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Review Article

Acquired Haemophilia A: An Intriguing Disease

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Abstract. Acquired Haemophilia A is a rare acquired bleeding disorder caused by Factor VIII autoantibodies, which neutralise FVIII activity. These inhibitors differ from alloantibodies against FVIII, which can occur in congenital Haemophilia A after repeated exposures to plasma-derived or recombinant FVIII products. In most cases, the disease occurs suddenly in subjects without a personal or familiar history of bleedings, with symptoms that may be mild, moderate, or severe. However, only laboratory alterations are present in ~30% of patients. The incidence varies from 1 to 4 cases per million/year; more than 80% of patients are elderly, males and females are similarly affected. There is a small peak of incidence related to pregnancy in young women aged 20–40 years. The disease may be underdiagnosed in the elderly. The diagnostic algorithm is based on an isolated prolonged activated partial thromboplastin time, normal thrombin time, absence of Lupus Anticoagulant, and a mixing test that reveals the presence of an inhibitor: the finding of reduced FVIII activity and the detection of neutralising autoantibodies against FVIII lead to the diagnosis. The disease is idiopathic in 44%-63% of cases, while in the others etiological factors are present. Bleeding prevention and treatment are based on therapeutic tools as by-passing agents, recombinant porcine FVIII concentrate or, in a limited number of cases, FVIII concentrates and desmopressin. As soon as the diagnosis has been made, immunosuppressive therapy must be started to eradicate the inhibitor. Better knowledge of the disease, optimal management of bleeding and eradication of the inhibitor have significantly reduced morbidity and mortality in most patients.

Keywords: autoantibodies against FVIII; bleeding symptoms; bleeding treatment; eradication therapy.

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Introduction. Acquired haemophilia A (AHA) is a rare acquired bleeding disorder due to the development of autoantibodies directed against different epitopes of Factor VIII (FVIII) molecule, so causing the neutralisation of the FVIII coagulant activity (FVIII:C), and thus miming a situation similar to that of congenital haemophilia A (HA). Neutralising inhibitors of AHA differ from alloantibodies against FVIII of HA patients: in fact, alloantibodies occur after repeated exposures to plasma-derived or recombinant FVIII products administered as replacement therapy. The cause of AHA is due to a breakdown of the immune control mechanism (immune-tolerance) for both genetic and environmental factors.[1,2,3,4] Generally, autoantibodies are immunoglobulins G (IgG). In most cases, the disease occurs suddenly in subjects without a

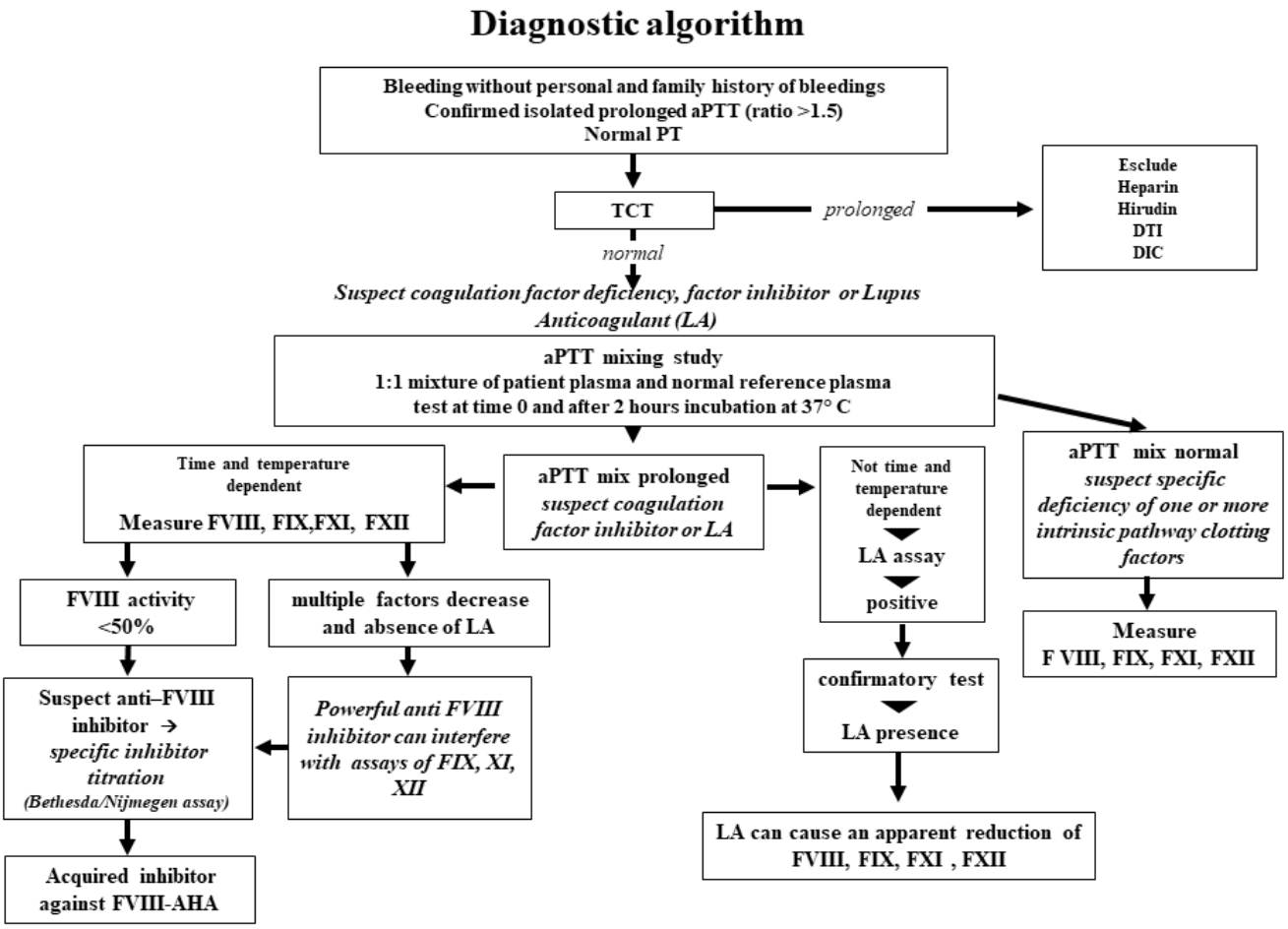
personal or familiar history of spontaneous bleedings and manifests itself with haemorrhagic symptoms that may be mild, moderate or severe. However, in about 30% of cases at the beginning of the disease, only laboratory alterations occur, namely an isolated prolonged activated partial thromboplastin time (aPTT). In many cases, AHA patients are admitted to the emergency or general medicine departments, where physicians are not specialists in the field. For this reason, the diagnosis may be delayed, and the patients may receive suboptimal treatment. On the contrary, immediate consultation with a Haemophilia Centre with expertise in the management of inhibitors against coagulation factors should be required, regardless of clinical features at presentation.[5,6]

