REVIEW

Acquired Haemophilia A: A Review of What We Know

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Abstract: Autoantibodies against plasma coagulation factors could be developed by some individuals inducing severe and sometimes fatal bleedings. This clinical entity is called acquired haemophilia. It should be suspected in subjects with acute abnormal bleedings, without personal or familiar history of congenital bleeding disorders with an unexplained prolonged aPTT. It is rare disease, although its incidence may be underestimated due to the low knowledge about it by many specialists, the frequent use of anticoagulant or antiplatelet therapies in the affected population that can mask the diagnosis and, sometimes, a so withering effect that avoid its confirmation. Mortality ranges between 9% and 33% depending on the series in the first 2 months after diagnosis. This mortality is attributed in up to 40% of the cases to infections in the context of immunosuppressive treatments used to eliminate the inhibitor. Factor VIII levels below 1% and high inhibitor titers are conditions of worse response rates. Advanced age, patient's ECOG, and underlying conditions are key prognostic factors for response to treatment and patient survival. To reduce morbidity and mortality in these patients, it is important to have clinical knowledge and access to guidelines to achieve an early diagnosis and to optimize the haemostatic and immunosuppressive treatment. This review aims to contribute to the dissemination of basic concepts on the epidemiology etiopathogenesis, diagnosis, treatment and management of these patients, as well as risk factors to get remission and the longest overall survival to allow individualized care. Especial awareness will be proposed in patients with some underlying conditions like cancer, autoimmune diseases, children, pregnancy or drugs.

Keywords: acquired haemophilia, inhibitors, coagulopathy, autoimmune, bleeding

Key Ideas

- AHA should be suspected in any patient with an unjustified prolonged aPTT and abnormal acute bleeding symptoms, with no personal or family history of coagulopathy.
- Do not exclude AHA as a potential diagnosis in patients anticoagulated or with antiplatelet treatment with abnormal bleeding or a change in their routine bleeding profile and the laboratory suggest it.
- Mortality and morbidity in AHA depend on the patient's age, the underlying pathology, hemoglobin at diagnosis, and response to eradication therapy.
- Immunosuppressive therapy should be started as soon as the diagnosis is made and should be individualized based on the characteristics of the patient.

Introduction

In a subject with abnormal bleeding in amount or location, no personal history of coagulopathy, and an unexplained prolonged activated partial thromboplastin time (aPTT), the presence of acquired haemophilia should always be ruled out.[1] This is an autoimmune organo-specific bleeding disorder secondary to the presence of autoantibodies against plasma coagulation factors. The most common antibodies are those directed against factor VIII (FVIII), that is why when we talk about acquired haemophilia in general, we do reference to acquired haemophilia A (AHA). It is included among the group of rare diseases, although its

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incidence may be underestimated due to the limitations of the available registries, the lack of knowledge about it, the high prevalence of concomitant anticoagulant or antiplatelet treatment given the advanced age of the patients, and, finally, to a clinical presentation so fulminant that it prevents its confirmation in some cases.[2] There are basically two groups of affected subjects, women during postpartum and the largest group consisting of aging people. Mortality ranges between 7% and 38% depending on the series.[3–8] Mortality is mainly related to bleedings during the first days after diagnosis and to infections related to immunosuppressive treatment indicated to eradicate the inhibitor or underlying conditions of patients.[3–8,10] To reduce morbidity and mortality, it is important that the physician responsible for the patient management knows the guidelines to follow to obtain an early diagnosis.

This review focuses on acquired haemophilia secondary to autoantibodies directed against FVIII, AHA. With this work, we intend to expose, updated, the cornerstones of the diagnosis and approach to AHA, based on a comprehensive review carried out on the available bibliography: through MEDLINE/PubMed, all identifiable works have been searched in Spanish and English using the terms "acquired h(a)emophilia", "acquired factor VIII inhibitor(s)", "acquired inhibitors", "autoantibodies"and "haemophilia with inhibitor" ["h(a)emophilia with inhibitor(s)"], until July 2022. The objective is to bring AHA closer to health professionals, especially to non-specialists in hemostasis, since, without clinical suspicion, the diagnosis of this entity is delayed, which poses a risk to the patient.

Epidemiology

The incidence of AHA ranges from 1 to 6 cases per million inhabitants per year.[3,9–11] These data should be treated with caution given the paucity of records and because the diagnosis may be underestimated in the absence of a high rate of clinical suspicion. The average age of onset is 65 years old, but it has a biphasic distribution. A first peak comprises young women starting in the postpartum period or in the presence of autoimmune systemic diseases. The second peak affects patients over 60 years of age with no clear gender differences.[3,7] Some pediatric cases have been reported with an estimated incidence of 0.045 per million per year.[12,13]

Although more than 50% of the cases are idiopathic (Table 1), AHA has been associated with postpartum, drugs and underlying diseases like autoimmune disorders such as rheumatoid arthritis or systemic lupus erythematosus, malignancies and infectious diseases.[14–18] Medications reported to be associated with AHAs include penicillin, sulfonamides, phenytoin, interferons and fludarabine.[14]

In the case of autoimmune diseases, the development of autoantibodies against FVIII occurs mainly in cases of systemic involvement (rheumatoid arthritis, SLE, Sjögren's syndrome, Goodpasture's syndrome, dermatomyositis or graft-versus-host disease in allogeneic liver or hematopoietic progenitors' transplantation).[19–21] Inhibitors in this group of patients, and in particular those associated with rheumatoid arthritis, are high titer ones, traditionally associated with few spontaneous remissions and poor response to steroids.[19,22]

In AHA secondary to neoplasia, there is no predominant oncological entity, although it seems more frequent among solid organ neoplasms.[23] Sometimes it precedes tumor diagnosis in months, so it can be labeled in this context as a paraneoplastic syndrome.[23–32] Sometimes, the detection of an inhibitor takes place after the start of treatment of the specific neoplasm, and it is very difficult to exclude the influence of other factors such as immunosuppressive treatment, chemotherapy and radiotherapy used in its genesis. Another hypothesis to take into account is the non-causal association between neoplasms and AHA, since both are pathologies of advanced age that could coexist.[23,29]

In the context of AHA and pregnancy, AHA generally occurs during the postpartum period, between 1 and 4 months, although cases have been described up to 1 year after delivery.[21,33–35] The most common symptoms are abnormal bleeds during the postpartum period; the rest of the clinical profile is similar to that of other patients with AHA.[34] Exceptionally, these inhibitors have been described during pregnancy, delivery or abortions. In these rare cases, severity is extreme because high risk of severe uterine bleeding and hysterectomy in most cases.[36–39] If we look at the EACH2 data, half of these women classified as postpartum AHA had an aPTT in the upper limit of normal already at the time of delivery, when in these circumstances it should be shortened, so probably AHA could be diagnosed in advance.[35] The etiopathogenesis of AHA in the context of pregnancy is not clear. Its usual presentation in the postpartum period suggests the possibility of an immune response from the mother when she is exposed to FVIII from the child during delivery.[40] Against this theory, there is low relapse rate because of anamnestic response in subsequent deliveries.[41]

