Acquired hemophilia

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Abstract

Acquired hemophilia (AH) is an autoimmune hemostatic disorder mediated by autoantibodies directed against factor FVIII:C. In 52 % of cases, the cause is unknown or is not associated with other pathological entities; in the rest, there are concomitant factors: lupus, rheumatoid arthritis, cancer, pregnancy, and medications. In Mexico, there is not a registry of AH, and awareness of the disease among health personnel is low. The groups with the highest incidence are women of childbearing age and individuals older than 70 years. It is characterized by severe bleeding, especially after trauma and normal childbirth or cesarean delivery, and large ecchymoses in the trunk and extremities. The suspicion is simple, it just takes for sudden, severe hemorrhage and a prolonged aPTT that is not corrected with plasma to concur in an individual. Treatment involves achieving hemostasis and eradicating the antibody. The former is achieved with recombinant activated factor VII or activated prothrombin complex concentrate. Cyclophosphamide, prednisone or rituximab are used to eradicate the antibody. Most cases of AH are not diagnosed, which translates into a high mortality rate. Given that awareness about the disease among physicians is low, it is not suspected, neither diagnosed, and nor is it treated. This document reviews the most recent data on AH and expands on its diagnosis and treatment.

KEY WORDS: Hemophilia. Acquired hemophilia. Factor VIII. Autoimmunity. Autoantibodies

Hemofilia adquirida

Resumen

La hemofilia adquirida (HA) es un trastorno hemostático autoinmune ocasionado por autoanticuerpos dirigidos contra el factor VIII:C. En 52 % de los casos, la causa se desconoce o no se asocia con otra entidad patológica; en el resto, existen factores concomitantes: lupus, artritis reumatoide, cáncer, embarazo y medicamentos. En México no existe registro ni conciencia de la enfermedad entre el personal de salud. Los grupos de mayor incidencia son las mujeres en edad reproductiva y los individuos mayores de 70 años. Se caracteriza por hemorragia grave, sobre todo posterior a traumatismos y parto o cesárea, y equimosis grandes en tronco y extremidades. La sospecha es simple, basta que concurren hemorragia súbita, grave y un TTPa prolongado que no se corrige con plasma. El tratamiento consiste en lograr la hemostasia y erradicar el anticuerpo; lo primero se logra con el factor VII activado recombinante o concentrado del complejo de protrombínico activado. La ciclofosfamida, prednisona o rituximab sirven para erradicar el anticuerpo. La mayoría de los casos no son diagnosticados y la mortalidad es alta. Ya que los médicos desconocen el problema, no se sospecha, no se diagnostica y no se trata. Este documento revisa los datos más recientes de la HA y abunda en el diagnóstico y tratamiento.

PALABRAS CLAVE: Hemofilia. Hemofilia adquirida. Factor VIII. Autoinmunidad. Autoanticuerpos.

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Introduction

Acquired hemophilia (AH) is a hemostatic disorder resulting from the development of autoantibodies (auto-Abs) mainly directed against factor FVIII:C (FVIII coagulant activity). These antibodies cause hemorrhages with a high risk of morbidity and mortality. In this review, most concepts refer to AH caused by anti-FVIII auto-Abs, although there are cases involving other factors: V, VII, IX, X, XII and XIII.¹

AH is an autoimmune condition. Most usually, it appears as a result of uncontrolled production, with no apparent cause, of IgG-type auto-Abs capable of neutralizing the effect of FVIII; therefore, these auto-Abs are also called “inhibitors”. Unlike congenital hemophilia A, where the inhibitor is an anti-FVIII alloantibody (allo-Ab) induced by the applied factor, in AH, auto-Abs appear without exposure to FVIII² (Table 1).

In 52 % of AH cases there are no concomitant diseases; however, in the rest, it coexists with other pathologies:

- Autoimmune conditions such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, pemphigus, chronic inflammatory bowel disease, asthma or severe allergic reactions.

Figure 1. Human FVIII domains.

- Lymphoproliferative conditions and solid tumors (lymphoma, leukemia, macroglobulinemia, prostate and lung cancer).
- In primiparous women within the first three months of postpartum³ (Figure 1).

Epidemiology

The incidence of AH is very low. The literature is limited to case series, records and single-center experiences. It is estimated at 1.3 to 1.5 cases/million people/year,⁴ which is why it is considered an “orphan” disease, although probably there are many undiagnosed cases.³ In Mexico there is no registry, but we can make inferences based on experience from La Raza National Medical Center of the Mexican Institute of Social Security, whose area of influence is three million population and only 13 cases have been recorded in 30 years (estimated incidence of 0.43 patients/year). However, this is a reference center and underdiagnosis of the disease seems therefore evident. The incidence graph shows a bimodal pattern. The first peak corresponds to fertile women aged between 19 and 40 years; the second occurs in older adults (median age: 73.9 years, range 64 to 78), with a predominance in males (1.4:1)^{4,5} (Figure 2).

