# Acquired haemophilia

# Nordic guidelines

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# 1 Summary

Acquired haemophilia (AH) is a severe bleeding disorder caused by inhibiting autoantibodies against a coagulation factor, most often factor (F) VIII (acquired haemophilia A, AHA), developing in a patient with no previous history of bleeding. Due to the rarity of acquired haemophilia B, with antibodies formed against FIX, all data available and presented in this guideline primarily concerns acquired haemophilia A.

It is a rare disorder with an incidence of about 1-2/one million per year. Mostly elderly persons are affected with the exception of the rare occurrence in females postpartum. The APTT is usually prolonged but other laboratory screening tests for haemostasis like platelet count and prothrombin time are normal. Patients with AH represent a demanding clinical challenge. The mortality rate is high (3.3%-22% in different studies)[1,2] and treatment involves the use of specific and expensive coagulation promoting products. The diagnosis requires identification of autoantibodies (inhibitors) with a specialized test. Consequently, both special laboratory facilities and clinical experience are required to deal with this group of patients. **The physician on duty at a haemophilia centre should be consulted.**

In recent years, valuable information was gathered regarding e.g. incidence, frequency of co-existing disorders, mortality and risk of bleeding as well as eradication therapy. These studies include: 1) a meta-analysis of 234 evaluated patients from the literature presented by Delgado et al. [3], 2) a surveillance study in the United Kingdom conducted by Dr Peter Collins [1], including altogether 172 patients diagnosed in England and Wales with acquired haemophilia A (AHA) during a two-year-period starting in 2001, and 3) the pan-European register, EACH/EACH2 [2], including 501 (266 male, 235 female) patients from 117 centres and 13 European countries. More recent studies include the prospective Surveillance des Auto antiCorps aucours de l'Haemophilie Acquise—SACHA [4] surveillance study including 82 patients, a retrospective Taiwanese study including 65 patients [5] as well as the prospective German, Austrian and Swiss Society on Thrombosis and Haemostasis including 102 patients [6].

# 2 Diagnosis

## 2.1 Incidence and co-morbidity

As mentioned above, AH is rare and the incidence is about 1.5/million per year. It is primarily a disease affecting the elderly (median age 64–78 years), but can also be associated with pregnancy. Most cases are idiopathic (43.6%-51.9%) but AHA is also associated with malignancy (6.4%-18.4%), autoimmune disorders (9.4%-17.0%), infections and dermatologic conditions [1–6]. Rarely, AH arises as idiosyncratic reactions to medication including antibiotics, psychiatric and immunomodulatory drugs [7]. The relative high number of co-existing autoimmune disorders in the patients or among his/her relatives may be striking. Therefore, findings suggesting polymorphisms in immune regulatory genes to be associated with the incidence of acquired haemophilia may be of importance [8,9]. It has also been hypothesized that encounter of antigenically different, allogeneic FVIII after blood transfusion may challenge inhibitor formation after presentation on MHC class II and support for this assumption was found in a study by Tiede et al [10].

## 2.2 Symptoms and signs and clinical course

Easy bruising with extensive enlargement, muscle haematomas and profuse bleeds after trauma and surgery are the most common symptoms in a patient who has never had any signs of bleeding tendency earlier. Muscle bleeds and gastrointestinal (GI) bleeds are also common, but in contrary to congenital haemophilia, joint bleeds are rare [1–3]. Haematuria with intermittent clotting and occlusion of ureter(s) may decrease renal function. Massive bleeds may occur after intravenous venipuncture if special care is not taken. Severe bleeds may be life-threatening. Because of the second-order kinetics of the anti-FVIII antibodies, FVIII levels are not predictive of bleeding risk and patients can have clinically significant bleeding despite only modestly reduced FVIII activity levels. Mortality in AHA is estimated to be 20% among patients >65 years and those with underlying malignancies. Although the primary cause of death is the underlying disease (46%) [2], the cause of death is unknown in many (38%) [11], reflecting limited follow-up in most studies. Immunosuppressive therapy (IST) to eliminate the antibodies and decrease bleeding risk is recommended but is associated

with high mortality, accounting for 16% of all deaths (4.2% of patients) in EACH2 [2]. Other fatal and nonfatal complications include thrombotic events such as myocardial infarction and stroke [4,6].

## 2.3 Laboratory screening methods

APTT is usually prolonged, while Prothrombin time, PT (INR) is normal. Platelet and leukocyte counts are generally normal. The erythrocyte count and the haemoglobin value may be low due to bleeds.

## 2.4 Specialized laboratory methods

The diagnosis should be confirmed at a specialized coagulation laboratory.

