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CRITICAL REVIEW

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Acquired hemophilia A: Updated review of evidence and treatment guidance

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Abstract

Acquired hemophilia A (AHA) is a rare disease resulting from autoantibodies (inhibitors) against endogenous factor VIII (FVIII) that leads to bleeding, which is often spontaneous and severe. AHA tends to occur in elderly patients with comorbidities and is associated with high mortality risk from underlying comorbidities, bleeding, or treatment complications. Treatment, which consists of hemostatic management and eradication of the inhibitors, can be challenging to manage.

Few data are available to guide the management of AHA-related bleeding and eradication of the disease-causing antibodies. Endorsed by the Hemostasis and Thrombosis Research Society of North America, an international panel of experts in AHA analyzed key questions, reviewed the literature, weighed the evidence and formed a consensus to update existing guidelines.

AHA is likely underdiagnosed and misdiagnosed in real-world clinical practice. Recommendations for the management of AHA are summarized here based on the available data, integrated with the clinical experience of panel participants.

1 | INTRODUCTION

Acquired hemophilia A (AHA) is a rare autoimmune disease with high risk for morbidity and mortality that is often initially encountered by emergency or internal medicine physicians.

Because of its rarity, AHA has limited data to support management. Thus, consensus recommendations considering available clinical trial/registry data and clinical experience are helpful for guiding the management of AHA. The recent advent of new data and new therapeutic products has occasioned the need for updated guidance.

2 | METHODS

An international expert panel (see authors), convened in 2015, conducted a comprehensive literature search of AHA through PubMed and Embase (all dates); key search terms included "Acquired hemophilia," "acquired factor VIII deficiency," "Hemophilia AND autoantibody," and "recombinant porcine factor VIII"; 886 citations were identified, duplicate records and single-patient case studies were removed, and outputs evaluated by at least two reviewers. Table 1 summarizes the largest registries and case summaries identified. Key questions were posed, pertaining data analyzed and discussed during an in-person meeting; evidence was weighted; and consensus was formed among the group. The aim was to build on and complement existing guidelines, with attention to the role of a newly available hemostatic agent.

The resulting guidance for the treatment of AHA, presented here, was endorsed by the Hemostasis and Thrombosis Research Society of North America.

Throughout the text, key questions are highlighted in **bold**, and consensus statements are presented in *italic* with supporting evidence from the literature following.

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TABLE 1 The largest population studies contributing information about the understanding of AHA to date

Study (reference)	Design	Year	N	Incidence	Median age at diagnosis, y (range)	Male-to-female ratio
International Survey (Green and Lechner)[1]	Retrospective survey	Before 1981	215	NA	NA	52.7/47.3
Delgado et al[2]	Meta-analysis	1984–2002	249 from 21 case series	NA	64 (8–93)	45/55
United Kingdom Haemophilia Centre Doctor's Organisation—UKHCDO (Collins et al)[3]	Prospective surveillance of a predefined population	2001–2003	172	1.48 cases/million/y	78 (2–98)	43/57
South Australian Center (Tay et al)[4]	Retrospective analysis	1997–2008	25	~1.2 cases/million/y	78 (27–99)	48/52
European Acquired Haemophilia Registry—EACH2 (Knoebl et al)[5]	Prospective multicenter (117 centers in 13 European countries)	2003–2008	501	NA	73.9 (61.4–80.4)	53/47
Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise—SACHA (Borg et al)[6]	Prospective surveillance in France	2001–2005	82	NA	76.7 (25–103)	61/39
Taiwan Centers (Huang et al)[7]	Retrospective analysis in 2 Taiwanese centers	1987–2010	65	NA	64 (18–94)	64/36
German, Austrian and Swiss Society on Thrombosis and Haemostasis—GTH-AH 01/2010 (Tiede et al)[8]	Prospective	2010–2013	102	NA	74 (26–97)	58/42

AHA: acquired hemophilia A; NA: not available.

3 | EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND PRESENTATION OF ACQUIRED HEMOPHILIA A

What is the epidemiology of AHA?

AHA is predominantly a disease of the elderly (median age 64–78 years),[1–8] but can be associated with pregnancy[1–7,9] and autoimmune disease in younger cohorts. Most cases are idiopathic (43.6%-51.9%),[1–7] but AHA is also associated with malignancy (6.4%-18.4%), autoimmune disorders (9.4%-17.0%, most commonly rheumatoid arthritis),[1–8,10] infections, dermatologic conditions, and certain medications (eg, interferon alpha).[5] Pediatric cases are rare; a review reported 42 cases in children, including six related to transplacental crossing of maternal antibody.[11]

What is the pathophysiology of AHA?

AHA is an autoimmune disease caused by the spontaneous production of neutralizing immunoglobulin G (IgG) autoantibodies (inhibitors) targeting endogenous FVIII.[12,13] Recent research suggests that the breakdown of immune tolerance is caused by a combination of genetic and environmental factors.[12,14,15]

What is the risk for bleeding in patients with AHA?

Although ~30% of patients do not require hemostatic treatment, bleeding severity varies and can be life threatening and/or limb threatening.[3,16,17] In a more recent study,[5] 94.6% of patients presented with bleeding: 77% with spontaneous and 70% with serious bleeding (hemoglobin [Hb] < 8 g/dL or a decrease in Hb of >2 g/dL). Because of the second-order kinetics of the anti-FVIII antibodies, FVIII levels are not predictive of bleeding risk and patients can have clinically significant bleeding despite only modestly reduced FVIII activity levels.[2]

What is the bleeding pattern in AHA?

Subcutaneous bleeding is most common in AHA (>80%),[3] followed by gastrointestinal bleeding (>20%); muscle bleeding (>40%); and genitourinary, retroperitoneal, and other sites of bleeding (<10%).[2] Intracranial hemorrhage is rare but can be fatal. In contrast to congenital hemophilia A, joint bleeding is infrequent with AHA.[3,5]

What is the risk and cause of death in AHA?