Incidence-Epidemiology. The incidence of AHA increases with age: it is sporadic in childhood, rare in adults, but more common in people older than 65. According to the most extensive available case series, the median age at presentation was 74[7] and 78,[8] respectively: more than 80% of patients were 65 years or older. The average incidence per million/year has been reported to be 0.3 in subjects aged 16-64, 9 in those aged 65-84 and 14.7 in those aged 85 or more.[9] The incidence in children under 16 years old is estimated to be 0.045 million/year.[8] The age distribution is typically biphasic with a small peak between 20 and 30 years and a larger pick between 68 and 80 years and over. Males and females are similarly affected, but in the extensive European Acquired Haemophilia Registry (EACH2) cohort, comprising 501 patients, a slight males' prevalence was found, that is 53.1% versus 46.9%, resulting in a male/female ratio of 1:0.88.[7] There is also a small peak related to pregnancy in young women aged 20–40 years: incidence of AHA in pregnancy within the United Kingdom was reported to be 1 case/350 000 births.[1,8] In summary, the literature reports an overall incidence of AHA from 1 to 4 cases per million/year[10] or 1-1.5 per million/year;[11] AHA is likely to be underdiagnosed in the elderly.

Diagnosis. Diagnosis should be considered on the basis of a prolonged isolated aPTT, not corrected by incubating equal volumes of patient and normal plasma (mixing test), [12] normal prothrombin time (PT) and absence of Lupus Anticoagulant (LA). The diagnosis is confirmed by the finding of reduced FVIII:C levels and by the detection of neutralising autoantibodies directed against FVIII:C utilising the Bethesda Nijmegen-modified assay, which allows the titration of the autoantibody in Bethesda Units/mL (BU/mL).[13,14] Inhibitors are time-and temperature-dependent, so in some cases, inhibition cannot be immediately demonstrated by the mixing test, but after a two-hour incubation at 37°C. In most cases, AHA autoantibodies are type 2 inhibitors and exhibit complex kinetics of inhibition and do not neutralise FVIII:C entirely, while alloantibodies of HA are generally of type 1 inhibitor and have second-order kinetics and inactivate FVIII:C completely. Heat treatment of the sample before assay (58°C for 90 minutes) may improve inhibitor detection sensitivity by eliminating residual FVIII:C; an anti-FVIII enzyme-linked immunosorbent assay (ELISA), particularly after thermal treatment of the samples, has also been proposed.[15,16] It is crucial to consider the presence of lupus anticoagulant (LA), which sometimes coexists with FVIII inhibitor: diluted Russel viper venom time (dRVVT) test is useful for LA detection in these cases. Heparins, heparinoids, and direct oral anticoagulants may interfere with inhibitor test results and mimic circulating inhibitors. Summarising, AHA is defined by the presence of a neutralising FVIII inhibitor $\geq$0.6 BU/mL and a FVIII:C <50%[17,18] **(Figure 1).**

Pathogenesis. Inhibitors against FVIII can be identified in about 20% of healthy donors:[19] these are directed against FVIII:C in pooled normal plasma, but not in autologous plasma, so, they are alloantibodies targeting an unidentified polymorphism and lacking clinical significance.[20] Autoantibodies in AHA occur for a breakdown of immune tolerance mechanisms, that regulate normal immune response to FVIII[21] and represent a polyclonal IgG population. A complex interaction between different CD4+ T cell subsets is implicated in the production of anti-FVIII antibodies: Th1cells which stimulate B cells to produce IgG1 antibodies and Th2 cells which stimulate B cells to produce IgG4 antibodies. Moreover, a correlation between the proportion of IgG4 anti-FVIII antibodies and high inhibitor titre has been found.[22,23] Autoantibodies of AHA are similar to alloantibodies of HA and IgG4 is usually a major component of the antibody population, although IgG4 represents only 5% of the total IgG in normal plasma; IgG1 and IgG2, and less often IgG3, are also present.[20] Isotypes and IgG subclasses were evaluated in a large AHA population at baseline: IgG4-subclass autoantibodies were found in 98% of cases, IgG1 in 88%, IgG2 in 77% and IgG3 in 41%; IgA and IgM autoantibodies were detected in 46% and 9% of cases, respectively. IgG4 and IgG1 correlated with the highest inhibitor titre. IgA autoantibodies that do not neutralise FVIII:C are potential predictors of recurrence and poor outcome of AHA, while IgG subclasses do not.[24] Inhibitor antibodies in AHA and HA are mainly directed against the A2 and C2 epitopes of FVIII molecule, but in AHA either anti-A2 or anti-C2 domain, autoantibodies are recognized, not both. The C2 domain is more frequently targeted.[20] Anti–FVIII C1 domain antibodies in AHA and HA were recently studied and were found in 78% of AHA and 57% of HA patients, respectively,

Figure 1.



