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REVIEW ARTICLE

Acquired haemophilia: an overview for clinical practice

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Abstract

Acquired haemophilia is a potentially life-threatening bleeding disorder caused by the development of autoantibodies against coagulation factors, most commonly against factor (F) VIII (acquired haemophilia A; AHA). In around half of patients, an underlying disorder is associated with AHA; the remaining cases are idiopathic. Typically, the disorder presents with bleeding, ranging from mild to life- and limb-threatening, in patients with no personal or family bleeding history. Diagnosis involves an isolated prolongation of the activated partial thromboplastin time, without correction in mixing studies, low FVIII activity levels and evidence of a FVIII inhibitor. As AHA is rare, a lack of familiarity of the condition may result in delayed diagnosis, and prompt haemostatic control is required to reduce morbidity and mortality. Bypassing agents (recombinant activated factor VII or activated prothrombin complex concentrates) can be used to control acute bleeding, and immunosuppression is necessary to eradicate the inhibitor. As clinical trials in this rare and heterogeneous disease are difficult, current evidence comes from observational studies, including registries. This review will focus on the diagnostic and therapeutic challenges of AHA and summarise how understanding of this complex condition has increased based on recent registry data.

Key words acquired haemophilia; autoantibodies; bypassing agents; diagnosis; epidemiology; management

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Acquired haemophilia is a bleeding disorder caused by the spontaneous development of autoantibodies (inhibitors) against endogenous coagulation factors in individuals with previously normal haemostasis (1). These inhibitory autoantibodies partially or completely neutralise the activation or function, or accelerate the clearance, of a specific clotting factor (2). Autoantibodies against all coagulation factors have been reported (3). As inhibitors are most commonly directed against factor VIII (FVIII) causing the acquired form of haemophilia A (4), this article provides an overview of acquired haemophilia A (AHA), focusing on the clinical, diagnostic and therapeutic challenges associated with this condition.

AHA is a rare condition with an estimated incidence of approximately 1.5 per million population per year (5). AHA represents a demanding clinical challenge, as lack of familiarity of AHA can result in delayed diagnosis and/or inadequate treatment, contributing to high mortality and morbidity rates (1, 6). Acute bleeding episodes may be very severe, and prompt haemostatic control is required to reduce morbidity and mortality (7). However, not all patients with AHA experience bleeding episodes and some events may be managed conservatively and do not require haemostatic therapy (e.g. subcutaneous bleeding). Moreover, patient characteristics at initial presentation are not predictive of major or fatal bleeding episodes (8). Patients remain at risk of life-threatening bleeding as long as the inhibitor persists. Therefore, treatment to eradicate the inhibitor should be initiated as soon as possible (1, 7, 8).

Large randomised clinical trials are considered unfeasible due to the rarity of AHA and the heterogeneity of patients and clinical manifestations of the condition. Thus, data from observational studies, including registries, provide a deeper insight into the demographics, underlying disorders and therapeutic management of AHA. This article summarises information presented at the 12th Novo Nordisk Symposium on

Haemostasis Management, considering how the understanding of this challenging condition has increased based on recent data from prospective registries, including the Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise (SACHA) registry from France, the registry of the Hemostasis and Thrombosis Research Society of North America (HTRS), and the European Acquired Haemophilia Registry (EACH2).

Clinical features of AHA

As summarised in Table 1, it is clear from the literature that the autoantibodies against endogenous FVIII acquired in AHA differ from the alloantibodies developed against therapeutically administered exogenous FVIII in patients with congenital haemophilia A (9–14). Although both types of inhibitors involve an effective deficit of FVIII function/activity, the clinical features of patients with AHA are distinct from those of congenital haemophilia A with inhibitors (Table 1). Unlike congenital haemophilia, which is an X-linked recessive trait (15), AHA occurs in both males and females (5). The incidence of AHA increases with age and is uncommon in children, with an estimated incidence of 0.045 per million per year in those aged 1–<16 years, rising to approximately 14.7 per million per year in the elderly (aged >85 years) (5). Recent data from EACH2, the largest prospective study of patients with AHA to date, have provided deeper insight into the demographics and underlying disorders associated with AHA. EACH2 data were collected for 501 patients (266 males and 235 females) with AHA from 13 European countries enrolled between January 2003 and December 2008 (14). In EACH2, the age and distribution of AHA patients at diagnosis is biphasic, showing a large preponderance of older individuals, with higher rates found in males, and a smaller peak of pregnancy-related cases in women aged 20–40 years (14). In agreement with previous large collections of patients with AHA (5, 16, 17), around half of AHA patients in EACH2 had an identifiable underlying clinical condition (malignancies, pregnancy, autoimmune disorders, infections, drug-induced and dermatological conditions); the remaining cases were idiopathic (14). Compared with pan-European databases, such as EACH2, the HTRS registry in the United States (US) derived its observations from a more ethnically diverse population, which included 24% of patients with AHA of black race/ethnicity (18). The incidence of AHA appears overrepresented compared with the percentage of black people within the US population [13.6% (19)] and suggests that black individuals could be preferentially affected by AHA, as they are for allo-FVIII antibodies (20).