Table 1 Underlying Conditions Associated with Acquired Hemophilia A

Idiopathic	**Dermatologic diseases** • Psoriasis • Pemphigus
Postpartum/Abort/Pregnancy	**Pulmonary diseases** • Asma • EPOC
Autoimmune diseases • Systemic lupus erythematosus • Multiple sclerosis • Rheumatoid arthritis • Temporal arteritis • Sjogren's syndrome • Autoimmune hemolytic anemia • Goodpasture syndrome • Myasthenia gravis • Graves disease • Autoimmune hypothyroidism • Inflammatory bowel disease • ITP	**Diabetes**
Drugs Penicillins and derivatives sulfonamides and quinolones, griseofulmin, Phenytoin, Chloramphenicol, methyldopa, Levodopa, alpha interferon, pegylated interferon, Fludarabine, BCG vaccine, Clopidogrel, Antidepressants (Thioxanthines, Flupenthixol, Fluphenazine), hydralazine acetaminophen	**Infectious diseases** HIV, HVB, HVC, SARS-CoV-2
Hematologic diseases • Chronic lymphocytic leukemia • Non-Hodgkin's lymphoma • Multiple myeloma • Waldenstrom's disease • Myelodysplastic síndrome • Myelofibrosis • Erythroleukemia	**Solid tumors** Prostate, Lung, Colon, Pancreas, Stomach, Bile duct, Head Neck, Cervix, Melanoma, Kidney

In a recent review that brings together pregnancy and postpartum AHA cases published up to 2021, in a total of 56 pregnancies, 69% were first pregnancies.[42] Of these women, only 13% had second and subsequent pregnancies, developing a new episode in 22% of them. The median time to CR was 12 months in women treated with steroids and 8 months with combinations of immunosuppressants, relapse rate 29% in the first year and 22% in a subsequent pregnancy. These data together with a mortality of 1.7%, although they define a more benign profile than other AHA, should warn us about the importance of ruling out other associated autoimmune and neoplastic pathologies and being more aggressive in inhibitor elimination treatments if the evolution is not adequate.

Dewarrat et al describe three neonates with incidents:[42] one with intracranial hemorrhage treated with intravenous immunoglobulins (iv Ig) and FVIII, a second one with post-puncture musculocutaneous hemorrhage that did not require haemostatic treatment and a third neonate with a gastrointestinal bleed treated with rFVIIa and FVIII with good evolution.

The etiopathogenesis of drug-associated AHA is not well understood.[14,43] They mostly occur after hypersensitivity reactions and, despite generally high inhibitor titers, they remit after a short period after drug withdrawal with a remission rate close to 80%.

Physiopathology of AHA

The mechanism of loss of tolerance to autologous FVIII that causes AHA remains to be elucidated. Tolerance against self-antigens is the result of the balance of different immunological processes. These include the elimination of autoreactive T lymphocytes during the maturation of the immune system and the anergy or loss of T and B lymphocytes with antigenic specificity. Like many other proteins, FVIII has epitopes that are universally recognized by CD4+ T lymphocytes. This response is modified over time and seems to depend on structural variability and the amount of antigen exposed in each case.[44] Tolerance is related to anergy due to CD4+ apoptosis secondary to continuous stimulation of circulating FVIII[14] (Figure 1). In AHA, the loss of tolerance causes the control of the response to FVIII to be compromised. There are several proposed triggering factors:[45–47]

- Modifications of T regulatory (Treg) lymphocytes, decreasing their response in favor of T helper (Th) lymphocytes. As justification, it has been observed in high inhibitor titer, higher proportion of anti-FVIII antibodies IgG4 (Th2 predominance) versus IgG1 (Th1 predominance).
- Existence of Th lymphocytes with receptors against FVIII related to more intense immune response (receptors Vβ2, Vβ5, Vβ9).
- Incidence of specific polymorphisms of the cytotoxic T lymphocyte antigen (CTLA-4) such as +49 A/G is higher in AHA population and could increase activity and expansion of Th lymphocytes.
- Polymorphisms of the FVIII gene and HLA could induce an abnormal recognition of FVIII. In patients with AHA associated with transfusion and postpartum, polymorphisms of the FVIII gene have been described, a substitution in domain B (D1241E) of FVIII. The combination of this polymorphism with certain profiles of the class II alleles of the HLA system could give rise to the loss of tolerance to FVIII in the subject himself.[48]

In 15% of the healthy population, low titers of anti-FVIII antibodies can be found. These are asymptomatic and have no underlying disease that justifies them.[49] These antibodies are IgG1 and IgG2 and are directed against the C2 domain of FVIII in most cases. The in vitro study of the plasma of these subjects confirms the inhibition capacity of FVIII by these antibodies, although it does not have a haemostatic effect. This is because they produce anti-idiotype antibodies that neutralize circulating autoantibodies against FVIII. This anti-idiotype neutralizing capacity is greater in the plasma of multiparous women and older men. Some authors have identified them in situations of sepsis, related to good prognosis for their recovery. It is theorized about a relationship between antibodies against FVIII and defense capacity against pathogens.[50]
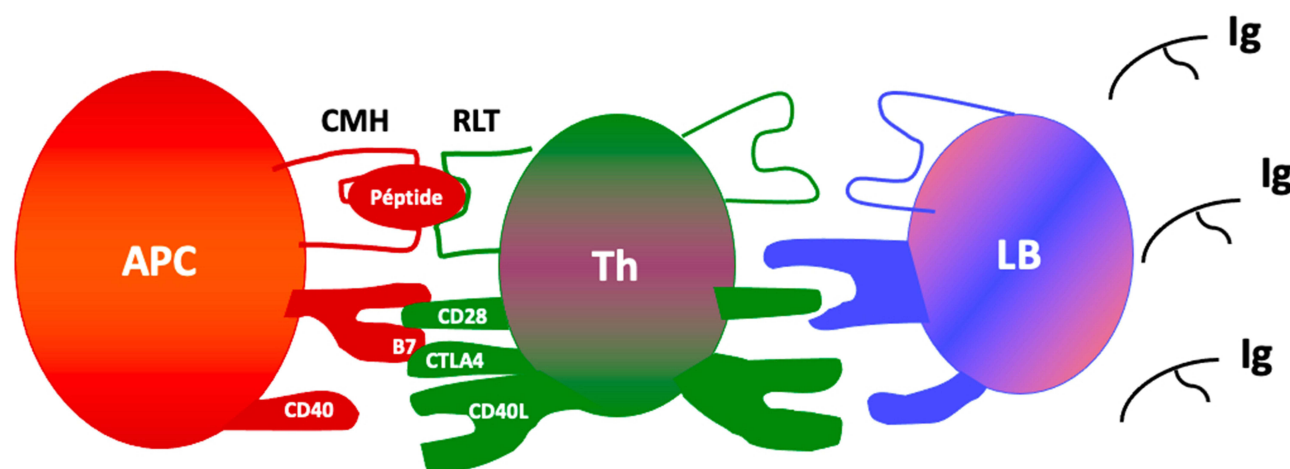

Figure 1 Mechanism of immune response to FVIII. FVIII is processed by the antigen-presenting cell (APC). Its function is to recognize and internalize it, giving rise to an endosome inside, which after merging with a lysosome leads to digestion of FVIII into peptide fragments that can bind to class II molecules of the major histocompatibility system. In case it is not assembled, the class II molecule will be degraded; otherwise, the complex will be transported to the surface of the APC, which presents it to the T cell receptor (TCR). The activation of T lymphocytes requires this union and the signals resulting from the interaction between various molecules such as CD28/B7 (pro-activation) or CTLA4/B7 (anti-activation). After this, there is an expansion of clone responsible for presenting FVIII to B lymphocytes. B lymphocytes (BL) are responsible for the production of specific antibodies (immunoglobulins [Ig]).