Legend. aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; DTI = direct thrombin inhibitor; FVIII = factor VIII; FIX = factor IX; FXI = factor XI; FXII = factor XII; PT = prothrombin time; ratio = test plasma time/normal reference plasma time; TCT=thrombin clotting time.

but their clinical relevance is unclear.[25] It seems that global coagulation is more suppressed in AHA than in severe HA due to the inhibition of Factor IX activated (FIXa)-dependent Factor X(FX) activation in the presence of anti-C2 autoantibodies against FVIII.[26] A study reported a stronger statistically significant response of autoantibodies against the A1*a*1-A2*a*2-B fragments of FVIII, particularly against the A1*a*1 domain, in the post-partum AHA group compared with the other AHA patients' groups. IgG4 subclass was predominant in all groups, but the anti-A1*a*1-A2*a*2-B and the anti-A1*a*1domains autoantibodies of the IgG1 and IgG3 subclasses were more frequently detected in post-partum AHA than in the other AHA groups. This finding may be due to the post-partum greater involvement of the Th1-driven response, while in the other AHA groups generation of Th2-driven IgG4 seemed to be predominant. This kind of Th1-driven response may contribute to a successful outcome of post-partum AHA.[27]

Bleeding Pattern. Clinical features of AHA differ from those of HA because bruising, retroperitoneal, muscle, gastrointestinal and urogenital bleedings are frequent, whereas haemarthroses are uncommon. Compartment syndrome and compression of nerves and blood vessels may also be found.[28] Gastrointestinal, intracranial and retroperitoneal haemorrhages are often fatal.[8] In most cases, bleedings occur suddenly, while in about 25% of the cases they are caused by a trauma or an invasive procedure.[29] Sometimes, AHA has been found in subjects receiving anticoagulant or antiplatelet drugs: in these cases, the diagnosis may be delayed, because the bleeding is assumed to be caused by these agents.[28] Therefore, excessive bruising or unexpected bleeding in patients taking antiplatelet or anticoagulant medications should be further investigated, especially in older adults, and whether evidence of an overdose of such drugs is lacking based on laboratory tests. In the past mortality related to bleeding had been reported to be 22-31%.[30,31] However, an incidence between 3% and 9% was found more recently, in particular, 3.2% in the EACH2 cohort,[7,8,32] maybe due to improved therapeutic approach, but mortality caused by infections appears to be increased.[33]

Associated Diseases/Conditions. In about 50% of cases, there are no underlying diseases or conditions associated with AHA; thus it has been described as idiopathic in many large case series at a rate ranging from 43.6% to 63.3%:[1,7,8,30] the EACH2 study reported that the disease was idiopathic in 51.9% of 501 patients. In comparison, in all other cases, etiological factors were autoimmune diseases (11.6%), malignancy (11.8%), pregnancy (8.4%), infections (3.8%), use of drugs (3.4%), monoclonal gammopathy of undetermined significance (2.6%), rheumatic polymyalgia (2.2%), dermatological diseases (1.4%), blood products transfusion (0.8%), and other disorders (2%).[7] The most common solid cancers are prostate cancer, followed by lung cancer.[34,35] Pregnancy-related AHA occurs mainly in the post-partum period, between 3 and 150 days after delivery[36] mostly after the first pregnancy, but the inhibitor is sometimes recognised during pregnancy in 2.5–14% of patients.[36,37] Moreover, it may become evident during labour, causing severe, unexpected bleeding; the transplacental passage of the autoantibodies to the foetus can lead to foetal bleeding.[22,38] Considering the largest available AHA cohorts, pregnancy-related AHA ranges between 2% and 15%.[8,30,39,40] In most cases, the inhibitor titre is rather low (median about 20 BU/mL).[37,41] The prognosis is favourable, with a low mortality rate (0-6%) and a high percentage of remission (77-86%), in some cases, even without treatment.[1,29,40]

Case Series. We considered eight case series published from 1981 to 2018, each including 40 or more evaluable patients with AHA.[1,7,8,30,42-45] One thousand four hundred eleven patients were recruited. Males' prevalence was found in 5 studies, ranging from 58% to 68%,[7,42-45] the prevalence was in favour of females in 2 studies, 55% and 57%, respectively,[1,8] while in the other one almost equal number of males and females was reported.[30] In 7 studies median patients' age ranged from 64 to 78 years[1,7,8,42-45] and in the other one, most patients were over 50 years;[30] in the French study, 69% of patients were over 70 years.[42] The incidence of AHA becomes more frequent with increasing age, but the likelihood of finding an underlying disease seems to decrease with age.[8] No AHA-associated disease was found in a median of 52% (46%-67%) of patients,[7,8,30,42-45] while the most frequent underlying disorders were autoimmune diseases and cancer, in young and older people, respectively.[42] Pregnancy-related AHA was reported in 7/8 case series, with a rate ranging from 2% to 15%.[1,7,8,30,42-44] Excluding pregnancy-related cases, AHA was described in young or very young people in 3 studies only.[1,8,30]

Severe bleedings at diagnosis were found to be 60%, 70% and 87% in 3 studies, respectively.[7,30,45] Mortality rate bleeding-related ranged from 2.9% to 9% (median 4.0%),[7,8,42,43] while mortality rate disease-related was reported to be 22%[30] and 11%,[1] respectively. Some prognostic factors were also identified. Age >65 years vs < 65, related diseases (malignancy vs post-partum vs others), inhibitor titre at diagnosis (>10 BU/mL vs <10 BU/mL), the achievement of inhibitor eradication (no vs yes) had a significant negative impact on overall survival (OS) on univariate analysis, but only inhibitor eradication, age at diagnosis and underlying diseases had a consistent, independent significant prognostic value on multivariate analysis. Regarding disease-related survival, the same four variables showed a significant prognostic value on univariate analysis, but only inhibitor eradication and age remained statistically significant on multivariate analysis.[1] Age appeared to be the only prognostic factor associated with survival in the UK study.[8] Age over the median of the studied group (76.3 years), low haemoglobin level at diagnosis, presence of neoplasia and failure of inhibitor eradication were significant negative prognostic factors in the EACH2 study, while gender, inhibitor titre and FVIII:C did not.[7] A study, aimed at identifying risk factors in patients treated with a uniform immunosuppressive regimen for inhibitor eradication, showed that the time to partial response to therapy did not depend significantly on age, gender, underlying disorder, and poor performance status (PS), *i.e.* WHO-PS >2; baseline FVIII:C<1% was significantly associated with time to partial response, while inhibitor titre >20 BU/mL did not; only baseline FVIII:C <1% remained significantly related with time to partial response on multivariate analysis. Baseline FVIII:C<1% and WHO-PS>2 were significantly associated with a lower rate of complete response to therapy, both on univariate and multivariate analysis. Patients with poor PS were more likely to die before achieving a complete response. Baseline FVIII:C <1%, inhibitor >20 BU/mL, age >74 years, WHO-PS >2, male gender, malignancy and renal failure were associated with a poor OS on univariate analysis, but only three baseline factors remained independent predictors of poor OS on multivariate analysis: FVIII:C <1%, WHO-PS >2, and malignancy.[43] In the same patients' population presence of anti-FVII, I IgA autoantibodies were identified as a potential predictor of recurrence and poor outcome of AHA.[24]

