

# Treatment of acquired hemophilia A

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**Summary.** Acquired hemophilia A (AH) is an autoimmune disease that leads to potentially severe bleeding. Management relies on rapid and accurate diagnosis, control of bleeding episodes and eradication of the inhibitor by immunosuppression. There is extensive literature about the disease but only few controlled data are available. This paper reviews the current literature on treatment strategies for hemostatic therapy and inhibitor eradication. Potential future developments are discussed.

**Keywords:** acquired hemophilia, bypassing agent, factor VIII, immunosuppression, inhibitor.

## Introduction

Acquired hemophilia A (AH) is an autoimmune disease caused by an autoantibody to factor VIII (FVIII). It is associated with a high morbidity and mortality secondary to bleeding, patient age, underlying diseases and the effects of immune suppression [1–5]. Early recognition and rapid diagnosis of AH is important to allow treatment of bleeds, avoidance of invasive procedures and inhibitor eradication. The incidence of AH is reported as 1.48 [6] and 1.34 [7] per million/year in the two studies in which patients were linked to a defined population. Both these studies describe cohorts from the UK and data related to incidence in other populations are awaited. The incidence of AH increases with age and is very uncommon in children (Fig. 1). The incidence in children under 16 years old is estimated to be 0.045 million<sup>-1</sup> year<sup>-1</sup> compared with 14.7 million<sup>-1</sup> year<sup>-1</sup> in those aged over 85 years [7]. It is also likely that AH is under diagnosed, especially in elderly patients. The incidence in males and females is similar except in 20–40 year olds where the effect of pregnancy results in a preponderance of females [2,7].

The pathogenesis, clinical associations and diagnosis of acquired hemophilia has previously been extensively reviewed [1–5,8]. This review will focus on the treatment of AH.

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The main principles of treatment for AH are to control bleeding, eradicate the inhibitor, treat underlying disorders and protect the patient against trauma and invasive procedures [9]. Up to one-third of patients do not require hemostatic therapy at diagnosis but remain at risk of severe bleeding until the inhibitor has been eradicated [7,10]. Patient education is important so that symptoms are reported early.

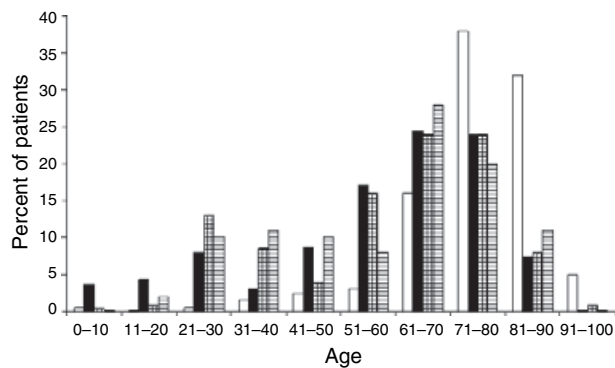
### Hemostatic management

Bleeding episodes may be very severe and prompt hemostatic control is required to reduce morbidity and mortality (Fig. 2). Treatment of bleeds in AH may be difficult and should be supervised by an expert in the field. Hemostatic agents do not have predictable efficacy, hence regular clinical review supported by appropriate imaging is necessary for optimal outcomes.

Hemostatic management depends on the site and severity of the bleed (Fig. 3). Imaging to assess the bleed is often useful and follow-up imaging, in combination with clinical observation, is often important to confirm hemostatic control and bleed resolution. Stabilization of the hemoglobin may also be a useful indicator of adequate hemostasis. Hemostatic therapy often needs to be continued at a reduced dose after initial hemostasis has been achieved to prevent relapse or recurrence. This is especially so after intracranial, muscle and retroperitoneal bleeds. Local measures to control bleeds should be used. Mucosal hemorrhage will benefit from concomitant therapy with an anti-fibrinolytic agent and topical fibrin glue may be useful in some cases.

The two options for hemostatic control are the use of bypassing agents and strategies to raise the level of circulating FVIII [9]. The choice between these strategies will depend on the site and severity of the bleed, patient characteristics and available facilities.

**Bypassing agents** Bypassing agents are currently the most commonly used first-line treatment [7] and both recombinant factor VIIa (rFVIIa) and factor eight inhibitor bypassing activity (FEIBA) have been shown to be efficacious in AH [11–13]. An analysis of 38 patients described retrospectively showed that in 60 bleeding episodes in which rFVIIa was used as non first line therapy a good response was reported in 75%, while in 14 bleeds treated as first line a good response was seen in 100%.



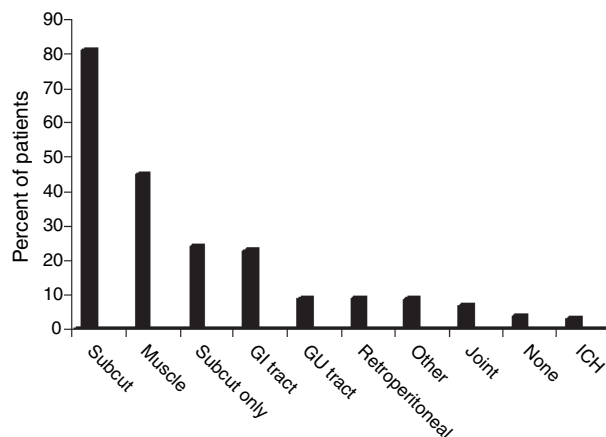
**Fig. 1.** Age-related incidence of acquired hemophilia A. Data are shown for percentage of patients presenting with acquired hemophilia A in each decade of life in four large studies. Black columns are from Green and Lechner [2], white columns are from Collins *et al.* [7], hatched columns are from Delgado *et al.* [1] and horizontal lined columns are from Morrison *et al.* [27].

