Nordic Hemophilia Council Hemophilia Guidelines 2024

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# 1. Introduction

## 1.1 Hemophilia A and B

* Hemophilia A and B are caused by deficiency of coagulation factor VIII (FVIII) or IX (FIX), respectively. The blood clotting is impaired, with risk of serious and life-threatening bleeding.

### 1.1.1 Inheritance

* Hemophilia A and B are inherited in an X-linked recessive manner and primarily affect males. Female carriers can have reduced factor levels and mild hemophilia, while a moderate or severe phenotype is rare.

### 1.1.2 Severity

* The clinical severity of hemophilia A and B closely correlates with the level of FVIII or FIX. In severe hemophilia, factor levels are less than 1% of normal; in moderate hemophilia 1-5% of normal, and in mild hemophilia over 5% and less than 40% of normal.
* Severe hemophilia inevitably causes spontaneous painful bleeding into joints and soft tissues. Iron deposition in the cartilage will lead to inflammation, hemophilic arthropathy and severe disability. Intracranial hemorrhage can cause paralysis and death. In mild hemophilia abnormal bleeding occurs following surgical procedures or trauma, whereas the clinical severity of moderate hemophilia varies from mild to severe.

### 1.1.3 Clinical presentation

* A family history of hemophilia is often the reason for referral, but 30-50% of new cases have no prior family history. Severe hemophilia can present with intracranial bleeding in infancy, bleeding from the umbilical stump or following circumcision and unusual bruises or hematomas in infant boys, sometimes leading to wrongful suspicion of child abuse. When the boy begins to crawl and walk, limping may occur due to hemarthrosis.

### 1.1.4 Treatment

* Hemophilia is currently treated with replacement of the missing coagulation factor or non-factor treatment.
* Upon starting factor replacement treatment around 30-40% of hemophilia A patients develop inhibitory antibodies against the replacement factor.
* Non-factor treatment allows for effective prophylaxis and prevention of disability even in patients with inhibitors.
* Gene therapy has recently been approved for adult patients with hemophilia A and B.

## 1.2 The Nordic history of hemophilia treatment

### 1.2.1 Life expectancy

* Prior to the availability of effective therapy, patients with severe hemophilia had a mean life expectancy of only about 16 years. However, since the late 1950’s the life expectancy of a newborn severe person with hemophilia (PWH) receiving some form of replacement therapy has increased steadily [[1](#ref-Ikkala1960)]. In 1960 the average life expectancy had risen to 23 years in Sweden, and it is now approaching normal in the Nordic countries, all of which now practice early and continuing prophylactic treatment.

### 1.2.2 1950: Fraction 1-0

* A plasma protein fraction correcting coagulation in hemophilia blood was first described in 1937 but only later termed coagulation factor VIII [[2](#ref-Patek1937)].
* In the 1950s, Margareta and Birger Blombäck at the Karolinska Institute in Stockholm while working on a method to purify fibrinogen by treating Cohn’s Fraction I with a glycine solution found that fibrinogen and Factor VIII (and as it later turned out, von Willebrand factor) remained as precipitates, while prothrombin, plasmin and other proteins were washed off.
* Together with Inga Marie Nilsson, a young scientist and physician from Malmö General Hospital, Margareta found that factor VIII could be almost completely recovered from this fraction designated “Cohn’s fraction 1-0” [[3](#ref-Nilsson1957)]. A sterile preparation of fraction 1-0 was injected for the first time to Inga Marie’s patient in May 1956 at the Malmö General Hospital. The patient was a young female patient with life-threatening menstrual bleeds and a prolonged bleeding time (i.e. with severe von Willebrand disease). The girl’s bleeding stopped promptly, her Factor VIII activity increased to a high level and her bleeding time was normalized.

### 1.2.3 1960: Anti hemophilic factor (AHF)

* After this, the Blombäcks began preparing Fraction 1-0 from plasma for PWHs with impressive efficacy. Industrial production of Fraction 1-0 by Kabi pharmaceuticals was started in 1964. Calling the product AHF, Kabi became one of the two first commercial producers of Factor VIII concentrates in the world. For more detailed description on the history of factor VIII discovery and production see also Ahlberg et al [[4](#ref-Ahlberg1965)].
* Although this first AHF concentrate was of low purity and contained large amounts of fibrinogen, it was used for many years to treat hemophilia and, as it also contained von Willebrand activity, for treating von Willebrand disease.
* Indeed, the introduction of Fraction 1-0 led to effective hemophilia care in Sweden, a decade earlier than in most other countries. It was only about 10 years after Inga Marie’s initial injection that effective therapy started elsewhere using cryoprecipitate.
* During the 1970’s and 1980’s increasingly more concentrated products were produced, and when the injection volume decreased the freeze-dried factor concentrates became available for home treatment.

### 1.2.4 1980: Hepatitis and HIV

* Until the mid-1980s, before virus inactivation of cryoprecipitate and later plasma-derived coagulation factor concentrates, there was a high rate of hepatitis B and C being transmitted to PWHs and, in the late 1970’s and early 1980’s, of HIV transmission in PWHs. Most PWHs were infected with HBV, some with HCV, but none with HIV were able to clear the virus. Close to 90% of severe PWHs receiving plasma derived factor concentrates before year 1986 in the Western world were infected with HIV and AIDS was a major cause of morbidity and mortality in PWHs in the 1980’s and 1990’s, before effective treatment was available. Hepatitis C has since become curable with modern drug treatment in most cases. Due to the use of locally produced plasma derived factor VIII concentrates in Norway only 14 patients were infected with HIV, in Finland only two patients and in Iceland none were infected. However, hepatitis C was transmitted to about 30-60% of patients in Norway, Finland and Iceland. Figures in Sweden reached just above 80%.
* Since 1986 all available plasma derived and recombinant concentrates have been virus inactivated preventing transmission of the above encapsulated viruses and, fortunately, no hepatitis B, C or HIV transmission has occurred. Nevertheless, patients and caregivers alike remain concerned that the current measures to eliminate viruses could not entirely prevent transmission of known and unknown non-encapsulated viruses and prions, e.g. variant Creutzfeldt-Jacob disease [[5](#ref-Mannucci2008)].

### 1.2.5 Prophylaxis in the Nordics

* Prophylactic factor replacement therapy has led to a dramatic improvement in the orthopedic outcome of PWHs in Sweden and the Nordic countries [[6](#ref-Nilsson1992)]. The value of costly prophylactic therapy was not generally recognized outside the Nordic area until many decades later when a prospective randomized trial finally conducted demonstrated the markedly improved clinical outcome of boys receiving early prophylaxis [[7](#ref-MancoJohnson2007)].
* Data from Malmö has shown that not only the joint score but, importantly, the overall quality of life of PWHs treated with prophylaxis has close to normalized, in those patients who have been treated with primary and continuing prophylactic therapy.
* With modern prophylactic treatment from toddler age, young adult men with severe hemophilia are healthy with no or minimal consequences of bleeding.

### 1.2.6 RECOMMENDATION

* **The aim is zero bleeds and healthy joints in severe hemophilia.**

# 

# 2. Organization of hemophilia care

## 2.1 Introduction

* The Nordic hemophilia care has a strong tradition ever since treatment with factor concentrate was initiated in Malmö, Sweden, in the 1950:ies and has paved the way for the hemophilia treatment worldwide.
* The Nordic Hemophilia council platform (since 1999) presents uniform recommendations for the diagnosis and management of coagulation disorders (www.nordichemophilia.org). The Council provides guideline documents, organizes annual meetings and forms working groups to address topical issues.
* European Association of Hemophilia and Allied Disorders (EAHAD) is the umbrella under which the Nordic Hemophilia care is networked with the other European major centers.
* European Hemophilia Comprehensive care centers (EHCCC) organizes the lifetime services provided by different disciplines around the patient’s medical needs ([www.eahad.org](http://www.eahad.org)).
* European Hemophilia Centers are of two types according to the services and facilities which they provide: European Haemophilia Treatment Centres (EHTCs) provide local routine care in conjunction with EHCCCs. European Haemophilia Comprehensive Care Centres (EHCCCs) provide the highest level of care and function as tertiary referral centres.

## 2.2 Responsibilities of the Nordic CCC’s

The Nordic hemophilia comprehensive care centers have the following responsibilities:

* To provide expert care, including regular replacement therapy or prophylaxis to avoid unnecessary bleeding complications.
* To provide on call services that secures expert management during emergency severe illnesses, major trauma and surgical interventions.
* To provide early diagnosis, pediatric and family care, through the adolescent years and transition clinics, genetic counseling, including attention to carrier and obstetric issues.
* To prospectively update patient registers nationally as well as the safety surveillance at the European level by EUHASS (European Haemophilia and Allied Disorders Safety Surveillance).

## 2.3 Responsibilities of the laboratory

One of the key players in the comprehensive care is the coagulation laboratory. In interaction with the hemophilia treaters It has the following responsibilities in hemophilia care:

* To establish the diagnosis of hemophilia.
* To provide assays to monitor prophylaxis, treatment of bleeds and management of major surgery with factor and non factor treatment and appropriate follow-up.
* To provide diagnosis of the complications of hemophilia, i.e. inhibitors.

## 2.4 Activities of the Nordic CCC’s

### 2.4.1 Networking activities

* Since our Nordic populations are concentrated in the large cities, networking activities are needed to provide access to care outside the cities.
* However, the Nordic cooperation has been ongoing since decades, over 50 years by organizing Nordic Coagulation meetings where bleeding disorders have always been included.

### 2.4.2 Multidisciplinary activities

* According to the recommendations of World Federation of Hemophilia and EAHAD, multidisciplinary activities should be readily available for patients with hemophilia.
* These CCC activities have been shown not only to reduce mortality but decrease morbidity, improve quality of life and days of absence from school and work.
* Management of joint disease, rehabilitation, and planning for interventions as a multi-expert effort should be well coordinated.
* Also, carrier, obstetric and perinatology issues need predesigned approach, written plans and consultation chains with multidisciplinary activities.

### 2.4.3 Registers and future development of hemophilia care

* Scandinavian centers have actively conducted and participated in hemophilia studies, including issues of inhibitor development and novel therapies.
* For the future the developing non-factor and gene therapies represent a significant progress, where joint platforms and registries are needed.
* The health economy of the current therapy in the era of the novel non-replacement therapies is an important task, which by linking the register data on patient follow-up and outcome can unravel the cost efficiency.

### 2.4.4 RECOMMENDATION

* **The national register capturing should be developed uniformly to enable comparison of treatment across centers and ease patient entering to into clinical studies.**
* **The treaters should raise active awareness of the costs of the treatment and look for the most cost-efficient individual solutions.**

# 

# 3. Laboratory diagnosis of hemophilia

## 3.1 Introduction

* A diagnosis of hemophilia is made with the support of laboratory service. This includes plasma-based coagulation tests and genetic testing in whole-blood.

### 3.1.1 RECOMMENDATION

* **Testing for diagnosis of hemophilia and monitoring of therapy needs experience in coagulation laboratory testing using equipment and reagents that have been validated for this specific purpose.**
* **Coagulation laboratories must implement quality assurance procedures e.g. participation in external quality assessment programs to ensure the reliability of laboratory testing.**

## 3.2 Coagulation laboratory testing

### 3.2.1 Pre-analytical aspects of hemophilia testing

* The pre-analytical phase is the time from the blood collection to the point when the sample is analyzed in the laboratory. Errors in this phase are often explained by incorrect patient identification or incorrect collection, handling, transportation, centrifugation or storage of the sample. In order to reduce the pre-analytical error rate, it is important to understand the sources of variability and mechanisms that may lead to false assay results.
* Coagulation tests are exceptionally susceptible to suboptimal sample quality as the sample collection itself will initiate a hemostatic response. Thus, improper sample collection technique and/or incorrect handling prior to analysis will increase the risk of coagulation activation and clot formation in the tube. Furthermore, coagulation factor VIII (FVIII) is one of the most labile coagulation factors and is rapidly degraded *in vitro*. In worst case scenario, erroneous results of screening and specific factor assays may be reported and lead to mismanagement of the patient. There are guidelines/recommendations, how to assure sample integrity during the pre-analytical phase [[8](#ref-Kitchen2021a),[9](#ref-Kitchen2021b)].

### 3.2.2 RECOMMENDATION

**For plasma-based coagulation assays the recommendations for sample collection are:**

* **Direct venipuncture: atraumatic phlebotomy with minimal tourniquet use.**
* **Collection tube and order of draw: 3.2 % (109 mmol/L sodium citrate, light blue stopper) tube first, or only after a non-additive tube.**
* **Fill the tube correctly to the mark (line).**
* **Mix blood with anticoagulant in the tube (reverse the tube immediately 5-10 times).**
* **Transport the whole-blood promptly at room temperature.**
* **Centrifuge preferentially within 1 hour after phlebotomy at a minimum of 1700 g for 15 min to obtain platelet poor plasma (<10 x 109/L).**
* **If laboratory testing cannot be performed within 4 hours, the plasma should be transferred by pipetting to another tube and frozen at -70 ºC for later analysis.**
* **Underfilling (<90%) of tubes or presence of clots lead to rejection of samples.**
* **The presence of anticoagulants in the sample, for example heparin contamination from a vascular access device, may interfere in the assay and give false test results.**

### 3.2.3 Initial testing for detection of hemophilia

* Global screening tests of coagulation, i.e. APTT and PT (INR), in addition to fibrinogen, are important for the initial laboratory evaluation of patients with bleeding disorders, and are available in most hospital laboratories. If congenital or acquired hemophilia A or B is present, the APTT will usually be prolonged and the PT (INR) remains within reference ranges. Deficiency of FXI and FXII might also cause an isolated prolonged APTT.
* APTT is a global plasma assay that measures the collective functional activity of 10 different coagulation factors including FVIII or FIX. If one or several of the coagulation factors are increased, a deficiency of one coagulation factor may be masked. Furthermore, during certain conditions such as an acute phase reaction, FVIII is increased and APTT may be within reference ranges.
* A normal APTT does not rule out mild hemophilia A or B and does not exclude a clinically relevant bleeding disorder. There are several commercially available APTT reagents that vary in their sensitivity for detecting coagulation factor deficiencies. To be accepted as a screening test for factor deficiency, it is recommended that the APTT reagent should give a prolonged APTT at FVIII and FIX activities ≤ 30% [[10](#ref-Kitchen2020)]. The presence of lupus anticoagulant may prolong the APTT and APTT reagents insensitive to lupus anticoagulant are advantageous.
* If APTT and/or PT (INR) is prolonged, a mixing test should be performed to distinguish between deficiency of coagulation factor(s) or presence of inhibitors/interfering anticoagulants. In congenital hemophilia the APTT will be corrected when patient plasma is mixed 1:1 with pooled normal plasma [[10](#ref-Kitchen2020)]. If mixing does not correct the prolongation of APTT, it may indicate the presence of an inhibitor (against coagulation factor VIII /IX in particular or lupus anticoagulant) or presence of other anticoagulants in the plasma (e.g. heparins).

### 3.2.4 RECOMMENDATION

* **For screening purposes, it is recommended that the APTT reagent gives a prolonged clotting time at FVIII or FIX activities ≤ 30%.**
* **A normal APTT result should not be used to rule out the presence of mild hemophilia A or B.**
* **It is important that the treating physicians are familiar with the local screening methodologies and reference intervals and understand the limitations of screening tests.**

### 3.2.5 Specific Factor VIII and IX assays

* FVIII:C or FIX:C in plasma represents the functional (coagulation) activity of the factors and can be measured with either clotting or chromogenic substrate assays [[10](#ref-Kitchen2020),[11](#ref-Peyvandi2016)]. These analyses are important in the diagnostic setting, during monitoring after administration of replacement products (measurement of trough and peak activity of the coagulation factor), and also for detecting the presence of inhibitory antibodies against endogenous and exogenous FVIII and FIX. When a family history is present, umbilical cord blood is tested in male infants at birth to determine FVIII:C or FIX:C. For prenatal diagnosis, see chapter “Carriers of hemophilia”.
* The FVIII:C and FIX:C assays should be calibrated with material that has traceability to the current international standard for FVIII or FIX in plasma [[10](#ref-Kitchen2020)]. In this way the unit is given in international units (IU) and one IU is the factor activity present in one mL of pooled normal plasma. The results should be reported in IU/mL or IU/dL, which indicates traceability to the international standard (IU/dL is the same as percentage in absolute numbers; i.e. 5 IU/dL= 5%).
* FVIII:C and FIX:C functional activity assays can be measured with both a one-stage clotting assay (OSA) or a chromogenic substrate assay (CSA).

### 3.2.6 RECOMMENDATION

* **FVIII:C and FIX:C can be measured with either one-stage clotting assays (OSAs) or chromogenic substrate assays (CSAs) and are used in the diagnostic setting, for monitoring of replacement therapy and detection of inhibitor development.**

### 3.2.7 Differential diagnosis

* Once a decreased FVIII activity has been confirmed, the differential diagnosis includes congenital hemophilia A, acquired hemophilia A and von Willebrand disease (VWD), type 2N VWD (Normandy) in particular. To determine the cause to low FVIII:C information about the case history, inheritance pattern and bleeding score is important, and the presence of lupus anticoagulant or interfering anticoagulants in plasma needs to be excluded. VWF antigen and activity should be measured and in some cases an inhibitor against VWF needs to be excluded. If the APTT is not corrected after mixing with pooled normal plasma measurement of antibodies against FVIII may be appropriate. If type 2N VWD is suspected a VWF:FVIII binding activity is recommended which determines the capacity of the patient’s VWF to bind FVIII. Definite diagnosis may be dependent on exon sequencing of the *F8/9* and *VWF* genes.

### 3.2.8 RECOMMENDATION

* **Low FVIII:C may be caused by congenital hemophilia, acquired hemophilia or von Willebrand disease (VWD).**
* **After measurement of von Willebrand factor (VWF) antigen and activity, extended investigation to detect antibodies against FVIII and VWF or measurements of VWF:FVIII binding activity may lead to a final diagnosis.**
* **In some cases, definite diagnosis may be dependent on exon sequencing of the *F8/9* and *VWD* genes.**

### 3.2.9 Factor VIII:C assays

* The OSAis the most frequently used assay principle in the world [[10](#ref-Kitchen2020),[11](#ref-Peyvandi2016)]. The main feature of the OSA is that it is based on the APTT test with the difference that the sample is pre-diluted in FVIII-deficient plasma before analysis. In this way, a test system is created that works with the simplicity of the APTT reaction but the pre-dilution procedure makes the FVIII activity in the sample the limiting factor, and thus determines the final clotting time. The ability of the sample to correct the APTT of a FVIII-deficient plasma can be expressed as the FVIII:C activity if the assay is calibrated with a plasma with known concentrations of FVIII:C.
* The performance of the OSA is affected by the type and quality of the APTT reagent and the FVIII-deficient plasma. The FVIII-deficient plasma can be obtained from a patient with severe hemophilia A (<1 IU/dL and without antibodies) or be immunodepleted. It is important to verify that new lots of FVIII-deficient plasmas are free from FVIII (<1 IU/dL) as this otherwise will compromise the test. Also, normal levels of VWF and other clotting factors of the FVIII-deficient plasma is recommended.
* The choice of APTT reagent will also have an impact on the general assay characteristics. It is important that the laboratory choose reagents that have proven capacity to detect all hemophilia categories i.e. mild to severe hemophilia A. The results obtained by OSAs may be affected by the presence of lupus anticoagulant, heparins, etc.
* Measurement of FVIII:C can also be performed by CSAs [[12](#ref-Bowyer2018)]. There are several commercial CSAsfor measurement of FVIII:C available. The assay procedure involves two separate reactions in a way that makes FVIII activity in the sample the rate-limiting factor. In the first step the diluted sample (or standard) is mixed with a reagent cocktail with purified FIXa, FX and phospholipids, leading to the formation of FXa. In the second step a specific chromogenic peptide substrate for FXa is added. Cleavage of the substrate yield a colour formation that is recorded spectrophotometrically. The amount of colour development is directly proportional to the FVIII:C in the sample. In general, the CSA has a lower detection limit than the APTT-based OSA and, due to the high dilution factor of the sample, the influence of interfering substances is less. CSA is common among the Nordic hemophilia centers. The CSA is also used by the pharmaceutical industry when the potencies of FVIII concentrates are assigned.

### 3.2.10 RECOMMENDATION

* **The OSA and CSA for FVIII:C should be performed with validated methods.**
* **It is important that the laboratory choose reagents that have proven capacity to detect all hemophilia categories i.e. mild to severe hemophilia A.**
* **Laboratories should ensure that new lots of FVIII-deficient plasmas are free from FVIII (<1 IU/dL).**
* **Normal levels of VWF and other clotting factors of the FVIII-deficient plasma is recommended.**

### 3.2.11 FVIII:C - Assay interpretation

* The different FVIII:C assays should give similar results in cases with severe hemophilia A. However, in some cases of mild/moderate hemophilia A patients, a significant assay discrepancy between OSA and CSA has been reported, with OSA FVIII:C at least 2-fold higher than CSA FVIII:C [[12](#ref-Bowyer2018),[13](#ref-Zwagemaker2023)]. Patients with certain mutations in the *F8* gene causing mild/moderate hemophilia A may therefore be undiagnosed using the OSA FVIII:C. On the other hand, there are some genotypes causing inverse assay discrepancy in patients with mild hemophilia, where CSA FVIII:C is higher than OSA FVIII:C. Thus, mild hemophilia A may be challenging to identify correctly in the laboratory.
* The recommendation in the current WFH guideline is to use both OSA and CSA in the initial diagnostic work-up [[10](#ref-Kitchen2020)]. For the management of hemophilia A, both methods should be performed to ensure detection of all mild/moderate cases and to correctly assess the severity.
* *Interpretation:* Hemophilia A patients have low FVIII:C. FVIII:C < 1 IU/dL (<1%) are seen in severe hemophilia A. Moderate deficiency is characterized by a FVIII:C between 1-5 IU/dL, and patients with mild deficiency have FVIII:C > 5 IU/dL up to 40 IU/dL. Carriers of hemophilia A usually have approximately 50% of the normal FVIII activity, but occasionally they have FVIII:C consistent with mild haemophilia A. FVIII is an acute phase reactant and the levels of FVIII may increase several fold under certain conditions (e.g. trauma, infection, etc).

