, the titers in these publications have been measured with quite different methods and are therefore not completely comparable.

4 Clinical Features of AHA

AHA can cause severe bleeding complications, with life-threatening bleeding episodes reported in 97% of patients [5, 17]. Patients with AHA can seemingly experience more severe bleeding episodes than those with congenital hemophilia with comparable FVIII levels.

The bleeding pattern seen in AHA is different from that observed in congenital hemophilia A (Table 3). Typically, bleeding episodes occur spontaneously and present with skin or soft-tissue bleeding in individuals with no personal or family history of bleeding. Extensive skin hematomas, severe muscle bleeding, retroperitoneal bleeding, epistaxis, hematuria, gastrointestinal bleeding, and even intracerebral bleeds are more frequent than joint bleeding. In comparison, hemarthroses account for approximately 70–80% of bleeding episodes in patients with congenital hemophilia A. Recent data from the EACH2 registry have provided detailed information on the bleeding phenotype of AHA [5] (Table 3). In the majority of patients (90%), a bleeding event triggered clotting testing and led to the diagnosis of AHA. Most of these bleedings (77.4%) were spontaneous, and less than 10% were associated with trauma, surgery, or pregnancy complications. Two-thirds of the patients had

Table 3 Bleeding phenotype of patients with acquired hemophilia A

Phenotype	Median (IQR) or (%)
Severity	
Severe	70.3
Non-severe	28.9
Not reported	0.8
Location ^a	
Skin	53.2
Deep muscle, retroperitoneal	50.2
Mucosa	31.3
Joints	4.9
Brain	1.1
No bleeding	6.6
Cause ^b	
Spontaneous	77.4
Traumatic	8.4
Surgery	8.2
Peripartal	3.6
Other	2.7
Time from bleeding to AHA diagnosis	
Median (days)	3 (0–12)
Up to 1 day	37.2
Up to 1 week	26.1
Up to 1 month	22.4
More than 1 month	11.1

Data are from the EACH2 registry, the largest collection of patients with AHA [5]

AHA acquired hemophilia A, IQR interquartile range

^aSome patients had more than one bleeding site

^bSome patients had more than one reason for bleeding

only one bleeding event, but one-third had one or more (up to six) relapses [5, 17].

Although the bleeding phenotype remains unchanged, the risk of dying from bleeding has reduced considerably with the development of effective hemostatic therapy. Green and Lechner [15] reported mortality from bleeding of 20% before 1981 [15], whereas only 2.9% of patients in the GTH trial from 2010 bled to death [7, 9].

5 Diagnosis of AHA

AHA should be suspected when new, unexpected bleeding occurs in a patient with no previous personal and family history of bleeding, especially in elderly or postpartum patients. Global coagulation tests usually show an isolated prolongation of the activated partial thromboplastin time (APTT) (normal prothrombin time, fibrinogen level, platelet counts). Such a constellation should prompt advanced

clotting tests to confirm the diagnosis. However, lack of familiarity with the disease can result in a considerably delayed diagnosis, which may affect treatment selection, initiation, and outcomes. The EACH2 registry showed that 37% of patients were definitely diagnosed with AHA within 1 day and 26% within 1 week of initial bleeding [5]. However, a considerable diagnostic delay was obvious in one-third of the patients (up to 1 month in 22%, more than 1 month in 11.1% of cases) [5]. Although diagnostic delay significantly prolonged the time to start of hemostatic therapy, no difference in response to therapy, intensity of therapy, or outcome was demonstrated. However, patients still remain at unnecessary risk of severe bleeding episodes until the inhibitor has been eradicated.

Extended coagulation testing should follow an algorithm [7] to rule out other causes of APTT prolongation or bleeding (Fig. 1). As most patients are older at diagnosis and probably being treated with anticoagulants for atrial fibrillation or arterial or venous thromboembolism, the effects of anticoagulants should be appropriately ruled out as a first step: a prolonged thrombin clotting time is always a sign for effects of heparin or direct thrombin inhibitor drugs, and a positive anti-Xa test is a sign for low-molecular-weight heparins, heparinoids, fondaparinux, or direct factor Xa inhibitor drugs. The effects of vitamin K antagonists would also lead to an abnormal prothrombin time. After ruling out anticoagulant effects, the next step would immediately be extended coagulation testing when available (single clotting factor activities of factors XII, XI, IX, and VIII; APTT with different reagents; plasma mixing studies to demonstrate circulating inhibitors). If no extended clotting testing is available, plasma mixing studies testing for APTT immediately after mixing and after 2 h of incubation at 37 °C are helpful to demonstrate that inhibitors are present in the patient's plasma, which should lead to extended clotting testing anyway.