Mortality in AHA is estimated to be ≥20% among patients >65 years and those with underlying malignancies.[18] Although the primary cause of death is the underlying disease (46%),[5] the cause of death is unknown in many (38%),[17] reflecting limited follow-up in most studies.

Deaths from bleeding are less common: 3.2% of patients (17.2% of all deaths) in EACH2[5] and 9.1% at a median of 19 days after presentation in the UK Haemophilia Centre Doctors' Organisation (UKHCDO) observational study.[3] Although bleeding as a direct cause of death is rare, it is usually a contributor to considerable morbidity that will extend hospitalization, delay healing, and can indirectly result in the death of the patient.

Immunosuppressive therapy (IST) to eliminate the antibodies and decrease bleeding risk is recommended but is associated with mortality, accounting for 16% of all deaths (4.2% of patients) in EACH2.[5]

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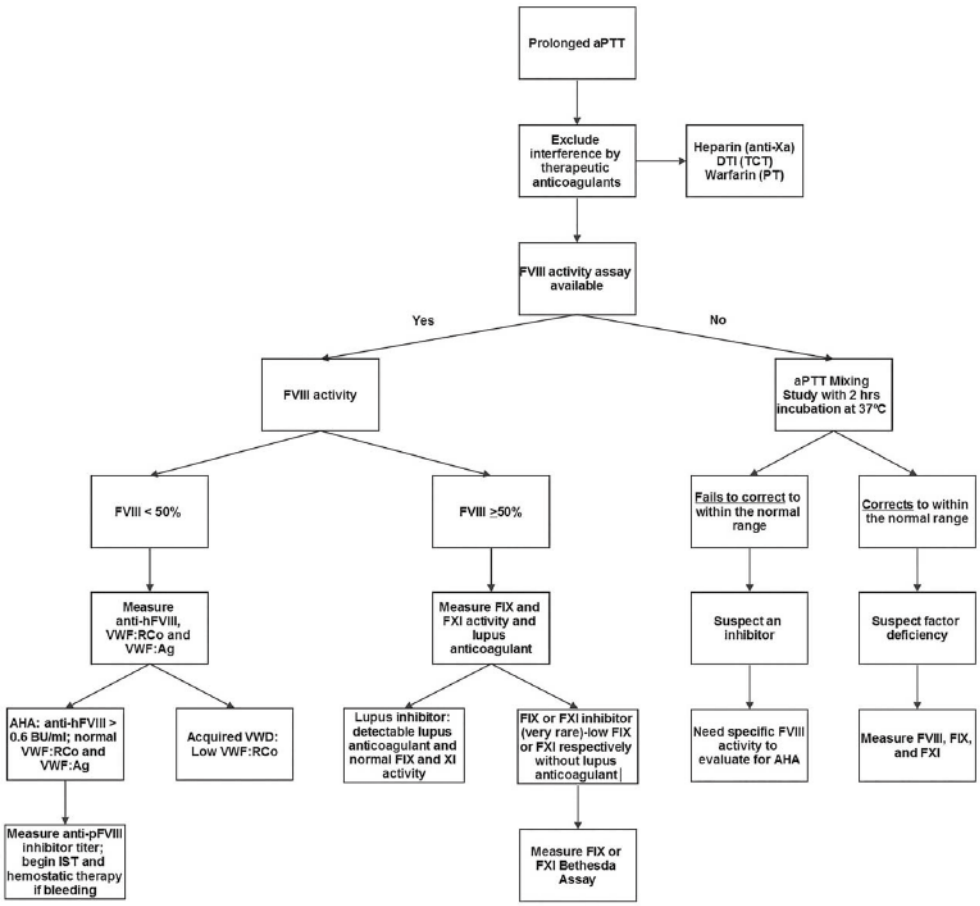

FIGURE 1 Laboratory diagnosis of AHA. AHA =acquired hemophilia A; anti-h-FVIII =anti-human factor VIII inhibitor; anti-pFVIII = anti-porcine FVIII; aPTT = activated partial thromboplastin time; DTI =direct thrombin inhibitor; FIX =factor IX; FVIII =factor VIII; FXI = factor XI; IST = immunosuppressive therapy; PT = prothrombin time; TCT =thrombin clotting time; VWD = Von Willebrand disease; VWF:Ag = von Willebrand factor-antigen; VWF:RCo = von Willebrand factor-Ristocetin co-factor

Other fatal and nonfatal complications include thrombotic events such as myocardial infarction and stroke.[6,8]

4 | DIAGNOSIS OF AHA

When should AHA be suspected?

- *AHA should be considered in patients, especially the elderly and peripartum and postpartum women, with recent onset of abnormal bleeding, an isolated prolongation in activated partial thromboplastin time (aPTT), and normal prothrombin time (PT).*
- *AHA should be suspected in a nonbleeding patient not on anticoagulation with an isolated prolonged aPTT, a mixing study consistent with an inhibitor, and a negative lupus anticoagulant (LA).*

How should AHA be diagnosed?

- *An isolated prolonged aPTT should always be investigated; an algorithm for diagnosing AHA is provided in* Figure 1
- *A FVIII inhibitor is confirmed and quantified by the Bethesda assay (BA), Nijmegen Bethesda assay (NBA), or in some laboratories by an enzyme-linked immunosorbent assay (ELISA) with anti-FVIII antibody.*[19]

What are the differential diagnoses and potential pitfalls in the laboratory diagnosis of AHA?