The bleeding pattern seen in AHA is different from that observed in congenital haemophilia A (Table 1). Typically, bleeding episodes occur spontaneously and present with purpura or soft tissue bleeding in individuals with no personal or family history of bleeding (1, 13). Severe muscle bleeding, epistaxis, haematuria, gastrointestinal bleeding and even intracerebral bleeds are more frequent than haemarthroses. In comparison, haemarthroses account for approximately 70–80% of bleeding episodes in patients with congenital haemophilia A (10). Recent baseline data from the EACH2 registry have provided detailed information on the bleeding phenotype of AHA (14). In the majority of patients, bleeding events precipitated a diagnosis of AHA (89.0%). Most initial bleeding events precipitating diagnosis were spontaneous (77.4%), with 8.4%, 8.2% and 3.6% associated with trauma, surgery and the peri-partum period, respectively. Bleeding sites were predominantly in the skin (53.2%) and deep muscle or retroperitoneum (50.2%); mucosal bleeding was reported in 31.6% of cases, while both haemarthroses (4.9%) and intracerebral bleeding events (1.1%) were rare. Bleeding was severe in 70.3% of cases and non-severe in 28.9%; in some cases, severe bleeding was experienced even in the

Table 1 Characteristics of acquired haemophilia A compared with congenital haemophilia A with inhibitors (data collated from references 9–14)

Characteristic	Congenital haemophilia A with inhibitors	Acquired haemophilia A
Antibody type	Alloantibodies against exogenous (therapeutically administered) FVIII (9)	Autoantibodies against endogenous FVIII (1)
Inhibitor incidence	20–30% (10)	$1.5/10^6$/year (5)
Inhibitor kinetics	Type 1 (11)	Type 2 (11)
Residual FVIII activity	Generally no detectable residual FVIII activity (11)	May have some residual FVIII activity (11)
Inhibitor development	Occurs at the beginning of therapy (<50 exposure days) (9)	Acute onset in individuals with no family or personal history of a bleeding disorder (1)
Typical bleeding manifestations	Haemarthroses or muscle bleeds (10)	Soft tissue haematomas, bruising, muscle bleeds, gastrointestinal and urinogenital bleeding (1)
Bleeding sites	Often involves recurrent bleeding into a 'target' joint (10)	May have multiple sites (1)
Aetiology	Inhibitor development is complex and multifactorial including genetic and non-genetic factors, and the main determinants are yet to be fully identified (12)	Autoimmune disease; presence of underlying diseases and conditions (1, 14)
Patient age and gender	Most frequent in children and males (9, 13)	Biphasic pattern: most common in older adults, but may occur postpartum in females of child-bearing age (14)

presence of relatively high levels of FVIII. A total of 159 (33.5%) patients had more than one bleeding episode following initial therapy (108, 35 and 16 patients had two, three and four or more bleeding episodes, respectively) (14).

AHA can cause severe bleeding complications, with life-threatening bleeding episodes reported to occur in 97% of patients (6). Patients with AHA can seemingly experience more severe bleeding episodes than patients with congenital haemophilia with comparable FVIII levels (21). This may be attributed, at least in part, to the kinetics of inactivation of FVIII by autoantibodies. In congenital haemophilia A, alloantibodies typically inactivate FVIII completely in a linear fashion (type I or first-order kinetics) in a manner that is dependent on both concentration and time (11). In contrast, in AHA, autoantibodies show a rapid initial inactivation phase followed by a slower equilibrium phase (type II kinetics) and some residual FVIII activity can be detected *in vitro,* even in cases of high-titre inhibitors. The Bethesda assay may therefore underestimate the *in vivo* inhibitor potency in AHA due to the complex nonlinear autoantibody pharmacokinetics. Consequently, FVIII activity or inhibitor titre cannot be used to predict the severity of bleeding events and identify patients with AHA who are at high risk of fatal bleeding episodes (5).

