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REVIEW ARTICLE

Rare inherited coagulation disorders: no longer orphan and neglected

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Abstract

Rare inherited coagulation disorders due to the deficiency or dysfunction of coagulation factors have until recently received less clinical attention than hemophilias and von Willebrand disease. This situation has changed in the last decades, mainly due to therapeutic progress with the availability of more and safer products for replacement therapy produced by plasma fractionation or recombinant DNA technology. This narrative review, based on the latest literature and expert opinion, emphasizes the progress achieved for each of the rare deficiencies, mentions the still unmet therapeutic needs, and sketches the perspectives for further progress.

KEYWORDS
coagulation rebalancing agents, nonfactor products, plasma-derived factors, prophylaxis, recessive coagulation disorders, recombinant coagulant factors

Essentials

- Rare inherited coagulation disorders have experienced much progress regarding treatment.
- Single-factor plasmatic or recombinant products are available for factor (F)VII, FX, FXI, and FXIII deficiencies.
- However, FV and prothrombin deficiencies are still missing a specific treatment agent.
- Coagulation rebalancing agents promise to fulfill the unmet needs of these patients.

1 | INTRODUCTION

In an early review article that dealt with rare bleeding disorders [1], it was emphasized that rare inherited coagulation disorders (RICDs) were neglected by the healthcare community at large, patient advocacy organizations, and drug manufacturers. Diagnostic workup with global screening tests such as the prothrombin and partial thromboplastin time plus factor assays were usually available even in the low- and middle-income countries where RICDs are more prevalent (Middle East, Iran, India, and Indonesia). However, there was a general scarcity of therapeutic agents, so fresh-frozen plasma (FFP) was often the main form of treatment, notwithstanding the risk of transmitting blood-borne infections such as viral hepatitis and HIV.

The situation has changed. The molecular basis of most RICDs is now more widely established [2], including next-generation sequencing approaches that offer to clinically severe cases the option of counseling, preimplantation and antenatal diagnosis. Moreover, an important step forward had been made by the European Network of Rare Bleeding Disorders in 2007 [3]. RICDs were newly classified not only on the basis of the plasma levels of the deficient coagulation factors, which are relatively poor predictors of the bleeding tendency, but also on the basis of the history of bleeding (Table 1) [3]. An additional pivotal contribution

TABLE 1 Categories of clinical bleeding phenotypes.

Clinical bleeding severity	Definition
Asymptomatic	No documented bleeding episodes
Grade I	Bleeding that occurred after trauma or drug ingestion
Grade II	Spontaneous minor bleeding: bruising, ecchymosis, minor wound and oral cavity bleeding, epistaxis, and menorrhagia
Grade III	Spontaneous major bleeding: hematoma, hemarthrosis, and CNS, GI, and umbilical cord bleeding

Clinical bleeding episodes were classified into 4 categories of severity relying on the location and potential clinical impact as well as unprovoked features of bleeding in order to have a standard definition of severity. Patients were classified as belonging to a certain category if they had at least 1 documented episode matching the defined bleeding severity and no episode matching the higher severity grade [3].

CNS, central nervous system; GI, gastrointestinal.

of the European collaborative effort is that for each RICD, trough plasma levels associated with the occurrence of provoked as well as unprovoked bleeding were established and helped to better design clinical trials and therapeutic strategies. The spectrum of medications became progressively wider, with the availability not only of plasma-derived (pd) single-factor products for fibrinogen, factor (F)VII, FX, and FXI deficiencies but also of those manufactured by recombinant DNA technology, at least for FVII and FXIII deficiencies. Owing to the clinical implications of the array of therapeutic agents currently available, we chose to update them in this narrative review based on the latest literature and expert opinions and to sketch for the practicing hematologist the perspectives for further progress in order to tackle the still unmet needs.

2 | FIBRINOGEN DEFICIENCY

Congenital fibrinogen deficiency is categorized as quantitative, characterized by unmeasurable or low fibrinogen levels (afibrinogenemia and hypofibrinogenemia), and qualitative, with normal or reduced antigen levels and disproportionately low functional activity (dysfibrinogenemia and hypodysfibrinogenemia) [4,5]. Congenital fibrinogen deficiency accounts for about 8% of RICDs, and the prevalence of afibrinogenemia has been estimated to be 1 in 10^6 people [3,6], with the most severe bleeding manifestations and an autosomal recessive pattern of inheritance [4].

