

Review

Factor VII Deficiency: Clinical Phenotype, Genotype and Therapy

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Abstract: Factor VII deficiency is the most common among rare inherited autosomal recessive bleeding disorders, and is a chameleon disease due to the lack of a direct correlation between plasma levels of coagulation Factor VII and bleeding manifestations. Clinical phenotypes range from asymptomatic condition—even in homozygous subjects—to severe life-threatening bleedings (central nervous system, gastrointestinal bleeding). Prediction of bleeding risk is thus based on multiple parameters that challenge disease management. Spontaneous or surgical bleedings require accurate treatment schedules, while patients at high risk of severe hemorrhages may need prophylaxis from childhood onwards. The aim of the current review is to depict an updated summary of clinical phenotype, laboratory diagnosis, and treatment of inherited Factor VII deficiency.

Keywords: inherited Factor VII deficiency; diagnosis; bleeding; replacement therapy; genotype

1. Introduction

Inherited Factor VII deficiency is the most common among rare autosomal recessive bleeding disorders. Coagulation Factor VII (FVII) is a plasma vitamin K-dependent serine protease produced by the liver. Factor VII is the unique coagulation factor with a small proportion (1%–3%) of free circulating activated form (FVIIa), even without coagulation activation [1]. Blood clotting is initiated by the interaction between tissue factor (TF) exposed on the vascular lumen upon injury and the activated factor VII (FVIIa)—a plasma vitamin K-dependent serine protease [2]. The FVIIa–TF complex is able to activate factors IX (to FIXa) and X (to FXa), which ultimately induce the formation of a stable fibrin clot [3]. All domains of FVIIa are involved in the interaction between TF and FVIIa: the catalytic domain, the gamma-carboxyglutamic acid domain, and the two epidermal growth factor (EGF)-like domains [4]. Only small amounts of FVIIa are needed to trigger coagulation. Inherited Factor VII deficiency is characterized by a wide spectrum of clinical phenotypes (Table 1) ranging from asymptomatic condition—even in homozygous subjects—to severe life-threatening bleedings including central nervous system (CNS) and gastrointestinal (GI) bleeding [5–7]. Studies on knockout mice indicate that the absence of FVII is incompatible with life; thus, FVII deficiency could not be associated with a complete lack of functional FVII [8,9]. FVII plasma levels can be influenced by FVII gene polymorphisms [10]. Several studies on the molecular structure and genetic diagnosis of FVII have been performed [7,11–14]. Due to the rarity of the disease, the optimal definition of clinical symptoms and treatment has however been reached mainly thanks to international multicenter

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studies like the International Registry on Congenital Factor VII Deficiency (IRF7) [5] and the Seven Treatment Evaluation Registry (STER) [13].

Table 1. High-risk and low-risk patients with inherited Factor VII deficiency, based on bleeding history and coagulation Factor VII (FVII) activity.

Heading	Bleeding	FVII: c (%)	Personal History	Familial History
High risk *		<2	CNS bleeding, UC stamp bleeding, hemarthrosis, GI bleeding	Life-threatening bleeding, death for hemorrhage in a first degree relative
Low risk ‡		>20	Negative for spontaneous bleeding	Negative for spontaneous bleeding

CNS: Central Nervous System; FVII: c: FVII coagulant; GI: Gastro-intestinal; UC: Umbilical Cord. * Some patients with FVII: c < 1% may be asymptomatic; ‡ Some patients may bleed with FVII: c > 20%.

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2. Clinical Manifestations

Inherited FVII deficiency has a wide range of clinical manifestations; mild (muco-cutaneous) bleeds (like in platelet disorders) are the most frequent, while 10% to 15% exhibit potentially life- or limb-threatening hemorrhages (CNS, GI, or hemarthrosis) [1,6,14]. About one-third of patients with FVII deficiency tend to remain asymptomatic during their life [5]; these subjects are diagnosed as part of family studies or hemostatic screenings. The most frequently reported bleeding symptoms among “platelet-like” FVII deficiency are epistaxis (60%), gum bleeding (34%), easy bruising (36%), and menorrhagia (69% of females) [5]. These manifestations usually do not require any systemic replacement therapy and are well-controlled by local hemostatic agents [5,15], even if in some cases (i.p. menorrhagia) prophylaxis may be indicated [16]. Excessive menstrual blood losses have been objectively determined in women with inherited Factor VII deficiency [17]; they affect two thirds of patients of fertile age, with a negative impact on quality of life [18]. Women with Factor VII deficiency can furthermore suffer from ovarian cysts and ovulatory bleeding; they also have an increased risk of post-partum hemorrhage [19,20].