Immunological aspects

AH occurs as a result of the production of polyclonal IgG1 and IgG4, with kappa light chains, directed against hot spots of FVIII A1, A2 and C2 domains. Although auto-Abs can be generated against any hemostatic factor, FVIII characteristics make it a preponderant target. It is not clear why tolerance to FVIII is lost, but genetic and environmental factors are argued.² Genetic predisposition (immune response

Table 1. Main differences between acquired and congenital hemophilia

Acquired hemophilia	Congenital hemophilia
Mainly older adults	Usually during childhood
Has no hereditary pattern	X chromosome-linked inheritance pattern
Male:female ratio is 1:1	Most are males
Hemarthrosis is rare	Hemarthrosis is common
Auto-Ab with type 2 kinetics	Allo-Ab with type 1 kinetics
No correlation between FVIII:C concentration and hemorrhage severity	Correlation between FVIII:C concentration and hemorrhage severity
Elevated mortality	No immediate impact on mortality

Taken from Webert KE. Acquired hemophilia A. *Semin Thromb Hemost* 2012;38:735-741.

Figure 2. Distribution of acquired hemophilia cases from the European registry EACH2.³

Figure 3. Acquired hemophilia distribution according to its primary or secondary nature (taken from reference 15).

genes and HLA genotype) is suggested due the association between AH and cytotoxic T-lymphocyte antigen-4 polymorphisms (CTLA-4 + 49 G) and expression of HLA class II DRB1*16 and DQB1*050210 alleles.² There is an abnormal balance of TCD4 + Th1 and Th2 cells, which enables the production of the auto-Ab. The predominance of the IgG subclass induced by CD4-Th2 T-cells is associated with higher concentrations of auto-Ab and a poorer prognosis; when Th1 T-cells predominate, the response to immunosuppressive therapy increases.⁶

AH-associated auto-Abs inhibit FVIII function or increase its clearance, which induces a drop in the hemostatic effect. Figure 3 shows a diagram of this factor's molecule. By reacting against FVIII, auto-Abs inhibit its interaction with activated FIX (a) and with FX (A2-A3 domains). This inhibition alters thrombin and fibrin generation. The C2 domain is where FVIII binds to vWF and phospholipids, so that if this domain is intervened, FVIII stabilization provided by vWF is modified, which shortens the half-life of the latter.⁷

Clinical presentation and diagnoses

AH presentation is characterized by two elements. The first one is clinical, usually in the form of typical extensive ecchymoses, mucosal hemorrhage or even internal hemorrhage in patients without a bleeding history. Almost always, AH occurs abruptly, severely and aggressively in previously healthy patients. Less frequently, there is an underlying or primary pathology

that is exacerbated by hemorrhage or anemic syndrome due to blood loss. The second element is paraclinical, characterized by isolated activated partial thromboplastin time (aPTT) prolongation that is not corrected when mixed with normal plasma. AH is suspected in patients without a hemorrhagic history, with or without apparent bleeding and who, without receiving anticoagulants, have isolated and unexplained prolonged aPTT. The suspicion increases if the patient has any risk factor: autoimmune disease, cancer, age older than 60 years and pregnancy or puerperium. Other hemostatic tests (platelets, prothrombin time, fibrinogen and thrombin time) are usually normal. AH should be ruled out in patients without apparent hemorrhage, but with prolonged aPTT that is not corrected with normal plasma and who are not positive for lupus anticoagulant.⁸

Almost 94 % of patients have hemorrhage, which is associated with a mortality of 9 to 33 %.⁷ The hemorrhage appears upon unrecognizable ("spontaneous") stimuli or is post-traumatic. Severe hemorrhages account for 80 to 90 % of events and the most common sites are the central nervous system, gastrointestinal, prostate, retroperitoneum and lung. Sometimes, bleeding is caused by diagnostic or therapeutic interventions. Death from bleeding usually occurs within the first weeks of evolution; late mortality is associated with the primary disease and immunosuppressive treatment.⁴ Although AH is a rare disease with high risk of morbidity and mortality, clinical experience is limited because most evidence comes from isolated cases.⁹ When AH is associated with a primary pathology, its characteristics impose its clinical hallmark.