Diagnosis of AHA

As AHA it is not associated with a personal or family history of bleeding episodes and the condition is rare, lack of familiarity can result in delayed diagnosis, which may impact on treatment selection, initiation and outcomes. EACH2 data showed that although 37% and 26% of patients were definitely diagnosed with AHA within 1 d and 1 wk of initial bleeding, respectively, a considerable diagnostic delay of >1 wk to 1 month, 1–6 months and >6 months occurred in 22%, 10% and 1% of cases, respectively (14). Although diagnostic delay significantly prolonged the time to start of haemostatic therapy ($P < 0.0001$), no difference in response to therapy, intensity of therapy or outcome was demonstrated. However, patients still remain at risk of severe bleeding episodes until the inhibitor has been eradicated.

AHA should be suspected when an individual with negative personal or family bleeding history (not receiving anticoagulant therapy) presents with unexplained bleeding diathesis with typical clinical features of the disorder (described above), especially elderly or postpartum patients. Diagnosis should be confirmed by laboratory investigation, with initial diagnosis based on the demonstration of an isolated prolongation of the activated partial thromboplastin time (aPTT), not corrected by a mixing study (i.e. incubation of patient plasma with pooled normal plasma (1:1) for 1–2 h at 37°C) (1). Once lupus anticoagulants and acquired von Willebrand syndrome have been ruled out (these conditions will also cause an aPTT prolongation of the mixture/normal plasma at time 0 and after incubation), AHA diagnosis is confirmed by reduced FVIII levels and evidence of a FVIII inhibitor, estimated with the Bethesda assay (Fig. 1) (1). However, not all patients with AHA present with bleeding symptoms (8).

The diagnosis and management of AHA is complex and ideally should be coordinated by haemophilia centres with clinicians and laboratory staff experienced in the management of inhibitors (7, 8). A recent quantitative case-based survey of 302 physicians across a range of specialties (haematology, emergency medicine, geriatrics, internal medicine, rheumatology and critical care medicine) illustrated a general lack of consideration and response to the presenting symptom of bleeding and prolonged aPTT in AHA (22). To provide an educational resource to support the evaluation of laboratory results as part

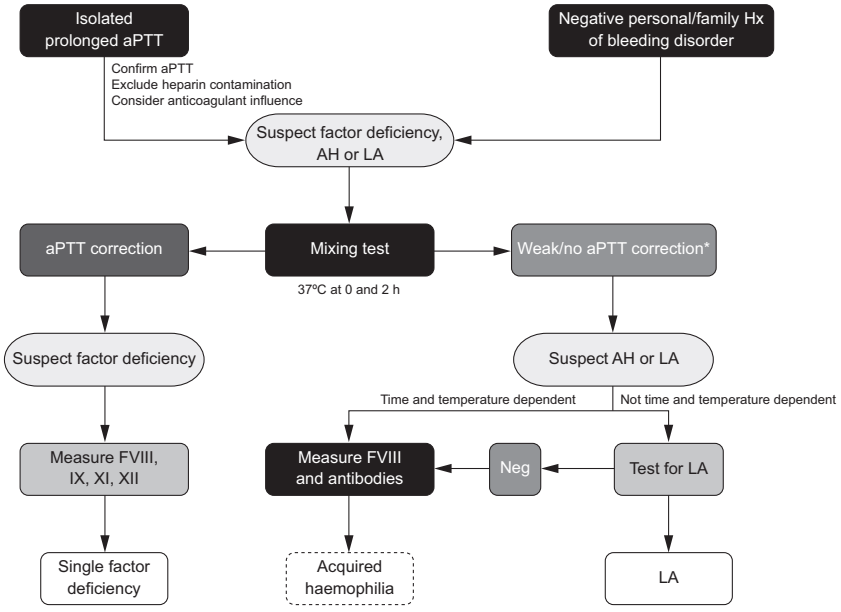


Figure 1 Algorithm for the diagnosis of patients with suspected acquired haemophilia [Adapted from (1)]. *Exclude acquired VWD. AH, acquired haemophilia; aPTT, activated partial thromboplastin time; F, factor; Hx, history; LA, lupus anticoagulant; neg, negative; VWD, von Willebrand disease.

of the diagnosis of bleeding disorders, an iOS/Android/Web/Desktop application (app) has been developed. Coags Uncomplicated™ (www.coagsuncomplicated.com) includes tools that facilitate laboratory value analysis and algorithmic approaches to diagnosis of AHA and 65 other bleeding disorders. The app is a reference tool and should be used with clinical correlation and consultation with a haematologist to ensure an accurate diagnosis. Given the rarity of AHA, case studies can provide an additional source of data and can be used as a useful tool to educate healthcare professionals. In Box 1, we briefly describe two cases of AHA to illustrate the heterogeneous nature of the condition and outline the laboratory analyses performed that led to the definitive diagnosis of AHA.