2.1 | Management

The main goals are the prevention and treatment of bleeding and obstetrical complications with fibrinogen replacement therapy (FRT). The preferred options approved in multiple countries by medicine regulatory agencies are fibrinogen concentrates (FC; Table 2), which have the advantages of small reconstitution volume, intravenous administration and low likelihood of transfusion reactions and circulatory overload [7]. Cryoprecipitate and FFP can also be used when FCs are unavailable [8–10]. FFP can be made virally safer by the addition of a solvent-detergent (SD) mixture, but this product (SD-FFP) is not widely available and is expensive. The therapeutic targets of plasma fibrinogen during prophylaxis and at the time of major and minor surgery are shown in Table 3 [11–13]. The majority of fibrinogen-deficient individuals undergo on-demand treatment, and regular primary prophylaxis is typically unnecessary. However, short-term prophylaxis is needed to stop unprovoked severe bleeds at the time of surgery, pregnancy, delivery, and postpartum [8,13].

2.2 | Products available and dosages

Fibrinogen concentrates listed in Table 2 are manufactured from pooled human plasma [14,15], provided in a lyophilized form containing approximately 1000 mg/vial, and require small fluid volumes for reconstitution [16]. The risk of blood-borne viral infection is minimized by the adoption of virus-inactivation methods (Table 2).

Recovering plasma fibrinogen activity of 100 to 150 mg/dL in a 70 kg adult is expected following a typical concentrate dose of 4 to 6 g [8]. Long-term prophylaxis is usually recommended in cases of afibrinogenemia with development of central nervous system (CNS) bleeding with the goal of maintaining factor activity levels above 50 mg/dL [17]. Because of the large variability of individual pharmacokinetics, the intervals between repeated doses depend on the plasma levels as monitored in each patient, and no fixed dosage schemes are recommended [18,19]. Notwithstanding pharmacokinetic differences between patients, FC doses of 50 to 100 mg/kg every 2 to 4 days that achieve levels of 100 to 150 mg/dL are usually sufficient for treatment/prevention of spontaneous or surgical bleeding [8]. In cases with severe bleeding or undergoing major surgery, more frequent dosing intervals are preferred to increased dosages [19,20]. When only cryoprecipitate is available, the US Food and Drug Administration recommends 14 bags in a 70 kg adult to raise fibrinogen by approximately 50 to 100 mg/dL and the British Society for Haematology recommends 10 bags to attain levels of at least 100 mg/dL [21].

While there is concern regarding the risk of thrombosis associated with FRT, establishing a causal relationship between the 2 events is elusive [9]. FRT-related thrombosis was reported in 2 afibrinogenemic cases in the context of a systemic review and in an additional afibrinogenemic case in the Prospective Rare Bleeding Disorders Database (Pro-RBDD) study [22,23]. Patients with a history of thrombosis should be considered for thromboprophylaxis with low-molecular-weight heparins when undergoing FRT [17], particularly at the time of conditions associated with hypercoagulability such as surgery and pregnancy/parturition.

TABLE 2 Coagulation factor concentrates available for rare inherited coagulation disorders.

