

Nordic Hemophilia Guidelines

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History of hemophilia in the Nordic countries

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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 patient with hemophilia (PWH) receiving some form of replacement therapy has increased steadily [1]. 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 factor replacement therapy.

A plasma protein fraction correcting coagulation in hemophilia blood was first described in 1937 but only later termed coagulation factor VIII [2]. 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 also 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]. 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. 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 (antihemophilic factor), 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].

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.

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 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].

Prophylactic factor replacement therapy has led to a dramatic improvement in the orthopedic outcome of PWHs in Sweden and the Nordic countries [6]. 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]. Data from Malmö has shown that not only the joint score but, importantly, the overall quality of life of PWHs treated with prophylaxis in Malmö has close to normalized, in particular in those patients who have been treated with primary and continuing prophylactic therapy [8].

Currently, all Nordic countries practice primary prophylaxis in severe hemophilia using preferably recombinant products.

Organisation of hemophilia care

Revision by: Riitta Lassila (Helsinki)

Since the early days of the treatment of hemophilia and other bleeding disorders the aim of the management has been to transform the severe disease form to a moderate, and currently to a mild one. The expert care, including regular replacement therapy or prophylaxis to avoid unnecessary bleeding complications, is best tailored, overseen and followed-up by the comprehensive care centers (CCC). 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 CCC (EHCCC) organizes the lifetime services provided by different disciplines around the patient's medical needs (www.eahad.org). On call services at necessity secures the expert management during emergency; severe illnesses, major trauma and surgical interventions. Provision of early diagnosis, pediatric and family care, through the adolescent years and transition clinics, genetic counseling, including attention to carrier and obstetric issues (see chapter "Carriers of hemophilia"), leads to the optimal comprehensive management to all patients and families with this inherited diseases. The prospective patient registers nationally and the safety surveillance at the European level by EUHASS (European Haemophilia and Allied Disorders Safety Surveillance) are of major importance to gather important outcome and safety data on most of the known bleeding disorders.

In the future, medical challenges among the ageing hemophilia population will call upon new bleeding disorder-specific approaches in the multidisciplinary management of co-morbidities, such as cancer and cardiovascular disease [9]. In Europe the national responsibility is to organize the centralized care of rare diseases overall, and the case of hemophilia provides a benchmark, as this inherited disease has organization of care and treatment options. The local policies, support from the authorities, national bodies and patient organizations should be engaged to the above aims. The EUHANET project has a EU- and pharmaceutical industry -funded has harmonized hemophilia care across Europe (www.euhanet.org).

The historical role from the first injection of a FVIII concentrate given in Sweden to the developed modern care has paved the way for the hemophilia treatment worldwide [6]. The fundamentals rely on the close interaction between the laboratory and

clinics. This interaction establishes the diagnosis, provides opportunities to tailor prophylaxis, treatment of bleeds and management of major surgery with proper dosing of coagulation factor and appropriate follow-up. Also, the diagnosis of the significant complications of hemophilia, i.e. inhibitors and infections, are based on laboratory medicine. In fact, the laboratory services are to be arranged to cover emergency services by the EUHANET criteria (Table 1), which match with the current practices in our Nordic centers. Under the current economical constraints the center leaders and practical staff should establish the health economical guidance, to maintain and strengthen the discipline locally in front of the regulators.

The two EUHANET center categories include European Hemophilia Treatment Centers (EHTC) and EHCCC. Since our Nordic populations are concentrated in the large cities, networking activities are needed to provide access to care. This Nordic Hemophilia council platform presents uniform recommendations for the diagnosis and management of coagulation disorders (www.nordichemophilia.org). The Nordic cooperation has been ongoing since decades and was formalized in 1999 as the Council. The Council provides guideline documents, organizes annual meetings and forms working groups to address topical issues.

Multidisciplinary activities

According to the recommendations of World Federation of Hemophilia, EAHAD and EUHANET, multidisciplinary activities should be readily available for patients with hemophilia [10,11]. These CCC activities have been shown not only to reduce mortality but decrease morbidity and days of absence from school and work [11]. The patients need consultation line to the Center in any practical daily life and acute problems. Algorithms for emergency care aim at securing immediate management to avoid complications and increased treatment costs due to delayed replacement therapy. 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.

Scandinavian centers have actively conducted and participated to hemophilia studies, including issues of inhibitor development and novel therapies.

Registries

Surveillance of treatment safety and health economics is of utmost importance in hemophilia. The traditional inhibitor frequency may alter, new concentrates with their short pre-registration follow-up enter the market and new viral entities may appear, demanding continued surveillance. The Nordic CCCs have reported to the prospective EUHASS, which monitors mortality and the main health hazards including incidence of inhibitors, infections and thrombotic and any unexpected complications associated with treatment of hemophilia and allied disorders. The national register capturing should be developed uniformly to enable comparison of the treatment across centers and entering to clinical studies according to the daily routines to ease the patient recruitment [12].

Outcome analysis, QoL and health economy

The outcome evaluation of the patient should occur based on an established protocol including a functional self-assessment and objective performance, and the status of the joints should be evaluated and data collected to a register for comparisons. The basic SF-36/EQ5 quality of life (QoL) assessment tool or other QoL methods should be implemented to the patient management as an objective tool to evaluate the impact of the replacement therapy.

The regular prophylaxis is 4-8-fold more expensive than on demand mode of treatment, but good QoL is within reach if the prophylaxis is well tailored.. The treaters should raise active awareness of the costs of the treatment and look for the most cost-efficient individual solutions. Active individualization of the therapy should be based on clinical and pharmacokinetic (PK) evaluation (WAPPSHemo recommended as the global population based-PK) as the standard of care. 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.

Table 1: EUHANET criteria [13] for the center status of EHCCC and EHTC

-
- * Delivery of hemophilia care
 - * Standard and general requirements
 - * General policy and objectives, policies and procedures
 - * Record and data collection
 - * Organization, personnel appraisal and continuing education
 - * Supply and management of therapeutic products, reagents and medical devices
 - * Quality planning, evaluation and improvement
 - * Participation in registries related to inherited and acquired bleeding disorders
 - * Participation in clinical research
 - * Awareness, information and education of patients and their families
 - * Diagnosis of hemophilia and other related bleeding disorders and all forms of acquired hemophilia
 - * Therapy of hemophilia and other related bleeding disorders and all forms of acquired hemophilia
 - * Treatment program, prophylaxis, home treatment plan
 - * Treatment of acute bleeds and prevention, emergencies, treatment outside normal working hours
 - * Elective surgery
 - * Treatment of patients with inhibitors, including immune tolerance
 - * Treatment of patients with chronic viral infections
 - * Treatment of patients with acquired hemophilia and acquired vWD
 - * Periodic clinical and multidisciplinary review
 - * Genetic services
 - * Outcome indicators
 - * Advisory service
 - * Network of clinical and specialized services in conjunction with the hemophilia team
-

Laboratory diagnosis

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Recommendations

- The global test APTT will usually be prolonged and can be used as screening test in haemophilia A and B. The factor sensitivity for different APTT-reagents varies.
- Factor VIII:C and IX:C, functional activity assays can be measured with either one-stage clot-based (OSA) or chromogenic method (CSA). Assay discrepancies can be caused by different mutations but also analytical factors. OSAs are generally more prone to interferences.
- Nijmegen-Bethesda assay is the recommended method for neutralizing FVIII or FIX antibodies. It is most reliable in patients without measurable factor activity (ie severe haemophilia).
- Discrepant results between OSA and CSA (difference of 20-30%) exists and are generally accepted when postinfusion levels of rFVIII or rFIX products are monitored.
- For more than one modified EHL-product, a difference larger than 30% has been obtained between different OSAs or between OSA and CSAs.
- For diagnostic and monitoring purposes, it is therefore of importance that the laboratory has access to more than one method for FVIII:C and FIX:C, respectively. Preferably one CSA and one OSA method.

Pre-analytical aspects of hemophilia testing

The pre-analytical phase is often equal with the time from the blood collection to the point when the sample is analyzed in the laboratory. Errors at this phase are often explained by incorrect specimen collection, handling, transportation or storage. Important aspects are also the blood sampling technique. Especially: Underfilling of tubes or presence of clots due to incorrect mixing, might 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. 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 having the coagulation system activated to such an extent that the results of screening and specific factor assays can lead to mismanagement of the patient. This is particularly true for hemophilia testing as FVIII is one of the most labile coagulation factors and is degraded with time *in vitro*.

There are published guidelines/recommendations, how to assure sample integrity during the pre-analytical phase [14,15].

For plasma-based coagulation assays the recommendation is:

- Direct venipuncture: Ensure atraumatic phlebotomy with minimal tourniquet use.
- Collection tube and order of draw: 3.2 % (109 mmol/L sodium citrate, light blue stopper) first or only after a non-additive tube for screening and specific coagulation factor analyses.
- Fill tube correctly to the mark (line).
- Adequately and thoroughly mix with anticoagulant (reverse tube immediately 5-10 times).
- Transport the whole-blood promptly at room temperature.

- Centrifuge within 1 hour of phlebotomy to obtain platelet poor plasma ($<10 \times 10^9/L$).
- If testing can not be performed within four hours, the plasma should be transferred by pipetting to another tube and frozen at -70°C for later analysis.

Screening for hemophilia

Coagulation screening assays, i.e. activated partial thromboplastin time (APTT) and prothrombin time (PT), 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 normal limits. Furthermore, in congenital hemophilia the APTT will be corrected when patient plasma is mixed 1:1 with normal plasma [16]. If mixing does not correct the prolongation it may indicate the presence of an inhibitor (against a coagulation factor or lupus anticoagulant) or other anticoagulant present in the plasma. There are several commercially available APTT reagents that vary in their sensitivity for coagulation factor deficiencies. Some reagents are relatively insensitive to lupus anticoagulant and these may be advantageous. To be accepted for factor-deficiency screening, it is recommended that the APTT reagent in use should give a prolonged clotting time at a factor activity of $\leq 30\%$ [16]. It is also important to understand that the APTT is a global plasma assay that depends on the sum effect of 10 different coagulation factors and low FVIII or FIX levels, compatible with mild hemophilia A or B, may be masked by increases of one or several of the other factors during certain conditions such as an acute phase reaction, resulting in a normal APTT. Thus, it is important that the treating physicians are familiar with the local screening methodologies and reference intervals.

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 clot-based or chromogenic assays [16,17]. These analyses are important in the diagnostic setting, during therapy (measurement of trough and peak levels after administration of replacement products) and also to detect the presence of inhibitory antibodies. When a family history is present, umbilical

cord blood is tested in male infants at birth to determine FVIII or FIX levels. For prenatal diagnosis, see chapter “Carriers of hemophilia”.

The FVIII:C and FIX:C assays should be calibrated with material that has traceability to current international standard for FVIII or FIX in plasma [16]. In this way the unit is given in international units (IU) and one IU is the factor activity present in one mL of normal plasma. In most of the Nordic countries the results are given in kIU/L or IU/mL but in the Anglo-American sphere it is common to use IU/dL (IU/dL, the same as percentage in absolute numbers; ie 5 IU/dL= 5%).