At first-contact services (emergency department, obstetrics & gynecology, family medicine, internal medicine and oncology),¹⁰ the disease is not suspected and invasive maneuvers are indicated for

comprehensive care, but since this is a hemostatic problem, they turn out being counterproductive as they increase the risk and intensity of hemorrhage or bring the situation to critical states due to massive or vital organ bleeding. Final diagnosis is usually late (up to 30-day delay).⁸ The responsibility is huge because there should be a high index of suspicion in order to establish an early therapy that improves the prognosis, since acute treatment almost always falls on these specialists, while the stable and definitive resolution phase depends more on the hematologist.

Unlike congenital hemophilia, AH occurs with large, diffuse, painful ecchymoses that can generate anemia. Other manifestations include muscle and gastrointestinal and genitourinary mucous membrane hematomas. Hemorrhage also complicates the situation of the post-operative patient or patients with wounds. There may be retroperitoneal hemorrhage,^{9,11} but joint or intracranial bleeding is less frequent.¹¹ Muscle hemorrhage can lead to large blood loss and, if not properly and promptly treated, it generates vascular or nervous ischemia due to compression.¹² Large hematomas in the legs can be misdiagnosed as deep vein thrombosis;¹² if anti-thrombotic agents are indicated, they will induce massive hemorrhages. Abscess formation is another complication if treatment is delayed. Deep muscle hemorrhage, as in the psoas, is difficult to diagnose and is confused with acute abdomen, indicative of subsequent surgery. Any surgery is complex due to high hemorrhagic risk and can result in death even with dental extractions, biopsies or central catheter placement.

Screening or confirmatory tests can be misinterpreted. Any mild or moderate hereditary coagulopathy can go unnoticed but manifest itself lately as bleeding. This is ruled out by anamnesis and hemostatic tests correction by mixing the patient's plasma with normal plasma. Correction suggests factor deficiency and rules out the presence of inhibitors. Another confounding condition is lupus anticoagulant, auto-Ab associated with prolonged aPTT and a pattern of non-correction with normal plasma. There are differences between the AH auto-Ab, which requires time and temperature to fully manifest itself, and lupus anticoagulant, which requires neither time nor temperature, in addition to being associated with thrombosis.¹³ A highly complicated scenario occurs when both auto-Abs coexist. Although disseminated intravascular coagulation should be considered in differential diagnosis, it is ruled out if coagulation tests show a multiple factor deficiency profile, in addition to data consistent with consumption, such as D-dimer increase and thrombocytopenia.¹⁴

Acquired hemophilia and pregnancy

Symptoms are heterogeneous in terms of presentation and intensity. Hemorrhage is always moderate or severe, and in 50 % there is no triggering factor.¹⁵ Up to 75 % of pregnancy-associated AH occurs in primigravid women.¹⁶ Hemorrhages are almost always subcutaneous, mucosal or retroperitoneal, and hemarthrosis is very rare. Occasionally, bleeding appears up to six weeks after delivery. AH rarely complicates pregnancy; it has a better prognosis because spontaneous remissions occur (maternal auto-Ab can disappear even without treatment) and the mortality rate is lower (up to 6 %).^{17,18} When prenatal monitoring is adequate, diagnosing AH is feasible with aPTT as part of the preoperative workup or if mild bleeding appears, by assessing whether aPTT is prolonged in isolation. Up to one third of patients do not require treatment;¹⁹ however, serious bleeding may occur any time until the inhibitor is eradicated.¹⁷

There are cases of in-utero transfer of the inhibitor to the fetus, although bleeding in the child is rather unusual.¹⁸ When the fetus clears the maternal auto-Ab, the clinical picture disappears if it occurred; there is no chance of this problem coming back. The most effective and least expensive way to monitor the child is with aPTT, which shortens until normalizing in a maximum of six weeks.

Laboratory diagnosis

Testing begins with aPTT, a simple test that is available in almost any hospital, which is quick, standardized and economical. In the emergency department, any prolonged aPTT should always be studied. It is prolonged in relation to the normal control and is not corrected by adding a plasma mixture (also called pooled or control plasma), which suggests the presence of an inhibitor that blocks the flow of enzymatic reactions reflected in the aPTT (Figure 4). Almost always, aPTT is prolonged in isolation and if so, the patient should be rigorously interrogated looking for data consistent with bleeding.

The next step for laboratory diagnosis is to measure functional FVIII:C, which will be below normal range. The third and final step is to quantify the potency of the inhibitor using the Bethesda or Nijmegen-Bethesda tests, which evaluate the inhibitor titer in Bethesda units (BU). Variation of these tests is high, which translates into false positive and negative results. There is an ELISA test for these anti-FVIII auto-Abs, although it also yields false negative results.^{20,21} Other more specific tests are

Figure 4. Approach to the patient with prolonged activated partial thromboplastin time.