### 2.4.1 Blood sampling and transport

Blood samples are drawn in vacutainer tubes containing 3.2% (0.109 M) trisodium citrate by direct venipuncture.

- Fill tube correctly to the mark (line) and mix thoroughly with anticoagulant (reverse gently the tube(s) immediately 5-10 times).
- Centrifuge within 1 hour of phlebotomy to obtain platelet poor plasma ($<10x10^9$/L) at 2000 g for 20 minutes.
- If testing cannot be performed within four hours from phlebotomy, the plasma should be transferred by pipetting to another tube and frozen at -70°C for later analysis.
- Frozen plasma must be transported on dry ice.

### 2.4.2 Testing at the coagulation laboratory

Mixing test (can also be performed at non-specialized laboratories): Patient plasma is mixed with an equal volume of normal plasma (NPP; 1+1) and APTT analyzed

immediately and/or incubated for 1-2 h at 37°C. In normal conditions, the APTT will lengthen slightly if incubated 1-2 h at 37°C, because of a spontaneous decay of the labile FVIII. A prolonged APTT in a factor deficient plasma will be corrected when the plasma is mixed 1:1 with normal plasma, whereas presence of an inhibitory antibody against a coagulation factor or lupus anticoagulant, does not give a correction after mixing (anticoagulant in the plasma must be excluded). In acquired haemophilia, weak affinity inhibitors can sometimes only be detected if a longer incubation time (1-2h) is used prior to analysis (see below autoantibodies).

## 2.5 Specific methods

The functional activity of FVIII or, occasionally, other coagulation factors such as FIX, can be measured with either clot-based or chromogenic assays. Autoantibodies to other factors are extremely rare. The recommended procedure for diagnosing inhibitory antibodies to coagulation factors is the Bethesda-Nijmegen method [12]. The antibody titer is expressed in Bethesda units (BU). One Bethesda Unit is defined as the quantity of antibody, which reduces the FVIII activity by half in normal plasma. A test sample is prepared by mixing equal volumes of patient plasma with NPP and then measure the residual factor activity in the plasma mixture after 2h incubation. A control sample is prepared in parallel with NPP mixed with an equal volume of FVIII-deficient plasma. Both test and control samples are incubated for 2 h at 37°C and then the factor activities in both samples are measured. The factor activity is measured using a clot-based or chromogenic method. The Bethesda assay is most suitable for patients that do not have measurable factor activity. If the patient has an activity $> 0.10$ kIU/L (10%), we recommend heat-inactivation of the plasma sample endogenous activity at 56 $^{\circ}$C for 1h before analysis.

## 2.6 Characteristics of the autoantibodies

Autoantibodies against FVIII are composed predominantly of IgG, most often of the IgG4 subclass, and have a preponderance of kappa light chains. The main antigenic epitopes of the FVIII molecule are the A2 and C2 domains. Bound inhibitors block the binding of FVIII to phospholipids, von Willebrand factor and cofactors of the FVIII molecule. The autoantibodies follow a type II inactivation pattern, which means

that there is incomplete neutralization of FVIII activity. Therefore, variable levels of residual FVIII activity may be detectable in patient plasma despite the concomitant presence of high titers of the FVIII inhibitor. The complex type II kinetics makes it difficult to clinically evaluate the inhibitor titer and factor levels. This is in contrast to alloantibodies seen in patients with congenital haemophilia which follow type I kinetics characterized by complete inactivation in a linear relationship between antibody titer and residual FVIII activity.

## 2.7 Recommendations

- Acquired haemophilia should be suspected in patients with prolonged APTT, but normal INR and signs of bleeding.
- If coagulations factor analyses is not readily available, a mixing test could be performed to strengthen the suspicion. The presence of an inhibitory antibody against a coagulation factor does not give a correction of APTT after mixing with normal plasma.
- The diagnosis should be confirmed at a specialized coagulation laboratory.
- The recommended procedure for diagnosing inhibitory antibodies to coagulation factors is the Bethesda-Nijmegen method.
- Type II kinetics of the antibodies results in poor correlation between antibody titer and FVIII levels and caution is warranted when interpreting the results.

# 3 Treatment of bleeding

## 3.1 Principles

The majority of patients with acquired haemophilia present with bleeds (89% for patients with AHA) [2]. Bleeds often constitute a medical emergency and can recur during treatment. In a British cohort, bleeding was the cause of death in 9% of the patients [1]. Approximately 70% of patients with acquired haemophilia require haemostatic treatment [3]. The choice of haemostatic agent and strategy is depending on the severity of bleeding, patient characteristics as well as the availability of specific products.

