Nordic Hemophilia Council Acquired Hemophilia Guidelines

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# Introduction

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

AHA is a rare disorder and the majority of those affected are elderly, except for the rare cases of pregnancy associated AHA in younger women. The activated partial thromboplastin time is usually prolonged while other laboratory screening tests for hemostasis such as platelet count and prothrombin time are within the normal range. Patients with AHA pose clinical challenges, often being elderly and frail with additional comorbidities. The mortality rate is high (3.3% - 22% in different studies) [[1](#ref-Collins2006),[2](#ref-Knoebl2012)] 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 manage this group of patients.

In recent years, valuable information has been collected regarding e.g. incidence, frequency of co-existing disorders, mortality, and bleeds as well as the use of eradication therapy of inhibitors. This information has been gained from several studies including the study by the Nordic Haemophilia Council, published in 2023 [[3](#ref-Lindahl2022)] ([Table 1](#table-1-overview-of-bleed-treatment)).

## General recommendation

* **The physician on duty at a hemophilia center should be consulted.**

# Diagnosis

## Incidence and co-morbidity

AHA is rare and the incidence is about 1.5/million per year [[1](#ref-Collins2006)]. 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%-27.0%), infections and dermatologic conditions [[1](#ref-Collins2006),[2](#ref-Knoebl2012),[4](#ref-Borg2013)–[7](#ref-Tiede2015)]. Rarely, AHA arises as idiosyncratic reactions to medication including antibiotics, psychiatric and immunomodulatory drugs [[8](#ref-Franchini2007)]. The relatively 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 hemophilia may be of importance [[9](#ref-Pavlova2008),[10](#ref-Oldenburg2008)]. 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 [[11](#ref-Tiede2010)].

## Symptoms, signs and clinical course

Easy bruising with extensive enlargement, muscle hematomas 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 hemophilia, joint bleeds are rare [[1](#ref-Collins2006)–[3](#ref-Lindahl2022),[5](#ref-Delgado2003)]. Hematuria 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.

In the Nordic study, mortality related to AHA was 21% [[3](#ref-Lindahl2022)]. Immunosuppressive therapy (IST) associated mortality was high, accounting for 16% of all deaths (4.2% of patients) in EACH2 [[2](#ref-Knoebl2012)] and 15% of all deaths (8.8% of patients) in the Nordic study [[3](#ref-Lindahl2022)]. Other fatal and nonfatal complications include thrombotic events such as myocardial infarction and stroke [[3](#ref-Lindahl2022),[4](#ref-Borg2013),[7](#ref-Tiede2015)].

## Laboratory screening methods

Activated partial thromboplastin time, APTT is usually prolonged, while Prothrombin time and PT (INR) are within the normal range. Platelet and leukocyte counts are generally normal. The erythrocyte count, hemoglobin and hematocrit values may be low due to bleeds.

APTT-mixing test: 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 patient 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 [Characteristics of the autoantibodies](#characteristics-of-the-autoantibodies)) [[12](#ref-Srivastava2020)].

## Specialized laboratory methods

The diagnosis should be confirmed at a specialized coagulation laboratory. For plasma-based coagulation assays the recommendations for sample collection and transport are the same as in the general recommendation for hemophilia (See [NHC hemophilia Guideline Chapter 3](https://guidelines.nordhemophilia.org/hemophilia/03Laboratory.html)).

### FVIII assays

The functional activity of FVIII (FVIII:C) or, occasionally, other coagulation factors such as FIX, can be measured with either clot-based (OSA) or chromogenic assays (CSA), the latter being less prone to interference from i.e. lupus anticoagulant that can be a diagnostic problem. Autoantibodies to other factors are extremely rare. In the diagnostic situation the patient can have a significant amount of factor activity, which can interfere with the measurement of the titer of inhibitory antibodies.

### FVIII inhibitor assay

The recommended procedure for diagnosing inhibitory antibodies to coagulation factors is the Bethesda-Nijmegen method [[13](#ref-Verbruggen1995)]. 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 37ºC and then the factor activities in both samples are measured. The factor activity is measured using OSA or CSA method. The Bethesda assay is most suitable for patients that do not have measurable factor activity. If the patient has an activity > 0.05 IU/dL (5%), heat-inactivation of the plasma sample endogenous activity at 56˚C for 1h before analysis is recommended.

