Acquired haemophilia A: A 2013 update
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Summary
Acquired haemophilia A (AHA) is a rare but often severe bleeding disorder caused by autoantibodies against coagulation factor VIII (FVIII). AHA occurs more frequently in the elderly and in association with several conditions, such as the post-partum period, malignancies, autoimmune diseases or drug exposure; however, approximately 50% of reported cases are apparently idiopathic. Beside the elimination of the underlying disorder, the therapeutic approach to AHA should be directed toward the control of acute bleed and the eradication of FVIII autoantibody production. In this narrative review, we summarise the current knowledge on the epidemiology, diagnosis and clinical features of AHA, focusing in particular on advances in the management of this challenging bleeding disorder.

Keywords
Acquired haemophilia A, FVIII, auto-antibodies, bleeding, inhibitors, therapy

Introduction
Acquired haemophilia A (AHA) is a rare autoimmune disorder caused by circulating auto-antibodies that inhibit the coagulant activity of factor VIII (FVIII) (1-7). Such acquired inhibitors are clearly distinct from FVIII alloantibodies occurring in patients with congenital haemophilia A following exposure to therapeutically administered FVIII (7). AHA is often a demanding clinical challenge and a life-threatening condition. Beside the severity of bleeding and of the underlying diseases, underestimation of symptoms, diagnostic delays and inadequate therapeutic approaches contribute to the high mortality rate reported (2-4). Recent national and international studies have increased our knowledge about clinical presentation, diagnosis, treatment modalities and outcomes of AHA (8, 9), providing the basis for recommendations on clinical management (10, 11). This article will review these topics, focusing particularly on therapeutic aspects. We performed a search on PubMed using the following terms with no time limits: ‘acquired haemophilia A’, ‘acquired haemophilia and factor VIII’, ‘acquired factor VIII inhibitors’, ‘autoantibodies and coagulation factors’, ‘anti-factor VIII antibodies’, ‘factor VIII autoantibodies’, ‘autoimmune factor VIII inhibitors’, ‘haemophilia and autoantibodies’, ‘spontaneous inhibitors and factor VIII’. The date of the last search was April 30, 2013. The references of all retrieved articles were assessed for additional relevant articles.

Clinical aspects
Epidemiology
Acquired inhibitors against FVIII occur rarely in the non-haemophilic population, with a reported incidence of approximately one case per million/year (12, 13), although epidemiologic data are likely to be underestimated in elderly patients. The incidence of AHA increases with age, being a very uncommon disease in children (14, 15). Indeed, the incidence in children under 16 years has been estimated to be 0.045 per million/year compared with 14.7 per million/year in the elderly over 85 years (8, 16). The median age of diagnosed patients was 78 and 74 years in the two largest available cohorts, the prospective UK study (8) and the European Acquired Haemophilia (EACH2) registry (9), more than 80% of patients being 65 years or older. The incidence in males and females is similar, with an exception in the 20-40 year age interval due to pregnancy-related cases (17-20).

Diagnosis
AHA is usually recognised following the laboratory investigation of abnormal bleeding in subjects with negative family and personal bleeding history, although occasionally patients are diagnosed during routine blood tests with no prior clinical evidence of bleeding. The initial diagnosis is typically based on the detection of an isolated prolongation of the activated partial thromboplastin time (APTT), which cannot be corrected by incubating equal volumes of patient and normal plasma (mixing study) (21). The diagnosis is confirmed by the subsequent identification of reduced FVIII levels
with evidence of FVIII neutralising activity (titrated using the Bethesda assay or the Nijmegen modification) (Figure 1) (4, 22). Similar to the alloantibodies occurring in congenital haemophilia A, FVIII autoantibodies are reported as being polyclonal and belonging predominantly to IgG1 and IgG4 subclasses. Moreover, both auto- and alloantibodies appear to react with the same regions of the FVIII molecule (mainly the A2, A3 and C2 domains), thus interfering with interaction with FIXa, phospholipids and von Willebrand factor (3).

