Factor VII deficiency

Practical Nordic guideline for diagnosis and management

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Version 1. Published 2019/02/07. Valid 3 years from publication.
Electronic version available at www.nordhemophilia.org

Content

Abbreviations

BI – Bolus injections

CNS – Central nervous system

EGF - Epidermal growth factor-like domains

EN-RBD – European Network of Rare Bleeding Disorders

F7 - human factor VII gene

FII – Coagulation factor II

FV - Coagulation factor V

FVII – Coagulation factor VII

FVII:C - Coagulation factor VII activity measured by a clot-based assay

FVIIa – Activated coagulation factor VII

FIX - Coagulation factor IX

FX - Coagulation factor X

FXa - Activated coagulation factor X

FXIII - Coagulation factor XIII

GI - Gastrointestinal

Gla - gamma-carboxyglutamic acid

h - hour

ICH – Intracranial heamorrhage

IU – International units

pd – Plasma derived

RBD – Rare bleeding disorders

rFVIIa – Recombinant activated factor VII

TF – Tissue factor

TFPI - Tissue factor pathway inhibitor

ttd – Three times daily

TXA – Tranexamic acid

VKDB – Vitamin K deficiency bleeding

Preface

The Nordic Haemophilia Council commissioned the work on Practical Nordic Guideline for diagnosis and management of FVII deficiency. A working group with representatives from six haemophilia treatment centers in four Nordic countries was formed. The work was partly based on the recent ph.d. thesis by Dr. Hoa Tran, Oslo, Norway, and owing to the high prevalence of severe factor VII deficiency in Norway and the accumulated expertise, the work was supervised by professor Pål André Holme, Oslo, Norway. The final document was assembled and finalized by Eva Zetterberg, Malmö, Sweden and Ole Halfdan Larsen, Aarhus, Denmark. A hearing version was distributed to all relevant treatment centers in the Nordic countries prior to publication.

Litterature searches was performed by the individual subgroups. However, factor VII deficiency is a rare bleeding disorder, with very limited data available. Hence, the quality of evidence supporting the recommendations are generally weak, and using a systematic rating system in this setting was not found relevant. However, when clinical decisions cannot be based on hard evidence, the present practical consensus guideline on what is considered state-of-the art treatment in the Nordic Countries may hopefully be a helpful tool tailoring treatment in factor VII deficiency patients.

The present guideline is available as an e-publication at www.nordhemophilia.org.

0. Overview of recommendations

- *Recommendation for analysis of FVII activity*
    - For analysis of factor VII activity, human tissue or recombinant thromboplastin as clotting activator is preferred.
- *Recommendation for definition of FVII deficiency*

  FVII:C>50%: Normal

  FVII:C 35-50% : Low FVII level

  FVII:C < 35% : FVII deficiency
- *Recommendation for FVII genotyping*
    - In clinically severe factor VII deficiency, genotyping allows for prenatal counseling and is recommended. In moderate, mild or asymptomatic cases, genotyping is not recommended for routine care.
- *Recommendation for classification*
    - Severity of factor VII deficiency should be classified according to bleeding phenotype in addition to factor level.
- *Recommendations for antifibrinolytics*
    - Tranexamic acid can be applied as monotherapy for treatment or prevention of mild bleeding or as adjunctive therapy to factor replacement in more severe cases.
    - Intravenous injection with tranexamic acid 10 mg/kg body weight every 8 hours or an oral dose of tranexamic acid 20-25 mg/kg 3-4 times daily.
- *Recommendation for substitution therapy*
    - Substitution therapy should only be given to high-risk patients defined as:
        - Factor VII level <10%
        - Factor VII level 10-20% and a history of trauma induced excessive bleeding and/or frequent nosebleeds
        - Significant bleeding history (joint or intracranial bleeds) irrespective of FVII level
        - Paediatric patients (see paediatric section)
    - rFVIIa is recommended as the preferred substitution therapy
    - rFVIIa can be administered as bolus injections or continuous infusion

- *Recommendation for long-term prophylactic factor replacement therapy*
    - Long-term prophylactic factor replacement therapy should be considered in severe FVII deficiency with severe bleeding phenotype.
    - rFVIIa initially 15-30 µg/kg 2 -3 times weekly followed by individualised dose tailoring is suggested
- *Recommendation for follow-up in adult patients*
    - High-risk patients should be offered annual follow-up visits at a comprehensive haemophilia care center
- *Recommendations for pregnancy and delivery*
    - All patients with FVII deficiency should receive tranexamic acid at start of delivery or prior to caesarean section
    - Irrespective of mode of delivery, rFVIIa or other haemostatic agents should be available in the case of haemorrhages.
    - Prophylactic treatment with rFVIIa during vaginal delivery and caesarean section should only be considered in high-risk patients
    - rFVIIa is given 15-30 µg/kg prior to and post-partum every 4-6 hours for at least 3 days
- *Paediatric recommendations*
    - Paediatric reference ranges must be used when evaluating the levels of Factor VII in children
    - Vitamin K deficiency and liver disease should be ruled out before the diagnosis of factor VII deficiency can be made in children
    - Particularly young children may benefit from higher doses and more frequent administration of rFVIIa compared to adults
    - Prophylactic treatment with factor concentrates should be considered early in severe FVII deficiency with a severe bleeding pattern

1. Introduction

1.1 Factor VII and factor VII deficiency

In the early 50´s three independent research groups, Alexander et al. [1, 2], Koller et al. and Owren et al. discovered coagulation factor VII (FVII) [3, 4]. FVII, also known as serum prothrombin conversion accelerator (SPCA) or proconvertin is a vitamin-K dependent glycoprotein synthesised by hepatocytes and secreted into the blood as a single chain zymogen. Extrahepatic synthesis of FVII has been found in macrophages and in smooth muscle cells in atherosclerotic vessels where it was co-localized with TF [5]. Colon cancer cells have also been shown to synthetize FVII, but evidence about a possible role in tumour progression or metastasis is conflicting [6, 7].