### Interference

The specific treatments used in acquired haemophilia can affect measurement of both factor activity and inhibitor titre. This is relevant for many FVIII products as well as for bypassing agents. Of significant importance is that the clinicians discuss possible local measurement options before the initiation of a new treatment.

Emicizumab interferes in both APTT and APTT-based factor VIII activity assays and in CSA FVIII assays with reagents of human origin. A substantial shortening of APTT and overestimation of FVIII activity is observed.

For determination of FVIII activity and inhibitor level in patients receiving emicizumab, the use of a CSA containing bovine factor X is recommended. Confirmation of emicizumab levels requires a specific assay with emicizumab calibrators. Furthermore, porcine FVIII treatment can also give discrepant results in OSA and CSA and is not consistent between methods.

## 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 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 contrasts with alloantibodies seen in patients with congenital hemophilia, which follow type I kinetics characterized by complete inactivation in a linear relationship between antibody titer and residual FVIII activity.

## Recommendations for diagnosis

* **Acquired hemophilia should be suspected in patients with prolonged APTT, but normal INR/PT and signs of bleeding.**
* **If coagulation factor analyses are 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 using specific methods for functional factor activity measurement (FVIII:C) and the Bethesda-Nijmegen method.**
* **Type II kinetics of the antibodies results in poor correlation between antibody titer and FVIII:C and caution is warranted when interpreting the results.**
* **The specific treatments used can affect measurement of both factor activity and inhibitor titre. The local measurement options need to be discussed before treatment initiation.**

# Treatment of bleeding

## Principles

The majority (89%) of patients with acquired hemophilia present with bleeds [[2](#ref-Knoebl2012)]. 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](#ref-Collins2006)]. Approximately 70% of patients with acquired hemophilia require hemostatic treatment [[5](#ref-Delgado2003)]. The choice of hemostatic agent and strategy is depending on the severity of the bleeding episode, patient characteristics as well as the availability of specific products. Severe bleeding is defined as life or limb threatening, bleeding in the central nervous system, deep muscles, or retroperitoneal bleedings. Haemoglobin <80 g/L or haemoglobin drop >20 g/L is also considered severe bleeding. Mild bleeding is muscle and subcutanous bleeds without any substantial effect of function and without causing significant anemia.

Patients with persistent inhibitors should be monitored even following the initial disease phase, since major bleeds can occur even after many months [[1](#ref-Collins2006)]. 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 the choice of treatment [[1](#ref-Collins2006),[2](#ref-Knoebl2012)]. Blood red cells, plasma and thrombocytes should be transfused as required for management of major bleeding episodes. Specific hemostatic products include bypassing agents and coagulation factor concentrates. The results from the EACH2 study in patients with AHA showed that bleeding control with bypassing agents were superior to FVIII and desmopressin (bleeding control 93.3% vs 68.3%; *P* = .003) [[14](#ref-Baudo2012)]. Inhibitor titer, treatment monitoring and immediate availability should guide the decision [[5](#ref-Delgado2003)].

See [Table 1](#table-1-overview-of-bleed-treatment) for an overview of products and dosing.

## Bypassing agents

Two bypassing agents are commonly used in treating bleeds: 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 NovoSeven® which is recombinant, activated factor VII. The other activated factor VII (Sevenfact®) is not approved in Europe yet.

There is no conclusive data on whether one of those bypassing agents is superior, since both have showed comparable efficacy in controlling bleeds [[1](#ref-Collins2006),[14](#ref-Baudo2012),[15](#ref-Astermark2007)]. The initial choice depends therefore on factors such as availability and previous clinical experience. Combination treatment can be considered if monotherapy is inefficient [[16](#ref-Schneiderman2007)].

### aPCC (FEIBA®)

aPCC has been shown to be highly effective in treating bleeds. A retrospective analysis from a 10-year-survey in three tertiary medical centers 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 [[17](#ref-Sallah2004)]. 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 [[14](#ref-Baudo2012)]. 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 ± 7.7 U/kg and hemostatic 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 disseminated intravascular coagulation [DIC] and low fibrinogen) were recorded [[18](#ref-Borg2015)].

In a recent Nordic study on 181 patients [[3](#ref-Lindahl2022)] FEIBA® was used twice as often as NovoSeven® as primary hemostatic treatment and showed superior efficacy. However, bleeds treated with NovoSeven® were more severe and the retrospective nature of the study did not allow for the usage of predefined response criteria. The significance of those results is therefore unclear.