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may be the presenting symptom in a newborn.

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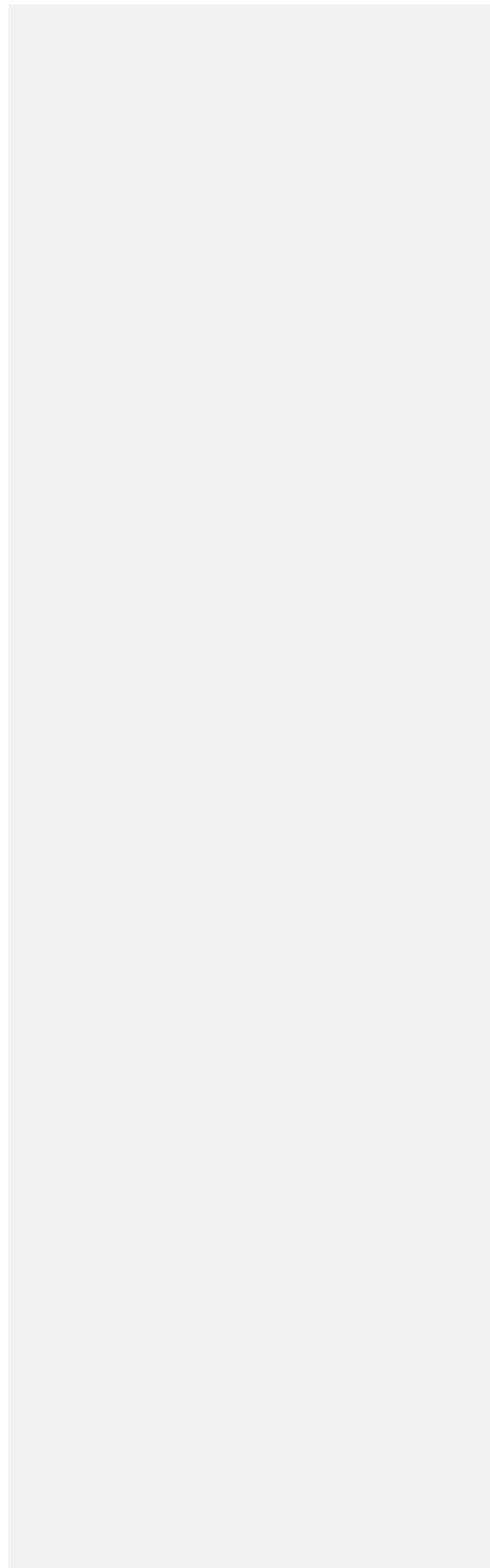
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Among the severe forms, recurrent hemarthrosis are frequent (19%), gastrointestinal bleeding is relatively frequent (15%), and central nervous system bleeding is less frequent (2.5%) but it can be the most serious and life threatening [5]. Severe bleedings usually occur soon after birth or in infants in severe inherited Factor VII deficiency; bleeding symptoms follow the same specific pattern of their onset. In particular, umbilical cord stump bleeds are associated with a high risk of developing further severe bleeds (CNS and GI) at a very young age [14]. Severe Factor VII deficiency may initially present in a newborn with intracranial hemorrhage (ICH). Bleeding after circumcision or heel stick during the neonatal period and dental extractions in childhood is quite common in inherited Factor VII deficiency [21]. There is a lack of correlation between clinical phenotypes and FVII coagulant activity (FVII: c). It is not rare to observe asymptomatic subjects with FVII:c below 1%, or on the other hand, patients with FVII:c level above 5% with a history of severe hemorrhages [1,6]. Heterozygous patients usually do not experience severe symptoms [22]. The minimal level Minimal levels of FVII: c able to protect from bleeding in different clinical scenarios is also not well defined, ranging from 8% [23] to 15–20% [24]. It is generally accepted that FVII:c levels above 20% can protect from spontaneous bleedings [6,25], and data from IRF7 and STER have shown a minimal clinical relevance to bleeding for FVII:c below 26% [14]. This unpredictable behavior could be related to the combined enhanced effect of TF–FVIIa complex, able to activate coagulation even with small amounts of FVII [4]. However, the risk of bleeding in asymptomatic individuals cannot be underestimated in circumstantial situations like major surgery [20,26]. Each bleeding event increases the likelihood of an early diagnosis of Factor VII deficiency, and asymptomatic individuals at diagnosis may experience _____ bleeding, if any, late in life [14].



