# Prophylaxis of bleeding episodes and surgical interventions in patients with rare inherited coagulation disorders

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Rare inherited coagulation disorders (RICD) represent a group of inherited deficiencies of clotting factors characterized by a low prevalence in the general population (usually around 1:1,000,000 inhabitants) and, in severe cases (homozygous or compound heterozygotes), by the invariable occurrence of bleeding after invasive procedures if not adequately treated. Furthermore, spontaneous or post-traumatic severe bleeding may occur, as usually observed in patients with haemophilia, although less frequently. The clinical picture of patients with RICD may, however, be complicated by particular situations not encountered in haemophiliacs, such as gynaecological bleeding. The availability of virally-inactivated plasma-derived concentrates of the missing factors, apart from factor V, has rendered surgery and prophylaxis more feasible in these disorders, thus reducing the risk of life-threatening episodes and significantly improving the quality of life of affected patients.

The goal for the future is to render this treatment accessible to all patients with these disorders, also to those living in developing countries.

**Key Words:** Prophylaxis, inherited coagulation disorders, clotting factor concentrates, rare bleeding disorders.

## Introduction

Rare inherited coagulation disorders (RICD) are a group of inherited deficiencies of clotting factors characterised by a low prevalence in the general population (usually around 1 case per 1,000,000 inhabitants) and a variable bleeding tendency which may sometimes resemble that seen in patients with severe haemophilia[1]. However, RICD patients show some particular bleeding symptoms and clinical situations that are not manifested by haemophilic patients, including those typical of females in reproductive age[2].

Furthermore, at variance with what occurs in about 15% of patients with severe haemophilia A, the risk of developing inhibitors against the missing clotting factor administered through replacement therapy is very rare in RICD, apart from factor XI (FXI) deficiency. Table I summarises the main clinical features of patients with RICD.

Patients with RICD and clinically significant bleeding manifestations are usually homozygous or compound heterozygous. Heterozygotes (parents and children of probands) have approximately half-normal levels of coagulation factors and are usually asymptomatic, although a recent North American survey[3] and other series[4] reported a significant rate of bleeding symptoms also in these subjects .

The rarity of these disorders makes it important that these patients are cared for in specialised centres that can provide global treatment and guarantee easy access to therapies which are not always immediately and widely available.

## Surgical and secondary prophylaxis

Surgery and invasive procedures can be managed easily provided sufficient amounts of replacement therapy are administered during such occasions. The availability of specific concentrates for these disorders makes therapy easier and safer[1]. However, in rare instances in which no concentrate is available (e.g., factor V [FV] deficiency), large amounts of plasma may be required with the inherent risk


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**Table I -** Main symptoms and features of recessively inherited coagulation disorders

| Deficient factor | Main clinical symptoms | Haemostatic levels | Concentrate availabile# | Secondary Prophylaxis | Plasma half-life |
|---|---|---|---|---|---|
| Fibrinogen | Umbilical cord, joint, and mucosal bleeding; recurrent miscarriages, rarely spontaneous thrombosis | 50 mg/dL | YES | In selected cases | 2-4 days |
| Prothrombin | Umbilical cord, joint, and mucosal bleeding | 20%-30% | Prothrombin complex concentrate | No data | 3-4 days |
| V * | Mucosal bleeding | 15%-20% | NO | No data | 36 hours |
| VII | Mucosal, joint, and muscle bleeding; rarely neonatal intracranial bleeding | 15%-20% | YES | Rare cases | ~ 4 hours |
| X | Umbilical cord, joint, and muscle bleeding, intracranical bleeding | 15%-20% | Prothrombin complex concentrate | Selected cases | 40-60 hours |
| XI | Post-surgical and traumatic bleeding | 15%-20% | YES | No data | 40-70 hours |
| XIII | Umbilical cord and intracranial bleeding recurrent miscarriages, impaired wound healing | 2%-5% | YES | Prophylaxis in all the patients | 11-14 days |
| V + VIII | Mucosal bleeding | 15%-20% | NO for FV; YES for FVIII | No data | 36 hours for FV and 10-14 hours for FVIII |
| Vitamin K-dependent, multiple deficiency | Umbilical cord and intracranial bleeding | 15%-20% | Prothrombin complex concentrate | No data | See corresponding factors |