There is no specific laboratory method for monitoring treatment with FEIBA®. The global hemostatic methods, such as thromboelastrography (ROTEM/TEG) and thrombin generation assays (TGA) have shown potential in the follow up and tailoring of treatment [[19](#ref-Sumner2007),[20](#ref-Varadi2003)]. ROTEM/TEG is the method most often available in 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 [[21](#ref-Holmstroem2012)]. Administration of tranexamic acid with FEIBA® is therefore not advised against, but it is recommended, whenever possible, to maintain an interval of six hours between administration of the products.

According to the results of one study [[22](#ref-Zanon2019)], 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.

### rFVIIa (NovoSeven®)

The optimal dosage of NovoSeven® in AH has not been defined. A dose of 90 µg/kg every 2-3 hours until hemostasis is achieved, is generally recommended to patients with congenital hemophilia with inhibitors.

Sumner et al. [[19](#ref-Sumner2007)] 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 µg/kg at 2-24 h intervals) or continuous infusion (8-50 µg/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 µg/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%) [[14](#ref-Baudo2012)].

A recent, single-centre study from China on 165 patients reported the usage of NovoSeven® to 13 patients, of which an overwhelming majority (12/13) achieved good hemostatic control. Since aPCC was not available in this area, no patients received FEIBA® [[23](#ref-Yu2024)].

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

## 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 localization 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 [[2](#ref-Knoebl2012),[14](#ref-Baudo2012)]. 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 and 90 U/kg every 2-3 hours [[24](#ref-Franchini2008)] 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](#ref-Knoebl2012)]. FVIII and FIX concentrates may be administered intermittently or as continuous infusion.

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

### Porcine FVIII

Porcine plasma FVIII (pFVIII) concentrate is also available (Obizur®) and has been shown to be effective in increasing FVIII:C even at dosages 100 U/kg [[25](#ref-KruseJarres2015)]. 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, although discrepant results in OSA and CSA assays that are not consistent, have been reported. There is also 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 IU/dL) while patients with antibodies had normal or sub-therapeutic levels of FVIII [[25](#ref-KruseJarres2015)]. This study also demonstrates 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 [[26](#ref-Fosbury2017)]).

## Tranexamic acid

Tranexamic acid (Cyklokapron®, Tranon®) is an efficient inhibitor of fibrinolysis. It may be useful in prevention of bleeds in AHA, both as mono therapy in minor bleeds and as a concomitant treatment. Tranexamic acid should be avoided in bleeds from the urinary tract. Caution is advisable when treating patients with significant cardiovascular comorbidities. Rare cases have been reported with thrombotic microangiopathy, using bypassing agents in conjunction with tranexamic acid. There are no available data on the use of tranexamic acid in patients treated with emicizumab.

## Desmopressin

Desmopressin (Octostim®, Minirin®) is a synthetic analogue of vasopressin, whichstimulates an endogenous release of FVIII, VWF and t-PA (tissue plasminogen activator). It has shown some effect in the treatment of minor bleeds [[24](#ref-Franchini2008)] and could be considered as second line treatment if no other hemostatic agents are available to patients with low inhibitor titre (<5 BU) and minor bleeding episodes. However, due to inferior efficacy [[14](#ref-Baudo2012)], it should not be used as first-line treatment.

## Emicizumab (Hemlibra®)

Emicizumab, known as Hemlibra®, is a bispecific antibody that bridges FIXa to FXa independently of the presence of neutralizing antibodies against Factor VIII. In recent years, several case reports have described the use of emicizumab in AHA to efficiently prevent bleeding with few thromboembolic complications [[27](#ref-Knoebl2020),[28](#ref-Thomas2021)]. In Japan, the indication to use Hemlibra® in AHA was approved in 2022, based on the AGEHA study; JapicCTI-205151. In this study, the dosage of emicizumab differed from that given in congenital hemophilia A with the aim of reaching steady state (>30 µg/mL) and bleeding control more quickly. Even if the study only contained 12 patients (the oldest 92 years old), the authors concluded that the dosage regimen and completion criteria may have a favorable benefit-risk profile [[29](#ref-Shima2023)]. One asymptomatic venous thrombosis was incidentally detected. Further two open-label, single-arm, multicenter, phase 2-studies have been initiated, using the same dosing regimen: one in Europe (in Germany and Austria: The GTH-AHA-EMI trial) and one in North America. In contrast to the Japanese study, IST was discontinued in the European study during the 12-week treatment period [[30](#ref-Tiede2023)]. The findings from the study on 47 patients (median age 76 years), indicated that emicizumab effectively prevented bleeding with low number of thromboembolic events, severe infections, and fatalities. Additionally, it suggested that IST could be deferred while patients are receiving emicizumab. The authors meant that this would be a benefit for high-risk patients, allowing them to wait starting IST until fit enough. One ischemic stroke occurred in week 20 (emicizumab was continued off-label because of low factor VIII activity at week 12). The patient had end-stage renal failure and a history of coronary artery disease. The North American study is still ongoing ([NCT05345197](https://clinicaltrials.gov/study/NCT05345197)).

