An overview in acquired hemophilia A

CHAPTER 10

Summary and general discussion

Acquired hemophilia A (AHA) is a rare, autoimmune bleeding disease characterized by a deficiency of coagulation FVIII secondary to autoantibodies directed against specific epitopes, which cause the accelerated neutralization and clearance of FVIII from plasma. AHA is extremely rare in children, presents a first peak in young women during pregnancy or puerperium, and becomes significantly more frequent in elderly people after 65 years old. AHA is a serious disease not only due to the incidence of severe bleeding, but also due to the high mortality, estimated to exceed 20% in older patients with other comorbidities.

In almost half of the cases the cause of AHA is idiopathic, while in the remaining 50% it is attributable to underlying diseases or clinical conditions, the main ones of which are shown in Table 1.

DISEASES OR CLINICAL CONDITIONS	CHARACTERISTICS
Oncologic diseases	Multiple myeloma, lymphomas, monoclonal gammopathy of uncertain significance (MGUS), myelofibrosis, myelodysplasia.
Rheumatic diseases	Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjogren's Syndrome, Goodpasture's Syndrome, Temporal

	Arteritis, Myasthenia Gravis, Thyroiditis, Multiple Sclerosis
Dermatological diseases	Psoriasis, pemphigus
Pregnancy or Puerperium	Within 1-4 months of delivery or miscarriage
Drugs	Some beta-lactam antibiotics, chloramphenicol, sulfonamides, clopidogrel, nonsteroidal anti-inflammatories (NSAIDs), fludarabine, interferon alpha
Other Diseases	Asthma, chronic obstructive pulmonary disease, acute hepatitis

***Table 1**. Diseases and clinical conditions associated to AHA (adapted from AICE Recommendations 2020)*

Typical onset manifestations of AHA, present in over 70% of cases, are large muscle and skin hematomas which generally affect the lower and upper limbs and the trunk, and which can cause severe anemization and/or compression of vessels and nerves (compartment syndrome). Other hemorrhagic manifestations may occur in the soft tissues, in the genitourinary tract or in the mucous membranes. Unlike congenital hemophilia, hemarthrosis or the feared intracranial hemorrhages are very rare.

An important role in the timely diagnosis of AHA is played by the laboratory (Figure 1) which must be able to exclude the presence of heparin, of other anticoagulant drugs (e.g. DOACs) and of Lupus Anticoagulant (LA), all associated to lengthening of the aPTT. The mix test, easily performed in most laboratories, aids in rapid diagnosis.

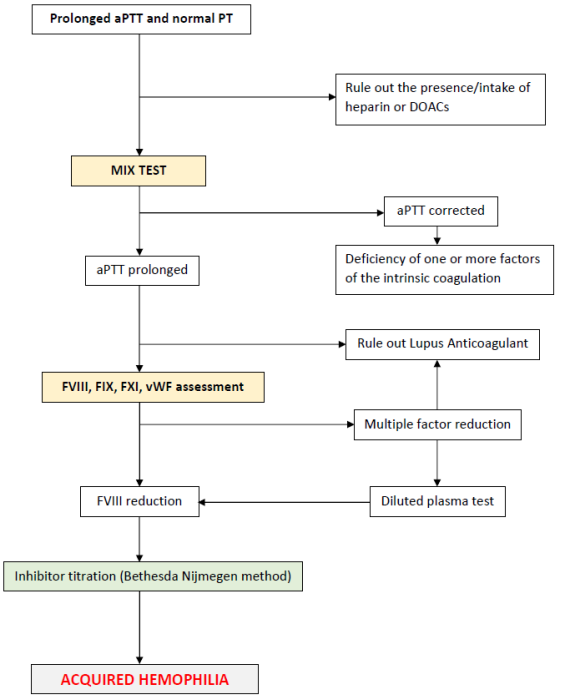

Figure 1. *Algorithm for the laboratory diagnosis of AHA (adapted from AICE Recommendations 2020)*

The management of a patient with AHA is complex, therefore it requires an in-depth knowledge of the disease, the most appropriate treatments and short- and long-term follow-ups. To help clinicians, there are precise algorithms that describe a differentiated clinical-diagnostic path for the hemophilia treatment centers (Figure 2), used to managing people with congenital and/or acquired bleeding disorders, and for peripheral hospitals (Figure 3) less accustomed to dealing with such emergencies.