Pathogenesis
The breakdown of immune tolerance mechanisms that regulate a normal immune response to FVIII is thought to be responsible for the development of autoantibodies (23). In particular, a complex interaction between different CD4+ T cell subsets, i.e. Th1 (which stimulate B cells to produce IgG1 antibodies) and Th2 (which stimulate B cells to produce IgG4 antibodies) cells, is implicated in the production of anti-FVIII antibodies. Indeed, a strong positive association between inhibitor titre and the proportion of Th2-driven IgG4 anti-FVIII antibody has been observed (24). Thus, a predominance of Th2-driven IgG4 anti-FVIII antibody is correlated with a more intense anti-FVIII response, with a high inhibitor titre and, ultimately, with failure to eradicate the inhibitor. Vice versa successful immunosuppressive therapy in AHA correlates with a predominance of Th1-driven anti-FVIII antibody. According to recent studies, the breakdown of immune tolerance in AHA appears to result from a combination of environmental and genetic factors. Among the latter, some human leucocyte antigen class II alleles and a single nucleotide polymorphism of cytotoxic T-lymphocyte antigen 4 (CTLA-4) gene seem to play an important role (25).

Bleeding pattern
The most striking difference between auto- and alloantibodies is their FVIII inactivation pattern. While antibodies arising in congenital haemophilia act with a first-order linear kinetic reaction, autoantibodies show a second-order non-linear inactivation pattern (21). Thus, the Bethesda assay, which quantifies the in vitro inhibitor titre, may underestimate the in vivo inhibitor potency, due to non-linear reaction kinetics (26). Consequently, inhibitor titres or residual FVIII activity do not correlate closely with the bleeding phenotype and severe bleeding may occur even in the presence of relatively high (up to 10-20% of normal) FVIII levels.

The bleeding pattern of AHA is rather different from that of congenital haemophilia A. Thus, most patients with FVIII autoantibodies have haemorrhages into the skin, muscles or soft tissues and mucous membranes (e.g. epistaxis, gastrointestinal and uro-
logical bleeds), whereas haemarthroses, a typical feature of congenital FVIII deficiency, are uncommon (13). Acquired haemophilia A is a very severe bleeding disorder, being associated with high morbidity and mortality rates. Severe or life-threatening bleeds, which involve most frequently the gastrointestinal tract and the retroperitoneal space, occur in 70-90% of patients, being fatal in 5-10% of cases (6). The clinical impact of AHA is also high, because the severity of bleeding is adversely affected by diagnostic delays, inadequate treatment and haemorrhagic complications during invasive procedures for controlling haemorrhages. These factors may also contribute the overall mortality rate (up to 41% reported in literature) (6), which is significantly increased by the underlying diseases and adverse events of treatment (infections or sepsis on immunosuppressive therapy), particularly in elderly patients and during the first few weeks after the onset of symptoms (8, 9, 27-30).

Associated diseases

Clinical conditions associated with AHA include solid tumours and lymphoproliferative malignancies (31-35), autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome or thyroid disorders) (36-40), skin diseases (pemphigus and epidermolysis bullosa), drugs (penicillin and interferon) and infections (hepatitis B and C viruses) (41-46). The post-partum state is another frequent setting in which AHA may occur (17-20, 47-49). Rates of pregnancy-associated AHA range between 2% to 15% in the largest available cohorts of patients (8, 18, 20, 27). Most commonly the inhibitor develops between three and 150 days after parturition, but sometimes during labour, leading to severe blood loss (48). When the inhibitor does develop during pregnancy, there is a risk of transplacental transfer of the IgG antibody and neonatal haemorrhage (50). On the whole, pregnancy-associated AHA shows a more favourable prognosis than AHA associated with other conditions, with low mortality rates (0-6%) and spontaneous or treatment-induced remissions in a high proportion of women (77-86%) (2, 18, 20). Figure 2 summarises the literature data on the distribution of idiopathic and secondary cases of AHA.

Management

A prompt diagnosis and start of an appropriate treatment is crucial in AHA for a favourable outcome, which also depends on the identification and treatment of possible concomitant diseases or triggering conditions that, in some cases may lead to the disappearance of the inhibitor (32, 36, 51). Due to the severity of bleeding manifestations and complexity of management, patients with suspected or confirmed AHA should be handled in collaboration with haemophilia centres with specialised laboratory and clinical experience in this setting (6).

Similarly to the treatment in case of FVIII alloantibodies, the management of AHA is directed to the control of bleeding episodes and the eradication of the inhibitor. A series of options are available for both therapeutic objectives (▶Table 1) (52-55).