- Both the BA and NBA may underestimate the inhibitor titer. Underestimates of the inhibitor titer may be result from nonlinear inactivation of FVIII and residual FVIII activity. Heat treatment of the

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sample prior to assay (58°C for 90 minutes) may improve inhibitor detection sensitivity by eliminating residual activated FVIII.[20,21]

- LA should be excluded as a potential cause of isolated prolonged aPTT.
  Studies of aPTT mixing will be abnormal with both AHA and a LA. While an aPTT mixing study could initially correct the aPTT prolongation, it will again prolong aPTT with incubation because of the time and temperature dependence of anti-FVIII antibodies. LA will usually show an immediate inhibitory effect in the mixing study. Confounding LA can usually be diagnosed through the use of dilute Russel viper venom time (dRVVT).[21–23]
- *Heparins,* heparinoids, *and direct anticoagulants may interfere with test results and resemble circulating inhibitors.*
  Although the effect of these agents on laboratory measurements are highly variable, thrombin clotting time, with or without reptilase time, may be helpful in distinguishing the effects of heparin and direct thrombin inhibitors from AHA.[21] To detect the effects of FXa-inhibiting anticoagulants (low-molecular-weight heparins, fondaparinux, danaparoid, and direct oral factor Xa inhibitors), an anti-Xa assay is helpful.

5 | PRINCIPLES OF MANAGEMENT IN AHA

The management of AHA focuses on the following goals:

1. Controlling and preventing bleeding (if present/significant).
2. Eradication of the inhibitor.
3. Treatment of the underlying disease (if applicable).

Who should manage patients with AHA?

- *A hematology specialist familiar with the management of patients with coagulation inhibitors, with access to possible hemostatic agents and frequent FVIII monitoring, is best suited to manage patients with AHA.*
  Available hemostatic agents do not always have predictable efficacy[16] and are administered to patients who often have underlying comorbidities and may have underlying prothrombotic risk factors. Immunosuppression creates a dynamically changing hemostatic environment that requires close monitoring. For these reasons, patients with AHA are best managed by, or in close consultation with, physicians experienced in AHA.[11,24–26]

6 | PREVENTION AND CONTROL OF BLEEDING

Which patients with AHA should be treated with hemostatic agents?

- *Invasive procedures should be avoided—if they are urgently needed, however, hemostatic therapy is required before and after the procedures.*
- *Patients with major bleeding and/or a decrease in hemoglobin require immediate hemostatic treatment.*
- *Patients with mild/moderate bleeding without a significant decrease in hemoglobin may not require immediate hemostatic therapy—but could developing severe bleeding at any time.*
- *Patients at high risk for bleeding (recent surgery, recent delivery, peptic ulcer, etc) require prophylactic hemostatic therapy.*

Because severe and potentially life-threatening/limb-threatening bleeding may occur, rapid diagnosis and treatment are critical.[1] Severity of bleeding at presentation does not predict recurrence or subsequent severity of bleeding.[3] Some soft tissue hemorrhage managed without hemostatic therapy can expand into compartment syndrome. Therefore, close monitoring, good patient education, and immediate inhibitor eradication are essential.[11,24,25]

How should bleeding be treated in patients with AHA?

- *Options for first-line hemostatic agents are listed in* Table 2
- *Determination of hemostatic control is largely based on clinical assessment and switch to an alternate hemostatic agent should be considered after 12–24 hours.*
- *Human FVIII (hFVIII) replacement, although effective in patients with low titers (<5 BU), is not effective in patients with high titer inhibitors (>5 BU).*
- *Desmopressin (DDVAP) is of limited utility in AHA.*
- *Antifibrinolytic agents may be a useful adjunct to therapy, particularly for mucosal bleeding, with the exception of renal tract bleeding (risk for urinary outflow obstruction induced by intraureteral or bladder clot formation).*

6.1 | Replacement therapy

Human FVIII replacement is not effective in the presence of high titer inhibitors.[27] If used in patients with lower titers (<5 BU), the dose must be increased sufficiently to overcome the inhibitor. Especially for patients in geographic locations where other hemostatic alternatives are not readily available, hFVIII replacement could be a sufficient first-line therapy and has proven effective in some patients.

Porcine FVIII (pFVIII) can achieve measurable FVIII levels and hemostasis in AHA, even if the human inhibitor is high. Recombinant porcine FVIII (rpFVIII, Obizur) was approved for the treatment of bleeding in AHA in the United States, Canada, and Europe based on a prospective study in adults with serious bleeding[28]: all 28 subjects had good hemostasis and FVIII activity levels >100% within 24 hours in response to rpFVIII. The FVIII activity on response to rpFVIII was dependent on a cross-reactive pFVIII inhibitor titer. Subjects without cross-reactivity (pFVIII inhibitor negative) achieved very high FVIII activity levels (118%-522%).

To predict the effectiveness of either hFVIII or rpFVIII in the treatment of AHA, it is essential to determine baseline concentrations of anti-human and anti-porcine FVIII antibodies (performed in specialty laboratories). Administration of rpFVIII will trigger an increase in the anti-rpFVIII titer in some patients,[28] and can subsequently decrease

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TABLE 2 Options for first-line hemostatic agents in AHA

Agent	Recommended dose	Comments
Replacement therapy		
Recombinant porcine FVIII (rpFVIII)	*If no anti-porcine FVIII inhibitor*[a]: 50–100 U/kg initially then monitor every 2–3 h with FVIII activity and redose as needed *If detectable anti-porcine FVIII inhibitor*[a]: 200 U/kg initially for severe bleeding 50–100 U/kg for less severe bleeding Monitor and redose as above	ADVANTAGE Can be monitored with one stage FVIII clotting assay Replaces missing component Proven efficacy DISADVANTAGE Less effective in case of cross-reactive anti-porcine antibody May develop anti-porcine FVIII antibody during therapy = needs close monitoring CONSIDER First LINE Where drug readily available No underlying rpFVIII inhibitor FVIII activity measurement readily available Life-threatening/limb-threatening bleeding
Bypassing Therapy		
Activated prothrombin complex concentrate (aPCC)	50–100 U/kg every 8–12 h Do not exceed 200 U/kg/d	ADVANTAGE Proven efficacy for clinical bleeding DISADVANTAGE No laboratory to monitor underdosing or overdosing Potential arterial or venous thrombotic risk CONSIDER First LINE Where drug readily available If underlying high titer rpFVIII inhibitor (>10 BU) FVIII activity measurement not readily available Non-life-threatening/limb-threatening bleeding
Recombinant FVII activated (rFVIIa)	70–90 mcg/kg every 2–3 h until hemostasis achieved, then prolong dosing interval	ADVANTAGE Proven efficacy for clinical bleeding DISADVANTAGE No laboratory to monitor underdosing or overdosing Short half-life (2 h) Potential arterial or venous thrombotic risk CONSIDER First LINE Where drug readily available If underlying high titer rpFVIII inhibitor (>10 BU) FVIII activity measurement not readily available Non-life-threatening/limb-threatening bleeding
Comments		
Patients should also be started on IST and FVIII level monitors regularly. Head to head comparison of these hemostatic agents have not been done and the first line agent should be chosen based on availability, prior efficacy in the patient and economic considerations. Hemostatic efficacy is largely based on clinical assessment and changing to an alternate hemostatic agent should be considered after 12–24 h. Once hemostasis is achieved, the dosing frequency of any hemostatic agent should be decreased as tolerated to prevent the risk for thrombosis. Hemostatic agents should not be given in a patient with rising factor levels and no active or increased risk for bleeding. In hospitalized patients consider thromboembolism prophylaxis when FVIII levels exceed 50 IU/dL.		