Emicizumab does not have an approved indication from the European Medicines Agency for preventing bleeds in patients with AHA. Even so, the GTH-AHA Working Group has published consensus recommendations (based on experts from 16 hemophilia centers in Germany and Austria) to provide guidance to physicians on the use of emicizumab in AHA that follows the results from the clinical trials [[31](#ref-Pfrepper2023)].

### Recommendations for emicizumab treatment in AHA

* **Treatment regimen with subcutaneous emicizumab (Hemlibra®) 150 mg/ml follows the protocol of the AGEHA study: 6 and 3 mg/kg on days 1 and 2, then 1.5 mg/kg once weekly.**
* **Lower or less frequent maintenance doses have been used in case reports after control of acute bleeding had been obtained with FVIII bypassing agents and may be considered if clinically motivated.**
* **If bypassing agent aPCC (FEIBA®) has been used to treat bleeds before treatment start, this must be stopped 48 hours before emicizumab treatment.**
* **In case of bleeding, bolus doses of rFVIIa (NovoSeven®) are administered.**
* **Due to lack of data in previous trails, it is suggested to avoid concomitant use of tranexamic acid with emicizumab. If used, high precaution is warranted as this is an elderly population with high cardiovascular morbidity.**
* **Treatment with emicizumab may be discontinued when remission is achieved.**
* **There is no restriction regarding the initiation of IST.**
* **Pregnant and breastfeeding women cannot be treated with emicizumab. For other contraindications, see also GTH-AHA-EMI trial (**[**NCT04188639**](https://clinicaltrials.gov/study/NCT04188639)**) before treatment start.**
* **If emicizumab is initiated, it is important to ensure that the patient provides informed consent for off-label treatment.**
* **For interference with laboratory assays, see paragraph 2.4 Specialized laboratory methods.**

## 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 hematomas. 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 (⍺-adrenergic vasoconstrictor) may be used in mucous membrane bleeds. Rigorous and repeated clinical evaluations of the bleeds in order to assess progress or regress are required.

## 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 hemophilia patients and thorough surgical hemostasis should be applied.

Since there are no large studies on the pre- and perioperative management of patients with AH, recommendations are often extrapolated from studies on patients with congenital hemophilia with inhibitors. Bypassing agents are considered as first-choice agents for pre- and perioperative prophylactic treatment in patients with acquired hemophilia. The dosages are similar to those required for bleeding control and it is generally recommended to maintain the perioperative dosage for 48-72 hours for major surgery, followed by tapering down [[32](#ref-Kempton2009)]. 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.

### Recommendations for treatment of bleeding

Treatment of bleeding in patients with acquired hemophilia is optimally carried out at a specialist center or, if referral is not possible, following early consultation with a coagulation expert.

#### First line treatment:

* **Bypassing agents are recommended for severe bleeds.**  
  **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.**
* **When reimbursed, emicizumab can be considered as prophylaxis for bleeding in patients with a bleeding phenotype as off-label use (for recommendations see** [**Emicizumab (Hemlibra®)**](#emicizumab-hemlibra)**.**
* **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 bleedings, 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.**

# Eradication therapy

## General aspects

Although spontaneous remission occurs, immunosuppressive therapy (IST) is recommended to eradicate the inhibitor 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 prognostic markers for remission rate and time to remission, and in frail low-risk patients, reduced intensity IST can be considered to reduce the risk of infections.

## First line treatment

The prospective, observational UK surveillance study and EACH2 registry have compared outcomes for first line treatments. The UK surveillance study (2007) found no significant difference between monotherapy prednisone and combination therapy with mostly cyclophosphamid in terms of complete remission (CR) rate and time to remission [[1](#ref-Collins2006)]. In the EACH2 registry, patients on combination therapy were more likely to achieve stable CR, and time to CR was shorter. There was, however, a higher proportion of adverse events with combination therapy [[33](#ref-Collins2012)].

