International recommendations on the diagnosis and treatment of patients with acquired hemophilia A

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ABSTRACT

Acquired hemophilia A (AHA) is a rare bleeding disorder characterized by autoantibodies directed against circulating coagulation factor (F) VIII. Typically, patients with no prior history of a bleeding disorder present with spontaneous bleeding and an isolated prolonged aPTT. AHA may, however, present without any bleeding symptoms, therefore an isolated prolonged aPTT should always be investigated further irrespective of the clinical findings. Control of acute bleeding is the first priority, and we recommend first-line therapy with bypassing agents such as recombinant activated FVII or activated prothrombin complex concentrate. Once the diagnosis has been achieved, immediate autoantibody eradication to reduce subsequent bleeding risk should be performed. We recommend initial treatment with corticosteroids or combination therapy with corticosteroids and cyclophosphamide and suggest second-line therapy with rituximab if first-line therapy fails or is contraindicated. In contrast to congenital hemophilia, no comparative studies exist to support treatment recommendations for patients with AHA, therefore treatment guidance must rely on the expertise and clinical experience of specialists in the field. The aim of this document is to provide a set of international practice guidelines based on our collective clinical experience in treating patients with AHA and contribute to improved care for this patient group.

Key words: acquired hemophilia, bleeding, inhibitors, treatment, recommendations.

Citation: Huth-Kühne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Lévesque H, Mingot Castellano ME, Shima M, and St-Louis J. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica 2009; 94:566-575. doi:10.3324/haematol.2008.001743

Introduction

Acquired hemophilia A (AHA) is a rare bleeding disorder with an incidence of approximately 1.5 cases/million/year[1] and is characterized by autoantibodies directed against circulating coagulation factor (F) VIII. These autoantibodies constitute the most common spontaneous inhibitor to any coagulation factor and may induce spontaneous bleeding in patients with no previous history of a bleeding disorder. An underlying medical condition can be identified in up to 50% of patients, including autoimmune diseases, solid tumors, lymphoproliferative malignancies and pregnancy.[1-4] Due to the variable bleeding phenotype of this disorder, the clinical picture ranges from life-threatening and traumatic bleeds to mild or no bleeding tendency. Patients with AHA are often elderly; co-morbidities and co-medications such as anti-platelet agents may also influence the clinical profile and require an individualized therapeutic approach.[5,6] There are few clinical parameters that can be used to guide patient management because the bleeding phenotype rarely correlates with laboratory assessments.[1] In contrast to congenital hemophilia, no high-level evidence exists to support treatment recommendations for patients with AHA. Data generated in congenital hemophilia patients with or without inhibitors may occasionally be used to support treatment decisions in patients with acquired hemophilia, however treatment recommendations must generally rely on the expertise and clinical experience of physicians who have treated patients with this disorder. Although a number of comprehensive reviews on AHA have been published in recent

Funding: support for literature searches, meeting organization and medical writing support for manuscript preparation were provided by Physicians World GmbH, Mannheim, Germany. Costs incurred for travel, hotel accommodation, meeting facilities, honoraria, remote communication and manuscript preparation were supported by unrestricted educational grants from Novo Nordisk Health Care AG, Zurich, Switzerland. The opinions expressed in this manuscript are those of the authors alone. Representatives of Novo Nordisk were present at meetings where the guidelines were discussed, but did not contribute to writing the manuscript or exert editorial control over the content of the manuscript and did not review the manuscript prior to submission. Manuscript received October 9, 2008. Revised version arrived November 26, 2008. Manuscript accepted December 16, 2008. *Correspondence: Angela Huth-Kühne, SRH Kurpfalzkrankenhaus and Hemophilia Center Heidelberg gGmbH Bonhoefferstrasse 5, 69123 Heidelberg. E-mail: angela.huth-kuehne@kkh.srh.de*
The online version of this article contains a supplementary appendix.

years, an international consensus for clinical practice is lacking. In developing these recommendations, our aim was to compile a set of practice guidelines based on our collective clinical experience in treating a large number of patients with AHA. This document is intended for the specialist with experience in the diagnosis and treatment of patients with bleeding disorders.

Methods

Comprehensive literature searches were performed using the indexed online database MEDLINE/PubMed and the terms *Acquired h(a)emophilia, Acquired factor VIII inhibitors, Acquired inhibitors, h(a)emophilia with inhibitor*s. The scientific questions addressed in the literature survey are available in the *Online Supplementary Appendix*. Recommendations were formulated according to the method of Guyatt *et al.*,[7] where "we recommend" represents a strong (Grade 1) recommendation and "we suggest" a weak (Grade 2) recommendation. Table 1 lists our recommendations in the order in which they will be discussed in the Results section. Because virtually no high or even medium-level evidence exists to support treatment recommendations in patients with acquired hemophilia, the literature cited was not graded according to the level of evidence. A parallel manuscript for non-specialist physicians was also developed (Collins *et al.* in preparation). The author group comprises an international medical collaboration with an interest and expertise in the management of acquired hemophilia. The need for increased awareness of the disorder and practice-based guidelines was initially suggested by one member of the author group (CMK), and members invited to join the group based on country of origin and recognized expertise in the field by the chair (HL), who presided over its deliberation. The stated aims were to improve awareness, diagnostic criteria and treatment of acquired hemophilia among health care professionals to whom acquired hemophilia patients may initially be referred, but who are not necessarily familiar with the treatment modalities available for this disorder. The group was managed by Physicians World GmbH, Mannheim, Germany, and its activities were supported by unrestricted educational grants from Novo Nordisk Health Care AG, Zurich, Switzerland.