Clinical management: treatment of acute bleeding episodes

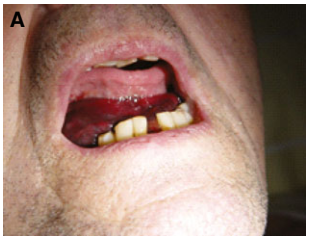
In AHA, autoantibodies interfere with the procoagulant activity of FVIII, rendering replacement FVIII therapy ineffective. In such cases, bypassing agents are the standard of care to stop acute bleeding episodes. Current guidelines recommend the use of recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk A/S, Novo Allé, 2880 Bagsvaerd, Denmark) or plasma-derived activated prothrombin complex concentrate (pd-aPCC; Factor VIII Inhibitor Bypassing Activity [FEIBA®], Baxter International) as first-line haemostatic therapy in this setting (7, 8). Either bypassing agent can be used, with the alternative product to be administered if the first agent is unsuccessful (Table 2) (23–25). Alternative therapeutic strategies such as extracorporeal immunoadsorption to help to lower the inhibitor titre, allowing treatment with high-dose FVIII, may be used when bypassing agents are not available or are ineffective (Table 2), but this technique is unattainable in many centres. After the symposium, and at the time of drafting this manuscript, the new treatment modality recombinant porcine sequence factor VIII concentrate (rpVIII, OBI-1, Obizur®, Baxter Healthcare Corp) became available in the US (26). [Note: rpVIII was not discussed during this workshop; data were unpublished and the product was not yet licensed.]

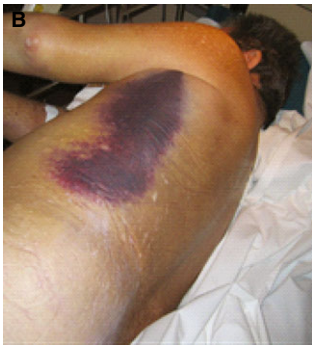
To date, the haemostatic efficacy of rFVIIa and pd-aPCC in AHA has not been directly compared in prospective head-to-head studies, likely due to the rarity of the disease. Also, diverse disease scenarios, differing degrees of severity and highly variable time intervals between presentation and definitive confirmation of actual cause of bleeding among

Box 1 Illustrative cases studies for acquired haemophilia A

Case 1

A 55-year-old man with a history of alcohol and tobacco abuse, in a bedraggled state, but with no history of trauma, presented with a large haematoma under the tongue (A) and a large psoas haematoma (B). Initial laboratory tests illustrated an isolated activated partial thromboplastin time (aPTT) (prothrombin time [PT], 12.5 s [97%]; aPTT, 55 s; fibrinogen levels, 2.5 g/dL). Unfractionated heparin or low-molecular-weight heparin effects were excluded [thrombin clotting time (TCT), 15.3 s; antifactor (F) Xa activity <0.1 U/mL]. Mixing studies revealed aPTT in control plasma of 28 s, aPTT in patient's plasma of 55 s and aPTT in a 1:1 mixture of the two plasmas of 52 s. Therefore, aPTT was not normalised after adding normal plasma to the patient's plasma, illustrating the presence of an inhibitor. Assays of specific factors showed activities of <1% for FVIII, whereas FIX, FXI and FXII were 93%, 75% and 65%, respectively, illustrating an isolated severe FVIII deficiency in this patient. A subsequent Bethesda assay demonstrated an inhibitor of 18 Bethesda Units (BU)/mL was present, confirming the diagnosis of acquired haemophilia A (AHA) in this patient.