In 60% of cases a good response had been seen by 8 h and responses at 8 and 24 h were generally predictive of overall response. A median of 28 doses (range 1–541) were required over a median of 3.9 (range 0–43) days [11]. Retrospective studies with FEIBA describe 34 severe and moderate bleeds treated, in the main, with  $75 \text{ U kg}^{-1}$  8–12 hourly. A median of six infusions were needed for moderate bleeds with 100% hemostatic efficacy at a median of 36 h compared with 10 infusions for severe bleeds with 76% hemostatic control at a median of 48 h [12].

The reports on the efficacy of rFVIIa and FEIBA can not be compared and there are no data to suggest that either agent has a superior hemostatic efficacy. Neither agent has predictable efficacy in all cases and close clinical monitoring of the patient is essential to determine response. The choice of agent should depend on considerations such as dosing schedule, use of plasma-derived products and cost. If first-line therapy fails the alternative bypassing agent may be successful. Both agents are associated with thrombotic events although these are less



**Fig. 2.** Bleeding in acquired hemophilia A. Acquired hemophilia A presenting as a forearm hematoma after venepuncture. The patient was taking alpha interferon for Castleman's disease both possible predisposing factors.



**Fig. 3.** Bleeding in acquired hemophilia. The bleeding pattern seen in a consecutive cohort of 172 patients with acquired hemophilia A [7]. Subcut is subcutaneous bleeding, subcut only means that subcutaneous bleeding was the only bleeding reported, no treatment means the patient did not require hemostatic therapy, GI tract is gastrointestinal bleeding, GU is genito-urinary and ICH is intracranial haemorrhage.

common if doses within the manufacturers' recommended range are used [14,15].

A strategy to escalate doses of rFVIIa above manufacturers recommendations has been described in the management of congenital hemophilia with inhibitors [16,17]. This approach should be used very cautiously in AH because there are no data to support that this practice is efficacious and patients are likely to have risk factors for arterial and venous thrombosis. However, in the management of severe bleeds uncontrolled by conventional doses, escalation may be justifiable on a case-by-case basis.

An important drawback for the use of bypassing agents is that currently there is no validated laboratory monitoring technique. While the use of thrombin generation assays [18,19] and modified thromboelastographic assays [20,21] hold promise, and changes in assay parameters can be demonstrated with *ex vivo* spiking and plasma taken from patients infused with bypassing agents, no data have been published that convincingly tie these results to hemostatic efficacy. Further data linking these assays to clinical endpoints are eagerly awaited. Extrapolation of results from inhibitors in congenital hemophilia to AH may not be valid as a result of the different inhibitor kinetics and bleeding phenotypes. If it is shown, however, that improvement of these assays with bypassing agents correlates with clinical efficacy a significant advance in the management of patients with FVIII inhibitors will have been made.

**Human FVIII** Human FVIII will usually be inadequate hemostatic therapy unless the inhibitor titer is low. The dose of FVIII required will need to be sufficient to overcome the inhibitor and provide an adequate hemostatic level. While formulae have been suggested for calculating the dose [4], the inaccuracies inherent in the laboratory measurement of inhibitor titers in AH makes these formulae at best very

rough approximations and regular monitoring of plasma FVIII level and clinical response is required.

The use of human FVIII in combination with immunoadsorption is more likely to result in hemostatic FVIII levels despite higher anti-FVIII inhibitor titers. This treatment strategy may be useful as first line or if bypassing agents or FVIII alone has failed. The technique relies on adequate venous access and FVIII levels must be closely monitored [22–25]. Many centers do not have access to immunoadsorption and it is technically difficult in small and acutely bleeding patients. Standard plasmapheresis is unlikely to be clinically useful.

**Porcine FVIII** In AH, the inhibitor titer to porcine FVIII is often 5–10% of the human titer and this may mean that porcine FVIII can achieve hemostatic levels in situations where human FVIII is ineffective [26,27]. If treatment with porcine FVIII is considered, an inhibitor titer should be measured to guide therapy and FVIII levels closely monitored. Porcine FVIII has been shown to have excellent or good hemostatic efficacy in 78% of 74 bleeds but no response in 9% [27]. It has been used successfully as a continuous infusion [28]. Plasma-derived porcine FVIII is not currently available for routine clinical use; however, a recombinant B-domain deleted porcine FVIII is undergoing phase II clinical trials in congenital hemophilia complicated by inhibitors and trials in AH are awaited.

**Desmopressin** Some patients with a low titer inhibitor and measurable baseline FVIII may respond to a desmopressin (DDAVP) infusion. A case report and literature review reporting on 22 cases found that in all 12 patients in whom with FVIII level was greater than 5%, DDAVP induced a rise in FVIII level to between 16–140%. The five patients in this group with Bethesda titers less than 2BU responded best, with peak FVIII levels >80% and a half life of 4–6 h. Amongst the 10 patients with FVIII levels <3%, seven had poor clinical and laboratory responses to DDAVP (FVIII post treatment <6%); three had an increase in FVIII to between 15% and 27%, with good clinical efficacy. The response to DDAVP is clearly unpredictable but its use can be considered for minor bleeding episodes [29].