AHA is diagnosed by reduced activity of factor VIII (below 50%). Acquired von Willebrand syndrome is also associated with bleeding and low factor VIII levels so must be ruled out. Very low (<1%) levels of factor VIII are associated with a lower rate of and a longer time to remission and with poorer overall survival [8, 9, 11]. Risk of bleeding is not associated with factor VIII level; even patients with somewhat higher levels may develop severe bleeding.

Quantification of the inhibitor titer is complicated in AHA because of the above-mentioned kinetics and the residual factor VIII activity. The classical Bethesda assay has many limitations [12, 13] that are partly solved by the Nijmegen modification [21] or other measures (heat treatment) [13, 22]. This leads to considerable inter-laboratory variations in inhibitor results [13]. Immunological methods (enzyme-linked immunosorbent assay [ELISA] assay testing for factor VIII binding antibodies) are limited in that even

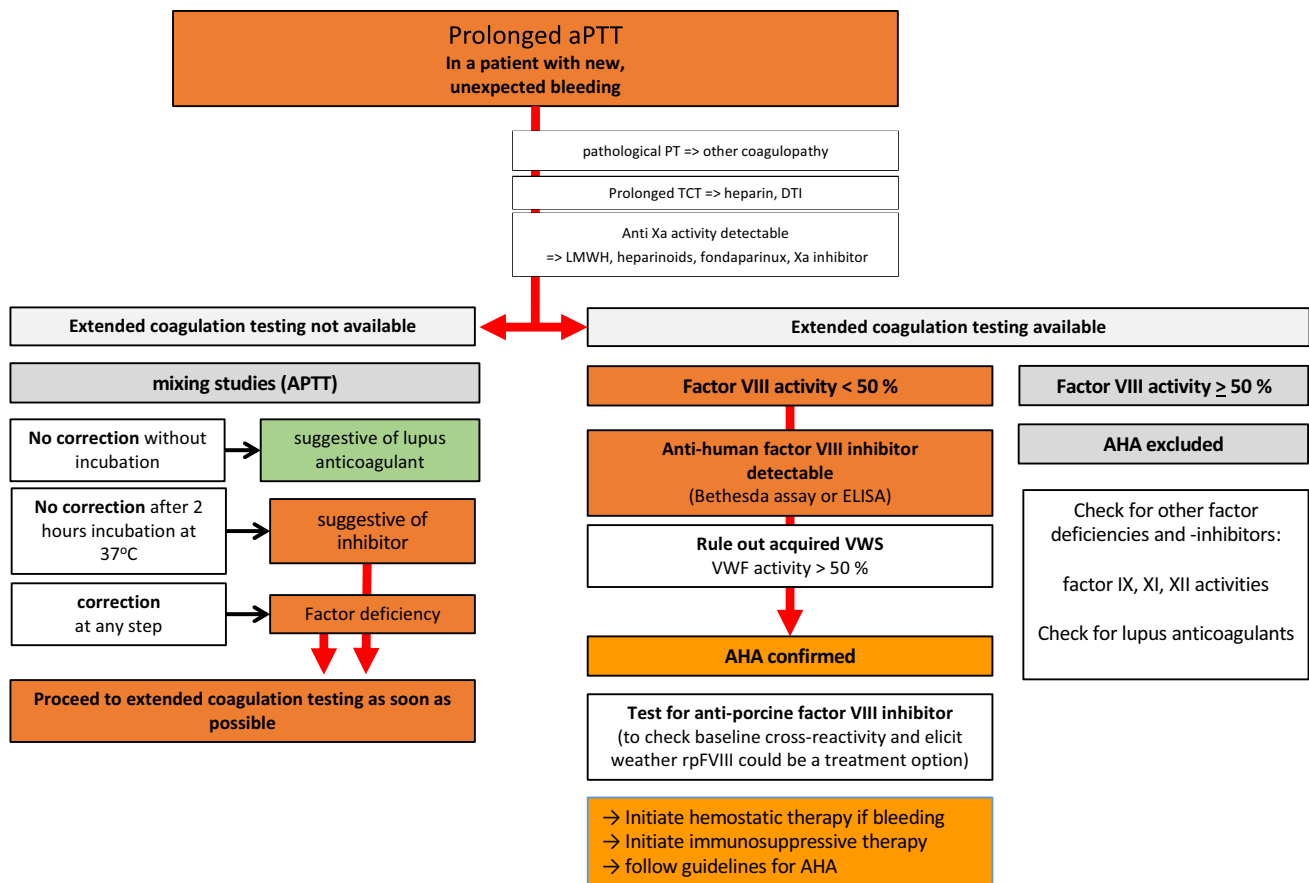


Fig. 1 Diagnostic algorithm for acquired hemophilia A. Modified from Kruse-Jarres et al. [7]. *AHA* acquired hemophilia A, *APTT* activated partial thromboplastin time, *DTI* direct thrombin inhibitor,

ELISA anti human FVIII antibody enzyme-linked immunosorbent assay, *LMWH* low molecular weight heparin, *PT* prothrombin time, *TCT* thrombin clotting time, *VWF* von Willebrand factor

non-inhibiting antibodies are detected. Depending on the applied method and the quality of the laboratory, the inhibitor titer may be a predictor for the rate and time to remission and may therefore be used to individualize the therapy of patients with AHA [9, 11].

6 Clinical Management

Clinical management of patients with AHA is based on four principles:

- hemostatic therapy of the acute bleeding event and prevention of further bleeding
- fast reduction of the inhibitor titer (if possible) to enable better hemostatic therapy
- termination of the underlying autoimmune process
- individualized supportive therapy.

These principles have been followed for many years, but recent developments in the understanding of the

pathophysiology, prognostic factors, hemostatic and immunosuppressive therapy, and extracorporeal methods have changed the philosophy of AHA management from acute, aggressive, and dangerous therapy to individualized, risk-adapted, mild methods to care for these vulnerable patients [7, 23, 24].