Figure 5. Type 1 and 2 inhibitor kinetics.

complex, expensive and poorly accessible in most hospitals.²²

There are several techniques for measuring FVIII:C and its inhibitor: functional and antigenic methods. The former include two classes: coagulometric and chromogenic. The ELISA technique is generally used for antigenic testing. Chromogenic tests have some advantages: they are technically robust, easy to use and the lupus anticoagulant does not interfere. Its disadvantages include its cost and interference of heparin, lipemia, hemolysis and direct oral anticoagulants. This technique usually yields lower FVIII:C results than coagulation testing, which resolves some inconsistencies of the latter. The coagulation testing technique is based on aPTT and has indisputable advantages: it is the most widely used and is automated and therefore it is the most recommendable. It

has drawbacks: it is affected by the quantity and quality of phospholipids used and requires activators. In addition, FVIII:C residual level may not be as accurate (FVIII:C quantification may be 50 to 100 % higher than with chromogenic testing). Any technique to measure inhibitors has variation. Once a method has been chosen, disease surveillance should be carried out with it.

Inhibitors should be assessed using the Bethesda method, which measures FVIII:C residual amount in a mixture of pooled plasma and patient plasma that is serially diluted (1:2, 1:4, 1:8, and so on and so forth), incubated for 2 hours at 37 °C.²³ FVIII increases with dilution. The inhibitor quantification ratio (1.0 BU) is reciprocal to a patient plasma dilution value that allows 50 % inhibition. Thus, 1 BU is the amount of inhibitor that neutralizes 50 % of circulating FVIII:C (2 BU neutralize 75 %, 3 BU 87.5 % and so on and so forth).

The Nijmegen modification is more accurate if inhibitor levels are very low; a buffer is added to the Bethesda test to keep the control plasma at physiological pH for 2-3 hours and allow FVIII stabilization.²¹

Although these tests are useful in congenital hemophilia, the determination of auto-Ab in AH is more difficult because of its type II kinetics (see below). Ideally, the concentration of the auto-Ab bound to FVIII should be measured in order to better evaluate the inhibitor²⁴ by ELISA, agarose gel, immunoprecipitation or with fluorescent microbeads.²⁵ The latter seems better because it is not affected by residual FVIII:C, lupus anticoagulant or heparin.

FVIII inhibitors in AH and congenital hemophilia A are different (Figure 5). Congenital hemophilia allo-Abs are type I inhibitors (first-degree kinetics) that inhibit FVIII in a linear relation to their concentration and fully inhibit the factor at high concentrations. FVIII:C residual activity drops with incubation time, by saturation and in a straight line until FVIII:C is zero. That is, inactivation by allo-Ab is linear and dependent on temperature and time. AH auto-Abs are nonlinear (type II), initially inhibit FVIII rapidly, but then are balanced and residual FVIII activity can be found, even after incubating with maximum inhibitor concentrations for an adequate period. That is, AH inhibitors induce an initial straight drop, such as type I kinetics, but then they acquire a plateau behavior and residual FVIII:C concentration does not drop to zero (Figure 5).¹⁷

Residual activity is not correlated with inhibitor titers or with bleeding tendency. In AH, the level of residual FVIII:C is not interpreted as in congenital hemophilia. A patient with AH and residual FVIII:C of 20 % behaves as congenital hemophiliac with much lower FVIII concentration;¹³ the patient with AH has more severe hemorrhages than a congenital hemophiliac at comparable levels of FVIII:C. Incubating FVIII in excess does not neutralize the type II inhibitor in vitro and high doses of FVIII are inefficacious in AH if the inhibitor titer is too high, which makes treatment difficult.

There are measurement and interpretation errors. For the former, it is important to remember that the inhibitor is a self-Ab that becomes evident by incubating at 37 °C; if this is omitted, the result is mixed up with lupus anticoagulant or with the effect of heparin or other anticoagulants. In interpretation, if the doctor requests other hemostatic factors (FIX, FXI or FX) coagulation activity measurement because aPTT is prolonged, their levels will be low, since the measurement of factors is based on aPTT, which is affected by the FVIII inhibitor; the result is falsely positive, with multiple factor deficiency being wrongly diagnosed. Since it is uncommon for an Ab to target several factors, antigenic or chromogenic functional measurement can be revealing. Another misinterpretation resulting from AH auto-A type II kinetics is to assume that a high level of FVIII:C (15-30 %) protects the patient; this is valid in congenital hemophilia (type I kinetics), but not for AH, where a FVIII:C of 20 % can be associated with severe bleeding.