Case 2

A 34-year-old woman presented with a 2-wk history of multiple ecchymoses in both upper and lower limbs and a history of menorrhagia (~20 years), which had worsened over the 2 wk prior to referral and had been treated with herbal remedies. Her past history was negative for constitutional or connective tissue disease symptoms or family history of bleeding complications. At presentation, she had no signs of synovitis, presence of organomegaly or palpable lymph nodes. The patient was a mother to four children, the most recent born 8 months before referral. A coagulation screen produced the following results, indicating an isolated prolonged aPTT: PT, 11.2 s; international normalised ratio. 0.97; aPTT, 77.9 s; fibrinogen, 4.4 g/L and TCT, 12.3 s. A mixing test did not correct the observed prolonged aPTT (aPTT mixing control at 0 h and 2 h, 37.6 s for both; aPTT mixing patient with normal plasma (1:1) at 0 and 2 h 44.2 and 55.2 s, respectively). FVIII activity was 3%, and an inhibitor titre of 8.00 BU/mL was obtained in the Bethesda assay. This patient was diagnosed with a postpartum FVlll inhibitor, associated with pregnancy-associated AHA.

Table 2 Recommendations for acute bleeding management in acquired haemophilia

Guidelines	Recommended first-line therapy	Recommended alternative treatment
Diagnosis and management of acquired coagulation inhibitors: a guideline from United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) (7)	Bypassing agent* • rFVIIa • pd-aPCC	• Alternative bypassing agent, if one bypassing agent fails • FVIII replacement combined with immunoadsorption or plasmapheresis for severe bleeding or if first-line therapy is unsuccessful • Tranexamic acid as adjunctive therapy
International recommendations on the diagnosis and treatment of patients with acquired haemophilia A (8)	Bypassing agent* • rFVIIa • pd-aPCC	• Alternative bypassing agent, if one bypassing agent fails • FVIII only if low-inhibitor titre, bleeding minor and bypassing agent not available • Activity levels of FVIII variable and unpredictable, no assurance of immediate or sustained haemostatic effect

pd-aPCC, plasma-derived activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.
*The approved rFVIIa dosing regimen for the treatment of bleeding episodes in patients with acquired haemophilia in the European Union is an initial dose of 90 μg/kg repeated every 2–3 h (23) [70–90 μg/kg every 2–3 h in the United States (US) label (24)]. In countries outside the US, the indicated dose for pd-aPCC in acquired haemophilia in countries outside the US is 50–100 U/kg, not exceeding a single dose of 100 U/kg and a maximum daily dose of 200 U/kg unless the severity of bleeding warrants and justifies the use of higher doses (25). For both agents, the duration of treatment and the interval between injections vary with the severity of the haemorrhage, the invasive procedures or the surgery being performed. Antifibrinolytics such as tranexamic acid should not be used for approximately 6–12 h after pd-aPCC administration (25). In the US, pd-aPCC is not indicated for the treatment of acquired haemophilia (37).

patients make it difficult to develop a therapeutic trial design that would be meaningful. However, analyses of data collected from the cited registries above give insight into haemostatic treatment usage and outcomes. In EACH2, patients were managed according to local practice, with data from 482 patients with at least one bleeding episode analysed (27). Of these, 144 (29.9%) patients with bleeding did not receive any haemostatic therapy. A total of 338 (70.1%) patients received treatment for a first bleed: 31 with ancillary therapy and 307 with a first-line haemostatic agent. rFVIIa was the most commonly used first-line therapy in 56.7% of patients (Fig. 2A), followed by pd-aPCC (20.5%) (27). Propensity score matching to allow unbiased comparison between treatment groups (controlled for bleed and patient characteristics) demonstrated that bleeding control was significantly higher with bypassing agents (93.3%) compared with replacement therapy (FVIII) and desmopressin (68.3%; $P = 0.003$) (Fig. 2B). Furthermore, the rFVIIa and pd-aPCC efficacy profiles were not statistically different from each other, both demonstrating a rate of bleeding control >90% (27). These data confirm that both bypassing agents have similar efficacy in AHA and should be among the haemostatic therapies of choice, over FVIII or desmopressin, for the first-line treatment of bleeding episodes in AHA.

Overall, both bypassing agents were generally well tolerated in EACH2, although pd-aPCC was associated with an anamnestic response to treatment of the first bleeding episodes in six patients (9.5%). EACH2 also provided important information about thrombotic adverse events, with a thrombotic event rate of 2.9% and 4.8% reported with rFVIIa and pd-aPCC, respectively (27). Thrombotic events were significantly associated with patient age ($P = 0.0341$) but not with underlying clinical conditions. Importantly, the bleeding mortality rate was 3.3% (27), lower than previously reported registry data (9%) (5). This may reflect improved awareness of the clinical condition, the availability of effective haemostatic agents and the centralisation of treatment for these bleeding disorders to Haemophilia Treatment Centres of excellence.