**Management of surgery** Invasive procedures are associated with significant risk and hemostasis can not be guaranteed. Only essential procedures should be considered and the benefits carefully weighed against the risks. Relatively few details are available on surgeries undertaken in acquired hemophilia. Excellent hemostatic efficacy with FEIBA was reported for a bone marrow trephine and Hickman line insertion [13] while three unspecified operations were performed under rFVIIa cover with good outcome [11].

### **Inhibitor eradication**

Immunosuppressive therapy to eradicate the inhibitor in AH should be undertaken as soon as the diagnosis has been

made [9]. This recommendation is based on the finding that, while many patients do not have severe bleeding at presentation and some may have a spontaneous remission, fatal bleeds can occur at up to 5 months after presentation if the inhibitor is not eradicated and bleed-related morbidity is high [7,10]. Furthermore, an individual patient's presenting characteristics do not predict risk of future fatal bleeds [7]. While numerous publications can be found in the literature on this aspect of management the data are difficult to interpret because different endpoints and definitions are used and studies are predominantly reports of cohorts without controls. The majority of papers are case reports, single center cohort studies or retrospective surveys [2,6,23,25,30–59]. This means that almost all reported cases are from specialist centers, potentially leading to the literature reflecting more severely affected patients. Furthermore, good outcomes are more likely to be reported by centers (and accepted by journals) than average or poor outcomes. This means that much of the literature needs to be treated with caution and conclusions that can be drawn from many studies are limited.

The main options for immunosuppression are steroids, cytotoxics (cyclophosphamide, azathioprine or combination therapy), cyclosporin A, intravenous immunoglobulin, rituximab, plasmapheresis or immunoadsorption and FVIII immune tolerance. These treatments have been combined in numerous ways. A regimen may be considered superior if more patients achieve complete remission (CR) or if this remission is achieved more rapidly. Studies must be interpreted in the light of the finding that four out of 16 patients achieved a spontaneous remission [10].

### *Steroids and cytotoxic agents*

One prospective randomized study is available in which 31 patients were treated with prednisone 1 mg kg<sup>-1</sup> for 3 weeks. At this time, 10 patients were in CR. Continued treatment with prednisone led to CR in three of the four (75%) patients. Of the 10 patients randomized to adding cyclophosphamide to prednisone, five (50%) achieved CR and of those in whom cyclophosphamide was substituted for prednisone three out of six (50%) achieved CR. There was no difference between the treatment arms and, therefore, no evidence to suggest that adding or changing to cyclophosphamide at 3 weeks was better than continuing with steroids alone [60].

A non-randomized study compared patients treated with steroids vs. steroids and cytotoxics. The 34 patients treated with steroids had 76% CR at a median (95% confidence interval) of 49 (31–62) days compared with 78% CR at 39 (34–57) days for the steroids and cytotoxics group. There was no statistically significant difference between the treatment arms and mortality was not different [7].

A review that combined data from 20 reports demonstrated that the use of steroids and cyclophosphamide resulted in more patients achieving CR compared with steroids. The higher CR rate was not translated into a lower mortality. The authors

speculated that this reflected toxicity in elderly patients and suggested that studies should report both inhibitor eradication and toxicity [1].

The combined data available from uncontrolled cohorts appears to suggest a benefit for combined steroids and cytotoxic agents (Table 1). However, combination of data in this way must be treated cautiously, particularly in the light of the trend to publish positive outcomes. If the aggregate response rates are calculated for only those studies that included both steroids alone and combined steroid and cytotoxic therapy the remission rates are 77% and 79%, respectively. Regimens involving cyclophosphamide or combination chemotherapy have been reported to have high success rates [32,39,46,50,54] but without comparative treatment groups the results must be treated with caution. Whichever regimen is used, 3 weeks appears to be too short a time to assess outcome because the median time to remission is 5–7 weeks.

#### Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) has been suggested to be a useful agent in AH. A study on 16 assessable consecutive

patients showed that three achieved an undetectable inhibitor titer and normal FVIII level. The starting inhibitor titer in these patients was 0.9, 1.0 and 1.0 BU mL<sup>-1</sup> and one patient received concomitant steroids. In three further patients a fall in inhibitor titer was seen although in only one did the FVIII level increase [52]. A study of six patients treated with steroids and IVIG reported a CR rate of 66% [36]. A larger study that compared non-randomized patients who either did or did not receive IVIG [7] and a literature review [1] both showed no benefit for IVIG. At the present time the available evidence suggests that IVIG as a single agent or in combination with steroids and cytotoxics is not useful in inhibitor eradication in AH, although it possibly has a role in patients with very low inhibitor titers.

#### Rituximab

Rituximab has been used to treat cohorts of patients with AH. In one study, three patients treated with rituximab and either steroids or steroids plus a cytotoxic agent achieved CR. The role of each agent is difficult to establish because all drugs were commenced within 7 days of each other [59]. The largest study reported on 10 patients, of whom eight achieved CR and the two non-remitters responded to subsequent intravenous cyclophosphamide [56]. This response rate of 80% is very similar to other immunosuppressive therapies. It has been suggested that rituximab may lead to more rapid remission and control of bleeding than other therapies but without comparative patients this is difficult to clarify [56]. A further study in six patients treated with rituximab and steroids with or without cytotoxic agents found a CR rate of 100%. CR occurred at 1, 2, 4, 8, 36 and 52 weeks, times similar to previous studies of other immunosuppressive agents [61]. The effect of rituximab on the immune system of elderly patients is not clear and patients should be carefully followed for infection. The available data support the use of rituximab as either first- or second-line therapy but do not support the assertion that rituximab is superior to other immunosuppressive agents for patients with higher titer inhibitors as suggested by some authors [30]. Rituximab is a useful option for patients who have failed first-line therapy [61].