Differential diagnosis

Once a decreased FVIII level has been confirmed, the differential diagnosis includes congenital hemophilia A, acquired hemophilia A and von Willebrand disease (VWD), type 2N VWD (Normandy) in particular. Appropriate investigation to sort this out includes the case history and inheritance pattern, bleeding score, ruling out the presence of lupus anticoagulant, measuring antibodies against FVIII and VWF activity, and, when appropriate, the VWF:FVIII binding which determines the FVIII binding capacity of patient’s VWF. Definite diagnosis may be dependent on sequencing of the F8/9 and VWD genes.

Factor VIII:C assays

The one-stage assay (OSA) is the most frequently used assay principle in the world [16,17]. 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 concentration of FVIII:C.

The performance of the OSA is affected by the type and quality of the APTT reagent and the FVIII-deficient plasma used. The FVIII-deficient plasma can be obtained from a patient with severe hemophilia A (<0.01 kIU/L and without antibodies) or be immunodepleted. It is important to verify that new lots of FVIII-deficient plasmas are

free from FVIII (<0.01 kIU/L) as this otherwise will compromise the test. Also, normal VWF concentrations of the FVIII-deficient plasma may be an advantage. According to the discussion about the APTT reagent above, 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.

Another version of the FVIII:C assay is the chromogenic substrate assay (CSA). The assay procedure involves two separate reactions in a way that makes FVIII:C in the sample being the rate-limiting factor. There are several commercial kits available for CSA of FVIII:C in which the end product is colour development from generation of activated FX that cleaves a chromogenic substrate. In the first step the diluted sample (or standard) is mixed with a reagent cocktail with purified factors IXa, X and phospholipids, leading to the formation of FXa. In the second step a specific chromogenic 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 activity 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. This assay is common among the Nordic hemophilia centers. The chromogenic assay is also used by the pharmaceutical industry when the potencies of FVIII concentrates are assigned.

The different FVIII:C assays should give similar results in most cases. However, in approximately 20% of genetically confirmed mild/moderate hemophilia A patients there is a significant assay discrepancy between OSA and CSA, with OSA FVIII at least 2-fold higher than CSA levels. Furthermore, patients with certain mutations in the F8 gene causing mild hemophilia A may be missed using the OSA FVIII assay. In general, the clinical phenotype corresponds better to the results of the CSA compared to the OSA. Also, there are some genotypes causing inverse assay discrepancy, with lower one-stage assay results in mild hemophilia A. Thus, mild hemophilia A may be challenging to identify correctly in the laboratory, if only one of the assay principles are used. For the management of hemophilia A, both OSA and CSA should be performed to ensure detection of all new mild/moderate cases and to correctly assess the severity [18,19].

Reference interval: Usually between 0.50-2.00 kIU/L, but local differences may apply.

Interpretation: Hemophilia A patients have low FVIII:C levels. Levels <0.01 kIU/L are seen in severe hemophilia A. Moderate deficiency is characterized with FVIII:C levels between 0.01-0.05 kIU/L and patients with mild deficiency have levels from >0.05 kIU/L up to 0.40 kIU/L. Carriers of hemophilia A have usually approximately 50% of the normal activity but can occasionally have levels in the mild hemophilia range leading to increased bleeding. FVIII is an acute phase reactant and the levels of FVIII may increase several fold under certain conditions (e.g. trauma, infection, etc).

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 kIU/L (see FVIII:C above).

Chromogenic FIX:C assays have become commercially available and is an alternative to the OSA. However, these assays are offered by few laboratories and have not yet been fully approved by regulatory bodies (EMA) for potency labelling. Nevertheless, local implementations in Nordic and other laboratories are encouraging and it is likely that these assays will display analytical advantages compared to the OSA as has been shown for the CSA for FVIII:C. Assay discrepancy, caused by mutations in the F9 gene, has been recently described also in hemophilia B [20].

Reference interval: Usually around 0.60-1.50 kIU/L but local differences may apply.
Interpretation: Congenital deficiency of FIX is the cause of hemophilia B. Acquired hemophilia B, caused by specific inhibitors exists but is less frequent than the rare acquired hemophilia A. The degree of the deficiency defines the different forms: Severe haemophilia B with FIX:C <0.01 kIU/L; moderate deficiency with FIX:C between 0.01-0.05 kIU/L and mild deficiency with levels from >0.05 up to 0.40 kIU/L. Carriers of hemophilia B express about 50% of the expected normal FIX:C activity.

Antibodies against FVIII or FIX

The hallmark of neutralizing anti-FVIII or anti-FIX antibodies (=inhibitors) is a prolonged APTT and normal PT (INR). The prolongation of the APTT is persistent also after mixing of the patient sample with an equal volume of pooled normal plasma. 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 two hours at 37°C during a mixing experiment in order to allow the antibody to have effect. Anti-FIX antibodies have faster kinetics and it is usually not necessary to incubate longer than 10 minutes. For anti-FVIII antibodies it is also important to use buffered pooled normal plasma (ie HEPES) as this stabilizes the pH and thus the FVIII activity during the incubation and this will reduce the risk of obtaining false positive results.

The recommended test procedure for quantitation of the inhibitor titer is the Bethesda-Nijmegen mixing test, which is an assay for inhibitory antibodies [3]. In brief, a test sample is prepared by mixing equal volumes of patient plasma with normal plasma and then measure the residual factor activity in the plasma mixture after 2h incubation. A control sample is prepared in parallel with pooled normal plasma mixed with an equal volume of FVIII-deficient plasma. Both test and control samples are incubated for 2 h at 37°C and then the factor activities in both samples are measured. There is usually a good correlation between the inhibitor results based on the OSA and CSA FVIII:C assays [21]. 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 before analysis until a residual activity within the 25-75% range is reached. The final inhibitor level is then calculated by multiplication with the dilution factor. If several dilutions result in residual activities in the 25-75% range then the dilution that is closest to 50% is chosen for calculation of the inhibitor titer. It is recommended to perform the Bethesda assay when there has been a washout of the concentrate (ie FVIII < 0.1 IU/ml) [22].

Reference interval: The cut-off for a positive result is by definition 0.4 BU/mL, as the recommendation was not to use any residual activity above 75% (75% residual activity

corresponds to 0.4 BU/mL). Many laboratories instead use 0.6 BU/mL as the cut-off for positivity as the test is less reliable in the low titer range (reduced risk of false positive results).

Interpretation: The presence of inhibitors may be suspected in patients with unexpected bleedings despite regular prophylaxis. 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 factor VIII or IX.

Note: The Bethesda assay is usually performed on patients with severe type of hemophilia that do not have measurable FVIII:C (or FIX:C) activity. If the patient has an activity of 0.10 kIU/L or higher this must be taken into consideration when the inhibitor titer is calculated. It is also possible to remove the endogenous activity by heat-inactivation of the plasma sample at 56°C before analysis [22]. The FVIII-mimetic emicizumab interferes with inhibitor measurements in clot-based assays, but a chromogenic assay with bovine reagents can be used.

Factor activity assays for monitoring treatment with factor concentrates with focus on EHL-products

For monitoring postinfusion levels of full length rFVIII 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 results 30% higher for CSA than OSA. 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 [17,23].

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) [17]. 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. The European Pharmacopoeia (8th ed. 2016) recommends the use of CSA for replacement factor potency labelling of FVIII and OSA for FIX. The FVIII and FIX sub-committee of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) recommendation is that if either the OSA or the

CSA for FVIII activity provides valid potency estimates relative to the WHO IS for concentrates, this assay can be used for potency labelling [24,25]. If both methods provide valid potency estimates, either assay can be used for potency labelling and if there are discrepancies between assays, the most appropriate assay for labelling must be identified. This issue has also been addressed by the European Medicines Agency (EMA) [26]. 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 levels when different APTT-reagents have been used in different OSAs [23,26]. 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 generally obtained with the chromogenic methods. However, it is a challenge that field studies with comparable data for different modified products still are lacking. Both ECAT and UK NEQAS (European external quality control providers in haemostasis) are performing larger field studies, and generalized product-by-product-based guidance about systematic under- or overestimation of activity for many reagent combinations can hopefully soon be given.

A possibility could be to use product-specific reference standards. For example, the use of a B-domain deleted rFVIII laboratory standard was previously shown to reduce the discrepancy between one-stage and chromogenic assays, allowing a more accurate assessment of FVIII activity levels in patient plasma samples [26]. This is perhaps a more theoretical than practical option. It is very cumbersome for the laboratory to validate such laboratory-developed tests for product-specific standards, and thus such assays might only be available at very few specialized central laboratories. It also requires that the laboratory is informed about the type of product used in every patient. The risk for miscommunication to the laboratory is evident.

Another possible approach to avoid incorrect measurements of modified rFVIII and rFIX products in post-infusion plasma samples would be for the manufacturers to provide information about the most suitable assays (i.e., reagent-instrument combinations) for treatment monitoring of specific products. The manufacturers should also give information about where patient samples can be sent for testing using the appropriate reagents for the replacement product used. However, this is a strategy that can not be used in emergency situations.

Other options 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.

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 method. With the information available it seems the chromogenic method is the more consistent laboratory method that can adequately measure the levels of most EHL-products.

In conclusion:

- Modified rFVIII and FIX replacement products show significant APTT-reagent dependent recovery in OSA, whereas the recovery is more consistent in CSA.
- There is only limited comparable data from field studies comparing several EHL-products in OSAs with various combinations of reagents, including also the CSAs commercially available in the same study, from which generalized product-by-product-based guidance about systematic under- or overestimation of activity can be given.
- Ideally, similar recovery results should be obtained in post-infusion samples with the same method as used for potency labelling and these data must be available from the manufacturers of the products.
- A significant challenge to the laboratories and also to clinicians will be to communicate to the laboratory the specific factor replacement product used by each patient.

Genetic diagnosis

Genotyping is clinically useful to predict the risk to develop inhibitor and for carrier- and prenatal diagnosis. For a detailed description of the genetic diagnosis of hemophilia, we refer to the UKHCDO 2015 document “Guideline on Clinical Genetics Services for Haemophilia” of the UK Haemophilia Centre Doctors’ Organisation (UKHCDO) [27]. 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 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 [28]. Approximately 40% of cases of severe hemophilia A is caused by intron 22 inversion. Similarly, an inversion involving intron 1 has also been discovered in 1-2% of severe cases which can also be screened for with a PCR technique. In the remaining cases of severe hemophilia A as well as all other cases the whole F8 gene, 26 exons, must be sequenced since most patients have their own unique mutation. Mutations such as nonsense and deletions, “null-mutations”, will obviously cause severe hemophilia since the DNA reading frame will be altered, mRNA aberrant and protein will not be synthesized. A missense mutation will usually produce a dysfunctional protein with reduced clotting activity but may also result in a ‘neutral mutation’ or a polymorphism. In such cases it is important to know if the same mutation has been reported previously in patients with hemophilia, in databases such as ‘FVIII variant Database’ [29], or ‘CHAMP’ and ‘CHBMP’ databases [30]. One may also use various mutation prediction programs to evaluate the deleterious effect of a mutation. In a few percentage, mutations will not be found despite sequencing of the whole gene, some of these cases having a more complex genetic background. The MLPA technique may reveal deletions or duplications.