AHA: acquired hemophilia A; FVIII: factor VIII; IST: immunosuppressive therapy; rpFVIII: recombinant porcine factor VIII.
[a]rpFVIII dosing recommendations differ from package inset and are based on the postmarketing clinical experience with this medication.

treatment efficacy. Baseline and postinfusion FVIII levels should be used to guide dosing and intervals.

6.2 | Bypassing agents

Recombinant factor VIIa (rFVIIa, NovoSeven®) and activated prothrombin complex concentrate (aPCC, FEIBA®—plasma-derived, containing factors II, IX, and X and VIIa) are both appropriate first-line bypassing treatments. Dosing recommendations are listed in Table 2.

In EACH2—prior to approval of rpFVIII—most patients treated with hemostatic agents received rFVIIa (56.7%); others received aPCC (20.5%), hFVIII (18.2%), or DDAVP (4.6%).[16] Overall, bleeding was controlled most successfully with bypassing agent (91.8%), with no difference between rFVIIa (91.8%) and aPCC (93.3%). Replacement with hFVIII concentrate was less successful in controlling bleeding (69.6%).

6.3 | Other hemostatic approaches

The use of DDVAP for the management of bleeding should be reserved for minor bleeding in patients with low inhibitor titers (<2 BU/mL) and FVIII levels >5 IU/.[16,20,24,29] The ability of DDVAP to release FVIII from endothelial cells is unpredictable and DDVAP is associated with a substantial risk for adverse events in elderly patients.

Tranexamic acid (TA) in combination with either aPCC or rFVIIa normalizes clot stability,[30,31] and case reports on combination of TA

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TABLE 3 Thromboembolic risk in patients receiving bypassing agents

Study	Treatment	N	Thromboembolic events
Sumner et al[40]	Recombinant factor VIIa	139	6 events in 4 patients (2.9%)
Ingerslev et al[41]	Combined or alternating bypassing agents	9	55%
Baudo et al[16]	Recombinant factor VIIa	174	2.9%
	aPCC	63	4.8%
	Factor VIII/desmopressin	70	0%
Seita et al[42]	Recombinant factor VIIa	132	2.3%
Borg et al[6]	Recombinant factor VIIa	28	0%
	aPCC	6	0%
Tiede et al[8]	Recombinant factor VIIa	63	5%
	Recombinant factor VIIa + tranexamic acid	21	10%

aPCC: activated prothrombin complex concentrate; factor VIIa: activated factor VII.

with rFVIIa[32] and aPCC[33,34] provide support for efficacy. Solutions of antifibrinolytic agents can be used topically to treat oral or skin bleeding.

The modified Bonn-Malmö Protocol (MBMP) combines immunoadsorption with FVIII replacement and immunosuppression and can achieve rapid and safe control of acute bleeding.[35] This strategy is mainly implemented in Europe because immunoadsorption columns are not available in the United States.

What is the definition of response to hemostatic therapy?

- *Response to therapy is determined clinically.*
- *Response to human and porcine FVIII replacement can be monitored with FVIII activity assays.*
- *There is no established laboratory monitoring assay for bypassing agents.*

Monitoring response relies on clinical assessment, hemoglobin, and imaging studies. No laboratory tests have been standardized for monitoring hemostatic response to bypassing agents.[36–38] Routine FVIII levels using 1-stage coagulation assays can be used to measure human or porcine FVIII concentrates.[39] FVIII levels should be obtained in real time (turnaround of 1–2 hours) to be clinically useful and guide subsequent management, which is not possible at many institutions. The more readily available aPTT will normalize when replacement results in FVIII levels >30%-50% (laboratory dependent), but it is not a predictor of supra-therapeutic levels. Thus, aPTT level is not a good surrogate marker to guide treatment.

Are there factors that predict response to hemostatic therapy?

Neither residual FVIII activity levels nor inhibitor titers correlate with the severity or responsiveness of bleeds.[3]

What are the risks associated with the use of bypassing agents?

- Patients receive bypassing agents are at risk for arterial and venous thromboembolism, and should be monitored closely.
- Particular caution is recommended in older patients and patients with predisposing conditions (eg, underlying malignancy or personal history of thrombosis).

The risk for thromboembolic complications, including disseminated intravascular coagulation, among patients who are treated with bypassing agents is increased (Table 3).[6,8,16,40–42] Thrombotic events appear to be associated with age and underlying conditions, such as previous thrombosis, immobilization, malignancy, indwelling catheters, artificial heart valves, vascular grafts, atrial fibrillation, and pregnancy/postpartum.[16]

The economic impact of hemostatic management

Replacement and bypassing agents are expensive. Their cost is calculated per unit (per microgram), thus the dose amount and dosing frequency will bear significant economic impact. No studies have compared the increased cost of these hemostatic agents with the resulting decreased morbidity, mortality, and length of hospitalization from their use. Continuous economic appraisal is recommended during the therapeutic course.