All statements that refer to rFVIIa are based on data for NovoSeven®, (Novo Nordisk A/S, Bagsvaerd, Denmark). All statements that refer to aPCCs are based on data for FEIBA VH Anti-Inhibitor Coagulant Complex (Baxter AG, Vienna, Austria). The safety and efficacy of any rFVIIa or aPCC products available in the future will need to be established in patients with AHA before the recommendations made here can be generally applied.

Results and Discussion

Diagnosis

Patients with autoantibodies to coagulation FVIII may present initially to physicians in a variety of specialties, who may not have experience with this rare disorder. Any acute or recent onset of bleeding symptoms in a patient with no previous history of bleeding, especially in elderly or post-partum patients, and an unexplained isolated prolonged activated partial thromboplastin time (aPTT) suggest the diagnosis of AHA, and prompt further investigation is indicated. Not all patients with AHA present with a significant prolongation of the aPTT or ongoing bleeding, and a close collaboration between clinicians and laboratory staff and a hemophilia center experienced in the management of inhibitors is important.[8-9]

We recommend that the diagnosis of AHA be considered whenever an acute or recent onset of bleeding is accompanied by an unexplained prolonged aPTT.

Table 1. International consensus recommendations on the diagnosis and treatment of patients with acquired hemophilia A.

Diagnosis
We recommend that the diagnosis of AHA be considered whenever an acute or recent onset of bleeding symptoms is accompanied by an unexplained prolonged aPTT.
Anti-hemorrhagic treatment
We recommend that anti-hemorrhagic treatment be initiated in patients with AHA and active severe bleeding symptoms irrespective of inhibitor titer and residual FVIII activity.
We recommend the use of rFVIIa or aPCCs for the treatment of severe bleeding in patients with AHA.
We suggest bolus injection of rFVIIa 90 μg/kg every 2-3 h until hemostasis is achieved.
We suggest a bolus injection of aPCCs between 50-100 IU/kg every 8-12 h to a maximum of 200 IU/kg/day.
We suggest the use of recombinant or plasma-derived human FVIII concentrates or desmopressin only if bypassing therapy is unavailable.
We suggest that alternative treatment strategies be considered after failure of appropriate first-line treatment.
We recommend the prophylactic use of bypassing agents prior to minor or major invasive procedures.
Inhibitor eradication
We recommend that all patients diagnosed with AHA receive immunosuppressive therapy immediately following diagnosis.
We recommend that all AHA patients be treated initially with corticosteroids alone or in combination with cyclophosphamide to eradicate autoantibodies.
We suggest corticosteroid therapy for inhibitor eradication at a dose of 1 mg/kg/day PO for 4-6 weeks, either alone, or in combination with cyclophosphamide at a dose of 1.5-2 mg/kg/day for a maximum of six weeks.
We suggest second-line therapy with rituximab if first-line immunosuppressive therapy fails or is contraindicated.
We suggest the application of immunotolerance regimens with immunoabsorption in AHA patients only in the case of life-threatening bleeds or in the context of clinical research studies.
We do not recommend use of high-dose intravenous immunoglobulin for inhibitor eradication in patients with AHA.
We recommend follow-up after a complete sustained response using aPTT and monitoring of FVIII:C monthly during the first six months, every 2-3 months up to 12 months and every six months during the second year and beyond, if possible.
We recommend thromboprophylaxis according to ACCP guidelines following inhibitor eradication and sustained response in former AHA patients, especially those with very elevated FVIII:C levels.

Mixing tests

A prolonged aPTT may be attributable to coagulation factor deficiencies, lupus anticoagulant or heparin therapy. So-called mixing tests are customarily performed to distinguish between factor deficiency and the presence of an inhibitory substance. FVIII inhibitors are time and temperature-dependent, therefore mixing studies performed immediately and after 2 h of incubation should be compared. Prolongation of the aPTT in a mixture of patient and normal plasma after a 1-2 h incubation compared to an immediate mix is typical of FVIII autoantibodies.[10] Immediate correction of the aPTT with normal plasma does not exclude AHA, however, and if the clinical presentation is suggestive, these patients should be investigated for an FVIII inhibitor as well as for other potential causes of hemorrhagic symptoms. Irrespective of the result of mixing tests, further investigation is required, and specific factor assays should be performed in parallel to facilitate an early diagnosis.