In hemophilia B, the 8 exons of the F9 gene are sequenced and in almost all cases the mutation 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. 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 mutation and is thus a carrier. In the remaining 20-30% of cases a mutation can not be found and these women may be true non-carriers or being gonadal mosaics, i.e. it is not possible to conclude if she is a non-carrier or carrier. Mosaicism may cause a problem when genotyping mothers of a sporadic case of hemophilia A. Studies indicate that, depending on the type of mutation, approximately 20% are gonadal mosaics [31]. However, in hemophilia B this seems to be rare [32].

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 in order

to determine fetal sex and in male fetuses be used to diagnose the mutation within 2-3 working days. 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 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 female foetus. Pre-implantation genetic diagnosis (PGD) enabling the implantation of female or unaffected male embryos has become possible [33–35]. PGD is a demanding procedure which however may be indicated in selected cases.

Prophylaxis and on demand treatment

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Recommendations

- Recombinant rather than plasma derived products should be used when available. In families with high risk of inhibitors, the choice should be discussed (see Inhibitor chapter)
- Primary prophylaxis in severe hemophilia should start around the age of one before joint bleeds occur.
- Patients with moderate hemophilia with a factor level of 1-2% should also be offered primary prophylaxis.
- The goal is prevention of joint disease and intracranial bleeds.
- Prophylaxis is initiated with a dose of standard FVIII around 25 IU/kg once or twice a week, or standard FIX around 50 IU/kg once a week.
- In hemophilia B, the first five injections should be done in a hospital setting, due to the risk of anaphylactic reactions.
- As soon as venous access allows, the frequency is increased. A central venous access device may be considered.
- The aim is full scale prophylaxis with 20-40 IU/kg standard FVIII every second day, or at least three times weekly, for patients with hemophilia A, and 30-40 IU/kg standard FIX every third day, or twice weekly, for patients with hemophilia B.
- The dose is tailored according to clinical response. Dose per kg body weight can often be lowered with age. At routine checkup, the previous factor infusion should be registered in detail (time point, dose), and a blood sample taken, for pharmacokinetic calculation (PK).

- FVIII EHL can be considered to improve troughs. In less active patients, FVIII EHL can be considered to reduce frequency of injections.
- FIX EHL should be considered, especially when there are break through bleeds on prophylaxis with standard FIX, or adherence issues.
- When switching to EHL products, PK measurement is recommended. PK sampling should be prolonged to 72 h for EHL FVIII, and 162 h for EHL FIX, with a minimum sampling schedule after 0.5-1h and before next dose (trough). Frequency of injections should be planned individually, according to patient activities and need for peak levels, and doses adjusted according to trough and bleeding pattern. Trough levels should be reassessed at steady state, after 5 doses.
- Young children with severe or moderate hemophilia are monitored every 6 months. Older children and adults are monitored every 12 months.
- Assessment of individual clinical response should include bleeding rate, recorded by the patient/parents, and joint score by a physiotherapist (see chapter on physiotherapy). Ultra sound (US) is recommended as a supplement in joint assessment. Quality of life (QOL) should be monitored.
- Acute bleeds during prophylaxis are initially treated with a single or a double prophylactic dose, depending on severity of the bleeding.
- Potentially life-threatening bleeds, such as head trauma, are initially treated with a double dose, to reach a factor level of minimum 70-80%.
- Patients with mild hemophilia are monitored every three years.
- In patients with moderate or mild hemophilia, treatment of acute bleeds on demand is tailored to reach a factor level of 40-60% in minor bleeds, and 70-80% in severe or life-threatening bleeds.
- In mild hemophilia A, DDAVP should be tested as alternative to factor replacement therapy (see surgery chapter).

Background

Treatment only when acute bleeds occur is called treatment on demand. Even if the bleeding stops, pain subsides, and mobility improves, blood remains in the joint, with harmful long-term effects on the articular cartilage. Unnoticed minimal bleeding could occur during on-demand treatment as well as during prophylaxis, causing joint damage when patients have not registered any symptomatic bleeding.

Replacement therapy in hemophilia has been called prophylactic treatment. The goal of prophylactic treatment 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.

Prophylaxis may be primary or secondary. Primary prophylaxis aims to start prior to initiation of joint disease. Meanwhile, we do not know how many joint bleeds it takes before cartilage destruction starts, the bleeding phenotype differ between patients, and subclinical bleeds may occur. It is therefore not surprising that the definition of prophylaxis differs among countries. However, international bodies have tried to define prophylaxis and the SSC of the ISTH published their definition [36], Table 3. Cohort studies, especially from Sweden and the Netherlands, clearly show the long-term benefit of prophylaxis [37,38]. In comparison with on demand treatment, the outcome of the Swedish prophylactic strategy was superior but at a much higher cost [38].

In a Swedish health technology assessment [39] it was concluded that concentrate treatment is efficacious, and prophylaxis is superior to on demand treatment on demand in terms of number of bleeds. Prophylaxis from early age protect against development of hemophilic arthropathy. These conclusions are strongly supported by a randomized clinical trial in children, comparing prophylaxis and treatment on demand [7]. It showed a much better outcome on prophylaxis after only 5 years follow up.

Several studies classify prophylaxis into ‘high-dose’ and ‘intermediate-dose’ categories. “High-dose” prophylaxis as in Sweden is designed to enable individuals with hemophilia to live as normal as possible. The factor concentration is maintained over 1% to avoid breakthrough bleeds. This usually requires the administration of standard factor products 10-15 IU/kg/daily or 20-40 IU/kg FVIII every second day or at least three times weekly for patients with hemophilia A, and 30-40 IU/ kg FIX every third day or

twice weekly for patients with hemophilia B. The minimal through to obliterate joint bleeds and hemophilic arthropathy is not known and may vary from patient to patient. Factor concentrates modified to extend the half-life (EHL) are now marketed in the Nordic countries, with varying availability and pricing. 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 with FC, prolongs the average half-life to 18.4 to 19 hours. In clinical trials [40], 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. Maintaining the frequency, and aiming for higher troughs, is an alternative use of EHL FVIII in patients with break through bleeds on prophylaxis with a standard FVIII product. Depending on the price per unit, switching to FVIII EHL can be cost beneficial, aiming for the same frequency and trough. Independent of the reason for switching, individual PK analysis and close follow up will be important for patients switching from standard to EHL FVIII concentrates.

Extension of FIX half-life has been more successful. Pegylation or fusion with FC or albumin, has resulted half-life's of 85 to 105 hours, with dosing every 7-14 days in clinical trials [40]. EHL FIX have a clear advantage compared to standard FIX products, and EHL FIX will allow for once weekly dosing in most patients. Alternatives to replacement therapy are emerging. Emicizumab is the first non-factor product for hemophilia A to reach the market, and EMA recently granted a marketing authorization for prophylaxis in patients with hemophilia A 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 of loading dose. Emicizumab cannot stand alone as monotherapy, as patients eventually will need supplemental on demand treatment with FVIII in case of break through bleeds, trauma or surgery. The effect of emicizumab is not readily measured with standard coagulation assays.

Assessment

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 centre and taken into consideration when planning dosing schedules.

Quality of life

To evaluate quality of 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.

Physical score

Physical score is performed mainly by physiotherapists 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 [41]. The HJHS assesses structural changes. HJHS has been widely implemented as an assessment tool in clinical studies, also in adults. Other scores 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.

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 [42–44].

Evaluation with a new 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.

Pediatric issues

The aim of early prophylactic treatment is to enable the child to live a life as normal as possible without hemorrhages and overprotection. The trend in Europe and other well-off countries (Canada, Australia) has been towards primary prophylaxis. The rationale behind an early start is that even a small number of joint bleeds can result in irreversible damage, as well as that damage may progress despite prophylactic therapy. It has also been shown that the time point at which prophylaxis is begun is an independent factor for good joint outcome. However, it must not be forgotten that the aim of prophylactic treatment is to avoid not only arthropathy but also other serious bleedings such as intracranial hemorrhage.

Choice of factor product

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 [45]; 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.

Starting prophylaxis

In many centers, an early therapeutic approach is initiated by giving a dose of standard FVIII around 25 IU/kg once or twice a week, or standard 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. 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 most patients 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 [46,47]. Even if intensive early treatment due to major bleed raises the risk of inhibitors [[48]; [49]; [50]], there is no support for the role of port implantation as a risk factor for inhibitor development [48,51].

Especially at the first exposure but also during the subsequent 20 exposures, intensive treatment and treatment during inflammatory states should be avoided if possible. In contrast, vaccinations do not increase inhibitor risk, see chapter on inhibitor.

The goal is to reach full-scale primary prophylaxis, which usually involves the following: in hemophilia A, standard factor VIII is administered at a dose of 20-40 IU/kg/day every second day or three times weekly; in hemophilia B, standard factor IX is given at a dose of 30-40 IU/kg/day every third day or twice weekly. A large multicenter study comparing three different prophylaxis regimen, 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) [52]. Full-scale prophylaxis also offers almost complete protection against intracranial haemorrhage (ICH) [53]. However,

both the dose and the dose interval must be individually tailored for each child 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.

In older children with hemophilia A, it is possible to optimize the cost-benefit ratio of treatment by daily injections of standard FVIII (10-20 IU/kg) [54]. Switching to EHL FVIII can be considered as alternative. However, it is the clinical outcome, not the achieved through levels, that determines whether the given dose is adequate. In hemophilia B rFIX EHL should be considered in PTPs when there are problems with venous access or break through bleeds on prophylaxis with standard FIX (see chapter Factor product treatment including prophylaxis, Background). Most children can be treated at home by their parents, and from the age of 10-12, the child can usually start self-injections.

Adolescence

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Recommendation

- A transition program is recommended to secure continuous adherence in adolescents during transfer from pediatric to adult service.

Adolescence is the time of rapid physical, social and cognitive development which occurs during the transition from childhood to adulthood, usually between the ages of 10 and 24 years. This is a challenging time for any teenager and even more so for those with a chronic disease. For them it is often harder to break family ties, harder to feel accepted by their peer group and to be realistic about their future. Young teenagers need to move towards independence and for people with hemophilia this includes achieving self-management, maintaining adherence to therapy and coping with the impact of hemophilia on lifestyle [55].

The developmental tasks of adolescence include emotional separation from parents and establishment of autonomy. Peers have a central role in building up the personality. Adolescents seek new experiences and higher levels of rewarding stimulation, and often engage in risky behavior without considering future outcomes or consequences. Poor compliance with hemophilia therapy during adolescence in combination with risky behaviors, may result in serious and recurrent bleeding episodes with impact on future outcomes. The teenager may for the first time question their medical regimen and be ashamed of the diagnosis [56].

In a global survey of treatment strategies in hemophilia A involving 147 hemophilia treatment centers, compliance was rated according to age. Compliance with all types of prophylactic therapy was the highest in children up to 12 years of age, with more than half achieving high ($\geq 90\%$) adherence. The number achieving this adherence level dropped to 13%, however, in adolescents aged 13-18 years [57].

A Scandinavian survey in young men with severe and moderate hemophilia showed that the average age for a patient to take over responsibility for their treatment was

14 years, but 25% required parental assistance in hemophilia-related care until a mean age of 17.2 years. A majority (68%) treated bleeds immediately and 60% used extra infusions when needed. Thus one-third of them put themselves at risk for complications by an unwillingness to recognize the need for treatment. Over 40% had at some time failed to follow the treatment regimen [58].

Caregivers can support adherence by education, encouragement, and by providing positive feedback to the patient.