FVII consists of an N-terminal gamma-carboxyglutamic acid domain (Gla domain) followed by two epidermal growth factor-like (EGF1 and EGF2) domains and a C-terminal protease domain. Activation of FVII results in a two-chain FVIIa molecule consisting of a light chain (the Gla-EGF1-EGF2 domains) and a heavy chain (the protease domain) held together by a single disulphide bond [8]. FVIIa is the factor that initiates the TF-dependent pathway of coagulation [9]. During coagulation, in the presence of calcium, the TF/FVIIa complex activates factor IX (FIX) and factor X (FX) on the surface of activated platelets, converts prothrombin to thrombin resulting in fibrin formation through proteolytic reactions involving factor V (FV), fibrinogen and factor XIII (FXIII) [10]. In contrast to the procoagulant property of FVIIa, zymogen FVII has inhibitory effect on thrombin generation by competing with FVIIa for binding to TF. This inhibitory effect has been suggested to be important for regulation of the haemostatic response [11].

FVII has the shortest half-life of all coagulation factors (3-6 hours). The FVIIa-TF complex is inhibited by the tissue factor pathway inhibitor (TFPI), a serine protease inhibitor synthesised by endothelial cells that consists of 3 Kunitz type domains. The mechanism of inhibition involves binding of activated FX (FXa) to domain 2 of TFPI and then to the TF/FVIIa complex through domain 1 [12]. Binding to FXa makes TFPI a much more potent inhibitor of the TF/FVIIa than TFPI alone. No direct protease inhibiting functions have been demonstrated for domain 3 [13].

The human factor VII (*F7*) gene is located at chromosome 13q34, close to the gene encoding for FX and comprises nine exons [14, 15]. FVII deficiency is an autosomal recessive inherited bleeding disorder caused by *F7* gene mutations [16]. In a multicenter study carried out by the Study Group of the Greifswald Registry of FVII Deficiency, 131 different gene mutations in 717 subjects have been identified [16, 17]. Data from the Mutation Database found that missense mutations were the most common, accounting for about two thirds, whereas the remainder were null mutations.

FVII-activity is measured by the clotting method. In patients with mutations FVII Padua (Arg304Gln), FVII Nagoya (Arg304Trp), and FVII Shinjo (Arg79Gln) there are discrepancies in FVII activities depending on the type of tissue thromboplastin used in the assay. Animal derived thromboplastin results in lower FVII levels without corresponding bleeding tendency [18].

Recommendation for analysis of FVII activity
For analysis of factor VII activity, human tissue or recombinant thromboplastin as clotting activator is preferred.

1.2 Clinical manifestations and classification

FVII deficiency is the most common of the rare congenital bleeding disorders with a prevalence of about 1:500,000. There is however large variation in prevalence between different countries [19-21]. Clinical phenotypes range from asymptomatic individuals to severe bleeding tendency. Epistaxis, bruising and menorrhagia are the most frequent bleeding manifestations but more serious manifestations such as gastrointestinal (GI), intracranial, or joint and muscle bleeds may occur [22, 23]. Interestingly, thrombosis has been reported in FVII deficiency although in most instances the thrombotic event occurred in association with substitution therapy or in the presence of known risk factors for thrombosis [24-26].

There is currently no available assays to predict the bleeding tendency in FVII deficient individuals. A study based on data from The European Network of Rare Bleeding Disorders (EN-RBD) included 224 patients with FVII deficiency and found a weak correlation between

the coagulation factor activity level and clinical bleeding severity [27]. The registry also found that the haemorrhagic diathesis varied in persons with similar FVII:C activity level and genotype [16]. Severe FVII deficiency cases with factor VII levels less than 2% were all either homozygous or compound heterozygous for mutations disrupting appropriate expression such as promotor, splice-juction or frameshift mutations. Patients with mild to moderate clinical phenotypes were homozygous or compound heterozygous for missense mutations. However, some missense mutations were also associated with a severe phenotype [16]**.** A more recent study suggested that the presence of large deletions is underestimated [28]. As the bleeding phenotype cannot be predicted from the mutation, genotyping is not recommended as standard of care.

FVII deficiency-definition

The diagnosis of FVII deficiency is currently made by analyses of FVII:C, but different cut-off levels are applied as diagnostic in the literature. In a French study on surgery, levels below 35% are taken as diagnostic, but given the variability between assays, patients with levels up to 40% were included in the study (41). In a recent update from the Ad-Hoc Study group that included 123 patients (28) FVII:C less than 50% was used as cut off. In this population only 33% were symptomatic and severe bleeding occured only in patients with FVII:C below 10%.

From a practical point of view our recommendation would be to avoid the diagnosis of FVII deficiency in patients with levels between 35-50% and no bleeding symptoms. They should be informed that they have low levels of FVII, that affects the result of other coagulation assays (INR), but has no clinical implications.