Clotting factor measurement

Patients with a prolonged aPTT and a clinical picture suggestive of AHA should have FVIII, IX, XI and XII levels measured. An isolated low FVIII level is suggestive of AHA. In some cases, all intrinsic factors are decreased, which may represent an *in vitro* artefact due to depletion of FVIII in the substrate plasma by the inhibitor.[11] A lupus anticoagulant can also cause artefactual lowering of factor levels due to inhibition of phospholipid in the assay, and specific tests for a lupus anticoagulant should be performed. In addition, factor assays should be repeated at higher serial dilutions of the test plasma, which will attenuate the effect of the inhibitor or lupus anticoagulant on the factor measurement.

Quantification of the inhibitor titer

The Bethesda assay was developed to quantify FVIII alloantibodies, which display linear type 1 kinetics. Acquired inhibitors to FVIII display complex and non-linear type 2 kinetics, therefore the Bethesda assay may not be able to estimate the true potency of the autoantibody,[12-14] and the titer corresponding to the dilution that is closest to 50% inhibition should be reported. Occasionally, in the presence of low FVIII activity, an inhibitor that is not initially apparent may become detectable only after several days, therefore re-screening may be necessary to confirm an inhibitor. The inhibitor titer to porcine FVIII should be quantified if this treatment option is available; usually the inhibitor titer to porcine FVIII is lower than that to human FVIII.[3]

Lupus anticoagulant

A lupus anticoagulant may also be associated with a prolonged aPTT that does not correct with normal plasma, low intrinsic factor levels and a positive Bethesda assay.[15] Lupus anticoagulants are not time-dependent, and specific tests for a lupus anticoagulant should be undertaken to establish a differential diagnosis.[16] Autoantibodies to FVIII and a lupus anticoagulant may be present in the same sample, and in complex cases, a FVIII antibody ELISA may be useful to distinguish between a lupus anticoagulant and an acquired FVIII inhibitor.[17,18] An aPTT reagent insensitive to lupus anticoagulant activity may be useful in patients with detectable lupus anticoagulant activity or low FIX, FXI and/or FXII levels.

Anti-hemorrhagic treatment

The incidence of fatal bleeding in acquired hemophilia patients is high, ranging between 22%[2] and 31%[19] in older reports when therapeutic options for acute bleeding were limited, and 9% (13/143) in a more recent study.[1] Death within the first week was caused by gastrointestinal and lung bleeding, and later deaths were predominantly due to intracranial and retroperitoneal hemorrhages. Fatal bleeding can occur up to five months after the first presentation, if the autoantibody is not eliminated, and morbidity related to bleeding remains high.[1,19]

General anti-hemorrhagic treatment strategy

Although not all patients with acquired hemophilia bleed and not all types of bleeding require intervention, control of acute bleeding in AHA is generally the immediate priority.[1,19] In view of the potential side effects of hemostatic agents, particularly in elderly patients with comorbidities, the risks, benefits and costs of treatment must be weighed carefully and on an individual basis. Not all possible situations can be foreseen, but in general, retroperitoneal or retropharyngeal hematomas, muscle bleeds with or without compartment syndromes, intracranial hemorrhage, gastrointestinal, pulmonary or postoperative bleeding, severe hematuria and bleeding from multiple sites require anti-hemorrhagic treatment. Ecchymosis and subcutaneous hematomas, even if extensive, may require only close observation but no specific treatment. In addition to clinical assessment, frequent monitoring of the hemoglobin (Hb) or hematocrit (Hct) is often a more reliable indicator of significant bleeding than radiological imaging.

We recommend that anti-hemorrhagic treatment be initiated in patients with AHA and active severe bleeding symptoms irrespective of inhibitor titer and residual FVIII activity.

The lack of correlation between inhibitor titer and bleeding phenotype in AHA has recently been recognized, but remains poorly understood.[1,20,21] The inhibitor titer should therefore not influence the decision to initiate treatment for significant bleeding or guide the choice of therapy. Table 2 presents a summary of the main therapeutic options for the treatment of acute bleeding episodes in AHA.

We recommend the use of rFVIIa or aPCCs for the treatment of severe bleeding in patients with AHA.

We suggest bolus injection of rFVIIa 90 mcg/kg every 2-3 h until hemostasis is achieved.

We suggest a bolus injection of aPCCs between 50-100 IU/kg every 8-12 h to a maximum of 200 IU/kg/day.

FVIII inhibitor bypassing agents

First-line treatment to achieve an efficient hemostasis in patients with AHA includes recombinant activated FVII (rFVIIa) and activated prothrombin complex concentrates (aPCCs). Neither of these agents is effective in all patients, and no high-level evidence exists for the use of one product in preference to the other, though each has potential advantages and disadvantages that may be relevant in spe-

Table 2. Anti-hemorrhagic treatment strategies in acquired hemophilia A.