7 | INHIBITOR ERADICATION

Who should receive IST to facilitate inhibitor eradication?

- *IST is recommended in all adult patients with AHA.*

Although in some cases inhibitors can disappear spontaneously after several months,[1] while they are present, bleeding-related morbidity and mortality are substantial and hemostatic treatment is costly. Thus, IST is recommended for all adults with AHA. The role for pediatric patients is not well established because of a lack of data.[11]

What is the optimal strategy for inhibitor eradication?

- *Options for first-line IST are summarized in* Table 4
- *IST achieves remission in about 60%-80% of patients after a median of 5–6 weeks.*

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TABLE 4 Options for first-line immunosuppression in AHA

Recommended first-line immunosuppression	Recommended dose	Comment
Corticosteroids alone	Prednisone 1 mg/kg PO daily (alternative dexamethasone 40 mg PO daily × 4–7 d)[a]	Unlikely to be effective in ≤3 wk in patients with FVIII < 1 IU/dL or inhibitor > 20 BU/mL at presentation Monitor for adverse events (elevated glucose, infection, psychiatric disorders)
Corticosteroid and cyclophosphamide	Corticosteroid same as above; cyclophosphamide 1–2 mg/kg PO daily (alternative ~5 mg/kg IV q 3–4 wk)[a]	May have faster response rated than steroids alone, but higher adverse event profile Associated with the highest CR rate Monitor for marrow suppression (WBC, platelets) and infection
Corticosteroids and rituximab	Corticosteroid same as above; rituximab 375 mg/m^2 IV weekly × 4 (alternative 100 mg weekly × 4)[a]	Rituximab is not recommended as initial monotherapy unless other IST is contraindicated
Comments		
Median time to response (FVIII activity level restored to >50 IU/dL) is 5 wk. Patients with FVIII activity level < 1 IU/dL at baseline require significantly longer times to remission compared to patients with FVIII activity level ≥ 1 IU/dL and may require combination IST rather than corticosteroids alone. FVIII activity and inhibitor levels should be monitored at least weekly. Apply individualized therapy according to the patient's general condition, underlying and concomitant diseases, and prognostic factors (ie, FVIII < 1 IU/dL, inhibitor titer > 20 BU/mL, presence of anti-FVIII-IgA antibodies, etc), when available.		

AHA: acquired hemophilia A; CR: complete remission; IST: immunosuppressive therapy; IV: intravenous; PO: orally; WBC: white blood cell.
[a]Few data available in AHA, but reports available in other autoimmune disorders.

- *Some evidence suggests that time to remission may be shorter in patients receiving a combination of corticosteroids and cyclophosphamide, although long-term survival does not differ.*

The recommendations made here are largely derived from observations made in the UKHCDO surveillance study,[3] the EACH2 registry,[17] and the GTH-AH registry.[8] Both the UKHCDO study and EACH2 collected real-life, nonrandomized data comparing the efficacy of different treatments. The GTH-AH study prospectively investigated a standardized treatment.

The UKHCDO study showed no statistically different median time to remission between corticosteroids alone (usually prednisolone 1 mg/kg daily, n = 40; 49 days; 95% CI, 31–62) and corticosteroids/cytotoxic agents (same dose steroids and usually cyclophosphamide 1–2 mg/kg daily, n = 48; 39 days; 95% CI, 35–47).[3]

In EACH2, most patients received first-line treatment with steroids alone (n = 142), corticosteroids and cyclophosphamide (n = 83), or rituximab-based regimens (n = 51).[17] The highest remission rates and shortest time to remission were achieved with the combination of corticosteroids and cyclophosphamide (80%, 40 days, interquartile range [IQR] 18–80) versus rituximab-based regimens (61%, 64 days, IQR 82–206) and corticosteroids alone (58%, 32 days, IQR 15–51). Rituximab alone (n = 12) was used infrequently and appeared to be less successful (42%). After propensity score matching, time to negative inhibitor and FVIII level > 70 IU/dL was shorter in patients receiving corticosteroids and cyclophosphamide compared with patients receiving corticosteroids alone (hazard ratio [HR] 2.11; 95% CI, 1.38–3.21; $P < 0.001$). However, no difference was noted in the proportion of patients who were alive and inhibitor free at 1 year.

A meta-analysis of 20 studies enrolling a total of 249 patients also concluded that cyclophosphamide, with or without corticosteroids (n = 99), was more effective in achieving complete remissions than corticosteroids alone (n = 57) or no IST (n = 27).[2]

The GTH-AH study, representing the most robust prospective registry, used a predefined consensus protocol.[8] All patients (n = 102) were enrolled within 7 days of starting IST and initially received corticosteroids alone for 3 weeks. If remission was not achieved, oral cyclophosphamide was added (weeks 4–6). Rituximab (375 mg/m^2 weekly) was added at week 7–10 where needed. Partial remission (PR; defined as FVIII > 50 IU/dL, no active bleeding, no hemostatic drugs for >24 h) was achieved by 83%; complete remission (CR; defined as PR plus negative inhibitor, prednisolone tapered to <15 mg daily, any other IST stopped) was achieved by 61%. Time to PR and CR was 31 days (IQR 19–51) and 79 days (IQR 48–102), respectively.

Who is a candidate for second-line and later-line therapy?

- *Patients who fail to see a decline in the inhibitor titer or a rise in the baseline FVIII level after 3–5 weeks of first-line therapy should be considered for second-line therapy.*

Insufficient data are available to recommend specific second-line and later-line treatments for AHA. The risk for bleeding must be weighed individually against the risk of infection from intense or prolonged immunosuppression. Although evidence is limited, other reasonable second-line options include calcineurin inhibitors,[43–46] mycophenolate mofetil,[47] multiple immunosuppressive agents,[46] immune tolerance protocols,[48–50] or the combination MBMP.[35]

What is the role of intravenous immunoglobin (IVIG)?