Factor deficiency	Brand	Manufacturer	Viral inactivation and removal methods	Factor concentration
Fibrinogen	Haemocomplettan RiaSTAP	CSL Behring	Pasteurization	20 mg/mL
	Fibryga Fibryna	Octapharma AG	Nanofiltration	20 mg/mL
	FibCLOT Clottafact	LFB	Dry heat Virus filtration	15 mg/mL
	Fibrinogen HT	Yoshitomi, Inc	Dry heat Nanofiltration	NA
	FibroRAAS	Shanghai RAAS	SD	NA
	GCC-Fibrinogen	GC Pharma	NA	NA
FII	Kcentra (PCC4) Confidex (PCC4) Beriplex P/N (PCC4)	CSL Behring	Pasteurization Nanofiltration	31 IU/mL 20-48 IU/mL 31 IU/mL
	Uman Complex D.I. (PCC3)	Kedrion	Dry heat	25 IU/mL
	Kaskadil	LFB		37 IU/mL
	Octaplex	Octapharma	Nanofiltration	31 IU/mL
	Cofact	Sanquin	Nanofiltration	30 IU/mL
	PPSB-HT Nichiyaku	Nihon	Dry heat Nanofiltration	20 IU/mL
	Konyne	Bayer	Dry heat	38 IU/mL
	Prothrombinex-VF	CSL Bioplasma	Dry heat Nanofiltration	25 IU/mL
	Prothromplex TIM 3 (PCC3) Bebulin (PCC4)	Takeda	Vapor heating	30 IU/mL 24-38 IU/mL
FVII	Provertin-UM TIM3 FVII Facteur VII-LFB Acset (FIIa) Kcentra (Beriplex P/N in Europe) Octaplex	Takeda BPL LFB LFB CSL Behring Octapharma	Dry heat Dry heat SD NA Dry heat Nanofiltration SD Nanofiltration	60 IU/mL NA NA NA 10-25 IU/mL Octaplex 500, 180-480 IU/mL
	rFVIIa: NovoSeven	Novo Nordisk	-	1 mg/mL
FX	Coagadex	BPL	Nanofiltration Dry heat	FX, 100 IU/mL
	FX P Behring	CSL Behring	Pasteurization	FX, 30-60 IU/mL FIX, 30 IU/mL
FXI	FXI concentrate Hemoleven	BPL LFB	Dry heat Nanofiltration	100 IU/mL 100 IU/mL
FXIII	Recombinant (Tretten/ NovoThirteen)	Novo Nordisk	-	rFXIII, 833 IU/mL 667-1042 IU/mL
	Corifact/Fibrogammin	CSL Behring	Pasteurized	CORIFACT, 1000/1600 IU Fibrogammin, 250/1250 IU

F, factor; NA, no available data; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII; rFXIII, recombinant factor XIII; SD, solvent-detergent.

2.3 | Surgical management

In afibrinogenemia, prophylactic replacement therapy is needed before high bleeding risk surgical procedures [13]. Cases with moderate hypofibrinogenemia but no bleeding history can be managed without prophylaxis for low-bleeding risk procedures [13]. Regarding major surgery, the optimal daily plasma level is 150 to 200 mg/dL until wound healing is complete (Table 3). According to the United Kingdom Doctors' Haemophilia Organization (UKHCDO), a concentrate dose of 50 to 100 mg/kg is recommended for this purpose, continuing with lower doses at 2- to 4-day intervals with the goal of maintaining fibrinogen above 100 mg/dL until wound healing [2,8]. In minor

TABLE 3 Target plasma levels and dosages recommended of factor replacement products for surgery and prophylaxis in patients with rare inherited coagulation deficiencies [3].

Factor deficiency		Major bleeding/surgery (treat until wound healing is complete)	Minor bleeding/surgery (treat for 2-3 d)	Prophylaxis
Fibrinogen (plasma half-life, 3-5 d)	Target plasma level	150-200 mg/dL	50-100 mg/dL	>50 mg/dL
	Concentrate	50-100 mg/kg every 2-4 d	-	50-100 mg/kg once a week
	Cryoprecipitate	1 bag/5 kg	1 bag/10 kg	1 bag 3 times/wk 3 bags every 7-10 d
	FFP or SD-FFP	15-30 mg/kg	-	-
FII (prothrombin; half-life, 60-70 h)	Target plasma level	>20 IU/dL	>10 IU/dL	>10 IU/dL
	FFP or SD-FFP	15-25 mL/kg		
	PCC (3- or 4- factor)	20-40 IU/kg	-	20–40 IU/kg once a week
FV (half-life, 16-36 h)	Target plasma level	>15-20 IU/dL	10 IU/dL	15-20 IU/dL
	FFP or SD-FFP	15-25 mL/kg plus additional dose (10 mL/kg every 12 h)	-	20-30 mL/kg twice a week
FV + FVIII (FVIII half-life, 10-14 h)	Target plasma level	FV, 25 IU/dL FVIII, 50-70 IU/dL	FV, 25 IU/dL FVIII, 30-50 IU/dL	-
	FFP or SD-FFP	15-25 mL/kg plus supplementary FVIII (rFVIII, 20-40 IU/kg)	-	Rarely required
FVII (half-life, 4-6 h)	Target plasma level	15-20 IU/dL	15-20 IU/dL	>10 IU/dL
	rFVIIa	15-30 μg/kg (every 4-6 h)	-	20-40 μg/kg 3 times/wk
	pd concentrate	10-40 IU/kg (every 4-6 h)	-	
	FFP or SD-FFP	15-30 mL/kg	-	-
	PCC (4-factor)	20-30 IU/kg	-	-
FX (half-life, 40-70 h)	Target plasma level	20-30 IU/dL	20 IU/dL	>10 IU/dL
	pd concentrate	25 IU/kg	-	25 IU/kg
	pd concentrate (dual factors—with a known amount of FIX)	20-40 IU/kg	20-40 IU/kg	20-40 IU/kg
	FFP or SD-FFP	15-20 mL/kg	15-20 mL/kg	-
	PCC (3- or 4- factor)	20-30 IU/kg	-	20-40 IU/kg twice a week
FXI (half-life, 50-70 h)	Target plasma level	45 IU/dL	30 IU/dL	Rarely required
	pd concentrate	15-20 IU/kg	-	As above
	FFP or SD-FFP	15-25 mL/kg + tranexamic acid 15-20 mg/kg or 1 g 4 times daily for 5-7 d	-	As above