### 3.2.12 RECOMMENDATION

* **Both methods, OSA and CSA are recommended to use in the initial diagnostic work-up. Assay discrepancies can be caused by different mutations but also due to analytical factors such as presence of lupus anticoagulant. OSAs are generally more prone to interferences from lupus anticoagulant, heparin etc.**

### 3.2.13 Factor IX:C assays

* The principle of OSAs for FIX is similar as for FVIII described above, with the only difference that the sample is prediluted in FIX-deficient plasma before analysis. Thus, the main FIX:C assay principle is a test system based on the APTT with dilution of the sample (patient or standard plasma) in a plasma lacking FIX, which means that the activity of FIX in the sample is the limiting factor. The assay is calibrated with a standard that is traceable to the current international standard of FIX:C in plasma and results expressed as IU/mL or IU/dL (see FVIII:C above).
* CSAs for measurement of FIX:C have become commercially available as an alternative to the OSAs. However, these assays are to this date only available at few laboratories, and measurement of FIX:C in combination with the WHO IS for FIX plasma standard (for potency labelling) have not yet been fully approved by regulatory bodies such as EMA. However, FIX:C measured by CSA displays analytical advantages e.g. high dilution of sample, and may complement the measurement of FIX:C by OSAs. Assay discrepancy caused by mutations in the *F9* gene, has been described also in hemophilia B patients [[14](#ref-Kihlberg2017)].
* *Interpretation:* Congenital deficiency of FIX is the cause of hemophilia B. Acquired hemophilia B, caused by specific inhibitors exists but is even less frequent than the rare acquired hemophilia A. The degree of the deficiency defines the different forms:  
  Severe hemophilia B has FIX:C < 1 IU/dL (<1%); moderate deficiency has FIX:C between 1- 5 IU/dL, and mild deficiency has FIX:C > 5 up to 40 IU/dL. Carriers of hemophilia B often express about 50% of the expected normal FIX:C activity, but rarely FIX:C may be reduced into the range of mild hemophilia B.

### 3.2.14 RECOMMENDATION

* **FIX:C can be measured with either OSA or CSA. OSAs are generally more prone to interferences due to the presence of lupus anticoagulant, heparin etc.**

### 3.2.15 Antibodies against FVIII or FIX

* The development of neutralising inhibitors and non-neutralising antibodies (NNAs) is a complication of factor replacement therapy in hemophilia. The diagnostic methods generally available are based on defining the neutralising capacity in functional assays, i.e. original or Nijmegen-modified Bethesda assays for antibodies considered to be inhibitors [[15](#ref-Meijer2023)]. However, NNAs might also affect clearance of administered products, therefore immunological assays can be used to define all antibodies, including NNAs. In the Nordics, ELISA and xFLI methods for NNAs are available at the Coagulation laboratory in Malmö, Sweden.
* Neutralizing antibodies may develop against factor concentrates in individuals with hemophilia A or B and are termed alloantibodies. Alloantibodies are most frequent and have a fast and dose-dependent antigen-antibody reaction. In acquired hemophilia A, time-dependent autoantibodies with a low binding affinity can be present. For this reason, it is recommended to incubate the samples for 2 hours at 37 ºC during a mixing experiment in order to allow the autoantibodies to have effect. Anti-FIX antibodies have faster kinetics and a shorter incubation time can be used for neutralising anti-FVIII antibodies. It is also important to use buffered pooled normal plasma (ie HEPES). This stabilizes the pH and thus the FVIII activity during the incubation and the risk of obtaining false positive results is reduced.
* The recommended test procedure for quantitation of the inhibitor titer is the Bethesda-Nijmegen mixing test, which is an assay for inhibitory antibodies [[10](#ref-Kitchen2020),[15](#ref-Meijer2023)]. In brief, a test sample is prepared by mixing equal volumes of patient plasma with buffered pooled normal plasma and then measure the residual coagulation factor activity in the plasma mixture after 2 hours of incubation. A control sample is prepared in parallel with buffered pooled normal plasma mixed with 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. In a plasma sample with an unknown value for the inhibitor, a series of dilutions will need to be made. These samples are prediluted in FVIII-deficient plasma and handled as described above. There is usually a good correlation between the inhibitor results based on the OSA and CSA FVIII:C assays [[16](#ref-Potgieter2015)]. Any residual activity in the sample between 25 and 75% can be used for calculations of the inhibitor titer. By definition, one Bethesda unit (BU) is the inhibitor titer that neutralizes 50% of the factor activity in one mL plasma. If the residual activity is less than 25% it indicates an inhibitor titer above 2 BU/mL. Hence, these samples are prediluted in FVIII-deficient plasma until a residual activity within the 25-75% range is reached.
* It is recommended to perform the Bethesda assay when there has been a washout of the concentrate.  
  *Reference interval:* The cut-off for a positive result is by definition 0.4 BU/mL. Many laboratories instead use 0.6 BU/mL as the cut-off for positivity (reduced risk of false positive results) [[17](#ref-Mueller2022)].  
  *Interpretation:* The presence of inhibitors may be suspected in patients with unexpected bleedings despite regular prophylaxis with replacement therapy. This is also strengthened if the patient displays reduced recovery and half-life of the substituted factor.
* Patients with acquired haemophilia have very different clinical symptoms, caused by autoantibodies against FVIII or FIX.  
  Note: The Bethesda assay is usually performed on patients with a severe type of hemophilia without measurable FVIII:C (or FIX:C) activity. If the patient has an activity of 5 IU/dL or higher this must be taken into consideration. Then it is possible to remove the endogenous coagulation factor activity by heat-inactivation of the plasma sample at 56˚C for at least 30 min. After centrifugation of plasma, FVIII:C or FIX:C is measured [[15](#ref-Meijer2023)–[17](#ref-Mueller2022)]. The FVIII-mimetic emicizumab interferes with inhibitor measurements using OSAs, but a CSA with bovine reagents can be used (see below).

### 3.2.16 RECOMMENDATION

* **Nijmegen-Bethesda assay is the recommended method for measurement of neutralizing FVIII or FIX antibodies. It is most reliable in patients without measurable coagulation factor activity (i.e. severe haemophilia).**
* **It is recommended to perform the Nijmegen- Bethesda assay when there has been a washout of the coagulation factor concentrate.**
* **If the patient has an activity of 5 IU/dL or higher it is possible to remove the endogenous coagulation factor activity by heat-inactivation of the plasma sample at 56˚C before analysis.**

### 3.2.17 Coagulation factor activity assays for monitoring treatment with replacement therapy with focus on Extended half-life products

* For monitoring of post-infusion levels of full length recombinant (r)FVIII standard products, CSA results are generally reported to be about 20% higher than OSA results. Well-documented discrepancies have also been described for B-domain deleted rFVIII (ReFacto®), with CSA results 30% higher than OSA results. Calibration with B-domain deleted FVIII has therefore been recommended for OSA. For rFIX products, CSA results are instead in general 30% lower than OSA results [[11](#ref-Peyvandi2016),[18](#ref-Adcock2018)–[20](#ref-Augustsson2021)].
* There are a number of products modified for an extended half-life (EHL), both rFVIII and rFIX, recently on the market or under development (i.e. pegylated, glycopegylated, and fusion proteins) (See Chapter Prophylaxis). Some of the modifications affect factor assays and can result in under- or overestimation of results in postinfusion patient samples, which might have a potential impact on patient management [[11](#ref-Peyvandi2016),[18](#ref-Adcock2018)–[20](#ref-Augustsson2021)]. Ideally, similar recovery results should be obtained in post-infusion samples with the same method as used for potency labelling.
* For more than one of the modified products, a difference of > 30% has been obtained for factor activity levels when different APTT-reagents have been used in different OSAs. The recovery can be more consistent in CSAs. All reagent-product combinations have not been tested, and all reagents that contain the same activator (ellagic acid/phenol, silica/kaolin type) do not give the same results. More adequate factor levels are obtained with the chromogenic methods for some of the products. Comparable data about systematic under- or overestimation of coagulation factor activity for different modified products are still scarce for many instrument-reagent combinations.
* The laboratory need information about the type of product used in every patient. Product-by-product-based information must be verified with the methods used by the local laboratory to maintain patient safety. Both ECAT and UK NEQAS (European external quality control providers in haemostasis) are providing external quality control programmes for EHL products.
* Other options for measurement that are now beginning to be used in clinical routine settings, are other global coagulation tests, such as viscoelastic coagulation methods (ROTEM®, TEG®) and thrombin generation (CAT®, Ceveron alpha®), that can, if available, be used as a complement for monitoring purposes of certain products. However, standardisation of these methods is very much needed.
* For the management of hemophilia patients with EHL-products, it is important that the laboratory has access to more than one method for FVIII and FIX respectively, preferably one CSA and one OSA. With the information available to this date, CSA is a more reliable laboratory method that is able to adequately measure the levels of most EHL-FVIII products. Most importantly, WFH recommends laboratories to use assays that has been validated with the specific concentrates used for treatment.

### 3.2.18 RECOMMENDATION

* **It is important that the laboratory has access to more than one method for monitoring of FVIII and FIX in post infusion samples, preferably one CSA and one OSA method for each factor.**
* **It is recommended to communicate to the laboratory the specific factor replacement product used by each patient, and if the sample is drawn at a through or peak level**.

### 3.2.19 Factor activity assays for monitoring treatment with non-replacement therapy

* The bispecific FVIII mimetic Emicizumab affects all APTT-based laboratory methods and for determining FVIII:C levels in a patient on treatment, it is recommended to use a CSA FVIII activity assay containing bovine FX [14]. This assay is not able to detect emicizumab and is used for measurement of endogenous/exogenous FVIII in the presence of emicizumab. Also, for measurements of FVIII inhibitors a CSA containing bovine FX should be used. Anti-emicizumab antibodies may be indicated by a prolongation of the APTT.
* The concentration of Emicizumab can be measured and reported in µg/mL using a modified OSA calibrated with emicizumab.
* Discrepancies between OSA and CSA results have been reported after both FVIII and FIX gene therapy. Results of OSA FVIII:C have been approximately 1.5-fold higher than CSA results. Results of OSA FIX:C have varied with different reagents, but were higher with OSAs than with CSAs.

### 3.2.20 RECOMMENDATION

* **FVIII:C and inhibitor levels in patients receiving emicizumab can be measured using a CSA FVIII:C assay containing bovine FX.**
* **Discrepancies between OSA and CSA results have been reported after both FVIII and FIX gene therapy, with generally higher results with OSAs compared to CSAs.**

## 3.3 Genetic diagnosis

### 3.3.1 Indications for testing

* For people with hemophilia, obligate carriers, females with low FVIII:C or FIX:C, or individuals with suspected hemophilia and potential carriers, measurement of FVIII:C and FIX:C activity l and VWF antigen and activity testing is recommended prior to genetic testing.
* Genotyping is clinically useful to predict the risk of developing an inhibitor against coagulation factor, response to immune tolerance induction (ITI), phenotype severity and for carrier- and prenatal diagnosis. For a detailed description of the clinical interpretation of genetic variants, we refer to the 2019 UK Haemophilia Centre Doctors’ Organisation Good Practice Paper) [[21](#ref-Gomez2019)]. Depending on the experience and competence of the hemophilia team and the local organisation of genetic services, a clinical geneticist or counsellor can be part of the hemophilia care team.
* Genetic information should include a discussion of the experimental limits and possibility of incidental findings.

### 3.3.2 RECOMMENDATION

* **Measurement of coagulation factor activity is generally recommended prior to genetic testing.**
* **Genotyping is clinically useful to predict the risk of developing an inhibitor and for carrier- and prenatal diagnosis.**

### 3.3.3 Strategy and techniques for genetic testing

* Genetic diagnosis of severe hemophilia A starts with screening for the intron 22 inversion of the *F8* gene which is caused by homologous recombination involving intron 22 and related sequences outside the *F8* gene [[22](#ref-Lakich1993)]. Approximately 40% of cases of severe hemophilia A is caused by intron 22 inversion. Similarly, an inversion involving intron 1 found in 1-2% of severe cases can also be screened for with a PCR technique. In the remaining cases of severe hemophilia A as well as all moderate and mild cases, the whole *F8* gene, 26 exons, must be sequenced usually through Sanger or next-generation sequencing (NGS) methodologies.
* Most patients have their own unique mutation/pathogenic variant and today a broad spectrum of more than 3000 variants are known to cause hemophilia A and almost 2000 causing hemophilia B. Variants such as nonsense and deletions, “null-mutations”, will obviously cause severe hemophilia since the DNA reading frame will be altered, mRNA aberrant and the FVIII protein will not be synthesized. A missense variant will usually produce a dysfunctional protein with reduced clotting activity but may also result in a ‛neutral/silent variant’ or a benign variant/polymorphism. In such cases it is important to know if the same variant has been reported previously in patients with hemophilia and exists in databases such as the European EAHAD Coagulation Factor Variant Databases (<http://dbs.eahad.org>) or the American CDC Hemophilia Mutation Project databases CHAMP/CHBM [[23](#ref-EAHAD),[24](#ref-CDC)].
* The clinical interpretation of a new or an unpublished genetic variant in the *F8* or *F9* genes, as well as other genes, should be based on guidelines published by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [[24](#ref-CDC)]; as pathogenic – likely pathogenic – variant of unknown significance (VUS) – likely benign - benign. One may also use various *in silico* variant prediction programs to evaluate the deleterious effect of a variant. In a small percentage, disease causing variants/alterations will not be found despite sequencing of the whole gene, some of these cases having a more complex genetic background. The MLPA technique (Multiplex Ligation-dependent Probe Amplification) may show deletions or duplications not revealed on conventional Sanger sequencing.
* In hemophilia B, the 8 exons of the *F9* gene are sequenced and in almost all cases the disease-causing variant will be found. Inversions are not present in the *F9* gene, but some patients have complete gene deletions, a strong predictor for development of inhibitors or anaphylactic reactions on FIX treatment.

### 3.3.4 RECOMMENDATION

* **Genetic diagnosis of severe hemophilia A starts with screening for intron 22 inversion (approximately 40% of cases of severe hemophilia A).**
* **An inversion involving intron 1 is found in 1-2% of severe cases.**
* **For remaining cases of severe hemophilia A as well as all moderate and mild cases, the whole *F8* gene, 26 exons, must be sequenced usually through Sanger or NGS methodologies.**
* **In hemophilia B, the 8 exons of the *F9* gene are sequenced and in almost all cases the disease-causing variant will be found.**
* **The clinical significance of a new or an unpublished genetic variant in the *F8* or *F9* genes should be evaluated according to ACMG criteria to be reported as: pathogenic – likely pathogenic –VUS – likely benign - benign.**
* Carrier diagnosis in sporadic case of hemophilia A or B, which encompasses around 50-60% of all newly diagnosed cases, may be a problem. In about 70-80% the mother of a sporadic case also carries the pathogenic variant and is thus a carrier. In the remaining 20-30% of cases a pathogenic variant cannot be detected and these women may be either true non-carriers or being somatic and/or gonadal mosaics, i.e. it is not possible with conventional less sensitive techniques to conclude if she is a non-carrier or a mosaic carrier.
* Mosaicism may cause a problem when genotyping mothers ofa sporadic case of hemophilia A with conventional techniques but may be detected by more sensitive techniques such as ddPCR or NGS [[25](#ref-Richards2015)–[27](#ref-Manderstedt2020a)]. Studies indicate that, depending on the type of pathogenic variant, approximately 20% may be somatic or gonadal mosaics [[28](#ref-Leuer2001)]. In hemophilia B this seems to be unusual but is not sufficiently studied with sensitive techniques [[29](#ref-Green1999)].
* Prenatal diagnosis (PND) can be achieved by chorionic villus sampling during the 11 to the 13th week of gestation and karyotype analysis can be performed to determine the sex of the fetus, and in cases of male fetus, if it carries a gene causing hemophilia. The reasons for PND may be to prevent the birth of an affected boy by termination of the pregnancy, to prepare the obstetrical procedures or, for the parents-to-be, to psychologically prepare for having a child with hemophilia. Later in pregnancy amniotic fluid can be used as source of fetal DNA. Fetal sex determination can also be made by Y-chromosome analysis in blood from the pregnant woman very early in pregnancy and thus avoiding invasive diagnostic procedures in pregnancies with a female fetus. Pre-implantation genetic diagnosis (PGD) enabling the implantation of female or unaffected male embryos has become possible [[30](#ref-Lavery2009),[31](#ref-Laurie2010)]. PGD is a demanding procedure which however may be indicated in selected cases.

### 3.3.5 RECOMMENDATION

* **In about 70-80% of sporadic cases, the mother also carries the pathogenic variant and is thus a carrier. In the remaining 20-30% of cases a pathogenic variant is not found.**
* **Mosaicism may cause a problem when genotyping mothers of a sporadic case of hemophilia A with conventional techniques.**

# 

# 4. Prophylaxis

## 4.1 Introduction

### 4.1.1 Prophylaxis

* The goal of prophylactic treatment in hemophilia is to prevent bleedings, primarily joint bleeds, with subsequent development of arthropathy. Importantly, prophylactic treatment will also offer protection from other serious bleeds such as intracranial bleeds, muscle bleeds and intra-abdominal bleeds.
* Cohort studies, especially from Sweden and the Netherlands, clearly show the long-term benefit of prophylaxis [[32](#ref-Fischer2013),[33](#ref-SteenCarlsson2003)]. In comparison with on demand treatment, the outcome of the Swedish prophylactic strategy was superior but at a much higher cost [[33](#ref-SteenCarlsson2003)]. A Swedish health technology assessment [[34](#ref-Berntorp2011)] concluded that concentrate treatment is efficacious, and prophylaxis is superior to on demand treatment in terms of number of bleeds.

### 4.1.2 Primary prophylaxis

* Primary prophylaxis aims to start prior to initiation of joint disease. Even a small number of joint bleeds can result in irreversible damage and damage may progress despite prophylactic therapy [[7](#ref-MancoJohnson2007)]. The randomized clinical trial by Manco-Johnson et al. showed a much better outcome on prophylaxis after only 5 years follow up. The number of joint bleeds before starting prophylaxis has a stronger association with outcome than the age at which prophylaxis starts [[35](#ref-Nijdam2015)].
* The aim of early prophylactic treatment is to enable the child to live a life as normal as possible without hemorrhages and overprotection.

### 4.1.3 RECOMMENDATION

* **Primary prophylaxis is recommended in severe hemophilia from around the age of one before joint bleeds occur.**

### 4.1.4 RECOMMENDATION

* **Patients with moderate hemophilia with a factor level of 1-2 IU/dL should be offered primary prophylaxis.**

### 4.1.5 RECOMMENDATION

* **Prophylaxis should continue during adulthood and in elderly patients**.

## 4.2 Choice of prophylactic treatment

### 4.2.1 Plasma-derived or recombinant factor products

* Recombinant rather than plasma derived FVIII/IX products should be used when available due to the possibility of the transmission of infectious agents. The first randomized study comparing recombinant and plasma derived FVIII products showed higher rate of inhibitors using recombinant FVIII concentrate [[36](#ref-Peyvandi2016a)]; however, Pharmacovigilance Risk Assessment Committee of the European Medicines Agency judges that the evidence is not sufficient to show difference between the different classes of FVIII concentrates. As the question is currently unsolved, it is suggested that the choice of factor concentrate and inhibitor risk is discussed with high-risk families, i.e., those with history of inhibitors in the family.

### 4.2.2 Extended half-life factor products

* Recombinant factor concentrates modified to extend the half-life (EHL) are marketed in the Nordic countries, with varying availability and pricing. EHL products can be considered as an alternative to standard factor products also for initiating prophylaxis in PUPs.
* For FVIII, modifications of the manufacturing process using single chain FVIII, using a human cell line instead of a hamster cell line, or optimizing post-translational glycosylation and sulfation, has resulted in half-life’s of on average 14.2 to 14.4 hours. Pegylation, or fusion of recombinant FVIII to the human IgG1 Fc-domain, prolongs the average half-life to 18.4 to 19 hours. In clinical trials [[37](#ref-Berntorp2016)], this has in selected cases allowed for prolonging the interval between infusions up to 3 to 7 days. However, reducing injection frequency means fewer peak concentrations, a challenge for physically very active patients. Infants and young children have short half-life’s even with EHL FVIII products, not allowing for injection every third day.
* The PUPs A-LONG study demonstrated that the inhibitor development, including high-titre inhibitors, were consistent with or lower than rates reported for standard FVIII products [[38](#ref-Konigs2020)].
* Extension of FIX half-life with pegylation or fusion with the human IgG1 Fc-domain or albumin has resulted half-lives of 85 to 105 hours, with dosing every 7-14 days in clinical trials [[37](#ref-Berntorp2016)]. EHL FIX have a clear advantage compared to standard FIX products, and EHL FIX will allow for once weekly dosing in most patients. EHL FIX products has been reported to be effective and well tolerated, with an adverse event profile as expected in PUPs with HB [[39](#ref-Nolan2021)].

### 4.2.3 Non-factor replacement therapy

* Emicizumab is the first non-factor product for hemophilia A to reach the market, approved for prophylaxis in all age groups, in patients with moderate or severe hemophilia A with or without inhibitors.
* Emicizumab is monoclonal antibody binding FIX and FX and thereby playing the role of FVIII in the coagulation cascade. It is administered subcutaneously once weekly to every second or fourth week. Steady state is reached after the first month with loading dose.
* Emicizumab cannot stand alone as monotherapy, as patients eventually will need supplemental on demand treatment with FVIII in case of trauma or surgery.
* The effect of emicizumab is not readily measured with standard coagulation assays. Emicizumab concentration can be indirectly measured with a modified FVIII OSA or Chromogenic assay with human reagents. ROTEM/TEG are used to some extent in all Nordic centers.
* Emicizumab prophylaxis may be associated with adverse events such as thrombosis, thrombotic microangiopathy, anti-drug antibody development, breakthrough bleeds and loss of efficacy [[40](#ref-Hassan2021),[41](#ref-Teo2021)].
* It is an unsolved question how to maintain FVIII tolerance during emicizumab treatment in patients who have been successfully tolerized to FVIII, and how to avoid de novo inhibitor development. The Nordic centers do not routinely continue regular FVIII exposure after switch to emicizumab in non-inhibitor patients.
* Emicizumab is reimbursed in all Nordic countries in hemophilia A with inhibitors. In Sweden and Finland emicizumab is reimbursed in all patients with severe hemophilia A. In Denmark, reimbursement in non-inhibitor patients is restricted to patients where factor replacement is not possible, e.g., venous access does not allow for sufficient prophylaxis with factor replacement to avoid breakthrough bleeds. Emicizumab is not reimbursed in non-inhibitor patients in Norway.