Patients with persistent inhibitors should be monitored even following the initial disease phase, since major bleeds can occur even after many months [1]. There is no consistent correlation between the titres of inhibitors or the residual factor level and the severity of the bleeding symptoms; thus, it is the phenotype, rather than the inhibitor titre, which should guide choice of treatment [1,2]. Blood red cells, plasma and thrombocytes should be transfused as required for management of a major bleeding. Specific haemostatic products include bypassing agents and coagulation factor concentrates.

Treatment, including management of bleeds, in patients with acquired haemophilia is optimally carried out at a specialist centre or, if referral is not possible, following early contact with a coagulation expert.

## 3.2 Specific treatments

There is no definitive data on which haemostatic agent (recombinant factor concentrates or bypassing agent) should be primarily considered as first-line treatment. The results from the EACH2 study in patients with AHA showed that bleeding control was similar in patients treated with rFVIII and with bypassing agents, however bypassing agents were superior to FVIII and desmopressin (bleeding control 93.3% vs 68.3%; P = .003)[13]. Inhibitor titer, treatment monitoring and immediate availability should guide the decision [3].

### 3.2.1 Bypassing agents

Two bypassing agents are commonly used in treating bleeds: i) FEIBA®, which is an activated prothrombin complex concentrate (aPCC), a plasma-derived, virus-inactivated product, containing small amounts of activated factors II, VII, IX and X and ii) NovoSeven® which is recombinant, activated factor VII.

There is no conclusive data on whether one of those bypassing agents is superior, since both have showed comparable efficacy in controlling bleeds [1,13,14]. The initial choice depends therefore on factors such as availability and previous clinical experience. Combination treatment can be considered if monotherapy is inefficient [15].

**3.2.1.1 aPCC (FEIBA®)** FEIBA® has been shown to be highly effective in treating bleeds. A retrospective analysis from a 10-year-survey in three tertiary medical centres included 34 patients with 55 bleeding episodes who received FEIBA® at a mean dose of 75 U/kg every 8-12 h. Complete bleeding control was achieved in 76 % of the severe and in 100 % in the moderate bleeding episodes [16]. According to the results from the EACH2 registry, FEIBA® as first-line treatment was administered at median initial dosage of 67 U/kg and was effective in 93% of the cases [13]. Treatment was well tolerated, with 4.8% of the patients suffering thrombotic episodes.

The French FEIBHAC registry included 34 patients with AHA who were treated with FEIBA® for a median duration treatment of 4 (2.2-8) days. The mean initial dosage was 75.4 U/kg $\pm$ 7.7 U/kg and haemostatic control was achieved in 88% of the bleeding episodes, whereas 6 serious adverse events (either thrombosis or events related to a potentially hypercoagulable state, such as DIC and low fibrinogen) were recorded [17].

There is no specific laboratory method for monitoring treatment with FEIBA®. The global haemostatic methods, such as thromboelastrography (ROTEM/TEG) and thrombin generation assays (TGA) have shown potential in the follow up and tailoring of treatment [18,19]. ROTEM/TEG is the method most often available in the clinical practice and can therefore be used for monitoring the efficacy of treatment with FEIBA®.

Although systemic use of tranexamic acid concomitantly with FEIBA® has been previously not recommended, more recent studies have not shown that there is an increased risk of thrombosis [20]. Administration of tranexamic acid with FEIBA® is therefore

not advised against, but it is recommended that, whenever possible, to maintain an interval of six hours between administration of the products.

According to the results of one study [21], administration of low dose FEIBA® to 15 patients for a mean of 20.5 ± 17.6 days following remission after initial treatment, led to lower rates of bleeding relapse compared to the rest of the cohort (n=41) which did not receive prophylactic treatment. The authors reported no thromboembolic events. However, due to the small size of the cohort, no recommendation on secondary prophylaxis following remission can be given.

**3.2.1.2 rFVIIa (NovoSeven®)** The optimal dosage of NovoSeven® in AH has not been defined. A dose of 90 $\mu$g/kg every 2-3 hours until haemostasis is achieved, is generally recommended to patients with congenital haemophilia with inhibitors. Sumner et al [18] reviewed 139 patients with AH who were treated with NovoSeven® at 124 non- surgical and 57 surgical situations. The dose regimens and length of treatment were similar for all patients with administration either as bolus injection (46-150 $\mu$g/kg at 2-24 h intervals) or continuous infusion (8-50 $\mu$g/kg/h). Most patients were treated for $<$ 7 days. The overall clinical response was evaluated as excellent or effective in 74.7% and partially effective in 13.7%. Ten thrombotic events were recorded.

In the EACH2 registry, the median initial dosage of NovoSeven® was 90 $\mu$g/kg (84.71-102.86) at an initial interval of 3 hours, and a median number of 12 dosages/patient. Out of the 174 patients, 5 suffered a thrombotic complication (2.9%)[13].