#### Cyclosporin A

A number of cases have been reported in which cyclosporin A has induced CR after failed first-line therapy [31,40,47,51,62].

#### Immune tolerance

The use of FVIII in conjunction with immunosuppressive agents in AH is reported. A stated rationale for this approach is that FVIII may stimulate antibody producing cells into division making them more susceptible to cytotoxic agents [45]. The lack of adequate controls means that direct assessment of the role of FVIII can not be made.

**Table 1** Inhibitor eradication therapy

Study	Steroids		Steroids and cytotoxics		Study reference
	n	% CR	n	% CR	
Saxena <i>et al.</i>	3/3	100	4/4	100	[50]
Ji <i>et al.</i>	7/8	88	–	–	[71]
Bossi <i>et al.</i>	9/10	90	14/16	88	[33]
Sallah <i>et al.</i>	8/9	89	8/14	57	[49]
Yee <i>et al.</i>	3/4	75	9/11	82	[57]
Mazzucconi	3/4	75	–	–	[72]
Dykes <i>et al.</i>	4/6	66	–	–	[36]
Di Bona <i>et al.</i>	5/8	63	1/3	33	[35]
Spero <i>et al.</i>	7/16	44	–	–	[55]
Grunewald <i>et al.</i>	1/3	33	6/6	100	[39]
Sohngen <i>et al.</i>	0/1	0	7/7	100	[54]
Shaffer <i>et al.</i>	–	–	9/9	100	[53]
Bayer <i>et al.</i>	–	–	8/8	100	[32]
Lian <i>et al.</i>	–	–	6/6	100	[46]
Burnet <i>et al.</i>	–	–	4/6	66	[34]
Sallah <i>et al.</i>	–	–	1/3	33	[48]
Godreuil <i>et al.</i>	2/3	66	0/2	0	[37]
Lian <i>et al.</i>	–	–	11/12	92	[45]
Green	7/10	70	–	–	[38]
Holme <i>et al.</i>	–	–	5/11	45	[41]
Huang <i>et al.</i>	–	–	4/5	80	[42]
Collins <i>et al.</i>	2/3	66	10/12	83	[6]
Ng <i>et al.</i>	–	–	8/12	75	[73]
Aggregate	42/67	62	97/116	83	

Papers reporting on inhibitor eradication therapy identified from the literature are presented. Although the percentage of patients achieving complete remission (CR) does not take into account the length of time patients were followed it allows a broad comparison between treatment groups. Not all patients from each study are included because treatment details or outcome could not be discerned. The results of a number of these studies were combined into a meta-analysis by Delgado and colleagues [1].

A report of patients treated with 3-weekly infusions of FVIII combined with vincristine, cyclophosphamide and steroids resulted in a 92% CR rate in 12 patients after 1–3 courses [45]. The same group, however, later published a report in six patients who were treated with vincristine, cyclophosphamide and steroids without FVIII and found 83% CR after 1–7 courses [46]. These data are difficult to interpret, the CR rates are not dissimilar to other published studies given the numbers of patients involved but the time to remission appears to be relatively short. The role of FVIII in these results is unclear because the intensity of immunosuppression was greater than for many other published protocols.

Infusion of FVIII on a daily basis (30 IU kg<sup>-1</sup> day<sup>-1</sup> for 1 week, 20 IU kg<sup>-1</sup> day<sup>-1</sup> for a second week and 15 IU kg<sup>-1</sup> day<sup>-1</sup> for a third week) combined with intravenous cyclophosphamide and methylprednisolone reported CR in 93% of 14 patients after a median 4.6 weeks, compared with 67% remission at a median of 28.3 weeks in six historical controls treated with steroids ± cyclophosphamide [63]. Although this is a relatively high CR rate the median time to response is similar to studies that did not use FVIII and the median time of 28.3 weeks to CR in the controls appears to be long.

Taken together these reports are insufficient to conclude that immune tolerance with FVIII is beneficial in AH and the cost of FVIII therapy in these protocols should be taken into account. Controlled studies appear to be the only way that this question can be answered.

#### *Immunoabsorption*

Immunoabsorption has been used to treat bleeding episodes by reducing the inhibitor titer but also as part of regimens aimed at inhibitor eradication. A cohort of 35 patients with AH and severe bleeding was treated with a combination of oral cyclophosphamide 1–2 mg kg<sup>-1</sup> daily, prednisolone 1 mg kg<sup>-1</sup> daily, immunoabsorption days 1–5 weekly, IVIG 0.3 g kg<sup>-1</sup> days 5–7 weekly and FVIII 100 u kg<sup>-1</sup> daily. Rapid control of bleeding was reported with an undetectable inhibitor at a median of 3 days (95% CI 2–4) and CR in 88% of patients at a median of 14 days (95% CI 12–17) [25]. The same group have extended the data to 48 patients with similar results and report no relapses after 48 weeks follow up [58]. Although no control patients are included, the CR rate is similar to other protocols and the cost of the FVIII considerable, this treatment regimen appears to rapidly control bleeding and induce CR. It is also not possible to state what role is played by the various components of the protocol. The main drawback of this type of treatment approach is that immunoabsorption is not available in many centers, is technically difficult particularly in small patients and may require invasive procedures to gain adequate access. It may also be difficult to perform in acutely bleeding patients.