(Continues)

TABLE 3 (Continued)

Factor deficiency		Major bleeding/surgery (treat until wound healing is complete)	Minor bleeding/surgery (treat for 2-3 d)	Prophylaxis
FXIII (half-life, 10-15 d)	Target plasma level	30 IU/dL	30 IU/dL	10-20 IU/dL
	rFXIII A-subunit	35 IU/kg	35 IU/kg (no clear indication)	35 IU/kg every 4 wk
	pd concentrate	10-40 IU/kg + tranexamic acid 15-20 mg/kg or 1 g 4 times daily	20-40 IU/kg	10-40 IU/kg every 4-6 wk
	Cryoprecipitate	2-3 bags	-	2 bags every 3 wk
	FFP	3-5 mL/kg	3-5 mL/kg	-

This table serves as a general guide for the management of bleeding. Dose adjustment may be required depending on the severity of bleeding and factor activity levels. PCCs generally are not used in cases of minor bleeding or minor surgery due to their potential prothrombotic risks.

F, factor; FFP, fresh-frozen plasma; PCC, prothrombin complex concentrate; pd, plasma-derived; rFVIIa, recombinant activated factor VII; rFVIII, recombinant factor VIII; rFXIII A-subunit, recombinant factor XIII A-subunit; SD, solvent-detergent.

surgery, oral tranexamic acid without replacement therapy is sufficient at a dose of 15 to 20 mg/kg or 100 mg 4 times a day [8]. This antifibrinolytic medication may also be sufficient for mild bleeding episodes, particularly in mucosal tracts.

2.4 | Obstetrical management

Due to their high risk of placenta abruption, spontaneous abortions, and postpartum hemorrhage, pregnant women with afibrinogenemia warrant prophylaxis [17]. Suggested plasma levels during pregnancy and at labor are 100 mg/dL and 150 mg/dL [8,24]. Placental abruption can be prevented by continuous infusions targeted to maintain levels higher than 200 mg/dL [17]. Typical recommended doses vary from 200 mg twice a week in the initial trimester up to 500 mg 3 to 4 times weekly near term [20]. If necessary, increasing the frequency of administrations rather than dosage is suggested.

Also, patients with hypofibrinogenemia and dysfibrinogenemia may experience obstetrical complications [4,23]. Therefore, they require prophylaxis if they have a history of bleeding or fibrinogen levels of less than 100 mg/dL. In cases with mild to moderate deficiency (ie, fibrinogen activity 50-100 mg/dL), trough target levels should be approximately 100 mg/dL throughout pregnancy in order to decrease the risk of placental abruption [17]. In hypofibrinogenemia, FRT is advised during labor and delivery, whereas its use during pregnancy should be considered only when there is a history of recurrent miscarriage or bleeding during pregnancy.

In dysfibrinogenemia, management is challenging owing to the varied clinical manifestations and lack of guidelines. Fibrinogen activity lower than 50 mg/dL is associated with a greater risk of spontaneous abortion and postpartum bleeding. However, FRT should be individualized. In women with bleeding phenotypes, the target should be at least 150 mg/dL for vaginal delivery and 200 mg/dL or more for cesarean delivery [16]. The management of dysfibrinogenemia cases with recurrent miscarriage is uncertain. Based on a few reports, treatment options may include fibrinogen replacement, anticoagulation, or a combination of both [20].