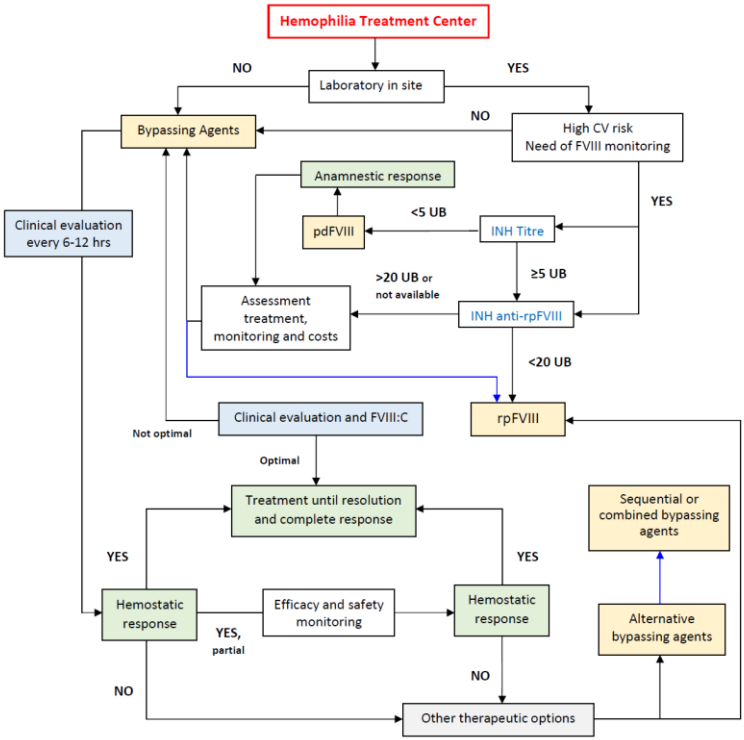

Figure 2. *Algorithm for AHA management at Hemophilia Treatment Centers (adapted from AICE Recommendations 2020)*

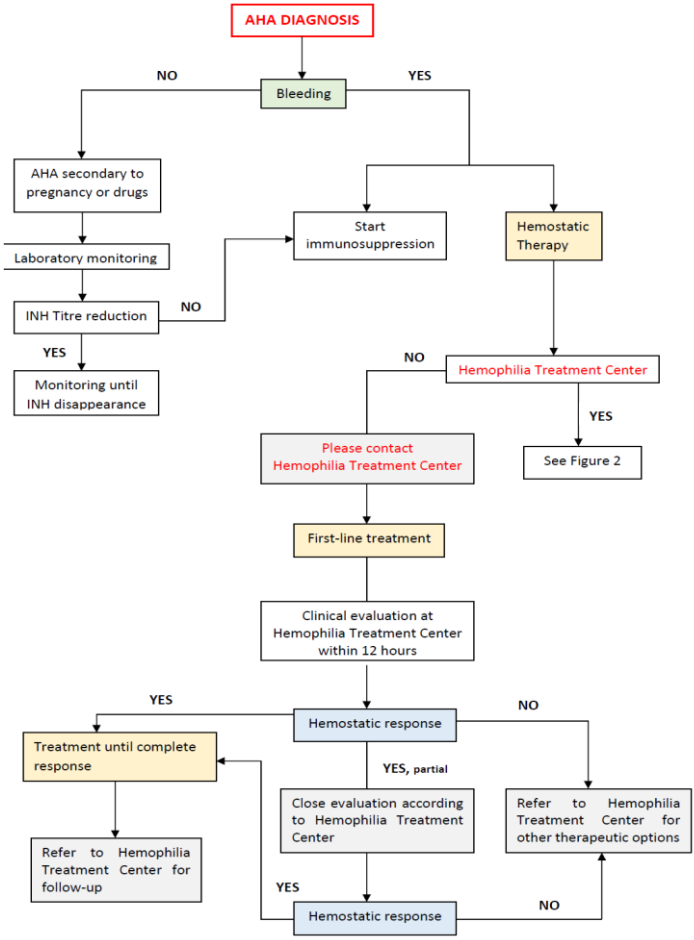

Figure 3. *Algorithm for AHA management at different hospitals (adapted from AICE Recommendations 2020)*

National and international guidelines recommend intervening as soon as possible to resolve bleeding and to eradicate inhibitors. Nowadays there are several possibilities of anti-hemorrhagic treatment, illustrated here in Table 2, while the immunosuppressive therapy is represented by corticosteroids alone, corticosteroids associated to cyclophosphamide or, in case of fail of these drugs, rituximab.