The perception that treatment is a normal part of life is shown to increase adherence to therapy in adolescents and treatment individualized to patients' bleeding pattern and lifestyle can improve compliance.

The challenges faced by the adolescent should be addressed in the years before transition to the adult clinic. Arranging efficient and caring transfer for young people with hemophilia is one of the great challenges in the coming century.

Transition programs are necessary even when pediatric and adult services are in the same hospital, as geographical closeness often does not translate into a close professional relationship. A joint pediatric-adult clinic is very useful to introduce adolescents to adult physicians and to hand over clinical issues. Joint clinics between pediatric and adult health-care teams can improve the transfer and help young people to communicate with the new team.

Inhibitors

Revision by: Jan Astermak (Malmö) and Fariba Baghaei (Gothenburg)

Introduction

The development of antibodies is a serious complication of factor replacement therapy. The antibodies bind to the factor VIII or IX molecule and in many cases neutralize (inhibit) the hemostatic efficacy. The incidence of inhibitory antibodies in patients with severe hemophilia A is about 30%, whereas less common in patients with a milder form of the disease. Among persons with hemophilia B, inhibitors are less frequent and usually <5%.

The formation of inhibitory antibodies is a complex immunological process involving both genetic and non-genetic factors [59]. Due to its complexity, an evidence based approach to base the clinical management of patients on is difficult to achieve, but clearly genetic factors including first of all the type of causative mutation and HLA but also several immune response genes will have an impact. In addition, the intensity of treatment with higher doses over several days has been defined as a risk. Only one randomized study has been published with the aim to evaluate one of the potential non-genetic risk factors i.e. the type of concentrate [45]. In this study, in which the cohort of PUPs and MTPs was more or less equally split between prophylaxis and on-demand treatment, plasma-derived factor VIII was associated with less inhibitors. However, in the case of high-titer inhibitors, no significant difference was observed. Even though the data are of interest, several issues remain to be settled and the decision on which product type to use in the individual case, should be based on safety, efficacy and availability in an open dialogue with the family. In addition, the inhibitor incidence with the new EHL molecules in PUPs is not yet available.

The presence of an inhibitor is confirmed using the “Bethesda inhibitor assay” with Ni-jmegen modifications and classified according to the peak titer into “high” (>5 BU/mL) or “low responding” (<5 BU/mL). The antibodies usually appear within the first 50 treatment doses, but may occur throughout life.

Inhibitory antibodies at low titer can be overcome by saturating levels of the deficient factor, whereas bleedings in patients with high titer need to be treated with “bypass-

ing 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; one plasma-derived activated prothrombin complex concentrate (aPCC) and one recombinant coagulation factor VIIa (rFVIIa). These agents are also used in inhibitor patients for the cover of surgical procedures and in the prevention of bleeds (prophylaxis). The most favorable option for inhibitor patients is the eradication of the inhibitor by immune tolerance induction (ITI) therapy. In this therapy, regular infusions of factor concentrates (factor VIII or IX) are administered (usually daily and at high doses) for weeks to years with or without immune-modulating drugs. We recommend that the ITI should be performed according to an international protocol and the patients should be recruited to international studies whenever possible.

Bypassing agents for the treatment of bleeds

Recommendations

- FVIII and FIX should be used as the first option in patients with a current low inhibitor titer, in order to saturate the inhibitor and reach a hemostatic factor level. In the case of life-threatening bleeds, irrespective of inhibitor response, FVIII/IX:C should be monitored at least daily. The risk of allergic reactions associated with FIX concentrates should be taken into consideration.
- The use of bypassing agents at the doses of aPCC 50-100 IU/kg every 6-12 h or rFVIIa 90-120 $\mu\text{g}/\text{kg}$ every 2-3 h is indicated for patients with inhibitor levels >5 BU/mL for treatment of any bleed and in those with high-responding inhibitors but a current low level (<5 BU/mL) in case of a non-life-threatening bleed. Children may need higher doses up to 270 $\mu\text{g}/\text{kg}$ of rFVIIa as an initial dose followed by lower doses depending on the hemostatic effect.
- rFVIIa is preferred in patients with a known anamnestic response prior to start of ITI, as well as in patients previously not being exposed to plasma products.
- Antibody removal by immunoadsorption might be considered in patients with high inhibitor titers in order to allow treatment with FVIII/IX concentrates.
- Concurrent use of tranexamic acid should always be considered with rFVIIa treatment, but also in association with aPCC to improve the hemostatic effect.

- Higher doses of rFVIIa (up to 270 $\mu\text{g}/\text{kg}$) and/or shorter intervals ($<2\text{hrs}$) should be considered in young children and in the case of treatment failures.
- The daily dose of aPCC should routinely not exceed 200 IU/kg.
- In hemophilia B patients with inhibitors, rFVIIa is preferred. FIX-containing agents e.g. aPCC should not be routinely used.
- In the case of bleeds resistant to monotherapy with each bypassing agent, a sequential use in the order of aPCC (50-75 IU/kg) and rFVIIa (90-100 $\mu\text{g}/\text{kg}$) with an interval of ≥ 2 hrs or a combined use of aPCC (20-30 IU/kg) and rFVIIa (30-60 $\mu\text{g}/\text{kg}$) may be considered. The risk of thromboembolic complications however always needs to be taken into account.

Most of the studies of rFVIIa and aPCC are retrospective and observational with low scientific value if one applies strict scientific criteria, but both agents have shown to be effective in the majority of cases. One drawback using these drugs is the cost. Therefore, the treatments with rFVIIa and aPCC need to be optimized to the extent possible. Two randomized head-to-head-studies have been conducted showing a similar high hemostatic effectiveness with both products. However, a difference in efficacy was observed with the respective products in one and the same patient, suggesting that predictive markers for the treatment response need to be identified [60,61].

The randomized study by Young et al [60] compared not only rFVIIa with aPCC, but also two treatment doses of rFVIIa in a blinded design. The results suggest in accordance with other case series and cohort studies, that rFVIIa can be administered at a dose of 270 $\mu\text{g}/\text{kg}$ on a single occasion, instead of three doses of 90 $\mu\text{g}/\text{kg}$, without reducing the efficacy or exposing the patient to risk [61].

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 [62]. The risk of thromboembolic complications however always needs to be taken into account [63], in particular in patients with a central venous access device, and the parallel use of them used cautiously and for the time being only in resistant cases. An algorithm for the use of aPCC and rFVIIa has been defined [64].

Prevention of bleeds

Recommendations

- Prophylaxis with rFVIIa (90 to 270 $\mu\text{g}/\text{kg}$) once daily intravenously, aPCC (85 IU/kg) every other day intravenously or emicizumab subcutaneously (3 mg/kg for 4 weeks followed by 1.5 mg/kg weekly) should be considered in patients with inhibitors following a severe/life-threatening bleed and/or repeated bleeds requiring by-pass therapy before, during or after ITI with or without immunosuppression. **Note that Emicizumab will only be an option for patients with hemophilia A.**
- In patients with ITI-failure emicizumab might be considered as the first choice treatment for prevention of bleeds.
- For treatment of break through bleeds requiring additional hemostatic drug intervention during prophylaxis with emicizumab, rFVIIa should be used as first-line option and the initial dose of rFVIIa should not exceed 90 $\mu\text{g}/\text{kg}$. Doses of 45 and 90 $\mu\text{g}/\text{kg}$ at a dose interval of 2 to 4 hours may be considered. Due to the hemostatic effect of emicizumab, the number of doses of rFVIIa should be minimized.
- If aPCC and emicizumab together will be required as second line treatment and/or resistant severe bleeds, the initial dose of aPCC should not exceed 50 U/kg. Then, if a second dose of aPCC is considered, the patient should be referred to the hospital for treatment and surveillance for TMA. The total dose of aPCC should not exceed 100 U/kg/d and - as a routine - not provided for more than 24 hours per treatment episode. The recommendation regarding by-pass therapy together with emicizumab should be followed for 6 months after the infusion of emicizumab.
- For all three prophylactic agents, a hemostatic improvement of the bleeding phenotype should be required defined as a reduction in the number of significant bleeds with $\geq 50\%$.

Bypassing agents have for several years been used to prevent bleeds in patients with inhibitors. This is a costly treatment, but should be considered in persistent inhibitor

patients and/or phenotypic bleeders to protect against harmful bleeds while waiting for the inhibitor to become eradicated. Recently, another option for the prevention of bleeds, emicizumab, was approved for subcutaneous administration by the FDA and EMA in patients with hemophilia A and inhibitors (≥ 12 years). In the case of the previously used two bypassing agents, i.e. aPCC and rFVIIa, no head-to-head comparison has been performed, but available data show that both drugs can be used prophylactically to reduce the number of bleeds [65–67]. A reduction in the bleeds up to approximately 60% have been reported for rFVIIa in daily doses of 90 to 270 $\mu\text{g}/\text{kg}$ and up to around 70% with aPCC in the dose of 50 to 85 U/kg 3 times weekly or every other day.

Emicizumab, is a humanized antibody that bridges activated FIX and FX, mimicking FVIII function. A total of 169 haemophilia A 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. 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. Participants who had previously received prophylactic treatment with bypassing agents were also enrolled and switched to emicizumab prophylaxis, which resulted in a lower bleeding rates (treated bleeds) compared to previous prophylaxis with bypassing agents, but these figures cannot be directly compared [68].

Bypassing agents (rFVIIa or aPCC) were used for treatment of bleeds.

The most reported adverse events were injection-site reactions. Thrombotic microangiopathy (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.

In patients with low-responding inhibitors, prophylaxis with the deficient factor can be used to prevent against bleeds as well as potentially induce tolerance.

Other non factor replacement strategies such as anti-TFPI and RNAi therapeutic antithrombin (Fitusiran) and zymogen like FXa might have a potential for management of haemophilia patients with inhibitors in future, but these agents are not yet available for routine clinical use [69].

Immune tolerance induction (ITI) therapy

Recommendations

- The principal goal in all patients with inhibitors should be to eradicate the immune response and to tolerize the patient.
- All children with confirmed low-responding inhibitor should continue on regular replacement therapy to induce tolerance.
- Adults with a low-responding inhibitor should if persistent and, preferentially if bleeds are not successfully treated on demand with the deficient factor, be offered regular replacement therapy to induce tolerance.
- Children with high-responding inhibitor, but no bleedings may wait with ITI until decline of the inhibitor - preferentially below 10 BU/mL. In case of bleedings, ITI should however be started immediately.
- Adult patients with high-responding inhibitors should be offered ITI as for children.
- A high factor dose seems to reduce the time to reach a negative inhibitor titer, and since bleeds mainly occur during this period, a dose of 100-200 IU/kg/d should be first-line option whenever possible. Lower dose may however be used with a similar final outcome – at least in so called good risk patients.
- No consistent data indicate the beneficial use of one type of product over the others, but in patients who fail the initial attempt of ITI with high purity FVIII, a VWF-containing FVIII concentrate should be considered. The potential role of EHL products for tolerization in resistant cases is currently not known.
- 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 resistant cases and in poor risk patients as well as in adults, the combined use of the deficient factor and immunosuppression should be considered - even as first-line treatment in adult patients.