3 | PROTHROMBIN DEFICIENCY

Prothrombin (FII) deficiency is one of the rarest coagulation deficiencies (less than 1 in 10^6), distinguished in hypoprothrombinemia (characterized by concomitantly low levels of antigen and activity) and dysprothrombinemia (characterized by normal levels of a dysfunctional protein) [1,25,26]. The inheritance pattern is autosomal recessive [1]. No cases of aprothrombinemia have been reported, suggesting incompatibility with life [1]. Low FII plasma levels (<5 IU/dL) lead to severe bleeding that requires replacement therapy for the episodic management of bleeding or prophylaxis before major surgery [26] (Table 3). There are no FII concentrates from recombinant or plasma sources. However, FII is contained in 3- and 4-factor prothrombin complex concentrates (PCCs) and in FFP [27] (Table 2). PCCs contain approximately equivalent amounts of FIX and FII activities, and FII recovery is 2 IU/dL per International Unit per kilogram. A typical therapeutic dose of PCC of 20 to 30 (FIX) IU/kg is expected to increase FII activity to 40 to 60 IU/dL. Similar doses at 2- to 3-day intervals may be required [8,27]. If PCC is not available, FFP or SD-FFP at a dose of 15 to 25 mL/kg is anticipated to raise FII activity to 30 to 40 IU/dL [8]. Although data on long-term prophylaxis are limited, it is worth considering in patients with life-threatening bleeding [28].

3.1 | Surgical management

For severe bleeding or major surgery, PCC is recommended at a dose of 20 to 40 IU/kg (FIX), followed by additional doses of 10 to 20 IU/kg every 48 hours if necessary, with the goal of sustaining FII activity higher than 20 IU/dL [8]. For mild bleeding or surgery, tranexamic acid at a dose of 15 to 20 mg/kg or 1 g every 6 hours is enough for hemostasis [8].

3.2 | Gynecologic and obstetrical management

Menorrhagia is a frequent manifestation in deficient women and, when severe, can be controlled by prophylaxis [26]. A woman with FII lower than 10 IU/dL received PCC prophylaxis (25 IU/kg) once a week, with additional doses of PCC (25 IU/kg) on day 1 and day 3 or 4 of menses [29]. This regimen instead of hormonal treatment resulted in normal menstrual logs [29]. Because FII remains low during pregnancy, in women who in the third trimester have FII activity lower than 20 IU/dL, PCC 20 to 40 IU/kg at labor or before cesarean section is recommended to achieve 20 to 40 IU/dL according to the Royal College of Obstetricians and Gynaecologists guideline [8,30]. It may be necessary to administer additional PCC (10-20 IU/kg) at 48 hours to maintain FII above 20 IU/dL for more than 3 days [8]. If a PCC is not available, FFP or SD-FFP at a dose of 15 to 25 mL/kg are alternatives [8]. PCCs may cause thrombotic complications due to their content of multiple vitamin K–dependent coagulation factors. To control this risk, vitamin K–dependent factors should be monitored and factors other than FII should be kept below 150 IU/dL in plasma [1].

4 | FV DEFICIENCY

FV deficiency has an autosomal recessive inheritance pattern with a prevalence of 1 in 10^6 [31]. Activity levels lower than 10 IU/dL usually lead to more severe bleeding, and cases with levels above 10 IU/dL are typically asymptomatic or mild bleeders [8]. Yet, there are cases with FV above 10 IU/dL in which patients experience hemarthrosis and intracranial bleeding, as well as deficient cases with FV below 10 IU/dL with less bleeding than anticipated [32–34]. Due to the lack of a pdFV concentrate, FFP or SD-FFP is at the moment the only available treatment, so there is still an unmet need for these patients [35]. The recommended starting dosage is 15 to 20 mL/kg, which increases FV by 15 IU/dL with the goal of preventing spontaneous, traumatic, and surgical bleeding [8,36]. Because of the relatively short plasma half-life of FV (16-36 hours), daily infusions are required to keep FV at hemostatic levels (ie, above 20 IU/dL) [37]. Because normal platelets contain FV that localizes at the site of bleeding [38], a combination of platelet concentrates and SD-FFP has been used when SD-FFP alone was ineffective [8]. Off-label recombinant FVIIa (rFVIIa) was successfully used in cases with FV inhibitors (not infrequent) or allergy to FFP or to avoid volume overload [8,39,40].