6.1 Treatment of Acute Bleeding Episodes

Hemostatic therapy in AHA is indicated in patients with acute major bleeding (defined as unstable hemoglobin/hematocrit levels, need for transfusions, deep muscle, retroperitoneal, gastrointestinal or cerebral bleeding). In such situations, hemostatic therapy needs to be easily available and applicable, reliable and highly efficacious, and with a low rate of side effects. In patients with high factor VIII inhibitor titers (> 5 BU/mL), replacement with human factor VIII concentrates, even at very high doses, is ineffective, as the antibodies will immediately block all the factor VIII administered. Porcine factor VIII may be an option,

but cross-reactivity is possible, and the initial efficacy is not predictable. Therefore, to date, bypassing agents and recombinant porcine factor VIII are approved for this indication, are recommended by current guidelines, [6, 7, 17, 24]. Table 4 summarizes the currently approved possibilities for hemostatic treatment of patients with AHA.

Patients with mild or no bleeding may also need hemostatic therapy to prevent bleeding, as they are at high risk for (spontaneous or induced) severe bleeding. Such patients need a different approach: dosing of bypassing agents can be lower, porcine (and even human) factor VIII can be tried, and in vivo recovery and trough levels can be measured. In future, even emicizumab can be a good option for such patients (see Sect. 6.1.3.1).

Nevertheless, any injury to or breach of the body's integrity will immediately lead to severe bleeding. Therefore, any invasive interventions need to be strictly avoided. Even large hematomas or deep muscle bleeding will resolve within a few days when sufficient hemostatic therapy is applied; hematoma evacuation or fasciotomy is not indicated.

6.1.1 Bypassing Agents

Bypassing agents improve hemostasis in patients with hemophilia and inhibitors, as well as in AHA, by bypassing the need for factor VIII to generate sufficient thrombin. Recombinant human activated factor VII (rhFVIIa) and activated prothrombin complex concentrates (APCC) are available and used in the majority of patients with AHA [12, 23, 25]. Both substances are equally effective in this indication, with a

93% rate of success [17]. Thus, bypassing agents remain the treatment of choice for AHA [7, 23, 26].