Specific AHA Populations. Some publications are mainly addressed to specific AHA populations: children, older people and pregnant or post-partum women. As for children, a review[38] showed that 42 cases of inhibitors against coagulation factors were collected in childhood: 37 reported *de novo* inhibitors and five transplacental transmissions of maternal inhibitors; the M/F ratio was 1.1. The inhibitor was directed to FVIII in 28/37 cases (75.7%). An underlying autoimmune disorder was found in 16.7% of cases, but the inhibitor was frequently associated

with infections (16.7%) or use of antibiotics (22.2%), especially penicillin or penicillin-like antibiotics; 33.3% of cases were idiopathic. The outcome was favourable: the inhibitor disappeared in 80.6% of cases, after a median of 2.5 months, the highest remission rate (100%) was associated with infections or antibiotics use. Other cases have been described regarding 7 children (4 males, 3 females) diagnosed with AHA at a median age of 10 years (range 5-14).[46-52] Symptoms described at diagnosis were muscle haematomas,[46,47,52] ankle haemarthrosis,[46] severe bleeding after tooth extraction.[49] Associated conditions were: previous HSCT and concomitant staphylococcus aureus infection,[50] streptococcal infection and amoxicillin treatment,[51] previous course of amoxicillin.[52]

Two papers have recently regarded AHA in the elderly: one review from 80 studies, including 159 cases[53] and a cases report concerning a small number of patients.[54] In the first one, most patients were men (64%) with a mean age of 76.1. Mortality was high, despite the number of therapies used for inhibitor eradication, probably due to the lack of rapid diagnosis and to inadequate management and monitoring. The other one described only 6 patients, but, interestingly, 4 were 90 or older: The Authors underlined that AHA shows a wide variety of symptoms in the elderly, indicating the need of individualised management.

Regarding pregnancy-related AHA, a survey carried out in 42 Italian Haemophilia Centres, identified 20 cases of post-partum AHA among 96 patients (20.8%), diagnosed during 15 years: 19/20 cases were idiopathic, and in six the inhibitor was identified because of surgical bleeding. Nine women did not require haemostatic treatment. The inhibitor was diagnosed for the occurrence of significant bleeding at a median time after delivery of 60 days (1–150). Eighteen women received treatment for inhibitor eradication with an excellent outcome. In two patients without bleedings, the inhibitor disappeared without therapy. No relapse was recorded in subsequent pregnancies occurred in 4 women.[39] In the EACH2 registry,[40] 42 cases (8.4%) of peripartum-associated AHA were diagnosed over 6 years. Evidence of antepartum inhibitors was found in 8 women, and 2 babies had postnatal bleeding, suggesting a transplacental transfer of the autoantibody. The median time between delivery and diagnosis of AHA was 89 days (21–120). Bleedings were successfully managed, and most women achieved inhibitor eradication. In conclusion, pregnancy-associated AHA is rare, but the awareness of it is crucial for rapid and appropriate management. Relapses during the subsequent pregnancies are very rare.[18]

Treatment and Prevention of Bleeding. Patients with AHA must be treated immediately as soon as major bleeding occurs or haemoglobin levels decrease significantly. Prophylactic haemostatic treatment must be given in subjects at high risk of bleeding (surgery, delivery, peptic ulcer, etc.). Invasive procedures should be avoided if not strictly necessary. Replacement therapy with plasma-derived or recombinant FVIII concentrates is not effective in the presence of high inhibitor titre. In case of low titre (<5BU/mL), the dose must be adequately adjusted to overcome the inhibitor. However, the risk of anamnestic response, that is a rise of inhibitor titre, should be seriously taken into consideration and careful control of FVIII:C levels and inhibitor titre is mandatory. Desmopressin (DDAVP), alone or associated with FVIII concentrates may be useful in case of minor bleedings if the inhibitor titre is low (<2 BU/mL[18] and basal levels of FVIII:C are over 5%.[22,55,56] In the EACH2 study, FVIII concentrates were successful in controlling bleeding in 69.6% of cases.[57] Products derived from porcine FVIII were administered in the past, with good results, because porcine FVIII shows a reduced cross-reactivity against anti-human FVIII inhibitors, but in 2004 their use was suspended, for viral safety concerns.[58,59] A recombinant porcine FVIII (rpFVIII, susoctocog alfa, Obizur^{R}) concentrate was sub sequentially developed; it has been approved for the treatment of bleedings in AHA in the United States, Canada and Europe. It is a glycosylated B-domain deleted, recombinant FVIII with porcine sequence and low cross-reactivity towards anti-human FVIII antibodies; it is produced in a well-characterised BHK cell line and manufactured using two viral clearance steps, solvent detergent and 15-nm nanofiltration.[60,61] It shows a favourable safety and efficacy profile and therefore constitutes a valid therapeutic option for the treatment of AHA.[62] In the first prospective phase 2/3 multicenter, international, open-label registration study concerning 28 adults with AHA, suffering from serious bleedings, rpFVIII demonstrated good clinical efficacy, reaching a bleeding control in 24/28 patients. The response of FVIII:C levels to rpFVIII infusion depends on the presence of an inhibitor with cross-reactivity towards porcine FVIII in the patient's plasma. Patients without cross-reactivity reached very high FVIII activity levels (118%-522%), after an initial loading dose of 200IU/Kg. For this reason, it is mandatory to determine baseline concentrations of anti-porcine FVIII antibodies to predict the effectiveness of rpFVIII. Moreover, infusion of rpFVIII may trigger an increase of the inhibitor titre or a *de novo* occurrence of an anti-rpFVIII inhibitor in some cases, with a subsequent reduction of efficacy. In this study, 5/28 (17.9%) treated patients, who did not have detectable anti-porcine FVIII at baseline, developed a *de novo* anti-rpFVIII inhibitor. Therefore, accurate search and monitoring of both anti-human and anti-porcine inhibitors and determination of FVIII:C levels are mandatory before and during treatment.[63] Two