4.1 | Surgical management

FV levels during surgical procedures should be kept above 15 to 20 IU/dL (Table 3) in severely deficient cases, as well as in those with a history of spontaneous or perioperative bleeding [17]. In addition to an initial preoperative dose of FFP or SD-FFP (15-25 mL/kg), an extra dose (10 mL/kg every 12 hours) is recommended for major surgery to maintain plasma FV above 15 to 20 IU/dL until wound healing [8]. For minor surgery, tranexamic acid may be sufficient [8].

4.2 | Gynecologic and obstetrical management

Menorrhagia, a common bleeding manifestation in deficient women, can be managed with oral contraceptives, antifibrinolytics, and replacement therapy [17]. Women with very low FV are at an increased risk of miscarriage and postpartum hemorrhage [17]. Therefore, FFP or SD-FFP is recommended to achieve at least 20 to 40 IU/dL with a single dose of 15 to 25 mL/kg at the time of labor or before cesarean section. Further doses of 10 mL/kg at 12-hour intervals are suggested to maintain FV above 20 to 40 IU/dL for at least 3 days [8].

5 | COMBINED FV AND FVIII DEFICIENCY

This autosomal recessive disorder has a low prevalence (1 in 2×10^6), and affected patients typically experience mild to moderate bleeding [1,41]. Therefore, treatment is mainly employed for traumatic bleeding or to prevent surgical or obstetrical bleeding, and prophylaxis should be considered only in the rare cases presenting with hematoma and hemarthrosis [8]. Agents that correct both FV and FVIII deficiencies are FFP or SD-FFP [8]. The recommended starting dosage is 15 to 25 mL/kg, to be repeated daily to keep FV at hemostatic levels (more than 20 IU/dL), but this is not sufficient for FVIII. Since FVIII has a shorter half-life than FV (10-14 vs 16-36 hours), FFP and SD-FFP are less effective in maintaining adequate plasma levels, and supplementary sources of FVIII may be needed [8]. Desmopressin and recombinant FVIII were effectively employed to raise FVIII when post-FFP levels were deemed insufficient [42–44]. rFVIIa has also been reported to control bleeding when FFP is ineffective or associated with allergy [8].

5.1 | Surgical management

Replacement of both factors using FFP or SD-FFP is warranted for severe bleeding or high-risk surgery (Table 3), along with supplementary FVIII by means of recombinant FVIII (20-40 IU/kg) or desmopressin (0.3 μg/kg) [8]. Further treatment at 12-hour intervals is required to maintain FV and FVIII above 15 IU/dL and 50 IU/dL, respectively. For minor surgery, tranexamic only is suggested [8].

5.2 | Gynecologic and obstetrical management

Even though menorrhagia is one of the most common bleeding symptoms in FV/FVIII deficiency, data on management are scarce. The incidence of miscarriage is also unknown. However, the high risk of postpartum hemorrhage in women with the combined deficiency demands attention during delivery [45]. There is an increase of FVIII during pregnancy, but FV remains stable in plasma. Thus, the risk of bleeding during labor and puerperium depends particularly on FV levels [46]. It is recommended to maintain FV and FVIII above 15 IU/

dL and 50 IU/dL, respectively, during labor with FFP or SD-FFP (15 mL/kg), with additional doses (10 mL/kg every 12 hours) for 3 days or more [8]. For women undergoing cesarean section with FV below 15 IU/dL, it is advisable to continue factor replacement until wound healing [41].

6 | FVII DEFICIENCY

It is the most common RICD and has an autosomal recessive pattern of inheritance, with prevalence of 1:300,000 to 500,000 for homozygous and 1:350 for heterozygous deficiency [1,47]. Typically, homozygotes or compound heterozygotes have severe FVII deficiency (<10 IU/dL), and heterozygotes have levels of 20 to 60 IU/dL [48–50]. Clinical manifestations range from asymptomatic to severe bleeds poorly correlated with factor activity levels [26], so homozygotes or compound heterozygotes with severe deficiency may be asymptomatic, but heterozygotes may have significant bleeding [26]. The preferred therapeutic choice is rFVIIa [51]. FFP, SD-FFP, or pdFVII concentrates can be used when rFVIIa is unavailable, while the 4-factor PCC is not commonly used [26].