ROTEM/TEG and TGA may be useful in tailoring the treatment for the individual patient [18,22].

Generally, tranexamic acid is added during treatment with NovoSeven®.

### 3.2.2 Factor concentrates

FVIII concentrates may be useful in patients with FVIII autoantibodies. FIX concentrates may be useful in patients with FIX autoantibodies, which only occur rarely.

The success of treatment with factor concentrates is dependent on, above all, the inhibitor titre but also the severity and localisation of the bleeding. Factor concentrates are generally not effective in patients with high antibody titres, >5-10 BU.

For AHA, recombinant factor VIII is recommended [13]. For a newly diagnosed patient with a moderate or severe bleeding, a high bolus dose of 100-200 U FVIII/kg may be used. Alternative dosages suggested by other studies are 20 U of factor concentrate for each BU, with an additional 40 U/kg [1] and 90 U/kg every 2-3 hours [23] until bleeding control. According to the results of the EACH2 trial, the incidence of thromboembolic complications in patients treated with rFVIII was 2.9% [2]. FVIII and FIX concentrates may be administered intermittently or as continuous infusion.

Very high doses of FIX concentrate should be avoided, as a risk of developing thrombosis cannot be entirely excluded, especially in elderly patients.

Human FVIII concentrates are recommended primarily if bypassing agents and recombinant FVIII concentrates are unavailable [13,24,25], since they can generally not be given in such dosages as to overcome the inhibitor.

### 3.2.3 Porcine FVIII

Porcine plasma FVIII (pFVIII) concentrate is also available (Obizur®) and has been shown to be effective in increasing FVIII even at dosages 100 U/kg [26]. Due to its different sequence from human FVIII, porcine FVIII concentrate has lower risk of inactivation by inhibitors. Its main advantage is the possibility to monitor treatment response by routinely used FVIII:C measurements. However, there is a significant variability in the response to the product, mainly dependent on pre existing pFVIII antibodies and the appearance of such under treatment. In the initial study that led to registration of the product, a loading dose of 200 U/kg was used. In patients without anti-pFVIII, FVIII reached supra therapeutic levels (>400%) while patients with antibodies had normal or subtherapeutic levels of FVIII [26]. This study also demonstrate that FVIII levels do not rise as rapidly in the first 24 h in patients with a pre-existing anti-pFVIII antibody as in those without, but therapeutic levels could still be achieved. To predict the response of therapy it is thus, advisable that an assay to measure anti-pFVIII is available. However, by using a lower loading dose (100 U/kg) and measure the FVIII in vitro recovery, the adequate dose of subsequent doses can be calculated. A practical limitation is the high number of vials needed per dose (28 vials to achieve a dose of 200 U/kg in a 70 kg person [27].

### 3.2.4 Tranexamic acid

Tranexamic acid (Cyklokapron®, Tranon®) is an efficient inhibitor of fibrinolysis. It may be useful in prevention of bleeds in AH but is rather to be considered as a concomitant medication in the majority of bleeds. It can, however, be used as monotherapy in patients with mild bleeds.

### 3.2.5 Desmopressin

Desmopressin (Octostim®, Minirin®) is a synthetic analogue of vasopressin, which stimulates the endogenous release of FVIII, VWF and t-PA (tissue plasminogen activator). It has been previously shown some effect in treating mild bleedings [23] and has been included in the treatment recommendations. It could be considered as second line treatment if no other hemostatic agents are available. However, due to inferior efficacy [13] and adverse effects (see Table 1 below), it should not be used as first-line treatment.

### 3.2.6 Emicizumab (Hemlibra®)

Emicizumab (Hemlibra®) is a bispecific antibody against FIXa and FX, mimicking the co-factor activity of FVIII. It has been approved as treatment for inherited haemophilia A with inhibitors. It has been used in some cases of acquired haemophilia A [28,29]. As reported in [29], four patients received 3mg/kg sc. weekly/4weeks, then 1.5mg/kg and good haemostatic effect was reported. An elderly patient with comorbidities suffered a minor stroke after three injections, in association with rhFVIIa. Clinical studies to systemically evaluate efficacy and safety are ongoing (NCT04188639).

Emicizumab is currently not included in the treatment algorithm for AHA but can be considered upon failure of first- and second line treatment.

### 3.2.7 Local treatment

Immobilization of a limb may help to relieve pain and stabilize the clot. This should, however, be merely a temporary measurement, since immobilization in combination with administration of (primarily) bypassing agents could increase the risk for thrombosis.