3. Diagnosis

Inherited Factor VII deficiency is usually diagnosed with a laboratory workup performed after a bleeding episode or during familial screening in cases with a known history of the disease. Factor VII deficiency can also be a serendipitous finding. Basic diagnostic work-up includes routine assays (prothrombin time, PT, ~~and~~ activated partial thromboplastin time, ~~aPTT~~ and platelet count) followed by FVII coagulant activity measurement for isolated prolonged PT, corrected by mixing studies. To confirm diagnosis, FVII assay should be repeated at least once. The assay of the other vitamin K-dependent clotting factors is not necessary but useful to rule out the combined deficiencies of vitamin K-dependent factors in which case, however, the aPTT is also prolonged [27].

FVII deficiency is usually distinguished into two types: type I (quantitative defects, with decreased FVII:c and FVII antigen, FVII:Ag), type II (qualitative defects, with low FVII:c and normal FVII:Ag). FVII coagulant activity is determined with a one-stage assay mixing citrated plasma sample, FVII-deficient reagent, and thromboplastin [28]. The accuracy of FVII:c assay is ~~thus~~ related to the sensitivity of the thromboplastin used, calibrators, and the quality of ~~reagents for the~~ FVII:c-deficient reagent [29]. Thromboplastins contaminated with small amounts of FVIIa may activate plasma and decrease the sensitivity to FVII:c assay [30]. This is particularly important for the diagnosis of type II defects, like FVII Padua. The Padua variant of FVII deficiency (Arg304Gln in exon 8) shows a different reactivity toward different tissue thromboplastins and determines normal results when brain thromboplastin is ~~adopted~~ employed [31]. On the contrary, type I defect has ~~ever~~ been reported to display variable reactivity toward different thromboplastins [32].

FVII antigen levels can be determined by enzyme-linked immunosorbent assays or ~~immune~~ immuno-turbidimetric assays, with monoclonal epitope-specific antibodies. FVII:Ag assay allows distinguishing between type I and ~~typing~~ type II defects. ~~Testing FVII:Ag first could however miss qualitative FVII:c defects.~~ Furthermore, FVII:Ag does not allow the prediction of bleeding tendency, but ~~it~~ may contribute to clarifying the role of specific mutational mechanisms of the defect.

FVIIa assays have been adopted to monitor the treatment with recombinant activated FVII (rFVIIa) in patients with FVII-deficiency and in hemophilia with inhibitors. The method adopts recombinant TF, acting as a cofactor for FVIIa but unable to activate FVII [33]. New, chromogenic or fluorogenic assay methods for FVIIa are now available for research purposes. FVIIa assay—even if more effective in monitoring treatment with rFVIIa than FVII:c assay [34]—is not recommended in the diagnosis of FVII deficiency.

4. Genetic Diagnosis

Correlation between genotype–phenotype indicates that modifiers (environmental and/or inherited factors) modulate the expressivity of FVII deficiency, as mirrored by patients with the same gene mutation ~~but~~ and discordant clinical phenotypes. FVII gene mutations are heterogeneous.

The FVII gene was sequenced for the first time in 1987; ~~its~~ its ~~is~~ is the whole sequence has been widely studied by DNA sequencing. Nowadays, direct gene sequencing allows detection of the mutation in 90–92% alleles. Whole gene sequencing is the recommended method for molecular diagnosis of FVII due to a high frequency of single nucleotide (point) mutations, a low recurrence of the same mutations, and a short length of the gene. In up to 10% of FVII deficiencies, a gene mutation has not been identified by DNA sequencing. This could be related to mutations in a different gene [9]. To further understand clinical variation ~~among~~ among individuals with the same gene mutation, studies have investigated the issue of clinical picture modifiers (i.e., common thrombophilia markers) not reaching firm conclusions [35]. Tissue factor, von Willebrand factor, or platelets could also be involved in the expression of bleeding tendency in FVII deficiency. Unknown regulators are not excluded either [20].