TREATMENTS	DOSAGE	ADVANTAGES	DISADVANTAGES
rpFVIII (Obizur®)	Initial dose of 200 IU/Kg, subsequent doses based on clinical response and FVIII levels (performed 30' and 3 hours after infusion) to be maintained depending on the type of hemorrhage, usually infusions every 4-12 hours	Easy monitoring and efficacy	Possible anti-rpFVIII development; not available in some hospitals; high costs, needing laboratory h.24.
rFVIIa (NovoSeven®)	90-120 µg/Kg every 2-3 hours until achieving secure hemostasis, then at longer intervals	Easily available in all hospitals; efficacy; small infusion volume	No validated monitoring; risk of events arterial or venous thrombosis; short half-life (2-3 hours)
aPCC (Feiba®)	50-100 IU/Kg every 8-12h. Do	Easily available in all hospitals;	No validated monitoring; risk

	not exceed 200 IU/ kg /day	efficacy	of events arterial or venous thrombosis; high volume of infusion
pdFVIII or pdFVIII/vWF	Variable based on bleeding severity, inhibitor titer, infusion mode (single boluses or continuous infusion)	Easily available in all hospitals; efficacy (especially in case of low-titer inhibitors); easy monitoring	Possible anamnestic response; need for high doses; daily laboratory control

Table 2 *Different treatments for AHA, dosage, advantages, and disadvantages (adapted from AICE Recommendations 2020)*

Patients with AHA often remain hospitalized for a long time, usually in internal medicine wards, requiring many treatments, those specific to this bleeding disorder, but also those necessary to cure their underlying diseases, sometimes very complex therapies consisting of biological drugs, such as for example belimumab for the treatment of lupus, enteracept for rheumatoid arthritis or imanitib for some forms of leukemia. Clinicians must therefore be constantly trained in order to better manage these patients. Periodic training meetings, managed by experts from hemophilia centers, would be necessary to ensure peripheral hospital staff have minimal skills in managing the AHA. Medical and graduate schools should also include the AHA in their courses in order to provide students and young doctors with the basics so that they are not unprepared if they are faced with one of these cases.

The main goal that we set ourselves in the study presented in **Chapter 2** was to evaluate whether plasma-derived products could still have a role in the treatment of AHA and possibly highlight which patients could benefit from this therapy. Two different groups of patients with different inhibitor titers were treated with pdFVIII, with and without von Willebrand factor (vWF), in an immunotolerance regimen or in continuous infusion. Some patients also had underlying diseases at high thromboembolic risk which made treatment with bypassing agents more critical. All treatments resulted ineffective stopping of bleeding, but the duration was markedly shorter in the case of pdFVIII/vWF used in continuous infusion, similar to that obtained with bypassing agents or with rpFVIII. Conversely to what is recommended in international guidelines[1,2], plasma-derived concentrates were also effective in patients who already had a high titer of inhibitors at the onset of AHA. This may therefore be a valid therapeutic option in many patients, especially when first-line drugs for the management of AHA are lacking.

The efficacy and safety of aPCC in the acute treatment of AHA is the subject of **Chapter 3**. The FAIR study is a multicenter Italian study involving 12 hemophilia centers, the data collection covered a period of 10 years and a total of data from 56 patients were collected. The aPCC was used as first-line therapy in 82.2% of subjects, while it was effective in 96.4% of cases, the latter data being consistent with that reported in the EACH2[3,4], but unlike what is reported in this registry, in

the FAIR study no patient experienced side effects using this drug.

The efficacy of a new recombinant B-domain deleted porcine FVIII (rpFVIII)was proven in the OBI-1 Study[5], in which the positive response to treatment was achieved in all enrolled patients within 24 hours from the first dose. This drug was then licensed in Italy in 2016. The real-world use of susoctocog-alfa in the treatment of patients with AHA was described in **Chapter 4**. Nine different cases were described, 88.9% were males, mean age 78.7 years. 44.4% were idiopathic AHAs. Seven patients presented muscular bleeding, one intracranial hemorrhage and the remaining hematuria with concomitant knee hemarthrosis. Seven patients also presented concomitant diseases, among these 71.4% were cardiovascular. Susoctocog-alfa as first line therapy was used in one third of cases. In contrast to the recommended loading dose of 200.0 IU/kg[5], the median loading dose used in this study was 100.0 IU/kg; median subsequent doses were 50 IU/kg with a median frequency of 12 hours and with a median number of doses of 8, data similar to those reported in other studies[6,7]. Treatment was continued for a median of 4 days (IQR 1-32).The inhibitor against rpFVIII was not tested before treatment with susoctocog-alfa, only two patients developed a low titer rpFVIII-inhibitor. rpFVIII was considered effective and safe in all cases and was associated with antifibrinolytics in 22.2% of cases.

