How to diagnose and treat acquired hemophilia: a consensus statement of the Working Party on Haemostasis of the Swiss Society of Haematology

Acquired hemophilia (AHA) has to be suspected in case of acute or recent onset of bleeding symptoms in a patient without personal or familial bleeding history and isolated prolonged aPTT. Invasive procedures in patients with AHA can lead to serious complications – abstain from all invasive procedures (except limb- and life-saving procedures) until a diagnosis is established.

1. Diagnosis

- Diagnosis must 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.

1.1 Diagnostic steps

a) Coagulation screening tests (PT, aPTT, Fibrinogen and platelet count).

b) APTT-mixing assay
- This test is poorly standardized and cannot be used to rule in or rule out AHA, but it may be of some help if specific tests are not readily available.
- Further investigations 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 1 or 2h at 37°C. Additional mixing ratios are optional.

1.2 Specific assays

a) Factor VIII:C assay
- Chromogenic or one-stage coagulation end-point assay.

b) Von Willebrand factor assay.

c) FVIII-Inhibitor assay
- A modified Nijmegen-Bethesda assay should be used (often FVIII autoantibodies in AHA displays complex or non-linear type 2 kinetics).
- FVIII inhibitors >20 BU/ml against human FVIII are usually cross-reactive with rpFVIII.
- Repeat if negative.

d) rpFVIII 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 spiked in FVIII deficient plasma (1 U/mL).

1.3 Underlying disease

While half of AHA cases are idiopathic, an underlying and/or associated diseases can be identified in the other half. In up to 15% solid tumors or hematological neoplasms; 15% autoimmune diseases (SLE, RA, etc.); 8% pregnancy associated; in 4-5% infections, 3-4% certain drugs. Appropriate investigations should be initiated.

2. Bleeding treatment

2.1 Treatment of acute bleeding

- Treatment of acute should be initiated as soon as the diagnosis is made (after point 1.2 a) of the diagnosis procedure).
- Of note, severity of bleeding in AHA does not necessarily 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 as a first line therapy, 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 every 2-3h until hemostasis is achieved.
- Extend dosing interval when bleeding is controlled.
- Switch to another 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.
- Extend dosing interval when bleeding is controlled.
- Switch to another treatment option if ineffective.

2.2.3 rpFVIII (Obizur®)

- Start with 100 U/Kg:
    - If FVIII activity recovery after this initial dose is ≥50%, a 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 <50%, a high titer anti-rpFVIII cannot be ruled out, and this treatment should be re-considered.

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

- They can be used only if none of the above-mentioned products is available and if the FVIII inhibitor is < 5 BU/ml.
- Start with 50-100 U/Kg followed by targeted dosing.

3. Hemostatic maintenance therapy

- If AHA is not associated with acute bleeding or at distance of the treatment of the acute bleeding event, no prophylactic hemostatic agent is mandatory, but should be considered on a case-by-case basis.
- Emicizumab (Hemlibra®) has been reported to be effective in AHA and may be considered in selected cases (but at least 48h after the last aPCC dosing, or together with rFVIIa if an active bleeding is still ongoing until hemostasis is achieved).
- 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

- Treatment of the underlying disease is essential for long-term remission and may guide the choice of the immunosuppressive therapy (IST).

- The goal of the IST is to suppress the autoantibody production, thereby shortening the time to remission of AHA and the reduction of the bleeding risk.

Complete remission (CR): No detectable FVIII inhibitor by the Nijmegen-Bethesda assay, FVIII:C > 50% and IST stopped.
Partial remission (PR): FVIII:C >50%, stable for >24h, after administration of any hemostatic treatment and no active bleeding, with IST ongoing.

4.2 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.

4.2.1 Patients with FVIII ≥ 1% and inhibitor titer ≤20 BU/ml 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 inhibitor titer and FVIII activity, pursue the corticosteroids alone
- In patients not responding to steroids after 3 weeks, a second-line IST should be started (see below).

4.2.2 Patients with FVIII < 1% or inhibitor titer >20 BU/ml

- First-line treatment with corticosteroids combined with second-line IST: rituximab or an immunosuppressive agent such as cyclophosphamide or possibly mycophenolate mofetil.
    - Rituximab should be administered at a dose of 375 mg/m2 weekly for a maximum of four infusions.
    - Cyclophosphamide should be administered at a dose of 1.5–2 mg/kg/day PO for a maximum of 6 weeks.
    - Mycophenolate mofetil should be administered at a dose of 1 g/day for 1 week, followed by 2 g/day.
    - Close monitoring for leukopenia, thrombocytopenia, kidney function and infections is required during treatment with any cytotoxic agent. Prophylactic anti-infectious agents should be considered while on these treatments (i.e., Trimethoprim/Sulfamethoxazole and Valaciclovir).
- A lower threshold of inhibitor titer for this strategy can be considered on individual basis.

4.3 Reduction scheme after at least PR is reached

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

4.4 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) Thomas VM, Abou-Ismail MY, Lim Y et al. Off-label use of emicizumab in persons with acquired haemophilia A and von Willebrand disease: A scoping review of the literature. Haemophilia 2022 Jan;28(1):4-17

4) Tiede A, Alberio L. The Art of Detecting Antibodies against Factor VIII. Hamostaseologie. 2020 Nov;40(4):485-490

5) Dix C, Tee A, McFadyen J, Tran H. Acquired hemophilia A: Insight unto treatment and outcomes from an Australian tertiary referral centre. Haemophilia, 2022, 28, e49-e52