#### *Relapse*

Relapse has been reported in 20% of 102 patients at a median of 7.5 months (range 1 week to 14 months). In this study, no

underlying disease was predictive of relapse and a second CR was induced in 10 (56%) patients and in a further four (22%) the inhibitor was eradicated, factor VIII normalized but immunosuppression could not be stopped without relapse. In four (22%) patients a second remission could not be achieved [7].

#### *Conclusions on inhibitor eradication*

There is general consensus that immunosuppression aimed at eradicating the inhibitor should be started as soon as the diagnosis of AH is made [1,4,5,9]. There are no convincing data to suggest that one immunosuppressive regimen is superior to any other or that the choice of regimen should be based on the inhibitor titer or FVIII level. First-line therapy is at the discretion of the clinician based on the clinical circumstances and taking into account the potential side effects of each treatment option. Although the median time to CR is about 4–6 weeks, response demonstrated by a fall in inhibitor titer or increase in FVIII level, is usually seen earlier. If a patient does not respond to first-line steroids then a cytotoxic agent or rituximab can be added. Similarly, if a patient fails first-line rituximab then steroids and cytotoxic agents may be successful. Cyclosporin A is a useful second-line option. A regimen based on high-dose FVIII and immunoabsorption can be considered for patients with severe bleeding.

#### **Pregnancy related acquired hemophilia**

There are features of pregnancy related AH that appear to be different from other patients. AH is a rare complication of pregnancy, estimated to affect 1 in 350 000 births in the UK [7] and 20 cases in 15 years were reported in a survey of 42 specialist Italian centers [64]. Patients usually present with bleeding at the time of delivery or within the first 1–4 months post-partum, although some present ante-partum [65] and cases up to a year after delivery have been reported [64–67]. The reason for the late presentations is unclear; however, some patients had been symptomatic for several months and may represent delayed diagnosis rather than late onset disease. The bleeding phenotype is similar to other patients with AH with the addition of bleeding related to vaginal delivery and Caesarean section [66].

These patients are younger and may have a different natural history and response to inhibitor eradication therapy [66]. Retrospective reviews have reported that in pregnancy related AH, the time to achieve remission is longer than in patients with other underlying etiologies, although conversely spontaneous remissions are recognized [64–66]. Similar to other patients with AH the available data are insufficient to convincingly conclude that outcome is affected by choice of immunosuppressive agents and treatment decisions should take into account the age of the patients and the potential side effects of drugs in women of child-bearing age [9]. A reasonable option is to treat initially with steroids alone and add a cytotoxic agent or rituximab if the response is not adequate.

Relapse in subsequent pregnancies appears to be relatively uncommon but women should be warned that this is a possibility. In one study it was observed that AH recurred in four out of six subsequent pregnancies in three patients [65]; however, no relapses were reported in nine subsequent pregnancies [68] in another study and an Italian Registry reported no relapses amongst four patients [64]. The antibody may affect the FVIII level of the fetus and this must be considered at the time of delivery [69].

Bleeding episodes vary between fatal and mild with some patients requiring no blood products [64,65]. Treatment of bleeds should follow the principles outlined for AH in general but caution about the risk of venous thromboembolism in the post-partum period should be borne in mind.

### Acquired hemophilia in children

AH in children is very uncommon with an incidence of  $0.045 \text{ million}^{-1} \text{ year}^{-1}$  in one study [7]. A survey of hemophilia centers in USA reported six cases and a literature review revealed another eight presumed or definite cases [70]. A large retrospective study reported a further six cases [2]. Patients appeared to present with similar bleeding patterns to adults and responded to standard immunosuppression. Reported underlying disorders included juvenile rheumatoid arthritis, positive anti-nuclear antibody, infection/antibiotic use, Goodpasture's syndrome, liver disease and gastritis [70].

### Future developments

Clinical progress in AH is hampered by the small numbers of patients and difficulties in performing randomized studies. In the area of bleed control, it is recognized that the hemostatic efficacy of all agents is unpredictable. A laboratory assay that has been clinically validated to predict successful hemostasis would be a very significant step forward. In this context, understanding why the bleeding phenotype in AH differs from congenital hemophilia may lead to a better understanding of the mechanism of hemostatic failure and possibly translate into improved hemostatic management. Access to new hemostatic agents is important and, if clinical trials show efficacy and safety, the B domain-deleted recombinant porcine factor VIII molecule will be a useful addition to the treatment armamentarium.

Studies in the field of inhibitor eradication are a major challenge, demonstrated by the fact that the literature contains only one randomized prospective clinical trial [60]. Trials that compare conventional steroid and cytotoxic agents with rituximab or investigate the role of FVIII would be useful. These trials will need to recruit hundreds of patients to be adequately powered and require international collaboration and significant resources to perform. It must be recognized that these trials may not be possible and the use of international registries may provide the only feasible source of data at present.

### Conclusion

The understanding of AH has progressed slowly as a result of difficulties in conducting randomized studies. The only viable option is establishing international collaboration supported by adequate resources.

### Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

### References

- Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol* 2003; **121**: 21–35.
- Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to Factor VIII. *Thromb Haemost* 1981; **45**: 200–3.
- Hay CR. Acquired haemophilia. *Baillieres Clin Haematol* 1998; **11**: 287–303.
- Kessler C, Asatiani E. Acquired inhibitors to factor VIII. In: Lee CA, Berntorp E, Hoots WK, eds. *Textbook of Hemophilia*. Oxford: Blackwell, 2006: 86–90.
- Morrison AE, Ludlam CA. Acquired haemophilia and its management. *Br J Haematol* 1995; **89**: 231–6.
- Collins P, Macartney N, Davies R, Lees S, Giddings J, Majer R. A population based, unselected, consecutive cohort of patients with acquired haemophilia A. *Br J Haematol* 2004; **124**: 86–90.
- Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, Keeling DM, Liesner R, Brown SA, Hay CR, UK Haemophilia Centre Doctors' Organisation. Acquired haemophilia A in the UK: a two year national surveillance study by UK Haemophilia Centre Doctors' Organisation. *Blood* 2007; **109**: 1870–7.
- Lollar P. Pathogenic antibodies to coagulation factors. Part one: factor VIII and factor IX. *J Thromb Haemost* 2004; **2**: 1082–95.
- Hay CRM, Brown SA, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol* 2006; **133**: 591–605.
- Lottenberg R, Kentro TB, Kitchens CS. Acquired hemophilia. A natural history study of 16 patients with factor VIII inhibitors receiving little or no therapy. *Arch Intern Med* 1987; **147**: 1077–81.
- Hay CR, Negrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. *Thromb Haemost* 1997; **78**: 1463–7.
- Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. *Haemophilia* 2004; **10**: 169–73.
- Tjonnfjord GE. Activated prothrombin complex concentrate (FEIBA) treatment during surgery in patients with inhibitors to FVIII/IX: the updated Norwegian experience. *Haemophilia* 2004; **10**(Suppl. 2): 41–5.
- Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. *J Thromb Haemost* 2004; **2**: 1700–8.
- Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa vs factor VIII inhibitor bypass activity – reply to a rebuttal. *J Thromb Haemost* 2005; **3**: 822.
- Parameswaran R, Shapiro AD, Gill JC, Kessler CM. Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia* 2005; **11**: 100–6.
- Santagostino E, Mancuso ME, Rocino A, Mancuso G, Scaraggi F, Mannucci PM. A prospective randomized trial of high and standard dosages of recombinant factor VIIa for treatment of hemarthroses in hemophiliacs with inhibitors. *J Thromb Haemost* 2006; **4**: 367–71.