Autoantibodies Against FVIII Characteristics

Inhibitory autoantibodies against FVIII are usually polyclonal IgG4 molecules and they have shown specificity against a single epitope of the FVIII molecule.[51] Clonality is a rare phenomenon but with a predominance of kappa light chains[52] and in these cases there is specificity against functional epitopes of more than one domain of the FVIII[53] protein. The identification of autoantibodies of the IgA and IgM isotypes is an epiphenomenon typical of AHA associated with lymphoid neoplasms and paraproteinemias.[54] Approximately, 60% of the inhibitors are directed against the A2 or C2 domain of the FVIII molecule, not against both at the same time. This is a difference compared to inhibitors of congenital haemophilia, in which 85% have specificity against several domains at the same time.[56,57] Inhibitors against A3 and B domain epitopes are sporadic.

FVIII inhibitors neutralize their procoagulant activity through different pathways: inhibiting the procoagulant function of FVIII directly by binding to functional regions of the protein or accelerating its catabolism and clearance.[58] These inhibitors are characterized by being time and temperature dependent in their action. FVIII–autoantiFVIII complexes do not fix complement, so there is no possibility of tissue damage secondary to deposits of immune complexes. Finally, unlike alloantibodies against FVIII, autoantibodies against FVIII are present in most cases with nonlinear inactivation kinetics type II or second order.[53,59–61] In this type of kinetics, FVIII is incomplete neutralized with an initial phase of rapid inactivation followed by a slower equilibrium phase where sometimes small amounts of FVIII can be detected because there is no complete saturation of the inhibitor (Figure 2).

Signs and Symptoms, Laboratory Diagnosis

Patients with AHA present with acute or recent abnormal bleeding symptoms, without a previous bleeding diathesis or family history, and laboratory tests showing an isolated prolonged activated partial thromboplastin time (aPTT).[15] Characteristic bleeding pattern is subcutaneous bleeds (Figure 3) being the most common (observed in 80% of the patients), followed by muscle, gastrointestinal, genitourinary, and retroperitoneal bleeds.[3,5,10,43] A relevant fact, revealed by the Spanish registry,[5] is that up to a third of the patients received anticoagulant or antiplatelet treatment at the time of diagnosis, due to the high age of onset. The use of anticoagulant or antiplatelet drugs could delay diagnosis by confusing bleeds because of AHA with bleeds because of these drugs.

A prolonged aPTT may be due not only to decreased FVIII but also to other causes,[62,63] including deficiency of other factors of the intrinsic pathway, Willebrand disease or the effect of some anticoagulant drugs such as heparin or dabigatran. Therefore, an unexplained aPTT prolongation should be investigated if it is encountered before surgery or
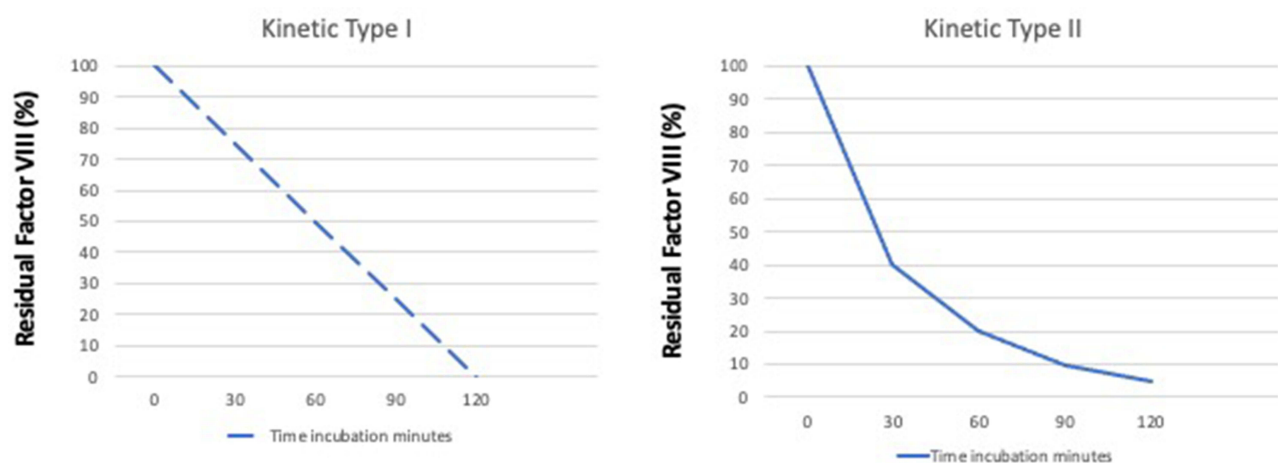

Figure 2 Kinetics of inhibition of FVIII activity by autoantibodies. The inhibition profile of FVIII activity which most often exhibit the autoantibodies characteristic in acquired haemophilia responds to a second order kinetics (triangles), in which a first phase of inhibition resulting from a linear pattern is followed by an equilibrium phase in which the inhibition rate slows markedly, a fact that allows the detection of residual FVIII activity in vitro. However, autoantibodies directed against FVIII rarely interact with this following a first-order kinetics (circles), in which the inhibition profile corresponds to a linear pattern and leads to the complete disappearance of FVIII activity, this being a more typical behavior of anti-FVIII alloantibodies that can occur in congenital haemophilia.
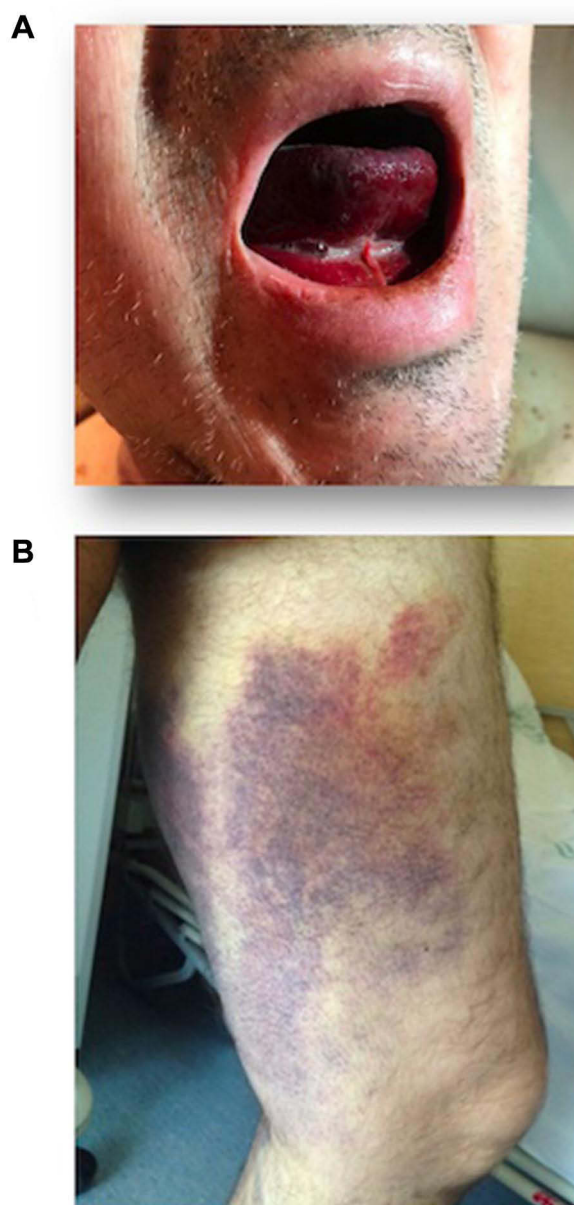
Figure 3 Examples of AHA bleeding profile. (**A**) Lingual and soft palate haematoma in patient with AHA. (**B**) Haemorrhagic infiltration of subcutaneous tissue due to abductor muscle bleeding in a patient with AHA.