Recommendation for definition of FVII deficiency

FVII:C > 50% : Normal
FVII:C 35-50% : Low FVII level
FVII:C < 35% : FVII deficiency

A recent study found that major bleeding at diagnosis is an independent predictor for the patients' bleeding risk in FVII deficiency [23]. Another study suggested that the type and number of bleeding symptoms might be used to classify the clinical phenotype, ranging from severe, moderate to mild to guide substitution therapy**.** The EN-RBD suggests that the bleeding phenotype in FVII deficiency should be classified as outlined in table 1 [27]. The clinical utility of this classification has not been validated.

Table 1. Categories of clinical bleeding severity according to *Peyvandi et al. [27]*.

Clinical severity	Definition
Asymptomatic	No clinical bleeding tendency
Grade I	Bleeding after trauma or drug
Grade II	Spontanous minor bleeding
Grade III	Spontanous major bleeding

Recommendation for FVII genotyping

In clinically severe factor VII deficiency, genotyping allows for prenatal counseling and is recommended. In moderate, mild or asymptomatic cases, genotyping is not recommended for routine care.

Recommendation for classification

Severity of factor VII deficiency should be classified according to bleeding phenotype in addition to factor level.

1.3 Management of factor VII deficiency

Treatment principles for FVII deficiency are similar to treatment of haemophilia, i.e replacement of the deficient coagulation factor to a haemostatic level that prevents or stops bleeding [29]. Prophylaxis therapy may be indicated in patients with frequent joint or muscle bleeds with subsequent increased risk of long-term joint destruction and impaired daily life performance.

Several treatment options are available for treatment of FVII deficiency. Recombinant FVIIa (rFVIIa) is the recommended first line therapy because it is highly effective and is associated with low prevalence of serious adverse events.
The dose needed in FVII deficiency (15-30 µg/kg) is lower than required in haemophilia patients with inhibitors where a high dose (90 – 270 µg/kg) is necessary to achieve haemostasis [30]. During major surgery or major bleeds the short half-life of rFVIIa of 2-3 hours necessitates repeated bolus injections for sustained haemostasis [31].
Other FVII containing products such as plasma-derived (pd) FVII, four factor prothrombin complex concentrates (PCC) and fresh-frozen plasma (FFP) have also been demonstrated useful [29, 32]. However, some safety concerns have been raised as venous thrombosis has been reported in association with the use of pdFVII and PCC [24]. Although known risk factors for venous thrombosis (VT) were present in these cases, the reports demonstrate that FVII deficiency does not protect the patients from thrombotic complications and replacement therapy should be used with caution in this patient population. FFP contains only a small amount of FVIIa, and carries a potential risk of volume overload and blood borne viral infections [33]. However, FFP may be a valuable haemostatic agent in case rFVIIa, pdFVII or PCC are not available for treatment or prevention of bleeds in FVII deficient patients.

1.4 Current challenges and future perspectives

There is currently no validated laboratory method to predict bleeding risk in patients with FVII deficiency. It is therefore challenging to select the patients who will benefit from replacement therapy before bleeds occur. Some patients have increased bleeding tendency and carry a high risk of developing haemarthroses. These patients will likely benefit from regular prophylactic treatment similarly to that in haemophilia patients. Nevertheless, selection of patients, optimal dosing and frequency of infusions remains to be established. It was hypothesized that global haemostatic assays might have the potential to predict the bleeding risk in patients with severe FVII deficiency but as shown by Tran et al. this was not useful [34]. Furthermore, more insight into mechanisms underlying the diversity in genotype-phenotype in factor FVII deficiency is warranted in order to extend our understanding of the coagulation process.
During surgery, rFVIIa is commonly administered as frequent bolus injections (BI) to prevent bleeding in patients with FVII deficiency but the optimal dose and frequency of

BI remain to be determined. Furthermore, continuous infusion has been shown to be haemostatically equivalent and more economic, since less concentrate is needed [35]. Continuous infusion is therefore recommended at centres where handling of intravenous pumps at the surgical wards is a safe option.

2. Overview of haemostatic treatment options

2.1 Treatment of FVII-deficiency

The relationship between factor VII level and bleeding tendency is poor and thus, the clinical bleeding history (phenotype) is the most important predictor for bleeding tendency and surgical complications.

Treatment recommendations on bleeding episodes and optimising haemostasis during invasive procedures and child delivery are all dependent on:

- The phenotype of FVII deficiency
- The severity of the bleed or surgical procedure
- The local supply of factor concentrates and/or plasma products.

2.2 Factor substitution therapy options

2.2.1 Recombinant FVIIa (rFVIIa) – NovoSeven®

rFVIIa has an approved indication for treatment and prevention of bleeding in FVII deficiency. It is a prohaemostatic drug containing recombinant FVII in an active form and has a shorter half-life (2-3 hours) compared to non-activated FVII. rFVIIa acts locally on the injured vessel by accelerating thrombin formation and platelet activation.

Treatment recommendations

Commonly, a low bolus dose of 15-30 µg/kg body weight is given and repeated every 4 to 6 hours until bleeding is controlled [36]. More recent publications have demonstrated that one dose daily with an intermediate dosage of 60 µg/kg body weight is sufficient to treat spontaneous bleeding, though more severe haemorrhages such as intracranial and gastrointestinal bleeds need repeated infusion for optimal effect [37]. For surgical procedures, repeated frequent bolus doses or an initial bolus dose followed by

continuous infusion of rFVIIa are applied [35]. Please see below for more detailed recommendations.