Prenatal diagnosis—in particular genetic analysis of cord blood [36]—is recommended for families with a history of severe or life-threatening bleeding episodes. FVII:c could also be assayed on cord blood obtained after cordocentesis between the 17th and 21st weeks of gestation; however, in this last case a confirmation test is needed after birth [37].

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Genetic testing is not routinely adopted ~~in~~ for the diagnosis of FVII deficiency. unless prenatal diagnosis is required.

5. Replacement Therapy

Bleeding risk prediction and treatment options for acute spontaneous bleeding episodes or surgery are challenging. FVII:-c levels alone cannot drive the management of the disease, as they are not able to accurately predict the bleeding risk tendency ~~and~~ ~~–~~ Currently, guidelines for the management of this rare bleeding disorder are lacking. ~~For Replacement replacement therapy, administration considers~~ ~~the analysis of a multiple number of factors is required~~, such as the rarity of the disorder, the type, availability, and supply of products, as well as economic and geographical factors.

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Results from multicenter observational studies like STER and IRF7 have provided important ~~elements of~~ evidence related to the efficacy and safety of replacement therapy (RT) ~~as well as the~~ schedules for spontaneous bleeding episodes [15], major surgery [38], invasive procedures [39] and prophylaxis [16]. These trials have ~~furthermore~~ contributed to ~~prediction of~~ the bleeding risk of patients with inherited FVII deficiency mainly based on the first bleeding symptom, ~~the~~ personal clinical history, and FVII:-c levels [14]. Several therapeutic options are currently available for ~~the~~ ~~treatment of~~ inherited FVII deficiency: ~~i.~~ (recombinant activated Factor VII, ~~ii.~~ plasma-derived Factor VII, ~~iii.~~ fresh frozen plasma ~~and iv.~~ prothrombin complex concentrates).

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Recombinant FVIIa (rFVIIa) is the most ~~adopted~~ ~~used~~ replacement therapy, when available. Pharmacokinetic studies in patients with inherited Factor VII deficiency at steady state have shown a large volume of distribution and a prolonged pharmacodynamics effect of the drug [40].

Data from STER (Table 2) have shown that one day RT with “intermediate” doses (median 60 µg/kg) of rFVIIa [15] can be effective and safe ~~to treat for the treatment of bleeding bleeds symptoms~~ like hemarthrosis, muscle/subcutaneous hematomas, epistaxis, and gum bleeding. Single- or multiple-dose schedules can be ~~effective for-used for the treatment of~~ menorrhagia, ~~while~~ ~~Short- or~~ long-term prophylaxis ~~may be optimal~~ ~~is indeed warranted~~ for the ~~patients with the~~ most severe ~~bleeds~~ ~~bleeding picture~~ (CNS, GI) [16]. Heavy menstrual bleeding in women with inherited bleeding disorders should be managed with a multidisciplinary approach, based also on the ~~wish~~ ~~objective of~~ ~~to preserve~~ ~~preserving~~ fertility [41]. ~~Other Medical-medical~~ ~~therapies~~ ~~–~~ of menorrhagia includes hemostatic agents like tranexamic acid and hormonal treatments (combined oral contraceptives, levonorgestrel intrauterine devices), ~~combined in combination~~ or not with RT [42]. Progesterone-releasing intra-uterine systems can be ~~more~~ effective in suppressing ovulation, thereby reducing the risk of ~~ovulation~~ bleeding in these women. RT alone may be ~~ineffective or~~ difficult to accept—in particular for young women after menarche [43].

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Table2. Replacement therapies with rFVIIa in inherited Factor VII deficiency (data from STER studies).