- *IVIG has a limited role in the treatment of AHA.*

In the EACH2 study, adding IVIG to other immunosuppressive agents as first-line therapy provided no benefit.[17] A similar result was seen in the UKHCDO surveillance study[3] and in a subsequent literature review.[2] IVIG is part of the MBMP[35] and may serve a purpose in the context of this combination therapy.

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Are there any clinical characteristics that predict response to first-line immunosuppression?

- *FVIII < 1 IU/dL and poor performance status are associated with lower remission and survival rates.*

Underlying etiology, age, or, sex do not influence time to remission,[8,17] but a multivariate analysis in the GTH-AH study indicated that FVIII concentration < 1 IU/dL and poor performance status were independently associated with lower CR rate and overall survival.[8] Patients with a FVIII ≥ 1 IU/dL and inhibitor titer < 20 BU/mL had a 53% chance of achieving a FVIII > 50 IU/dL by 21 days with corticosteroids alone, compared with a 9% with a FVIII < 1 IU/dL or an inhibitor titer ≥ 20 BU/mL.

What is the risk of relapse after initial remission?

- *After achieving remission, patients should be closely monitored for relapse.*
- *Patients with anti-FVIII autoantibodies of the immunoglobulin A (IgA) class appear to have a particularly high risk of relapse.*

In EACH2, relapse occurred in 18% of patients who achieved remission with corticosteroids alone, and in 12% receiving corticosteroids/cyclophosphamide, with similar time to relapse (134 and 139 days, respectively). Patients achieving remission after rituximab-based regimens had a lower relapse rate of 3%. After a median observation time of 262 days, the proportion of patients who were alive and inhibitor free was similar (steroids only, 67%; steroids and cyclophosphamide, 62%; or rituximab-based regimens, 71%).[17] In the GTH-AH study, the median observation time was 403 days, with 48% of patients alive and in stable CR at database closure.[8]

In a post hoc analysis of the GTH-AH study, anti-FVIII autoantibodies of the IgA isotype, detected in 46% of patients, were a potential marker for early relapse.[51]

No evidence is available to recommend specific treatment regimens for patients who relapse. In the GTH-AH study, the last effective dose of corticosteroids was recommended if FVIII activity decreased to <50 IU/dL and achieved remission in 18 of 19 patients.[8]

What are the complications of IST?

- *Complications of IST are frequent and can be fatal.*
- *Patients should be monitored closely for signs of infection and other adverse effects of IST.*

IST increases infectious risk in this elderly, fragile population. In the UK surveillance study, sepsis was reported in 33% and contributed to death in 12%.[3] In the GTH-AH study, 54 infections were recorded in 37 of 102 patients.[8] Infections occurred after a median of 54 days (IQR 33–137) of starting IST, and 16 of 102 patients died from infection. A similar rate of death from IST (12%) was reported in the SACHA (Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise) registry.[6] In the EACH2 registry 4.2% died from complications of IST. Prophylactic antibiotic therapy has not been studied in AHA.

Other well-recognized complications of steroid therapy include raised blood sugar levels (12%), gastrointestinal ulcers (4%), muscle disorders (4%), and psychiatric disorders (3%).[3,8]

How should patients be monitored?

- *Inhibitor titer and FVIII activity should be monitored at least weekly during immunosuppressive treatment.*

In the absence of data to support a specific monitoring and tapering schedule, the consensus of the expert panel was to monitor with FVIII activity levels and inhibitor titers weekly until the inhibitor becomes undetectable and FVIII activity levels normalize. Tapering of IST should be initiated once the inhibitor is undetectable and FVIII is rising. FVIII activity should be monitored for some period after IST is stopped to assess for recurrence.

It is important to educate patients on the urgent and immediate need to return to the clinic in case of bleeding symptoms, which could be a sign of inhibitor recurrence.

When is thromboprophylaxis appropriate?

- *Nonbleeding hospitalized patients with FVIII activity levels > 50 IU/dL should receive thromboprophylaxis.*
- *If a patient has a prior indication for aspirin or anticoagulation, it should be restarted when the FVIII activity consistently exceeds 50 IU/dL.*

Data are limited on thrombotic risk in patients receiving hemostatic agents and responding to IST (Table 3) but may be increased in the elderly and those with predisposing underlying conditions (ie, personal history of thrombosis, malignancy or pregnancy). Many centers, as well as this expert panel, recommend thromboprophylaxis in hospitalized nonbleeding patients when endogenous FVIII exceeds 50 IU/dL. This could be either mechanical or pharmacological prophylaxis. Individuals with a prior need for full anticoagulation should restart such at this point.

8 | PREGNANCY-RELATED AHA

- *Pregnancy-associated AHA may resolve spontaneously.*
- *IST with corticosteroids alone should be considered as first-line therapy to avoid potential bleeding complications in the mother and baby.*
- *Cyclophosphamide is not safe during pregnancy/lactation.*

Pregnancy-associated AHA typically occurs with the first pregnancy. It is usually diagnosed several days to months postpartum but can present peripartum,[1–7,10,52] and the transplacental crossing of the IgG antibodies poses a potential hemorrhagic risk for the neonate.[11] Bleeding patterns are of similar severity and distribution as other AHA, with the addition of significant uterine/vaginal bleeding.[52] Hemostatic management is achieved as with other patients with AHA, although no data are available on the use of rpFVIII during pregnancy. Overall survival is superior to patients with AHA associated with other etiologies.[52]

AHA associated with pregnancy (rather than other etiologies) may require a longer time to remit fully, although the rate of spontaneous

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remission may be higher.[53–55] Relapse during subsequent pregnancies appears uncommon.[55,56]

Steroids are a safe and effective way to eradicate inhibitors around pregnancy.[52] Few data are available on the efficacy and safety of IST for pregnancy-associated AHA. A single-center case series suggests that rituximab is effective in this setting.[57]

9 | CONCLUSIONS

AHA is a rare disorder with high potential for morbidity and mortality. Because it occurs in patients without a known bleeding disorder, the internist or emergency department provider is often the first to evaluate the patient. For most patients, AHA is eminently treatable, with clear benefits from prompt recognition and appropriate management. Both hemostatic and immune therapy impose considerable risks and require close monitoring to ensure safety.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

Dr Craig Kessler and Rebecca Kruse-Jarres had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors
Acquisition, analysis, or interpretation of data: All authors
Drafting of the manuscript: All authors
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: n/a
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Study supervision: All authors

REFERENCES

[1] Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to Factor VIII. *Thromb Haemost*. 1981;45:200–203.