### 4.2.4 RECOMMENDATION

* **Recombinant rather than plasma derived products should be preferred when available. In families with high risk of inhibitors, the choice should be discussed (see chapter** [**Inhibitors**](file:///Users/christq/hemophilia24/_book/06Inhibitors.qmd)**).**

### 4.2.5 RECOMMENDATION

* **EHL is recommended for prophylaxis in PUP’s.**

### 4.2.6 RECOMMENDATION

* **FVIII EHL is recommended to improve troughs. In less active patients, FVIII EHL can be considered to reduce frequency of injections**.

### 4.2.7 RECOMMENDATION

* **FIX EHL is recommended for most patients with hemophilia B, especially when there are break through bleeds on prophylaxis with standard FIX, or adherence issues.**

### 4.2.8 RECOMMENDATION

* **Emicizumab is recommended for prophylaxis in patients with hemophilia A and inhibitors (see chapter** [**Inhibitors**](file:///Users/christq/hemophilia24/_book/06Inhibitors.qmd)**).**

### 4.2.9 RECOMMENDATION

* **When reimbursed, it is recommended to discuss the choice of emicizumab prophylaxis in non-inhibitor patients.**

### 4.2.10 RECOMMENDATION

* **Adjusting intervals to use whole vials of emicizumab is recommended when possible.**

## 4.3 Initiating prophylaxis with factor products

* A large multicenter study comparing three different prophylaxis regimens, i.e. 1) full early prophylaxis, 2) early initiation with increasing frequency as soon as possible (asap) and 3) starting and increasing frequency according to bleeding phenotype, showed that the full early prophylaxis was most effective in prevention of joint bleeds before the age of four years (32% full vs. 27% asap and 8% phenotype), though at the cost of using most CVADs (88% full vs. 34% asap and 22% phenotype) [[35](#ref-Nijdam2015)]. Full-scale prophylaxis also offers almost complete protection against intracranial hemorrhage (ICH) [[42](#ref-Andersson2017)].
* An early therapeutic approach is initiated by giving a dose of FVIII around 25 IU/kg once or twice a week, or FIX around 50 IU/kg once a week via a peripheral vein, with the aim of increasing the frequency of administration as soon as possible. It is common to apply anesthetic cream to the skin of the child to minimize pain.
* The aim is full scale prophylaxis. For hemophilia A, that corresponds to a dose of 20-40 IU/kg standard FVIII every second day, or at least three times weekly, or 20-50 IU/kg EHL FVIII two or three times weekly. For hemophilia B the dose is 30-40 IU/kg standard FIX every third day, or twice weekly, or 30-50 IU/kg EHL FIX once weekly.

### 4.3.1 CVAD

* Achieving venous access via a peripheral vein will be successful in most cases. However, with difficulties with venous access it may be necessary to consider a central venous access device (CVAD) – usually a subcutaneous fully implanted central venous catheter (port). In fact, current practice differs and in Finland and Denmark where most PUP’s used to get ports.
* A port ensures reliable venous access, enables early home treatment carried out by parents and helps to prevent major bleeds especially when distance to the hemophilia center is long. The decision to use a central venous port is often a compromise between the medical goal, the bleeding tendency and familiarity with the devices at the hemophilia centre.
* The most frequent complications with CVADs are infections, mechanical problems and catheter related thromboses (usually clinically silent). Most ports can be used for several years without complications [[43](#ref-Vepsaelaeinen2015),[44](#ref-Khair2017)].
* To avoid inhibitor development especially in hemophilia A, intensive treatment should be avoided until after the first 20 FVIII exposure days, as intensive treatment longer than 5 days raises the risk of inhibitors [[45](#ref-Maclean2010)–[47](#ref-Gouw2013)]. However, there is no strong support for the role of port implantation as a risk factor for inhibitor development [[45](#ref-Maclean2010),[47](#ref-Gouw2013),[48](#ref-Vepsaelaeinen2016)]. According the RODIN study [[47](#ref-Gouw2013)], a surgery for central venous access during the first 75 EDs did not enhance ID risk.
* Most children can be treated at home by their parents, and from the age of 10-12, the child can usually start self-injections.

### 4.3.2 RECOMMENDATION

* **Prophylaxis is initiated with a dose of FVIII around 25 IU/kg once or twice a week or FIX around 50 IU/kg once a week.**

### 4.3.3 RECOMMENDATION

* **The** **frequency is increased as soon as venous access allows**.

### 4.3.4 RECOMMENDATION

* **CVAD is recommended when necessary to initiate prophylaxis.**

### 4.3.5 RECOMMENDATION

* **When reimbursed, prophylaxis with emicizumab is recommended over CVAD for prophylaxis.**

## 4.4 Initiating prophylaxis with non-factor products

### 4.4.1 The risk of intracranial hemorrhage

* The aim of prophylactic treatment is to avoid not only arthropathy but also other serious bleedings such as intracranial hemorrhage (ICH). Prophylaxis offers good protection against ICH [[42](#ref-Andersson2017)].
* However, since prophylaxis is commenced at one year of age and full-scale prophylaxis often takes several months to establish, ICH remains a threat. Infants have a high risk for head traumas and ICH may occur even without trauma in severe hemophilia, sometimes with life-threatening consequences.

### 4.4.2 RECOMMENDATION

* **When reimbursed, it is recommended to discuss initiation of ICH prophylaxis with emicizumab in infants at 6 months of age.**

## 4.5 Assement

### 4.5.1 Pharmakokinetics of factor treatment

* Both the dose and the dose interval must be individually tailored owing to bleeding phenotype, the patient’s physical activity and pharmacokinetic differences between patients. PK analysis using the Bayesian method should be used to describe and optimize treatment. The Canadian WAPPS HEMO website offer PK calculations without cost.

### 4.5.2 Bleeding frequency

* The patients should be instructed to document bleedings and home treatment in a prospective diary, either on paper or electronically. To motivate patients, the reports should be actively used during consultations with the haemophilia center and taken into consideration when planning dosing schedules.

### 4.5.3 Quality of life

* To evaluate quality life standardized quality of life formulas can be used where the simplest is EQ-5D but also SF-36 is used in many centres. The EQ-ED assess pain and mobility. Hemo-QoL is a validated, disease specific QoL instrument useful in children which exist in different versions depending on the need. As generic instruments, SF-36 may be used.

### 4.5.4 Physical score

* Physical score is performed mainly by physiotherapist (see chapter [Physiotherapy](file:///Users/christq/hemophilia24/_book/13Physiotherapy.qmd)) and the recommended score is HJHS (hemophilia joint health score) which takes into consideration function, pain and signs of arthropathy.
* HJHS was developed to study early joint disease in hemophilia and has been validated in children up to the age of 18 years [[49](#ref-Feldman2011)]. The HJHS asseses structural changes. HJHS has been widely implemented as an assessment tool in clinical studies, also in adults.
* Other scores such as the Gilbert score are not sensitive enough in patient with no or just minimal joint damage but are still used in some clinical trials.

### 4.5.5 Imaging technique scores

* Different imaging techniques exist, and MRI is the most sensitive method to detect early signs of joint damage. MRI is also used in clinical studies.
* Due to the high cost MRI cannot be recommended for routine assessment of joint damage.
* The method of choice when physical signs of joint damage occur is X-ray of the joint, and in selected cases subsequently MRI.
* Validated scoring systems exist for plain X-ray (Pettersson score), MRI (IPSG score and several others) and are being developed for US [[50](#ref-Pettersson1980)–[52](#ref-Lundin2012)].

### 4.5.6 Ultra-sound

* Evaluation with a ultrasound-based scoring system, Hemophilia Early Arthropathy Detection with UltraSound (HEAD-US) performed by non-imaging specialists, such as physiotherapist, hemophilia nurse or doctor, has recently emerged as a complement to the clinical score and seems to correlate well with HJHS.
* HEAD-US may be more sensitive in detecting early signs of hemophilia arthropathy than HJHS but longer follow-up studies are required to show the relevance of findings by HEAD-US and the need for intervention.

### 4.5.7 RECOMMENDATION

* **Bleeding rate and joint score should be assessed.**

### 4.5.8 RECOMMENDATION

* **Ultrasound is recommended as a supplement in joint assessment.**

### 4.5.9 RECOMMENDATION

* **QOL should be assessed.**

# 

# 5. Transition

## 5.1 Introduction

* Transition is an organized, coordinated process that aims to ensure the young patient with a chronic disease a safe and consistent crossing from pediatric care to adult care. Transition is typically initiated around the age of 12 and continues until the patient is transferred to adult care.

### 5.1.1 Transition in a Nordic perspective

* In the Nordic countries HTCs are not organized uniformly and models of care delivery differ. Some centers transfer patients to a new facility with a new HCP team typically at the age of 18. Other clinics keep the patients at the same facility and adjust the composition of the HCP team. Consequently, all patients have a need for a planned transition process from child to adult care, but not all patients will experience a transfer.

### 5.1.2 Purpose off transition

* The overall purpose of transition is to increase the young person’s understanding of disease and selfcare, studies have shown that a lack of coordinated transition from pediatric to adult care leads to higher morbidity and higher mortality among young people with chronic disease [[53](#ref-Kennedy2007)].
* In the transition to adult care the young person becomes responsible for; treatment, engagement in dialogue with HCP, attending appointments, and disease management. It is these new and substantial challenges the transition must prepare the young person for. The treatment of hemophilia is demanding, and many affected young people need parental assistance even in their later teen age years [[54](#ref-Breakey2014)].

### 5.1.3 International guidelines for transition

* While there currently is no consensus on the best approach to transition and transfer specific to young people with hemophilia. However, the latest decades have provided a selection of international guidelines for young people with chronic disease, guidelines developed with well-designed case-control-studies, experts opinions and rapports from expert committees [[55](#ref-Adelman2016)–[60](#ref-RCN2024)].

## 5.2 Planning and timing

* Involve an identified transition-coordinator.
* Provide the young person with a transition plan, adapted to the young person’s development, maturity, and cognitive abilities.
* Development adapted care consider the young person’s bio-psychosocial status as the basis for any transition strategy. Special attention must be paid to each young person’s capabilities, needs, and hopes. The process should be adapted to match the young person’s ever-changing needs and circumstance ex education, housing, substance use and fertility [[61](#ref-ACI2022)].
* Most international guidelines recommend that the transition starts at the age of 12 (but there are variations in the guidelines) but no later than a year before transfer. Importantly the time of transfer take place at a time of relative stability in the young person’s life, and not solely be based on a rigid age threshold [[61](#ref-ACI2022)].

## 5.3 Communication

* Adolescents are often challenged by insufficient adherence, and health professionals’ way of communicating has proved to be strongly linked to successful transition and adherence [[62](#ref-Betz2004),[63](#ref-Hanghoej2014)].
* Meet the young person with empathy and a non-judgmental tone.
* The young person must be involved in the planning of the intervention and the transition plan must take his/her understanding of disease, physical limitations, and future goals into account.
* The communication must be aimed at the young person and not the parents.
* Split visits are one way to strengthen the young person’s competencies and support the natural development towards independence. Split visits are a central part of transition and is internationally recommended [[55](#ref-Adelman2016),[64](#ref-TPHC2017)–[68](#ref-Thomsen2020)].
* Furthermore, studies have shown that that the use of communicational and linguistical tools such as motivational interviews and structured youth interview models such as the HEADS-model, helps alleviate insecurities and make the young person feel at ease, while the HCP can explore signific subjects regarding the young person’s resources and challenges including sensitive and personal matters [[62](#ref-Betz2004),[63](#ref-Hanghoej2014),[69](#ref-Chadi2017)].
* The primary barriers to adherence to prophylaxis adherence for young people with hemophilia have been identified to encompass a desire to be normal and perceived negative impact on activities and social participation [[70](#ref-LeeMortensen2018)].
* Encourage the young person to share concerns in relation to ex. school, friends, and social relations.

## 5.4 Aim

* During the transition process, it is the task of the treatment team and transition-coordinator to educate and train the young person in self-sufficiency concerning health matters [[71](#ref-Hanghoej2016)].
* The young person must be supported in the process towards self-efficacy and independence.
* The aim is for the young person to acquire knowledge that renders him/her capable off planning and keeping appointments, understanding relevant medical terminology, and understanding when and whom to contact in case of emergency and/or questions.
* To acquire the skills necessary to order, administer, and register medicine.
* To develop attitudes supporting adherence to treatment plans.
* In addition, the young person must be introduced to his/her future treatment team and department [[72](#ref-White2018)].

### 5.4.1 Measuring the effect of transition

The impact of the intervention must be evaluated. Relevant outcome indicators for assessing the intervention can include:

* Adherence to treatment plan.
* Number of missed appointments.
* Patient and parent satisfaction.
* Self- efficacy skills.
* Change in bleed pattern.
* Understanding of haemophilia and its treatment.
* Number of emergency contacts.
* Number of contacts from parents instead of the young person [[73](#ref-WFH2020)].

### 5.4.2 RECOMMENDATIONS

* **Children with haemophilia should be gradually involved in their treatment in accordance with their age specific development starting from time of diagnosis.**
* **All centers should have transition programs that support the gradual education of the patient.**
* **The program should support the referral and development of responsibility, knowledge, and skills for the patient.**
* **From the age of 12 a structured transition plan should be developed in collaboration with the patient, caregivers, and comprehensive healthcare team.**
* **The effect of the program should be evaluated and adjusted accordingly.**

# 

# 6. Inhibitors

## 6.1 Introduction

* The development of inhibitory antibodies (inhibitors) is a serious complication of factor replacement therapy occuring in about 30% of patients with severe hemophilia A (HA) and 10-15% of patients with severe hemophilia B (HB).
* Genetic and, for HA, non-genetic factors like intensity of treatment and choice of product have been identified as risk factors.
* In severe HA, inhibitor development happens most likely during the first 50 FVIII exposures; in median at 11 exposure days (EDs). Regular screening is recommended, e.g. initially every 5th ED and/or after the treatment of bleeding with FVIII-concentrates.
* The presence of an inhibitor is confirmed using the “Bethesda inhibitor assay” with Nijmegen modifications and classified according to the peak titer into “high”titre (>5 BU/mL) or “low titre” (<5 BU/mL).
* If an inhibitor is detected, repeated measurements are recommended since some inhibitors can be transient.
* In patients in HA with low-titre inhibitors, it is recommended to continue earlier prophylactic regimen and not start ITI immediately as early start with ITI can lead to the the development of high-titre inhibitors.
* In hemophilia B, inhibitor development often occurs together with allergic reactions and after re-exposure to FIX there is possiblility of development of nephrotic syndrome. FIX treatment cannot be continued in these cases.
* rFVIIa for the treatment of acute bleeds can be used in HA and HB inhibitor patients.
* Today, aPCC is used rarely, mostly as second line treatment since it should not be combined with emicizumab and can cause allergic reactions due to containing FIX in HB.
* The clinician will have to decide on a strategy for the acute treatment of bleeds, prophylactic treatment for the prevention of bleeds, and immune tolerance induction (ITI).

The development of inhibitory antibodies (inhibitors) is a serious complication of factor replacement therapy. The antibodies bind to factor VIII or IX and neutralize (inhibit) the hemostatic efficacy. The incidence of inhibitors in severe hemophilia A is about 30% [[74](#ref-Gouw2013a)], while patients with a moderate or mild HA develop inhibitors less frequently [[75](#ref-Abdi2021)]. In HB, inhibitors are rarely seen in patients with non-severe disease, but 10-15% inhibitor rates have been reported in severe HB [[76](#ref-Kihlberg2021),[77](#ref-Male2020)]. The formation of inhibitors is a complex immunological process involving both genetic and non-genetic factors [[78](#ref-Andersson2023)]. For HA, non-genetic factors like the intensity of the treatment with high doses of FVIII and the type of concentrate have been reported as risk factors for inhibitor development [[47](#ref-Gouw2013),[79](#ref-Mannucci2007)]. In a randomized study, plasma-derived factor VIII was associated with lower incidence of inhibitor development but this finding has not been confirmed in large cohort-studies [[80](#ref-Fischer2023),[81](#ref-Fischer2015)].

In severe HA, inhibitor development happens most likely during the first FVIII exposures; in median at about 11 exposure days (EDs), with most inhibitors developing before 50 ED [[82](#ref-Berg2019)]. Regular screening is recommended, e.g. every 5th ED and/or after a surgical procedure and the treatment of bleeding with FVIII.

The decision on which product type to use in previously untreated patients, should be based on safety, efficacy and availability of the product in an open dialogue with the family. Today, extended half-life (EHL) products are widely used with clinically similar inhibitor profiles [[80](#ref-Fischer2023),[83](#ref-Frampton2016)].

The presence of an inhibitor is confirmed using the “Bethesda inhibitor assay” with Nijmegen modifications and classified according to the peak titer into high-titre (>5 BU/mL) or low-titre inhibitor (<5 BU/mL). The highest titre the patient ever recorded – the historical peak titre -defines if the patient has a low-responder or high-responder inhibitor. If an inhibitor is detected, repeated measurements are recommended since some inhibitors can be transient.

In patients with HA and newly detected low-titre inhibitors, it is recommended to continue earlier prophylactic regimen rather than the direct initiation of ITI since this can lead to the development of high-titre inhibitors, if the bleeding pattern allows [[84](#ref-Mancuso2017)]. In HB, inhibitor development often occurs together with allergic reactions and may lead to nephrotic syndrome. FIX treatment cannot be continued in these cases.

Both HA and HB inhibitor patients can present with a high bleeding frequency and the clinician will have to decide on a strategy for the acute treatment of bleeds, prophylactic treatment, and immune tolerance induction (ITI).

ITI means regular infusions of factor concentrates (factor VIII or IX) for weeks to years with or without immune-modulating drugs to achieve tolerization. While there are several studies on ITI in HA, less is known about the use of ITI in HB.

While inhibitory antibodies in HA at a low titre could be overcome by saturating levels of the deficient factor, acute severe bleedings in patients with high titer inhibitors need to be treated with “bypassing agents”. These agents will not be affected by the factor VIII or IX inactivating antibodies but induce hemostasis. There are two bypassing agents currently available in Nordic countries: recombinant coagulation factor VIIa (rFVIIa)- which is first line therapy in patients with HA on emicizumab and HB - and plasma-derived activated prothrombin complex concentrate (aPCC), which should not be routinely be used in combination with emicizumab or HB patients since it contains FIX. These agents are also used in inhibitor patients for surgical procedures. For prophylaxis, emicizumab administered subcutaneously is now available, and has been effectively used for patients with HA.

Until some years ago, the main treatment option for inhibitor patients was the eradication of the inhibitor by immune tolerance induction (ITI) therapy. However, since emicizumab has become available, and effectively reduces the bleeding tendency also in inhibitor patients, the use of ITI has become more individualized due to the need for venous access, costs and uncertainties of keeping tolerance. However, ITI should be discussed with the patient and the family, since it is by now the only way of eradicating the immune response and making the patient eligible for all future treatment options. However, opinions on this matter are diverse and have to be discussed regularly within the heamophilia community [[85](#ref-Ranta2023)].

## 6.2 Prevention of bleeds

### 6.2.1 Recommendations for HA

* Inhibitory antibodies at a low titer can be overcome by saturating levels of FVIII by continuing regular prophylaxis, but regular measurements for recovery and inhibitor titre are recommended.
* Emicizumab subcutaneously (3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly or 3 mg/kg every 2nd week with the aim to use whole vials and possibility to adjust the interval) should be considered as a first-line prophylactic option in patients with HA and inhibitors where FVIII prophylaxis is not sufficient and can be used both during ITI and in the case of ITI failures.
* Emicizumab should not routinely be combined with aPCC and always at doses below 100 U/kg and day due to the risk of thrombotic microangiopathy (TMA) and thromboembolic events.
* The second-line option for prophylaxis in HA is rFVIIa (90 to 270 µg/kg) once daily intravenously.
* A hemostatic improvement should be assessed as a decrease of the number of significant bleeds with ≥ 50%.

### 6.2.2 Recommendations for HB

* First-line option for prophylaxis in hemophilia B is rFVIIa (90 to 270 µg/kg) once daily intravenously.
* Second-line option is aPCC (dosing above). aPCC contains FIX and cannot be given to patients with allergic reactions to FIX or nephrotic syndrome.
* Re-balancing therapies as concizumab or fitusiran or Serpin PC are part of ongoing studies for inhibitor patients with HA or HB and no recommendation can be given at this state. However, compassionate use of these therapies could be discussed as prophylactic regimen in HB patients with inhibitors and severe bleeding phenotype.

For both, HA and HB, patients with low-responding inhibitors, prophylaxis with the deficient factor can be used to prevent against bleeds as well as potentially induce, tolerance. However, the bleeding pattern, recovery and inhibitor titre has to be followed closely. Also, in HB the risk for allergic reactions and nephrotic syndrome is apparent: in a recent Nordic study, 92% of patients developed allergic reactions and 25% a nephrotic syndrome [[86](#ref-Kihlberg2022)]; FIX cannot be used in these patients.

While some inhibitors are transient or persistent at a low titre, most inhibitors in HA – in about 2/3 of cases - rise and become a high-titre inhibitor [[78](#ref-Andersson2023)].

For the prevention of bleeds, emicizumab with subcutaneous administration can be used in patients with HA and inhibitors at all ages, and it offers good bleed protection in HA patients with inhibitors. Emicizumab, is a humanized antibody that bridges activated FIX and FX, mimicking FVIII function. Several studies on emicizumab in various patient groups (HAVEN studies) have been performed. In the HAVEN study on HA patients with inhibitors, a total of 169 HA patients with inhibitors, 12 years of age or older, were enrolled in the pivotal study. Patients were given 3 mg/kg once-weekly for 4 weeks followed by 1.5 mg/kg weekly thereafter. Patients with emicizumab prophylaxis (s.c) had 87% lower bleeding rate (treated bleeds) than patients with no prophylaxis (p<0.001). The ABR was 2.9 events in prophylaxis group versus 23.3 events in participants with no prophylaxis. Also, compared to previous prophylaxis with bypassing agents, the bleeding rate was significantly lower [[87](#ref-Oldenburg2017)]. TMA and thromboembolic events were reported among 5 participants after treatment with aPCC with average doses of more than 100 U/kg daily for more than one day. Therefore, aPCC is not recommended as first-line option for the treatment of bleeds during emicizumab. If aPCC would be necessary, the dose should be as low as possible.