Data collected from SACHA, a prospective collection of patients with AHA from France, have also included outcomes for haemostatic treatment of initial bleeding episodes. SACHA data were collected on 82 patients from French haemophilia centres (50 males and 32 females) with AHA between September 2001 and September 2005 (with follow-up until September 2006) (28). Haemostatic therapy was selected by physicians based on recommended treatment regimens according to French practice, which were provided at study inclusion. Of 82 enrolled patients, the initial bleeding episode was treated in 38 (46.3%) of patients. rFVIIa administered alone was the most common therapy in 28 of 38 (73.7%) patients, with rFVIIa used in sequential regimens in an additional two cases (Fig. 2C). Complete resolution or improvement of initial bleeding was observed in 22 of 27 (81%) of patients treated with rFVIIa only and in all six patients receiving pd-aPCC (Fig. 2D). Bleeding resolved or improved in the four patients treated with other treatment regimens. No thromboembolic complications were observed in patients receiving rFVIIa or pd-aPCC. The mortality rate due to bleeding was low in SACHA (4%)

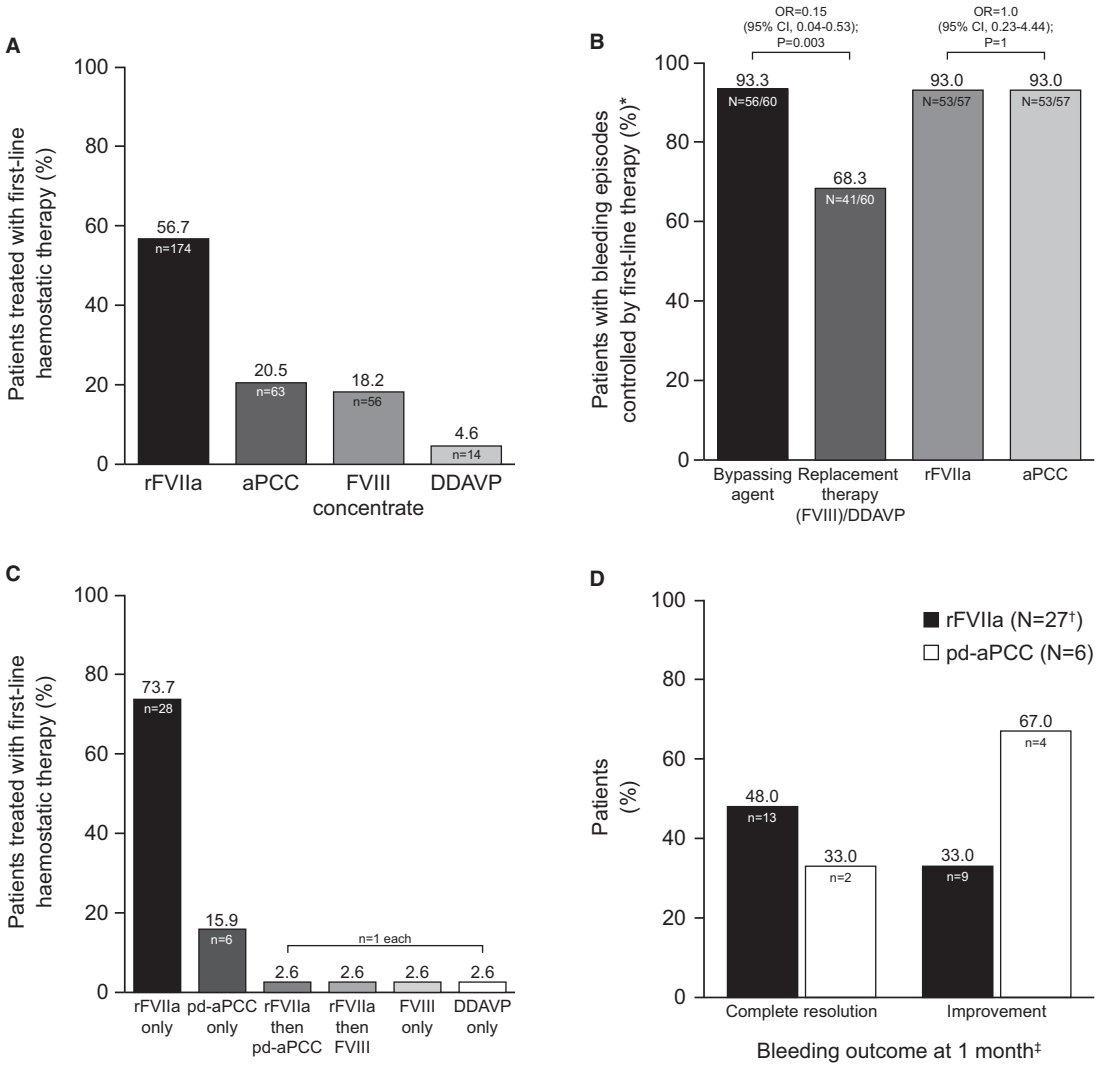


Figure 2 First-line haemostatic therapy usage and efficacy rates for first bleeding episodes in patients with acquired haemophilia A from EACH2 (panels A and B) (27) and SACHA (panels C and D) (28). aPCC, activated prothrombin complex concentrate; CI, confidence interval; DDAVP, 1-desamino-8-D-arginine-vasopressin; FVIII, factor VIII; OR, odds ratio; pd-aPCC, plasama-derived activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII. *Propensity score-matched rates of control for first bleeding episodes adjusted for age at diagnosis, sex, FVIII level and inhibitor titre at time of the bleeding episode, haemoglobin value at diagnosis, bleeding site, bleeding severity, delay of therapy and cause of bleeding. †One patient receiving rFVIIa died from sepsis at Day 13. ‡Efficacy haemostatic treatment criteria: complete resolution = absence of new or active bleeding (no bleeding); improvement = improved according to local physician.

(28), consistent with the rate reported in EACH2 (3.3%) (27). These data from SACHA support the findings from EACH2, confirming the efficacy and safety of bypassing agents in controlling bleeding in patients with AHA. Moreover, recent data from the Acquired Hemophilia Surveillance project have reaffirmed that rFVIIa is efficacious and well tolerated in AHA, with a low rate of thrombotic complications (29).

More recently, preliminary data have been published on the favourable safety and efficacy profiles of rFVIIa in the surgical setting from the HTRS registry (30). This is a longitudinal US database established in 1999 to study treatment strategies for patients with bleeding disorders and monitor the postapproval use of rFVIIa, which since 2006 (date of approval of rFVIIa for AHA in the US) has provided post-marketing surveillance on rFVIIa-treated patients with AHA. We await the full publication of the HTRS data set (18, 30, 31) with interest.