Heading	Treatment Days, Median (Range)	Daily Dose rFVIIa, Median (Range)	Single Dose rFVIIa, Median (Range)
Spontaneous bleeding	1 (1–14)	80 (35–210)	60 (10–3600)
Major Surgery	3.5 (1–16)	31.9 (12–120)	18.7 (6.5–87)
Minor Surgery	1 (1–4)	20 (7.2–300)	20 (19–60)
Prophylaxis	Three/two times per week	--	90 (30–120)

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Doses are expressed as mg/kg/bw. rFVIIa: recombinant activated Factor VII (Novoseven®).

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In the management of major surgical procedures (particularly during the first 24 h after the procedure), replacement therapy with rFVIIa is effective ~~when if~~ administered at a minimum dose of 13 µg/kg/body weight per single dose, in at least three administrations [38]. For invasive procedures and minor surgery, 1-day RT resulted sufficient, with an “average” total dose of rFVIIa of 20 µg/kg/body weight, possibly in more than one administration [39]. RT with rFVIIa has a very good safety-to-efficacy ratio [38,39,44,45]. Continuous infusion of rFVIIa during surgery has also been reported as effective, safe, and well-tolerated in patients with inherited Factor VII deficiency [46].

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Adverse events (AEs)—mainly inhibitors to FVII and thrombosis—reported from STER had a low ~~to~~ ~~very-low~~ incidence [44], with three cases of thrombosis and two cases of confirmed inhibitors among 245 reported treatments with rFVIIa.

Plasma-derived FVII (pd-FVII) concentrates may be an alternative option to rFVIIa. Large volume infusions and the short half-life (4–6 h) of FVII make this administration option **less appealing** **difficult**, particularly in children. One IU of pd-FVII induces a plasma level increase of 1.9%. Currently, the **mean administered average** pd-FVII **doses dosages used** are 15–20 IU/kg for mucosal bleeding, and **up to** 30–40 IU/kg in severe or life-threatening hemorrhages [47].

Fresh frozen plasma (FFP) can be more easily available; however, its effectiveness is limited by a high risk of fluid overload following repeated infusions [48]. FFP **is currently** given at a mean dose of 15–30 mL/kg **at a variable frequency related to** **depending on** the site and severity of bleeding **was shown effective in the control of CNS hemorrhages and hemarthrosis** [15].

Antifibrinolytic agents like tranexamic acid—alone for mild bleedings or in combination with RT—can **also** be effective [16,49].

Long-term prophylaxis is **generally** indicated in patients with a severe clinical phenotype (CNS and GI bleedings) since childhood and soon after the first bleeding event [16,24]. Data from **the** STER showed that recombinant activated factor VII prophylaxis schedules based on “frequent” administrations (three times weekly) **and a** of 90 µg/kg total weekly dose resulted effective. Short-term or intermittent prophylactic schedules **can also be considered**, **could also be evaluated**, particularly in conditions like menorrhagia **or severe hemarthroses** [16,20]. Early long-term administration of primary prophylaxis with rFVIIa 15–30 µg/kg/dose, **given two to three times weekly** in children with severe **inherited Factor— FVII deficiency at with** very high bleeding risk **is was proved to be** safe and effective [50].

Plasma-derived FVII concentrates have been prophylactically administered for periods from 9 months to 9 years at dose schedules **from** 10–50 U/kg/three times per week **to** 50 U/kg **or** on alternate days **and was shown to be**. Prophylaxis was effective in reducing the frequency and/or severity of bleeding [51]. Available evidence does not support a long-term prophylaxis with FFP, due to **persistent significant persistence of significant** bleeding in patients on FFP [52].

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6. Conclusions.

We have here **reported clinical—described clinical** manifestations, diagnosis, and treatment principles **of in** inherited FVII deficiency—a rare but complex bleeding disorder. Available data is mainly based on results **stemming** from observational studies **and** case series; **the registries, however have provided convincing evidence that this disorder may be managed with success with little burden of adverse events,** **and reports, partly support clinicians;** **treatment—Treatment, however, is** still challenged by product availability worldwide, **and guidelines may improve FVII deficiency care.**

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Author Contribution: N.M. collected available data, revised the literature and wrote the paper, S.S. **wrote helped to write** the paper. G.M. conceived the paper and critically revised the manuscript.

Conflicts of interest: The authors declare no conflict of interest.

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