Bypassing agents have earlier been used to prevent bleeds in patients with inhibitors, especially in HA, but since there is excellent prophylactic therapy with emicizumab available for HA patients, bypassing agents for preventing bleeds will mostly not be the choice of therapy anymore. However, bypassing agents – mainly rFVII due to possible allergic reactions with aPCC - are still an option for patients with HB and inhibitors and bleeds [[88](#ref-Konkle2007),[89](#ref-Antunes2013)]. A reduction in bleeds up to approximately 60% has been reported for rFVIIa in daily doses of 90 to 270 µg/kg and up to around 70% with aPCC in the dose of 50 to 85 U/kg 3 times weekly or every other day compared to on-demand treatment.

Re-balancing therapies as concizumab [[90](#ref-Matsushita2023)] – which got approval recently in Canada -, fitusiran [[91](#ref-Kenet2024),[92](#ref-Young2023)] or Serpin PC [[93](#ref-Aymonnier2020)] are part of ongoing studies and seem to have a potential role especially in HB patients with persistent inhibitors and bleeds. No recommendation can be given at this state, but compassionate use could be discussed from patient case to patient case.

## 6.3 Treatment of acute bleeds in inhibitor patients

### 6.3.1 Recommendations

* Tranexamic acid should always be considered, both in minor bleeds alone or in combination with emicizumab or bypassing agents.
* In HA with low inhibitor titer and a minor bleed, FVIII could be used as the first option to saturate the inhibitor and reach a hemostatic factor level.
* In HB with low inhibitor titer and minor bleed, FIX could be used if no allergic reactions or signs of nephrotic syndrome are apparent and a clinical response can be achieved. Patients with short half-lifes may not respond to this treatment.
* In HA/HB with low inhibitor titer and a major severe bleed, FVIII/IX might initially be infused, but in that case frequently monitored - at least daily - and rFVIIa provided if and when the half-life becomes too short, the inhibitor titer rises or the patient does not show clinicala response. If FVIII/IX cannot be monitored, rFVIIa should be considered as a first-line option.
* In HA with high inhibitor titer and a major bleed, rFVIIa 90-120 µg/kg every 2-3 h is indicated for treatment.
* Children may need higher doses up to 270 µg/kg of rFVIIa as an initial dose followed by lower doses depending on the hemostatic effect.
* Due to the hemostatic effect of emicizumab, the number of doses of FVIII/rFVIIa can most often be reduced in HA patients using emicizumab. The first dose of rVIIa is however recommended to be 90 µg/kg.
* In HA, rFVIIa is preferred over aPCC due to increased risk of thrombotic complications when used in combination with emicizumab.
* In HB, rFVIIa is preferred over aPCC due to possible allergic reactions.
* aPCC dosing in non-emicizumab patients could be started with 50-100 IU/kg every 6-12 h but the daily dose of aPCC should not exceed 200 IU/kg.
* For patients with emicizumab and need for aPCC a maximum of 50 IU/kg are recommended and the dose of 100 IU/kg/day should not be exceeded.
* If bleeds are resistant to monotherapy with each bypassing agent , a sequential use in the order of aPCC (50 IU/kg) and rFVIIa (90 µg/kg) with an interval of ≥ 2 hrs or a combined use of aPCC (20-30 IU/kg) and rFVIIa (30-60 µg/kg) may be considered but the risk of thrombosis should always be considered. Experience on the use of sequential therapy with aPCC and rFVIIa under emicizumab is very limited.

For both HA and HB, tranexamic acid should be offered in case of a bleed. Since most patients with HA and persistent inhibitors receive emicizumab, breakthrough bleeds occur less often in this patient group. If breakthrough bleeds require additional hemostatic drug intervention besides tranexamic acid, rFVIIa should be used as first-line option. For patients on emicizumab, the initial dose of rFVIIa should not exceed 90 µg/kg and if neede, repeated doses of 45 upp to 90 µg/kg at an interval of 2 to 4 hours may be considered.

If aPCC and emicizumab together will be required as second line treatment and/or in resistant severe bleeds, the initial dose of aPCC should not exceed 50 U/kg and total daily dose should not exceed 100 IU/kg due to risk for thrombosis and TMA [[87](#ref-Oldenburg2017),[94](#ref-Makris2019)]. For HB patients, aPCC can be used with caution due to possible allergic reactions.

Studies before the era of emicizumab of rFVIIa and aPCC have shown to be effective in majority of cases [[95](#ref-Astermark2006)]. Several studies have shown that rFVIIa can be administered at a dose of 270 µg/kg on a single occasion, especially in children, instead of three doses of 90 µg/kg, without reducing the efficacy or exposing the patient to complication risk [[96](#ref-Young2007)], in patients not receiving emicizumab.

The mechanisms of action differ between aPCC and rFVIIa. Therefore, a sequential or combined use of them has been studied and suggested to improve efficacy in bleedings hard to control [[97](#ref-Ingerslev2011)]. However, the risk of thromboembolic complications – especially in patients with HA treated with emicizumab or patient with other thrombogenic factors like central venous lines - needs to be taken into account and these agents should be used very cautiously, when used in parallel, and only in resistant cases.

## 6.4 Immune tolerance induction (ITI) therapy

### 6.4.1 Recommendations for HA

* In patients with mild/moderate HA, the possibility of spontaneous remission (≈ 20%) should be taken into consideration and a watch and wait strategy might be advisable before treatment.
* Children and adults with confirmed low-responding inhibitor treated with factor VIII prophylaxis should continue on regular factor VIII treatment to induce tolerance  with repeated measurements of inhibitor titres and assessment of recovery. In persistant inhibitors or patients with bleeds, emicizumab could be offered.
* Children and adults with high-responding inhibitor are recommended to use emicizumab for bleeding control during ITI.
* ITI should be discussed with the patient and the family, since it is by now the only way of eradicating the immune response and making the patient eligible for all future treatment options. However, since emicizumab offers efficient bleeding control in inhibitor patients with HA, the requirement of ITI should be discussed individually since venous access, costs and issues about keeping the tolerance are obstacles in ITI.
* ITI can be started immediately independent on the inhibitor titre.
* For patients on emicizumab, low-dose ITI with FVIII SHL or EHL such as 50 IU/kg 3 times weekly is recommended as a starting ITI regime.
* For patients not on emicizumab, a high factor dose regimen seems to reduce the time to reach a negative inhibitor titer, and since bleeds mainly occur during this period, a daily dose of 100-200 IU/kg/d should be used.
* No consistent data indicate the beneficial use of one type of product over the others. In case of ITI failure, the addition of immunosuppression should be considered.
* Switch of ITI protocol or discontinuation of ITI should be considered when no further significant decline or improvement in clinical phenotype has occurred for 4-6 months.
* In patients with hemophilia A and persistent  high-responding inhibitors failing ITI protocols, the approach to further ITI therapy should be discussed.
* After successful tolerance, the dosing should be tapered to regular prophylactic treatment. For patients using emicizumab, currently no data is available on the frequency and dosing of FVIII after tolerization of the patient.

### 6.4.2 Recommendations for HB

* The principal goal in all patients with inhibitors – both children and adults - should be to eradicate the inhibitor and to tolerize the patient.
* Children and adults with confirmed low-responding inhibitors without allergic reactions to FIX could continue on regular factor IX therapy to induce tolerance.
* Besides inhibitor measurements, also FIX recovery is important to indicate the most optimal therapeutic strategy. HB patients can have a low inhibitor titre but very short half-lifes.
* For patients with persistent high-titer inhibitors without allergic symptoms, a dose of 100-200 IU/kg/d could be used.
* Immunosuppression should be considered as first-line treatment in all HB patients with allergy to FIX and in high-titre patients, e.g. rituximab or “Beutel-protocol”, especially in patients with allergy to FIX.
* In patients with hemophilia B and persistent  inhibitors failing ITI protocols with and without immunosuppression or allergy to FIX, ITI may be stopped and compassionate use of re-balancing therapies could be discussed.
* After successful tolerance, the dosing should be tapered to regular prophylactic treatment.

### 6.4.3 ITI in mild/moderate hemophilia A

In HA, up to 25% of new inhibitors occur in patients with mild or moderate disease altering the bleeding phenotype from mild/moderate to severe even after 50 ED [[75](#ref-Abdi2021),[98](#ref-Abdi2018)]. Inhibitors most commonly arise following an intensive episode of replacement therapy for surgery or major trauma and appear to be associated with s high-risk factor VIII gene mutations [[99](#ref-Eckhardt2013)]. Importantly, some inhibitors might be transient and disappear spontaneously.

The limited data available in patients with non-severe hemophilia A suggests that when eradication treatment is indicated, strategies that modulate the immune system, such as the use of rituximab may have greater benefit than ITI with FVIII concentrates only [[100](#ref-Kempton2012)]. Therefore, the clinician will have to decide if a watch-and wait strategy, immunosuppression and/or ITI should be started [[101](#ref-Castaman2016)].

### 6.4.4 ITI in severe hemophilia A

Also in severe HA, the inhibitor could be transient in around 20% of cases and a watch-and-wait-strategy should be used with a re-measurement of the inhibitor before intitiating ITI. Also, in children and adults with confirmed low-responding inhibitor treated with factor VIII prophylaxis should continue on regular factor VIII treatment since early initiation of ITI could induce high-titre inhibitors [[84](#ref-Mancuso2017)]. Repeated measurements of inhibitor titres and assessment of recovery and bleding pattern are important in this patient group. In low-titre patients with bleeds, emicizumab could be offered with parallel FVIII exposure. Emicizumab should be offered to high-titre inhibitor patients.

In patients with persistant inhibitors, especially high-titre inhibitors, emicizumab is recommended since it offers bleeding control but ITI treatment should also be discussed, since it is by now the only way of eradicating the immune response and making the patient eligible for all future treatment options. The benefits of ITI with the tolerization of the patient to FVIII has to be weighed against the need for venous access, costs and issues about keeping the tolerance are obstacles in ITI.

The principle consists of repeated exposures for the deficient factor with or without the concomitant use of immunosuppressive agents by at least three exposures per week of FVIII intravenously. Most studies show tolerance to be induced in 60-80% of the cases with HA [[102](#ref-Oomen2023)] with several different regimens. One of the first protocols used was the “Bonn-protocol” using 200IU FVIII daily, published by Brackmann et al. in 1977 [[103](#ref-Brackmann1977)]. In the International Immune Tolerance study, patients were randomized into high (200 IU/kg/d) and low dose (50 IU/kg 3 times/week) FVIII regimens. No difference in success rate between the treatment arms was seen, but the time to achieve a negative titer, i.e. the phase with most frequent bleedings, was significantly shorter with the high dose regimen [[104](#ref-Hay2012)]. A higher efficacy rate of von Willebrand-containing FVIII products to induce tolerance compared with more highly purified products has been suggested, but it has not been possible to confirm these findings [[105](#ref-Velzen2014)]. Newer studies on EHL products show similar success rates to SHL [[106](#ref-Malec2023)]. ITI can be started without the inhibitor to drop below 10 BU.

Today, emicizumab treatment for prevention of bleeds is started in most high-titre inhibitor patients and those with persistent inhibitor and bleeds. The choice of ITI regimen has therefore changed, with studies still ongoing. A low-dose regimen with about 50 IU/kg three times weekly is recommended under emicizumab since high-dose regimens have  shown a risk for thrombotic events in recent studies and success rate seems to be similar compared to high-dose regimens.

After successful tolerance, the dosing should be tapered to regular prophylactic treatment. For patients using emicizumab, currently no data is available on the frequency and dosing of FVIII after tolerization of the patient with different strategies at the moment [[85](#ref-Ranta2023)].

A switch of ITI protocol or discontinuation of ITI should be considered when no further significant decline or improvement in clinical phenotype has occurred for 4-6 months.

### 6.4.5 ITI in hemophilia B

For HB, ITI treatment may be jeopardized by the occurrence of an allergic or anaphylactoid reaction or nephrotic syndrome. The use of ITI in these patients therefore needs careful monitoring and should initially be provided in the hospital setting. Children and adults with confirmed low-responding inhibitors without allergic reactions to FIX could continue on regular factor IX therapy to induce tolerance.

In all other cases, immunosuppressive drugs should be considered as first line therapy, such as the use of steroids, rituximab, cyclophosphamide, cyclosporine, mycophenolate mofetil and/or other agents, e.g. the “Beutel-protocol” or treatment with immunosuppressive drugs and extracorpral adsorption as in the “Malmö-protocol” [[107](#ref-Hauch2009),[108](#ref-Berntorp2000)]. The FIX inhibitor should not only be judged by BU but also recovery since there can be mismatches. The success rate in HB might be lower in patients with HB compared to HA, but can be achieved even after several attempts [[86](#ref-Kihlberg2022)] . After successful tolerance, the dosing should be tapered to regular prophylactic treatment.

In patients with hemophilia B and persistent inhibitors failing ITI protocols with and without immunosuppression or allergy to FIX, ITI may be stopped and compassionate use of re-balancing therapies could be discussed.

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# 7. Surgery in hemophilia

## 7.1 Introduction – preoperative planning

* Surgical and invasive procedures can be performed safely in PWHs.
* Due to the increased risk of bleeding complications during surgery, thorough planning is essential before surgery.
* Coordinated standard pre-, intra-, and postoperative assessment and planning are essential for optimizing surgical outcomes, resource utilization, and minimizing the risk of bleeding and other adverse events during and after surgery.
* Due to the concentration of expertise and experience at hemophilia treatment centers (HTC), it is recommended that all surgery in patients with hemophilia, and especially inhibitor patients, be planned and executed in conjunction with an HTC [[109](#ref-Kulkarni2012)].
* It is important to discuss the patient’s expectations for surgery and recovery before an orthopedic procedure. The hematologist should provide a written detailed treatment plan that outlines the duration and dosage of hemostatic therapies, as well as the rehabilitation phase.
* The patient’s hemostatic function should be screened before surgery. Laboratory tests, including platelet count, APTT, prothrombin time, FVIII/FIX level, inhibitor test, fibrinogen, blood group including irregular antibodies, and recovery test, should be performed.
* If an inhibitor test and in vivo response assessment for the factor concentrate that will be used during surgery have not been performed recently, they should be performed shortly before surgery to plan the factor replacement regimen during and after surgery.
* It is important that an inhibitor test is performed recently before surgery and that an in vivo response assessment is performed to test the recovery of a standard dose of the factor concentrate selected for substitution during surgery. Data from these tests can be used to plan the substitution program during and after surgery.
* Based on the in vivo response assessment results (recovery), a factor replacement regimen should be developed. This regimen should specify the exact number of units of coagulation factor to be used, the timing of concentrate infusions during surgery and the entire postoperative period, and whether bolus or continuous infusions are preferred.
* The factor replacement regimen should also specify whether prophylactic treatment is needed during the rehabilitation training program, both in the hospital and at home.
* Factor FVIII/FIX levels should be monitored closely in the immediate postoperative period and at least once daily during hospitalization to adjust the factor levels achieved [[110](#ref-Ingerslev2006)].
* If possible, surgery should be postponed during the first 20 exposure days to reduce the increased risk of inhibitor development.
* Thromboprophylaxis should not be routinely administered to PWH. In patients with a previous venous thromboembolism (VTE) or severe risk factors, such as obesity and active cancer, thromboprophylaxis may be considered.

### 7.1.1 RECOMMENDATION

**Surgical and invasive procedures can be performed safely in PWH.**

### 7.1.2 RECOMMENDATION

**All surgery in PWH, especially inhibitor patients, should be planned and executed in close collaboration with an HTC.**

### 7.1.3 RECOMMENDATION

**PWH undergoing surgery should have their factor levels monitored daily.**

## 7.2 Substitution principles

* Two main approaches to factor replacement therapy are used in the clinical management of surgical episodes in PWH: bolus injections every 6-12 hours and continuous infusion via a pump delivery system [[111](#ref-Holme2017)].

### 7.2.1 Continuous infusion

* Continuous infusion (CI) has been used in some hemophilia centers for many years.
* One of the main advantages of continuous infusion is that it provides the patient with a safe and constant level of the coagulation factor by matching the rate of infusion with the rate of clearance.
* A reasonably constant factor level may reduce or eliminate the risk of early and late re-bleeding, and continuous infusion may reduce factor concentrate spending compared to bolus injections by avoiding peaks in factor level.
* Some concerns have been raised about continuous infusion (CI) practices, such as the theoretical risk of infection and/or factor concentrate degradation during storage at room temperature. However, extensive studies have shown that these risks are not significant within 72 hours of CI, as determined by laboratory testing of stability and sterility.
* A common complication is battery failure or other malfunction of the delivery pump system.
* Phlebitis at the infusion site was once common with CI but is now very rare after the addition of small amounts of heparin or low-molecular-weight heparin to the infusion bag.
* Finally, suspicion has been raised that CI may be associated with development of inhibitors, especially in non-severe hemophilia, but there is no strong scientific evidence to support this claim.

### 7.2.2 Bolus injections

* Bolus injections are pre-planned doses of factor concentrate given at regular intervals.
* The response to bolus injections is dependent of the dose administered.
* A sufficient factor level in blood is one that does not go below a predetermined trough level (immediately before the next dose) and that prevents excessive bleeding. This means that the trough level should be the lowest factor level that ensures adequate hemostasis in the clinical situation.
* Because the hemostatic efficacy of bolus-administered factor concentrate depends on the trough level, a certain degree of spillage may be required to maintain that level.
* While the trough level is a critical determinant of bleeding risk, the post-dose factor level can vary greatly.
* A clear disadvantage of using bolus injection strategy is the requirements for frequent injections at 6–12-hour intervals.
* Another disadvantage of bolus injection methods is related to the substitution program and its costs. The peak value of factor in blood probably represents an overshoot of factor needed, and thus a relative risk of overuse of factor concentrates.

### 7.2.3 RECOMMENDATION

**Factor replacement for PWH undergoing surgery can be given as either repeated bolus infusions or continuous infusions.**

## 7.3 Major surgery including orthopedic surgery

* FVIII/IX level 7-100 IU/dL immediately before a surgical procedure and replacement therapy for 7-10 days after major surgery are to be targeted.
* Prophylaxis should then be continued.
* Tranexamic acid (25 mg/kg p.o / 10 mg/kg i.v.) should be combined with factor replacement 3-4 times daily for 7-10 days.
* For the bolus infusion: A bolus dose of approximately 50 IU/kg (FVIII) should be administered just before anesthesia.
* The dose for giving a steady state level is calculated for the next 24 h according to the formula (clearance (CL) x BW x 24) where default values of 3 and 4 can be used as CL for FVIII and FIX respectively.
* Two hours after the bolus dose (see above) it is recommended to give another 2.000 IU to an adult patient and the total dose for the next 24 h according to the formula is then given in 6-hour intervals for FVIII and 8-hour intervals for FIX.

### 

### 7.3.1 Continuous infusion

Recovery calculation to determine the initial bolus dose:

* Clearance(mL/h/kg) is often measured. It varies between individuals and products, especially for FIX:
* **Hemophilia A**: Adult: 3, Children: 5
* **Hemophilia B**: Adult: 6
* Desired FVIII/IX levels in the patients for continuous infusion and trough levels for the bolus injection group:
* Day 1-3: 70 IU/dL
* Day 4-6: 0.50 IU/dL
* Day 7-9: 0.30 IU/dL
* Then tapering off - bolus infusions before physiotherapy [[111](#ref-Holme2017)].

## 

## 7.4 Minor surgery

* In general, a factor level of 50 IU/dL is recommended before the surgical procedure and replacement therapy for 1-5 days depending on the procedure.

## 7.5 Specific surgery

### 7.5.1 Dental extraction

* For invasive surgical intervention it is recommended to increase the factor level 50 IU/dL before surgery and use an oral antifibrinolytic agent (tranexamic acid) agent before and after surgery in combination with local therapy [[112](#ref-Srivastava2012)].

### 7.5.2 Circumcision

* A general recommendation for circumcision is a factor level of 70-100 IU/dL at the start of surgery and a level >50 IU/dL maintained for at least 2-3 days (some recommend 7-10 days) together with antifibrinolytics.
* When performing circumcision in patients with mild hemophilia A, desmopressin (DDAVP) 0.3 µg/kg intravenously before the initiation of surgery and an additional dose on the second day can be considered in DDAVP responding patients [[113](#ref-Ljung2012)].

### 7.5.3 Liver biopsy

* In patients undergoing liver biopsy, the preoperative factor level should be as for major surgery 70-100 IU/dL and replacement therapy should be continued for at least 3 days with concomitant use of tranexamic acid as described below [[114](#ref-Hermans2009)].
* Bed rest for 8-12 h after the biopsy is recommended.

### 7.5.4 Tonsillectomy/adenectomy

* In children undergoing tonsillectomy preoperative factor level should be 70-100 IU/dL and replacement therapy should be continued for 7-10 days with concomitant use of tranexamic acid as described below [[113](#ref-Ljung2012),[114](#ref-Hermans2009)].

### 7.5.5 Prostatectomy

* Prostatectomy should be considered as major surgery. However, substitution therapy should be continued for at least 2 weeks due to the increased risk of late bleeding complications [[114](#ref-Hermans2009)].

### 7.5.6 Mild hemophilia

* Surgery in persons with mild hemophilia A can be performed using desmopressin (DDAVP) when FVIII can be raised to an appropriate therapeutic level.
* Administration of desmopressin (DDAVP) can raise FVIII level adequately (three to six times baseline levels) in patients with mild, and possibly moderate, hemophilia A.
* Testing for DDAVP response prior to surgery should be performed after one and four hours.
* Desmopressin does not affect FIX levels and is of no value in hemophilia B.
* **Dose:**

– 0.3 mg/kg i.v. or s.c.

– 300 mg i.n. (spray) (150 mg if BW <30 kg)

* **Intravenously (i.v.):** slow injection of DDAVP (diluted in 10 mL saline) for 15 minutes or infusion (diluted in 50-100 mL saline) for 30 minutes diluted in 50-100 mL saline. Peak FVIII/VWF levels are observed at 60 minutes.
* **Subcutaneously (s.c.):** Peak FVIII/VWF levels are reached after about 120 minutes.
* Octostim® solution (15 mg/mL) is the most suitable for s.c. administration, due to its high concentration. Often a single 15 mg dose s.c. will suffice in adults.
* An additional dose of DDAVP is infused on the second day (12/24h).
* DDAVP may cause fluid retention, which deserves special attention in the youngest children (<4 years) in whom FVIII concentrate should be considered. A fluid restriction of 1-1.5 L is recommended.