in bleeding patients.[14] Measuring FVIII, factor IX or factor XI levels and testing for conditions able to prolong aPTT such as lupus anticoagulant (LA) and factor XII deficiency may be performed.[15]

The aPTT coagulation waveforms generated by coagulation analyzers using optical detection methods provide freely available information that can help in the detection of acquired FVIII inhibitors.[64] The aPTT derivative maxima and minima curve differed significantly between acquired FVIII inhibitors and other diagnostic categories. The presence of an abnormal double-peaked first derivative curve had a sensitivity of 83.3% and specificity of 81.6% for identification of acquired factor VIII inhibitors in cases with aPTT >50 seconds.[64]

To distinguish a factor deficiency from the presence of an inhibitory substance, mixing tests should be performed. FVIII inhibitors from AHA are time- and temperature-dependent, so aPTT results obtained immediately following the 1:1 volume

mixture of normal and patient plasma and after a 2 hours incubation at 37°C should be compared.[65] A significant prolongation of the incubated mixture identifies a circulating inhibitor in the patient plasma. Further investigation is always required, and specific factor activity assays should be performed in parallel to detect the factor neutralized by the inhibitor and allow early diagnosis. An isolated low FVIII level suggests diagnosis of AHA. However, other causes of low FVIII as von Willebrand disease, congenital haemophilia A or acquired von Willebrand syndrome, must be excluded.[66]

Lupus anticoagulant (LA) behaves as a circulating anticoagulant; it can be excluded by a negative diluted Russell viper venom test (DRVVT), which is typically not affected by FVIII inhibitors.[67] On the other hand, interference of LA on FVIII activity can be excluded by using chromogenic substrate assays that are usually insensitive to LA.[68] Alternatively, a normal chromogenic assay FVIII excludes AHA in cases in which LA decreases one-stage FVIII assay results. Fluorescence immunoassay is a technique under development that could be useful to differentiate an inhibitor from a LA.[69] Viscoelastic tests could also be useful for this purpose, since the prolonged clotting time (CT) is clearly greater in the AHA than in the presence of a LA,[70] although the real value could be the verification of shortening CT (ROTEM®) or R (TEG®) with bypass agents treatment.[71] However, it should be noted that AHA and LA are both autoimmune disorders that can co-exist in the same patient.[72]

AHA must also be differentiated from disseminated intravascular coagulation (DIC). Although symptoms could be quite similar, in DIC an haemostatic exhaustion occurs due to the consumption of multiple coagulation factors, not just a specific one, and the prolonged APTT is corrected by mixing the patient's plasma with normal plasma. There is also a decrease in the platelet count and an increase in D-dimer level.[73]

There are several tests for the detection and quantification of inhibiting autoantibodies,[74] but the most used is Bethesda assay.[75] The inhibitor titer is equal to the reciprocal of the plasma dilution that results in 50% inhibition of FVIII in normal plasma after incubation for 2 hours at 37°C.[76] Inhibitor titers are measured in Bethesda units (BU) where 1 BU is equal to the amount of antibody that neutralizes 50% of FVIIIC activity in the normal pooled plasma.[14] It was developed to detect and quantify FVIII alloantibodies in congenital haemophilia A that display linear type 1 kinetics, but it may be also useful in detecting FVIIIC inhibitors in AHA, although these often display a complex non-linear type 2 kinetics (Figure 3) and so the assay may not be able to estimate the true potency of the autoantibody.[16,61] An important consequence is that a lack of correlation between FVIII or inhibitor titer and bleeding phenotype in AHA has been described in many studies.[3,9,10] Sensitivity and specificity of the Bethesda assay is improved by the Nijmegen modification (buffering the normal plasma) and heat inactivation of the patient's plasma at 56°C (to precipitate circulating residual FVIII) prior to assessment of the test.[77,78] The incubation time can also have an effect on the estimation of the inhibitor by facilitating its binding to FVIII.[79] Samples exhibited inhibitory effects within 0.5 hours, with the higher titer sample being more inhibitory; then the curve in their polygram tended to be flat at >1.0 hours, and the inhibitory trends were almost the same for both levels. Altogether, it is feasible to incubate 1.0–2.0 hours for the aPTT mixed test and the Bethesda assay.[79]

Finally, if recombinant porcine FVIII (rpFVIII) is a therapeutic option, then a Bethesda assay specific to rpFVIII should be considered as it may help guide treatment decisions.[15]

Enzyme-linked immunosorbent assays (ELISA) can be used to diagnose FVIII antibodies, but these cannot distinguish neutralizing capacity and are seen to some degree in the normal population.[14]

Thus, diagnosis should be made by a stepwise approach.[14–16] A proposal for a diagnostic algorithm is presented in Figure 4.

General Treatment Recommendations

In AHA, the risk of bleeding is independent of the inhibitor titer and the residual FVIII. Until FVIII levels are at least greater than 50% and inhibitor is undetectable, the risk of bleeding remains.[1,80] Therefore, early diagnosis and the prescription of immunosuppressive treatment to eliminate the inhibitor are key to patient safety, up to day. Delays in diagnosis are associated with a greater consumption of haemostatic agents.[81]

Treatment of acquired haemophilia has four pillars: Prevent bleeding episodes and basic care, treatment of the underlying disease, haemostatic treatment and eradication of the inhibitor. General recommendations could be:[1,10,16,82–84]
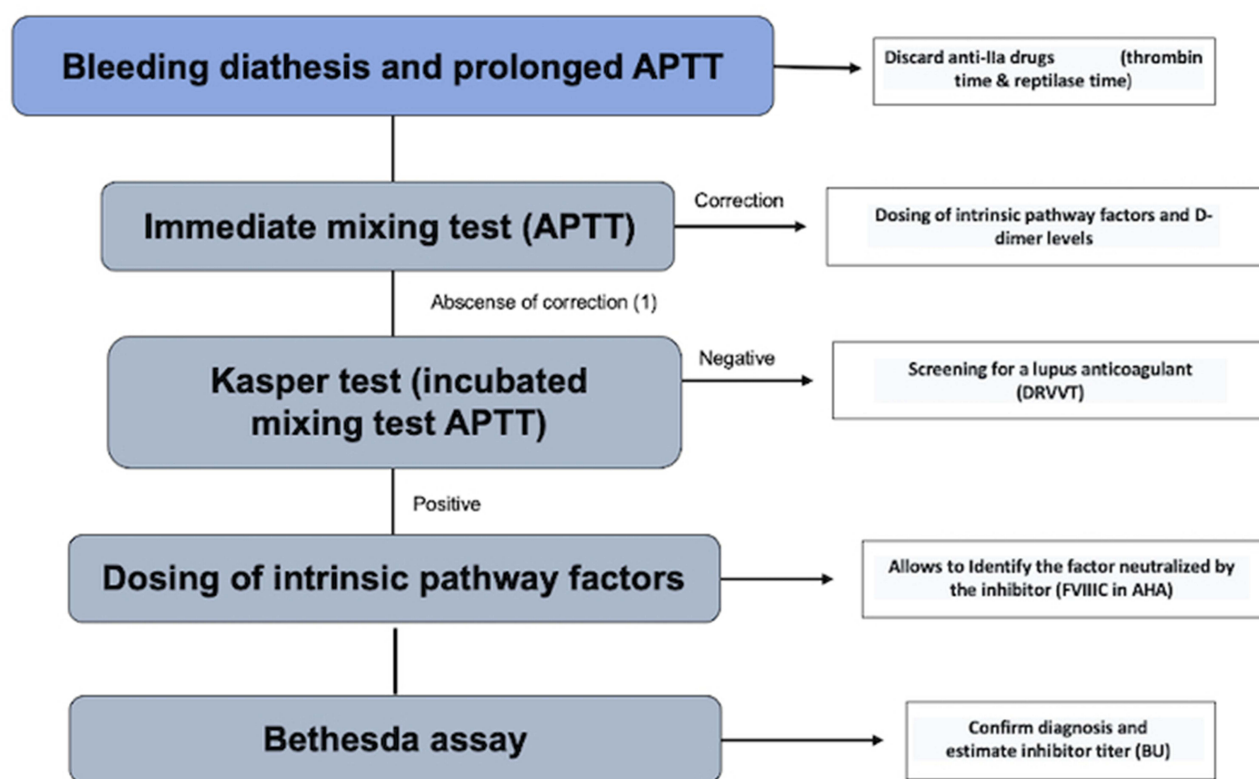
Figure 4 Diagnostic algorithm for a prolonged APTT. Kasper test and Bethesda assay requires incubation 2 hours at 37°C of the mixing samples. (1) No evidence of correction is defined as a test time 8 seconds longer than the control time.
Abbreviations: BU, Bethesda units; DRVVT, dilute Russell viper venom test.