First-line treatment
rFVIIa
aPCC
Alternative treatment – if bypassing therapy unavailable
Human FVIII
DDAVP
Alternative treatment – currently unavailable
Porcine FVIII
Alternative treatment – if first-line treatment fails
Immunoadsorption and/or plasmapheresis

cific clinical situations. A recombinant agent may be more appropriate in post-partum women, for example. The dosage of these agents is based largely on experience in congenital hemophilia and product prescribing information provided by the manufacturers.[22,23] No data on the duration of treatment are available. We suggest that therapy be continued until bleeding is controlled. Depending on the site, type and severity of the bleeding, 24-72 h may be appropriate, although this may not be necessary in all cases. Further treatment after hemostasis has been achieved may be appropriate to prevent re-bleeding in some situations. There are no validated laboratory tests available with which to determine whether a therapeutic level has been achieved,[24,25] therefore management must generally rely on the clinical assessment.

Recombinant activated FVII (rFVIIa)

The efficacy of rFVIIa has been demonstrated in congenital hemophilia patients with inhibitor,[26-30] but its use is less well documented in AHA. Effective hemostasis is reported in an overview of compassionate-use programs that includes the Hemophilia and Thrombosis Research Society Registry and a few published reports.[27] Treatment was administered for spontaneous bleeds in the majority of the cases, and regimens included bolus injection (46-150 mcg/kg every 2-24 h) or continuous infusions (8-50 mg^3/kg/h). Overall, the response to treatment was rated effective or partially effective in 90% (111/124) of non-surgical bleeding [102/115 (89%) spontaneous; 9/9 (100%) traumatic] and 86% (49/57) of surgical cases.[31] Two earlier studies reported rFVIIa efficacy as first-line or as salvage therapy. An effective response was observed in 100% of the episodes in which rFVIIa was used as first-line therapy; effective or a partial response was observed in 75% and 17% of the episodes when used as salvage therapy respectively.[32] In a prospective study that included 14 patients (20 bleeding episodes) who received rFVIIa as first-line therapy and one patient after failure of desmopressin and porcine FVIII, treatment was very effective or effective in 13/15 patients (86.6%) and in 18/20 bleeding episodes (90.0%) within 24 hours with no difference between intermittent and continuous infusion.[33]

The rarity of thromboembolic complications in congenital hemophilia patients with inhibitors cannot be readily transferred to the generally older AHA population, in which risks such as smoking, hypertension, previous cardiovascular events, type 2 diabetes and high body mass index are frequently present. An overview of acquired hemophilia[31] reported a relatively high incidence of 10, predominantly arterial, thrombotic events in 139 patients (7.2%) treated with rFVIIa. A recent review reported 30 thromboembolic events (<1%) associated with an estimated 800,000 rFVIIa infusions in patients with congenital or acquired hemophilia with inhibitors, however results for the two patient groups were not reported separately.[34] Caution should also be used when evaluating patients in whom tissue factor may be expressed, such as advanced atherosclerotic disease, crush injury, septicemia or disseminated intravascular coagulation (DIC). The risk of a potential interaction between rFVIIa and other coagulation factor concentrates is unknown, and experience with concomitant administration of anti-fibrinolytics and rFVIIa treatment is limited in patients with AHA. The risk of developing antibodies to rFVIIa is low in patients with congenital hemophilia, although rare cases have been reported in patients with FVII deficiency.[27,35]

Activated prothrombin complex concentrates (aPCCs)

aPCCs are widely used in the treatment of FVIII inhibitors in congenital hemophilia,[36-38] but experience in AHA is limited. The standard dose ranges between 50 and 100 IU/kg every 8-12 h. In a retrospective study of acquired hemophilia patients who received aPCCs as first-line treatment for acute bleeding episodes (n=34) at a dose of 75 IU/kg (n=29) or 100 IU/kg (n=5), 76% of patients with severe and 100% of patients with moderate bleeding episodes showed a complete response. Moderate bleeding episodes showed a faster median response time (36 *vs.* 48 h) and lower number of infusions per bleeding episode (6 *vs.* 10) than severe bleeding episodes.[39] aPCCs at a dosage of 35-80 IU/kg every 8-24 h as first-line therapy was judged effective in 89% of 55 bleeding events in 17 patients.[40] Six patients from a single center who received first-line therapy for severe bleeding episodes at a dose of 70 IU/kg every 8 h showed a 100% response rate.[41] Treatment of acute bleeding with aPCCs as first or second-line therapy was reported to be effective in 10 patients in two separate reports.[5,42]

The results of retrospective series and case reports have shown that aPCCs are well tolerated, with few adverse events.[43] DIC has been observed after administration of a 100 IU/kg bolus or 200 IU/kg/day, and contraindications include patients with significant signs of DIC. Anti-fibrinolytic agents should be avoided for 12 h after administration of aPCCs.[23] Anamnestic response with increase in the FVIII inhibitor titer has been reported in both congenital and acquired hemophilia.[44,45]

At present, evidence on the thrombogenicity of rFVIIa and aPCC is limited. We do suggest caution in elderly patients and in patients with underlying cardiovascular disease or risk factors for thromboembolic complications.[46,47] However, bypassing therapy should not be considered absolutely contraindicated when facing a life-threatening or severe bleed.