However, they do have some clinical shortcomings: it is not possible to monitor these drugs with conventional laboratory assays, even not with the modern thrombin-generation assays. Therefore, only clinical response of the bleeding is helpful to guide treatment (increase or reduce dose and/or intervals), which is rather unsatisfactory for such expensive medications. Moreover, there is a higher risk for thromboembolism, especially in elderly and comorbid patients.

6.1.1.1 Recombinant Human Activated Factor VII (Novoseven®) rhFVIIa has been approved for many years for the treatment of patients with congenital and acquired hemophilia with inhibitors, for factor VII deficiency, and for Glanzmann's thrombasthenia [27, 28]. Excess of activated factor VII leads to a burst of thrombin generation without the need for factor VIII. As the half-life of rhFVIIa is short, it is typically dosed at 90 µg/kg body weight every 2 h. Dose and/or intervals may be modified according to clinical response. Trial and registry data show that rhFVIIa is used in the majority of patients with AHA with a high rate of success and a low rate of associated thromboembolic complications [5, 14, 17, 20, 29–32]. Data from EACH2 show that patients were treated with a median of 12 doses in 3-h intervals for their initial bleeding. rhFVIIa is available in most hospitals, as it is frequently used (off-label) in trauma centers or emergency departments as a potent hemostatic medication.

Table 4 Hemostatic therapy for acquired hemophilia A

	Bypassing agents		Factor VIII concentrates	
	Recombinant human activated factor VII	Activated prothrombin complex concentrate	Human factor VIII concentrate (plasma-derived or recombinant)	Recombinant porcine factor VIII concentrate
Brand name	Novoseven®	FEIBA®	Various	Obizur®
Indication in AHA	Independent of inhibitor titer	Independent of inhibitor titer	Low inhibitor titer (< 5 BU/mL) and good post-infusion recovery	Dependent on cross reactivity
Initial dose	90 µg/kg every 2 h	70 U/kg every 8 h max. 200 U/kg/day	70 U/kg every 8 h	50–200 U/kg; interval dependent on recovery
Laboratory monitoring	Not possible	Not possible	Factor VIII activity	Factor VIII activity
Therapeutic target	Clinical response	Clinical response	Clinical response; factor VIII trough level > 50%	Clinical response; factor VIII trough level > 50%
Advantages	High efficacy No maximum dose	High efficacy	Laboratory monitoring possible Antibody saturation lower treatment costs	Laboratory monitoring possible
Disadvantages	Short dosing intervals High treatment costs	Maximum dose Risk of coagulopathy High treatment costs	Low efficacy	Possible cross reactivity; induction of anti-porcine antibodies High treatment costs

AHA acquired hemophilia A

6.1.1.2 Activated Prothrombin Complex Concentrates (APCC; FEIBA®) APCC has been approved for many years for the treatment of patients with congenital and acquired hemophilia with inhibitors [33–35]. As APCC comprises activated clotting factors, mostly activated factor VII, its mechanism of action is similar to that of rhFVIIa [36, 37]. APCC is usually administered at a dose of 70 U/kg every 8 h (with a warning not to exceed 100 U/kg single dose and 200 U/kg daily dose). Doses and/or intervals may be modified according to clinical response. Trial and registry data show that APCC is used frequently in patients with AHA with a high rate of success and a low rate of associated thromboembolic complications [9, 14, 17, 20, 29]. However, there is a low risk of consumption coagulopathy, especially in patients with other risk factors (active cancer, infection, higher age, trauma, surgery, etc.), and APCC should be used with special attention in such patients (monitoring of platelet counts and fibrinogen, D-dimer, and antithrombin levels) [33].