In our experience, the main factor that delays diagnosis is the lack of knowledge about this pathology due to its low prevalence and because it is not taught

during medical training. First-contact doctors usually have no information about it. Even in hematology residence, AH is not characterized with the dimensions of a diagnostic and therapeutic emergency. In addition, there is a need for laboratories specialized in hemostasis that have good quality control, a profile that often is not met by tertiary care centers either.

Complications and prognosis

Delaying the diagnosis worsens the prognosis. This depends on the course of the disease, which is parallel to hemorrhagic severity and underlying disease. Complete “spontaneous” remissions occur in 25-36 % of cases, especially in those associated with pregnancy and medications.^{19,26} Overall survival is 69 to 78 %, and once remission is reached, it is similar to that of the general population or that of individuals affected by the primary disease. Up to 8 % die soon (median: 19 days post-diagnosis), usually due to uncontrollable bleeding.¹⁹ Death within the first week post-diagnosis is almost always due to gastrointestinal or pulmonary hemorrhage. Intracranial and retroperitoneal hemorrhage is associated with later mortality.²⁷ Death is associated with AH, concomitant disease or with side effects secondary to the management of primary disease. Mortality due to primary disease treatment is similar to or higher than mortality due to hemorrhage.¹⁶ Pregnancy-associated AH is the exception, since survival reaches 13 months in 100 %.¹⁶

The factors associated with poor prognosis for remission and survival are: FVIII:C < 1 IU/dL at diagnosis, a score > 2 on the performance status scale of the World Health Organization, association with neoplasms and not achieving a complete remission. Age older than 65 years at diagnosis decreases survival.^{4,8} The factors of good prognosis include achieving complete remission, having FVIII activity > 1 IU/dL and an inhibitor titer < 16 BU.⁸ In general, AH is potentially curable with immunosuppressants or immunomodulators, which eradicate the auto-Ab.

If remission is achieved, clinical and laboratory monitoring should be frequent due to the risk of recurrence; 20 % relapse within the first two years.^{8,28} Inhibitor and FVIII:C titers are measured weekly while immunosuppressants are indicated. Once remission has been achieved, assessments are monthly for the first six months, every two or three months the following six months and every six months during follow-up for two years.^{1,29} For pregnancy-associated AH, recurrence in subsequent pregnancies is low and the patient should

Table 2. First-line hemostatic agents for acquired hemophilia

Agent	Recommended dose	Comments
Replacement therapy		
rpFVIII	–If there is no anti-rpFVIII inhibitor: 50-100 U/kg every 2 to 3 hours and adjust dose as needed. –If there is anti-rpFVIII inhibitor: 200 U/kg for severe hemorrhage. –50-100 U/kg for moderate hemorrhage. –Adjust dose as needed.	–First-line treatment (if available), especially in most severe cases. –Can be monitored with aPTT. –Replaces the deficient component. –Proven efficacy. –Less effective if there are cross-reacting antibodies. –Potential generation of antibodies –Requires close monitoring. –First line if there are no anti-rpFVIII antibodies, if there is FVIII quantification and hemorrhage puts limb at risk.
Bypassing agents		
Activated prothrombin complex concentrate	–50-100 U/kg every 8 to 12 hours. –200 U/kg/day should not be exceeded.	–Proven efficacy. –No tests for monitoring. –Thrombotic potential. –First line if there is no rpFVIII, if anti-rpFVIII Ab titer is > 10 BU, if there is no FVIII quantification and in non-severe hemorrhage.
Recombinant activated FVII	–70-90 µg every 2 to 3 hours until hemostasis is achieved. –Subsequently, adjust dose as needed.	–Proven efficacy. –No tests for monitoring. –Short half-life. –Thrombotic potential. –First line if there is no rpFVIII, if anti-rpFVIII Ab titer is > 10 BU, if there is no FVIII quantification and in non-severe hemorrhage.

Simultaneously with the treatment, immunosuppressive therapy should be started. FVIII activity should be continuously monitored. There are no studies comparing all these therapeutic alternatives, and thus the choice of the agent is based more on availability, on physician experience and on economic issues. Hemostatic efficacy is based on clinical assessment, and change to another agent should be considered after 12 to 24 hours. Once hemostasis is achieved, the dosing frequency of any treatment should be reduced as much as possible to prevent thrombosis. These treatments should not be indicated if the level of FVIII is increasing, if there is no high risk of bleeding or if there is no active bleeding. It is very important to consider antithrombotic prophylaxis if FVIII level is higher than 50 %. rpFVIII = recombinant porcine factor VIII.

be informed of this possibility. Relapse is managed with the initially instituted treatment.