### 7.5.7 Tranexamic acid

* Tranexamic acid is an antifibrinolytic agent.
* Administration can be oral, intravenous, or topical (e.g., as mouthwash).
* It can be used in combination with DDAVP, FVIII/FIX and rFVIIa.
* To increase its effectiveness, tranexamic acid should be given prior to elective procedures and in repeated doses to ensure adequate tissue concentrations.
* **Dose:**

– Orally 25 mg/kg 3-4 times daily for 7-10 days.

– Intravenously 10 mg/kg 3-4 times daily for 7-10 days.

– Mouthwash 10 mL of a 5% solution 4 times daily, which can be swallowed.

#### 7.5.7.1 Limitations

* Contraindicated in the management of upper urinary tract bleeds.
* Dose reduction is necessary in patients with renal insufficiency.
* Should be avoided, or its usage minimized, in patients with a recent thromboembolism and/or a previous personal or family history of thromboembolic disease.
* No data are available on the use of tranexamic acid in newborns.

#### 7.5.7.2 Adverse effects

* Nausea, vomiting, diarrhea, and abdominal pain.

### 7.5.8 RECOMMENDATION

**Major surgery: FVIII/IX level 70-100 IU/dL immediately before a surgical procedure and replacement therapy for 7-10 days.**

### 7.5.9 RECOMMENDATION

**Tranexamic acid (25 mg/kg p.o / 10 mg/kg i.v.) should be combined with factor replacement 3-4 times daily for 7-10 days.**

## 7.6 Postoperative management

* Adequate pain control is essential for successful postoperative management and rehabilitation.
* However, neuraxial anesthetic and analgesic techniques (such as epidural anesthesia) are generally contraindicated postoperatively due to the risk of bleeding. Nerve blocks may be used in this patient population with caution and under replacement coverage.
* Acetylsalicylic acid and Cyclooxygenase-1 (COX-1) inhibitors should also be avoided since they induce platelet dysfunction and thereby contribute to impaired hemostasis.
* COX-2 inhibitors are suitable with proton pump inhibitors unless there is renal insufficiency.
* Patients undergoing elective orthopedic surgery should be assessed for pre- and post-operative rehabilitation by a physical therapist experienced in the management of hemophilia.
* The physical therapist should communicate frequently with the other members of the hemophilia treatment team.

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## 7.7 Orthopedic aspects

* Orthopedic surgery in PWH is a team effort, involving the surgeon and the comprehensive hemophilia center team to address important considerations.
* The optimal timing of orthopedic surgery in hemophilic patients is uncertain, but young people’s demanding social and professional lives often favor early correction of joint disease.
* This has led to a trend towards earlier orthopedic intervention, with a shift in focus from pain relief to restoring functional ability.
* **Recommended plasma factor levels before and after surgery:**

|  | Hemophilia A and B |  |
| --- | --- | --- |
|  | Desired level kIU/L | Duration (days) |
| **Major surgery** |  |  |
| Pre-op | 0.7-1.0 |  |
| Post-op | 0.6-0.8 | 1-3 |
|  | 0.4-0.6 | 4-6 |
|  | 0.3-0.4 | 7-9 |
| **Minor surgery** |  |  |
| Pre-op | >0.5 |  |
| Post-op |  | 1-5 depending on procedure |
|  |  |  |

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## 7.8 EHL products and surgery

* Prophylaxis during and after surgical procedures using an extended half-life product (EHL) should follow the same principles as when using a standard half-life (SHL) product for both hemophilia B and A.

## 7.9 Non-factor replacement therapy and surgery in non-inhibitor patients

* Minor and major surgeries with ongoing emicizumab treatment with or without substitution of SHL-FVIII products have been successfully reported. All surgical or invasive procedures on prophylaxis must be managed by the HTC.

### 7.9.1 Minor surgery

* Prophylaxis with FVIII concentrate is not strictly necessary for minor surgery or invasive procedures (such as central venous catheter insertion, endoscopy with biopsy, or dental/oral procedures).
* Tranexamic acid administered as mouthwash is particularly useful for dental/oral procedures. However, FVIII concentrate should be promptly available in adequate doses to be administered if bleeding complications occur.

### 7.9.2 Major surgery

* For surgery or invasive procedures at high risk of bleeding, replacement treatment with FVIII concentrate is advised, aiming at maintaining FVIII levels >50 IU/dL.
* To this purpose, plasma FVIII daily monitoring by using a chromogenic assay with bovine reagents should be carried out [[115](#ref-Coppola2020)].

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# 8. Surgery in PWHs with inhibitors

## 8.1 Introduction

* Surgery in persons with hemophilia and high-titer inhibitors is a clinical challenge and was for a long time considered as almost impossible.
* Despite an increased risk of bleeding compared to non-inhibitor patients, surgical outcomes using bypassing agents have been generally good over the past 20-25 years [[116](#ref-Tjoennfjord2004)]. While surgery remains a major challenge for patients with inhibitors, they should not be denied access to surgery.
* All surgical procedures in patients should be conducted by a specialized surgeon in association with a hemophilia comprehensive care center.
* Currently, there are no standardized laboratory tests to monitor the effectiveness and optimal dosage of bypassing products after surgery.
* Preoperative evaluation of hemostatic response to bypassing agents using thrombin generation test (TGT) or thromboelastography has been shown to predict and optimize hemostatic outcomes during the peri- and postoperative phases [[117](#ref-Dargaud2010),[118](#ref-Holmstrom2012)].

### 8.1.1 RECOMMENDATION

**All surgery in PWH should be planned and executed in close collaboration with an HTC.**

## 8.2 aPCC and rFVIIa

* The bypassing agents aPCC - factor eight inhibitor bypass activity (FEIBA®, Baxter AG, Vienna, Austria), and recombinant activated factor VII (rFVIIa) (NovoSeven®, NovoNordisk A/S, Bagsvaerd, Denmark) are the treatments of choice in patients with inhibitors if the inhibitor level exceeds 5 BU/mL.
* The choice of bypassing agent depends on several factors, including the patient’s age, prior history of response, cost, and safety.
* aPCC has been used for many years. It can be dosed every 8-12 hours, which is an advantage over rFVIIa that must be infused every 2-3 hours.
* rFVIIa has the advantage of being less likely to be contaminated with infectious agents, even though that risk is now very low due to improved safety precautions.
* Both products are effective in achieving hemostasis. If the first choice fails, switch to the other product.
* Both aPCC and rFVIIa can cause side effects such as venous thrombotic events, disseminated intravascular coagulation (DIC), and myocardial infarction, but these risks are very low when used within the manufacturer’s recommended dosage range.
* The main disadvantages of rFVIIa compared to aPCC are high cost and frequent infusions (see chapter [Inhibitors](file:///Users/christq/hemophilia24/_book/06Inhibitors.qmd)).

### 8.2.1 Management of substitution therapy in the peri- and postoperative phase

* For patients with low-titer (<5 BU) or low-responding inhibitors, high-dose FVIII or FIX concentrates may be used initially to overcome the inhibitor. However, be prepared to switch to a bypassing agent at any time, as an anamnestic response may occur.

### 8.2.2 aPCC - FEIBA®

* During the last 20 years more than 200 surgical procedures have been reported in case reports using aPCC as replacement therapy in patients with inhibitors.
* Initial doses, frequency, and duration of aPCC treatment are variable, but continuous infusion has not been studied.
* The hemostatic efficacy in these case series have been reported from 75-100% [[119](#ref-Rangarajan2012)].
* The Norwegian experience using aPCC for surgery counts 37 surgical procedures, 17 major and 20 minor [[116](#ref-Tjoennfjord2004)–[118](#ref-Holmstrom2012),[120](#ref-Holme2011)].
  + APCC was delivered by short-time infusions (15-20 min) three times daily.
  + A preoperative loading dose of 100 IU/kg was given.
  + The following doses were adjusted to a total daily dose of 200 IU/kg/d.
  + Following the third postoperative day, the dose of aPCC was tapered to a daily dose 150 IU/kg and from the 7th postoperative day tapered gradually to 100 IU/kg.
  + 50 IU/kg every second day was given as post-surgical prophylaxis and prior to physical therapy.
  + A good or excellent hemostatic outcome was observed for all minor procedures and in 15/17 (88%) of the major procedures.
* A few consensus reports for using aPCC as replacement therapy in inhibitor patients undergoing surgery based on the present literature have been published [[119](#ref-Rangarajan2012),[121](#ref-Teitel2009)].
* Common in these recommendations are a preoperative bolus infusion of 50-100 IU/kg and then a dose of 75-100 IU/kg every 8-12 h with a maximum daily dose of 200 IU/kg and depending on the clinical condition and type of surgery the dose may be tapered until discharge ([Table 1](#tbl-dosing1)).

### 8.2.3 rFVIIa - NovoSeven®

* Many small case series have reported successful hemostatic outcomes with rFVIIa for various surgical procedures in PWHs with inhibitors, but there is wide variation in doses and protocols, and only two small prospective randomized studies have been published on dosing and administration [[122](#ref-Gilchrist1998),[123](#ref-Mathew2007)].
* Shapiro and colleagues compared the effect of two doses of rFVIIa in 29 patients with inhibitors for minor and major operative procedures.
  + The patients were randomized to 35 mg/kg vs 90 mg/kg every 2 h for 2 days, then every 2-6 h for total 5 days.
  + Concerning major surgery, the effectiveness at day 5 was found to be 40% for the low dose whereas 83% for the high dose concluding that rFVIIa 90 mg/kg is an effective first-line option for major surgery in patients with inhibitors.
  + Concerning minor surgery, 70% and 100% of the procedures were found to be effective or partially effective for the low dose and high dose, respectively.
* Pruthi and colleagues [[123](#ref-Mathew2007)] studied the efficacy and safety of administering rFVIIa after an initial bolus dose of 90 mg/kg and then randomization to either repetitive bolus infusion (BI) (90 mg/kg) every two hours or continuous infusion (CI) 50 mg/kg/h for 5 days in 22 major surgical procedures in hemophilia A or B patients with inhibitors.
* They found comparable hemostatic efficacy and safety of BI and CI, however the treatment was considered as ineffective in three subjects in each arm.
* Valentino and colleagues reported from the Haemophilia and Thrombosis research registry and literature, which also incorporated a small number of medical procedures (n=45), in addition to surgical and dental procedures, and found rFVIIa to be effective in 333 (84%) of the 395 cases represented [[124](#ref-Valentino2011)].
* Thromboembolic complications attributable to rFVIIa were reported in 0.025% of these procedures.
* Based on the present literature a few general expert recommendations have been given for using rFVIIa to cover surgical procedures [[121](#ref-Teitel2009),[125](#ref-Makris2012)] [Table 1](#tbl-dosing1) .
* The initial bolus dose should at least be 90 mg/kg given immediately preoperatively and then every 2 h for at least 48 h.
* However, due to observed bleeding complications in a minority of procedures an even higher initial bolus dose of 120-180 mg/kg have been proposed. After 2 days the dosage interval may be increased to 3, 4 the 6 h on days 3, 5, and 8 respectively, and continued until discharge.
* Pretreatment with 90 mg/kg is recommended before each physical therapy session.
* In case of unexpected peri- or postoperative bleeding episodes using bypassing agents, one should increase the dose of already initiated treatment agent to maximum dose for rFVIIa (up to 270 mg/kg) or aPCC (200 IU/kg/d).
* If hemostasis is not achieved, rapidly implement an alternative bypassing agent, as in unresponsive severe bleeding episodes.
* If monotherapy with either bypassing agent at maximum doses is ineffective, sequential or concomitant treatment with both bypassing agents may be considered for salvage treatment.

### 8.2.4 RECOMMENDATION

**APCC and recombinant activated factor VII (rFVIIa, NovoSeven®) are the treatment of choice in patients where the inhibitor level exceeds 5 BU/mL. For dosage see** [**Table 1**](#tbl-dosing1) **.**

## 8.3 Emicizumab, Hemlibra®

* Emicizumab is a humanized monoclonal antibody that bridges activated factor IX (FIXa) and FX and replaces the function of activated FVIII [[126](#ref-Kitazawa2012)].
* Emicizumab was approved by the United States Food and Drug Administration in 2017 and the European Medicines Agency in 2018, for prophylaxis in PWH with or without FVIII inhibitors.
* Although emicizumab prophylaxis has been shown to be highly efficient in preventing spontaneous bleeds [[87](#ref-Oldenburg2017)], patients may require additional administration of bypassing agents (BPAs) or clotting factors to control bleeding and during surgery.
* The scarcity of published reports of surgery in patients treated with emicizumab and the occurrence of thrombotic events following cumulative doses of aPCC in the HAVEN 1 emicizumab trial (thrombotic microangiopathy and thrombosis reported in two participants each who had received multiple infusions of aPCC for breakthrough bleeding) (>100IU/kg/24 h) [[87](#ref-Oldenburg2017)] have led to recommendations from the United Kingdom Haemophilia Centres Doctors’ Organisation (UKHCDO) [[127](#ref-Collins2018)].
* However, recommendations how to mitigate risks are given, like those present in a recent review of the literature by an international expert group with practical recommendations [[128](#ref-JimenezYuste2021)]. This review lists experiences from 10 major surgeries all of which were arthroplasties, as well as from 25 minor surgeries including 15 central venous catheter device insertion/replacement/removal, 4 circumcisions and 6 dental procedures.
* Since then, additional reports have been published, such as a single center American report describing results from 20 minor and 5 major surgeries performed in 17 and 5 patients, respectively [[129](#ref-Lewandowska2020)]. In all major and in 15 minor surgeries additional coagulation factor therapy was given and there were no major bleeds, thrombotic events, or deaths.
* In addition, a report published in 2021 describes the results from a questionnaire sent to 144 hemophilia treatment centers (HTC) in 21 European countries. In this study, results from a total of 52 inhibitor positive patients underwent surgery (17 major and 45 minor) while on emicizumab.
  + Major surgeries were mainly covered with rFVIIa by 93.3% of HTCs (n = 14), while 6.7% (n = 1) preferably managed them with emicizumab alone.
  + Minor surgeries were primarily treated with tranexamic acid (57.1%; n = 12), followed by treatment with emicizumab alone (23.8%; n = 5) and treatment with rFVIIa (19.0%; n = 4).
  + Nineteen HTCs answered questions on efficacy of emicizumab during surgery: hemostasis was unsatisfactory in 1 out of 16 (6.3%) major procedures and in 4 out of 43 (9.3%) minor procedures [[130](#ref-Krumb2021)].
* Therefore, since all reported data is observational, evidence-based guidelines cannot be given on the use of emicizumab treated patients during surgery, but for simplicity we refer to the practical guidelines given by Jiménez-Yuste et al [[128](#ref-JimenezYuste2021)].
* For major surgery, it is recommended that emicizumab should be dosed as per the prescribed maintenance regimen throughout the pre-, peri- and post-operative period but that caution regarding emicizumab administration should be taken when more than one-third of whole blood volume is lost during surgery, because the distribution of emicizumab into the third extracellular compartment has not been described in detail.
* For major surgery in patients with high titer inhibitors (>5 Bethesda Units [BU]), concomitant hemostatic treatment with rFVIIa should be given (for dosing see [Table 2](#tbl-dosing2)).
* APCC should only be given to patients not responsive to rFVIIa and in reduced doses ([Table 2](#tbl-dosing2)).
* If inhibitor titre is low (<5 Bethesda Units [BU]), high doses of FVIII could be used to achieve hemostasis.
* For minor surgery administration of BPAs should be considered on an individual basis, and in some cases, no BPAs may be required.
* If a BPA is indicated, rFVIIa should be used (for dosing, see [Table 2](#tbl-dosing2)) and aPCC only to patients not responsive to rFVIIa and in reduced doses.

## 8.4 Alternative treatments

### 8.4.1 Recombinant porcine FVIII

* Recombinant porcine FVIII (r-pFVIII, Obizur®) has been approved by the EMA for treatment of acquired hemophilia A but has also been used for patients with congenital hemophilia A with inhibitors.
* In a small phase II study, eight or fewer injections of r-pFVIII successfully controlled all 25 bleeding episodes in nine patients without anti-pFVIII antibodies. r-pFVIII was well tolerated, with no serious adverse events reported [[131](#ref-Mahlangu2016)].
* The use of r-pFVIII in a surgical procedure has only been described in one case report where a 5-year-old male, refractory to ITI, was operated because of a progressively symptomatic aortic coarctation [[132](#ref-Croteau2017)].
  + r-p FVIII was preferred over aPCC or rFVIIa because of the ability to assay FVIII levels throughout the procedure.
  + Haemostasis with r-pFVIII was excellent but because of declining peak and trough levels of FVIII suggesting a rising porcine inhibitor titre, he was switched to aPCC after the procedure.
* The cost of r-p VIII is substantially higher than that of the other bypassing agents and cannot be recommended to be used in patients with congenital HA with inhibitors until more data on its efficacy is available.

### 8.4.2 Bypassing agents and antifibrinolytics

* The antifibrinolytic agent tranexamic acid (TXA) increases clot stability and is used concomitantly with coagulation factor replacement to improve hemostasis in PWHs without inhibitors.
* It is not contraindicated to combine rFVIIa with TXA to improve hemostasis although it is not systematically studied.
* In contrast to rFVIIa, aPCC has not been recommended to be given together with TXA unless a time lag of 6 h between administrations of the two drugs.
* The reason for this caution is safety concerns with an estimated increased risk of thrombotic events and disseminated intravascular coagulation (DIC). However, strong evidence supporting this precaution is lacking.
* At least whenever possible applied locally either as mouth rinse or moistened dressings the combination of TXA and aPCC is considered as safe.
* The dose of tranexamic acid commonly used is 10 mg/kg intravenously or 25 mg/kg orally 3-4 times daily for 7-10 days.

### 8.4.3 Bypassing agents and thromboprophylaxis

* Although thrombosis might be a concern using bypassing agents, postoperative anticoagulation (e.g., low-molecular-weight heparin) is not recommended in patients with inhibitors.
* For most of the patients the use of graduated compression stockings and early mobilization are sufficient to prevent venous thromboembolism.
* According to current knowledge, the presence of emicizumab does not affect the efficacy or safety of tranexamic acid.

## 

## 8.5 Tables

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 1: Recommended dosage of rFVIIa and aPCC for surgery in patients with hemophilia and inhibitors   |  | **Preoperative dose** | **Postoperative management** | | --- | --- | --- | | **rFVIIa** |  |  | | Minor surgery | 90 µg/kg | 90 µg/kg every 2 h up to four times, then every 3-6 h until discharge. | | Major Surgery | 90-120 µg/kg | 90 µg/kg every 2 h the first 48 h, then 90 µg/kg every 3, 4 the 6 h on days 3, 5, and 8 respectively until discharge. CI\*: 50 µg/kg/h. | | **aPCC** |  |  | | Minor surgery | 50-100 IU/kg | 50-75 IU/kg every 8-12 h until discharge. | | Major surgery | 75-100 IU/kg | 70 IU/kg every 8 h for at least 3 days with a maximum daily dose of 200 IU/kg. Dose may be tapered from day 4 to 50-75 IU/kg every 8 h. | |

\*CI: Continuous infusion

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 2: Recommended dosage of rFVIIa and aPCC for surgery in patients with hemophilia and inhibitors treated with emicizumab   |  | **Preoperative dose** | **Postoperative management** | | --- | --- | --- | | **rFVIIa** |  |  | | Minor surgery | 90 µg/kg | 90 µg/kg rFVIIa (single dose) and/or tranexamic acid 10 mg/kg i.v. (x4 doses).  In the event of excessive post-operative bleeding, an additional 90 µg/kg rFVIIa may be considered. | | Major Surgery | 90-120 µg/kg  Tranexamic acid 10 mg/kg i.v. | Perioperatively:   * 90 µg/kg rFVIIa every 2 h. * Adjust dosing according to bleed volume. * In the event of excessive bleeding, increase the rFVIIa dose (maximum single dose should not exceed 270 µg/kg) or shorten the duration between rFVIIa doses. * In the absence of bleeding, or presence of very minor bleeding, consider reducing rFVIIa dose (90 µg/kg every 3–4 h).   Post-operative dosing recommendations:   * Days 1–2 (0–48h) post-procedure: 90 µg/kg rFVIIa every 2–3h + tranexamic acid 10 mg/kg i.v. (×4 doses). * Days 3–4 (48–96h) post-procedure: 90 µg/kg rFVIIa every 4 h + tranexamic acid 10 mg/kg i.v. (×4 doses). * Days 5–7 (96–168h) post-procedure: 90 µg/kg rFVIIa every 6 h + tranexamic acid 10 mg/kg i.v. (×4 doses). * Adjust dosing according to bleed volume. | | **aPCC** |  | **Only patients not responsive to rFVIIa** | | Minor surgery | < 50 IU/kg | Individualized low doses (<50 IU/kg per dose) every 8–12 h until bleeding is resolved. | | Major Surgery | < 50 IU/kg | Individualised low doses (<50 IU/kg per dose) every 8–12h until bleeding is controlled. | |

# 

# 9. Treatment of bleeds

## 9.1 Introduction

* Treatment only when acute bleeds occur is called treatment *on demand*. In mild and mild-moderate hemophilia spontaneous bleeds a rare, and patients are mostly treated on demand.
* In severe and moderate-severe hemophilia, patients might suffer bleeds despite prophylactic treatment.
* Acute bleeds are treated with factor products to target a factor level of 40-60 IU/dL for minor bleeds, and 70-100 IU/dL for major bleeds.
* For potentially life-threatening bleeds such as head trauma, bleeding in the throat and neck and gastrointestinal bleeding the target is 70-100 IU/dL with repeated dosing every 6-8th hours until the bleeds resolves.
* For further details on treatment of specific bleeds, see the WFH guideline <https://guidelines.wfh.org/chapter/treatment-of-specific-hemorrhages/>.
* In mild hemophilia A, DDAVP should be tested as alternative to factor replacement therapy for treatment of acute bleeds as well as prophylaxis before surgery (see chapter [Surgery in hemophilia](file:///Users/christq/hemophilia24/_book/07Surgery.qmd)).
* For non-inhibitor patients in emicizumab prophylaxis, minor bleeds often resolve without treatment.
  + In case a minor bleed requires treatment, the recommended dose is 25 IU/kg.
  + Major bleeds should be treated with a dose of FVIII of 50 IU/kg and repeated dosing can be necessary.
  + The factor level can be measured with a chromogenic FVIII assay with bovine reagents.
* For inhibitor patients, see chapter [Inhibitors](file:///Users/christq/hemophilia24/_book/06Inhibitors.qmd).