6.1.2 Factor VIII Replacement Therapy

Replacement with factor VIII to increase factor VIII activity levels is possible when the anti-factor VIII inhibitor titer is low, but even low titers considerably reduce post-infusion in vivo recovery peak and trough levels. Therefore, very high doses of factor VIII concentrates are necessary to overcome the inhibitors. This applies for both human and porcine factor VIII concentrates. In contrast, if sufficient post-infusion levels can be obtained, replacement therapy can easily be guided with conventional factor VIII activity assays, and treatment is cheaper than with bypassing agents. In addition, there is some evidence that high doses of factor VIII replacement may saturate the circulating inhibitors and lead to a faster elimination, similar to the immunotolerance-induction protocols for congenital hemophilia [38]. However, classical immunotolerance is not an option for AHA, as endogenous factor VIII is always present.

6.1.2.1 Human Factor VIII Concentrates (Plasma-Derived or Recombinant) Human factor VIII concentrates, either plasma derived or recombinant, have been available for many years for the treatment of hemophilia A. As mentioned, the circulating inhibitors in AHA mean human factor VIII concentrates need to be administered at high doses (starting with 70 U/kg every 8 h), guided by the factor VIII levels obtained [12, 23, 24]. During treatment with human factor VIII concentrates, regular measurements of factor FVIII plasma levels (trough levels and post-infusion levels and in vivo recovery) are necessary to guide dosing. Particularly in patients with active bleeding, factor VIII trough levels of > 50% are necessary. Hemostatic efficacy of human factor VIII concentrates is much lower than with bypassing

agents, as demonstrated in various studies (i.e., the EACH2 data) [17].

Attempts to lower the inhibitor titers with extracorporeal immunoadsorption have been shown to be effective (in terms of a faster switch from bypassing agents to factor VIII replacement and considerably reduced treatment costs), but recent developments (availability of adsorption columns and devices; knowledge of antibody subclasses; changes in immunosuppression by use of rituximab; upcoming availability of non-factor therapy; etc.) means the use of immunoadsorption in AHA has almost ceased in most centers [39–43].

6.1.2.2 Recombinant Porcine Factor VIII Concentrate (Obizur®) Factor VIII concentrates from other species have a slightly different amino acid sequence than that from humans, such as a different antigenic structure. This means the autoantibodies would not (or to a lower extent) bind and inhibit and that this factor VIII could be used as replacement therapy when no cross reactivity of the autoantibodies with porcine factor VIII is detectable. A recombinant porcine sequence factor VIII (rpFVIII) concentrate (Obizur®) was recently approved in the USA, Canada, and Europe for the treatment of bleeding in AHA [44–46] based on a prospective, open-label, phase II/III study in 28 adults with serious bleeding [47]. In that study, treatment was initiated with a single 200 U/kg dose of rpFVIII, and subsequent dosing was adjusted according to clinical response and factor VIII activity. Patients without cross reactivity of the antibodies achieved very high post-infusion factor VIII levels (between 118 and 522%), suggesting that a much lower initial dose may also be sufficient [48, 49]. After 24 h of repetitive infusions, all 28 patients had a good response, suggesting saturation of the remaining antibodies. Bleeding was controlled in 85.7% of patients. To predict the effectiveness of rpFVIII in the treatment of AHA, it is essential to determine the baseline anti-porcine factor VIII inhibitor titer (cross reactivity), but this is possible only with special reagents. Administration of rpFVIII may also lead to an increase in or new development of anti-rpFVIII antibodies, which may also target the (human) factor VIII of the patient [47]. During treatment with rpFVIII, factor FVIII plasma levels must be measured regularly (trough levels and post-infusion levels and in vivo recovery) to guide dosing and detect antibody development.

6.1.3 Non-Factor Therapies

6.1.3.1 Emicizumab (Hemlibra®) Emicizumab is a bispecific, factor VIIIa mimetic antibody. It targets both factor IXa and X, leading to faster activation of factor X, thus acting like factor VIIIa [50]. It is already approved and available for the prevention of bleeding in patients with hemophilia A with inhibitors. However, clinical trials have been