Treatment

Achieving a favorable outcome in AH depends on expedite diagnosis and selection of the best management. Treatment rests on two pillars:

- Control the hemorrhage if its present or prevent its occurrence.
- Eradicate the inhibitor.¹⁷

Since the patient can die rapidly,²⁶ prompt hemostatic treatment should be indicated depending on the severity and location of the bleeding. Invasive procedures such as evacuation of hematomas should not be performed unless they are absolutely necessary, preferably until the inhibitor has been eradicated,⁸ since there is no reliable test to assess the coagulant response and minimal hemostasis cannot be ensured.¹⁹ Many life-threatening hemorrhages are caused by medical interventions: venous punctures,

insertion of catheters and tubes, biopsy taking and other invasive diagnostic or monitoring procedures such as frequently taking blood pressure.³⁰ We suggest avoiding any invasive procedure that is not strictly necessary. If required without postponement, only if hemostatic treatment is already implemented. This simple action reduces iatrogenic hemorrhages.³¹

The patient should be informed about the appearance of early hemorrhagic symptoms and on trauma prevention and on especially avoiding non-steroidal analgesic medications. It should be emphasized that he/she must seek attention in case of unjustified bleeding.

Between 20 and 30% of patients do not require hemostatic treatment at diagnosis, e.g., extensive ecchymosis. Immediately eradicating the inhibitor should be attempted and, unless there is obvious hemorrhage or hemodynamic decontrol due to hypovolemia, no hemostatic treatment is started immediately. Patients with inhibitors and FVIII:C functional deficiency but without bleeding do not require treatment either.

Patients who must receive immediate hemostatic treatment are those with high hemorrhagic risk or with clinical or paraclinical hemorrhage: muscular, genitourinary, gastrointestinal, retroperitoneal, articular, pulmonary or central nervous system. If the patient undergoes a major or minor invasive procedure, he/she must receive hemostatic treatment before and after it.²⁸

Since the treatment is limited by availability of resources, the considerations hereafter may seem utopian, although it is necessary to know the existing options. Hemostatic treatment intensity is defined by hemorrhagic location and severity.^{1,14} Although the treatment of choice is with bypassing agents and recombinant porcine FVIII, if they are not available and if inhibitor titer is < 5 BU and FVIII:C recovery can be frequently monitored (maintaining it at > 5%), it is enough to provide oxygen, general support and increase FVIII concentration with desmopressin.³² Tranexamic acid is recommended in some mucosal hemorrhage guidelines. If activated prothrombin complex concentrate (aPCC) is used, tranexamic acid should never be indicated within the first 12 hours.¹

Unfortunately, most hemorrhages in AH are severe and even fatal, with anemia being another factor that influences on treatment. As the hemorrhage progresses, more hemostatic therapy and monitoring of its efficacy is required, with clinical improvement and hemoglobin level being assessed.

Severe hemorrhage initial treatment is with bypassing agents. aPCC contains factors II, VII, IX and Xa, which are able to bypass FVIII to generate thrombin³³ (Table 2). The dose is 50 to 100 IU/kg every 8 to 12 hours or even 35 to 80 IU/kg every 8 to 24 hours³⁴ (200 IU/kg/day should never be exceeded); it is useful in 76 to 89 % of cases.³⁴ In patients with chronic and mild bleeding, 50 % of the dose is used prophylactically. Recombinant activated FVII (rFVIIa) allows bypassing hemostasis from the extrinsic pathway, thus avoiding the intrinsic one.^{35,36} Evidence of rFVIIa as first line treatment in AH is large. Ninety to 120 µg/kg are used every two to three hours and the dose is decreased according to the response.^{1,14,8} Its efficacy reaches 100 % (81 to 100 %).^{1,37} Effectiveness and safety are slightly higher with rFVIIa vs. aPCC, but higher with both than with FVIII or desmopressin (93.3 versus 68.3 %, $p = 0.003$).⁵ There are no studies that make either one preferable.^{8,38} It should be borne in mind that the doses for AH are extrapolated from congenital hemophilia with inhibitors, that treatment optimal duration is unknown although it can

Table 3. Risk of thrombosis in patients treated with bypassing agents

Study	Treatment	n	%
Summer ¹	rFVII	139	2.9
Ingerslev ²	Combined or alternate agents	9	55
Baudo ³	rFVII	174	2.9
	aPCC	63	4.8
	FVIII/desmopressin	70	0
Seita ⁴	rFVII	132	2.3
Borg ⁵	rFVII	28	0
	aPCC	6	0
Tiede ⁶	rFVII	63	5
	rFVII/tranexamic acid	21	10

rFVII = recombinant factor VII, aPCC = activated prothrombin complex concentrate.