Clinical management: inhibitor eradication

While haemostatic control with bypassing agents is the priority in acute bleeding events, patients remain at risk of severe and fatal haemorrhage until the inhibitor has been eradicated. Although spontaneous remissions have been reported (32), treatment guidelines recommend immunosup-

pressive therapy as soon as AHA diagnosis is made to eradicate the inhibitor (1, 7, 8). However, immunosuppression may be associated with severe side effects (1). Indeed, immunosuppressive regimens should be carefully adjusted according to patient age, general condition and comorbidities, with the benefits of inhibitor eradication balanced against the risk of side effects.

Eradication of FVIII autoantibodies has been reported with a variety of immunosuppressive regimens using corticosteroids, alone and in combination with cytotoxic drugs or rituximab (1, 7). In the absence of randomised controlled trials, registry data add to the evidence base to guide patient management. Data from 331 patients entered into EACH2 indicated that steroids combined with cyclophosphamide resulted in more patients achieving a stable complete remission (70%) than either treatment with steroids alone (48%) or rituximab-based regimens (59%; Fig. 3A) (33). Propensity score-matched analysis controlling for age, sex, FVIII level, inhibitor titre and underlying aetiology confirmed that stable remission was more likely with steroids and cyclophosphamide than steroids alone [odds ratio 3.25 (95% confidence interval, 1.51–6.96; $P < 0.003$)]. Despite this, survival was not significantly different between immunosuppressive treatment groups (Fig. 3B). This might reflect the increased toxicity of the regimens involving cyclophosphamide compared with the other immunosuppressive regimens used in EACH2. Data from EACH2 also indicated that a presenting inhibitor titre <16 BU/mL and higher FVIII levels are associated with achievement of stable remission (33). Preliminary data from the GTH AH-01/2010 study, the largest prospective study of AHA treated according to a standardised immunosuppressive treatment protocol ($n = 102$), also suggested that baseline FVIII activity may be considered to guide individually tailored immunosuppression in future studies (34). An alternative approach to total eradication of the auto-FVIII antibody has been described in the Budapest immune tolerance induction (ITI) protocol (using FVIII concentrates, cyclophosphamide and methylprednisolone) (35). Although the success and durability of this ITI regimen remains to be reproduced by others, the dramatic 93% success rate published by Nemes and Pitlik (35) cannot be overlooked.