### 9.1.1 RECOMMENDATION

* **When treating minor bleeds, the target is a factor level of 40-60 IU/dL.**

### 9.1.2 RECOMMENDATION

* **When treating major bleeds, the target is a factor level of 70-100 IU/dL.**

### 9.1.3 RECOMMENDATION

* **DDAVP is recommended for on demand treatment in patients with mild hemophilia A.**

### 9.1.4 RECOMMENDATION

* **Major or life-threatening bleeds under emicizumab prophylaxis in non-inhibitor patients should be treated with FVIII 50 IU/kg.**

# 

# 10. Gene therapy

## 10.1 Introduction

* Gene therapy has proved to be effective in hemophilia management and may offer the potential to overcome some of the limitations of current therapeutic options [[112](#ref-Srivastava2012),[133](#ref-Pipe2022),[134](#ref-Mancuso2021)].
* The treatment is approved by EMA and used in some European countries for routine clinical practise.
* Currently, it is not available outside clinical trials in the Nordic region, but a potential health technology assessment (HTA)-approval of gene therapy in the near future should be considered, since, whenever approved and reimbursed, it will present a challenge and require an extensive preparation and partly re-organization of the hemophilia infrastructure in each Nordic country.
* To this end, a Nordic preparatory project was initiated in 2022 in order to facilitate and implement an effective infrastructure for the safe introduction of gene therapy and other potential genetically modified organism (GMO) agents with a function-based working model,addressing critical milestones including organization, patient selections and eligibility, product handling, administration, and follow-up [[135](#ref-Astermark2023)].

## 10.2 Principles

* The current concept of gene therapy for hemophilia includes the delivery of functional copies of the factor VIII or IX gene by viral vectors into the patient’s cells, enabling an endogenous production of the deficient factor [[112](#ref-Srivastava2012),[133](#ref-Pipe2022)].
* Various vectors serve as delivery mechanisms to introduce the genetic material into the patient’s cells, mainly the hepatocytes. The most used and studied type of vector over the last decade has been the adeno-associated viruses (AAVs), but also other approaches such as lentiviruses have provided promising results and will be further evaluated.
* AAVs have been favored for their safety profile with a low risk of integration in the host genome and ability to deliver genetic material to non-dividing cells, making them suitable for long-term expression.
* Lentiviruses, on the other hand, can integrate the therapeutic gene into the patient’s genome, potentially providing a stable and enduring correction in also dividing cells making it more suitable for the growing child.
* The current treatment options for both hemophilia A and B evaluated in phase 3 trials and approved by EMA all include various subtypes of AAV vector delivery [[136](#ref-Pasi2020),[137](#ref-Pipe2023)], and research is on-going with the aim to refine the treatment and to ensure effective delivery, minimize the immune responses, and to enhance the overall success.
* The specific factor levels achieved with gene therapy in hemophilia vary depending on the type of vector and individual patient characteristics, many of which are currently unknown, but basically a long-term expression for several years have been established in the majority of patients enabling them to reach sustained factor levels in the mild range i.e. sufficient levels to reduce or eliminate the need for regular factor replacement therapy.

## 10.3 Organization

* The ‘hub-and-spoke’ model has been proposed as a framework of gene therapy [[138](#ref-Miesbach2019)–[140](#ref-Miesbach2021)].
* Based on the structure of the health care in the Nordics, the original hub-and-spoke model will however not be fully applicable, but each country will potentially have one to three infusion sites with or without a collaboration with spoke center(s). In all countries, the local hospital and/or mobile teams will be involved for optimal sampling and follow-up.
* To meet future requirements to establish GMO treatment in hemophilia, the multidisciplinary team will ideally include not only a hematologist, nurse, physiotherapist, orthopedic surgeon, but also a psychologist, social worker and hepatologist. This may require a collaboration between centers. In addition, how to access laboratory analyses within 24 hours of collection should be discussed and defined, including the availability of both the one-stage clotting assay and the chromogenic substrate assay.
* The pharmacy unit will play a key role in the preparation and administration of the vector (gene therapy product) at each center, but the set-up will differ between countries and centers.
* For future management of GMO products, Advanced Therapy Medicinal Product (ATMP) centers are currently being organized in several of the University hospitals. These centers will presumably in most locations be involved in vector preparation and delivery, but supervised by and in close collaboration with the local multidisciplinary hemophilia care team.

## 10.4 Patient selection

* Early information and counselling about treatment options and expectations of gene therapy should be provided on several occasions to all potentially eligible patients during the pre-dosing process.
* Patients should understand that although gene therapy may convert them from a severe to a mild phenotype, they should not be considered as cured and they will continue to need clinical monitoring independent of the expression level.
* In addition to what is stated in the Summary of Product Characteristics (SmPC) about contraindication/cautiousness for vector delivery, the review of therapeutics and co-morbidities, all candidates must be given sufficient information in order to understand and consent to the commitments and potential risks involved.
* The requirement post-infusion for abstinence from alcohol for up to a year after the vector is administered need an extra focus and discussion, as does the need for the use of barrier and effective contraception throughout the period of vector shedding (see below).
* The likelihood of a cytotoxic immune response occurring, and the subsequent need for treatment with immunosuppressive agents (mainly corticosteroids) for several weeks post-infusion should also be addressed.
* Patient education should take individual health, literacy, diverse social and educational background, language barriers and learning mechanisms into account. A broad pallet of educational tools should be provided, including face-to-face sessions, and the provision of written and visual aid materials are of paramount importance in providing equal access to gene therapy.
* A shared decision-making process based on a designed pre-infusion checklist has been defined to ensure that all preparatory work has been performed and that adequate information has been provided to the patient/family ([Figure 1](#fig-table1)).

## 10.5 Eligibility testing

* The eligibility criteria for gene therapy may differ, and should follow the guidelines in the relevant SmPC.
* Accurate measurement of anti-AAV antibodies will be crucial, and each manufacturer will presumably offer mandatory companion diagnostics to be used.
* In addition, a centralized method for AAV-serotype testing at one or more of the Nordic centers have been discussed to enable the possibility of testing for different serotypes of AAV independent of the product manufacturer.
* An initial first screening in the early phase of communication, during the pre-infusion period, should be performed followed by a follow-up testing closer to the time of dosing – preferably 3-4 weeks pre-infusion.
* An accurate and appropriate liver assessment for evaluating patient eligibility will be important [[141](#ref-Miesbach2023)].
* The decision limit of liver enzyme levels for eligibility for gene therapy should also follow the guidance that is stated in the relevant SmPC, but all pathological findings need to be scrutinized.
* Active infections need to be ruled out, and subjects who have been treated and cured of hepatitis C virus infection must have two negative viral assays performed by polymerase chain reaction at least 6 months apart.
* Fibroscan, liver ultrasound and fibrosis-4 score for liver fibrosis should be performed on all eligible patients to screen for advanced liver fibrosis or liver cirrhosis.

## 10.6 Vector infusion

* A general working sheet or checklist for the preparation and delivery of the vector should be developed at each center and include a planning of all logistics with the patient, ward, emergency equipment, intensive care unit and the pharmacy two weeks pre-infusion.
* The dose (vg/kg) to be administered and infusion rate will follow the SmPC for each agent.
* The patient should be carefully observed during the entire infusion period including frequent blood pressure, heart rate and temperature according to a pre-defined protocol.
* On day 1 post-infusion before discharge, the procedure should be reviewed with the patient, follow-up discussed and the commitments confirmed, as well as any post-infusion thoughts/concerns identified.

## 10.7 Follow-up

* Follow-up visits will generally be performed at the hemophilia comprehensive care (infusion) center and include a general laboratory work-up including liver assessment, inflammatory markers, factor activity levels including inhibitor testing whenever indicated.
* The content and minimal timing of these visits/sampling time points will mainly follow the recommendations of the World Federation of Hemophilia (WFH), as outlined in [Figure 2](#fig-table2), but during the first 3-6 months, sampling and monitoring will be performed more frequently, basically every week.
* For patients living far away from the center, blood sampling may be performed at the patient’s local hospital and/or by mobile teams. Anagreement, between the mobile unit/nurses and the responsible center, should be signed and responsibilities defined.
* A turn-around-time (TAT) of 24 hours for both factor activity analyzes and liver enzymes will be required, and availability of these analyzes at weekends may require extra consideration.
* In addition to the plasma laboratory work-up, and irrespective of any fibroscanning, ultrasound of the liver is recommended – as for all other patients with a history of hepatitis B and/or C infection – every 6-12 months, for early identification of hepatocellular carcinoma.
* Vector shedding should be assessed according the SmPC of each approved GMO product. During the period of vector shedding, all patients (also including vasectomized patients) should use contraception including condoms, and not donate any cells and/or tissues including semen – usually up to 6 months post-infusion – and longer if required.

## 10.8 Registry

* Proper data collection and registration in the national registries will be crucial and each national registry in the Nordics will harmonize the parameters to be documented together.
* In addition, data will be provided to the WFH Gene Therapy Registry, manually or automatically, and the Nordic centers will take part in the planned accreditation process by EAHAD.

### 10.8.1 RECOMMENDATION

* **Gene therapy should be considered as a new treatment option for adult patients with severe hemophilia.**

### 10.8.2 RECOMMENDATION

* **An infrastructure for the safe introduction of gene therapy in the routine clinical setting should be established at each infusion center.**

### 10.8.3 RECOMMENDATION

* **Education of patients and the expanded health care professional team will be the key to successful and optimal clinical management and a shared decision making process.**

### 10.8.4 RECOMMENDATION

* **Close long-term follow-up and proper data collection with registration in the national registries as well as WFH gene therapy registry will be crucial for optimal clinical management.**

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## 10.9 Tables

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| Figure 1: Table 1 |

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| Figure 2: Table 2 |

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# 11. Comorbidities in the ageing patients with hemophilia

## 11.1 Introduction

* Improved treatment has extended life expectancy for PWHs during the last three to four decades making them susceptible not only to complications of hemophilia, but also to age related co-morbidities same as in the general population [[142](#ref-Franchini2010)–[146](#ref-Harrison2018)].
* Apart from the initial devastating effects on morbidity and mortality associated with the transmission of viral pathogens during the 1980’s and early 1990’s, the availability of factor concentrates, and improved treatment regimens have had a favorable influence on longevity and quality of life of PWHs.
* At present with only scarce evidence-based data available, little is known about how to manage these “new” concomitant illnesses in a scientific manner, apart from hemophilic arthropathy and chronic infections with HIV (human immunodeficiency virus) and HCV (hepatitis C virus).
* Comorbidities like metabolic syndrome, cardiovascular and renal disease, along with infection related issues and cancer represent a series of challenges to physicians treating PWHs.
* Comorbidities should be managed appropriately as they may emphasize problems associated with hemophilia and impact the patient’s quality of life. Thus, expertise from specialists in e.g. cardiology, neurology, oncology, nephrology, and urology, as well as collaboration with patients’ primary care physician need to be included in the multidisciplinary team of physicians treating elderly PWHs in comprehensive hemophilia care centers [[147](#ref-Hollingdrake2016),[148](#ref-Boccalandro2017)].

## 11.2 Current status and recommendations / managing suggestions

### 11.2.1 Joint disease

* The most prominent co-morbidity in middle-aged and older PWHs is irreversible joint arthropathy [[142](#ref-Franchini2010),[143](#ref-Khleif2011),[149](#ref-Stephensen2012)].
* Recurrent hemarthroses result in initial synovial hypertrophy and neoangiogenesis further increasing the risk of bleeding and later result in degenerative changes of the joint.
* This leads to limited use of the affected, often weight-bearing joint, causes pain, muscle atrophy, anchylosis (reduces range of motion), contractures and osteoporosis, the latter express by a reduced bone mineral density (BMD) or impaired bone structure.
* The goal of treatment is to try to improve joint function, relieve pain and assist the patient in resuming to normal activities of daily living.
* Physiotherapy is an important treatment modality to improve or maintain muscle function and joint motion, may reduce the risk of falls, and encourage an interest for an active lifestyle.
* Appropriate pain management including suitable medication needs to be carried out to prevent further deterioration, but also needs to be monitored closely for side effects [[150](#ref-Mannucci2009)].
* Lifestyle changes e.g., weight loss and regular exercise, is beneficial for joint health.
* The use of secondary prophylaxis (regular treatment with factor concentrate after onset of arthropathy) reduces bleeding frequency and facilitates rehabilitation but does not alter established degenerative changes that worsen with age.
* Despite adequate treatment and even in the absence of an inhibitor, target joint bleeds might require procedures, such as radiosynovectomy to control synovial hypertrophy or at times angiographic embolization to stop joint bleeding from arterial origin [[150](#ref-Mannucci2009),[151](#ref-Konkle2012)].
* To reduce severe pain and disability arthroscopy, arthrodesis or arthroplasty are efficient interventions.
* Consultations services and multidisciplinary programs with rehabilitation medicine, orthopedics and pain clinics should be an integral part of the hemophilia care team [[148](#ref-Boccalandro2017)].

### 11.2.2 RECOMMENDATION

* **To protect and improve joint function and relieve pain the use of factor prophylaxis, physiotherapy, regular exercise and when appropriate, weight loss, pain management, and orthopedic procedures are recommended.**

### 11.2.3 Osteoporosis

* Osteoporosis is frequently occurring in PwH [[152](#ref-Wallny2006)] .
* There are many predisposing factors for patients with hemophilia, such as prolonged periods of immobility, reduced weightbearing and co‐morbidities associated with bone loss [[153](#ref-Gerstner2009)].
* Osteopenia can be prevented or reduced through a supplement of calcium, vitamin D and weight bearing exercise, while osteoporosis necessitates specialist treatment with one or several drugs including bisphosphonates, estrogens, calcitonins and monoclonal antibodies [[154](#ref-Konkle2009)].
* Assessment of bone mineral density (BMD) by imaging studies (DEXA scan) and laboratory evaluation are recommended as part of comprehensive hemophilia care in patients with high risk or multiple risk factors.

### 11.2.4 RECOMMENDATION

* **Assessment of bone mineral density status by imaging studies (DEXA scan) and laboratory evaluation are recommended as part of comprehensive hemophilia care.**

### 11.2.5 RECOMMENDATION

* **Osteopenia can be prevented or reduced by supplement of calcium, vitamin D and exercise, while osteoporosis necessitates specialist treatment with bisphosphonates, estrogens, calcitonins or monoclonal antibodies.**

### 11.2.6 Infection related issues / complications

* HAART (highly active antiretroviral treatment) increases the risk of metabolic syndrome, diabetes, renal insufficiency, and atherosclerotic CVD (cardiovascular disease) in non-bleeding patients. A similar impact is suspected to apply to PWHs [[142](#ref-Franchini2010),[150](#ref-Mannucci2009)]. Close laboratory monitoring is therefore recommended.
* HAART has also been reported to increase frequency and severity of hemarthrosis in hemophilia [[154](#ref-Konkle2009)].
* HCV is a major cause of chronic liver disease. Modern antiviral hepatitis C therapy, combinations of direct-acting antiviral agents including HCV protease inhibitors, has markedly improved virological response rates [[155](#ref-Isfordink2021)].
* Infectious disease issues should be handled by hepatologist and infectious disease specialist as part of comprehensive hemophilia care.
* Treatment decisions should follow the national guidelines when available.

### 11.2.7 RECOMMENDATION

* **HAART may increase the risk of metabolic syndrome, diabetes, renal insufficiency and atherosclerotic cardiovascular disease and frequency and severity of hemarthrosis, thus close laboratory monitoring and follow-up is recommended.**

### 11.2.8 Metabolic syndrome

* The term describes a complex of signs that increase the risk for type 2 diabetes, stroke, and coronary artery disease.
* Effective prevention strategies throughout life are most important, as management of thrombotic complications in PWH is a special challenge.
* Diagnostic criteria include increased body mass index (BMI) >30 kg/m2, hypertension, dyslipidemia, and hyperinsulinemia.
* Middle-aged PWHs have an increased risk of becoming obese and inactive due to severe arthropathy. On the other hand, high BMI has been associated with a significant limitation in range of motion, increased arthropathic pain and increased risk of developing target joints.
* Lipid profile should be measured in ageing hemophilia patients at risk of cardiovascular disease and treatment initiated according to the general guidelines.
* Glucose levels should be checked annually, especially in those patients who are overweight.
* HAART can result in hypertension, ischemic heart disease and dyslipidemia.
* Patients need appropriate treatment management, regular clinical and laboratory follow-up, which should also be coordinated with the primary care physician, with consultation services from internal medicine and endocrinology as needed [[156](#ref-Coppola2013)].

### 11.2.9 RECOMMENDATION

* **Effective prevention strategies are necessary throughout life.**

### 11.2.10 RECOMMENDATION

* **Lipid profile should be measured in ageing hemophilia patients at risk of cardiovascular disease and treatment initiated according to the general guidelines. Glucose levels should be checked annually, especially in overweight patients.**

### 11.2.11 RECOMMENDATION

* **Treatment management, regular clinical and laboratory follow-up should be coordinated with the primary care physician, with consultation services from internal medicine and endocrinology.**

### 11.2.12 Cardiovascular disease

* Conflicting data exist on whether hemophilia protects against development of atherosclerosis and cardiovascular events [[151](#ref-Konkle2012),[154](#ref-Konkle2009),[157](#ref-Dolan2010),[158](#ref-Coppola2010)], but there is evidence that PWH develop atherosclerosis at similar rates to those in the general population [[159](#ref-BiereRafi2012)].
* The same risk factors that affect the general population also seem to have impact on ageing PWHs.
* Increasing age, obesity, smoking, arterial hypertension, diabetes and dyslipidemia and inflammation contribute to cardiovascular disease.
* An institutional non-evidence-based Dutch guideline covers acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI), where, after substitution with the deficient factor, the PWH is treated as close to general guidelines for non-PWHs as possible [[160](#ref-Schutgens2009)].
* The WFH guidelines ([wfh.org](https://wfh.org/)) similarly state that PWH with cardiovascular disease should receive routine care adapted to the individual situation, in discussion with a cardiologist. DDAVP (desmopressin) should be avoided as a hemostatic due to non-specific thrombogenic effects.
* Thrombolysis is not recommended.
* In case of PCI, we recommend discussing with the cardiologist on which stent to be used to enable as short dual anti platelet therapy (DAPT) as possible. Radial artery access site is preferred over femoral, to minimize retroperitoneal or groin bleeds. Heparin can be administered according to standard cardiologic treatment protocols. Glycoprotein IIb/IIIa inhibitors used in PCI with stenting can be administered.
* When treating valvular heart disease, a material should be chosen that does not necessitate anticoagulation.
* Anticoagulation and antiplatelet therapies are possible taking in consideration of the baseline factor level and goals of replacement therapy [[161](#ref-Martin2016),[162](#ref-Schutgens2023)].
* Emphasis should be made on not to “overtreat” during replacement therapy especially with bypassing agents to avoid thrombotic events.
* A way to avoid hazardous peak levels during substitution therapy can be achieved by administering the needed coagulation factor by continuous infusion instead of bolus injections.
* Treatment strategy should be tailored to the individual; however, a minimum trough FVIII/IX level must be maintained to allow for necessary treatment.
  + For single anti platelet therapy (aspirin or clopidogrel) a minimum trough factor level of 1-5IU/dL is recommended [[162](#ref-Schutgens2023)].
  + For dual antiplatelet therapy a minimum trough factor level of 20 IU/dL is recommended [[162](#ref-Schutgens2023)].
  + For oral anticoagulation (vitamin K antagonist or direct oral anticoagulant) a minimum trough factor level of 20 IU/dL is recommended [[162](#ref-Schutgens2023)].
* Virtually no data are available for defining treatment strategies for cerebrovascular and peripheral artery disease [[158](#ref-Coppola2010)].
* Some recommendations are available based on case series regarding non-valvular atrial fibrillation and venous thromboembolism [[161](#ref-Martin2016)].
* For atrial fibrillation, no anticoagulation, DOAC or warfarin are considered depending on basal factor levels and stroke risk.
* Erectile dysfunction can be seen as the first manifestation of vascular disease and endothelial dysfunction. It can accompany the metabolic syndrome or be caused by age-related changes in hormonal, neurological and psychological function [[163](#ref-Bar-Chama2011)].

### 11.2.13 RECOMMENDATION

* **PWH with cardiovascular disease should receive routine care adapted to the individual situation, in discussion with a cardiologist.**

### 11.2.14 RECOMMENDATION

* **DDAVP (desmopressin) should be avoided, and thrombolysis is not recommended.**

### 11.2.15 RECOMMENDATION

* **In case of PCI, we recommend discussing with the cardiologist on which stent to be used to enable as short dual anti platelet therapy (DAPT) as possible.**

### 11.2.16 RECOMMENDATION

* **Radial artery access site is preferred to reduce bleeding risk.**

### 11.2.17 RECOMMENDATION

* **For valve replacement, material that does not necessitate anticoagulation should be chosen.**

### 11.2.18 RECOMMENDATION

* **Anticoagulation and antiplatelet therapies are possible with replacement therapy.**

### 11.2.19 RECOMMENDATION

* **For atrial fibrillation, no anticoagulation, DOAC or warfarin are considered depending on basal factor levels and stroke risk.**

### 11.2.20 Renal disease

* In young PWHs, hematuria often is a benign, transient, usually idiopathic event.
* In older patients this bleeding symptom can be caused by several different conditions and etiology should be evaluated [[164](#ref-Holme2015)].
* In chronic renal disease uremia and anemia via platelet dysfunction increase the risk for kidney bleeding [[164](#ref-Holme2015),[165](#ref-Holme2015a)]. So does hypertension that can be caused by chronic renal disease and at the same time represents a risk factor for development of cardiovascular disease as well as cerebral hemorrhage.
* HIV-associated nephropathy and immune complex glomerulonephritis, nephrotoxicity of HAART and co-infection with HCV make up a large proportion of causes for renal insufficiency.
* If dialysis is needed, peritoneal dialysis could be the preferred choice since no anticoagulation is needed. This however could contain the risk for infection and peritoneal hemorrhage especially in patients co-infected with HIV and HCV [[151](#ref-Konkle2012),[157](#ref-Dolan2010),[166](#ref-Franchini2009)].
* For hemodialysis patients prophylactic factor dosing needs to be carefully tailored for access surgery and to allow the required anticoagulation.