be maintained until bleeding is controlled, that, empirically, additional doses are recommended to prevent the reappearance of hemorrhage,¹⁴ and that there are no laboratory tests to monitor it (clinical evaluation is the best surveillance tool). Finally, rFVIIa and aPCC can be alternately administered in severe hemorrhages resistant to monotherapy at maximum doses and frequency.^{14,32,38} It is an option in hospitalized patients under the supervision of a doctor with experience in coagulopathies.

Direct adverse effects of bypassing agents are scarce but assessment for severity is justifiable. Thrombosis is the most dreaded complication. A significant number of patients with AH have prothrombotic primary pathologies, and thus it is crucial to adhere to the recommended dosage and stop the treatment at the right moment, as, for example, in elderly patients with high atherothrombotic risk and cancer or postpartum women, i.e., with prothrombotic states. Although thrombogenicity of both aFVIIr and aPCC is low, thrombosis should always be considered^{5,39} (Table 3). Due to the rarity of AH, there is no evidence for indicating thromboprophylaxis or antithrombotic treatment. This is a decision-making problem, since patients often have thrombogenic risk factors for total anticoagulation but are candidates for potent hemostatic treatment for the management of AH. There are only expert recommendations suggesting general thromboprophylactic lines: elastic stockings or intermittent pneumatic compression as long as FVIII:C is < 50 %, since, once this level is reached, the patient can receive thromboprophylaxis or therapeutic

Table 4. First-line options for immunosuppressive therapy

First-line immunosuppression	Recommended dose	Comment
Steroids	–Prednisone 1 mg/kg/day. –Dexamethasone 40 mg/day/4-7 days.*	–Unlikely to be effective before 3 weeks in patients with FVIII < 1 % or with inhibitor titer > 20 BU at diagnosis. –Monitor for adverse events.
Steroids and Cyclophosphamide	–Steroids at similar doses to those above. –Oral cyclophosphamide 1-2 mg/kg/day. –Intravenous cyclophosphamide 5 mg/kg every 3-4 weeks.*	–Quicker responses but higher likelihood of adverse events. –Higher likelihood of complete responses. –Monitor for myelosuppression.
Steroids and rituximab	–Steroids at similar doses to those above. –Intravenous rituximab 375 mg/m ² /week for 4 weeks. –Rituximab 100 mg/week for 4 weeks.*	–Rituximab is not recommended as initial monotherapy unless the other therapies are contraindicated.

Average time to response (FVIII > 50 %) is 5 weeks. Patients with FVIII < 1 % at diagnosis require significantly longer periods to achieve remission in comparison with patients with > 1 % FVIII activity and maybe rather require combined therapy. FVIII activity, as well as that of inhibitors, should be monitored at least once a week according to clinical evolution. The therapy is individualized according to patient clinical status, primary disease, concomitant conditions and prognostic factors (FVIII < 1 %, inhibitor > 20 BU, presence of anti-rpFVIII antibodies, etc.), if available. *Poor evidence in acquired hemophilia, but with published data in other autoimmune pathologies.

anticoagulation.^{5,36} Obviously, treatment should always be customized.

Laboratory monitoring of AH is difficult and therefore clinical response is the most applicable strategy.⁴⁰ In the patient with hemophilia A and inhibitors, calculating FVIII effect is hypothetically possible because inhibitors are type I. In AH, inhibitors are type II, which hinders laboratory surveillance evaluation. The problem is more evident in patients with high inhibitor titers (> 16 BU) and, therefore, the most effective alternative is to frequently monitor clinical status and quantify FVIII and aPTT.

The next therapeutic step is to seek the cure by eradicating the inhibitor with immunosuppressant agents. The patient achieves complete remission if inhibitor titers are < 0.6 BU and FVIII:C is > 50 %.⁸ Relapse is defined when, upon immunosuppressant discontinuation, the inhibitor reappears at increasing titers associated with a progressive decrease in FVIII:C.⁵ Stable remission is the persistence of complete remission after therapy is discontinued.