subsequent publications have shown that lower initial doses of rpFVIII (100 IU/Kg) achieved the same efficacy as that obtained in the registration studies with higher doses.[64,65] However, in the first one, one patient developed a *de novo* anti-rpFVIII inhibitor and another suffered from a lower-limbs deep vein thrombosis; in the second one, a *de novo* anti-rpFVIII inhibitor occurred in 2 patients. In both studies, the Authors highlighted the efficacy of lower doses of rpFVIII and the need to titrate the rpFVIII doses, using close monitoring of FVIII:C. Before the availability of the rpFVIII concentrate, the alternative to FVIII replacement therapy was represented by the products capable of by-passing the inhibitor activity ("by-passing agents"), namely the activated prothrombin complex concentrates (APCCs) and the recombinant factor VII activated (rFVIIa). They circumvent the inadequate activation of FX. Both rFVIIa and APCCs are effective in the treatment of bleedings, but no comparative studies are showing greater efficacy of one product than the other.[22,57] Many case series have been published concerning the use of both products. Since1997, treatment with rFVIIa (NovoSeven®) has been reported either as a first-line therapy tool or after the failure of other therapeutic approaches.[57,66-69] A large number of bleedings were treated with rFVIIa with efficacy ranging from 83% to 100% and, when it was administered as second-line therapy, from 66% to 75%.[57,66-69] The doses ranged from 40 to 180µg/Kg (average 90) every 2-6 h, for a variable duration, according to bleeding severity, clinical situation and disease status.[70] A 10-year post-marketing surveillance analysis was recently published: NovoSeven® was used in 371 bleeding episodes occurred in 132 AHA patients; efficacy was recorded in 92% of cases. Interestingly, the response rate was significantly better in patients who received an initial dose of ≥90µg/Kg than of <90µg/Kg. Treatment with rFVIIa was more effective if given immediately after the start of bleeding.[69] Regarding APCCs, a retrospective study[71] described the efficacy of APCC (FEIBA®) in 34 AHA patients: most of them received FEIBA® at a single dose of 75IU/Kg repeated every 8-12 hours: the complete response was reached in 100% of moderate and in 76% of severe bleedings, respectively. In the EACH2 study, 19% of bleeds were treated with APCC and 51% with rFVIIa: both by-passing agents showed similar efficacy rate (FEIBA® 93%, rFVIIa 91%).[57] A French registry collected data on 34 AHA patients (mean age 81.8 years) who received FEIBA® for bleeding episodes or prophylaxis for invasive procedures. Mean initial dose of FEIBA® for acute bleeding was 75.4IU/Kg, mostly administered twice daily. The median duration of treatment was 4 days. Efficacy was recorded in 88.0% of bleeding episodes, although 4 patients experienced six serious adverse events possibly related to FEIBA®.[72] A retrospective/prospective multicentre Italian study ("FAIR study") was recently published and regarded 56 patients (median age 69.9 years) enrolled in 12 Italian Haemophilia Centres. FEIBA® was given as first-line therapy in 82.2% of cases, at a mean dose of 72.6IU/kg for a median period of 8 days; efficacy was reached in 96.4% of bleedings. Antifibrinolytic agents were used with FEIBA® in 39. 6% of treated cases at clinician's discretion. Low-dose FEIBA® for short-term prophylaxis (mean dose 54.2IU/Kg), was administered in 26.8% of the patients after the first episode to prevent bleeding relapse at an average frequency of 24 hours. In the FAIR study, an anamnestic response was recorded in 5.9% of cases; no thromboembolic events occurred.[73] The thromboembolic risk was seriously considered for both by-passing agents. Sumner *et al.* reported 12 thrombotic events in 10 patients treated with rFVIIa;[68] 11 thrombotic events (arterial 7 and venous 4) were described in the EACH2 cohort, with a similar incidence for rFVIIa (2.9%) and APCCs (4.8%).[57] Amano *et al.*[69] reported 5 thromboembolic events in 3 elderly patients with comorbidities treated with rFVIIa (2.3%). Tiede *et al.*[43] described that the rate of fatal vascular events was 5% in patients treated only with rFVIIa and 10% in those who received a combination of rFVIIa and tranexamic acid (TA). Risk of thrombotic events can increase if both by-passing agents are administered in a combined or sequential way: thromboses occurred in 5/9 AHA patients treated with this modality (55%).[74] Interestingly, in French registry[72] and in "FAIR study"[73] no thromboembolic events were reported. However, careful monitoring of patients should be performed, especially in the elderly and in those with comorbidities or predisposing conditions, such as previous thrombotic events or thrombophilia. Antifibrinolytic drugs, such as TA, are considered a useful tool for the treatment of bleeding, especially of mucous origin, except haematuria, in patients with congenital or acquired bleeding disorders; TA contributes to the clot stability, but doubts remain about its use in association with APCCs, due to the risk of thromboembolic complications. Mouthwashes with TA are safe and effective for mouth bleeds, also during treatment with APCCs. The association of antifibrinolytics with FEIBA® in AHA patients was recently evaluated in 39.6% of 101 treated bleedings: no thromboembolic events were recorded, despite a large portion of patients showed serious comorbidities or severe cardiovascular diseases. However, these findings need to be confirmed in proper, larger clinical trials.[75] In AHA patients with high inhibitor titre APCCs have been considered a cost-effective therapy option when compared to rFVIIa.[76] We can conclude that both by-passing agents are still suitable and effective first-line treatments of AHA, despite the availability of the rpFVIII. In rare cases, characterised by serious life-threatening haemorrhages and a very