Pros

- Effective
- Small amounts needed
- No risk of virus transmission

Cons

- Expensive
- Not available in all hospitals
- Theoretical risk for development of inhibitors

2.2.2 Other available sources of Factor VII

Plasma – fresh-frozen, fresh-stored or OctaplasLG®

Plasma contains all coagulation factors and inhibitors. Plasma can be given as fresh-frozen or fresh-stored plasma. In FFP the concentration of FVII is relatively stable compared to FV and FVIII which are halved within 24 hours. FFP needs 45 minutes to defrost, whereas the fresh-stored plasma is preferred in an emergency situation despite the concentration of coagulation factors is slightly lower. Norway and Finland only apply OctaplasLG® aiming to reduce the risk of adverse effects from plasma particularly the risk of transmitting infectious agents, severe allergic reactions or TRALI. OctaplasLG® is solvent/detergent (processed and filtered) treated FFP from male blood donors. All coagulation and haemostatic parameters are equivalent to the raw product, FFP, except the lower levels of protein S and antiplasmin.

Treatment recommendations:

Start dose for treatment or prevention of bleed: 10-15 ml per kg body weight. This should increase the patient's plasma coagulation factor levels, including FVII by 0.15-0.25 IU/ml. If haemostasis is not achieved, increased doses are needed.

Pros:

- Lower costs compared to rFVIIa and factor concentrates
- Available at most hospitals

Cons:

- Risk for volume overload when repeated infusions are needed
- Insufficient in severe FVII-deficiency
- Risk for virus transmission

Prothrombin-complex concentrates (PCC) - Confidex®, Octaplex®, Prothromplex®

The human plasma-derived 'Prothrombin-complex concentrate' (PCC) contains the K-vitamin dependent coagulation factors and inhibitors; FII, FVII, FIX, FX as well as protein C and protein S.

In the Nordic countries, there are three approved PCC products by the national medical product agencies; Confidex®, Octaplex® and Prothromplex®

Treatment recommendations:

Recovery for FVII is estimated so that 1 IU of FVII per kg body weight increase the plasma activity of Factor VII with 1.7% or 0.017 IU/ml.

The amount of PCC needed is calculated by:

PCC content of Factor VII needed (IU) = Body weight [kg] x desired increase of FVII [IU/ml] x (1/0.017).

The concentration of FVII varies between products and batches and must be taken into account when calculating the doses.

Pros:

- Compared to FFP smaller volumes are needed
- Efficient

Cons

- Costs
- Wide variability in the concentration of FVII between batches
- Repeated doses of PCC may led to accumulation of the other K-vitamin dependent coagulation factors due to longer half-life compared to FVII, and thereby increase the risk of thrombotic complications

- PCC contains low amounts of heparin implying a risk of heparin-induced thrombocytopenia – HIT (low)
- Risk for viral transfusion (low)
- Development of inhibitors (low)

Plasma derived factor VII

Is rarely applied. PdFVII is available in Denmark, but not in the other Nordic countries.

2.3 Antifibrinolytics: Tranexamic acid - Cyklokapron®

Tranexamic acid is an inhibitor of fibrinolysis and can be used alone or as adjunctive therapy to factor concentrates such as rFVIIa. The general use of tranexamic acid for treatment and prevention of bleeding has recently been thoroughly described by Tengborn *et al.* [38]. The British Guidelines on rare coagulation disorders do not comment on tranexamic acid (TXA) as adjunctive therapy to factor concentrate, but only recommend that is should be considered as monotherapy in mild bleeding [39]. Tranexamic acid as adjunctive therapys is largely absent in case series on bleeding in FVII deficiency available from the literature. However, tranexamic acid is widely used in Scandinavia as adjuntive therapy in bleeding disorders including FVII deficiency [35]. In other patient groups, it is clearly demonstrated that tranexamic acid reduces bleeding, and may often be sufficient treatment of non-severe mucosal haemorrhages [38]. Tranexamic acid has also been shown to reduce the risk of death in bleeding trauma patients, particularly when administered within 3 hours of traumatic injury [40, 41].

Recommendations for antifibrinolytics

Tranexamic acid can be applied as monotherapy for treatment or prevention of mild bleeding or as adjunctive therapy to factor replacement in more severe cases. Intravenous injection with tranexamic acid 10 mg/kg body weight every 8 hours or an oral dose of tranexamic acid 20-25 mg/kg (max. 2 g) 3-4 times daily.

2.4 Monitoring of therapy

FVII has a short half-life of four to six hours, why factor replacement treatment needs to be closely monitored. Normalised PT/INR in the upper reference levels (<1.2) is roughly close to 50 percent of the reference FVII plasma concentration. For more accurate monitoring, the FVII activity (FVII:C) needs to be measured [32, 35].

3. Management during surgery

3.1 Which patients require substitution therapy during surgery?

As previously stated the correlation between FVII levels and risk of bleeding in FVII deficiency is very weak. In one retrospective study where substitution was only given if a severe bleeding phenotype was present (irrespective of FVII level), bleeding complications were present in 15.3% of performed operations [42]. Bleeding frequency was not increased in "high-risk" operations (assessed by the surgeon) and the highest bleeding frequency was observed in tonsillectomy, hernia and circumcision (20, 25 and 40% respectively). History of trauma induced excessive bleeding and frequent nosebleeds predicted risk of bleeding, but bleeding during previous surgery did not. A ROC analysis made from these data determined that a FVII level below 7% would justify replacement therapy during surgery [42].