The German, Austrian and Swiss Thrombosis and Hemostasis Society (GTH) (2015) report a prospective observational study of 102 patients with AHA receiving IST according to the escalating protocol of the GTH [[7](#ref-Tiede2015)]. 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:C 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 [[34](#ref-Tiede2020)].

A retrospective Dutch cohort study (2020) including 143 patients treated first line with monotherapy corticosteroids (67%), in combination with cyclophosphamide (12%) or rituximab (12%), reported remission rates of 33%, 80% and 67% respectively [[35](#ref-Schep2020)]. A high inhibitor titer was associated with lower CR rates. Infections occurred significantly more often with combination therapy than monotherapy corticosteroids, and mortality was mostly due to infections (19%) compared to fatal bleeds (7%) [[33](#ref-Collins2012)].

In a retrospective Nordic registry study of 181 patients with data from 6 haemophilia centres, the overall remission rate was 57% [[3](#ref-Lindahl2022)]. Corticosteroid monotherapy was the most frequently used first-line IST in 75% of cases (effective in 55%), followed by corticosteroids combined with cyclophosphamide in 13% (effective in 58%) and rituximab-based regimens in 9% (effective in 82%). Death from AHA related bleeding was reported in 12% of patients and IST related infectious death in 9%. The high rate of steroid monotherapy was considered related to the lower rate of overall CR.

In 2023, the first randomized study of IST in AHA was published. In a multicentre, open-label, randomized noninferiority trial by Wang et al, steroids combined with a single dose of rituximab 375 mg/m2 was compared to steroids combined with cyclophosphamide with daily dose of 2mg/kg until the inhibitor titre was negative [[36](#ref-Wang2023)]. The study included 63 patients and demonstrated noninferiority, with CR rate of 77.4% in the rituximab group and 68.8% in the cyclophosphamide group, without differences in treatment related adverse events.

In the recent GTH-AHA-EMI study, the group investigated a treatment strategy of subcutaneous emicizumab prophylaxis for 12 weeks without any IST [[30](#ref-Tiede2023)]. After the study period of 12 weeks, one out of 47 enrolled patients had reached spontaneous remission while two had increased FVIII to 49 and 50 IU/dL, respectively with detectable inhibitor. Most patients (62%) received IST after the study period of 12 weeks as outpatients and at 24 weeks, 30% reached remission. The GTH AHA working group concluded that emicizumab is effective for bleed prophylaxis and should be considered from the time of diagnosis, and that IST should be offered to patients on emicizumab if they are eligible based on physical status [[31](#ref-Pfrepper2023)].

## Second line treatment

In parallel with the escalating GTH study from 2015 [[7](#ref-Tiede2015)], second line therapy is considered when the patient does not show any sign of remission within 3 weeks.

## Other treatment options

### Azathioprine and ciclosporine

Other options for IST are azathioprine [[37](#ref-Tay2009)], ciclosporine or tacrolimus [[38](#ref-PardosGea2012)] that has been reported as successful first line treatment in combination with steroids.

### Human immunoglobulin for intravenous use (IVIG)

Adding IVIG to other IST did not improve outcome in the UK surveillance study or EACH2 [[1](#ref-Collins2006),[2](#ref-Knoebl2012)].

### Factor VIII concentrate

Nemes [[39](#ref-Nemes2004)] 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 [[40](#ref-Lian1989)]. 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 [[41](#ref-Lian2002)]. The role of FVIII co-administered with IST is not clear, and due to high cost, not recommended.

### Immunoadsorption/MBMP

Zeitler et al. [[42](#ref-Zeitler2005)] 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 bleedings.

Based on a later report of 20 patients suffering from less severe AH, Goldman et al. [[43](#ref-Goldmann2015)] argue that immunoadsorption could be considered as first line therapy. The patients with residual FVIII >1 IU/dL and/or non-transfusion requiring bleedings at first presentation received first line IST consisting of cyclophosphamide 1 mg/kg/day and/or prednisolone 1 mg/kg /day. Despite the initial non-severe presentation and recommended first line treatment, bleeding was 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.

## Relapse

The relapse rate after first CR was about 20 % in the 90 patients with available data in the UK surveillance study [[1](#ref-Collins2006)]. The outcome was comparable in the EACH2, where 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%).

In the EACH2 study relapses occurred up to 14 months after stopping IST, with a median of 4 months [[33](#ref-Collins2012)]. 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.