*FV deficiency is the only RICD for which there is no plasma-derived concentrate available
# Fresh-frozen plasma is useful in all the deficiencies

of fluid overload since prolonged treatment is usually necessary to cover surgical procedures. The role of prophylaxis in haemophilia has recently been established by the demonstration of a better quality of life and orthopaedic function in paediatric patients treated with regular infusions of recombinant factor VIII (FVIII) compared to those treated with an enhanced on-demand schedule[5]. Although the usefulness of this approach for patients with RICD has not been formally established by controlled studies, there is evidence of its relevance for some of these disorders. Of course, the decision to use prophylaxis depends on several conditions being fulfilled. The clinical premises for the use of prophylaxis are the frequency of bleeding, the risk of severe spontaneous bleeding, and the risk of long-term disability associated with bleeding in a particular district of the body despite on-demand treatment (e.g., joint bleeding). Furthermore, there are situations that are not characterised by overt bleeding but for which the adoption of prophylaxis with the missing factor may result in significant clinical benefits, such as the possibility of carrying a pregnancy successfully to term, by preventing early miscarriages, as in afibrinogenaemia[6] or factor XIII (FXIII) deficiency[7]. In addition to the clinical features indicating the usefulness of a prophylactic regimen, the availability, safety and efficacy of the therapeutic products is of the utmost relevance, along with the half-life of the transfused factor. The production of concentrates that are easy to administer and can deliver the required amount of the missing factor has been the outstanding progress in the treatment of haemophilia, since very few millilitres of concentrate are sufficient, compared to the previously required large volumes of plasma. Furthermore, unlike cryoprecipitate, which is still used for some of these RICD, especially in developing countries, these concentrates are now virally-inactivated. Not all situations in patients with RICD are manageable with a


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plasma concentrate (e.g., FV deficiency) and in some cases no pure factor concentrate is available (e.g., factor X [FX] deficiency). Furthermore, safety issues should not be ignored, since there have been reports of thrombotic episodes associated with the use of some concentrates[8].

Finally, for some situations, such as FXI deficiency, the pros and cons of replacement treatment should be weighed, taking into consideration the real risk of bleeding against the risk of inhibitor development[9]. On this background, the results of prophylaxis for surgery and the role of secondary prophylaxis in some specific RICD are reviewed.

## Afibrinogenaemia

Fibrinogen is a complex glycoprotein involved in the final step of the coagulation cascade as the thrombin substrate for fibrin generation and is required for platelet aggregation to occur by binding to glycoprotein IIb/IIIa ($\alpha_{IIb}\beta_3$) exposed on the platelet membrane after platelet activation[10]. Fibrinogen is synthesised in hepatocytes as a hexamer composed of two sets of three polypeptide chains (Aα, Bβ, and γ)[10].

Each chain is encoded by a separate gene, *FGA*, *FGB,* and *FGG*; these three genes are clustered in a 50-Kb region on chromosome 4q32.1[10].

Inherited disorders of fibrinogen are classified on the basis of whether there is a complete lack of fibrinogen in plasma (afibrinogenaemia), a partial deficiency (hypofibrinogenaemia) or an abnormal circulating molecule (dysfibrinogenaemia)[10]. Hypofibrinogenaemia is considered the heterozygous condition of afibrinogenaemia and usually does not confer an increased risk of bleeding, while patients with afibrinogenaemia generally have a severe, life-long bleeding tendency.

Post-operative bleeding has been reported to occur in about 40% of patients with untreated afibrinogenaemia and thus prophylaxis during surgery is always recommended[11]. There is consensus that trough fibrinogen levels >50 mg/dL and possibly around 100 mg/dL should be achieved by regular infusions of fibrinogen concentrate or cryoprecipitate. There have been reports of successful pregnancies in afibrinogenaemic women in whom prophylaxis with fibrinogen concentrate, started as soon as possible to prevent early miscarriage, has been adopted throughout the pregnancy. A recent mail survey by Peyvandi *et al.*[12] gathered data on surgical procedures in afibrinogenaemic patients given prophylaxis with concentrate (52%) or cryoprecipitate (42%), with excellent results in more than 90% of instances. In addition, 19 patients had received prophylaxis for recurrent severe bleeds or life-threatening bleeding, 59% of whom with a weekly dose of fibrinogen concentrate or cryoprecipitate. Most of these patients remained symptom-free, while a few bleeding episodes occurred in some, probably due to delayed timing of infusions or an inadequate dose of fibrinogen. The optimal schedule for the prophylactic regimen in these patients remains to be firmly established.