Ice bags on towels can be applied on muscle haematomas. Fibrin glue, spongostan and similar products can be used locally, e.g. after tooth extractions. Tranexamic acid can be administered locally, for example to treat epistaxis or oral bleeds. A solution of lidocainhydroklorid + nafazolin ($\alpha$-adrenergic vasoconstrictor) may be used in mucous membrane bleed. Rigorous and repeated clinical evaluations of bleeds in order to assess progress or regress are required.

## 3.3 Pre- and perioperative management

Surgery or other invasive procedures should be avoided in patients with AH until the inhibitor is eradicated because of the risk of uncontrollable bleeds. If surgery is inevitably necessary, it should be undertaken with rigorous precautions. The surgeon must be familiar with operations on haemophilia patients and thorough surgical haemostasis should be applied.

Bypassing agents are considered as first-choice agents for pre- and perioperative prophylactic treatment in patients with acquired haemophilia. If bypassing agents are not available, administration of rFVIII/IX concentrate, intermittently or as a continuous infusion, would be efficient treatment if the levels of FVIII/IX are increased after injection (a test dosage should be administered prior to surgery in order to evaluate the effect). Porcine FVIII may also be considered after evaluating the in vitro recovery.

Factor concentrates or bypassing agents should be administered as soon as possible in severe manifestations associated with bleeding to avoid complications such as ileus or compartment syndrome, thus rendering invasive procedures unnecessary.

## 3.4 Recommendations

**First line treatment:**

- Bypassing agents are recommended for significant bleeds[1]. Choice of agent depends primarily on availability and clinical experience. Upon treatment failure with one agent, it is recommended to use the other. When switching treatments, an interval of at least 3 hours (when switching from NovoSeven® to FEIBA®) and 6 hours (when switching from FEIBA® to NovoSeven®) is recommended. Combination treatment can be considered if monotherapy is inefficient.

- Factor VIII concentrates in high dosages can be used as first line treatment in patients with AHA, if bypassing agents are not available and especially in patients with low antibody titres and if daily measurement of FVIII is possible.
- Tranexamic acid can be used as concomitant treatment both in patients receiving bypassing agents and factor concentrates. In mild[2] bleeds, tranexamic acid can be used as monotherapy or in combination with desmopressin.

**Second line treatment:**

- Either factor concentrates or bypassing agents can be used as second line treatment, depending on the medication used as first line treatment.
- Porcine FVIII is recommended if adequate bleeding control is not achieved on treatment with bypassing agents.

[1]Life or limb threatening, central nervous system, deep muscle or retroperitoneal bleeds. Haemoglobin <80 g/L or haemoglobin drop >20 g/L [3].

[2]Muscle and extensive superficial bleeds without any substantial effect on skin and function and without causing significant anaemia.

Table 1: **Dosing, adverse effects and monitoring of treatment**

| Treatment options | Dosing | Contraindications | Adverse effects | Monitoring and prevention of side effects |
|---|---|---|---|---|
| FEIBA® | 50-100 U/kg (i.v.) every 6-12 hours, at maximum 200 U/kg daily. | Acute venous or arterial thrombosis. DIC. | Arterial and venous thrombosis. Gastrointestinal symptoms. Dyspnoea. Coughing. | Clinical monitoring and ROTEM/TEG (alt. another global haemostatic method) can be used when available. |

Table 1: **Dosing, adverse effects and monitoring of treatment** *(continued)*

| Treatment options | Dosing | Contraindications | Adverse effects | Monitoring and prevention of side effects |
|---|---|---|---|---|
| NovoSeven® | 70-90 ug/kg (i.v.) at an initial interval of 2-3 hours until hemostasis is achieved, thereafter increasing the interval (4, 6, 8, 12 hours). An initial dosage of up to 120 ug/kg can be used. | | Arterial and venous thrombosis. DIC. Elevation of hepatic enzymes. Headache. Rash. Nausea. | Clinical monitoring and ROTEM/TEG (alt. another global haemostatic method) can be used when available. |

Table 1: **Dosing, adverse effects and monitoring of treatment** *(continued)*

| Treatment options | Dosing | Contraindications | Adverse effects | Monitoring and prevention of side effects |
|---|---|---|---|---|
| Factor concentrates (human) | 100-200 U FVIII/kg. Alternative dosages: 20 U of factor concentrate for each BU, with an additional 40 U/kg and 90 U/kg every 2-3 hours. (dosage based on recommendations for AHA) | (Depends on the factor concentrate) | (Depends on the factor concentrate) | Clinical monitoring and measurement of factor level. Monitoring of APTT (if initially prolonged). Factor levels should be determined at least once daily initially in order to evaluate the continued treatment. A level of 0.30 kIU/L or more should be aimed at. There is, however, no definite correlation between plasma levels and the clinical response, therefore the clinical condition must be carefully evaluated on a daily basis. |