high inhibitor titre, extracorporeal removal of the autoantibody by plasmapheresis, or immunoadsorption on staphylococcal protein A or polyclonal sheep antibodies against human immunoglobulins has been used to remove the autoantibody temporarily and allow the administration of FVIIII concentrates.[77] A novelty in the treatment of HA has been identified in an innovative drug, emicizumab. Emicizumab is a bi-specific, humanised monoclonal antibody which bridges FIXa and FX to replace the physiologic function of missing activated FVIII in HA patients, thereby restoring haemostasis. Some randomised and non-randomised clinical trials carried out in adults and in children with HA, with or without inhibitor against FVIII, have shown remarkable effectiveness of emicizumab, administered as prophylaxis therapy, in preventing bleedings.[78-81] Although the results of these studies have already led to the approval of treatment with emicizumab in many countries around the world, including Europe, its use in AHA is not currently allowed. However, some case reports were recently published describing emicizumab treatment in some elderly AHA patients. Emicizumab was effective when given after failure of previous agents, such as rpFVIII and APCC.[82-85] Moreover, a recent study has demonstrated, in an experimental model, that the ex-vivo addition of various concentrations of emicizumab to plasma samples of AHA patients has been capable of restoring thrombin generation. Therefore, emicizumab can improve the ex-vivo coagulation potential in plasma of patients with AHA and, based on these results, its therapeutic use could also be effective in AHA[86] (**Table 1).**

Table 1. Bleeding treatment or prevention.

Agent	Dosages	Comments
Recombinant porcine FVIII (rpFVIII)	**Initial dose** *if no anti-porcine FVIII inhibitor* ● 50-100 IU/Kg-> perform clinical and laboratory monitoring (FVIII activity) every 2-4 h for successive doses planning *if present anti- porcine FVIII inhibitor* ● 200 IU/Kg if severe haemorrhage or if less severe ● 50-100 IU/Kg-> perform the same monitoring and planning as above	**Pros**: - real replacement therapy - good safety and efficacy profile - possible FVIII activity monitoring (one stage assay) **Cons**: - poor or no efficacy in case of anti- porcine FVIII inhibitor at baseline - risk of development of a *de novo* anti-rpFVIII inhibitor during therapy - risk of anamnestic response **Conclusions**: - treatment must be carried out at a Haemophilia Centre or under its supervision and in an inpatient regimen. - laboratory monitoring must be available. - rpFVIII can be considered as first-line therapy in absence of anti-rpFVIII inhibitor and if easily available. - easiness of administration
Activated prothrombin complex concentrate (APCC)	● 50-100 IU/Kg every 8/12 h without exceeding 200IU/Kg/ day	**Pros:** - good efficacy and acceptable safety - easily available - administration in hospitalized patients, outpatients and at home. **Cons**: - laboratory monitoring impossible - only clinical surveillance - potential thrombotic risk - association with tranexamic acid is not recommended **Conclusions**: - still suitable and effective first-line therapy - avoid administration in combined or sequential way with recombinant FVII activated.
Recombinant FVII activated (rFVIIa)	● 90-120µg/Kg every 2-4 h until haemostasis is reached, then doses interval may be prolonged	**Pros:** - good efficacy and acceptable safety - easily available - administration in hospitalized patients, outpatients and at home. **Cons:** - laboratory monitoring impossible - only clinical surveillance - short half-life (2 h) - potential thrombotic risk. **Conclusions:** - still suitable and effective first-line therapy - avoid administration in combined or sequential way with APCC
Desmopressin (DDAVP)	● 0.3µg/Kg every 12-24 h	**Pros:** - effective in case of minor bleedings, if the inhibitor titre is < 2 BU/mL and basal FVIII activity is >5%

		- easily available - possible laboratory monitoring. **Cons:** - reduction or loss of efficacy after 4-5 doses (tachyphylaxis) **Conclusions:** -useful in a limited number of cases of mild disease

Inhibitor Eradication: Immunosuppressive Therapy (IST). Patients with AHA, although asymptomatic at diagnosis, remain at risk of bleeding as long as the inhibitor persists. Although up to 36% of patients achieve spontaneous disappearance of the autoantibody without immunosuppressive therapy (IST),[1] the inhibitor must be eradicated by IST, administered immediately after diagnosis in order to induce remission of the disease, as soon as possible.