- 18 Turecek PL, Varadi K, Keil B, Negrier C, Berntorp E, Astermark J, Bordet JC, Morfini M, Linari S, Schwarz HP. Factor VIII inhibitor-bypassing agents act by inducing thrombin generation and can be monitored by a thrombin generation assay. *Pathophysiol Haemost Thromb* 2003; **33**: 16–22.
- 19 Varadi K, Negrier C, Berntorp E, Astermark J, Bordet JC, Morfini M, Linari S, Schwarz HP, Turecek PL. Monitoring the bioavailability of FEIBA with a thrombin generation assay. *J Thromb Haemost* 2003; **1**: 2374–80.
- 20 Sorensen B, Ingerslev J. Thromboelastography and recombinant factor VIIa-hemophilia and beyond. *Semin Hematol* 2004; **41**(Suppl. 1): 140–4.
- 21 Sorensen B, Ingerslev J. Whole blood clot formation phenotypes in hemophilia A and rare coagulation disorders. Patterns of response to recombinant factor VIIa. *J Thromb Haemost* 2004; **2**: 102–10.
- 22 Freedman J, Rand ML, Russell O, Davis C, Cheatley PL, Blanchette V, Garvey MB. Immunoabsorption may provide a cost-effective approach to management of patients with inhibitors to FVIII. *Transfusion* 2003; **43**: 1508–13.
- 23 Guillet B, Kriaa F, Huisse MG, Proulle V, George C, Tchernia G, D'Oiron R, Laurian Y, Charpentier B, Lambert T, Dreyfus M. Protein A sepharose immunoabsorption: immunological and haemostatic effects in two cases of acquired haemophilia. *Br J Haematol* 2001; **114**: 837–44.
- 24 Rivard GE, St Louis J, Lacroix S, Champagne M, Rock G. Immunoabsorption for coagulation factor inhibitors: a retrospective critical appraisal of 10 consecutive cases from a single institution. *Haemophilia* 2003; **9**: 711–6.
- 25 Zeidler H, Ulrich-Merzenich G, Hess L, Konsek E, Unkrig C, Walger P, Vetter H, Brackmann HH. Treatment of acquired hemophilia by the Bonn-Malmö Protocol: documentation of an in vivo immunomodulating concept. *Blood* 2005; **105**: 2287–93.
- 26 Hay CR, Lozier JN, Lee CA, Laffan M, Tradati F, Santagostino E, Ciavarella N, Schiavoni M, Fukui H, Yoshioka A, Teitel J, Mannucci PM, Kasper CK. Safety profile of porcine factor VIII and its use as hospital and home-therapy for patients with haemophilia-A and inhibitors: the results of an international survey. *Thromb Haemost* 1996; **75**: 25–9.
- 27 Morrison AE, Ludlam CA, Kessler C. Use of porcine factor VIII in the treatment of patients with acquired hemophilia. *Blood* 1993; **81**: 1513–20.
- 28 O'Gorman P, Dimichele DM, Kasper CK, Mannucci PM, Santagostini E, Hay CR. Continuous infusion of porcine factor VIII in patients with haemophilia A and high-responding inhibitors: stability and clinical experience. *Haemophilia* 2001; **7**: 537–43.
- 29 Mudar R, Kane WH. DDAVP in acquired hemophilia A: case report and review of the literature. *Am J Hematol* 1993; **43**: 295–9.
- 30 Aggarwal A, Grewal R, Green RJ, Boggio L, Green D, Weksler BB, Wiestner A, Schechter GP. Rituximab for autoimmune haemophilia: a proposed treatment algorithm. *Haemophilia* 2006; **11**: 13–9.
- 31 Au WY, Lam CC, Kwong YL. Successful treatment of acquired factor VIII inhibitor with cyclosporin. *Haemophilia* 2004; **10**: 98–100.
- 32 Bayer RL, Lichtman SM, Allen SL, Budman DR, Buchbinder A, Fettes J, Kolitz J, Loscalzo J. Acquired factor VIII inhibitors – successful treatment with an oral outpatient regimen. *Am J Hematol* 1999; **60**: 70–1.
- 33 Bossi P, Cabane J, Ninet J, Dhote R, Hanslik T, Chosidow O, Jouan-Flahault C, Horellou MH, Leynadier F, Liozon E, Pouchot J, Robin JP, Sanderson F, Schaeffer A, Sicard D, Staikowsky F, Wechsler B, Zittoun R. Acquired hemophilia due to factor VIII inhibitors in 34 patients. *Am J Med* 1998; **105**: 400–8.
- 34 Burnet SP, Duncan EM, Lloyd JV, Han P. Acquired haemophilia in South Australia: a case series. *Int Med J* 2001; **31**: 556–9.
- 35 Di Bona E, Schiavoni M, Castaman G, Ciavarella N, Rodeghiero F. Acquired haemophilia: experience of two Italian centres with 17 new cases. *Haemophilia* 2006; **3**: 183–8.
- 36 Dykes AC, Walker ID, Lowe GD, Tait RC. Combined prednisolone and intravenous immunoglobulin treatment for acquired factor VIII inhibitors: a 2-year review. *Haemophilia* 2001; **7**: 160–3.
- 37 Godreuil S, Navarro R, Quittet P, Landreau L, Schved JF, Biron-Andreani C. Acquired haemophilia in the elderly is a severe disease: report of five new cases. *Haemophilia* 2001; **7**: 428–32.
- 38 Green D. Oral immunosuppressive therapy for acquired hemophilia. *Ann Intern Med* 1998; **128**: 325.
- 39 Grunewald M, Beneke H, Guthner C, Germowitz A, Brommer A, Griesshammer M. Acquired haemophilia: experiences with a standardized approach. *Haemophilia* 2001; **7**: 164–9.
- 40 Hart HC, Kraaijenhagen RJ, Kerckhaert JA, Verdel G, Freen M, van de WA. A patient with a spontaneous factor VIII:C autoantibody: successful treatment with cyclosporine. *Transplant Proc* 1988; **3**(Suppl. 4): 323–8.
- 41 Holme PA, Brosstad F, Tjonnfjord GE. Acquired haemophilia: management of bleeds and immune therapy to eradicate autoantibodies. *Haemophilia* 2005; **11**: 510–5.
- 42 Huang YW, Saidi P, Philipp C. Acquired factor VIII inhibitors in non-haemophilic patients: clinical experience of 15 cases. *Haemophilia* 2004; **10**: 713–21.
- 43 Hultin MB, Shapiro SS, Bowman HS, Gill FM, Andrews AT, Martinez J, Eyster EM, Sherwood WC. Immunosuppressive therapy of Factor VIII inhibitors. *Blood* 1976; **48**: 95–108.
- 44 Kain S, Copeland TS, Leahy MF. Treatment of refractory autoimmune (acquired) haemophilia with anti-CD20 (rituximab). *Br J Haematol* 2002; **119**: 578.
- 45 Lian EC, Larcada AF, Chiu AY. Combination immunosuppressive therapy after factor VIII infusion for acquired factor VIII inhibitor. *Ann Intern Med* 1989; **110**: 774–8.
- 46 Lian EC, Villar MJ, Noy LI, Ruiz-Dayao Z. Acquired factor VIII inhibitor treated with cyclophosphamide, vincristine, and prednisone. *Am J Hematol* 2002; **69**: 294–5.
- 47 Pardos-Gea J, Ordi-Ros J, Altisent C, Balada E, Perez-Lopez J, Vilarde M. Acquired haemophilia A: successful treatment with immunosuppression, methylprednisolone pulses and oral cyclosporin. *Thromb Haemost* 2006; **95**: 735–7.
- 48 Sallah S, Singh P, Hanrahan LR. Antibodies against factor VIII in patients with solid tumors: successful treatment of cancer may suppress inhibitor formation. *Haemostasis* 1998; **28**: 244–9.
- 49 Sallah S, Wan JY. Inhibitors against factor VIII in patients with cancer. Analysis of 41 patients. *Cancer* 2001; **91**: 1067–74.
- 50 Saxena R, Mishra DK, Kashyap R, Choudhry VP, Mahapatra M, Bhargava M. Acquired haemophilia – a study of ten cases. *Haemophilia* 2000; **6**: 78–83.
- 51 Schulman S, Langevitz P, Livneh A, Mortinowitz U, Seligsohn U, Varon D. Cyclosporine therapy for acquired factor VIII inhibitor in a patient with systemic lupus erythematosus. *Thromb Haemost* 1996; **76**: 344–6.
- 52 Schwartz RS, Gabriel DA, Aledort LM, Green D, Kessler CM. A prospective study of treatment of acquired (autoimmune) factor VIII inhibitors with high-dose intravenous gammaglobulin. *Blood* 1995; **86**: 797–804.
- 53 Shaffer LG, Phillips MD. Successful treatment of acquired hemophilia with oral immunosuppressive therapy. *Ann Intern Med* 1997; **127**: 206–9.
- 54 Sohngen D, Specker C, Bach D, Kuntz BM, Burk M, Aul C, Kobbe G, Heyll A, Hollmig KA, Schneider W. Acquired factor VIII inhibitors in nonhemophilic patients. *Ann Hematol* 1997; **74**: 89–93.
- 55 Spero JA, Lewis JH, Hasiba U. Corticosteroid therapy for acquired F VIII:C inhibitors. *Br J Haematol* 1981; **48**: 635–42.
- 56 Stasi R, Brunetti M, Stipa E, Amadori S. Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. *Blood* 2004; **103**: 4424–8.
- 57 Yee TT, Taher A, Pasi KJ, Lee CA. A survey of patients with acquired haemophilia in a haemophilia centre over a 28-year period. *Clin Lab Haematol* 2000; **22**: 275–8.