3.2. What haemostatic therapy should be used?

Currently ***rFVIIa*** is recommended as first line therapy since it is highly effective, has few adverse events and low risk of virus transmission. However, no direct comparisons between available treatment options exists. Historically prothrombin complex concentrate (PCC) and pdFVII have also been applied [43]. ***Tranexamic acid*** has been found to reduce perioperative blood loss and transfusion requirements in hip and knee replacement, and concomitant treatment with rFVIIa in recently published case series did not lead to thrombotic complications [43, 44].

3.3 What dose of rFVIIa?

The STER (Seven Treatment Evaluation Registry) committee evaluated 41 operations where rFVIIa was administered to patients with FVII levels below 20% [45]. In line with

the previous recommendations they identified a minimum dose of rFVIIa of 13 μg/kg administered at least 3 times in order to prevent bleeding complications [36]. In a recent report of 5 patients undergoing orthopaedic surgery a dose of 18-37 μg/kg three times daily was used with no bleeding or thrombotic complications[46].
The short half-life of rFVIIa necessitates repeated bolus injections [31]. It was recently shown that by administering rFVIIa as continuous infusion the amount of rFVIIa and hence medication costs could be reduced by 70–90% when compared to expected costs of bolus injections [35]. No prospective randomized trials comparing bolus injections with continuous infusion of rFVIIa have been performed, but both approaches appear safe and efficacious.

3.4 Recommendations for management during major surgery:

3.4.1 rFVIIa replacement using bolus injections

Shortly before start of surgery, rFVIIa 15-30 μg/kg is administered depending on type of surgery. The dose is rounded up or down to closest vial size to avoid waste of product. This dose is given every 6 hours for the first 24 hours. The first postoperative day the same dose is given every 8 hours and the second postoperative day every 12 hours. The dose is thereafter tapered depending on type of surgery and occurrence of bleeding complications.

3.4.2 rFVIIa replacement using continuous infusion

An intravenous bolus injection of 0.6 mg from a vial of 1 mg, is given immediately before the start of the surgery, followed by continuous infusion. The rFVIIa, given by continuous infusion, is prepared by diluting 5.4 mg NovoSeven (of a 5 mg vial and the remaining 0.4 mg from an already opened vial) in 50 mL sterile water to a final concentration of 108 μg mL). The reconstituted rFVIIa is delivered at an infusion rate of 15 mL per 24 hours (h), corresponding to approximately 0.9 ug/kg/h, for the first 3 days. The medication cassette should be prepared to last for 24–72 h, as rFVIIa activity previously has been reported to be preserved at room temperature for at least 3 days. To avoid local thrombophlebitis at the infusion site, a parallel infusion with saline at 20 mL/h should be administered.

3.4.3 Tranexamic acid

Just before start of surgery tranexamic acid is given at 10 mg/kg iv. The dose is repeated after 4 hours. Tranexamic acid is then given orally at 20-25 mg/kg x 3-4 times daily for 4-7 days.

3.4.4 Laboratory monitoring of treatment

Plasma levels of FVII are measured once daily weekdays. The target range of FVII:C is 0.5–0.8 IU/mL when receiving the bolus dose, and 0.3–0.4 IU/ mL when receiving the maintenance continuous treatment during the first days after surgery.

3.4.5 Thromboprophylaxis

The risk for venous thromboembolism (VTE) is considered low after factor replacement therapy in rare bleeding disorders, and thromboprophylaxis is therefore not routinely recommended [47].

Recommendation for factor substitution therapy during major surgery
Substitution therapy should only be given to high-risk patients defined as:
-Factor VII level <10%
-Factor VII level 10-20% and a history of trauma induced excessive bleeding and/or frequent nosebleeds
-Significant bleeding history (joint or intracranial bleeds) irrespective of FVII level
-Paediatric patients (see paediatric section)

rFVIIa is recommended as the preferred factor substitution therapy
rFVIIa can be administered as bolus injections or continuous infusion

3.6 Management of minor surgery and procedures

3.6.1. Bleeding complications in minor surgery

The risk of bleeding complications in minor surgery, diagnostic interventions and dental procedures have been systematically documented in one study [42] comprising 83 unrelated patients with FVII deficiency (FVII:C levels: 0.6 – 35 %) that underwent 157 procedures, *without* coagulation factor replacement. Bleeding complications were seen

in 15 % of procedures performed. This includes dental extractions (10/52 patients), nose-throat procedures (4/22 patients), circumcision (2/5 patients), abdominal hernia repair (2/8 patients) cesarean section (1/6 patients), breast surgery (1/4 patients), haemorrhoid operation (1/1 patients), episiotomy (1/2 patients), elective induced abortion (1/10) and GI-endoscopy (1/3)[42].

3.6.2. Recommendations for rFVIIa replacement and tranexamic acid during minor surgery and procedures

Please see appendix A for suggested treatment regimens in specific minor surgery and procedures.