- In patients with hemophilia A and resistant high-responding inhibitors failing ITI protocols with and without immunosuppression, ITI may be stopped and emicizumab provided prophylactically for bleed protection.
- Immunosuppression may be considered as a first-line option in patients with hemophilia B and a causative gene defect such as a gene deletion and/or nonsense mutation.
- After successful tolerance the dosing should be tapered to regular prophylactic treatment.
- In patients with mild/moderate hemophilia, the possibility of spontaneous remission ($\approx 20\%$) should be taken into consideration and a watch and wait strategy might be advisable before treatment. If persistent, immunosuppression e.g. Rituximab should be considered as a first line option with or without the combined use of the deficient factor based on the bleeding phenotype of the patient.

ITI treatment with the intent to induce tolerance was described in the 1970s and should be the ultimate goal when possible in all patients with a persistent inhibitor to reduce the risk of harmful bleeds. Successful treatment also has a cost-saving potential [70]. The principle mainly consists of a repeated exposure for the deficient factor with or without the concomitant use of immunosuppressive agents. Several different regimens have been described, many of which seem to have a similar outcome. A decline of the pre-ITI titer to low levels and a low peak before or during ITI seems to mirror a beneficial immune response. One randomized study has so far been conducted - in patients with “good risk” severe hemophilia A and high titer inhibitors comparing high (200 IU/kg/d) and low dose (50 IU/kg 3 times/week) FVIII. No difference in success rate (about 70% in the intention-to-treat analysis) between the treatment arms was seen. However, the time to achieve a negative titer, i.e. the phase with most frequent bleedings, was significantly shorter with the high dose regimen [71].

The other non-randomized studies reported in the literature are difficult to compare since the agents, doses, dose intervals, and definitions of tolerance vary. However, most of the retrospective analyses show tolerance to be induced in up to 60-80% of the cases regardless of the type of agent and dose [72]. A higher efficacy rate of von Willebrand-containing FVIII products to induce tolerance compared with more highly purified products has been suggested in patients with unfavorable prognosis [73]. However,

additional studies and data are needed to confirm these findings and whether product type including the new EHL products will impact success rate is still not settled.

ITI and mild/moderate hemophilia

In hemophilia A, up to 25% of new inhibitors occur in patients with mild or moderate disease and changes the bleeding phenotype from mild/moderate to severe [74]. Inhibitors most commonly arise following an intensive episode of replacement therapy for surgery or major trauma. The risk of inhibitor development also appears to be associated with some high-risk factor VIII gene mutations [75]. The limited data available in patients with non-severe hemophilia A suggests that when treatment is used, strategies that modulate the immune system, such as the use of rituximab may have greater benefit than ITI performed with only the deficient factor, but additional studies are needed to confirm these findings. Importantly, the inhibitors might be transient and disappear spontaneously. Therefore, the necessity of eradication treatment should be critically examined for each individual patient [76].

ITI and hemophilia B

ITI treatment in hemophilia B seems to be associated with a less successful outcome compared with hemophilia A. The reasons for this are not known. In addition, the procedure is, in some cases, jeopardized by the occurrence of an allergic/anaphylactoid reaction and nephrotic syndrome. The use of ITI in these patients therefore needs careful monitoring and should initially be provided in the hospital setting. To reduce the exposure for the deficient factor IX molecule, lower dose and immunosuppressive drugs should be considered, such as the use of steroids, rituximab, cyclophosphamide, cyclosporine, mycophenolate mofetil and/or other agents [77,78].

Surgery in hemophilia - practical guidelines

Revision by: Pål Andre Holme (Oslo)

Recommendations

- Surgical and invasive procedures can be performed safely in PWHs
- Any surgery in patients with hemophilia and especially inhibitor patients should be planned and executed in close conjunction with a hemophilia treatment center (HTC)
- PWH undergoing surgery should be daily monitored with daily factor measurements
- Factor replacement in PWH undergoing surgery can either be given as repetitive bolus infusions or continuous infusion
- Major surgery: FVIII/IX level 0.7-1.0 kIU/L immediately before a surgical procedure and replacement therapy for 7-10 days
- 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

Preoperative planning

Surgical and invasive procedures can be performed safely in PWHs. Due to the increased risk of bleeding complications during surgery, thoroughly planning should be performed prior to surgery. Coordinated standard pre-, intra and postoperative assessment and planning are mandatory (intended) to optimize surgical outcome and utilization of resources, while minimizing the risk for bleeding and other adverse events during and after surgery. Because of the concentration of expertise and experience, it is recommended that any surgery in patients with hemophilia and especially inhibitor patients are planned and executed in conjunction with a hemophilia treatment center (HTC) [79].

The patient's expectations regarding surgical outcome and recovery are also important to explore upfront of an orthopedic procedure. The hematologist should provide a

written detailed treatment plan including duration and dosage of hemostatic therapies, also covering the rehabilitation phase.

The patient's hemostatic functions should be screened prior to surgery. Laboratory test as: Platelet count, APTT, prothombin time, FVIII/FIX level, inhibitor test, fibrinogen, blood group including irregular antibodies and recovery test prior to surgery should be performed. 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 response (recovery), a substitution program should be outlined, giving exact information on the number of units of coagulation factor to be used and the timing of concentrate infusion during surgery and the entire post-operative period and whether repetitive bolus infusions or continuous infusion are preferred. The substitution schedule should also provide information about the need for prophylactic treatment during the rehabilitation training program both in hospital and home.

Factor FVIII/FIX should be monitored peri- immediately postoperative and at least once daily in the hospitalized period to adjust the factor levels achieved [80].

Due to an increased risk of inhibitor development during the first 20 exposure days surgery should be postponed if possible.

Thromboprophylaxis should not be administered routinely. In patients with previous VTE, with severe risk factors, such as obesity and active cancer, thromboprophylaxis might be considered.

Substitution principles

In clinical management of surgical episodes in patients suffering from hemophilia, two major substitution principles have been adopted: Bolus injections of factor concentrate every 6-12 h and continuous infusion of factor concentrate by means of a pump delivery system [81].

Continuous infusion

The continuous infusion (CI) principle has been in use in some hemophilia centers for numerous years. One of the strongest arguments favouring continuous infusion is its superiority in providing the patient with a safe and constant level of the coagulation factor in question by balancing input with clearance. At a reasonably constant factor level, the risk of early and late re-bleeding may be diminished or abrogated. Further, continuous infusion may reduce concentrate spending compared to bolus injections, since peaks of factor level are avoided. However, there are some issues concerning CI practices. The bag system most often used with the pumps has the theoretical risk of infection and/or factor concentrate degradation during storage at room temperature. These questions have been extensively studied and appear not to be a problem within 72 h of CI determined by laboratory testing of stability and sterility. Phlebitis at the infusion site was regularly reported using CI, however this problem is nowadays very seldom seen after small amounts of heparin or LMW-heparin was added to the infusion bag. A quite frequently reported complication is related to loss of battery power or other failures of the delivery pump system. Finally, suspicion has been raised that continuous infusion may be associated with development of inhibitors, especially in non-severe hemophilia, although medical evidence in standard terms are lacking.

Bolus injections

Bolus injections refer to administration of pre-planned doses of factor concentrate infused at scheduled time intervals. The response to bolus injections is dependent of the dose administered. A sufficient factor level in blood is the one that does not go below a predetermined trough level of factor (immediately before the next dose) and that does not cause untoward bleeding. This means that the immediate pre-dose sample should illustrate the minimum target level of factor that ensures, in the clinical situation, adequate hemostasis. While this value is a critical determinant of bleeding risk, the post-dose factor level may vary a great deal.

A clear disadvantage of using bolus injection strategy is the requirements for frequent injections at 8-12 hour intervals. Since the hemostatic efficacy of concentrate with bolus administration is dependent of the trough level, a certain degree of spillage may be demanded to maintain that particular level. 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 concentrate.

Major surgery including orthopedic surgery

FVIII/IX level 0.7-1.0 kIU/L 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 IX 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.

Continuous infusion

Recovery calculation to determine the initial bolus dose:

$$Recovery = \frac{Increase\ in\ factor\ level\ (\%) \times BW}{Test\ dose\ IU}$$

$$Bolus\ dose = \frac{Desired\ increase\ in\ factor\ level\ (\%) \times BW}{Recovery}$$

$$Infusion\ rate = Clearance \times desired\ factor\ level\ (IU/kg)$$

$$Daily\ dose = Infusion\ rate \times BW \times 24\ h$$

$$Clearance = \frac{Infusion\ concentration\ kIU/L \times infusion\ rate\ mL/24\ h}{Measured\ factor\ level\ kIU/L}$$

Clearance (mL/h/kg) often measured. 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: 0.70 kIU/L
- Day 4-6: 0.50 kIU/L
- Day 7-9: 0.30 kIU/L

Then tapering off - bolus infusions before physiotherapy [81].

Minor surgery

In general, a factor level of 0.5 kIU/L is recommended before the surgical procedure and replacement therapy for 1-5 days depending on the procedure.

Specific surgery

Dental extraction

For invasive surgical intervention it is recommended to increase the factor level >0.5 kIU/L pre-operatively and use an oral antifibrinolytic agent (tranexamic acid) agent pre-and post operatively in combination with local therapy [82].

Circumcision

A general recommendation for circumcision is a factor level of 0.7-1.0 kIU/L at the start of surgery and a level >0.5 kIU/L maintained for at least 2-3 days (some recommend 7-10 d) together with antifibrinolytics. When performing circumcision in patients with mild hemophilia A desmopressing (DDAVP) $0.3 \mu\text{g}/\text{kg}$ intravenously before the initiation of surgery and an additional dose on the second day can be considered in DDAVP responding patients [83].

Liver biopsy

In patients undergoing liver biopsy, the preoperative factor level should be as for major surgery 0.7-1.0 kIU/L and replacement therapy should be continued for at least 3 days with concomitant use of tranexamic acid as described below [84]. Bed rest for 8-12 h after the biopsy is recommended.

Tonsillectomy/Adenotomy

In children undergoing tonsillectomy preoperative factor level should be 0.7-1.0 kIU/L and replacement therapy should be continued for 7-10 days with concomitant use of tranexamic acid as described below [83,84].

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 [84].

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.

- 0.3 $\mu\text{g}/\text{kg}$ i.v. or s.c.
- 300 μg i.n. (spray) (150 μg if BW <30 kg)

Intravenously (i.v.): slow injection of DDAVP (diluted in 10 mL saline) during 15 minutes or infusion (diluted in 50-100 mL saline) during 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 µg/mL) is the most suitable for s.c. administration, due to its high concentration. Often a single 15 µg 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.

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 with repetitive dosing to ensure concentrations in tissues as well.

- 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

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

Adverse effects

Nausea, vomiting, diarrhea and abdominal pain.

Postoperative management

Adequate pain control is an important factor in successful postoperative management and rehabilitation. However, in general, neuraxial anesthetic and analgesic techniques (epidural anesthesia) are contraindicated postoperatively due to the risk of bleeds. However, nerve blocks may be used in this patient group (with caution and under replacement coverage). Acetylsalicylic acid and Cyclooxygenase-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.

A physical therapy plan to assess pre- and postsurgical rehabilitation is advisable to patients undergoing elective orthopedic surgery and the physical therapist should be experienced in the management of hemophilia and in frequent communication with the other members of the hemophilia treatment team.