Therapy of bleeding

Efficient haemostasis and control of bleeding can be achieved with a variety of methods that may be used in combination: normalisation/correction of FVIII deficiency (human plasma derived or recombinant FVIII concentrates, desmopressin), bypassing the inhibitor activity (activated prothrombin complex concentrates [APCC] and recombinant activated factor VII [rFVIIa]) and removal of the inhibitor by plasmapheresis or immunoadsorption (54). Bypassing agents are recommended as first-line treatment of bleeding episodes (54) and both rFVIIa and APCC are effective, although there are no comparative trials to demonstrate superior efficacy for either product (55-62) (▶Table 2). Sallah (58) retrospectively analysed the efficacy of Factor Eight Inhibitor Bypassing Activity (FEIBA), the most widely used APCC, in 34 AHA patients. FEIBA doses ranging between 50 and 100 IU/Kg every 8-12 hours (h) provided an excellent or good haemostatic efficacy in 76-100% of treated bleeds, with higher efficacy (100%) reported in moderately severe episodes (58). More data are available on the use of rFVIIa in AHA, with average doses of 90 µg/kg (range, 40-180) every 2-6 h for a widely variable duration of treatment ranging from 1-60 days (61). In a retrospective analysis of 38 patients, Hay et al. (59) reported a good response in 100% of patients.
when rFVIIa was used as a first-line treatment, and in 75% of patients when it was used as salvage therapy after failure of blood products. Sumner et al. (60) collected the available data on the use of rFVIIa in AHA from compassionate use programs, the Haemophilia and Thrombosis Research Society (HTRS) registry and the published literature. A total of 139 patients were treated with rFVIIa for 204 bleeding episodes. The overall efficacy rate (complete or partial) of rFVIIa was 88% (161/182 bleeding episodes valuable). rFVIIa as a first-line treatment was effective in 95% of bleeding episodes, compared with 80% when it was used as salvage therapy after failure of other haemostatic agents. rFVIIa was the most frequently used first-line therapy in the EACH2 Registry (51% of bleeds vs 19% APCC and 18% FVIII concentrate) and both bypassing agents showed similar rates (93%) of bleeding control (62). For both these agents the main safety concern remains the thromboembolic risk (63-65). Eleven thrombotic events (7 arterial and 4 venous) were reported in the EACH2, with a similar incidence for rFVIIa (2.9%) and APCC (4.8%) (62). This incidence, which appears to be higher than that reported in congenital haemophilia, is probably due to the older age and additional age-related cardiovascular risk factors in AHA patients.

Alternative therapeutic strategies aimed to raise the levels of circulating FVIII are suggested only when bypassing agents are not available (11), because data from the EACH2 Registry confirm a significant higher rate of bleeding control in patients treated with bypassing agents than in those receiving replacement therapy with FVIII concentrates or desmopressin (93.3% vs 68.3%, p=0.003) (62). Indeed, human FVIII is usually inadequate for haemostasis, unless the inhibitor titre is low and FVIII is administered at doses that overtake the inhibitor, so that haemostatic plasma levels are achieved. Moreover, the risk of anamnestic response and the need for careful monitoring FVIII levels are challenging in the management of patients. Desmopressin (alone or in association with FVIII concentrates) may be useful in treating minor bleeds in patients with low inhibitor titres and basal FVIII levels above 5 IU/dl (66, 67). Due to the reduced cross-reactivity with human FVIII inhibitors (usually 5-10%), FVIII derived from porcine plasma was successfully used in the past (68). A recombinant B-domain deleted porcine FVIII product (OBI-1) is currently under investigation in AHA (69, 70). In patients with high inhibitor titres and severe haemorrhages, the extracorporeal removal of the autoantibody by therapeutic plasmapheresis, or its immunoadsorption on staphylococcal protein A or polyclonal sheep antibodies against human immunoglobulins, can be used in order to achieve a prompt, although transient, inhibitor removal and then make possible treatment with human FVIII concentrates (71-74).

### Table 1: Therapeutic options for AHA.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Bypassing agent</th>
<th>Patients / bleeds (n)</th>
<th>Efficacy (%)</th>
<th>Severe adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bleeds</td>
<td>rFVIIa</td>
<td>38/74</td>
<td>100–75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>One patient developed DIC</td>
</tr>
<tr>
<td>Inhibitor eradication</td>
<td>Prednisone (1 mg/kg/d, 4–6 weeks) alone or with cyclophosphamide (1.5–2 mg/kg/day, maximum 5 weeks)</td>
<td>15/20</td>
<td>87</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 2: Summary of the results of the most important studies on the use of bypassing agents in AHA.