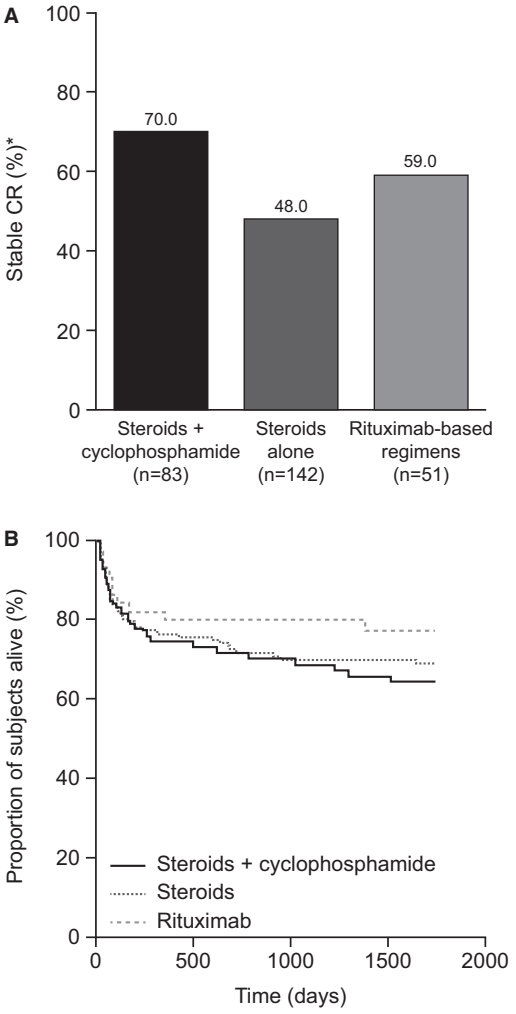


Figure 3 Treatment of patients with acquired haemophilia A in EACH2 with immunosuppressive regimens showing initial response to first-line treatment (panel A) and survival at final follow-up (panel B) (33). CR, complete response. *Inhibitor undetectable, factor VIII level >70 IU/dL and immunosuppression stopped and no relapse during follow-up. Republished with permission of the American Society of Hematology, from Collins P, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *Blood* 2012; 120: 47–55; permission conveyed through Copyright Clearance Center, Inc.

Unmet needs in acquired haemophilia

Clinical research in AHA is hampered by the rarity of the disease and observational findings from international registries provide the only feasible large-scale data source at present. Although many efforts have been made to fill the gap in knowledge of AHA, further efforts of cooperation and organisation must still be made in terms of registry data collection. Potential improvements for harmonised data collection include longer follow-up of patients, additional detailed information regarding dosing regimens and local clinical practice, use of a more standardised treatment protocol and collection of more data on surgery in AHA. Furthermore, detailed data analyses could be performed to identify patient groups responding to certain therapies and risk factors for recurrence of bleeding episodes and/or poor outcomes; analysis of patient subgroups (e.g. cancer patients) might also be helpful.

It is still not fully understood why patients with congenital haemophilia A and inhibitors and those with AHA differ in their clinical presentation. An improved understanding of the function of FVIII and strategies to avoid hindrance by inhibitory antibodies may help account for these differences, and research is currently underway in this area (36).

Conclusions

Although AHA is rare, development of autoantibody inhibitors against endogenous FVIII can be life-threatening. Early recognition and initiation of therapy is essential in reducing morbidity and mortality associated with the condition. However, the diagnosis of AHA is often difficult due to the lack of personal or family history of bleeding and the heterogeneous nature of the condition. Bypassing agents, rFVIIa or pd-aPCC, should be used as first-line therapy for the treatment of bleeding episodes in AHA. A combination of steroids plus cyclophosphamide should be considered as the most effective approach to eradicate the FVIII autoantibody, immediately following diagnosis. Further data collection in international registries will inform the best treatment approaches in the future.

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Author contributions

Craig M. Kessler (CMK) and Paul Knöbl (PK) were involved in the drafting and the approval for submission of this manuscript.

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CMK has received research and education grants and travel subsidies and fees for participation on consultant advisory boards from Novo Nordisk and Baxter, pertinent to the scope of this activity. He has not participated in any speakers bureaux. PK has received research and travel grants and speaker and consultancy fees from Novo Nordisk and Baxter.

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