### Recommendations for eradication therapy

#### First line treatment

* **Start IST as soon as possible after diagnosis in patients eligible for treatment.**
* **Corticosteroids in combination with rituximab or cyclophosphamide is recommended as first line therapy.**
* **Corticosteroids as monotherapy can be considered in low-risk patients with FVIII > 0.01 IU/dL and low ( < 5 BU) inhibitor titer at presentation.**
* **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.**

#### Relapse

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

See [Table 2](#_Table_2:_Overview) for overview of eradication therapy.

# Monitoring

This section may serve as frameworks for how to monitor patients with AHA but need to be adapted based on clinical context and the availability of specialized laboratory analyses.

## Acute Phase

Daily examination of the whole bodysuit is essential to identify new and follow ongoing bleeds and to evaluate the effectiveness of treatment.

* Mark skin bleeds with a skin-safe marker.
* Measure the extent of arm and/or leg involvement in extensive bleeding as there is a risk of compartment syndrome.
* Central access e.g. central venous catheter or PICC line should be considered to facilitate a) blood sampling, b) intravenous treatment, and c) reduce the risk of skin bleeding caused by vein puncture.
* If there is an obvious risk of infection (ongoing IST, elderly and/or fragile), consider administering antibiotic prophylaxis upon insertion.

**Blood tests:**

CRP, blood count, electrolytes, B-glucose are checked daily. APTT\* and/or FVIII:C twice or more weekly. FVIII-inhibitors once weekly.

Fibrinogen and D-dimer; if concerns are raised for thrombotic microangiopathy caused by extensive treatment with activated factor concentrates with/without fibrinolysis inhibitors.

**Vital signs:**

Blood pressure, pulse, temperature daily. Weight two or more times per week.

## Post acute phase (in hospital)

Bleeding is under control and IST has been initiated.

**Blood test:**

B-glucose, APTT\*, FVIII:C and FVIII-inhibitors, CRP, blood count, and neutrophils\*\* are checked once weekly. The frequency of testing depends on how the patient responds to prednisolone.

**Vital signs:**

Blood pressure, pulse, temperature daily. Weight two or more times per week.

## Remission, complete treatment response to IST

Remission is achieved at FVIII:C > 0.50 IU/dL without measurable FVIII-inhibitors [[44](#ref-Holstein2020)].

**Blood test:**

APTT\* and/or FVIII:C, blood counts and neutrophils\*\* should be checked monthly the first three months after the remission, then every third month. Monitoring ends one year after remission.

*\*APTT interferes with emicizumab. Emicizumab has a half-life of four weeks with expected detectable concentration long time after discontinuation.*

*\*\*Patient on certain IST such as rituximab have a risk of neutropenia.*

# Table 1: Overview of bleed 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 hemostatic method) can be used when available. |
| **NovoSeven®** | 70-90 mg/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 mg/kg can be used. |  | Arterial and venous thrombosis.  DIC.  Elevation of hepatic enzymes.  Headache. Rash. Nausea. | Clinical monitoring and ROTEM/TEG (alt. another global hemostatic method) can be used when available. |
| **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. |
| **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 mmol/L. | Acute venous or arterial thrombosis.  DIC.  Haematuria (should not be used if bleeding from the upper urinary tract is suspected). | 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. |
| **Desmopressin** | 0.3 µg/kg i.v. or s.c., or 300 µg (nasal spray). The dose may be repeated twice with 12 or 24 h intervals.  Tranexamic acid should be administered concomitantly, if not contraindicated. | SIADH.  Unstable angina.  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. 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 a forementioned formulations: allergic reactions can occur as an adverse event and hypersensitivity to the product or component of the formulation is a contraindication.

# Table 2: Overview of eradication therapy

| **Treatment options** | **Dosing** | **Side effects** | **Monitoring and prevention of side effects** |
| --- | --- | --- | --- |
| Corticosteroids | 0.5-1 mg prednisolon/kg BW p.o. once daily until clear increase in FVIII:C, thereafter 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, D-vitamin and proton pump inhibitor 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. |
| Rituximab | Rituximab 375 mg/m2 intravenously one dose. HIV and hepatitis B virus screening should be performed prior to start. | Asthenia, pain in bowel, back, chest, muscles or joints, lymphadenopathy, thrombocytopenia, neutropenia, anemia, hypertension, bradycardia, tachycardia, arrhythmia, postural hypotension, neurological symptoms, diarrhea, 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. |
| 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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