Corticosteroids alone or associated with cyclophosphamide have been used as first-line treatment, while other immunosuppressants or the monoclonal anti-CD20 antibody, rituximab, have been given as second/third-line therapy. In the only randomised study published until now, 31 AHA patients were initially treated with prednisone, if the autoantibody persisted and there was no rise in FVIII:C, patients were randomised to either prolong prednisone for other 6 weeks or taper prednisone and start cyclophosphamide or continue prednisone and add cyclophosphamide. About 1/3 of patients responded to prednisone alone, while in 50% of prednisone-resistant patients, cyclophosphamide-containing regimens achieved eradication of the inhibitor. In conclusion, patients should be initially treated with prednisone, while cyclophosphamide appeared to be an effective second-line therapy for prednisone-resistant patients.[87] In a metanalysis concerning 234 patients, cyclophosphamide with or without prednisone was found to be more effective in inducing inhibitor eradication than corticosteroids or no immunosuppressive treatment at all. However, the superiority of cyclophosphamide over prednisone was not confirmed with regard to OS, probably for increased infection-related mortality due to haematological toxicity of this drug.[1] In a prospective, non-randomised study, no statistically significant difference was found regarding the eradication rate of the inhibitor and the median time to complete remission (CR), namely FVIII:C normal, inhibitor undetectable, IST stopped or properly reduced, between patients treated only with corticosteroids (mostly prednisolone) and patients receiving corticosteroids combined with a cytotoxic drug, (mostly cyclophosphamide): CR were 76% and 78%, reached at median time of 49 and 39 days, respectively. In another meta-analysis, concerning 359 patients, CR (absence of FVIII inhibitors and normalisation of FVIII:C) was recorded in 68% of patients treated with prednisone alone, in 82% of those treated with dual therapy (prednisone and cyclophosphamide or azathioprine) and in 94% of those treated with combined chemotherapy (prednisone, cyclophosphamide and vincristine). Inhibitor eradication was more probably achieved by patients treated with IST than by those untreated at all; in addition, patients undergoing combination therapy had a lower risk of death.[88] In the EACH2 study, first-line IST was evaluated in 294 patients: corticosteroids were given alone in 142 patients and combined with cyclophosphamide in 83; rituximab-based regimens were administered in 51 patients, 18 patients were treated with other regimens. Complete remission (CR) was defined as complete disappearance of inhibitor, factor VIII:C over 70%, IST stopped; stable CR was considered as persistent CR without relapses during follow-up. The median time to FVIII:C>70% and undetectable inhibitor in patients treated with corticosteroids alone were 32 and 34 days, respectively, while in those receiving corticosteroids and cyclophosphamide 40 days and 32 days, respectively. Complete remission was reached at a median time of 108 days in patients receiving corticosteroids alone and of 74 days in those undergoing corticosteroids and cyclophosphamide and CR rates were 58% and 80% in the two groups, respectively. Complete remission was obtained by 61% of patients treated with rituximab-based regimens. Relapses occurred in 18% of patients treated with corticosteroids alone, while in those receiving combined therapy or rituximab-based regimens in 12% and 3%, respectively; stable CR was recorded in 48%, 70% and 59% of each group, respectively. Underlying disease or sex did not affect the remission; age showed a moderate influence; on the contrary, baseline low inhibitor level (<16BU/mL) and higher FVIII:C were significantly associated with faster inhibitor eradication and normalisation of FVIII:C level. At last follow-up (median 262 days), death rates were similar among the groups: 28% in patients treated with corticosteroids only, 33% in those treated with corticosteroids and cyclophosphamide and 20% in those treated with rituximab-based regimens; 4 patients receiving corticosteroids and cyclophosphamide died for sepsis due to the immunosuppression, one of them was neutropenic.[89] Another study investigated prospectively standardised IST:102 patients received prednisolone initially for 3 weeks; then oral cyclophosphamide was added if remission was not reached, (weeks 4–6); then rituximab was given with prednisolone (weeks 7-10) if lack of response. Partial remission (PR) was defined as FVIII:C>50%, no active bleeding, no haemostatic drugs for 24 h, CR as PR plus inhibitor absence, prednisolone tapered to less 15mg/day and any other

immunosuppressive therapy stopped; PR was achieved by 83% and CR by 61% of patients, respectively. The median time to PR and CR was 31 days and 79 days, respectively. Forty-eight % of the patients were alive in stable CR after a median observation time of 403 days.[43] In resistant or relapsed patients, other therapeutic approaches have been experienced: cyclosporine alone or in combination with corticosteroids, mycophenolate mofetil or multiple immunosuppressive drugs, with variable results.[18,22] Based on the experience gained in congenital HA with inhibitor, immunotolerance induction (ITI) protocols has been proposed in very selected cases for inhibitor eradication: Budapest protocol[90] and the modified Bonn-Malmo protocol (MBMP).[91] However, these expensive procedures require ad hoc specialised clinical departments. High-dose intravenous immunoglobulins (IVIG), alone or in combination with corticosteroids, are no longer considered suitable for the inhibitor eradication.[1,8,89] Rituximab has been used since the early 2000s for the treatment of AHA: two reviews were recently published on its placement in the first-line therapy or subsequent lines. Both publications concluded that rituximab may be considered a safe and useful treatment for AHA, but that it should be placed on second-line therapy in resistant or relapsed patients after first-line treatment.[92,93] Rituximab is also effective in pregnancy-related AHA.[94-96]

Complications of IST are frequent and sometimes fatal: patients, especially if elderly, should be monitored for the occurrence of adverse events, particularly infections. In the UK study, sepsis occurred in 33% of cases and led to death in 12% of them;[8] in the GTH-AH 01/2010 study, 54 infections were diagnosed in 37/102 patients, and 16/102 died from sepsis;[43] in the SACHA registry death rate for IST was 12%[42] and in the EACH2 study 4.2%.[89] Complications of corticosteroid therapy include: increased blood sugar levels (12%), gastroduodenal ulcer (4%), muscle disorders (4%), and psychiatric disorders (3%).[8,43] After inhibitor eradication elevated levels of FVIII:C are often observed and constitute an independent thrombotic risk factor.[97] In a recent study, a cohort of 111 AHA patients, followed for a median time of 25.6 months, was evaluated for relapse pattern. In 14% of them, one or more relapses occurred after remission obtained with IST. Median time from diagnosis and from the first remission to the first relapse was 13.4 months and 12.0 months, respectively. Underlying lymphoproliferative diseases were predictive of relapse; older age and male gender appeared to be more frequently associated with recurrence, while FVIII:C and inhibitor levels at diagnosis were not. Moreover, relapse was not associated with worse OS. The authors suggested that the patients should be followed up after remission for at least 2 years[98] (**Table 2).**

Guidelines. The knowledge of AHA, based on publications of case reports and large case series has led to the development of *ad hoc* guidelines, as consensus recommendations of experts' panels, regarding diagnosis and therapeutic approach of the disease.[9,18,28,99,100] In 3 of these[28,100,101] the "GRADE system" was used to quote the levels of evidence and the strength of the recommendations.[102]

Recommendations and suggestions derived from guidelines are summarised and listed below.

Table 2. Immunosuppressive treatment.

