

## **How to diagnose and treat acquired hemophilia: a consensus statement of the Working Party on Hemostasis of the Swiss Society of Hematology**

Acquired hemophilia (AHA) has to be suspected in case of acute or recent onset of bleeding in a patient without personal or familial bleeding history and isolated prolonged aPTT.

### **1. Diagnosis**

- Diagnosis has to be confirmed in a Reference Center with experience in the diagnosis and treatment of hemophilia as well in the treatment of patients with high risk of severe bleeding.
- Diagnosis and treatment of AHA should be carried out in Reference Centers with experience in the diagnosis and treatment of hemophilia.

#### **1.1 Diagnostic steps**

- a) Coagulation screening tests (PT, aPTT, Fibrinogen and platelet count).
- b) Factor VIII:C assay
  - Chromogenic or one-stage coagulation end-point assay.
- c) Von Willebrand factor assay.
- d) APTT-mixing assay (optional)
  - This test is poorly standardized and cannot be used to establish or exclude AHA
  - Further investigation are always required, and specific factor activity assays should be performed in parallel to facilitate early diagnosis.
  - First mixing 1:1 with normal plasma, assay immediately and after 2h at 37°C. Additional mixing ratios are optional.
- e) Factor VIII-Inhibitor assay
  - A Bethesda assay, Nijmegen modification should be used (often AHA displays complex or non-linear type 2 kinetics autoantibodies).
  - Repeat if negative.
- f) Anti-porcine inhibitor titer
  - The porcine FVIII inhibitor titer should be quantified if rpFVIII is considered as a treatment option.
  - The assay is performed in the same way as the Bethesda assay, but with rpFVIII as the substrate instead of normal human plasma.
- g) Look-up for an underlying disease

- Tumor screening (solid and hematologic, MGUS), Autoimmune disease (SLE, RA), drug history, infection or acquired von Willebrand disease.

## **2. Bleeding treatment**

### **2.1 Treatment of acute bleeding**

- Treatment should be initiated as soon as the diagnosis is made (after point c of the diagnosis procedure).
- Of note, severity of bleeding in AHA does not always correlate with FVIII levels or FVIII inhibitor titer.
- The goal of the treatment is to restore hemostasis as soon as possible to stop bleeding by overcoming the role of endogenous FVIII by a replacement therapy.
- Several treatment options are available, such as rFVIIa (NovoSeven®), aPCC (FEIBA®) or rpFVIII (Obizur®), according to the availability of these agents in each treatment center.
- If the patient has a particularly high thrombotic risk, rpFVIII (Obizur®) may be preferred.
- In case of delay or non-availability of these agents, FVIII concentrates could be tried (probably more effective in patients with low inhibitor titer).
- Addition of tranexamic acid may be considered.
- The use of IVIg and DDAVP is not recommended.

### **2.2 Hemostatic agent options in case of acute bleeding**

#### **2.2.1 rFVIIa (NovoSeven®)**

- Start with 90 ug/Kg BW every 2-3h until hemostasis is achieved.
- Increase dosing interval if bleeding is controlled.
- Switch treatment option if ineffective.

#### **2.2.2 aPCC (FEIBA®)**

- Start with 50-100 U/Kg every 8 to 12h, up to a maximum of 200 U/kg/d, until hemostasis is achieved.
- Increase dosing interval if bleeding is controlled.
- Switch treatment option if ineffective.

#### **2.2.3 rpFVIII (Obizur®)**

- Start with 100 U/Kg:
  - o If FVIII activity recovery after this initial dose is above 50%, high titer inhibitor can be ruled out. Then the patient can be treated with rpFVIII with tailored dosing according to the clinical situation. Of note, close monitoring of FVIII levels is mandatory as cross-reacting anti-rpFVIII inhibitors can develop during the treatment course.

- If FVIII activity recovery after this initial dose is below 50%, high titer inhibitor cannot be ruled out, and this treatment should be re-considered since there may be poor effectiveness and insurance coverage issues.

### **2.2.4 Human factor VIII concentrates (recombinant or plasma-derived)**

- They can be used only if none of the above-mentioned products are available and if the inhibitor titer is low.
- Start with 50-100 U/Kg followed by targeted dosing.