• Given the potential severity of the bleeding and the complexity of the haemostatic and immunosuppressive treatment, whenever the patient's conditions allow it, patient should be referred to an experienced center or at least have their advice until transfer is possible.

• To avoid the use of anticoagulants or antiplatelets. Restart these therapies in the subjects for whom they were indicated when the FVIII is greater than 50% and no bleed.

• Do not perform arterial punctures, intramuscular injections or invasive procedures without appropriate haemostatic treatment and always within the framework of adequate justification.

• In case of major or minor surgery, delay the procedure until the inhibitor is eradicated and if it is not possible to perform the most effective haemostatic coverage, under the supervision of experienced health personnel.

• Patients can have an outpatient follow-up except in the case of uncontrollable bleeding in these circumstances or associated with important comorbidities or environment that compromise their follow-up.

• The patient should be trained in recognizing the warning signs and symptoms that require consultation, with guaranteed access to said consultation 24 hours a day.

Regarding the follow-up of the evolution of the hemorrhagic symptoms, a detailed clinical assessment together with the strict control of the hemoglobin and ferritin levels can be valid parameters in both mild and severe cases. FVIII and aPTT are valuable tools to follow patient evolution every 7 days or less, performing inhibitor quantification every 7 to 15 days according to FVIII evolution.[1,84] Imaging tests such as CT or MRI are very useful for diagnosis, but they are not always available. For this reason, a valid and cost-effective option is ultrasound in the diagnosis and, above all, in the follow-up of hemorrhagic symptoms without the cumulative effect of radiation.[1,84]

We must emphasize that the indication of complementary tests, to exclude associated pathology or make differential diagnoses, must be carefully assessed based on the acute and future clinical situation of the patient. The purpose of this is to avoid blood tests that increase the risk of bleeding or those that, despite facilitating a diagnosis, cannot be

Table 2 Goals of AHA Treatment and Studies Recommended to Rule Out Underlying Conditions in Patients Suffering from AHA

Goals of AHA Treatment	Recommended Studies
• Treat bleeding symptoms considering cardiovascular risk • Treat underlying condition as soon as possible • Individualize immunosuppressive treatment to prevent adverse events	• Cervical and thoraco-abdominal CT • Blood count • Ferric metabolism and maturational factors • Peripheral blood smear • Biochemistry: basic, hepatic, renal and lipid profile • Lactate dehydrogenase (LDH) • Proteinogram • Viral serology (herpes-virus, HIV, hepatotropic viruses) • Thyroid tests • Antinuclear antibodies and anti-DNA. • Rheumatoid factor, RPC

Abbreviations: CT, computed tomography; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; RPC, reactive protein C, TP, trough/peak ratio.

accompanied by the treatment and management indicated for it due to the patient's comorbidities.[1] Table 2 describes some of the studies recommended to rule out underlying conditions, able to be treated.

Finally, it must be taken into account that 75% of the adverse events (bleeding and infections) in these patients occur in the first 100 days of diagnosis and 50% of mortality in the first 2 months of diagnosis.[5,85] For this reason, the follow-up of these patients should be weekly until the elimination of the inhibitor and monthly until 6 months later.[1] From then on, the frequency of evaluations could be between 3 and 6 months depending on patient's necessities.

With regard to AHA and pregnancy, the probability of recurrence is 22%, so follow-up should be at least monthly during pregnancy.[42] Fetus and neonate follow-up should similar to persons with haemophilia during pregnancy and childbirth, since the autoantibody against FVIII is usually an IgG and crosses the placental barrier, increasing the risk of severe hemorrhagic complications in the fetus. This risk will disappear after delivery with progressive decrease in IgG levels transferred from the mother to the child in 1 to 4 months.[36,86–88] The recommendations are to avoid invasive procedures, instrumentalized deliveries and close monitoring with transfontanelle ultrasound in the first 24–48 hours after birth to identify possible intracranial hemorrhages early.[89]

Haemostatic Management

Haemostatic treatment of AHA is based on the use of so-called by-pass agents like recombinant factor VIIa (rFVIIa, eptacog alfa activated, NovoSeven®)[90] and activated prothrombin concentrate complex (aPCC),[91] and on recombinant porcine factor VIII (rpFVIII, susoctocog alfa, Obizur®).[92] Factor VIII concentrates and desmopressin (DDAVP) are not very effective, even at low inhibitor titers (<5 BU),[8,93] so they should only be used if no other option is available.[1–3] In the Chinese registry, FVIII concentrates effectiveness was 34%, compared to 84–100% of bypass agents.[8] In the EACH2, by-pass agents also demonstrated their superiority with haemostatic effectiveness of 93% compared to 71% of the FVIII factors in multivariable analysis adjusted by age, gender, FVIII level, inhibitor titer, hemoglobin level, site, severity and cause of bleeding.[93]

Time to start haemostatic treatment and its intensity will depend on location and severity of bleeding symptoms. If haemostatic treatment is indicated, it should be started early to avoid the progression of a haemorrhagic event and its complications.[1,15,84] In EACH2 registry, the difference between patients who presented, or not, good haemostatic response was the delay in its administration.[93] The selection of the haemostatic drug is based on the experience of the center, availability and previous patient response, if it is known.[1,84,85]

It is recommended to treat in case of uncontrolled bleeding, WHO grade 2 or higher hemorrhage or in case of need for surgery to prevent bleeding[1,15,82,84] (see Table 3). Approximately 70% of the patients with AHA require haemostatic treatment.[5,10,93] Spanish experience described 77.4% of the patients with AHA and anticoagulant or antiplatelet treatment and diagnosis versus 68.5% of the rest, but this difference is not statistically significant.[5] In case of bleed with no indication for haemostatic treatment, close monitoring is necessary because serious and fatal bleeding events could occur

Table 3 Suggested Surgical Prophylaxis in Adults with Acquired haemophilia[94]