4. Management of spontaneous and traumatic bleeds

4.1. Haemostatic treatment of bleeding episodes in factor VII deficiency

Key data on haemostatic treatment of bleeding episodes in factor VII deficiency has been provided by the STER. The patients prospectively evaluated in the STER had 1-20 % residual FVII:C activity and were all symptomatic. In this group, rFVIIa is clearly beneficial in the treatment of spontaneous and traumatic bleeds [37].
Intracranial haemorhages (ICH) are among the most feared bleeding complications. The prospective evaluation from the STER group registered 9 CNS bleeds (8 spontaneous and 1 traumatic). Eight patients were treated with rFVIIa (a minimum of 3 doses of 15-30 µg/kg). Clinically, more than one dose was needed to stop the bleeding and resolve symptoms in all but one case. In general, the outcome was found to be in the spectrum of "partly effective" to "excellent"[37].
Based on the reported effectiveness of single doses of rFVIIa, Mariani and collegues suggest an intermediate dose of 60 µg/kg for optimal efficacy. Antifibrinolytics are rarely used in reports from the STER[37].

4.2. Recommendations for rFVIIa replacement and tranexamic acid in spontaneous and traumatic bleeds

Spontaneous or traumatic bleeds in FVII deficiency can be haemostatically treated following the same principles as described for patients undergoing surgery.
However, considering the seriousness of ICH, rFVIIa may be considered in all patients with reduced FVII levels below 40%. In addition, an intermediate dose of rFVIIa 60 µg/kg may be considered initially in severe bleeds.
Eventhough there is a lack in published data, continuous infusion of rFVIIa should also be considered for treatment of severe spontaneous or traumatic bleeds.

Please see appendix B for suggested treatment regimens in specific spontaneous or traumatic bleeds.

5. Long-term prophylactic factor replacement therapy

The use of long-term prophylactic factor replacement therapy was recently reviewed by Siboni and colleagues identifying 74 patients[48]. rFVIIa 20-30 µg/kg 2 -3 times weekly as well as pd-FVII 10-30 U/kg 2-3 times weekly, was described to be effective as prophylaxis in severe FVII deficiency with severe bleeding phenotype. No side effects or thrombotic complications were reported [48]. This corresponds to data from the STER registry reporting that rFVIIa administered three times weekly at a total weekly dose of 90 µg/kg was effective with no thrombotic events or new inhibitors occurring [49].

Recommendation for long-term prophylactic factor replacement therapy
-Long-term prophylactic factor replacement therapy should be considered in severe FVII deficiency with severe bleeding phenotype.
-rFVIIa initially 15-30 µg/kg 2 -3 times weekly followed by individualised dose tailoring is suggested

6. Follow-up in adult patients

Most patients with FVII deficiency have a mild bleeding phenotype and regular check-ups are not necessary. When the diagnosis is confirmed the patient should be evaluated

by a coagulation specialist and be informed on the genetic basis of the disorder, inheritance pattern, bleeding risks and treatment options. The patients should be advised to contact the coagulation center in any case of bleeding or surgery. High-risk patients (as defined above) should be offered annual follow-up visits at a comprehensive haemophilia care center, and receive team-based care including physiotherapy and consultations by an orthopaedic surgeon in line with recommendations in the Nordic Haemophilia Guidelines.

Recommendation for follow-up in adult patients High-risk patients should be offered annual follow-up visits at a comprehensive haemophilia care center

7. Management during pregnancy and delivery

7.1. Prophylactic treatment during pregnancy

Due to a weak correlation between the FVII activity level and the bleeding tendency in FVII deficiency, prophylaxis with rFVIIa is only recommended in high-risk patients (as defined above). In pregnant women with menorrhagia rFVIIa 15-30 μg/kg 2-3 times per week should be considered.

7.2. Haemostatic treatment during delivery

A systematic review of the literature between 1953-2011 identified 94 deliveries by women with a median FVII activity level of 5.5 % (range 0.5-49%). 10% of women receiving haemostatic prophylaxis experienced post-partum bleeding complications compared to 13% of women not recieving prophylaxis [50]. However, the number of caesarean deliveries were lower than the number of vaginal deliveries, 53 versus 31 cases in the whole group.

Only one portal vein thrombosis was reported and occurred six months postpartum in a patient that did not receive thromboprophylaxis at delivery.

Recommendations for pregnancy and delivery

-All patients with FVII deficiency should receive tranexamic acid at start of delivery or prior to caesarean section

-Irrespective of mode of delivery, rFVIIa or other haemostatic agents should be available in the case of haemorrhages.

-Prophylactic treatment with rFVIIa during vaginal delivery and caesarean section should only be considered in high-risk patients

-rFVIIa is given 15-30 μg/kg prior to and post-partum every 4-6 hours for at least 3 days

8. Paediatric considerations

8.1 Background

The haemostatic system of a healthy newborn, while functionally adequate, can be considered "immature". Maternal coagulation factors do not pass through the placenta; the level of the vitamin K-dependent coagulation factors including FVII in a healthy full term newborn are about half of adult values. The levels of FVII increases gradually and reach adult values by the age of 16 years, however the largest differences compared to adult levels are seen the first 6 months of age [51]. Vitamin K is required for post-translational modification of FVII and children are vitamin K deficient at birth. Vitamin K deficiency bleeding (VKDB, haemorrhagic disease of the newborn) with deficiency of all K-dependent proteins should be considered in newborns with bleeding symptoms. This condition is rare since Vitamin K substitution (i.e. Vitamin K 1 mg IM at birth or repeated doses of Vitamin K orally the first 1-3 months) is used worldwide to prevent this condition [52].