Table 1: **Dosing, adverse effects and monitoring of treatment** *(continued)*

| Treatment options | Dosing | Contraindications | Adverse effects | Monitoring and prevention of side effects |
|---|---|---|---|---|
| Porcine FVIII | 50-200 U FVIII/kg as initial treatment. Subsequent dosing dependent on in vitro recovery and presence of anti pFVIII antibodies. | Previous anaphylactic reaction on administration of the product. | Allergic reactions, anti pFVIII antibodies. No thrombosis in 29 patients evaluated. | Clinical monitoring and measurement of factor level. |
| Tranexamic acid | 10 mg/kg (i.v.) or 20 mg/kg (p.o.) every 6-8 hours. The dosage has to be adjusted if the serum creatinine is >120 ugmol/L. | Acute venous or arterial thrombosis. DIC. Haematuria (should be used with caution if bleeding from the upper urinary tract is suspected). Convulsions. Parenteral treatment: subarachnoidal haematoma (short-term treatment might be considered). | Diarrhoea, vomiting, nausea. Allergic dermatitis. Thrombosis, anaphylactic reaction, convulsions (unknown incidence). | Clinical monitoring. There is a risk for accumulation in patients with kidney failure, please refer to dosing and product resume. |

Table 1: **Dosing, adverse effects and monitoring of treatment** *(continued)*

| Treatment options | Dosing | Contraindications | Adverse effects | Monitoring and prevention of side effects |
|---|---|---|---|---|
| Desmopressin (for AHA) | 0.3 ug/kg i.v. or s.c., or 300 ug (nasal spray). The dose may be repeated twice with 8, 12 or 24 h intervals. Tranexamic acid should be administered concomitantly, if not contraindicated. | SIADH. Unstable angina. Uncompensated heart insufficiency (and other conditions requiring treatment with diuretics). Habitual or psychogenic polydipsia. Von Willebrand disease type 2B. Hyponatraemia. | Fatigue, temporary hypotensive episode, nausea, headache. Dizziness. Hyponatremia. Thrombosis (unknown incidence). | Clinical monitoring and measurement of FVIII. Treatment increases risk for fluid retention and hyponatremia, and the patient's fluid intake should be limited. Should be administrated with caution to patients with creatinine clearance <50 ml/min. Electrolytes should be monitored throughout treatment duration. |

* The physician should refer to product resume prior to administration for more detailed report, this list is considered incomplete. Concerns all aforementioned formulations: allergic reactions can occur as an adverse event and hypersensitivity to the product or component of the formulation is a contraindication.

# 4 Eradication therapy

## 4.1 General aspects

Although spontaneous remission occurs, immunosuppressive therapy (IST) is recommended to eradicate the inhibitors as soon as possible to reduce the length of time the patient is at risk for severe bleeding. Factor VIII level and inhibitor titer at presentation are not useful for predicting the severity of bleeding events [1].

## 4.2 Corticosteroids, cyclophosphamid and rituximab

There are no randomized studies of IST in AHA, and treatment recommendations are based on observational studies. Most centres have used corticosteroids, cytotoxic drugs, or a combination of the two, originally studied by Green [30]. Rituximab has emerged as a second line option, recommended by most guidelines [31–33]. The prospective, observational UK surveillance study and ECHA2 registry have compared outcomes for first line treatments.

The UK surveillance [1] study included 174 patients, IST at the discretion of the local clinician according to the national guideline at that time [34]. Out of the 144 patients where remission data was available, 40 patients were treated with steroid monotherapy, almost invariably prednisolone 1 mg/kg and 48 were treated with prednisolone in combination with a cytotoxic agent usually oral cyclophosphamide 1-2 mg/kg. The groups were comparable regarding age, sex, and underlying disorder. Complete remission (CR) was defined as normal FVIII, no detectable inhibitor, and immunosuppression stopped or reduced to doses used before AH developed. CR was achieved in 76% and 78%, respectively, after 49 days (95% CI, 31-62) compared to 39 days (95% CI, 34-57), P=0.51, i.e. not statistically significant. Neither was there any difference in mortality between the two groups.