Orthopedic aspects

Orthopedic surgery in PWHs is truly a collective effort, involving not only the surgeon but also collaboration with the comprehensive hemophilia center team to address serious considerations. The optimal timing of orthopedic surgery during the lifetime of the hemophilic patient is unknown. However, the more demanding social and professional life of youth also favour the early correction of joint disease. These factors have contributed to the tendency towards early orthopedic intervention, and the focus of such procedures has shifted from relief of pain towards the correction of functional disability.

Table 2: 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

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 product both for Hem B and A. However, the data so far are very limited so thorough monitoring should be performed.

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. However, the data so far are very limited [85].

Surgery in PWHs with inhibitors

Revision by: Eva Zetterberg (Malmö)

Recommendations

- APCC and recombinant activated factor VII (rFVIIa) (NovoSeven®) are the treatment of choice in patients with if the inhibitor level exceeds 5 BU/mL. For dosage see Table 3.

Table 3: 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

Surgery in persons with hemophilia and high-titered inhibitors is a clinical challenge and was for a long time considered as almost impossible. However, surgical experience during the last 10-15 years using bypassing agents have shown that despite increased bleeding risk compared to non-inhibitor patients the results are in general good [86]. Consequently, patients with inhibitors should not be denied surgical procedures. Nevertheless, surgery continues to pose a major challenge in these patients, as the costs are significantly higher than in patients without inhibitors in addition to a higher risk of bleeding.

All surgical procedures in patients should be conducted by a specialized surgeon in association with a hemophilia comprehensive care center.

Currently, there are today no standardized laboratory assays to monitor the efficacy and optimal dosing of bypassing products following surgery. However, preoperative evaluation of hemostatic response to bypassing agents using thrombin generation test (TGT) or thromboelastography has been reported as a means to predict and optimize the hemostatic outcome during the peri- and postoperative phase [87,88].

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 treatment of choice in patients with if the inhibitor level exceeds 5 BU/mL. Which one to use depends on several factors as the age of the patient, prior history of efficacy to a product, costs and safety. APCC have been used extensively for a long period of time and has the advantage of dosing every 8-12 h, whereas rVIIa must be infused every 2-3 h. rFVIIa offers the advantage of being a recombinant protein, and therefore unlikely to be contaminated with infectious agents, as opposed to aPCC which is plasma derived. However, the risk is minimized as aPCC is now double virus inactivated and no transmission of blood born infectious agents has been reported since these precautions were undertaken. Both products are effective in achieving hemostasis, and one should switch to the other product if the first choice fails. Side effects including venous thrombotic events, disseminated intravascular coagulation (DIC) and myocardial infarction have been reported using both aPCC and rFVIIa, although at a very low incident rate, if doses within the manufacturers recommended range are used. The main disadvantages of rFVIIa compared to aPCC

are high cost and frequent infusions (see chapter Inhibitors).

Management of substitution therapy in the peri- and postoperative phase

In patients with a low-titer (<5 BU) or a low responding inhibitor the use of high dose FVIII or FIX concentrates to overcome the inhibitors might be applicable in the initial phase. However, an anamnestic response may occur and one should be prepared to switch to a bypassing agent at any time.

aPCC - FEIBA®

During the last 15 years more than 200 surgical procedures have been reported in case reports using aPCC as replacement therapy in patients with inhibitors. The hemostatic efficacy in these case series have been reported from 78% to 100%. Variable initial doses, frequency and duration of treatment using aPCC have been reported however, continuous infusion has not been studied.

The Norwegian experience using aPCC for surgery counts 37 surgical procedures, 17 major and 20 minor [86–89]. 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 [90,91]. 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 3).

rFVIIa - NovoSeven®

Many case series with a small number of patients have reported a good hemostatic outcome using rFVIIa for different surgical procedures in PWHs with inhibitors. However, variable doses and protocols have been reported and only two small prospective randomized studies have been published addressing the dose and mode of administration [92,93]. 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 either 35 $\mu\text{g}/\text{kg}$ vs 90 $\mu\text{g}/\text{kg}$ 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 $\mu\text{g}/\text{kg}$ 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 [93] studied the efficacy and safety of administering rFVIIa after an initial bolus dose of 90 $\mu\text{g}/\text{kg}$ and then randomization to either repetitive bolus infusion (BI) (90 $\mu\text{g}/\text{kg}$) every two hours or continuous infusion (CI) 50 $\mu\text{g}/\text{kg}/\text{h}$ 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 [94]. 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 [90,95] (Table 3). The initial bolus dose should at least be 90 $\mu\text{g}/\text{kg}$ 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 $\mu\text{g}/\text{kg}$ 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 $\mu\text{g}/\text{kg}$ is recommended before each physical therapy session.

In case of unexpected peri- or postoperative bleeding episodes using bypassing agent one should increase the dose of already initiated treatment agent to maximum dose for rFVIIa (up to 270 $\mu\text{g}/\text{kg}$) or aPCC (200 IU/kg/d). If hemostasis is still not achieved an alternative bypassing agent should be rapidly implemented similarly to unresponsive severe bleeding episodes (Figure 1). If monotherapy with either of the products at maximum doses have been ineffective sequential or concomitant treatment with both bypassing agents might be considered for salvage treatment.

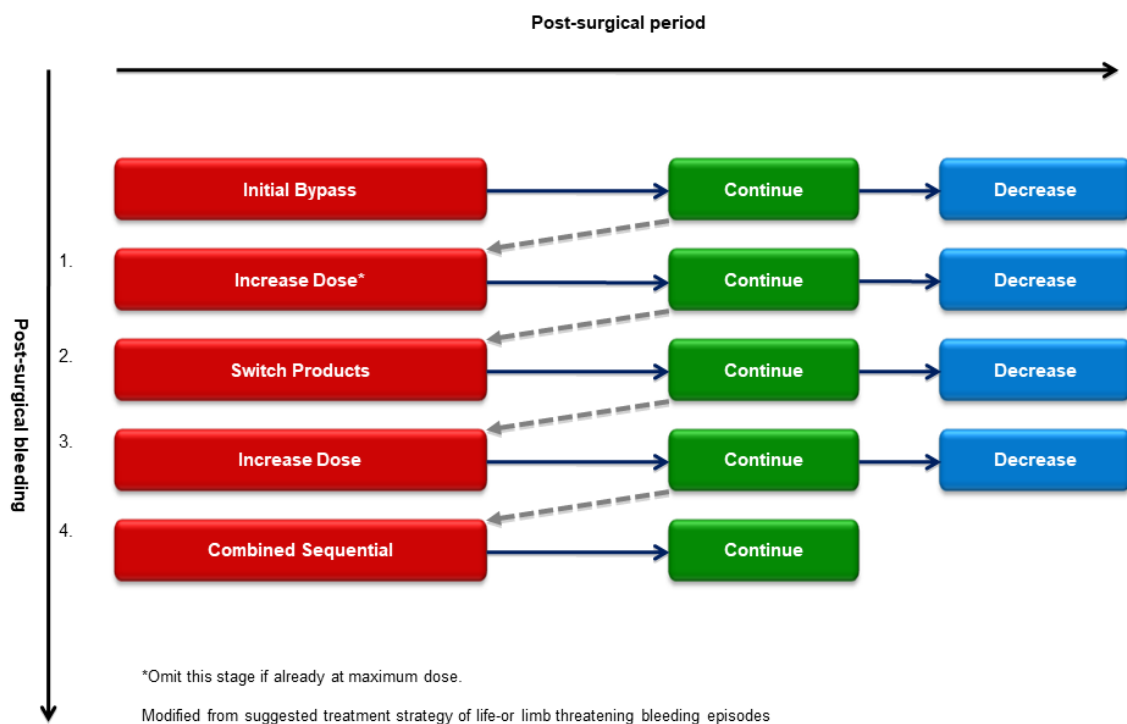


Figure 1: Algorithm to manage post-surgical bleeding episodes in patients with high-titer inhibitors

Alternative treatments

Recombinant porcine FVIII

Recombinant porcine FVIII (r-p FVIII, Obizur®) has recently 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 small phase II study involving 25 bleeding episodes in nine patients, none of which had anti p FVIII antibodies, all bleedings were successfully controlled with eight or fewer injections of r-pFVIII. r-p FVIII was well tolerated and no treatment-emergent serious adverse events were reported [96].

The use of r-p FVIII 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. 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.

pd-FVIIa/FX

In November 2014, a new bypassing agent, Byclot®, was introduced in Japan. This agent is a complex concentrate of plasma-derived activated factor VII (FVIIa) and factor pd-FVIIa/FX. It contains less plasma-derived coagulation factors than pd-aPCC. The efficacy has been evaluated in a phase III study [97] and its use in one orthopedic procedure has been described [98], but it is not available in the Nordic countries.

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. A recently clinical study showed good hemostatic results and no episodes of thromboembolic events or DIC and hypercoagulability in inhibitor patients that had previously been refractory to monotherapy treatment [86,89]. 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.

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 the majority of the patients the use of graduated compression stockings and early mobilization are sufficient to prevent venous thromboembolism.

Comorbidities in the ageing patients with hemophilia

Revision by: **Elina Lehtinen (Helsinki)**

Summary of recommendations

- 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.
- Joint disease: The goal is to try to protect and improve joint function, relieve pain and assist the patient in resuming normal activities of daily living by secondary factor prophylaxis, physiotherapy, lifestyle changes, pain management, and orthopedic procedures.
- Osteoporosis: Assessment of bone mineral density status by imaging studies (DEXA scan) and laboratory evaluation are recommended as part of comprehensive hemophilia care. 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.
- Infection related issues: HAART treatment 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.
- Metabolic syndrome: Effective prevention strategies are necessary throughout life. 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 if overweight. Treatment management, regular clinical and laboratory follow-up should be coordinated with the primary care physician, with consultation services from internal medicine and endocrinology.
- Cardiovascular disease: PWH with cardiovascular disease should receive routine care adapted to the individual situation, in discussion with a cardiologist. DDAVP (desmopressin) should be avoided and thrombolysis is not recommended.

Bare-metal stent should be favored over drug-eluting stent or alternatively coronary artery bypass grafting. Radial artery access site is preferred to reduce bleeding risk. For valve replacement, material that does not necessitate anticoagulation should be chosen. Anticoagulation and antiplatelet therapies are possible with replacement therapy. For atrial fibrillation, no anticoagulation, low-dose aspirin or warfarin are considered depending on basal factor levels and stroke risk.

- Renal disease: Etiology for recurrent hematuria should be evaluated especially in older patients. Peritoneal dialysis could be the preferred choice since no anticoagulation is needed. Hemodialysis is performed with tailored prophylactic factor dosing.
- Cancer: 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. For prostate cancer diagnostics and treatment, antifibrinolytics should be used with caution.

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 male population [99–103]. 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 [104,105].

Current status and recommendations / managing suggestions

Joint disease

The most prominent co-morbidity in middle-aged and older PWHs is irreversible joint arthropathy [99,100,106]. Due to lack of treatment, recurrent hemarthroses result in initial synovial hypertrophy and neoangiogenesis further increasing the risk of bleeding and later on result in degenerative changes of the joint. This leads to limited use of the affected, often weight-bearing joint, causes pain, muscle atrophy, ankylosis (reduces range of motion), contractures and osteoporosis, the latter expressed 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 [107]. Lifestyle changes, e.g. weight loss and regular exercise, would also be beneficial. 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 require procedures, such as radiosynovectomy to control synovial hypertrophy or at times angiographic embolization to stop joint bleeding from arterial origin [107,108]. To reduce severe pain and disability arthroscopy, arthrodesis, arthroplasty or total joint replacement are efficient interventions. Consultation services and multidisciplinary programs with rehabilitation medicine, orthopedics and pain clinics are integral part of the hemophilia care team [105].