We suggest the use of recombinant or plasma-derived human FVIII concentrates or desmopressin only if bypassing therapy is unavailable.

FVIII concentrates

The administration of human plasma-derived or recombinant FVIII concentrates can only be advocated for the treatment of acute bleeding episodes associated with AHA when the inhibitor titer is very low, the bleeding manifestations or potential are minor and no bypassing agent is available. Published reports recommend that a bolus loading dose be administered to neutralize the inhibitor [calculated as inhibitor titer (BU) x plasma volume (mL)] and to achieve the hemostatic level (usually 20-50 IU/kg in accordance with the severity of bleeding), followed by subsequent doses given by bolus (20-50 IU/kg every 6-8 h) or by continuous infusion (3-4 IU/kg/h) for maintenance.[48] However, this approach results in variable and unpredictable FVIII activity levels in the patient, and the second order kinetics of the autoantibody provide no assurance of immediate or sustained hemostatic effect. No prospective, randomized, controlled clinical studies are available to validate this approach in AHA.

Desmopressin

Some of the same limitations to the use of human FVIII concentrate in AHA patients also apply to the use of desmopressin, a synthetic vasopressin analog (DDAVP; 1-deamino-8-D-arginine). DDAVP (0.3 mcg/kg) is best reserved for minor bleeding episodes and very low titer inhibitors; however, the experience using DDAVP in acquired hemophilia is anecdotal.[49-52] The usefulness of this agent is compromised by the inability to predict efficacy and whether tachyphylaxis will occur following subsequent dosing. In addition, the adverse event profile of this drug should be taken into consideration, particularly given the typical elderly population affected by AHA. Water retention, with consecutive hyponatremia and convulsions may occur following repeated injections of DDAVP.

Porcine FVIII

Porcine plasma-derived FVIII concentrate was formerly available and effective in the treatment of AHA, particularly since human FVIII auto-antibodies often have a low cross-reactivity with porcine FVIII.[3,53] Plasma-derived porcine FVIII concentrate is not presently available, however a recombinant porcine B-domain-deleted FVIII molecule is under development.[54,55] Should this agent demonstrate adequate efficacy and safety profiles in acquired hemophilia, it may be recommended in an updated version of this document.

We suggest that alternative treatment strategies be considered after failure of appropriate first-line treatment.

Efficacy of treatment must be assessed clinically in terms of bleeding tendency, size of hematoma, stability of Hb/Hct and pain caused by the hematoma. Table 3 lists some criteria that define treatment failure in AHA. Relapse or spontaneous re-bleeding from a site at a later time point following initial control of bleeding is not necessarily a sign of ineffective treatment.

In case of treatment failure with one first-line bypassing agent, we suggest switching to the alternative agent. A few recent case reports describe favorable responses to the administration of both bypassing agents (in alternating sequence) in refractory congenital hemophilia patients with inhibitors and insufficient control of bleeding with a single agent.[56,57] However, these results may not apply to patients with acquired hemophilia. In view of the estimated rate of arterial thrombosis and other thromboembolic complications,[31,43] combination therapy with rFVIIa and aPCC should be restricted to life- or limb-threatening bleeds. The use of anti-fibrinolytic agents in association with bypassing therapy remains controversial. Tranexamic acid is contraindicated in conjunction with aPCC administration according to the prescribing information.[58] Although little data is available, most members of the author group have routinely combined tranexamic acid and rFVIIa when treating bleeding in AHA,[33] particularly in the presence of mucosal bleeding.

Table 3. Definition of treatment failure in acquired hemophilia A.

Overt bleeding; no change in blood loss/unit time
Hb unchanged or decreased despite red blood cell replacement
Increasing dimensions of internal bleed on imaging studies
Evidence of continued bleeding after 48 hours of appropriate treatment (24 h if site critical)
Bleeding at a new site while on anti-hemorrhagic treatment
Increasing pain associated with hematoma despite treatment

Under special circumstances, including the management of a refractory bleeding episode or necessary surgical intervention, acute reduction or removal of the inhibitor to facilitate hemostasis using plasmapheresis or immunoadsorption may be applied.[59-62] Auxiliary topical thrombin or fibrin glue may be applied at some sites, for example, nasal and oral cavities, skin lesions and surgical sites.

We recommend the prophylactic use of bypassing agents prior to minor or major invasive procedures.

Prevention of iatrogenic bleeding is important in the management of patients with AHA, and even minor procedures such as peripheral venous access may result in significant bleeding.[21,63] Invasive procedures and surgery should be delayed until inhibitor eradication, if possible, or performed with extreme caution. Central venous access and surgery, depending on the type, require cover with a bypassing agent.

Inhibitor eradication

We recommend that all patients diagnosed with AHA receive immunosuppressive therapy immediately following diagnosis.