The EACH2 registry report prospectively collected IST data from 289 patients [35] treated according to local guidelines. Two hundred seventy four patients were included in the propensity score-matched analysis. It showed that patients treated with prednisone and oral cyclophosphamide were more likely to achieve a stable CR than those treated with prednisone alone (OR 3.25; 95% CI, 1.51-6.96, P=.003). Furthermore, in the matched groups, time to a negative inhibitor and normal factor VIII and time to

CR (adjusted for presenting inhibitor titer) was shorter for the steroid and cyclophosphamide group compared with steroids alone (HR 2.11; 95% CI, 1.38-3.21, P=.001 and HR 2.36; 95% CI, 1.49-3.74, P=.001, respectively). A higher proportion of patients treated with steroids and cyclophosphamide experienced at least 1 adverse event (41%), compared with steroids alone (25%). The proportion of patients experiencing adverse events was similar comparing those that received oral cyclophosphamide (30 of 74, 41%) and intravenous cyclophosphamide (4 of 9, 44%). Mortality was comparable, (22% and 33%, respectively). Fifty one patients in the EACH2 registry were treated with rituximab, either as monotherapy ([12]) or in combination with another immunosuppressant [37]. Stable remission was achieved in 5 (42%) on monotherapy rituximab, compared to 25 (64%) on combination regimens, with a median time to remission of 65 days (IQR 29-144 days). Relapse was uncommon in the rituximab group (3%) [35].

The German, Austrian and Swiss thrombosis and hemostasis society (GTH) report a prospective observational study of 102 patients with AHA receiving IST according to the escalating protocol of the GTH [6]. Forty eight patients achieved PR with prednisone monotherapy, 25 of them within 3 weeks. Forty four patients were escalated to rituximab [9] or cyclophosphamid [35], and 12 received third line therapy with rituximab added to cyclophosphamid. Fourteen patients died before remission. Patients with baseline FVIII <1 IU/dL achieved PR less often and later (77%, 43 days) than patients with ‡1 IU/dL (89%, 24 days). Low FVIII was also associated with a lower rate of complete remission and decreased survival. Based on this observation, GTH suggest tailoring first line treatment intensity according to presenting FVIII-level.

At present there are two ongoing larger trials randomising between 1st line cyclophosphamide and rituximab, both in combination with steroids (NCT01808911 and NCT03384277).

## 4.3 Azathioprine and ciclosporine

Other options for IST are azathioprine (Tay et al 2009), ciclosporine or tacrolimus [38] that has been reported as successful first line treatment in combination with steroids.

## 4.4 Human immunoglobulin for intravenous use (IVIG)

Adding IVIG to other IST did not improve outcome in the UK surveillance study or EACH2 [1].

## 4.5 Factor VIII concentrate

Nemes [39] has been successful using a model for induction of tolerance in AHA with a combination of FVIII concentrate and cyclophosphamide 200 mg/day up to a total of 2-3 g and prednisolone 100 mg/day gradually tapering off. A complete remission was obtained in 24 of 26 patients, typically in 4 weeks. Another group reported 12 patients with CR rates of 92% after 3 weekly infusions of FVIII combined with vincristine, cyclophosphamide and steroids [37]. The same group later reported six patients who were treated with vincristine, cyclophosphamide and steroids without FVIII and found 83% remission after 1–7 courses [40]. The role of FVIII co-administered with IST is not clear, and due to high cost not recommended.

## 4.6 Immunoadsorption/MBMP

Zeitler et al. [41] presented 35 patients with high titre AHA and severe bleeding, treated according to the Modified Bonn/Malmö protocol (MBMP) combining immunoadsorption, IST, IVIG and FVIII infusions. Treatment cycles (days 1-7) were repeated until clinical and laboratory response were achieved. They underwent 1) large-volume adsorption 2.5 to 3 times the total plasma volume on days 1-5, 2) IVIG 0.3 g/kg on days 5-7, 3) prednisolone 1 mg/kg and cyclophosphamide 1-2 mg/kg daily until remission, and 4) FVIII concentrate infusion in a dosage of 100 up to 200 IU/kg every 6 h which was reduced when satisfactory response was achieved. With this regimen inhibitors were undetectable rapidly within 2-4 days, FVIII concentrate was stopped with a median of 12 days and the total treatment process was completed within 12-17 days. Guidelines generally recommend MBMP as third line treatment or in case of acute surgical intervention, situations of high bypassing agent consumption and life threatening bleeds. Based on a later report of 20 patients suffering from less severe AH, Goldman et al. [42] argue that immunoadsorption could be considered as first line therapy. The patients with residual FVIII >1% and/or non-transfusion requiring

bleedings at first presentation received first line IST consisting of cyclophosphamide 1 mg/kg BW/d and/or prednisolone 1 mg/kg BW/d. Despite the initial non-severe presentation and recommended first line treatment, bleeding were progressive in 5 patients. They switched to the full MBMP protocol, allowing FVIII recovery to normal after median 14 apheresis sessions. In contrast to IST treated patients, disease flares during immunosuppressive tapering were not seen.