conducted only in patients with congenital hemophilia, where emicizumab impressively reduced the annualized bleeding rate to almost zero [51–53]. These patients, who previously required prophylactic intravenous injections of bypassing agents, can now be better treated with a subcutaneous injection of emicizumab every 1 or 2 weeks. It is also effective in congenital hemophilia without inhibitors, with as little as one subcutaneous injection every 4 weeks [54]. Some patients with AHA have been treated with emicizumab outside clinical studies with interesting responses [55]. The principle of action would allow the use of emicizumab in this indication. The advantages would be the possibility of effective hemostatic prophylaxis with weekly or bi-weekly subcutaneous therapy, possibly in an outpatient setting because of the long half-life. The total treatment costs would also be considerably lower than with bypassing agents. Disadvantages include that therapeutic levels are reached after 3 weeks when administered subcutaneously, and acute bleedings cannot be treated this way. Although an intravenous push infusion is possible, which leads to therapeutic levels within minutes, that form of administration is not approved, and adverse effects cannot yet be estimated. Treatment monitoring is complicated: chromogenic factor VIII assays need to be used, inhibitor assays cannot be performed with conventional reagents [56], and the timepoint of remission cannot be determined exactly; combination with APCC is strictly contraindicated because of the high risk of (lethal) thrombotic microangiopathy [53]. Combination with rhFVIIa is possible but with an increased risk of thromboembolism. Combination with factor VIII concentrates (human or porcine), and even endogenous factor VIII in AHA, will compete with emicizumab from its binding sites (and maybe prolong its half-life) but not lead to thromboembolism.

6.1.3.2 Anti-Tissue-Factor Pathway Inhibitor Therapy Blocking the tissue-factor-pathway inhibitor (TFPI) is a way to enhance hemostasis by inhibiting regulatory pathways. TFPI downregulates the extrinsic pathway of blood coagulation, thus modulating thrombin generation. Several antibodies and aptamers, targeting various domains of TFPI are under development. Concizumab, PF-06741086, BAY 1093884, and ARC19499 are currently under clinical development for patients with congenital hemophilia with and without inhibitors [57], but no study is active for AHA. Nevertheless, these drugs have the potential to be effective in AHA, but the possible prothrombotic risk in the elderly or comorbid patient must be considered.

6.1.3.3 Other Non-Factor Therapy Inhibition of regulatory pathways by blocking antithrombin synthesis with fitusiran, inhibition of protein C with antibodies or constructed ser-

pins, or inhibition of protein S have been shown to enhance hemostatic activity *in vitro*. Fitusiran has been further developed and studied in patients with congenital hemophilia. All these substances may also have the potential to improve hemostasis in AHA in the future, although no clinical studies in such patients are planned as yet [58].

6.2 Inhibitor Eradication

Modern hemostatic therapy is highly effective in stopping and preventing bleeding but has no effect on the underlying autoimmune process. Patients remain at risk of bleeding until the inhibitors have been eradicated. Spontaneous remissions have been reported, and patients with low titer inhibitors and higher factor VIII levels in particular may be candidates for a “watch and wait” strategy when not bleeding, but current treatment guidelines generally recommend immunosuppressive therapy to eradicate the inhibitors [7, 19, 23]. However, immunosuppression may be associated with severe side effects, which limits the benefits for patients. Leukopenia, severe infections and sepsis, thrombocytopenia, steroid-induced diabetes, and psychosis have been reported in up to 37% of patients, with a mortality rate of up to 16% [9, 18, 20, 29]. Thus, immunosuppressive regimens should be carefully adjusted according to patient age, general condition, and comorbidities, with the benefits of inhibitor eradication balanced against the risk of side effects. In addition, treatment and, ideally, elimination of an underlying condition is mandatory to stop the production of antibodies.

A variety of drugs and treatment protocols for immunosuppression have been published, but no controlled trial has investigated these strategies. Most commonly, corticosteroids (either daily prednisone with 1–2 mg/kg or pulsed high-dose dexamethasone) alone or in combination with cyclophosphamide (bolus intravenous infusion or daily oral medication) have been used for many years [59]. Other immunosuppressive regimens include azathioprine, bortezomib, and mycophenolate mofetil, among others [6, 18, 60, 61]. Recently, rituximab has gained increasing acceptance because of the low rate of adverse events, although it is used off label in this indication [18, 62–64]. Data from the EACH2 registry showed a 58% remission rate with steroids alone, 80% with steroids and cyclophosphamide, and 61% with rituximab-containing combinations [18]. Median time to complete remission (ceased immunosuppression and normal factor VIII levels) was 32, 40, and 64 days, respectively. Adverse events occurred in 25, 41, and 37%, respectively, with a mortality rate from complications due to immunosuppression of 3.8%. The GTH AH-01/2010 trial studied 102 patients with AHA using an escalating immunosuppressive protocol with an initial 3-weeks phase with steroids alone, addition of cyclophosphamide in non-responding patients, and switch to rituximab after 3 further weeks in patients with