Patients diagnosed with AHA should undergo immediate inhibitor eradication to restore normal hemostasis.[21,46,64-66] In their survey of 215 patients, Green and Lechner reported a mortality of 22% and major bleeding episodes in 87%.[2] In another study, 64% of 28 untreated patients died due to inhibitor-related complications.[67] According to a recent review of 249 patients, the overall mortality without any treatment is 41%. With immunosuppressive treatment, mortality is reduced to 20%, with 11% mortality directly related to the inhibitor. The high overall remaining mortality has been attributed to complications of immunosuppressive therapy or co-morbidity.[21] Although one study reported that 36% (5/16) of patients receiving no treatment experienced spontaneous remission, this outcome is unpredictable.[19] In addition, patient characteristics at initial presentation are not predictive of major or even fatal bleeding episodes.[46] Patients with

acquired hemophilia and only a mild or non-spontaneous bleeding tendency may bleed as a result of traumatic injury.[19] Because inhibitor levels are not predictive of bleeding risk, the inhibitor level should not be a criterion to determine whether to administer immunosuppressive therapy. The only context in which the inhibitor level may play a role is with respect to the predicted response to immunosuppressive therapy. Low-level evidence suggests that patients who respond best to immunosuppressive therapy have lower baseline inhibitor titers.[68-70]

General inhibitor eradication strategy

The optimal therapeutic strategy for AHA inhibitor eradication has not yet been defined, but for the last two decades, immunosuppressive regimens applied most successfully to suppress autoantibody production have included corticosteroid therapy alone or in combination with cyclophosphamide.[21] Recently, rituximab has emerged as a promising new agent for the eradication of inhibitors in patients with acquired hemophilia.[8,69,71-74] Initial treatment should therefore usually consist of corticosteroids, either alone or in combination with cyclophosphamide, especially if the patient has already been treated with corticosteroids for other medical conditions.[64,75] If no response is observed after 4-6 weeks, treatment with rituximab alone or in combination with corticosteroids is an alternative. The use of other cytotoxic agents such as azathioprine,[76] vincristine,[77] mycophenolate[78] or cyclosporine[79-82] has also been described (Table 4).

We recommend that all AHA patients be treated initially with corticosteroids alone or in combination with cyclophosphamide to eradicate autoantibodies.

We suggest corticosteroid therapy for inhibitor eradication at a dose of 1 mg/kg/day PO for 4-6 weeks, either alone, or in combination with cyclophosphamide at a dose of 1.5-2 mg/kg/day for up to six weeks.

The literature on immunosupressive therapy consists of small, referral center case collections or larger retrospective surveys.[75] One prospective randomized study (n=31) compared prednisone alone with cyclophosphamide[68] or combination therapy and found that 42% (13/31) of patients responded to prednisone alone while 50% responded to cyclophosphamide (3/6) or combination therapy (5/10) after failed prednisone treatment. An analysis of published reports (n=44) found an 84% complete response among AHA patients treated with prednisone and cyclophosphamide.[70]

Data from a retrospective registry in the United Kingdom suggests that prednisolone alone (1 mg/kg/day) eradicates the inhibitor in 60-70% of patients, while 70-80% of patients respond to a combination of prednisolone and oral cyclophosphamide (50-150 mg/day),[1] however the overall survival and disease-free survival showed no difference between corticosteroid alone and corticosteroid plus cytotoxic therapy. Neither inhibitor titer nor FVIII level was found to be significantly associated with outcome. Another prospective study[83] (n=48) reported complete remission at one month in 31% and at three months in 61% of acquired hemophilia patients treated with corticosteroids alone or in combination with cytotoxic therapy, with no significant difference in 3-month survival between 22 patients treated initially with corticosteroids alone compared to the 26 patients who received combination therapy.

Table 4. Inhibitor eradication treatment strategies in acquired hemophilia A.

First-line treatment
Corticosteroids
Corticosteroids + cyclophosphamide
Second-line treatment
Rituximab
Alternative treatment
Azathioprine
Vincristine
Mycophenolate
Cyclosporine
Not recommended
Intravenous immunoglobulins

We suggest second-line therapy with rituximab if first-line immunosuppressive therapy fails or is contraindicated.

Immunosuppressive regimens that include rituximab are based largely on experience in patients with lymphomas and other autoimmune diseases.[74] Recent reports have shown promising results in eradicating inhibitors in patients with acquired hemophilia at a common dose of 375 mg/m^2/week for up to four weeks[8,69,71-73,84-86] however because the drug is new, the amount of data available is limited compared to the older treatment modalities, and carries a risk of bias in reporting positive outcomes. Furthermore, the effectiveness of rituximab alone has not been established because the drug is seldom administered in the absence of other immunosuppressive treatment. Rituximab may be useful as first-line therapy in patients for whom corticosteroids or chemotherapeutic agents are contraindicated. A recent literature review[70] based on uncontrolled studies or case reports suggests that this drug may be useful in treating acquired hemophilia patients, with remission obtained in 79% of patients (n=43) and no reported cases of opportunistic infections. As more data become available, the efficacy and long-term safety profile of this drug may justify a recommendation for first-line therapy in an updated version of this document.