FVII is synthesised in the liver and the levels decrease if the hepatocellular function is impaired. FVII has a short half-life and may therefore be the first coagulation factor deficiency observed in acute liver failure. Reduced levels of both pro-and anticoagulant factors are often seen in chronic liver failure. Children with cholestasis are also at increased risk for VKDB [53].

8.2 Diagnosis of factor VII deficiency in children

In severe FVII deficiency, FVII<10%, bleeding symptoms in the neonatal period are frequent. As the mode of inheritance for severe FVII is autosomal recessive, a negative family history does not exclude this bleeding disorder. Pre-and postnatal age should be considered while interpreting the FVII levels in very young children and paediatric reference ranges must be used until 16 years of age [51, 54]. Low FVII values should be measured repeatedly, especially if the child is below 6 months of age, before the diagnosis of FVII deficiency can be made. Vitamin K deficiency must be ruled out by vitamin K supplementation before testing and liver disease needs to be excluded. Prenatal diagnose can be made in families with clinical severe FVII deficiency and known genotype.

8.3 Treatment in children

8.3.1 Treatment of bleeding episodes and at surgery

The principles of treatment are the same as for the adults. Tranexamic acid can be used safely in children, with dosing 20-25 mg/kg/per dose orally and 10mg/kg/dose intravenously. The recommendations regarding treatment with rFVIIa, including bolus doses, repeated doses and continous infusions, earlier in this document (section 2.2 and 3) are based on reports on adults, children and infants and can thus be applied also in children [35, 36, 55]. However, the risk of thrombosis in children is lower than in adults while the clearance of coagulation factor concentrates is increased. Therefore especially young children may benefit from doses in the higher dose range and more frequent administration. If available, monitoring of FVII for an individual dosing scheme is recommended.

8.3.2. Prophylaxis in children

Unlike haemophilia, there are no guidelines on when to initiate prophylaxis. The need for prophylaxis depends on the bleeding pattern: intracranial bleeding, recurrent haemarthroses, gastrointestinal bleeding, severe epitaxis, menorrhagia or other serious bleedings motivate prophylatic treatment. It may be necessary to start prophylaxis within the first year of life or early childhood to prevent lifelong disability. Primary prophylaxis may be considered. For example in children diagnosed prenatally with a

family history of early life-threatening bleeding symtoms [56]. In Israel, prophylaxis is recommended from one year of age if FVII levels are below 1%, and ultrasound post partum is applied in known severe cases (personal correspondence). The most common prophylactic regimen is rFVIIa 20-30 ug/kg 2-3 times a week [48, 49].

8.3.3 Liver transplantation

A few case reports regarding hepatocyte transplantation, auxillary- and orthotopic liver transplantation in paediatric patients with severe FVII deficiency have been published [57-59]. The hepatocyte transplantation only had a short-term effect. Orthotopic liver transplantation can cure FVII deficiency. However, it is a major procedure with risk of complications, need for lifelong immunosuppression and one of the transplanted patients developed antibodies against FVII [59]. Therefore, consideration of such intervention needs to be restricted to selected patients with severe FVII deficiency and complicated bleeding symptoms after careful evaluation by multidiciplinary teams in specialised centers.

8.4 Follow-up during childhood

Children with clear bleeding tendency or FVII levels below 25% should have regular follow-up at a paediatric coagulation center. Children with FVII deficiency not fullfilling these criteria should be informed about the FVII deficiency and instructed to contact the paediatric coagulation center before surgical interventions or in case of bleeding symptoms. A follow-up visit is also advised in adolescense to get accurate and updated information about their FVII deficiency.

Paediatric recommendations

-Paediatric reference ranges must be used when evaluating the levels of Factor VII in children

-Vitamin K deficiency and liver disease should be ruled out before the diagnosis of factor VII deficiency can be made in children

-Particularly young children may benefit from higher doses and more frequent administration of rFVIIa compared to adults

-Prophylactic treatment with factor concentrates should be considered early in severe FVII deficiency with a severe bleeding pattern

9. Appendix

9.1. Appendix A: Suggested treatment for minor surgery and procedures in high-risk patients

Clinical situation	**Treatment**
Minor surgery	Just before start of surgery, rFVIIa is given at 15 μg/kg iv in combination with tranexamic acid 10 mg/kg iv. The rFVIIa dose is repeated after 6 hours. Tranexamic acid is given orally at 20 mg/kg three times daily (ttd.) for 3-7 days
Regional, spinal and epidural anesthesia as well as diagnostic lumbar puncture	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv, in combination with tranexamic acid 10 mg/kg iv.
Endoscopic procedure without biopsy	No pre-treatment
Endoscopic procedure with biopsy	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv in combination with tranexamic acid 10 mg /kg iv. Thereafter tranexamic acid is given orally at 20 mg/kg ttd for 3 days
Implantation of external central venous catheter and subcutaneous venous ports	See “Minor surgery”
Renal biopsy	See “Minor surgery”
Minor dental procedures	Local application of tranexamic acid for one hour

Major dental procedures (extraction of multiple teeth)	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv in combination with tranexamic acid 10 mg/kg iv. Thereafter tranexamic acid is given orally at 20 mg/kg ttd. for 3 days
Acupuncture	Tranexamic acid is given orally at 20 mg/kg ttd the day of the procedure, starting in the morning
Bone marrow aspiration	No pre-treatment
Bone marrow biopsy	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv in combination with tranexamic acid 10 μg/kg iv. Thereafter tranexamic acid is given orally at 20 mg/kg ttd for 3 days
Angiography with puncture of the femoral vein	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv in combination with tranexamic acid 10 μg/kg iv. Thereafter tranexamic acid is given orally at 20 mg/kg ttd for 3 days
Injection of botox or hyaluronic acid	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv, in combination with tranexamic acid 10 mg/kg iv.
Transplantation of dermal grafts	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv in combination with tranexamic acid 10 μg/kg iv. Thereafter tranexamic acid is given orally at 20 mg/kg ttd for 3 days
Electro Convulsive Treatment (ECT)	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv in combination with tranexamic acid 10 μg/kg iv. Thereafter tranexamic acid is given orally at 20 mg/kg ttd for 3 days
Heart catheterisation	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv, in combination with tranexamic acid 10 mg/kg iv.