Dental Extractions
APCC, 50 to 75 IU/kg/12 h, 2 to 3 doses, starting just before surgery rFVIIa, 90 to 120 µg/kg/2h, 3 to 4 doses, starting just before surgery minor surgery
Minor Surgery
APCC, 50 to 100 IU/kg/8–12 h, without exceeding 200 IU/kg/day. Start just before surgery. Treatment 3–7 days depending on evolution rFVIIa, 90 to 120 µg/kg/2–3 hours for 24 hours. Start just before surgery. Repeat dose every 4 to 6 hours for 3 to 7 days depending on evolution
Major Surgery
APCC, 75 to 100 IU/kg/8–12 hours on days 1 to 6, then every 12 hours on days 7 to 15, not to exceed 200 IU/kg/day. Start just before surgery. Adjust according to evolution rFVIIa, 90 to 120 µg/kg/2 hours for 24 hours, every 2 to 3 hours on day 2, every 4 hours on days 3 to 5, every 6 hours on days 6 to 15. Start just before surgery. Adjust according to evolution

up to 5 months after AHA diagnosis in patients with a persistent inhibitor titer.[15] Despite the lack of correlation between residual plasma FVIII activity or inhibitor titer and bleeding severity described in the majority of series,[3,9,10,80] patients with inhibitor titer >100 BU/mL seemed to require more and more frequently haemostatic treatment than those with levels <10 BU/mL[5].

rFVIIa is one of the most widely used haemostatic drugs in AHA. In a recent review, a total of 12 studies were analyzed in a systematic review, including 671 patients and 1063 bleeding episodes treated with rFVIIa with dosing describing an interval of 2–3 hours between doses, and a median total number of doses of 10–28.[95] In the Spanish registry, rFVIIa was used mainly with a median duration of 7 days (3–13) and number of doses of 15 (5–48).[5] The recommended dose is 90 µg/kg every 2–3 hours until control of the bleeding episode.[15]

In the case of aPCC, the recommended dose is 50–100 U/kg every 8–12 hours, up to a maximum of 200 U/kg/day[1]. In the EACH2 registry, efficacy was similar compared to rFVIIa, with bleeding control rates greater than 90% when used as first-line therapy.[93]

Repeated rVIIa or aPCC infusions could increase risk of thrombotic events. Fortunately, these events seem rare. In EACH2, 2.9% (5/174) and 4.8% (3/63) of patients with AHA who received rVIIa or aPCC, respectively, presented thrombotic events.[93] These data are similar to those of other series; rFVIIa 0–5%, rFVIIa and antifibrinolytics 10%, and FEIBA 0–2.9%.[82] There are 13 cases, 8 arterial and 5 venous, the majority in subjects with vascular risk factors (atrial fibrillation, catheters, neoplasms, autoimmune diseases, arterial disease, etc). No infection by emerging pathogens has been reported in any of the bypass products discussed.

In subjects without an optimal response, we must rule out non-haemostatic causes that justify the bleeding and increase the dose and frequency of the chosen agent. If there is no improvement, switch to the unused bypass agent, and if control is not achieved with the new drug, increase its dose and frequency. In literature, there are published cases of sequential therapy alternating FEIBA and rFVIIa in patients with AHA and uncontrolled vital bleeding, with an effectiveness of 40%.[96–98] The doses used are disparate and the intervals between agents range between 6 and 12 hours, without communication of associated thromboembolic events. In any case, this will always be an exceptional option since it is not included in the summary technical of any of the two bypass agents. It would be indicated by professionals with experience in the management of coagulopathies, under hospitalization.

Recombinant porcine factor VIII, susoctocog alfa, was evaluated in a prospective clinical study that included patients with a major bleeding event, excluding those with an rpFVIII inhibitor titer >20 BU. The initial dose was 200UI/kg and the subsequent ones and the administration interval were variable at the discretion of the investigator, monitoring levels of FVIII in the laboratory. The objective was to maintain an FVIII activity of 80% in severe episodes and 50% in the rest. Effectiveness of rpFVIII was 86% of the patients.[99] Although the approved starting dose for rpFVIII is 200 U/kg, some studies suggest that starting doses of 100 U/kg appear to be sufficient in many patients.[100] It is recommended to know the

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inhibitor titer against rpFVIII prior to rpFVIII indication, but if this is not feasible, a dose can be administered performing a FVIII recovery 30 minutes later to assess the response.[101] If there is an inadequate recovery, it should be considered the use of bypass agents or close monitoring depending on the severity of the bleeding and its evolution.

Regarding rpFVIII safety, in the pivotal trial, no thromboembolic events were communicated by investigators as related to the study drug. Regarding the ability of the autoantibodies to neutralize rpFVIII, in the pivotal study, 10 of the 28 patients had antibodies against rpFVIII at the beginning and 5 developed it during the study (8–85 days). However, only in two patients, the treatment was interrupted due to lack of efficacy. In another serie, the incidence of these antibodies was 44%, the majority low titer.[102,103] When rpFVIII is used, it is recommended to monitor the activity of FVIII, using tests based on aPTT in order to adjust the dosage and identify patients with cross-reacting antibodies.[15] Turkantoz et al have published that 97% of the subjects with AHA and inhibitor titers higher than 100BU and 90% of those with FVIII lower than 3.7% will present cross-reactivity with rpFVIII.[102] In most cases, the inhibitor is directed against C1 domain.

There are guidelines and case series supporting the use of tranexamic acid in combination with rFVIIa or aPCC particularly for mucocutaneous bleeds or as a single agent for minor bleeds.[104,105] However, combined therapy may increase thrombotic risk, and the risks and benefits must be considered individually.[14]

There are no clear recommendations on the definition of bleeding response in AHA. Tiede et al[83] describe by Delphi consensus that the time to achieve an adequate haemostatic response should be between 6 and 24 hours depending on the location and severity. Complete haemostatic response is considered to be the absence of bleeding or rebleeding in the same location 48 hours after discontinuation of haemostatic treatment. Signs of poor evolution of bleeding are persistence or worsening of pain, persistence of anemia or non-stabilization of hemoglobin, need for transfusion, extension of muscular or subcutaneous bleed or persistence of externalization of it.

The concept of prophylaxis in patients with AHA has been published.[106] Zanon et al describe their experience in the use of aPCC at low doses as prophylaxis in subjects with AHA and a high frequency of bleeding, with a 50% reduction in bleeding.[106] The mean number of days in prophylaxis after major bleeding was 12.7 ± 5.7 days, mean units/kg administered was 1246.8 ± 952.1 (30–60IU/kg/2-3 doses per week). Anyway, there is no clear evidence to establish its general indication.