### 11.2.21 RECOMMENDATION

* **Etiology for recurrent hematuria should be evaluated especially in older patients.**

### 11.2.22 RECOMMENDATION

* **Peritoneal dialysis could be the preferred choice since no anticoagulation is needed.**

### 11.2.23 RECOMMENDATION

* **Hemodialysis is performed with tailored prophylactic factor dosing.**

### 11.2.24 Cancer

* If malignancies that are a consequence of viral infection are excluded only a few clinical studies have addressed the issue of cancer in the ageing hemophilia population.
* It is uncertain whether the incidence of cancer in PWHs differs from that observed in the general middle-aged population [[150](#ref-Mannucci2009),[166](#ref-Franchini2009)].
* Persons with severe hemophilia tend to have a higher rate of virus-related cancers whereas milder forms present an overweight of non-virus-related cancer types.
* Attention must be drawn to the importance of prompt evaluation if a middle-aged PWH experiences new, aggravated, or recurring bleeding episodes due to a second peak of inhibitor incidence at the age of 60 and above.
* Despite the increased risk of bleeding investigation and procedures should not be delayed or avoided in PWHs [[167](#ref-Astermark2012)]. Relevant hemostatic treatment must be given to prevent bleeds both in the setting of diagnostic interventions and later as well prior to surgical, chemo, or radiotherapeutic treatment.
* One specific cancer type need mentioning since it is one of the most frequent cancers in men, with increasing frequency up to the age of 70: prostate cancer [[168](#ref-Fogarty2012)]. Prostate specific antigen (PSA) screening has reduced the percentage of disseminated disease at diagnosis more then 20-fold.
* Despite hemostatic treatment bleeding occurs but is often mild to moderate and self-limiting.
* Antifibrinolytics should be used with caution and close observation for thrombus formation in the bladder and in the upper urinary tract with the risk of developing hydronephrosis.

### 11.2.25 RECOMMENDATION

* **New, aggravated or recurring bleeding episodes should be promptly investigated, and relevant hemostatic treatment must be given to prevent bleeds in the setting of diagnostic interventions and prior to surgical, chemo, or radiotherapeutic treatment.**

### 11.2.26 RECOMMENDATION

* **For prostate cancer diagnostics and treatment, antifibrinolytics should be used with caution.**

### 11.2.27 Conclusion

* Ageing PWHs present new challenges to hemophilia caretakers. Current management, in the absence of studies, is based on international consensus guidelines for the assessment, monitoring and follow-up of PWH. These include the WFH ([wfh.org](https://wfh.org)), the UKHCDO ([ukhcdo.org](https://www.ukhcdo.org/)) and the EHTSB (European Haemophilia Therapy Standardization Board) [[169](#ref-deMoerloose2011)].
* On-going and future studies will hopefully clarify the most appropriate preventive measures and treatment regimens for co-morbidities, which often create management challenges in view of the hemostatic status of the PWH.
* Centralized comprehensive hemophilia care is important throughout the life of PWHs.
* The challenges with comorbidities developing during aging are best managed in close multidisciplinary collaboration with different medical and surgical specialists and networking with patient’s local hematologist and primary care physician.

# 

# 12. Treatment of pain

## 12.1 Introduction

### 12.1.1 Pain in people with hemophilia

* Among people with hemophilia (PWH) pain is a very common condition affecting the quality of life [[170](#ref-SteenCarlsson2022),[171](#ref-Kennedy2022)].
* When evaluating pain, it is important to take the patient’s life situation into account. The pain could be acute and/or severe or chronic. Pain from joints or muscles is very common in PWH, especially if the patient has hemophilic arthropathy, in which case the pain often is chronic.
* Basic pain treatment can be symptomatic and, in some cases, also directed against the underlying disorder.
* Bleeding in a joint or muscle will cause acute pain and should be treated with relevant hemostatic drugs as soon as possible to stop the bleeding.
* If the PWH is not on a prophylactic treatment regimen and has a target joint, prophylaxis should be offered to avoid recurrent bleeding, inflammation, and pain.
* Several instruments exist for the evaluation of pain in PWH among which are the visual analogue scale (VAS), health-related quality of life (HRQoL), McGill Pain Questionnaire (arthritis), and others [[172](#ref-Riley2011)–[174](#ref-StLouis2022)].
* In many situations chronic pain should be managed by a multidisciplinary team where the patient is rehabilitated with the help of a specialized pain management team, physiotherapists, psychologists, doctors of other specialities (e.g., anesthesia, orthopedic surgery, physiatry), social workers, psychologists, in addition to hemophilia doctors and nurses [[175](#ref-Gualtierotti2022)].

### 12.1.2 RECOMMENDATION

* **For PWH with acute or chronic pain, the use of age-appropriate pain assessment tools such as VAS are recommended.**
* **Acute pain due to a joint or muscle bleed should be immediately treated with relevant hemostatic drug in addition to pain medication and other measures such as immobilization, compression to minimize the pain.**
* **Chronic pain should be managed by a multidisciplinary team consisting of specialized pain management teams in addition to the hemophilia comprehensive care centre’s team.**

## 12.2 Analgesics

### 12.2.1 Managing mild to moderate pain

* Mild analgesics are often used in the treatment of both acute and chronic pain. Paracetamol (acetaminophen) is the basic treatment and can if necessary be combined with tramadol or codeine.
* The analgetic effect of codeine is caused by codeine conversion to morphine. However, one should keep in mind that in approximately 10% of the Caucasian population, codeine is without an analgetic effect, due to an inability to convert codeine to morphine.
* Tramadol is a synthetic codeine analogue.
* Common side effects of treatment with codeine, tramadol, and morphine are nausea, vomiting, constipation and drowsiness.
* Codeine should be used with caution, especially in elderly patients because of the risk of cognitive side effects.
* Information about dosing of analgesics is very important for the prevention of toxicity e.g., liver toxicity with paracetamol in patients with chronic hepatitis or HIV.
* Aspirin inhibits platelet aggregation irreversibly and should not be used in the treatment of pain for PWH.
* If the pain is caused by inflammation in a joint, COX-2 inhibitors (celecoxib or etoricoxib) can be considered in selected PWH. COX-2 inhibitors do not inhibit platelet aggregation. However, even COX-2 inhibitors can have serious side effects like COX-1 inhibitors and should be used with caution.
  + One of the most serious side effects is gastroduodenal ulcers.
  + The risk of gastrointestinal ulcers is lower with COX-2 inhibitors compared to COX-1 inhibitors.
  + H2-receptor antagonists or proton pump inhibitors can be used to minimize the risk of ulcers.
  + Both COX-1 and COX-2 inhibitors can have severe gastrointestinal, renal, and cardiovascular (MI, stroke, and other arterial thrombosis) side effects.
* Among the NSAIDs COX-1 inhibitors e.g., ibuprofen has a reversible inhibition on platelet aggregation. COX-1 inhibitors should generally only be used on strong indications and with caution in the treatment of pain in PWH due to the increased risk of bleeding and other serious side effects. If there is a strong indication for the use of COX-1 inhibitors in PWH it is recommended to choose a drug with a short half-life. Ibuprofen has a short half-life, and the risk of side effects (gastrointestinal ulcers and cardiovascular events) is considered low when the daily total dosage is 1,200 mg and below.
* Some patients may benefit from using analgesics with prolonged effects, especially for the treatment of pain at night. Also, transdermal formulas can benefit many patients with chronic pain issues.

### 12.2.2 Managing severe and complex pain

* In the case of severe acute pain, morphine could be necessary to use at the start, but due to the risk of addiction, it should be given for a limited period.
* Patients with severe complex chronic pain should be preferably managed at a multi professional pain clinic.
* It is important to be aware that children often express pain in a different way than adults.
* Before injections, it is common to apply anesthetic cream to the skin of the child to minimize pain.
* In addition to the management of nociceptive pain, patients with chronic pain conditions can also benefit from medications aimed at modifying the pain response, such as serotonin and norepinephrine reuptake inhibitors (SNRI), gabapentinoids or tricyclic antidepressants.
* The non-pharmacologic, complementary management options are an important part of pain treatment. Examples of psychologic methods include meditation, distraction, mindfulness, relaxation techniques and acceptance and commitment therapy (ACT).
* ACT is a cognitive-behavioral therapy commonly used by psychologists and other healthcare professionals working with patients with chronic pain. The aim of the therapy is through mindfulness and acceptance increase valued action in the presence of pain [[176](#ref-Hughes2017)].
* Physical medicine techniques such as the use of cold, heat and electricity (e.g., transcutaneous electrical nerve stimulation (TENS) can also provide relief. Ice must be used with caution as it may interfere with coagulation.
* Physiotherapist also aid in finding pain relief. Methods include home-based exercises, hydrotherapy, manual therapy techniques, laser therapy, orthotics and aids, and advice for modifying physical activity [[177](#ref-McLaughlin2020)].
* Pain in PWHs could be managed as described below [141,142]:

### 12.2.3 RECOMMENDATION

* **Mild pain and/or chronic pain can be managed with paracetamol alone or combined with codeine or tramadol.**

### 12.2.4 RECOMMENDATION

* **Pain and joint inflammation can be managed with COX-2 inhibitors (celecoxib or etoricoxib) or in special circumstances with COX-1 inhibitor ibuprofen.**

### 12.2.5 RECOMMENDATION

* **Acute severe pain can be managed with morphine.**

### 12.2.6 RECOMMENDATION

* **Non-pharmacological methods are a useful complement to pain medications.**

## 12.3 Orthopedic surgery and treatment by the orthopedist

* Treatment by the orthopedic surgeon should always be considered if the pain is a symptom caused by joint damage and conservative management has failed to provide sufficient improvement in pain and function.
* Synovectomy with removal of the synovial membrane can often be used if the patient has inflammation without severe cartilage or bone destruction in the joint.
* If the joint is severely damaged a joint prosthesis is often the best solution to the pain problem.
* In some cases, the physiotherapist or orthopedist can help the patient with orthosis or heightening of shoe heels.

## 12.4 Intraarticular corticosteroid injection in joints with hemophilic arthropathy

* Intraarticular injection of corticosteroid for the treatment of inflammation and pain in joints with arthritis e.g. rheumatoid arthritis is a documented and established treatment modality [[178](#ref-Cheng2012)].
* If the PWH has a joint with inflammation, a corticosteroid injection into the joint can be used. It has been demonstrated in a few studies that intra-articular injection of corticosteroids can reduce pain in hemophilia joints with inflammation [[179](#ref-RodriguezMerchan2018)].
* A prophylactic dose of factor concentrate should be given prior to the injection of corticosteroid unless the patient uses non-factor replacement therapy.
* The intra-articular injection must be given under sterile conditions and if possible, effusions can be drawn from the joint.
* In case of suspicion of infection, the synovial fluid must be sent to further investigation to rule out infection and injection of corticosteroid should not be given. The most serious but also very rare complication of intra-articular corticosteroid is infection.
* The dose of corticosteroid depends on the size of the joint and the degree of inflammation. The dose of corticosteroid could be e.g. triamcinolone hexacetonide (Lederspan®) 10-40 mg or triamcinolone acetonide (Kenalog®) 20-80 mg.
* As it is essential to the effect of the treatment, that the corticosteroid is given into the joint, it is recommended that the injection is given by a physician, trained in giving injections into the joints. If possible, the injection could be given guided by ultrasonography to increase the precision of injection.
* After the injection the patient must avoid loading of the joint for at least 24 hours. When corticosteroid is used in arthritis the effect of the injection stays at least four to six weeks but usually for several months or even longer. Osteoporosis around the joint needs to be managed appropriately.
* Mild side effect is experienced in up to 10% of cases as flushing of the face and increased sweating in minutes to hours after the injection.
* In patients with arthritis, approximately 2% can experience worsening pain lasting the first 24 hours after the injection.
* Although the systemic effects of the corticosteroid injection are minimal, measurements of blood glucose should be done in patients with diabetes mellitus, as the blood glucose in some cases can be elevated in the first days after the injection.

### 12.4.1 RECOMMENDATION

* **Corticosteroid injections can be used in joints with inflammation.**

### 12.4.2 RECOMMENDATION

* **Care must be taken to avoid bleeding and that the treatment is given into the joint.**

### 12.4.3 RECOMMENDATION

* **Systemic effects of single corticosteroid injections are minimal.**

# 

# 13. Physiotherapy

## 13.1 Introduction

* The role of the physiotherapist in the treatment of people with hemophilia (PWH) has changed over the years because of the improvement of the medical treatment, from historically focusing on passive rehabilitation after acute events and limiting the damage of bleeds, to active rehabilitation, prevention, education and maximizing movement potential [[6](#ref-Nilsson1992),[180](#ref-deKleijn2006),[181](#ref-Boccalandro2022)].
* Despite improvements in treatment, there is still a need for physiotherapy for PWH to manage musculoskeletal (MSK) issues and help optimize function and participation. It is essential to monitor the MSK status of PWH, also related to new treatments opportunities [[182](#ref-Lobet2021),[183](#ref-Wells2020)].
* Physiotherapists at the hemophilia treatment center (HTC) have an expert role in supporting primary care physiotherapists in treatment regimens for PWH [[184](#ref-Timmer2021)], which may be particularly needed in the Nordic countries due to the geography of the Nordic region, with centralized hemophilia care, and many patients living far from treatment centres.
* Telehealth and virtual consultation could be a complement to in-person visits to the hemophilia treatment center for PWH living far away. PWH can thus get instructions for exercise, follow-up and support without travelling [[185](#ref-Flannery2020)–[188](#ref-ODonovan2020)].
* Physiotherapy for PWH can be divided in to three categories: Prevention, assessment and treatment/rehabilitation [[189](#ref-Mulder2021)].

### 13.1.1 RECOMMENDATION

* **Physiotherapy should be provided to all PWH to improve function and optimize movement potential and should include monitoring of musculoskeletal status.**

### 13.1.2 RECOMMENDATION

* **Physiotherapists at the HTC should support primary care physiotherapists treating PWH.**

## 13.2 Prevention

* People with more severe forms of hemophilia will receive prophylaxis with coagulation factor concentrates or novel treatment products from an early age, and can and should be physically active to the same extent as children without hemophilia, resulting in normal physical strength and mobility [[190](#ref-Engelbert2008)].
* Low physical activity can result in impaired bone mineralization and reduced bone mineral density in children with hemophilia compared to those without the condition [[191](#ref-TlacuiloParra2008)].
* Moderate intensity of aerobic walking exercise improves bone metabolism and hand grip strength in adult persons with moderate hemophilia A [[192](#ref-AlSharif2014)].
* Good function of muscles around the joints has been shown to prevent joint- and muscle bleeds. It is therefore essential to train muscle strength, endurance, and coordination from an early age [[193](#ref-Gomis2009)].
* Not only PWH, but everybody (both adults and children) should be physically active at moderate to vigorous intensity for 30–60 min every day [[194](#ref-Bull2020)]. The Nordic recommendations for physical activity are the same as those of the World Health Organization (WHO).
* PWH experience the same benefits of exercise as the general population, being physically healthier than if sedentary and enjoying a higher quality of life (QoL) through social inclusion and higher self-esteem [[195](#ref-Runkel2016),[196](#ref-Negrier2013)].
* PWH can also gain physical benefit from increased muscle strength, joint health, balance and flexibility achieved through physiotherapy, physical activity, exercise and sport [[196](#ref-Negrier2013),[197](#ref-Runkel2016a)].
* For PWH, physical activity may also help reduce joint and muscle bleeds via improvements in proprioception, balance, muscle strength, joint mobility, stability, and function [[198](#ref-Wang2016),[199](#ref-Harris2006)].
* Recent summarized research indicates increased physical activity in PWH along with improved medical treatment [[200](#ref-Kennedy2021)].
* The physiotherapist has an important role in informing and supporting PWH and their families about physical activity and sports that are appropriate for PWH [[201](#ref-Heijnen2008)]. The choice of types of physical activities should reflect the PWH’s preferences/interests, bleeding phenotype, physical condition and ability, local contexts, and available resources (including treatment intensity) [[196](#ref-Negrier2013),[202](#ref-Matlary2022),[203](#ref-Martin2020)].
* The physiotherapist can also educate parents how to examine the joint mobility of the youngest children for early detection of joint bleeding.

### 13.2.1 RECOMMENDATION

* **PWH should be regularly physically active as they can experience the same benefits of physical activity and exercise as the general population.**

### 13.2.2 RECOMMENDATION

* **Physical activity may help to reduce muscle and joint bleeds.**

### 13.2.3 RECOMMENDATION

* **PWH should consult a physiotherapist or other musculoskeletal specialist before engaging in sports and physical activities to discuss their appropriateness specific to the individual’s condition and their requirement for physical skills and/or protective gear.**

## 13.3 Assessment

* Assessment instruments that are disease specific for hemophilia have been developed over the past 10 years [[204](#ref-Beeton2006)].
* The physiotherapist should assess joint- and muscle function regularly, e.g. during the annual control at the HTC. This includes joint mobility, muscle strength, pain, joint and muscle contractures, axial changes in the joints, balance, and gait function. Ideally, standardized outcome measures should be used.
* In the case of a suspected bleed, a physiotherapist can help with differential diagnosis between joint bleeding and synovitis together with the physician.
* Ultrasound can aid the assessment for a correct diagnosis [[205](#ref-DiMinno2017)]. When ultrasound imaging is performed and scored by physiotherapists using Hemophilia Early Arthropathy Detection (HEAD-US) [[206](#ref-Alberighi2013)] there is a good overall repeatability of the protocol and this complements the physical examination when screening and monitoring joint health of PWH [[207](#ref-Stephensen2018)]. HEAD-US also correlate well with Hemophilia Joint Health Score (HJHS) in persons with hemophilia [[208](#ref-Maaseide2021)].
* The Hemophilia Joint Health Score (HJHS) was initially developed for children from 4 to 16 years of age [[209](#ref-Hilliard2006)]. It is currently validated and reliability tested for both children and adults (ages 4-18 [[49](#ref-Feldman2011),[209](#ref-Hilliard2006)], ages 14-30 [[210](#ref-Fischer2013a)], ages 18-82 years [[174](#ref-StLouis2022)]).
* It is now frequently used for the evaluation of joints in children and young adults, as well as for older populations [[209](#ref-Hilliard2006),[210](#ref-Fischer2013a)]. For adults and elderly patients, the HJHS needs to be complemented with assessment of possible age-related conditions for example problems with the hip and shoulder joints.
* Several other evaluation instruments may also be relevant to use is the functional assessment of PWH.
  + The visual analog scale (VAS) can be used to rate the pain experience in daily activities or at acute trauma/bleeding [[211](#ref-Callahan1987)].
  + The Hemophilia Activities List (HAL) can be used to get the patient’s own perception of their ability in terms of activity (a person carrying out a task or action) and participation (a person’s involvement in a life situation) [[212](#ref-vanGenderen2006)].
  + Furthermore, the Functional Independence Score in Haemophilia (FISH), which is a performance‐based tool, can be used to assess an individual’s functional ability. Eight activities of daily living are assessed: eating, grooming, dressing, chair transfer, squatting, walking, step climbing, and running [[213](#ref-Poonnoose2005)].
  + Finally, the generic self-administered questionnaire, Health Assessment Questionnaire Disability Index (HAQ-DI) could be used as a self-reported functional status when FISH or HAL is not useful [[214](#ref-DelaCorteRodriguez2017)].
* Based on clinical examination and other assessments, the physiotherapist can recommend relevant steps that can benefit PWH, such as rehabilitation, contact to an occupational therapist, and assistive devices for activities of daily living (ADL).

### 13.3.1 RECOMMENDATION

* **Musculoskeletal** **status in PWH should be monitored on a regular basis, and at least annually.**

### 13.3.2 RECOMMENDATION

* **MSK monitoring should be carried out by a physiotherapist with knowledge and experience in hemophilia.**

### 13.3.3 RECOMMENDATION

* **MSK assessment should include standardized outcome measures/protocols/tools.**

## 13.4 Intervention (treatment/rehabilitation)

* Muscle- and joint bleeds cause pain and swelling, and usually reduced range of movement and function.
* Repeated joint bleeds cause synovitis, cartilage damage and skeletal bone irregularities and osteophytes, also known as hemophilic arthropathy.
* The purpose of rehabilitation after an acute bleeding in the joint or muscle, or in hemophilic arthropathy, is to limit damage, reduce pain and restore or improve function.
* Active exercise under the guidance of a physiotherapist in combination with intensive treatment with factor concentrate/novel treatment products can improve function. The results are better the sooner physiotherapy begins [[215](#ref-Gurcay2007)].
* In the acute phase the early management can be summarized as “PRICE”, meaning Protection and joint Rest, relive acute pain with Ice and prevent and treat swelling with Compression and Elevation [[216](#ref-Hanley2017)].
* After the acute phase, the physiotherapist can plan and help execute an exercise program to speed recovery and restore lost function. Several studies show that mobility and strength exercise leads to faster normalization of the function and also significantly reduces the risk of permanent disability [[193](#ref-Gomis2009),[217](#ref-GuodemarPerez2018)].
* Treatment may include different types of mobility exercises (active, active unloaded, passive), posture instructions, careful manual therapy modalities for increased mobility and pain relief purposes, strength and endurance exercise, coordination training, etc.
* Aquatic exercise can be used for different types of intervention such as mobility, aerobic capacity and strength [[218](#ref-Neelapala2019)].
* Exercise in warm basin can also be useful as pain relief, as well as the use of TENS, heat and cool pack [[201](#ref-Heijnen2008),[216](#ref-Hanley2017),[219](#ref-Young2013)].
* There is, however, limited evidence for the use of physiotherapy intervention for pain relief in PWH [[177](#ref-McLaughlin2020)]. There is limited high-quality evidence for exercise in persons with hemophilia due to a small numbers of randomized controlled trials, but no adverse effects are reported in the different exercise intervention studies published [[220](#ref-Strike2016)–[224](#ref-Elshennawy2023)].
* Patients undergoing orthopedic surgery, for example synovectomy or different types of joint replacement should receive physiotherapy exercise both before and after surgery [[180](#ref-deKleijn2006),[225](#ref-Escobar2018)].
* Before surgery it is important to train muscle strength around the joints and maintain the mobility that exists. After surgery the patient trains their mobility and strength according to the relevant protocol at the orthopedic clinic for the current operation. If the hemophilic arthropathy has caused malalignment, stiffness and pain, the physiotherapist may prescribe or recommend orthotics and orthopedic shoes together with the attending orthopedic surgeon depending on the rules in different countries [[226](#ref-Heijnen2005)]. The physiotherapist also tests out walking aids and recommend other appliance needed in daily life.