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Study design</th>
<th>Bypassing agent</th>
<th>Patients / bleeds (n)</th>
<th>Efficacy (%)</th>
<th>Severe adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hay, 1997 (59)</td>
<td>Retrospective</td>
<td>rFVIIa</td>
<td>38/74</td>
<td>100–75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>One patient developed DIC</td>
</tr>
<tr>
<td>Baudo, 2004 (56)</td>
<td>Retrospective</td>
<td>rFVIIa</td>
<td>15/20</td>
<td>87</td>
<td>No</td>
</tr>
<tr>
<td>Sallah, 2004 (58)</td>
<td>Retrospective</td>
<td>APCC</td>
<td>34/55</td>
<td>85</td>
<td>No</td>
</tr>
<tr>
<td>Sumner, 2007 (60)</td>
<td>Registries, literature review</td>
<td>rFVIIa</td>
<td>139/204</td>
<td>83–66&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 patients had 12 thrombotic events</td>
</tr>
<tr>
<td>Baudo, 2012 (62)</td>
<td>Prospective, EACH2 Registry</td>
<td>APCC, rFVIIa</td>
<td>NR/63, NR/174</td>
<td>93, 91</td>
<td>Thrombotic events in 3.6% of treated patients, with a similar incidence between rFVIIa (2.9%) and APCC (4.8%)</td>
</tr>
</tbody>
</table>

APCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII.
Antibody eradication

Patients with AHA should receive immunosuppressive therapy in order to eradicate inhibitory autoantibodies immediately following the diagnosis, because they remain at risk of fatal bleeding until normal haemostasis has been restored, even when clinical presentation appears to be benign. Options for immunosuppression are corticosteroids alone or in combination with cytotoxic drugs (cyclophosphamide, azathioprine, 6-mercaptopurine and vincristine), rituximab, cyclosporin A and FVIII immune tolerance.

Corticosteroids/cyclophosphamide

The most commonly used therapeutic strategy, which achieves complete inhibitor eradication in approximately 70-80% of patients, is based on corticosteroids, alone (prednisone 1-2 mg/kg per day for at least 5 weeks) or in combination with cyclophosphamide (1-2 mg/kg per day) (53, 54, 74-76). However, the majority of available data stem from case reports or single-centre small retrospective studies that are very difficult to compare due to the heterogeneity of regimens and patient characteristics. The only randomised prospective trial in this setting was published in 1993 and dealt with 31 patients initially treated with prednisone alone at a dose of 1 mg/kg/day for three weeks (77). If the autoantibody was still detectable, patients were then randomised to receive for six weeks one of these regimens: the same dose of prednisone alone, prednisone plus oral cyclophosphamide (2 mg/kg/day) or cyclophosphamide alone. Approximately one third of patients responded to the initial prednisone course, about 50% of the steroid-resistant patients responded to cyclophosphamide-containing regimens. However, there was no difference between treatment arms pertaining to the rate of inhibitor eradication. Data from the prospective non-randomised UK cohort showed similar rates of inhibitor eradication in 34 patients treated with steroids alone and in 45 patients receiving combined steroids and cytotoxic drugs (76% at median 49 days vs 78% at 39 days, respectively) (8). No statistical difference was found even in mortality rates. On the other hand, according to the meta-analysis of data from 20 reports carried out by Delgado et al., cyclophosphamide was superior to prednisone alone in terms of inhibitor eradication but not in terms of overall survival. This was imputed to the increased toxicity associated with cyclophosphamide, in particular because of infection-related mortality (2). A more recent meta-analysis of 32 non-randomised studies found that patients receiving combination chemotherapy had a reduced likelihood of having persistent AHA (odds ratio [OR] = 0.04; 95% confidence interval [CI], 0.01-0.23) compared with steroids alone (OR = 0.38; 95% CI, 0.14-0.94) (78). Furthermore, patients treated with combination chemotherapy had a lower risk of death (OR 0.15, 95% CI 0.03-0.64). Significantly higher inhibitor eradication rates with combined steroids and cytotoxic drugs than with steroids alone have been reported in the frame of the EACH2 Registry (77% vs 58%), in spite of the fact that the prednisone alone arm received a higher dose of steroids (79). This difference remained statistically significant when stable eradication were considered, even after adjustment for age, weight, gender, FVIII level, inhibitor titre and underlying conditions (OR 3.25; 95% CI, 1.51-6.96; p<0.001). However, no difference in survival was found.