The concomitant use of antifibrinolytics and aPCC were detailed and discussed in **Chapter 5**. Antifibrinolytic

drugs exert their action inhibiting activation of plasminogen and reducing the plasminogen conversion to plasmin. Headache, abdominal pain, backache, and diarrhea are common side effects of these drugs, while pulmonary embolism or deep vein thrombosis are rare. Despite this, the association with another drug that acts on the coagulation cascade can greatly increase the thromboembolic risk. This leads clinicians to use caution in combining aPCC and antifibrinolytics, especially in the case of patients with AHA. Only rare reports are in fact available in literature[8]. In the detailed sub-analysis of the FAIR study 40/101 acute bleeds were overall treated with a combined use of aPCC and antifibrinolytics; there were 19/35 bleeds in the prospective group and 21/66 in the retrospective one, showing a statistically significant difference ($p<0.05$). In 35 patients in whom the combined treatment was used, two of them had a previous ischemic stroke, while other one had a history of myocardial infarction. In these subjects, the treatment duration was reduced (mean reduction 16.3%) up to a median of 7 days (IQR 1-48). Good tolerance to combined therapy and no thromboembolic events were reported during the study, also in subjects with severe cardiovascular diseases, suggesting that the combined use of aPCC and antifibrinolytics has a reasonable safety.

In **Chapter 6** we reported the case of a 71-year-old-man, who presented with spontaneous hematomas and severe anemia, and had a medical history of thromboendoarterectomy of the left carotid artery; aorto-iliac by-pass; acute myocardial infarction with consequent coronary artery by-pass graft (CABG) and

vascular cervical myelopathy with sensory and motor deficit in the right lower limb. He did not have a personal or family history of inherited coagulation disorders or autoimmune diseases. Idiopathic AHA was diagnosed at admission to hospital needing an immediate treatment to solve bleeding. At the time of this case report, only bypassing agents were available for the treatment of AHA, but their use in this subject with severe cardiovascular disease was risky. Despite the high titer of the inhibitor (28 BU/ml) and the lack of recommendations[1,2], we still decided to use pdFVIII/vWF in combination with corticosteroids. The bleeding resolved and one month after the start of treatment the FVIII plasma level returned to normal, and the inhibitor disappeared. No relapses occurred in the following months. This treatment has therefore proved to be a valid therapeutic alternative in a very complex patient.

In **Chapter 7** the attention is focused on the case of an elderly patient with many comorbidities including bilateral breast cancer and rheumatoid arthritis, who presents in hospital for acute myocardial infarction, severe anemia (5.7 g/dl) and extensive mucocutaneous hematomas. After the first emergency treatments for the ischemic heart disease, the patient was transfused with packed red blood cells to restore the hemoglobin level, and subsequently an AHA was diagnosed. The patient was immediately treated with cyclophosphamide/corticosteroids and a bolus of rpFVIII 100IU/Kg, followed by rpFVIII 50IU/Kg/tid; the bleeding resolved within 72h. One month later the patient had to undergo an emergency cholecystectomy

under cover with susoctocog-alfa 50IU/Kg/tid, without any complications. This was the first real-world case reported in the literature of an AHA patient undergoing surgery under rpFVIII coverage, while only few cases of subjects with congenital hemophilia A and inhibitors were available[9,10].

One of the major problems in managing the patient with AHA is the risk of relapse, which is around 20% of treated cases[4] and is more likely within a month of resolution of the first episode. The use of low-dose aPCC as post-acute treatment prophylaxis is the topic of **Chapter 8**. The efficacy of this prophylactic regimen had already been described in a previous Italian study[11]for a small number of patients, now the larger FAIR study has confirmed these results. Only three of the thirty-two total relapses occurred in the group of patients treated in prophylaxis with aPCC. However, further studies would be necessary to better define the most appropriate dosage of aPCC to be used and the duration of treatment.

A possible new therapeutic option for the treatment of AHA may derive from the use of emicizumab, a bispecific monoclonal antibody that mimics the action of FVIII, currently approved only for the treatment of hemophilia A with or without inhibitors[12,13]. In **Chapter 9** we reviewed the available literature regarding the use of emicizumab in AHA. From the analysis it clearly emerges that this drug finds its best use in short and long-term prophylaxis, the efficacy in preventing further bleeding has in fact emerged in all the publications analyzed. Given the need for a period of at least four

weeks to reach steady state and full efficacy, emicizumab is not widely indicated as first-line treatment of the acute event.

Furthermore, the level of FVIII must be constantly monitored in patients with AHA treated with emicizumab, in fact when it exceeds 50% the risk of thromboembolic events significantly increases.

In conclusion, with this thesis we wanted to underline the importance of not underestimating a disease such as acquired hemophilia, which is still today the cause of high mortality and, at the same time, we wanted to make an overview of the treatments currently available or under study.

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