## Factor VII deficiency

Factor VII (FVII) is a vitamin K-dependent glycoprotein of about 50 KDa. Large amounts of this clotting factor circulate in plasma in an inactive form (≈ 0.5μg/mL) and a small quantity (50-100 pmoles/L) in an active form, which binds to tissue factor[13]. The FVII gene (*F7*) maps to chromosome 13 (13q34) and consists of nine exons encoding a protein of 406 amino acids. FVII deficiency is the most frequent RICD, with an estimated prevalence of 1 case per 300,000-500,000 people. The bleeding pattern is highly heterogeneous, ranging from the occurrence of neonatal cerebral bleeding to the absence of bleeding even after triggering events[14]. Some of this variability is explained by the high prevalence of dysfunctional molecules, which are detectable by the use of thromboplastin from different animal sources. Recombinant activated FVII (FVIIa) has been used in several instances for the prevention of bleeding during surgery. Doses around 25 μg/kg every 3-4 hours for the first 24 hours and then followed by longer intervals (6-8 hours) for the remaining post-operative period have been used successfully[13]. This closely-spaced schedule is required because FVII has a half-life of around 4 hours, the shortest among the clotting factors. This short half-life would theoretically prevent the use of FVII for prophylactic regimens since repeated daily infusions would be required to maintain safe haemostatic levels (10-15%) throughout[13]. Surprisingly, however, there have been a few reports of successful prophylaxis in children with recurrent haemarthrosis or cerebral bleeding with twice or thrice weekly administrations of either plasma (10-50 U/kg) or recombinant FVIIa concentrate (1.2 – 4.8 mg)[15-17]. Further studies are needed to establish definitely the role of prophylaxis in this disorder.

## Factor X deficiency

FX is a vitamin-K-dependent protease synthesised by the liver and secreted into plasma as a two-chain (light and heavy) zymogen, with a concentration of around 10 μg/mL. FX is activated by activated factor IX (FIXa) or by FVIIa by cleavage of Arg194-Ile195 in the heavy chain[18]. The gene coding for FX maps to the long arm of

chromosome 13 (13q34), adjacent to *F7*, and consists of eight exons over 27 Kb of genomic sequence[18]. Inherited FX deficiency is one of the rarest RICD and the variable severity of symptoms correlates poorly with the laboratory phenotype[4]. The Greisfwald registry, started in 1998, has collected data on 102 patients with clinical manifestations of variable severity. Thirty-four of them have been treated for severe bleeding or surgical prophylaxis, with excellent results. Seven patients (six children), all with FX levels <1%, have been treated prophylactically with a prothrombin complex concentrate containing FX (FX P, CSL Behring, Marburg) at a dose of 10-20 U/Kg twice or thrice weekly for recurrent haematoma or haemarthrosis (more than 20 episodes/year), with a dramatic reduction of the number and severity of bleeding episodes[19]. Although prophylaxis appears to be required rather rarely in FX deficiency, this approach does seem to be efficacious and safe.

### Factor XI deficiency

FXI is a disulphide-linked homodimeric glycoprotein composed of two identical 80-KDa polypeptide chains. FXI is produced by hepatocytes and circulates in plasma in a non-covalent complex with high molecular weight kininogen. Upon activation, mediated by thrombin, activated factor XII (FXIIa) or FXI itself, it catalyses the conversion of FIX to activated FIX (FIXa) in the consolidation phase of blood coagulation[20].

The human FXI gene (*F11*) comprises 15 exons, and spans about 23 Kb on the long arm of chromosome 4 (4q35.2)[21]. FXI deficiency is a rare autosomal recessive bleeding disorder invariably caused by mutations in *F11*. This disorder is particularly common among Ashkenazi Jews with a heterozygote frequency of 9%[22]. Two mutations, designated as type II (E117X) and type III (F283L), account for 98% of the alleles in this population[23]. Homozygous and compound heterozygous patients usually have severe FXI deficiency (FXI <15%), whereas heterozygotes have mild/partial FXI deficiency (20 to 50%)[24]. The bleeding tendency in FXI-deficient patients seems to correlate poorly with plasma FXI levels and haemorrhagic episodes are usually associated with injury or surgery and sometimes require replacement therapy[23]. No reports on secondary prophylaxis have been published, and surgical management represents a puzzling aspect of this disorder. Overall, the odds ratio for bleeding after surgery in patients with severe deficiency has been estimated to be 13, while in heterozygotes it is around 2.6[25]. However, it has been suggested that the risk of bleeding after surgical procedures is particularly high if anatomical sites rich in fibrinolytic activity are involved. An important contribution to the elucidation of bleeding risk after surgery in FXI deficiency was recently provided by Salomon *et al.*[26]. These authors evaluated surgical interventions carried out without prophylaxis, but with antifibrinolytic agents or replacement therapy, in homozygous or compound heterozygous patients with severe FXI deficiency. Tonsillectomy, nasal surgery, oral surgery, tooth extraction and prostate surgery were followed by bleeding in 53% of 152 procedures, while appendectomy, abdominal surgery, herniorraphy, bone fractures, hysterectomy and circumcision were followed by bleeding in only 6.5% of the 122 procedures[26]. An additional study demonstrated that dental extraction and oral surgery could be successfully carried out by using an antifibrinolyic agent (tranexamic acid) alone even in patients with severe FXI deficiency (FXI activity < 14 U/dL)[27]. The importance of identifying the situations at risk of bleeding requiring replacement treatment is further underlined by the demonstration that plasma infusion is associated with an increased risk of inhibitor development in patients with homozygous E117X genotype (type II mutation)[9]. Furthermore, it should be borne in mind that the use of FXI concentrate is accompanied by an increased risk of thrombotic events, especially in older patients when post-infusion FXI levels are >80-90%. FXI levels above 20% and not exceeding 70% are deemed sufficient to avoid bleeding complications and the risk of thrombosis[8].