Thus, the current data suggest that the combination of steroids and cyclophosphamide is more likely to result in a stable autoantibody eradication than steroids alone, but that the final outcome is not improved, possibly reflecting increased toxicity of the regimens involving cyclophosphamide. Accordingly, this and other cytotoxic drugs should be used with caution especially in the elderly, tailoring the dose and the duration of treatment in order to reduce side effects.

Other immunosuppressants

Cyclosporine, usually in combination with steroids, has been successfully used as a second line treatment in AHA patients (80-82). By contrast, the available evidence indicates that immunomodulation with high-dose intravenous immunoglobulins (IVIG) as a single agent or in combination with steroids is not useful in antibody eradication in AHA (8).

Rituximab

Biotherapy with the anti-CD20 monoclonal antibody rituximab has been increasingly used to treat patients with AHA (83-89). Since the largest published cohort of 10 patients, showing inhibitor eradication in eight patients and subsequent response to intravenous cyclophosphamide in the remaining two non-responders (83), several other reports on small cohorts of patients documented the benefits of rituximab in AHA (84-88). A literature review of 71 patients treated with rituximab and a variety of immunosuppressive agents found a complete or partial eradication rate of more than 90%, the presence of high inhibitor titres (> 100 BU/ml) being a negative prognostic factor for response to rituximab (87). However, the authors were cautious in interpreting these data because of the presence of several treatment-related differences between studies. Another literature review reported that 42 patients treated with rituximab had similar outcomes to 44 patients treated with cyclophosphamide and steroids (88). Similar results were observed in the EACH2 registry: 30 of 51 (59%) patients treated with a regimen that included rituximab achieved a stable eradication. The 12 patients treated with rituximab alone had only a 42% response rate, whereas those treated with rituximab and another agent had a 64% stable inhibitor eradication, similar to 70% observed for patients treated with steroids and cyclophosphamide (79). Thus, there is presently no evidence to support the use of rituximab as first-line treatment, and this agent should be used only as a second-line approach, unless first-line treatment with steroids and cyclophosphamide is contraindicated (10).

Immune tolerance induction

Immune tolerance induction (ITI) protocols, like those used for the eradication of alloantibodies in congenital haemophilia (90), have been proposed also for the eradication of FVIII autoantibodies (91). The Budapest protocol (92), consisting of three weeks of treatment...
with a combination of FVIII concentrates (30 IU/kg/day for the first week, 20 IU/kg/day for the second week and 15 IU/kg/day for the third week), intravenous cyclophosphamide (200 mg/day for a total dose of 2-3 g) and intravenous methylprednisolone (100 mg/day for the first week, tapering the dose gradually over the next two weeks), resulted in inhibitor eradication in more than 90% of treated cases. Similarly, the modified Bonn-Malmö protocol (93), including a complex combination regimen based upon oral cyclophosphamide (1-2 mg/kg/day), prednisolone (1 mg/kg/day), large-volume immunoadsorption (2.5-3.0 times the plasma volume on days 1-5 weekly), IVIG (0.3 g/kg on days 5-7 weekly) and FVIII concentrates (100 IU/kg/day), obtained a rapid (median 14 days) eradication response in 88% (90% in the 2010 update) of patients (94).

Conclusions

Recent studies, reviews and meta-analyses and, above all, the results of the large international EACH2 registry have greatly contributed to increase our knowledge on the clinical presentation, natural history, outcome and management of AHA. A series of effective therapeutic options are presently available, giving the opportunity of tailoring the treatment to patient clinical features. A prompt recognition of this rare but life-threatening bleeding disorder and an early and aggressive treatment, preferably by specialised centres, are mandatory, as diagnostic delays or inadequate treatments are still associated with high mortality rates. For the treatment of bleeding episodes, the bypassing agents rFVIIa or FEIBA should be used as first-line therapy, while available data suggest that a combination of corticosteroids and cyclophosphamide should be considered as the most-effective approach to eradicate FVIII autoantibody even though this combined approach is not free from serious adverse events. Regimens including rituximab have not been shown to have any advantage in terms of inhibitor eradication rate over other immunosuppressive regimens.

Conflicts of interest

MF declares no conflict of interest. PMM has received honoraria as speaker at educational meeting organized by Bayer, Grifols, Kedrion Biopharma, Novo Nordisk. He has also served as paid consultant in advisory boards summoned by Bayer.

References


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