Osteoporosis

Osteoporosis is an under-recognized problem in males. There are many predisposing factors for patients with haemophilia, such as prolonged periods of immobility, reduced weight bearing and co-morbidities associated with bone loss [109]. 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 [110]. Thus, assessment of bone mineral density (BMD) by imaging studies (DEXA scan) and laboratory evaluation are recommended as part of comprehensive hemophilia care. Laboratory measurements include serum calcium, vitamin D levels, as well as markers of bone turnover, such as collagen I aminoterminal telopeptide (INTP or Ntx) from urine and procollagen I aminoterminal propeptide (PINP) from serum at baseline and as follow up of drug therapy. Testosterone levels and thyroid function studies are used for ruling out secondary causes for low bone density. Endocrinologist consultation should be utilized as needed.

Infection related issues / complications

With the introduction of HAART (highly active antiretroviral treatment) a substantial decrease in HIV infection related deaths (over time) were seen [110]. Also the HIV related occurrence of NHL (non-Hodgkin lymphoma) has declined. HAART 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 [99,107]. Close laboratory monitoring is therefore recommended. HAART has also been reported to increase frequency and severity of hemarthrosis in hemophilia [110].

HCV is the major cause of chronic liver disease since genotype 1 responds poorly to treatment with subcutaneous Peg-IFN (pegylated interferon) and oral ribavirin. Poor treatment response has also been seen in the numerous PWHs who have a HIV and HCV co-infection. Those who are co-infected also have a marked increased risk for progression in their liver disease with a later risk of transformation from liver cirrhosis into HCC (hepatocellular carcinoma [99,100,107]. Cirrhosis and portal hypertension with development of esophageal varices in combination with hypocoagulable state, including thrombocytopenia, increase the risk of bleeding [107]. The only curative option

is liver transplantation. Modern antiviral therapy including HCV protease inhibitors has markedly improved virological response rates. For patients not suitable for antiviral eradication therapy, disease progression should be followed according to current hepatology recommendations by utilizing laboratory (ALT, AFP) and modern imaging studies (fibroscan) as indicated [110]. Liver biopsies are rarely required. 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.

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 tend to become obese and inactive due to severe arthropathy. In 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. Mean cholesterol levels in patients with hemophilia have been reported to be lower than in the general population [111]. 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 treatment for HIV 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 [112].

Cardiovascular disease

Conflicting data exist on whether hemophilia protects against development of atherosclerosis and cardiovascular events [108,110,113,114]. 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 (detected with high sensitivity-CRP and elevated factor VIII levels in hemophilia B) 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 [115]. The WFH guidelines (www.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. If necessary, documented in case series, a bare-metal stent should be favored since only four weeks of dual antiplatelet therapy is needed, or alternatively a coronary artery bypass grafting (CABG) [99,114]. Radial artery access site is preferred over femoral, in order 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 [116].

Emphasis should be made on not to “overtreat” in the course of 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. Conversely, a certain empirical minimum factor level has to be maintained to allow for necessary antithrombotic treatment. In severe PWHs; >5% for aspirin alone and >30% for dual antiplatelet therapy [107]. Prolonged use of aspirin is not recommended in severe hemophilia, although its use in patients on regular intensive prophylaxis is possible.

Virtually no data are available for defining treatment strategies for cerebrovascular and peripheral artery disease [114]. Some recommendations are available based on case series regarding non-valvular atrial fibrillation and venous thromboembolism [116]. The use of low molecular weight heparin or warfarin could be considered for short term treatment. For atrial fibrillation, no anticoagulation, low-dose aspirin 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 [117].

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 [118]. In chronic renal disease uremia and anemia via platelet dysfunction increase the risk for kidney bleeding [118,119]. 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/or HCV [108,113,120]. For hemodialysis patients prophylactic factor dosing needs to be carefully tailored for access surgery and to allow the required anticoagulation.

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 [107,120]. 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. At times patients are diagnosed with acquired hemophilia due to unusual bleeding of a cancer. Attention must also 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 [121]. Relevant hemostatic treatment must be given to prevent bleeds both in the setting of diagnostic interventions and later on as well prior to surgical, chemo-, or radiotherapeutic treatment. One specific cancer type needs mentioning since it is one of the most frequent cancers in men, with increasing frequency

up to the age of 70: prostate cancer [122]. Prostate specific antigen (PSA) screening has reduced the percentage of disseminated disease at diagnosis more than 20-fold. Needle biopsy should be avoided if possible. 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. Several treatment options are available and seem to have equivalent survival rates.

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 (www.wfh.org), the UKHCDO (www.ukhcdo.org) and the EHTSB (European Haemophilia Therapy Standardization Board) [123]. 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.

Treatment of pain

Revision by: Lone Hvitfeldt (Aarhus) and Fariba Baghaei (Gothenburg)

Among PWHs pain is a very common condition affecting quality of life [124]. Basic pain treatment can be symptomatic and in some cases also directed against the underlying disorder. 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 PWHs especially if the patient has hemophilia arthropathy, in which case the pain often is chronic. Bleeding in a joint or muscle will produce an acute pain and should be treated with relevant hemostatic drug as soon as possible in order to stop the bleeding. The evidence is scarce for the use of ice to reduce bleeding and inflammation due to joint or muscle bleeding in hemophilia.

If the PWH is not on a prophylactic treatment regime with factor concentrate and has a target joint, prophylaxis should be offered to avoid recurrent bleeding, inflammation and pain.

Several instruments exists for the evaluation of pain in PWHs among which are the visual analogue scale (VAS), health related quality of life (HRQoL), McGill Pain Questionnaire (arthritis) and others [125,126].

In many situations chronic pain should be managed in a multidisciplinary team where the patient is rehabilitated with the help from pain management clinic, physiotherapists, psychologist, orthopedists, social workers, experts in management of pain in addition to the hemophilia doctors and nurses.

Analgetics

Mild analgetics 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 codeines conversion to morphine. In approximately 10% of the white population codeine is without analgetic effect, caused by inability to convert codeine to morphine. Tramadol is a synthetic codeine analogue.

Common side effect to treatment with codeine, tramadol and morphine is nausea, constipation, vomiting and drowsiness. Codeine should be used with caution, especially in elderly patients because of the risk of cognitive side effects.

Information about dosage of analgetics to the patients is very important for the prevention of toxicity e.g. liver toxicity in the use of paracetamol in patients with chronic hepatitis or HIV.

Aspirin has an irreversible inhibition on platelet aggregation and should not be used in treatment of pain for PWHs. If the pain is caused by inflammation in a joint COX-2-inhibitors (celecoxib or etoricoxib) can be considered in selected PWHs. 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 in specific patients. One of the most serious side effects is gastroduodenal ulcers. The risk of gastrointestinal ulcers is lower with COX-2 inhibitors than COX-1 inhibitors and 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 effect.

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 indication and with caution in the treatment of pain in PWHs 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 people with hemophilia 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 analgetics with prolonged effect especially for treatment of pain at night. Also transdermal formulas can benefit many patients with chronic pain issues.

In the case of severe acute pain morphine could be necessary to use at start, but due to the risk of addiction it should be given for a limited period of time.

Patients with severe complex chronic pain should be managed at a pain clinic. In the treatment of chronic pain gabapentin (medication for epilepsy) or tricyclic antidepressants can have an additive effect on the treatment with analgetics. It is important to be aware of 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 in order to minimize pain.

Pain in PWHs could be managed as described below [127,128]:

Mild pain and/or chronic pain

- Paracetamol alone or combined with
- Codeine or
- Tramadol

Pain and joint inflammation (NSAIDs)

- COX-2 inhibitors - celecoxib or etoricoxib
- COX-1 inhibitors – ibuprofen only in special circumstances

Acute severe pain

- Morphine

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. Synovectomy with the 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.

Intraarticular corticosteroid injection in joints with hemophilia 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 [129].

If the PWH has a joint with inflammation, 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 [130,131].

A prophylactic dose of factor concentrate should be given prior to the injection of corticosteroid. The intra-articular injection must be given under sterile condition 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 to intra-articular corticosteroid is infection.

The dose of corticosteroid depends on size of the joint and the degree of inflammation. The dose of corticosteroid could be e.g. triamcinolonehexacetonide (Lederspan®) 10-40 mg or triamcinolonacetonid (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 h. 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, increased sweating in minutes to hours after the injection. In patients with arthritis approximately 2% can experience worsening of the pain lasting the first 24 h after the injection. Although systemic effects of the corticosteroid injection is 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.

Physiotherapy

Revision by: Elisabeth Brodin (Göteborg)

Reviewed by Marianne Berg and Rut Elise Dybvik (Oslo), Karin Juel Hansen and Lise Karlmark (Copenhagen)

Recommendations

Summary of physiotherapy work at treatment centers in the Nordic countries:

- Informs about the joints and muscles function to parents, teenagers and adults
- Assess physical activity, joint mobility and muscle strength
- Proposes appropriate recreational and sporting activities
- Tests out and practicing assistive devices
- Designs exercise programs after a bleeding disorder
- Patients exercise to increase mobility and muscle strength
- Patients exercise before and after orthopedic surgery
- Treatments for pain relief
- Is a resource for colleagues outside the treatment center

Introduction

The role of the physiotherapist in the treatment of the hemophilia patients has changed over the years because of the improvement of the medical treatment [6].

Physiotherapy for the hemophilia patient is divided in to three categories: Prevention, assessment and treatment/rehabilitation.

Prevention

Patients will at an early age receive prophylaxis with coagulation factor concentrates and can be physically active to the same extent as non-hemophiliac children resulting in normal physical strength and mobility [132]. Low physical activity can result in impaired bone mineralization and reduced bone mineral density in children with hemophilia compared with healthy [133]. Moderate intensity of aerobic walking exercise improves bone metabolism and hand grip strength in adult persons with moderate hemophilia A [134]. 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 at an early age [135]. Not only patients with hemophilia, but everybody (both adults and children) should be physically active for 30–60 min every day. The physiotherapist has an important role in informing and supporting PWH and their families about physical activity and sports that are appropriate for PWH [136].

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 [137,138]. PWH can also gain physically from increased muscle strength, joint health, balance and flexibility achieved through physiotherapy, physical activity, exercise and sport [138,139]. The physiotherapist can also educate parents how to examine the joint mobility of the youngest children for early detection of joint bleeding.

Assessment

Assessment instruments that are disease specific for PWHs have been developed over the past 10 years [140]. The physiotherapist will assess the joint and muscle function during the annual control at the treatment center. This includes joint mobility, muscle strength, pain, joint and muscle contractures, axial changes in the joints, balance and gait functions.

In acute bleeding a physiotherapist can help with differential diagnosis between joint and muscle bleeding and synovitis together with the physician. Ultrasound can complete the assessment for a correct diagnose [141]. When US imaging performed and scoring by physiotherapists using Hemophilia Early Arthropathy Detection (HEAD-

US) [142] there is a good overall repeatability of the protocol and this complements the physical examination when screening and monitoring joint health of people with hemophilia [143].