Dermal excision	Tranexamic acid is given orally at 20 mg/kg ttd for 3 days starting in the morning the day of the procedure
Cataract surgery	No pre-treatment
Liver biopsy	See “Minor surgery”
Pleural tap	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv, in combination with tranexamic acid 10 mg/kg iv.
Prostate biopsy	Just before start of the procedure, rFVIIa is given at 15 μg/kg iv in combination with tranexamic acid 10 μg/kg iv. Thereafter tranexamic acid is given orally at 20 mg/kg ttd for 3 days
Tatoo	Tranexamic acid is given orally at 20 mg/kg ttd for 3 days starting in the morning the day of the procedure

9.2 Appendix B: Suggested treatment for spontaneous and traumatic bleeding episodes in high-risk patients

Clinical situation	Treatment
Intracerebral haemorrhage	rFVIIa: 15–30 µg/kg every 4–6 h for a minimum of 3 days or continuous infusion as described under major surgery. Tranexamic acid: initially 10 mg/kg i.v. ttd. then given orally at 20 mg/kg ttd. for a total of 3-7 days
Subarachnoidal haemorrhage	rFVIIa: 15–30 µg/kg every 4–6 h until aneurism is clipped/coiled or for a minimum of 3 days or continuous infusion as described under major surgery. Tranexamic acid: Application in subarachnoidal haemorrhage is controversial. Consider 1g i.v. immediately at diagnosis repeated every 6 hours until aneurism is clipped/ coiled or for a maximum of 72 hours [60].
Subdural haemorrhage	rFVIIa: 15–30 µg/kg every 4–6 h for a minimum of 6 doses or continuous infusion as described under major surgery. Tranexamic acid: initially 10 mg/kg i.v. ttd. then given orally at 20 mg/kg t.i.d. for a total of 3-7 days
Major traumatic bleeds	rFVIIa 15–30 µg/kg every 4–6 h until bleeding is stopped or continuous infusion as described under major surgery. Tranexamic acid: initially 10 mg/kg i.v. ttd. then given orally at 20 mg/kg t.i.d. for a total of 3-7 days

Haemarthrosis	rFVIIa: 15–30 μg/kg every 4–6 h for a minimum of 3 doses. Tranexamic acid: initially 10 mg/kg i.v. ttd. then given orally at 20 mg/kg ttd. for a total of 3-7 days
Muscle haematoma	rFVIIa: 15–30 μg/kg every 4–6 h for a minimum of 3 doses. Tranexamic acid: 10 mg/kg i.v. ttd. or 20 mg/kg p.o, ttd. for a total of 3-7 days.
Subcutaneous haematoma	Tranexamic acid: 20 mg/kg ttd. orally for a total of 3-7 days. rFVIIa: In gross haematomas consider a single dose of 15–30 μg/kg, repeated if needed after 4-6 hours.
Superficial cutaneous bleeding	Tranexamic acid: Locally applied 4 times daily, and/or 20 mg/kg ttd. p.o. for a total of 3-7 days
Epistaxis	Tranexamic acid: 20 mg/kg ttd. p.o. for a total of 3-10 days [61] rFVIIa: In gross bleeding consider a single dose of 15–30 μg/kg, repeated if needed after 4-6 hours.
Gum bleeds	Tranexamic acid: Mouthwash four times daily for a total of 3-7 days or 20 mg/kg ttd. orally for a total of 3-7 days rFVIIa: Consider a single dose of 15–30 μg/kg, repeated if needed after 4-6 hours.
Upper gastrointestinal bleeds	rFVIIa: 15–30 μg/kg every 4–6 h at least until gastroscopy or for a minimum of 3 doses

	Tranexamic acid: Consider 10 mg/kg i.v. ttd. or 20 mg/kg p.o t.i.d. for a total of 3-7 days
Lower gastrointestinal bleeds	rFVIIa: 15–30 µg/kg every 4–6 h until coloscopy or for a minimum of 3 doses Tranexamic acid: Consider 10 mg/kg i.v. ttd. or 20 mg/kg p.o ttd. for a total of 3-7 days
Menorrhagia	Oral contraceptives with estrogen/hormonal intrauterine devices Tranexamic acid: 20 mg/kg ttd. orally on days with heavy bleeding rFVIIa: Consider a single dose of 15–30 µg/kg, repeated if needed after 4-6 hours.
Upper urinary tract bleeds	rFVIIa: 15–30 µg/kg every 4–6 h for a minimum of 3 doses.
Lower urinary tract bleeds	rFVIIa: 15–30 µg/kg every 4–6 h for a minimum of 3 doses. Tranexamic acid: Consider 10 mg/kg i.v. ttd. or 20 mg/kg p.o. ttd. for as short a time period as possible

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