### 13.4.1 RECOMMENDATION

* **A suspected bleed should immediately be treated according to PRICE.**

### 13.4.2 RECOMMENDATION

* **Mobility and strength exercise should be provided after muscle- and joint bleeds, as this leads to faster normalization of the function and significantly reduces the risk of permanent disability.**

### 13.4.3 RECOMMENDATION

* **PWH undergoing orthopedic surgery, for example synovectomy or different types of joint replacement, should receive physiotherapy, including adapted exercise both before and after surgery.**

# 

# 14. Hemophilia in women and girls and hemophilia carriers

## 14.1 Introduction

* The hemophilia nomenclature distinguishes five clinically relevant categories of hemophilia in women/girls: women/girls with mild (FVIII/FIX >5% to <40%), moderate (FVIII/FIX 1-5%) or severe (FVIII/FIX <1%) hemophilia and symptomatic and asymptomatic hemophilia carriers (FVIII/FIX ≥40%) with and without a bleeding phenotype, respectively [[227](#ref-Galen2021)].
* The term hemophilia carrier is used in discussions relating to genetic counselling, including obligatory and potential carriers, and hemophilia or symptomatic carrier when referring to bleeding phenotype.
* Obligate carriers include any daughter of a father with hemophilia, any mother of a child with hemophilia who also have at least one family member with hemophilia or who is a known carrier of hemophilia and any mother of two or more children with hemophilia.
* Potential carriers include any daughter, sister, mother, maternal grandmother, aunt, niece or female cousin of a carrier of hemophilia and any mother of a child with hemophilia and without family history of hemophilia.
* The factor levels in carriers are expected to be about 50% of the levels of non-carriers, but due to X-chromosome inactivation, the factor levels may vary from very low to the upper limit of normal values [[228](#ref-Plug2006)].

### 14.1.1 RECOMMENDATION

* **Hemophilia carriers should be registered at a hemophilia treatment centre.**

### 14.1.2 RECOMMENDATION

* **Obligate and potential hemophilia carriers should have their FVIII/FIX levels measured to establish their baseline levels prior to invasive procedures and childbirth or if abnormal bleeding symptoms.**

## 14.2 Bleeding symptoms and treatment

* The most common manifestations among symptomatic carriers and women with hemophilia includes heavy menstrual bleeding (HMB), post-partum haemorrhage, and perimenopausal bleeding.
* In addition, symptomatic carriers and women with hemophilia are at risk of being affected by bleeding following trauma or medical interventions (e.g., dental extractions or surgery) [[228](#ref-Plug2006)].
* Symptomatic carriers and women with hemophilia should have a treatment plan prior to menarche [[229](#ref-DowlutMcElroy2015)].
* Excessive menstrual bleedings may appear with the first or any following menstrual bleeding during the period of adolescence.
* Hormonal therapy can be useful in managing HMB [[231](#ref-Pai2013)] and may be considered by a gynaecologist, with knowledge of bleeding disorders, working in collaboration with the HTC.
* Treatment options include oral or transdermal formulations containing oestrogen/progesterone/progestin and levonorgestrel intrauterine device (IUD).
* Haemostatic treatment options for the management of HMB include tranexamic acid, DDAVP and clotting factor replacements [[232](#ref-Chaudhury2020)].
* A screening for iron deficiency and anaemia should be performed at regular check-ups. If iron deficiency anaemia is diagnosed and substituted, a reassessment of current HMB treatment should be performed.
* For treatment options during trauma and surgery please see chapter [Surgery in hemophilia](file:///Users/christq/hemophilia24/_book/07Surgery.qmd) and chapter [Treatment of bleeds](file:///Users/christq/hemophilia24/_book/09TreatmentBleeds.qmd).

## 14.3 Genetic counselling and testing

* Genetic counselling is an essential component of comprehensive care for individuals and families with hemophilia.
* Genetic counselling help both obligate and potential carriers of hemophilia to understand their bleeding risk and genetic risk [[233](#ref-Alabek2015)].
* Genetic testing should be offered to potential carriers when mature enough to understand the consequences of diagnoses and to give consent [[234](#ref-Dunn2008)].
* It’s important that the girl as well as her family understand that a normal FVIII/FIX level does not exclude carriership.
* Before planning a family, the carrier and her partner should be offered contact with a genetic counsellor and an educational visit at the HTC.
* Counselling should include education regarding hemophilia and assessment of hemophilia inheritance risks. Prenatal genetic testing options and relevant reproduction options should be reviewed.

## 14.4 Psychosocial support

* Psychosocial assessment should be integrated in the comprehensive care and the hemophilia nurse have an important role in this supportive work.
* Professional psychosocial counselling may be required, not only during the fertile period, but during a carrier’s different stages of life.

### 14.4.1 RECOMMENDATION

* **Carriers of hemophilia should be offered counselling that includes reproductive implications and choices.**

## 14.5 Prenatal diagnosis

* Evaluation of carrier status should be performed before pregnancy. Evaluation should include measurement of factor levels in the non-pregnant state as well as genetic testing, as normal factor levels do not preclude carrier status.
* Preconception consultation at the hemophilia treatment centre or by a genetic counselor should be offered to all possible carriers and their partners. Counselling should include education regarding hemophilia, assessment of hemophilia inheritance risks and review of the prenatal testing options available and the associated risks of each method.
* Methods include preimplantation genetic diagnosis (PGD), invasive prenatal diagnosis (chorionic villus sampling (CVS), amniocentesis, and cordocentesis), and non-invasive determination of free foetal DNA (ffDNA) in the maternal circulation and ultrasound detection of foetal sex [[235](#ref-Chi2006),[236](#ref-Street2008)].
* PGD requires in-vitro fertilization and is an option for couples who would not consider giving birth to an affected infant or termination of an established pregnancy, and for those with concurrent infertility [[30](#ref-Lavery2009)].
* CVS is the most reliable method for prenatal diagnosis of hemophilia and is performed at 11-13 weeks of gestation. Later in pregnancy, an amniotic fluid sample can be used as DNA source for prenatal diagnosis. Both procedures are associated with a risk of miscarriage at approximately 1% [[237](#ref-Mujezinovic2007)].
* All invasive procedures require a factor level ≥ 50% and factor substitution should be provided as needed.

### 14.5.1 RECOMMENDATION

* **Possible carriers of hemophilia should be offered preconception counselling that includes reproductive implications and choices.**

### 14.5.2 RECOMMENDATION

* **Testing should include assessment of factor level and genetic testing.**

## 14.6 Pregnancy management and delivery

* Pregnancy and delivery should be managed by a multidisciplinary team of specialists, including a haematologist, an obstetrician/gynecologist and an anaesthesiologist.
* Female carriers of hemophilia A or B do not have increased risk of miscarriage [[230](#ref-Byams2011),[231](#ref-Pai2013),[238](#ref-Rizza1975)].
* Female carriers may have low factor levels that increases their risk of bleeding during pregnancy and in the postpartum period. Factor VIII levels rise during pregnancy but may not reach sufficient levels to prevent bleeding complications. FIX levels do not increase during pregnancy [[239](#ref-Chi2007)].
* Factor levels should be assessed in the third trimester around gestational week 32-34 to evaluate the need for factor replacement therapy during delivery and in the post-partum period.
* A clear plan for delivery should be made by the multidisciplinary team, shared with the patient, and documented in the medical record.
* Factor replacement therapy should be provided to carriers with subnormal factor levels in the third trimester. If required, factor replacement therapy should be administered to target levels of 100% for labour and delivery and maintained ≥ 50% for at least 3-4 days after vaginal delivery and at least 5-7 days after caesarean delivery [[239](#ref-Chi2007)–[241](#ref-James2014)].
* Factor levels ≥ 50% is required for insertion and removal of an epidural catheter and for spinal anesthesia [[242](#ref-Chi2009)].
* Tranexamic acid may be used as supplement to factor replacement therapy or as stand-alone treatment for carriers with factor levels within the normal range.
* Decisions regarding anaesthesia and method of delivery should be made by the multidisciplinary team and shared decision making with the patient.
* Vaginal delivery of an infant with severe hemophilia is not recommended against as the risk of intracranial hemorrhage is not significantly increased as compared to caesarean delivery [[243](#ref-Andersson2019)]. However, the obstetrician should carefully discuss with the carrier patient the maternal and foetal risks of vaginal delivery versus a planned caesarean delivery.
* Delivery of infants known or suspected to have hemophilia must be atraumatic regardless of route of delivery to decrease the risk of bleeding complications [[239](#ref-Chi2007)].
* Forceps and vacuum extraction vaginal delivery as well as invasive procedures to the foetus such as foetal blood sampling and internal foetal scalp electrodes should be avoided [[244](#ref-Kletzel1989)].
* Caesarean section should be considered early when vaginal labour does not proceed as expected. These instructions should be documented as part of the delivery plan in the patient’s medical record.

### 14.6.1 RECOMMENDATION

* **Pregnant carriers of hemophilia should have their factor VIII/IX levels measured in the third trimester (GA 32-34) in order to plan for factor replacement therapy during delivery and post-partum.**

### 14.6.2 RECOMMENDATION

* **Factor levels should be maintained ≥ 50% during delivery and post-partum.**

### 14.6.3 RECOMMENDATION

* **A delivery plan should be made by the multidisciplinary team (haematologist, obstetrician, anaesthesiologist) and shared decision making with the patient.**

### 14.6.4 RECOMMENDATION

* **Delivery should be atraumatic, and use of forceps, vacuum extraction as well as invasive procedures to the foetus avoided.**

### 14.6.5 Post-partum care

* Factor VIII levels in carriers return to baseline levels 7-10 days after birth [[245](#ref-Mauser2008),[246](#ref-Girgis2018)], but sometimes earlier and increases the risk of secondary post-partum bleeding.
* Bleeding may occur up to 35 days post-partum and should be monitored and treated accordingly with factor replacement therapy and tranexamic acid [[247](#ref-Sentilhes2015)]. DDAVP can occasionally be used in carriers of hemophilia A to improve haemostasis post-partum but should be used with caution in breast-feeding women.
* Haemoglobin, factor levels and bleeding should be monitored as needed 1-2 months post-partum.

### 14.6.6 RECOMMENDATION

* **Secondary post-partum bleeding may occur when factor VIII levels return to baseline.**

### 14.6.7 RECOMMENDATION

* **Bleeding, haemoglobin and factor VIII should be monitored and treated as needed in the entire post-partum period.**

### 14.6.8 New-born testing

* Cord blood should be collected from all male infants of carriers of hemophilia to assess clotting factor levels for early identification and management of hemophilia.
* Of note, while it usually is possible to diagnose severe and moderate hemophilia A at birth and often possible to diagnose severe and moderate hemophilia B at birth, detection of mild hemophilia A and B may require repeated screening at 6 months of age.
* Vitamin K should be administered orally to neonates with low factor levels [[248](#ref-Chalmers2011)].

### 14.6.9 RECOMMENDATION

* **Cord blood sampling and diagnostic testing is recommended for all male new-borns of hemophilia carriers.**

### 14.6.10 RECOMMENDATION

* **Vitamin K should be administered orally.**

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# 15. The role of the hemophilia nurse

## 15.1 Introduction

* The role of the hemophilia nurse may vary between the Nordic hemophilia centers; however, the foundation of the role is care, treatment, education, coordination, support~~,~~ and development of care.
* The comprehensive care for persons with hemophilia (PWH) and other inherited bleeding disorders is complex and requires a multidisciplinary team. The hemophilia nurse plays a key role in the comprehensive care for PWH.
* The nurse coordinates the care, educates PWH/caregivers in illness management, and has an important role in supporting the PWH and their families. The nurse is the first point of contact for PWH and their families [[249](#ref-Srivastava2020)–[251](#ref-Colvin2008)].
* The nurse has knowledge concerning the challenges in different life stages such as: Childhood, adolescence, early adulthood, and old age.
* The life stages affect and influences the treatment and management of hemophilia in different aspects, and the nurse adapts the care accordingly. Overall, person-centered care with shared decision making is crucial for the success of achieving self-managing and self-reliant PWH [[252](#ref-MyrinWestesson2018)–[256](#ref-Lindvall2013)].
* The role of the hemophilia nurse has changed during the last decade. Nurses are Increasingly involved in and conducts research in nursing care which leads to more knowledge about the specific caring process securing an evidence-based approach to care.
* The rapidly changing scene of hemophilia treatment with extended half-life products, gene therapy and non-factor treatment is challenging and changing the hemophilia nurses’ role and daily work.

## 15.2 Hemophilia nurse specific tasks

### 15.2.1 Care and treatment

* The hemophilia nurse administrates factor concentrates, non-factor treatments, organize and performs blood sampling for pharmacokinetic evaluation.
* The hemophilia nurse is responsible for initial clinical assessment, and for certifying that treatment is administered promptly in critical situations and likewise for managing continuous care and follow-up after bleeds [[250](#ref-Pollard2020)].
* The nurse recognizes the female PWH and is aware of the female-specific bleeding symptoms and the unique challenges this implies in life [[250](#ref-Pollard2020),[253](#ref-Harrington2015),[257](#ref-Galen2021a)].
* The hemophilia nurse has knowledge about hemophilia and complications that may occur from treatment or the illness itself.
* The nurse must be aware of problems associated with inhibitors and the necessary extensive treatment.
* The nurse makes home visits when needed and acts as a consultant to fellow nurse colleagues when PWH are hospitalized.

### 15.2.2 Education

* The hemophilia nurse educates PWH, caregivers and other family members about hemophilia.
* The nurse educates the PWH and caregivers in home treatment and other aspects of the illness. She/he encourages PWH and caregivers to increase their knowledge about the illness to enable independent home treatment and illness management. He/she provides information and education about the illness to preschool, school, nursing homes and to other health care providers.
* The hemophilia nurse has knowledge of the inherited aspects of the illness and can perform genetic counseling and support to carriers.
* The nurse educates the PWH/caregivers in how to manage and handle the advanced ITI treatment in a central venous access device [[250](#ref-Pollard2020),[252](#ref-MyrinWestesson2018),[256](#ref-Lindvall2013)] and educates PWH and their families about non-factor treatment, when needed.
* Hemophilia nurses will play a key role in the delivery of gene therapy for hemophilia giving information, counselling, and support throughout the process. This is as important for all PWH, eligible or ineligible for gene therapy [[258](#ref-Aradom2021)].

### 15.2.3 Coordination

* The hemophilia nurse has, when needed, close contact with local health care professionals and the PWHs’ primary care contacts.
* The nurse functions in a consulting role to colleague nurses when PWH are hospitalized. The nurse guides and educates other health care professionals in- and out of clinic.
* The coordination and counseling of PWH, caregivers, preschool, schools, nursing homes and other health care professionals are carried out face to face as well as by telemedicine.
* The nurse coordinates and facilitates the comprehensive team meetings and collaborates within the multidisciplinary team [[249](#ref-Srivastava2020),[250](#ref-Pollard2020),[252](#ref-MyrinWestesson2018),[253](#ref-Harrington2015)].
* The nurse keeps and updates hemophilia registries to enable quality of care and evaluate treatment.

### 15.2.4 Support

* The nurse plays an important role as a supporter of newly diagnosed children and their caregivers. She/he helps the family to adjust to the new situation with the illness and emphasizes the healthy aspects of the child [[250](#ref-Pollard2020),[252](#ref-MyrinWestesson2018),[253](#ref-Harrington2015)].
* The nurse recognizes and articulates the needs of the child, caregivers, and other family members to the hemophilia team.
* The nurse plays an important role in assisting young PWH and their families in the transition process from childhood and dependency, towards adolescence and self-management through individualized support and continued education [[252](#ref-MyrinWestesson2018),[253](#ref-Harrington2015),[256](#ref-Lindvall2013)–[260](#ref-Schrijvers2016)].
* The hemophilia nurse is a resource, that primary and secondary caregivers can contact when they need guidance regarding hemophilia in daily life [[250](#ref-Pollard2020),[252](#ref-MyrinWestesson2018),[253](#ref-Harrington2015)].
* The supporting function of the nurse is vital for the aging PWH and likewise for families affected by inhibitors [[252](#ref-MyrinWestesson2018)–[255](#ref-Petrini2007),[261](#ref-DeKoven2014a)].

### 15.2.5 Development of care

* Hemophilia nurses are involved in research to enable and enhance quality of care and evaluate treatment for PWH and their families.
* The involvement in research may vary from participating in clinical trials to conducting independent nurse lead research [[250](#ref-Pollard2020),[253](#ref-Harrington2015)].
* Nursing research in the comprehensive care of PWH is important to develope knowledge about the illness.
* The nurse participates in developing projects concerning the care of PWH, both in the hemophilia treatment center, nationally, and when needed internationally.

### 15.2.6 RECOMMENDATION

* **The Nordic Hemophilia Guidelines recommend that the nurse has hemophilia specific knowledge. This includes knowledge about both the nursing and medical aspects of hemophilia to enable evidence-based care.**

### 15.2.7 RECOMMENDATION

* **The NHG recommend that the hemophilia nurse works according to the principles of person-centered care.**

### 15.2.8 RECOMMENDATION

* **The NHG recommend that the hemophilia nurse is involved in the development of comprehensive care for PWH.**

### 15.2.9 RECOMMENDATION

* **The NHG recommend that the hemophilia nurse participate in scientific congresses and meetings, both nationally and internationally, to enable best practice.**

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# 16. Dental care

## 16.1 Introduction

* Regular check up at the dentist is important to prevent damage to the teeth and the mucosa of the mouth and thereby prevent bleeding from the gums and other oral diseases and the need for operations [[262](#ref-Zanon2000)–[265](#ref-Lee2005)].
* The staff at the hemophilia center can provide information to the patient and his/her dentist about which kind of hemostatic treatment could be given and which kind of treatment should be given at the department of oral and maxillofacial surgery affiliated with the hemophilia center.
* Most patients, both adults and children can have regular checkups at their own dentist for caries and cleaning of the teeth. All treatments which do not cause bleeding, such as treatment of caries, root canal treatment, tooth prosthesis and orthodontic tooth regulation can be performed at the patient’s own local dentist.
* Inhibitor patients should be treated in close collaboration between the dental clinic and the hemophilia center since they have special hemostatic treatment and increased risk of bleeding.
* Patients with inflammation in the gums often have problem with bleeding and should be offered treatment by dental hygienist.
* Surgical operations should always be performed at an oral and maxillofacial surgical department connected with the hemophilia center as this kind of procedure requires experience in treatment of PWHs and collaboration regarding the need of medication.
* Tooth extractions, implantations and jaw surgery should be performed at the department of oral maxillofacial surgery and in some cases prophylaxis with antibiotics is needed.

### 16.1.1 RECOMMENDATION

* **Close collaboration between the dentist, oral maxillofacial surgeon and the multidisciplinary team at the hemophilia center is of great importance.**

## 16.2 Hemostatic Treatment

* Prophylactic treatment with factor concentrates may be necessary for some patients depending on the severity of hemophilia and the character of the dental procedure.
* For patients on prophylactic treatment with factor concentrates, the dental procedure could be planned on one of the days when the patient receives prophylactic treatment with factor concentrate.
* Tooth extraction can often be managed by a single dose of factor concentrate combined with tranexamic acid tablets and mouth wash for 7 days. Compression of the wound with swaps containing tranexamic acid and topical hemostatics like fibrin glue can be useful. After tooth extraction cold liquid food is recommended for one to two days.
* Dental procedures on patients who are on non-factor replacement therapies like emicizumab could be performed with or without additional factor concentrates and/or by-pass agents (inhibitor patients) depending on the severity of the procedure. Tranexamic acid should be used as complementary treatment.
* In more advanced jaw or oral surgery repeated doses of factor concentrates might be necessary for hemostasis.
* Desmopressin (Octostim®) can be used in patients with mild hemophilia A who have an adequate rise in factor VIII. Desmopressin should be administered one hour before dental procedure regardless of route of administration. The dosage for subcutaneous and iv administration is 0.3 μg/kg bodyweight.
* Besides the treatment with factor concentrates, tranexamic acid is very useful in dental surgery as oral suspension of tranexamic acid 5% and/or as tablets and sometimes in combination with desmopressin. Mouthwash with 10 mL 5% oral suspension of tranexamic acid 4 times a day is an efficient adjuvant treatment after dental surgery or minor dental procedures for adul After mouthwash the patient should avoid eating or drinking for 30 minutes. Suspension of tranexamic acid for mouthwash is in some places produced by the hospital pharmacy. Suspension of tranexamic acid could be made by mixing one tablet containing 500 mg tranexamic acid and 10 mL lukewarm water or one soluble tablet containing one gram tranexamic acid in 20 mL lukewarm water. Tablets can also be chewed and the mouth can then be rinsed with a small amount of water keeping that for a couple of minutes in the mouth and then spit the liquid out.
* Treatment with tranexamic acid tablets is started before dental treatment in the dosage up to 15-25 mg/kg 3-4 times a day, as repeated dosing will raise the tissue concentration of tranexamic acid. Treatment with tranexamic acid should continue until wound healing or in the case of tooth extraction most often for seven days. Wounds can be treated with local hemostatic agents as fibrin glue and suturing.
* Eruption or exfoliation of teeth in children can be treated with tranexamic acid. Extraction of an exfoliating tooth might be necessary if there is continuous bleeding. Depending on the severity of hemophilia the following medication can be used alone or in combination:
  + Tranexamic acid tablets 15-25 mg/kg 3-4 times daily.
  + Tranexamic acid mouthwash 10 mL 5% suspension 4 times daily.
  + Desmopressin in mild hemophilia A.
  + Factor concentrates and/or by-pass agents for inhibitor patients when needed.
  + Local hemostatic agents.

### 16.2.1 RECOMMENDATION

* **The hemostatic treatment for dental procedures should be planned carefully in the MDT team and in close collaboration with the dentist or oral surgeon.**

### 16.2.2 RECOMMENDATION

* **For patients on prophylaxis regimen with factor concentrates we recommend to perform the dental procedure on the day of ordinary prophylactic treatment.**

### 16.2.3 RECOMMENDATION

* **Patients on prophylaxis regimen with non-factor replacement therapies might need additional treatment with factor concentrates or by-passing agents prior to dental procedure. However in most cases with minor dental procedures no additional treatment is needed except for tranexamic acid.**

### 16.2.4 RECOMMENDATION

* **We recommend use of tranexamic acid po or for topical use as additional treatment to the patient’s ordinary hemostatic treatment.**

### 16.2.5 RECOMMENDATION

* **Use of local hemostatics by dentist or oral surgeon are recommended.**

## 16.3 Anesthesia

* Anesthetic injections in the bottom of the mouth and mandibular injection (intramuscular) should be avoided unless prophylactic treatment to increase the level of the missing coagulation factor is given.
* Intra-ligamental injection or infiltration-anesthesia can be used without treatment with factor concentrate. Local anesthetics with or without adrenaline can be used.

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