Side effects of immunosuppressive therapy

Most immunosuppressive drugs are associated with side effects, including neutropenia-related infections and sepsis.[1,3,21,77,87-90] Lian *et al.*[77] treated 12 patients with cyclophosphamide, prednisone and vincristine, and 3 patients developed neutropenia-induced infections. Delgado[21] treated 17 patients with cyclophosphamide; 9 patients experienced therapy-related adverse events, including cytopenia, alopecia and toxic hepatitis. A French registry[83] reported that mortality secondary to sepsis (12.2%) was higher than bleeding mortality (3.6%), while the UK registry reported a 33% rate of sepsis, which contributed to mortality in 11% of cases.[1]

Because the majority of AHA patients are elderly and likely to have concomitant medical conditions, treatment regimens should aim to balance the need to eradicate the inhibitor quickly, thereby reducing the risk of severe bleeding episodes, and the time and exposure to the side

effects of immunosuppressive therapy. The dose of corticosteroid therapy should be rapidly tapered off after successful therapy or after a switch to second-line treatment. Cyclophosphamide therapy should be dosed according to hematologic tolerance and administered for a maximum of six weeks, because continued therapy may increase the risk of adverse effects.[91] Contraindications or grounds for a delay or adjustment in treatment include high fever of unknown origin, sepsis or severe infections, age and severe life-limiting co-morbidities. We suggest that the potential risks and benefits of immunosuppressive therapy be considered for each patient individually. For example, postpartum women should not be treated with cyclophosphamide or other alkylating agents due to the risk of infertility. If no response is achieved within 6-8 weeks, alternative combination therapies may be considered.

We suggest the application of immunotolerance regimens with immunoadsorption in AHA patients only in the case of life-threatening bleeds or in the context of clinical research studies.

Co-administration of FVIII and immunosuppressive agents in patients with acquired hemophilia has been implemented successfully by several investigators,[62,88,92,93] however it is not clear whether the addition of FVIII achieves any benefit. Immunotolerance should therefore only be used in conjunction with clinical research trials to define the real benefits of this new therapeutic modality, or in life- threatening bleeding situations with no response to standard therapeutic regimens.

Immunoadsorption protocols have been used successfully to eradicate inhibitors in patients with AHA, and may have a modifying effect on the immune response, but should only be performed by centers with the necessary experience and expertise. The modified Bonn-Malmö protocol combined immunoadsorption using a double column system comprising sepharose-coupled anti-human IgG sheep antibodies with high-dose FVIII, intravenous (IV) immunoglobulins and immunosuppression (n=45). Complete response was reported in 41/45 (91%) of patients; when cancer patients were excluded, the success rate was 41/42 (97%). The inhibitor was eliminated after a median three (95% CI: 3-7) days and treatment completed after a median 15 (95% CI: 13-17) days. No recurrent inhibitors were observed during a long-term follow-up of a median 48 (minimum 12) months.[93,94] Similar results were observed using the modified Heidelberg-Malmö protocol (n=8).[62] Immunoadsorption in patients with AHA has also been performed using staphylococcal protein A-bound sepharose columns as well single-use tryptophan-based columns.[95-97]

We do not recommend use of high-dose intravenous immunoglobulin for or inhibitor eradication in patients with AHA.

The usefulness of IV immunoglobulin was explored as a means of eradicating auto-FVIII antibodies;[98] however, at doses conventionally employed for chronic autoimmune thrombocytopenia (0.4 mg/kg IV daily for five days or 1 g/kg daily for two days), only 10% of inhibitors were completely suppressed, and only in patients with low titer inhibitors (<5 BU).[99] Similarly, a literature review of patients who received IV immunoglobulin with no other concomitant immunosuppressive therapy reported a 12% (3/26) complete response rate.[100] A prospective study[99] of 16 assessable patients (1000 mg/kg for two days or 400 mg/kg for five days, followed by maintenance doses as indicated) showed a response in only 4 (25%) patients who received IV immunoglobulin alone; an additional 2 responders received concomitant immunosuppressive therapy. A complete response was observed in only 3 patients, all of whom had initial inhibitor titers ≤1 BU. Four of the 6 responders received prior or concomitant immunosuppressive therapy. A meta-analysis showed no benefit of adding immunoglobulin to immunosuppression,[21] a result supported by a retrospective survey of 174 patients in the UK.[1] IV immunoglobulin has also been associated with thromboembolic complications.[101] Currently, there is no rationale for use of IV immunoglobulin as a single agent in AHA, although the agent has been used as an integral component of immune tolerance induction protocols for acquired hemophilia.[62,92,93]

We recommend follow-up after a complete sustained response using aPTT and monitoring of FVIII:C monthly during the first six months, every 2-3 months up to 12 months and every six months during the second year and beyond, if possible.

Complete inhibitor eradication is generally defined as undetectable inhibitor and normal FVIII levels. A sustained response is undetectable inhibitor (<0.6 BU) and a FVIII level >50% following immunosuppressive therapy.