refractory disease [9]. In this study, 48% of patients achieved partial remission on steroids alone, 21% with steroids plus cyclophosphamide, and 12% switched to rituximab. The overall rate of partial remission was 83% after a median of 31 days, and the rate of complete remission was 61% after 79 days. However, the rate of immunosuppression-related adverse events was as high as 30% with a 16% mortality. The study identified prognostic factors that predicted rates of partial and complete remission and survival [8, 9, 11] (Fig. 2). These data can be used to individualize immunosuppressive therapy to avoid overtreatment in low-risk patients and undertreatment in high-risk patients. In the UKHCDO study, 40 patients were treated with corticosteroids alone and retrospectively compared with 48 matched patients with additional cyclophosphamide [14]. The median time to remission was not statistically different (49 vs. 39 days). However, a meta-analysis comprising 20 studies with 249 patients demonstrated that cyclophosphamide with or without corticosteroids was more effective in achieving complete remission than corticosteroids alone or no immunosuppressive therapy [16].

Several groups have proposed an alternative approach to eradicating the inhibitors with very high doses of human factor VIII concentrates combined with immunoadsorption, steroids, and intravenous immunoglobulin infusions (Bonn-Malmö and Budapest protocols for immunotolerance induction) [38, 65]. The authors reported high success rates at the cost of in part enormous consumption of factor VIII concentrate (and other resource).

All the published data clearly demonstrate that difficulties for patients with AHA no longer related to bleeding

and hemostatic therapy but instead to immunosuppression. To prefer rituximab over cytotoxic drugs or steroids is one possibility to avoid the toxic effects of immunosuppression, but this has not yet been studied in controlled trials. Future developments will probably offer other possibilities: discussion about introducing emicizumab as a baseline hemostatic agent to reduce spontaneous new bleeding with a weekly or bi-weekly subcutaneous injection, and use rhFVIIa for short-term treatment of acute bleeding episodes is ongoing. If patients can be stabilized with this strategy, it buys time for a mild immunosuppression (or even none) to reduce inhibitor production or to wait for spontaneous remission. Again, this approach needs to be studied in a controlled clinical trial.

6.3 Monitoring of Patients with AHA During Therapy

Patients with AHA must be carefully monitored, as adverse events are common and may even be fatal (Table 5). During episodes of acute bleeding, assessment of bleeding locations and severity should be performed in short intervals (6–12 h). In addition, it is mandatory to look for efficacy, response, and side effects of the applied hemostatic and immunosuppressive therapy. Laboratory tests should cover not only blood counts and clotting factor levels but also parameters detecting neutropenia, infections, diabetes, disseminated coagulopathy, thromboembolism, muscle damage, and organ function. Imaging studies are often necessary to follow hematoma size.