The Hemophilia Joint Health Score (HJHS) has been developed for children from 4 to 16 years of age and its validity and reliability tested. It is used for the evaluation of joints in children and young adults [144,145]. 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.

Other evaluation instruments that may be present are visual analog scale (VAS) to rate the pain experience in daily activities or at acute trauma/bleeding [146]. 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) [147].

Based on our examination we can recommend relevant steps that can benefit PWH such as contact to occupational therapist, when the patients need assisted devices at home for the ADL (activities of daily living). A disease-specific ADL status is developed in India [148] but is not used in the Nordic Countries at the moment due to cultural differences between the countries that makes the manual not suitable for the Nordic conditions. 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 [149].

Intervention (treatment/rehabilitation)

The purpose of rehabilitation of hemophilia arthropathy and after an acute bleeding in the joint or muscle is to reduce pain, restore joint mobility and muscle strength. Repeated bleedings in a joint leads to cartilage damage and give a hemophilia-related joint disease (hemophilia arthropathy). Active exercise under the guidance of a physiotherapist in combination with intensive treatment with factor concentrate can break the vicious circle. The results are better the sooner physiotherapy begins [150].

In the acute phase the early management can summarize as PRICE meaning Protection and joint Rest, relieve acute pain with Ice and prevent and treat swelling with Compression and Elevation [151]. The physiotherapist plans an exercise program to

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 [135,152].

Treatment may include different types of mobility exercises (active, active unloaded, passive), posture instructions, careful manual extractions for increased mobility and pain relief purposes, strength and endurance exercise, coordination training, etc. Exercise in warm basin can be useful as pain relief like TENS, heat and cool pack [136,151,153]. Techniques used in routine clinical practice can be used if the person with hemophilia have appropriate treatment with clotting factor [151]. There is a lack of confidence in the evidence for exercise in persons with hemophilia due to small numbers of randomized controlled trials but no adverse effects are reported in the different exercise intervention studies published [154,155]. Recommended frequency is 3 times per week to reach desired results [136].

Patients undergoing orthopedic surgery, for example synovectomy or different types of joint replacement receive physiotherapy exercise both before and after surgery [156]. 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 actual programs/protocol at the orthopedic clinic for the current operation. If the hemophilia-related arthritis 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 [157]. The physiotherapist also tests out walking aids and recommend other appliance needed in daily life.

Carriers of haemophilia

Revision by: Anna Olsson (Gothenburg)

Background

Due to X-chromosome inactivation the clotting factor levels in carriers are expected to be about 50% of the levels of non-carriers. However, the factor levels may vary from very low to the upper limit of normal values [158]. Carriers with factor levels less than 0.40 kIU/L are diagnosed with haemophilia. In addition, carriers may have bleeding symptoms similar to mild haemophilia even with factor levels close to normal range. It is estimated that approximately 20% of carriers are symptomatic to some degree and may require haemostatic support during surgery, trauma and delivery [158]. The factor level of an obligate or possible carrier should be checked at a young age and especially prior to an invasive procedure or in case of bleeding symptoms. The timing of genetic testing for carriership needs careful consideration taking into account age and psychosocial issues [159]. It's also important that the girl as well as her family understand that a normal factor level does not exclude carriership.

Prenatal diagnosis

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 discussion of the genetic risk and the options of prenatal testing that are available [160].

Chorionic villus sampling (CVS) is the principal method used for prenatal diagnosis of haemophilia. The procedure is performed during the 11 to 13th week of gestation. If later in pregnancy, an amniotic fluid sample may be used as DNA source for prenatal diagnosis. Both procedures are associated with a risk of miscarriage at approximately 1% [161]. Haemostatic cover should be arranged prior to any invasive procedure if the factor level is <0.50 kIU/L. Knowledge of foetal gender allows appropriate management of labour and delivery. Ultrasound diagnosis can be used from late second trimester and is based on visualization of the external genitalia [162]. Analysis of free foetal DNA (ffDNA) in the maternal circulation is an alternative non-invasive means of determining

foetal sex [163]. Pre-implantation genetic diagnosis (PGD) may be an option for couples who would not consider termination of a pregnancy and for those with concurrent infertility. Since in-vitro fertilization is used, the technique is labour intensive and technically challenging [34].

Management of gynaecological and obstetrical bleedings

One of the first haemostatic challenges a carrier may be facing is menstrual bleeding. Girls with haemophilia should have a treatment plan prior to menarche for the possibility of excessive menstrual blood loss. Excessive bleedings may appear with the first or any following menstrual period during the adolescence. Haemostatic therapeutic options for the management of menorrhagia include tranexamic acid, DDAVP and clotting factor replacements. Hormonal therapy should be considered and, if appropriate, introduced by a gynaecologist with knowledge of bleeding disorders in collaboration with HTC [164].

During pregnancy the FVIII levels in carriers of haemophilia A may increase sufficiently to permit safe haemostasis during delivery. In carriers of haemophilia B the FIX level cannot be expected to increase to the same extent [165]. Factor level should be checked at gestation week 32-34 to allow appropriate management of delivery and to assess the need for prophylactic treatment. A written delivery plan should be drawn up in advance and the delivery should take place in a unit with suitable expertise. As a general rule, prophylactic treatment to prevent from bleeding during delivery and postpartum is given to carriers with subnormal factor levels. If treatment is required, factor levels of 1.0 kIU/L should be aimed for to cover labour, delivery and the immediate postpartum period. The treatment should be continued to maintain factor levels above 0.50 kIU/L for at least three to four days after vaginal delivery and five to seven days after caesarean section [164]. Tranexamic acid may be used in combination with replacement therapy and as a sole therapy for carriers with factor levels within normal range when clinically required. The risk for secondary postpartum haemorrhage is increased when clotting factors return to pre-pregnancy levels after delivery and tranexamic acid should be continued postpartum as needed [166]. DDAVP may be used in carriers of haemophilia A to improve haemostasis after the child is born. Factor levels > 0.50 kIU/L are required for insertion and removal of an epidural catheter and for spinal anaesthesia [167,168]. Vaginal delivery is recommended if no other obstetric

concerns, however caesarean section should be considered early when needed to avoid emergency caesarean. Assisted vaginal delivery, vacuum extraction and use of forceps, as well as foetal blood sampling and foetal scalp electrode should be avoided for male babies at risk of haemophilia [169–171]. Cord blood sampling and diagnostic testing is recommended for all male babies. Vitamin K should be administered by an oral regimen to neonates with low factor levels [172].

Hemophilia nurse functions

Revision by: Linda Myrin Westesson (Gothenburg) and Malin Axelsson (Malmö)

Recommendations

The functions of the haemophilia nurse may vary some in the centers of the Nordic countries, however the foundation of the function is care, education, communication and support.

The comprehensive care of persons with haemophilia (PWH) and other inherited bleeding disorders is complex and it requires a multidisciplinary team. The haemophilia nurse plays a key role in the comprehensive care of the PWH. The nurse educates PWH, parents and caregivers in illness management and has an important roll in supporting the PWH and the family. The nurse is a link between the PWH and the family, the haemophilia center and society [82]. The functions of the haemophilia nurse may vary some in the centers of the Nordic countries, however the foundation of the function is care, education, communication and support.

The haemophilia nurse educates PWH, parents and other family members about haemophilia. He/she provides information and education about the illness to preschool, school, nursing homes and to other health care providers. The nurse also has close contact with local health care professionals and the PWH primary care contact. The nurse makes home visits when needed, as well as acting as a consult towards nurse colleagues when PWH are hospitalized. Ideally the haemophilia nurse coordinates and facilitates the comprehensive team meetings and collaborates within the multidisciplinary team.

As the population with haemophilia is ageing and co-morbidities will add to the complexity of the illness, the haemophilia nurse needs to focus not only on haemophilia. It's also important to have a more holistic approach towards PWH and their families, if not to improve at least to maintain a good health-related quality of life for PWH [10,82].

The nurse plays an important role as a supporter for newly diagnosed children and parents. He/she helps the family to adjust to the new situation with the illness and

emphasize the healthy aspects of the child [173]. The nurse recognizes and articulates the needs of the child, parents and other family members to the haemophilia team. The nurse educates the parents in home treatment and other aspects of the illness and encourages the parents to increase their knowledge about the illness and to independently be able to perform home treatment. Another important function is to provide information about haemophilia to preschool and school. The nurse has knowledge about haemophilia and complications that may occur from treatment or the illness itself. The hemophilia nurse is a resource, which parents or others around the child can turn to when they need guidance regarding haemophilia in daily life [174].

The supporting function of the nurse is vital for families with children affected by inhibitors [175,176]. The nurse has to be aware of problem associated with inhibitors and the extensive treatment that the child needs. He/she educates parents on how to manage and handle the advanced ITI treatment in a central venous access device [177].

The nurse has knowledge about challenges at different life stages such as: childhood, adolescence, young adults and elderly. The life stages affect and influence the treatment and management of the haemophilia in different aspects and the nurse adapt her/his way of work and interacting. Over all, personal centre care is crucial for the success of achieving good self-management and self-reliant PWH [174,177–179].

The haemophilia nurse has knowledge of the inherited aspects of the illness and can perform basic genetic counseling. The nurse recognizes the female carriers and is aware of their bleeding risk [174].

The haemophilia nurse has many functions among which the most important are:

- Educate about illness management and home treatment
- Support PWH and their families
- Plan and participate in regular follow-ups at the haemophilia treatment center (HTC)
- Perform administration of factor concentrates and blood samples
- Telephone counseling to PWH, parents, preschool and other health care professionals
- Guide and educate other health care professionals in- and outclinic

Hemophilia nurse functions

- Consultant role to colleague nurses when PWH is hospitalized
- Inform preschool, school and nursing homes etc. about haemophilia
- Keep and update haemophilia registries
- Participate in research and clinical trails
- Participate in nursing research and developing project about haemophilia and other inherited bleeding disorders

Dental care

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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 [180–183]. The staff at the hemophilia center can provide information to the patient and his dentist about which kind of treatment could be given and which kind of treatment should be given at the department for oral and maxillofacial surgery affiliated with the hemophilia center.

Most patients, both adults and children can have regular check up at their own dentist for caries and cleaning of the teeth. Treatment of caries, root canal treatment, tooth prosthesis and orthodontic tooth regulation could also be done at the local dentist in most cases. All treatments which do not cause bleeding can be performed at the patient's own local dentist. Especially inhibitor patients should be treated in close collaboration between the dental clinic and the hemophilia center since they have a 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 for oral maxillofacial surgery and in some cases prophylaxis with antibiotics is needed.

Hemostatic treatment

Prophylactic treatment with factor concentrate may be necessary for some patients depending on the severity of hemophilia and the character of the procedure at the dentist. The treatment at the dentist/ surgeon could be planned on one of the days when the patient receives prophylactic treatment with factor concentrate. The procedure at the dentist should be done as soon as possible after the infusion of factor concentrate

within one to two hours. 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 swabs 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.

In more advanced jaw or oral surgery repeated doses of factor concentrate 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 administration is 0.3 µg/kg bodyweight.

Besides the treatment with factor concentrate 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 adults. 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 already 1-3 days prior to surgery, 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 or
- Factor concentrate
- Local hemostatic agents

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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