## 4.7 Relapse

The relapse rate after first CR was about 20 % in the 90 patients with available data in the UK surveillance study [1]. The outcome was comparable in the EACH2, were relapse was reported in 15 (18%) patients who achieved a CR with steroids alone, translating to stable CR after first-line treatment with steroid monotherapy in 68 of 142 (48%) patients. The steroid and cyclophosphamide group had a 12% relapse rate, resulting in a stable CR in 58 of 83 (70%) patients. Of note, only 1(3%) of patients reaching CR with a rituximab regimen relapsed. In GTH, relapse occurred in 15 of 62 patients (24%). Relapses occur up to 14 months after stopping IST, with a median of 4 months [35]. Most of these patients achieved a second CR although some needed a long-term maintenance immunosuppression. There are no studies to support choice of treatment in case of relapse.

## 4.8 Recommendations

**First line treatment:**

- Start IST as soon as possible after diagnosis.
- Corticosteroids in combination with rituximab or cyclophosphamide is recommended as first line therapy.
- Corticosteroids as monotherapy can also be considered.
- Rituximab monotherapy as first line treatment is not recommended due to longer time to remission.

**Second line treatment:**

- If the patient is not in responding within 3 weeks (ongoing bleeding, no increase in FVIII) consider adding second line treatment with rituximab or cyclophosphamide, whatever option not used as first line.
- Alternatively, azathioprine, cyclosporine or immunoadsorption can be used for second line treatment.
- In refractory bleeding consider immunoadsorption/MBPM.

**Follow-up:**

- Monitor clinical bleeding, FVIII and inhibitor level initially every 1-2 weeks after discharge form hospital.
- Follow-up should continue at least a year after IST is stopped.

**Relapse:**

- Repeat first line treatment with corticosteroids, and consider adding other IST.

Table 2: **Treatment options, dosing, side effects, and monitoring**

| Treatment options | Dosing | Side effects | Monitoring and prevention of side effects |
|---|---|---|---|
| Corticosteroids | 1 mg prednisolon/kg BW p.o. once daily for 6 weeks, there after tapering the dose rapidly. | Oedemas, hypertension, Cushing symptoms, atrophy of skin and muscles, osteoporosis, electrolytic changes, diabetes mellitus, mental disturbances. | Measure blood glucose. Prophylactic treatment with calcium and d-vitamin is recommended. Sulfamethoxazol-trimethoprim 400/80 mg 1 tbl. daily should be considered during combination therapy and 3 months after. |
| Cyclophosphamide | 1.5-2 mg/kg BW p.o. once daily at maximum 3-4 months, alternatively 10 mg/kg BW i.v. on 2 consecutive days, followed by 1.5-2 mg/kg BW p.o. for 8 days. | Leukopenia, thrombocytopenia, anemia, nausea, vomiting, alopecia, exanthema. Cyclophosphamide should not be given to fertile women or young men since it may cause infertility. | Blood count is checked 3 times the first week if i.v. doses are given, otherwise once a week the first month, thereafter once a month. |

Table 2: **Treatment options, dosing, side effects, and monitoring** *(continued)*

| Treatment options | Dosing | Side effects | Monitoring and prevention of side effects |
|---|---|---|---|
| Rituximab | Rituximab 375 mg/m2 intravenously once weekly for four weeks. HIV and hepatitis B virus screening should be performed prior to start. | Asthenia, pain in bowel, back, chest, muscles or joints, lymphadenopathia, thrombocytopenia, neutropenia, anemia, hypertension, bradycardia, tachycardia, arythmia, postural hypotension, neurological symptoms, diarrhoea, activation of herpes simplex or herpes zoster, respiratory symptoms, hyperglycemia. | Close surveillance of blood pressure, pulse and vital signs during infusion. Measure blood count, glucose and electrolytes. Prophylactic treatment with acyclovir is recommended. Sulfamethoxazol-trimethoprim 400/80 mg 1 tbl. daily should be considered. |
| Azathioprine | 2 mg/kg BW once daily for 6 weeks. Thereafter the dose is tapered slowly depending on the antibody titre and the factor level. | Leukopenia, thrombocytopenia, less often anemia, nausea, vomiting, alopecia, exanthema, liver dysfunction, susceptibility to infections. | Measure blood count and liver enzymes weekly initially, thereafter once a month. |

Table 2: **Treatment options, dosing, side effects, and monitoring** *(continued)*

| Treatment options | Dosing | Side effects | Monitoring and prevention of side effects |
|---|---|---|---|
| Cyclosporin | 5 mg/kg BW a day divided in two doses; if renal insufficiency is present the dose has to be reduced. | Renal dysfunction, liver dysfunction, tiredness, headache, abdominal pain, hypertension, nausea, vomiting, hyperlipidemia, electrolyte changes, muscle cramp. | Measure creatinine, liver enzymes, electrolytes, blood level of ciclosporin. |

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