Patients with AHA who undergo immunosuppressive therapy may be monitored on an outpatient basis, except in the presence of bleeding, high co-morbidity that involves hospitalization, invasive procedures, delivery or surgery. Monitoring should include a regular anamnesis and physical examination, hemogram, aPTT, FVIII activity and FVIII inhibitor titer assessments. During the first six weeks of therapy, monitoring should be performed weekly on an outpatient basis and twice weekly for hospitalized patients.

If complete remission is achieved, aPTT and FVIII:C plasma levels can be used to exclude recurrence of inhibitor. aPTT is an inexpensive and readily available option with these practical advantages over FVIII:C assays. Two studies showed that the median time to relapse is 7-9 months after cessation of immunosuppressive therapy (range: one week to 14 months).[1,21] From these data, we suggest that laboratory monitoring of former AHA patients for the first year following remission is prudent (Table 5). Testing should be initiated immediately if clinical symptoms suggest a relapse.

We recommend thromboprophylaxis according to American College of Chest Physicians (ACCP) guidelines following inhibitor eradication and sustained response in former AHA patients, especially those with very elevated FVIII:C levels.

Substantially elevated plasma FVIII levels are often observed in AHA patients following inhibitor eradication, and constitute an independent thrombotic risk factor.[102,103] Although no specific guidelines for thromboprophylaxis in

Table 5. Monitoring frequency following immunosuppressive treatment and autoantibody remission in patients with acquired hemophilia A.

Time after remission	aPTT	FVIII:C
<6 months	Monthly	Monthly
6-12 months	Every 2-3 months	Every 2-3 months
>12 months	Every 6 months	Every 6 months

former AHA patients exist, we recommend that these patients receive thromboprophylaxis according to ACCP guidelines[104] as in any other patient without a history of a hemorrhagic disorder.

Conclusions

AHA is a rare disorder presenting with heterogeneous bleeding phenotypes, therefore it may remain undiagnosed or its diagnosis delayed. Because AHA is still associated with high morbidity and mortality, there is an ongoing need to expand our understanding of optimal management that may be aided by advances in basic autoimmune research. The paucity of new cases presents an obstacle for the generation of high-level evidence based on randomized clinical trials; and the management of patients with AHA is often empirical or based on anecdotal or retrospective study data. We would therefore encourage physicians who treat patients with AHA to actively contribute cases to the growing number of registries that collect patient data on clinical characteristics, management and outcomes, which may serve as the basis for more evidence-based treatment. In addition, we suggest that the establishment of centers of expertise for AHA and the implementation of national or regional hemophilia center networks that provide 24-hour turnaround for sample assessment and diagnosis may assist in standardizing clinical practice in the management of this patient group.

Authorship and Disclosures

Subgroups of the authors met in November 2007 (FB, AH-K, HL, JSL) and January 2008 (FB, AH-K, HL, MEMC) to define the scope of the project, generate a list of preliminary questions to be addressed and develop a literature search strategy. The topic outline, strategy and questions were subsequently reviewed and revised by the entire author group using email and teleconferences. Three working groups were formed to address questions concerning "diagnosis" (PC, JI, MS), "anti-hemorrhagic treatment" (FB, CMK, JSL) and "inhibitor eradication" (AH-K, HL, MEMC), and outlines, draft recommendations and rationale for each section generated by the authors in each working group. Draft recommendations and final outlines for each rationale were discussed during a face-to-face meeting by the entire group (except PC, CK) in February 2008. The draft manuscript was discussed, revised and recommendations finalized by consensus during a further meeting (except PC, MS) in April 2008. Final manuscript revisions and approval were completed using email and teleconferences. All authors had full access to all of the literature described here, contributed to the intellectual development and writing of the manuscript, and take responsibility for the integrity of the data and the accuracy of the data analysis.

During the past three years, FB has received honoraria for consulting or lecturing from Bayer HealthCare and Novo Nordisk; PC has received honoraria for consulting or lecturing from Baxter, Novo Nordisk, Bayer and Ipsen, educational grants from Baxter and Bayer and institutional support from Baxter; AH-K has received honoraria for consulting or lecturing from Bayer HealthCare, Novo Nordisk and Wyeth; JI has received honoraria for consulting or lecturing from Baxter, Novo Nordisk, Bayer, Wyeth, educational grants from BioVitrum and institutional support from STER, Baxter and BioVitrum; CMK's institution receives research funding for clinical trials on his behalf from Baxter Immuno, Novo Nordisk, Octapharma, Grifols, Genentech and Bayer. He has received honoraria for consulting or lecturing from Wyeth, Octapharma, Bayer, Baxter Immuno, Ipsen and Novo Nordisk; HL has received honoraria for consulting or lecturing from Novo Nordisk; MEMC has received honoraria for consulting or lecturing for Novo Nordisk, Grifols, Baxter and Wyeth. No other relevant financial associations are reported by the Thrombosis and Hemostasis section of the Hematology department at the Regional University Hospital of Carlos Haya, Malaga (Spain); MS reported no relevant financial associations; JSL has received honoraria for consulting from Baxter and Novo Nordisk, educational grants from Bayer and research grants from Ipsen and Novartis.

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