[2] Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol*. 2003;121:21–35.

[3] Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. 2007;109:1870–1877.

[4] Tay L, Duncan E, Singhal D, et al. Twelve years of experience of acquired hemophilia A: trials and tribulations in South Australia. *Semin Thromb Hemost*. 2009;35:769–777.

[5] Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost*. 2012;10:622–631.

[6] Borg JY, Guillet B, Le Cam-Duchez V, Goudemand J, Levesque H. Outcome of acquired haemophilia in France: the prospective SACHA (Surveillance des Auto antiCorps au cours de l'Hemophilie Acquise) registry. *Haemophilia*. 2013;19:564–570.

[7] Huang SY, Tsay W, Lin SY, Hsu SC, Hung MH, Shen MC. A study of 65 patients with acquired hemophilia A in Taiwan. *J Formos Med Assoc*. 2015;114:321–327.

[8] Tiede A, Klamroth R, Scharf RE, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. *Blood*. 2015;125:1091–1097.

[9] Michiels JJ. Acquired hemophilia A in women postpartum: clinical manifestations, diagnosis, and treatment. *Clin Appl Thromb Hemost*. 2000;6:82–86.

[10] Gheisari R, Bomke B, Hoffmann T, Scharf RE. Clinical features and outcome of acquired haemophilia A: interim analysis of the Dusseldorf study. *Hamostaseologie*. 2010;30:156–161.

[11] Franchini M, Zaffanello M, Lippi G. Acquired hemophilia in pediatrics: a systematic review. *Pediatr Blood Cancer*. 2010;55:606–611.

[12] Oldenburg J, Zeitler H, Pavlova A. Genetic markers in acquired haemophilia. *Haemophilia*. 2010;16(Suppl 3):41–45.

1. **AHA is a rare disorder with high potential for morbidity and mortality. Because it occurs in patien...**
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[13] Ma AD, Carrizosa D. Acquired factor VIII inhibitors: pathophysiology and treatment. *Hematol Am Soc Hematol Educ Program*. 2006; 432–437.

[14] Tiede A, Eisert R, Czwalinna A, Miesbach W, Scharrer I, Ganser A. Acquired haemophilia caused by non-haemophilic factor VIII gene variants. *Ann Hematol*. 2010;89:607–612.

[15] Pavlova A, Zeitler H, Scharrer I, Brackmann HH, Oldenburg J. HLA genotype in patients with acquired haemophilia A. *Haemophilia*. 2010;16:107–112.

[16] Baudo F, Collins P, Huth-Kuhne A, et al. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) registry. *Blood*. 2012;120:39–46.

[17] Collins P, Baudo F, Knoebl P, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *Blood*. 2012;120:47–55.

[18] Bitting RL, Bent S, Li Y, Kohlwes J. The prognosis and treatment of acquired hemophilia: a systematic review and meta-analysis. *Blood Coagul Fibrinol*. 2009;20:517–523.

[19] Werwitzke S, Geisen U, Nowak-Gottl U, et al. Diagnostic and prognostic value of factor VIII binding antibodies in acquired hemophilia A: data from the GTH-AH 01/2010 study. *J Thromb Haemost*. 2016;14:940–947.

[20] Batty P, Moore GW, Platton S, et al. Diagnostic accuracy study of a factor VIII ELISA for detection of factor VIII antibodies in congenital and acquired haemophilia A. *Thromb Haemost*. 2015;114:804–811.

[21] Tiede A, Werwitzke S, Scharf RE. Laboratory diagnosis of acquired hemophilia A: limitations, consequences, and challenges. *Semin Thromb Hemost*. 2014;40:803–811.

[22] Keeling D, Mackie I, Moore GW, Greer IA, Greaves M, British Committee for Standards in Haematology. Guidelines on the investigation and management of antiphospholipid syndrome. *Br J Haematol*. 2012;157:47–58.

[23] Zhang L, Whitis JG, Embry MB, Hollensead SC. A simplified algorithm for the laboratory detection of lupus anticoagulants: utilization of two automated integrated tests. *Am J Clin Pathol*. 2005;124: 894–901.

[24] Collins PW, Chalmers E, Hart DP, et al. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). UK Haemophilia Centre Doctors Organization. *Br J Haematol*. 2013; 160:153–170.

[25] Huth-Kuhne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica*. 2009;94:566–575.

[26] Collins PW. Therapeutic challenges in acquired factor VIII deficiency. *Hematol Am Soc Hematol Educ Program*. 2012;2012:369–374.

[27] Nemes L, Pitlik E. New protocol for immune tolerance induction in acquired hemophilia. *Haematologica*. 2000;85:64–68.

[28] Kruse-Jarres R, St-Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. *Haemophilia*. 2015;21:162–170.

[29] Franchini M, Lippi G. The use of desmopressin in acquired haemophilia A: a systematic review. *Blood Transfus*. 2011;9:377–382.

[30] Hvas AM, Sorensen HT, Norengaard L, Christiansen K, Ingerslev J, Sorensen B. Tranexamic acid combined with recombinant factor VIII increases clot resistance to accelerated fibrinolysis in severe hemophilia A. *J Thromb Haemost*. 2007;5:2408–2414.

[31] Tran HT, Sorensen B, Rea CJ, et al. Tranexamic acid as adjunct therapy to bypassing agents in haemophilia A patients with inhibitors. *Haemophilia*. 2014;20:369–375.