### Factor XIII deficiency

FXIII is a transglutaminase which, in the presence of $Ca^{++}$ and thrombin, cross-links $\alpha$- and $\gamma$-fibrin chains, making fibrin stronger and insoluble[28]. FXIII is a heterotetramer composed of four subunits (A2B2), held together by non-covalent bonds with catalytic function being expressed by the A subunit while the B subunit functions as a carrier[29]. The gene encoding for the A subunit of FXIII (*F13A*) maps to chromosome 6 (p24-25) and spans a distance of 160 Kb. It consists of 15 exons encoding for a mature protein of 731 amino acids[30]. *F13B* is located on the long arm of chromosome 1 (q32-32.1) and contains 12 exons encoding for a mature protein of 641 amino acids[30].

Inherited FXIII deficiency is a rare severe bleeding disorder characterised by a life-long bleeding tendency, often presenting at birth with bleeding from the umbilical stump[30-32]. Recurrent miscarriages in females and spontaneous intracerebral or retroperitoneal bleeding are very frequent in this disorder [30,31,33].

There are two types of FXIII deficiency: XIIIA deficiency, caused by mutations in *F13A*, and XIIIB


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deficiency, which is rare and characterised by mutations in *F13B*. Patients with XIIIA deficiency have no detectable FXIIIA subunits in their plasma and mild (usually around 40-50%) FXIII subunit B deficiency, while .patients with severe XIIIB deficiency show consensual, marked reductions of FXIII subunits A and B.

The half-life of FXIII is the longest amongst coagulation factors and it has been suggested that levels around 2-5% are sufficient to prevent spontaneous bleeding and to avoid the risk of early foetal loss[34]. Experience with secondary prophylaxis for this disorder is the longest and the results are excellent. The use of prophylaxis with either plasma or FXIII concentrate (Fibrogammin P, CSL Behring, Marburg) has allowed women with FXIII deficiency who have had recurrent miscarriages to complete pregnancies successfully[7]. We have administered more than 1,200 infusions of FXIII concentrate (typically at ~ 10 U/kg every 4 weeks, larger doses in children) to six patients with FXIII deficiency over a maximum period of about 20 years and no adverse effects have been observed. Maintaining prophylaxis avoided any significant bleeding symptoms and a single bolus of 20-30 U/kg has been administered to cover surgical interventions, without mishap. The preliminary data of a French and an American study have been reported[35,36]. A total of 80 patients (61 in the USA and 19 in France) have been enrolled in a programme of continuous prophylaxis, with a maximum follow-up of 8 years. There has been no development of inhibitors, very few minor side-effects (mainly headache and myalgias) and no seroconversion. In the USA study, five bleeding episodes have been observed due to non-compliance with the prophylaxis schedule[36]. Overall, these data confirm that prophylaxis in severe FXIII deficiency is strongly recommended since it almost completely avoids any bleeding risk, allowing these patients a normal life-style.

## Conclusions

Nowadays, in western countries the availability of plasma-derived concentrates of missing clotting factors and the use of virally-inactivated plasma has rendered surgery and prophylaxis more feasible in patients with RICD, thus reducing the risk of life-threatening bleeding episodes and significantly improving their quality of life. It should, however, be borne in mind that treatment is still not so easily accessible to most patients living in developing countries. Extending state-of-the-art treatment to all RICD patients should be the goal of people treating patients with these disorders.

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