Emicizumab is a recombinant, humanized and bispecific monoclonal antibody with FVIII mimetic activity, recently authorized for the prophylaxis of patients with haemophilia A.[107] It is being used off-label in AHA.[108,109] In a recent publication, 24 patients with AHA treated with emicizumab were collected with a decrease in serious bleeding rate from 58% to 13%. One patient experienced a thrombotic event, and there were two deaths not classified as related with the drug.[110] In another study, 12 patients with AHA were treated with emicizumab, observing a rapid improvement in bleeding symptoms with a median of 3 days (range 2–15 days).[111] However, the safety and efficacy of emicizumab in AHA is unknown, so it only should be used within clinical trials. Emicizumab doses in AHA clinical trials are 6mg/kg on day 1 and 3mg/kg on day 2, then 1.5mg/kg weekly in the American group (NCT05345197)[112] and once weekly in the German group (NCT04188639, dose not described).[112]

Immunosuppressive Treatment to Eradicate Neutralizing Autoantibodies

Immunosuppressive treatment (IST) in AHA is, together with the haemostatic treatment, the cornerstone to achieve the best clinical result. The elimination of the autoantibody should be established as soon as the diagnosis is confirmed.[3,113,114] Complete remission is defined as reaching a normal FVIII level, without evidence of inhibitor or bleeding related to AHA in the absence of immunosuppressive treatment.[1,15,82] The German group has coined the term partial remission (PR), such as reaching VIII levels greater than 50% and no bleeding after discontinuing haemostatic treatment for 24 hours.[15] While there is detected inhibitor, patients are on a risk of bleeding, but the justification of PR definition could be the dramatic reduction of this risk when FVIII is greater than 50% in patients with AHA.[80] In any case, it is important to keep in mind that after inhibitor eradication, FVIII levels are upper normal, with level higher than 100% during the first weeks after response. If this does not happen in a patient, it could be suggested close monitoring to keep from a possible relapse.

The guidelines in IST vary according to national experiences. Immunosuppression with steroids and cyclophosphamide have been the most used protocol.[2–6,113–115] EACH2 with a total of 331 patients, the longest registry,[113] and

other national registries,[4–8] confirm that steroids alone or in combination with cyclophosphamide are the most used scheme, with good clinical results. In EACH2,[113] German group[4] and Spanish group,[5] they also include patients who did not respond adequately with the combination of steroids and cyclophosphamide, and who were treated with rituximab, alone or associated with corticosteroids. Cases treated first-line with rituximab alone or in combination have also been published.[5,82,113] Table 4 describes the effectiveness data of the different schemes used by the longest published registries. These three immunosuppressant drugs are the ones used universally; however, other drugs have been used in published case series like cyclosporine, syrolimus, azathioprine, bortezomid, iv Ig, etc, as second-line IST.[116,117]

Doses of steroids (in prednisone equivalents) start with 1 mg/kg/24h for 3 weeks, followed by gradual decrees. In general, it is accepted that, if there is no response to steroids after 3 weeks, cyclophosphamide or rituximab should be associated, if they have not been used previously. Recommended cyclophosphamide dose is 1–2 mg/kg/24h and rituximab dose is 375 mg/m^2/weekly, for a total of 4 doses.[4,113,115–117] However, there are published experiences with rituximab in AHA at doses of 100mg/m^2/weekly with good results.[118,119]

The results of IST from EACH2[113] show that the association of steroids and cyclophosphamide achieved a CR rate of 77%, steroids in monotherapy 48%, rituximab and other immunosuppressive drug 59% and rituximab in monotherapy scheme dropped to 42%. In addition, to avoid bias derived from the different clinical characteristics of the patients, they perform a statistical analysis using the "propensity score", to control age, gender, factor VIII levels, inhibitor titer and underlying pathologies, concluding that the combination of steroids with cyclophosphamide achieves a significantly higher CR rate (p<0.003).

In the German-Austrian group,[4] the authors note that FVIII < 1%, inhibitor title >20BU, ECOG >2 or IgA antibody titer higher than 1:20 are related to a lower rate of CR, and such patients should be candidates for dual IST with steroids and cyclophosphamide or steroids and rituximab. The results with the different combinations showed CR rate of 80% versus 47% in case of steroids alone. In the steroids group, the mean of days to achieve remission was 32 days, while dual therapy with steroids and cyclophosphamide achieved CR in a median of 40 days. However, patients treated with steroids plus rituximab needed a median of 65 days to achieve remission.

In Dutch serie,[6] there was no difference in effectiveness between steroids plus cyclophosphamide or plus rituximab (80% and 63% respectively), but both schemes of treatment were superior to steroids in monotherapy with an effectiveness of 35%. It took more than 10 weeks to achieve remission. They describe inhibitor titer higher than 20 BU, severe bleeding, and steroid monotherapy as adverse prognostic factors for remission.

Spanish experience[5] confirms the same data on the superiority of combined immunosuppression regimens over steroids in monotherapy (Table 4). It validates inhibitor titers greater than 20 BU and steroid treatment as monotherapy as poor prognosis factor for response. It does not confirm the influence on remission rate of FVIII <1% or age (ECOG or severity of bleeding not included in analysis). Other published prognostic factor for remission could be the specificity of autoantibodies with regard to FVIII epitopes. Those directed against light chain FVIII could be related to poor response.[55,120]

Patients who did not respond to the first-line IST and need a second line present a remission rate of 79% with steroids plus cyclophosphamide, and 65% with rituximab and steroids.[113]

Recently, the international recommendations for AHA diagnosis and treatment have been reviewed.[15] They recommend/suggest in patients with favorable prognostic factors the use of steroids in monotherapy, and in those with unfavorable prognostic factors use as first-line cyclophosphamide or rituximab associated with steroids. In the case of rituximab, they recommend the dose of 375mg/m^2, weekly maximum 4 cycles. High doses of Factor VIII and high-dose immunoglobulins are not recommended. Although in the recommendations,[15] FVIII <1% and an inhibitor titer >20BU are considered poor prognosis factor to get CR, only inhibitor titer >20BU has been validated for the majority of series.[4–7] In contrast, steroid monotherapy is persistently a poor prognostic factor for achieving remission,[5,6,113] and reduction in mortality due to infections in patients treated with steroids alone has been validated by some authors,[4,6,9] but not by others like EACH2,[5,7,113] the longest published registry. Perhaps, the recommendation should be restricted to the use of steroids in monotherapy in patients with inhibitor titer lower than 20BU and no fit, who may have a higher risk of infections and death. Other considerations in special populations are

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Table 4 Outcomes of Immunosuppressive Treatment of Longest AHA Registries.[4–8,113]

	Steroids		Steroids Plus Cyclophosphamide		Rituximab Plus Other Immunosuppressive Drug		Global Data (All Immunosuppressive Schemes)			
	Complete Response Time to Response	Relapse	Complete Response	Relapse	Complete Response	Relapse	Complete Response	Time to Complete Response (Median)	Relapse	Time to Relapse
Collis et al[113]	48%	19%	77%	14%	59%	4%	65%	5 weeks	11%	137 days
Borg et al[7]	–	–	–	–	40%	–	87%	20 weeks	0% (12 months follow-up)	–
Tiede et al[4]	47% 32 days	–	80% 40 days	–	80% 65 days	–	61%	14 weeks (79 days)	–	–
Sun et al[8]	62%	22%	88%	7%	91%	5%	68%	7–10 weeks	9.4% (7 months follow up)	–
Mingot-Castellano et al[5]	68%	27%	89%	3.7%	88%	3.4%	84%	5–7 weeks	7.1% (13 months follow-up)	–
Schep et al[6]	35%	27%	80%	10%	63%	23%	46% with first line	10.7 weeks	25%	102 days

- Neoplasms: Treatment of underlying neoplasm will facilitate the elimination of the inhibitor, although it does not substitute immunosuppressive treatment. In this group, immunosuppressive treatment should be individualized according to age, patient comorbidities and the type and prognosis of the tumor. Napolitano et al have reported response rates of 88% (79% patients treated with steroids and cyclophosphamide, 20% steroids and rituximab).[23]
- Pregnancy/postpartum: Mortality rates are lower, between 1.7% and 3%.[42] Despite this, IST should be started as soon as possible to prevent from severe or vital bleeding always exists. The first line of treatment recommended is steroids.
- AHA secondary to drugs: It may be a useful IST, but taken into account that this AHA usually regresses spontaneously when the drug is dicontinued.[14,43]
- Children: They present a high rate of spontaneous remissions. The recommended first-line treatment is steroids.[15] In neonates as a consequence of the transplacental transference of autoantibodies from mother, symptoms have been solved without IST.[42]