It should be mentioned that the ideal option is not known. The most commonly used first-line treatment is steroid administration (1 mg/kg/day), alone or associated with low-dose cyclophosphamide (1 to 2 mg/kg/day), for three to five weeks¹ (Table 4). Evidence is based on small, retrospective series. Only two small prospective studies showed almost 60 % of responses with the combination, which was better than with steroids alone (42 %).⁴¹ Other registries show a non-significant advantage of the combination over steroid monotherapy (80 versus 70 %).¹ Apparently, there is no significant difference for overall and disease-free survival between both treatments.²⁸ Immunosuppression, together with patient comorbidities

(age, multiple pathologies, current imbalance), entails the risk of cytopenia and secondary infections (33 to 53 %),²⁸ between 11 and 12 % of AH-associated mortality is attributed to these complications.⁸ In pregnancy-associated AH, cyclophosphamide may have a leukemogenic effect and perhaps an effect on fertility.²⁸ The second-line treatment of choice is rituximab (Table 4), if first-line therapy fails.^{1,14,28} Its effect is believed to be due to a decrease in anti-FVIII auto-Abs. It is started at 375 mg/m²/week for four weeks,⁸ with weeks or months of treatment being required. Eradication is achieved in 78.6 % of patients, regardless of the previous use or not of another immunosuppressant.⁴² It is a good alternative if inhibitor titer is > 200 BU,⁴³ however, evidence is scarce and, therefore, combined treatment should be started in these cases.⁴⁴

In general, the eradication rate is 60 %, ³⁶ and it is higher in patients treated with rituximab and other immunosuppressants versus monotherapy, although, in some series, rituximab was no better than steroids (77 versus 61 %) and time to remission was longer (median: 32 versus 64 days). The relapse rate with rituximab appears to be lower than with steroids plus cyclophosphamide or steroids alone (4, 14 and 19 %, respectively). There is positive evidence for rituximab at a dose of 100 mg/m².⁴⁵ In pregnancy-associated AH, rituximab appears to be efficacious, although the cases involved correspond to treatments after failure to steroids and high inhibitor titers.⁴⁶

There is no evidence that any immunosuppressant is superior or for choosing any based on hemorrhagic status or inhibitor titer. First-line therapy depends on assessment of the underlying disease and probable adverse events.³² Infections are not negligible and can

lead to death⁴⁷ and, as in any patient with prolonged immunosuppression, close immunological surveillance is necessary. In addition to immunosuppressants, azathioprine, cyclosporine, cyclophosphamide, mycophenolate, 6-mercaptopurine, tacrolimus, cladribine, azathioprine and vincristine are also used. Prednisone is used as monotherapy or combined with cyclophosphamide with important responses.^{28,32,41} High doses of intravenous Ig are also used.⁴ Combined chemotherapy treatment (cyclophosphamide, vincristine and prednisone) is indicated if the other options have failed. In AH associated with systemic lupus erythematosus, cyclosporine at a dose of 10-15 mg/kg/day seems useful.⁴⁸

There are two treatments that are not globally accepted or widely available: immunoabsorption and immune tolerance. In the former, patient plasma is passed through a sepharose column with adhered staphylococcus A protein, capable of eliminating auto-Abs; it is generally used in very acute and severe cases,⁴⁹ it is an expensive, complicated, scantily available treatment and whether eradication is sustained is not known. Immune tolerance, which is useful in congenital hemophilia, is expensive, its availability is limited and it does not ensure inhibitor sustained eradication either. FVIII chronic and high-dose administration induces immune regulation and increased auto-Ab-producing clone sensitivity to the immunosuppressant, thus modulating the generation of auto-Abs.⁶ Maybe it is only applicable in relapsing AH and its widespread use is unlikely.^{14,27}

Conclusions

The main problem with AH is delayed diagnosis due to lack of knowledge about the disease. Mid- and long-term educational strategies are imperative in order to raise awareness on this potentially curable entity in doctors so that they can include it in their diagnoses. It is not difficult to suspect AH; basic hemostatic tests and interpretation of clinical signs and symptoms in at-risk populations is sufficient. The next challenge is hematological laboratories at second and tertiary care levels, which should be made aware on their diagnostic role and the need to refine their processes to improve the quality of their tests. Another problem is the lack of a national hemophilia registry. We have advanced, although insufficiently, in congenital hemophilia (underreporting is 18 %); for AH, we only have the experience of large reference centers. We almost completely ignore AH epidemiology in Mexico; we

need data that provide feedback to the health system in order to develop really effective therapeutic policies and guidelines. As for treatment, patient fragility is a challenge, since he/she is sensitive to secondary immunosuppression and infection, which are factors that can cause death by sepsis. Since individuals with AH have several comorbidities (some require antithrombotic treatment), and are prescribed medications that generate thrombin (bypassing agents, high doses of FVIII, DDAVP and antifibrinolytic agents), some patients will require antithrombotic prophylaxis.

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