Agent	Dosages	Comments
Corticosteroids alone	● Prednisone/Prednisolone PO: 1mg/Kg/day for 3-4 weeks	Effective as first-line therapy in patients with non-severe disease (FVIII>1%, inhibitor <20 BU/mL at baseline) Monitor for adverse events (increased glucose, gastroduodenal ulcer, psychiatric disorders)
Corticosteroids plus cyclophosphamide	● Corticosteroids (same doses as above) plus cyclophosphamide:1-2 mg/Kg PO for 4-6 weeks. Cyclophosphamide can also be added to corticosteroids in unresponsive patients	Very effective first- line treatment, especially in patients with severe disease (FVIII:C <1%, inhibitor >20BU/mL at baseline), faster response than corticosteroids alone, highest CR rate. Monitor for adverse events (decrease of WBC and platelets for bone marrow toxicity) and infection occurrence. Cyclophosphamide should be used with caution in young patients and is contraindicated in women of childbearing age
Rituximab and corticosteroids	● Rituximab 375mg/m2/ IV weekly for 4 weeks, plus corticosteroids (same doses as above)	Effective second/third-line therapy. Rituximab can be used as initial treatment if other immunosuppressants are contraindicated.

Abbreviations: CR= complete remission; IV= intravenous; PO= *per os*; WBC= white blood cells.

Diagnosis: **suspect AHA** when a sudden abnormal haemorrhage occurs in subjects, not on anticoagulation, without personal or family bleeding history, who show an isolated prolonged aPTT (absence of LA) and a mixing study consistent with an inhibitor. An unexplained prolongation of aPTT before surgery or an invasive procedure should always be investigated. However, in~30% of cases, only laboratory alterations occur. **The diagnosis must be made by a Haemophilia Centre** with expertise on coagulation disorders and management of inhibitors against coagulation factors. **Test and monitor anti-FVIII inhibitor with Bethesda Nijmegen-modified assay. If treatment with rpFVIII concentrate is planned, test and monitor also anti-prFVIII inhibitors.**

- **Avoid invasive procedures: if necessary**, they must be performed in a Haemophilia Centre or after consultation with it.
- **Look for an underlying cause, or disease** as soon as the diagnosis of AHA has been made. Treat any underlying condition.
- **Treatment of bleeding. Start anti-haemorrhagic therapy in the presence of clinically relevant bleeding symptoms By-passing agents** (APCC, rFVIIa) must be considered as first-line treatment; if the by-passing agent, administered initially, is ineffective, the other one should be tried at an early stage. **Recombinant and plasma-derived FVIII concentrates and DDAVP** should be reserved to patients with measurable FVIII:C levels and low inhibitor titre, but accurate laboratory monitoring is necessary; **DDAVP is not recommended in the elderly**. **Porcine recombinant FVIII** is also considered as first-line treatment, but its use should be reserved for highly specialised Haemophilia Centres**. By-passing agents or rpFVIII should be used in the prevention of bleeding** in the event of surgery or invasive procedure. In exceptional cases (very severe bleeding and lack of response to standard treatments), plasmapheresis and/or immunoadsorption, in combination with high doses of FVIII concentrates can be considered.
- **Inhibitor eradication. All AHA patients should receive IST immediately after diagnosis**. **First-line treatment** should be oral **prednisone/prednisolone** either alone or associated with oral **cyclophosphamide**: this approach allows to reach a CR (persistent undetectable inhibitor, <0.6 UB/mL, and levels of FVIII:C >70% and IST stopped) in 60-80% of cases, after a median time of 5-6 weeks. **Rituximab** can be considered as first-line therapy when standard first-line treatment is contraindicated. **Second-line therapies** should be attempted if a response to first-line treatment is not reached within 3-5 weeks: **rituximab,** alone or in combination with corticosteroids, if never given before, **cyclosporin, mycophenolate mofetil or multiple immunosuppressive agents.** At present, **ITI** does not appear to be an advisable therapeutic approach. The use of high-dose **IVIG** is contraindicated. **Prognostic markers at baseline (FVIII:C ≥1% vs ≤ 1% and inhibitor titre ≥20BU/mL vs ≤ 20BU/mL) should be identified to optimise IST** regarding the combination of corticosteroids with cyclophosphamide or other immunosuppressants such as rituximab for first-line therapy.
- **Monitoring after response to IST: aPTT, FVIII:C and inhibitor titre** must be monitored monthly within 6 months, every 2-3 months between 6 and 12 months, and every 6 months after 12 months.
- **Thromboprophylaxis after response to IST:** mechanical or pharmacological thromboprophylaxis in hospitalised non-bleeding patients is indicated when FVIII:C is over 50%, while subjects with prior need for anticoagulation or antiplatelet therapy can restart it at this moment. Patients showing very high levels of FVIII:C, during or after IST, should be evaluated for thromboprophylaxis.
- **IST in children with AHA:** there are no particular recommendations, given the low frequency of cases. Anti-haemorrhagic and eradication treatments are similar to those of adults.
- **IST in pregnancy-associated AHA: prednisone/prednisolone must be considered as first-line therapy choice**; cyclophosphamide and other alkylating agents must be avoided; **rituximab is believed to be an appropriate second-line therapy.**

Comments and Conclusions. Acquired haemophilia A is a rare and intriguing disease. Its knowledge should be improved among non-specialised clinicians, because it may suddenly appear in people otherwise in good health and because the first approach might occur in emergency departments, where sometimes doctors do not have experience with the diagnosis and management of this disease. Ideally, a Haemophilia Centre, with adequate expertise, would be the best place for the first approach of AHA, but this is not always possible. Therefore, the establishment of a network would be necessary on the territory to allow immediate consultation with a reference Haemophilia Centre, for obtaining both early diagnosis and prompt therapeutic approach. Over the past years, therapies for bleedings have gradually improved, thanks to the use of increasingly effective and more widely available products. The availability of rpFVIII has made possible a real replacement therapy, thanks to low cross-reactivity of the rpFVIII with the autoantibody directed

against human FVIII. However, as mentioned above, this treatment should be carefully monitored and requires to be administered in specialised Centres. Excellent results can be obtained with IST: first-line therapy with corticosteroids, alone or combined with cyclophosphamide, has demonstrated high efficacy; moreover, rituximab in resistant or relapsed cases or even as first-line approach, when other immunosuppressants are contraindicated, is currently considered an effective treatment. In conclusion, the knowledge of the disease has been improved, therapy for bleeding has reached remarkable results and IST, set up as soon as possible, offers the possibility of the inhibitor eradication in most cases. Hence, morbidity and mortality of AHA have significantly decreased, even in the more advanced age groups.

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