- 58 Zeitler H, Ulrich-Merzenich G, Walger P, Dusing R, Vetter H, Brackmann HH. The modified Bonn Malmo protocol (MBMP) in the treatment of acquired haemophilia A. *Dtsch Med Wochenschr* 2006; **131**: 141–7.
- 59 Wiestner A, Cho HJ, Asch AS, Michelis MA, Zeller JA, Peerschke EI, Weksler BB, Schechter GP. Rituximab in the treatment of acquired factor VIII inhibitors. *Blood* 2002; **100**: 3426–8.
- 60 Green D, Rademaker AW, Briet E. A prospective, randomized trial of prednisone and cyclophosphamide in the treatment of patients with factor VIII autoantibodies. *Thromb Haemost* 1993; **70**: 753–7.
- 61 Adedayo AA, Skorupa A, Lal A, Ronsih E, Mercier RJ, Islam R. Rituximab in the treatment of acquired factor VIII inhibitors. *Thromb Haemost* 2006; **96**: 87.
- 62 Pfliegler G, Boda Z, Harsfalvi J, Flora-Nagy M, Sari B, Pecze K, Rak K. Cyclosporin treatment of a woman with acquired haemophilia due to factor VIII:C inhibitor. *Postgrad Med J* 1989; **65**: 400–2.
- 63 Nemes L, Pitlik E. New protocol for immune tolerance induction in acquired hemophilia. *Haematologica* 2000; **85**(Suppl. 10): 64–8.
- 64 Italian Association of Haemophilia Centres (AICE). Acquired factor VIII inhibitors in pregnancy: data from the Italian Haemophilia Registry relevant to clinical practice. *Int J Gynaecol Obstet* 2003; **10**: 311–4.
- 65 Solymoss S. Postpartum acquired factor VIII inhibitors: results of a survey. *Am J Hematol* 1998; **59**: 1–4.
- 66 Hauser I, Schneider B, Lechner K. Post-partum factor VIII inhibitors. A review of the literature with special reference to the value of steroid and immunosuppressive treatment. *Thromb Haemost* 1995; **73**: 1–5.
- 67 Michiels JJ, Hamulyak K, Nieuwenhuis HK, Novakova I, van Vliet HH. Acquired haemophilia A in women postpartum: management of bleeding episodes and natural history of the factor VIII inhibitor. *Eur J Haematol* 1997; **59**: 105–9.
- 68 Collier BS, Hultin MB, Hoyer LW, Miller F, Dobbs JV, Dosik MH, Berger ER. Normal pregnancy in a patient with a prior postpartum factor VIII inhibitor: with observations on pathogenesis and prognosis. *Blood* 1981; **58**: 619–24.
- 69 Ries M, Wolfel D, Maier-Brandt B. Severe intracranial hemorrhage in a newborn infant with transplacental transfer of an acquired factor VIII inhibitor. *J Pediatr* 1995; **127**: 649–50.
- 70 Moraca RJ, Ragni MV. Acquired anti-FVIII inhibitors in children. *Haemophilia* 2002; **8**: 28–32.
- 71 Ji L, Yang R, Yang D, Chen Z, Xing S, Tian M, Sun Y. Prednisone and low-dose activated prothrombin complex concentrates for FVIII inhibitor in nonhemophilic patients. *Haemophilia* 1998; **4**: 721–4.
- 72 Mazzucconi MG, Bizzoni L, Giorgi A, Morano SG, Peraino M, Russo M, Alimena G. Postpartum inhibitor to factor VIII: treatment with high-dose immunoglobulin and dexamethasone. *Haemophilia* 2001; **7**: 422–7.
- 73 Ng HJ, Tan DC, Lee LH. Treatment and outcome of acquired haemophilia A with a standard conventional regimen in a cohort without associated conditions. *Haemophilia* 2006; **12**: 423–8.