### **3. Hemostatic maintenance therapy**

- If AHA is not associated with an acute bleeding or at distance of the treatment of the acute bleeding event, no hemostatic agent is mandatory, although a prophylaxis with one of the above-mentioned products may be considered especially in selected patients with a high risk of infections (e.g. older frail patients)
- Emicizumab (Hemlibra®) has been reported as effective in AHA to reduce the need for early and aggressive immunosuppressive therapy (IST), at the posology of 6 mg/kg on day 1, 3 mg/kg on days 2 and 1.5 mg/kg weekly until week 12. Of note, this is an off-label indication.
- The use of emicizumab requires chromogenic FVIII test (with bovine reagents) to monitor native FVIII levels and anti-FVIII inhibitors levels.

### **4. Treatment of the antibody**

#### **4.1 Treatment goal**

- The goal of the immunosuppressive therapy (IST) is to reduce the risk of bleeding by shortening the time to achieve remission of AHA.

#### **4.2 Complete remission (CR)**

- No detectable FVIII inhibitor by the Bethesda assay, FVIII:C > 50% and IST stopped.

#### **4.3 Partial remission (PR)**

- FVIII:C > 50%, stable for >24h, after administration of any hemostatic treatment and no active bleeding, with IST ongoing.

#### **4.4 Treatment steps**

- The use of high-dose FVIII for immune tolerance induction is not recommended.
- IVIg for inhibitor eradication is not recommended.
- IST should be individualized according to the FVIII level and the inhibitor titer.

##### **4.4.1 Patients with FVIII $\geq$ 1 IU/dL and inhibitor titer $\leq$ 20 BU at baseline**

- First-line treatment with corticosteroids alone for 3–4 weeks.
- Start prednisone with 1 mg/kg/day for 4-6 weeks followed by tapered withdrawal.
- In patients who do not achieve CR with first-line IST but have continued improvement of FVIII activity and inhibitor titer, pursue the corticosteroids alone

- In patients not responding to steroids after 3 weeks, a second-line IST should be started (see below).

#### **4.4.2 Patients with FVIII < 1IU/dl or inhibitor titer >20 BU**

- First-line treatment with corticosteroids combined with second-line IST: rituximab or a cytotoxic agent (cyclophosphamide or mycophenolate mofetil)
  - o Rituximab should be administered at a dose of 375 mg/m<sup>2</sup> weekly for a maximum of four cycles.
  - o Cyclophosphamide should be administered at a dose of 1.5–2 mg/kg/day PO for a maximum of 6 weeks.
  - o Mycophenolate mofetil should be administered at a dose of 1 g/day for 1 week, followed by 2 g/day.
  - o Close monitoring for leukopenia, thrombocytopenia, kidney function and infections is required during treatment with any cytotoxic agent.

#### **4.5 Reduction scheme after at least PR is reached**

- Stop second-line IST.
- Tapered withdrawal of prednisone.
- If FVIII falls below 50% during reduction, continue with the last effective dose of steroids until FVIII>50% for one week.
- Continue the reduction scheme after FVIII>50%.

#### **4.6 Follow-up after CR**

- FVIII level should be monitored monthly during the first 6 months.
- Every 2–3 months up to 12 months.
- Every 6 months during the second year and beyond, if possible.

## **References**

- 1) Tiede A, Collins P, Knoebl P et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. *Hematologica* 2020 Jul;105(7):1791-1801
- 2) Hayden A, Candelario N, Moyer G. Recombinant porcine factor VIII in acquired hemophilia A: Experience from two patients and literature review. *Res Pract Thromb Haemost* 2022 Mar 27;6(2):e12688
- 3) Tiede A, Hart C, Knoebl P et al. Emicizumab prophylaxis in patients with acquired haemophilia A (GTH-AHA-EMI): an open-label, single-arm, multicentre, phase 2 study. *Lancet Haematol* 2023 Nov10(11):e913-e921.
- 4) Hart C, Klamroth R, Sachs UJ et al. Emicizumab versus immunosuppressive therapy for the management of acquired hemophilia A. *J Thromb Haemost.* 2024 Oct;22(10):2692-2701