Relapse

In AHA, relapse rate is 7.1% and 20% according to the most recent series.[4–8,10] Collins et al[10] describe a relapse rate of 20% out of a total of 90 patients who eliminated the inhibitor. Median time to relapse was 7.5 months, with a follow-up after remission of 13 months (range 0–37 months). A second remission was achieved in 10 of the relapsed patients. In EACH2, with a median follow-up of 262 days (range 30–603 days), relapse rates after treatment with steroids, steroids plus cyclophosphamide and rituximab-containing regimens were 18%, 12%, and 4%, respectively, with a median time to relapse of 139 days.[113] In Table 4, there are described relapse data from recent series.[4–8,10,113] In postpartum AHA, relapse rates reach 29% with a median time to relapse close to 8 months.[42]

In case of relapse, there are no recommendations on immunosuppressive schemes of treatment. In general, the choice would depend on patient's characteristics at that time and the possible associated causes, the duration of the response and tolerance to previous regimens.[1,15,84]

Mortality and Prognostic Factors
Morbidity

The mortality rate associated with AHA ranges between 7% and 38%.[3,10,116,121] Overall survival in EACH2 registry, with a median follow-up of the series of 262 days (range 30–603 days), were 67% for steroids, 62% for steroids plus cyclophosphamide and 71% for rituximab plus other immunosuppressive agent.[113]

The GTH-AH 01/2010 study found that the main negative prognostic factors for survival in AHA were FVIII levels equal to or less than 1%, a score on the World Health Organization performance status (WHO-PS) functional scale greater than 2, the presence of underlying neoplasia, and not achieving CR.[4] This group, in a post hoc analysis, described that the presence of isotype IgA autoantibodies against FVIII implies a higher rate of recurrences and therefore represents an unfavorable prognostic factor that would increase mortality.

Previous meta-analyses have associated greater overall survival and disease-free survival with achieving CR, no underlying neoplasm, and age at diagnosis under 65 years.[9,121] Patients older than 65 years have a higher mortality, with an odds ratio of 2.4. Regarding the associated pathology, in subjects with AHA and neoplasia, rates of 44% are described, compared to 19% of the idiopathic ones or 4% of those associated with postpartum.[3,121] Other factors related to higher mortality are lack of response to eradication treatment and low hemoglobin levels at diagnosis.[3,9] The Dutch registry[6] described age above 75 years, neoplasms and admission to Intensive Care Unit are poor prognostic factors for survival. Spanish registry found age superior to 65 years as the only poor prognostic factor for survival, non-validated neoplasia as underlying disease, inhibitor titer, FVIII level, get CR, scheme of immunosuppressive treatment or anticoagulant/ antiplatelet secondary prophylaxis before AHA diagnosis.[5]

In AHA, bleeds are usually the cause of early mortality due to delays in diagnosis and, therefore, in the treatment of severe hemorrhages that usually motivate the initial consultation. The iatrogenic nature of immunosuppressive treatment is the protagonist in late mortality.[3,9,121] It should not be forgotten that most of these patients are elderly and suffer from

many comorbidies. This, together with treatment with immunosuppressive drugs such as cyclophosphamide or steroids, turn this population into a "fragile" group in which the benefit of treatment must always be assessed on the basis of the morbidity it could induce. These recommendations are based on clear facts such as the incidence of infections in 30%[6] of these patients, which contributes to 15–47% of mortality linked to AHA.[3,4,9,10] The main causes of death today are infectious conditions in the registries of countries with adequate access to bypass agents[4–7,113] and hemorrhagic events in those that do not have them[8] (Table 5).

In the current registries, there are contradictory data regarding the increased risk of infections with steroid regimens in combination[6,9] or not.[5,113] There are no clear recommendations for the prevention of these infections. In benign hematological pathology, it could be suggested:[122]

- Pneumocystis: TMP/SMX, 80 mg TMP and 400 mg SMX daily or double dose 3 times a week, discontinue when steroids are discontinued. If TMP/SMX intolerance, use dapsone or nebulized pentamidine once a month. These schemes could be useful in patients under prednisone ≥30 mg daily ≥4 weeks; 15 mg to 30 mg daily ≥8 weeks or ≥10 mg daily and 2 or more of the following age >65 years, lung disease, association with another immunosuppressant
- Herpes Virus: In case of a history of previous infections, acyclovir 400mg/day could be used.
- Tuberculosis: If predniso(lo)ne would be used at doses higher than 10mg for more than 4 weeks, a tuberculin test should be performed. In case of positivity, it should be consulted with Infectious Diseases Department.
- Hepatitis B virus (HBV): In patients with positive HBVc Ab and positive HBV Ag, if prednisone were used at higher doses or 20mg for 4 weeks or more; or 10–20mg daily for 8 weeks or more, prophylaxis with entecavir or tenofovir should be performed. If HBVc Ab positive, but antigen negative, close monitoring should be used.

Table 5 Cause of Mortality in Longest AHA Registries.[4–8,113]

Study Dead Patients/Total Patients Percentage of Death	Infections	Bleeds	Underlying Disease	Cardiac or Thrombosis
Collis et al[113] 89/287 31%	12.4%	3.3%	11.2%	–
Borg et al[7] 27/82 33%	37%	11%	–	15%
Tiede et al[4] 34/102 33%	47%	9%	9%	18%
Sun et al[8] 11/165 6.7%	27%	55%	18%	–
Mingot-Castellano et al[5] 36/151 23.8%	41.7%	13.9%	14%	
Schep et al[6] 52/136 38%	19.2%	7.7%	13.5%	9.6%

Other measures to put into practice in case of steroid treatment beyond 4 weeks would be the prevention of osteopenia since up to 30% may present pathological fractures. Prophylaxis treatment should start from first dose of steroids with oral vitamin D at a dose of 800–1000 IU/day and calcium at a dose of 1000–1200 mg/day.[123]

Another morbidity to assess is the high cardiovascular risk of patients with AHA given their advanced age in most cases.[4–8,10,113] Elevation of FVIII levels to levels above normal after the eradication of the inhibitor has been clearly described.[1] Elevated levels of FVIII have been described as a cardiovascular risk factor,[124] which adds to the baseline elevated cardiovascular risk of most patients with AHA given their advanced age and comorbidity in most cases. For this reason, strict monitoring of thromboembolic disease prophylaxis is recommended in cases where it is indicated by the medical-surgical situation of the patient in these circumstances.[1] Other adverse effects are hyperglycemia, psychiatric disorders, or mucosal ulcers secondary to cytotoxic agents.[1,15,84]

Conclusions

In conclusion, acquired haemophilia A is a rare condition but in many cases supposes a hematological emergency, and the hematologist intervention is essential to achieve a rapid diagnosis, and to introduce the treatment as soon as possible. Since most of the publications represent national registries, there are no properly randomized studies that allow conclusions to be drawn with scientific evidence. But the available data provide us the best knowledge of this disease and to prescribe the optimal treatment for acquired haemophilia A. This treatment should be based on bypassing agents of recombinant porcine FVIII and immunosuppressive drugs according to patient comorbidities.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing financial interests for this paper.

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