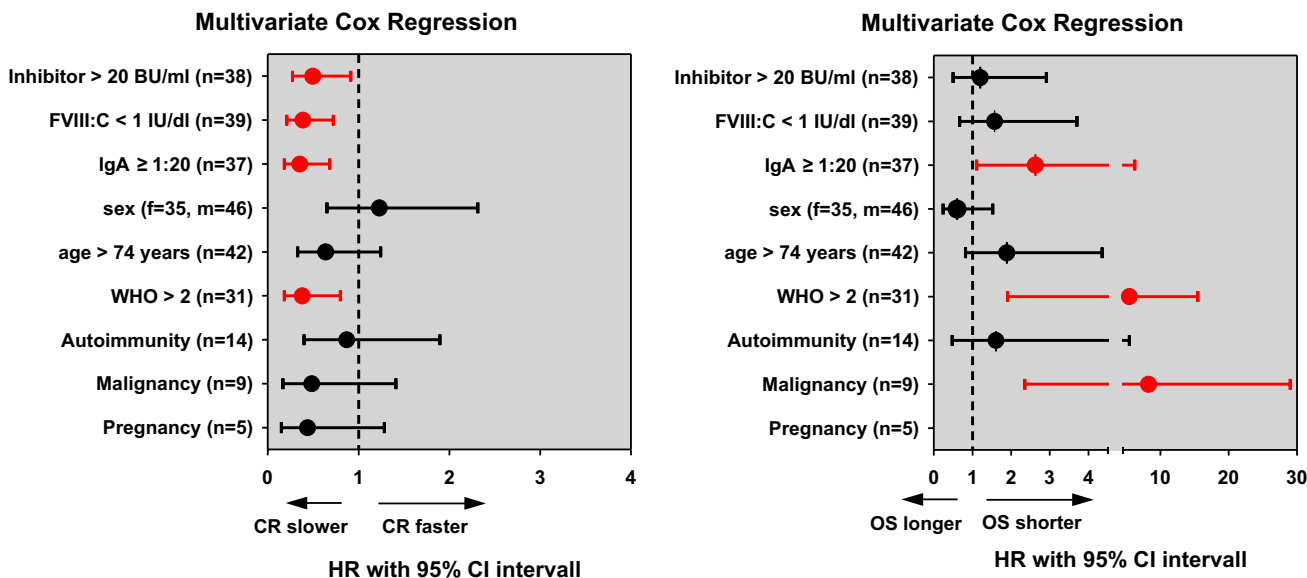


Fig. 2 Prognostic factors of patients with acquired hemophilia A. Data from the GTH AH 01/2010 Study [8, 9]. CI confidence interval, CR complete remission, HR hazard ratio, IgA immunoglobulin A, OS overall survival, WHO World Health Organization performance status

Table 5 Adverse events, outcomes, and follow-up of patients with acquired hemophilia A

	Green and Lechner [15]	Delgado et al. [16]	Collins et al. [14]	Knoebl et al. (EACH2) [5]	Borg et al. [29] (SACHA)	Tiede et al. [9] (GTH)	Kessler et al. (HTRS) [20]
Deaths reported	NR	20	42	26	33	33	NR
Estimated 1-year survival	NR	NR	55–72	72	62	68	NR
Fatal bleeding (%)	22	11	9.1	4.5	3.5	2.9	NR
Fatal CV complications	NR	NR	NR	NR	7.3	6	NR
Fatal IST-related complications	NR	NR	11	4.2	12.2	16	NR

Data extracted from publications and presented as %

CV cardiovascular, IST immunosuppressive therapy, NR not reported

During follow-up, patients should be monitored for factor VIII activity and inhibitor levels, new onset of bleeding, and side effects of immunosuppressive therapy.

6.4 Individualized Therapy and Supportive Care

AHA is a rare, quite heterogeneous disease in a heterogeneous population of patients. Therefore, clinical studies comparing various therapeutic strategies in a sufficient number of patients cannot be expected. Even the various recommendations that have been published recently can only give some guidance, but important individual circumstances are often not covered. Thus, treatment strategies (the choice of first-line hemostatic agent, response criteria, immunosuppressive regimen, patient's setting, monitoring, comedications, etc.) need to be individualized. Special attention is necessary for patients with active cancer, infection, poor general condition, diabetes, older age, major surgery, large hematomas, compression of vascular structures or other organs. Other concomitant factors enhancing the thromboembolic risk are atrial fibrillation, a history of thromboembolism, a high body mass index, intracoronary and other intravascular stents, immobilization, indwelling catheters, or artificial heart valves. Supportive care needs to include prophylaxis of thromboembolism and even therapeutic anticoagulation as soon as factor VIII levels increase, but that transition is challenging.

7 Conclusion

AHA is a rare disease complicated by a lack of knowledge, severe bleeding, multimorbid patients, complex and expensive hemostatic therapy, and severe immunosuppression-related side effects, making it one of the most challenging hematologic diseases. Increasing the awareness of AHA so it is recognized as the reason for bleeding is important so the disease is diagnosed quickly and correctly. However, disease management is the domain of specialized dedicated

hemophilia treatment centers to provide patients with the best available therapy. Future developments, including highly individualized therapy, new non-factor hemostatic agents, and better immunosuppressive regimens will change its management in the near future, but all these ideas should be studied in well-designed clinical trials.

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Compliance with Ethical Standards

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