[32] Fisher C, Mo A, Warrillow S, Smith C, Jones D. Utility of thromboelastography in managing acquired Factor VIII inhibitor associated massive haemorrhage. *Anaesth Intensive Care*. 2013;41:799–803.

[33] Holmstrom M, Tran HT, Holme PA. Combined treatment with APCC (FEIBA(R)) and tranexamic acid in patients with haemophilia A with inhibitors and in patients with acquired haemophilia A—a two-centre experience. *Haemophilia*. 2012;18:544–549.

[34] McCain S, Gull S, Ahmad J, Carey D. Acquired hemophilia A as a cause of acute upper gastrointestinal hemorrhage. *BMJ Case Rep*. 2014;2014:1–3.

[35] Zeitler H, Ulrich-Merzenich G, Hess L, et al. Treatment of acquired hemophilia by the Bonn-Malmo Protocol: documentation of an in vivo immunomodulating concept. *Blood*. 2005;105:2287–2293.

[36] Varadi K, Negrier C, Berntorp E, et al. Monitoring the bioavailability of FEIBA with a thrombin generation assay. *J Thromb Haemost*. 2003;1:2374–2380.

[37] Dehmel H, Werwitzke S, Trummer A, Ganser A, Tiede A. Thrombelastographic monitoring of recombinant factor VIIa in acquired haemophilia. *Haemophilia*. 2008;14:736–742.

[38] Ay Y, Balkan C, Karapinar DY, Akin M, Bilenoglu B, Kavakli K. Feasibility of using thrombin generation assay (TGA) for monitoring bypassing agent therapy in patients with hemophilia having inhibitors. *Clin Appl Thromb Hemost*. 2013;19:389–394.

[39] Kempton CL, Abshire TC, Deveras RA, et al. Pharmacokinetics and safety of OBI-1, a recombinant B domain-deleted porcine factor VIII, in subjects with haemophilia A. *Haemophilia*. 2012;18:798–804.

[40] Sumner MJ, Geldziler BD, Pedersen M, Seremetis S. Treatment of acquired haemophilia with recombinant activated FVII: a critical appraisal. *Haemophilia*. 2007;13:451–461.

[41] Ingerslev J, Sorensen B. Parallel use of by-passing agents in haemophilia with inhibitors: a critical review. *Br J Haematol*. 2011;155: 256–262.

[42] Seita IAK, Higasa S, Sawada A, Kuwahara M, Shima M. Treatment of acute bleeding episodes in acquired haemophilia with recombinant activated factor VII (rFVIIa): analysis from 10-year Japanese post-marketing surveillance. *J Thromb Haemost*. 2013;11:119.

[43] Pardos-Gea J, Altisent C, Parra R, Vilardell-Tarres M, Ordi-Ros J. Acquired haemophilia A. First line treatment with calcineurin inhibitors and steroid pulses: a 10-year follow-up study. *Haemophilia*. 2012;18:789–793.

[44] Pfliegler G, Boda Z, Harsfalvi J, et al. Cyclosporin treatment of a woman with acquired haemophilia due to factor VIII:C inhibitor. *Postgrad Med J*. 1989;65:400–402.

[45] Schulman S, Langevitz P, Livneh A, Mortinowitz U, Seligsohn U, Varon D. Cyclosporine therapy for acquired factor VIII inhibitor in a patient with systemic lupus erythematosus. *Thromb Haemost*. 1996; 76:344–346.

[46] Au WY, Lam CC, Kwong YL. Successful treatment of acquired factor VIII inhibitor with cyclosporin. *Haemophilia*. 2004;10:98–100.

[47] Rech J, Hueber AJ, Leipe J, Manger B, Schett G, Kallert S. A case report of plasma exchange, steroids, mycophenolate mofetil and cyclophosphamide in acquired factor VIII inhibitors. *Ther Apher Dial*. 2008;12:406–408.

[48] Nemes L, Piklik E. Ten years experience with immune tolerance therapy in acquired hemophilia. *Haematologica*. 2003;88:106–110.

[49] Lian EC, Larcada AF, Chiu AY. Combination immunosuppressive therapy after factor VIII infusion for acquired factor VIII inhibitor. *Ann Intern Med*. 1989;110:774–778.

[no notes on this page]

[50] Lian EC, Villar MJ, Noy LI, Ruiz-Dayao Z. Acquired factor VIII inhibitor treated with cyclophosphamide, vincristine, and prednisone. *Am J Hematol.* 2002;69:294–295.

[51] Tiede A, Hofbauer CJ, Werwitzke S, et al. Anti-factor VIII IgA as a potential marker of poor prognosis in acquired hemophilia A: results from the GTH-AH 01/2010 Study. *Blood.* 2016;127:2289–2297.

[52] Tengborn L, Baudo F, Huth-Kuhne A, et al. Pregnancy-associated acquired haemophilia A: results from the European Acquired Haemophilia (EACH2) registry. *BJOG* 2012;119:1529–1537.

[53] Baudo F, de Cataldo F, Italian Association of Haemophilia Centres. Register of acquired factor Vi. Acquired factor VIII inhibitors in pregnancy: data from the Italian Haemophilia Register relevant to clinical practice. *BJOG* 2003;110:311–314.

[54] Hauser I, Schneider B, Lechner K. Post-partum factor VIII inhibitors. A review of the literature with special reference to the value of steroid and immunosuppressive treatment. *Thromb Haemost*. 1995;73:1–5.

[55] Solymoss S. Postpartum acquired factor VIII inhibitors: results of a survey. *Am J Hematol.* 1998;59:1–4.

[56] Coller BS, Hultin MB, Hoyer LW, et al. Normal pregnancy in a patient with a prior postpartum factor VIII inhibitor: with observations on pathogenesis and prognosis. *Blood.* 1981;58:619–624.

[57] Dedeken L, St-Louis J, Demers C, Meilleur C, Rivard GE. Postpartum acquired haemophilia: a single centre experience with rituximab. *Haemophilia.* 2009;15:1166–1168.

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