Patients with severe deficiency may rarely suffer from intracranial bleeding, particularly after head trauma and in neonates after vaginal delivery. The majority of bleeding episodes can be effectively treated with a mean daily rFVIIa dose of 30 to 60 μg/kg [49]. pdFVII, with a dosage of 10 to 40 IU/kg at 4- to 6-hour intervals, can treat and prevent bleeding with an efficacy similar to that of rFVIIa [2]. A typical dose of FFP is 15 to 30 mL/kg, depending on the site and severity of bleeding [50]. Long-term prophylaxis is generally not needed in FVII deficiency, relying for this choice on the history of clinical bleeding rather than on factor levels alone. Prophylaxis is considered at a rFVIIa dosage of 20 to 40 μg/kg or pdFVII dosage of 10 to 30 IU/kg twice/thrice a week in patients with factor levels below 1 IU/dL and a history of severe bleeding, including those who had intracranial bleeding (Table 3) [17,52].

6.1 | Surgical management

For severe bleeding or major surgery, the recommended rFVII dosage is 15 to 30 μg/kg administered every 4 to 6 hours (Table 3) [53]. For mild bleeding episodes or minor surgery, a reported dose is 20 μg/kg in single or multiple daily doses [54]. Tranexamic acid (at a dosage of 15-20 mg/kg or 1 g 4 times daily) is sufficient for minor surgical procedures and mucosal tract bleeding (Table 3) [8].

6.2 | Gynecologic and obstetrical management

FVII deficient women may present with gynecologic bleeding that can be controlled by rFVII or pdFVII administered on the first and second day of menses [55]. Cases with plasma levels below 10 IU/dL are 5-fold more likely to have menorrhagia than those with higher levels [56]. Replacement therapy duration varies from 1 to multiple days, with no apparent difference in efficacy [57]. FVII increases 4-fold in plasma during pregnancy in heterozygotes but not in homozygotes [58], so postpartum hemorrhage is a potential complication. Because the postpartum rate of bleeding in deficient women who received peripartum prophylaxis was comparable to those who did not, prophylaxis should be individualized on the basis of the bleeding history and delivery method [59–61]. Women with FVII below 20 IU/dL and with a history of bleeding or requiring cesarean section should be candidates for rFVII prophylaxis (15-30 μg/kg every 4-6 hours for at least 3 days) [8]. For the remaining deficient women, rFVIIa 15 to 30 μg/kg is recommended only in case of abnormal bleeding [8]. FVII deficiency does not apparently increase the risk of vaginal bleeding, miscarriage, or antepartum hemorrhage [62]. The use of tranexamic acid is recommended following miscarriage until bleeding settles [62].

7 | FX DEFICIENCY

It is one of the most severe RICDs, transmitted with an autosomal recessive pattern and a prevalence of 1 in 10^6 in the general population [1]. Patients with very low coagulant activity (<1 IU/dL) may present with severe and unprovoked bleeding early in life, including umbilical stump, CNS, or gastrointestinal bleeding [63]. While a proportion of cases with low factor levels have severe bleeding (24%), those with factor activity above 40 IU/dL usually remain asymptomatic [3]. Treatment options include PCCs, FFP, SD-FFP, a dual FIX/FX pd concentrate with known amounts of both factors, and a single-factor pdFX concentrate approved in both the United States and Europe [64–66]. FX recovery after PCC is 20 IU/dL, suggesting that a dose of 20 to 30 IU/dL FIX may increase FX by 40 to 60 IU/dL [8]. The high-purity pd concentrate is of particular interest for the relatively high proportion of patients, most commonly neonates, who develop intracranial hemorrhage after vaginal delivery (9%-26%) [67]. In addition, this concentrate may overcome the risk of thromboembolic complications or circulatory overload associated with PCCs or FFP. Because FX levels between 10 and 40 IU/dL have been reported to be hemostatically effective and on the basis of a FX half-life of 24 to 40 hours, a concentrate dosage of 25 IU/kg every 24 hours should generally suffice if continuous prophylaxis is needed [8], with the goal of maintaining trough levels above 10 IU/dL [68]. Prophylactic regimens with the pd concentrate for children and adults are indicated to be 40 to 50 IU/kg and 25 IU/kg twice a week, respectively [17].

7.1 | Surgical management

Similar to on-demand treatment, surgical treatment has recently evolved toward the use of the pd concentrate. Three prospective, open-label, multicenter clinical trials and 2 multicenter retrospective studies have been conducted in patients with factor levels below 20 IU/dL [66]. In particular, cases undergoing surgery received the concentrate preoperatively with the goal of raising FX to 70 to 90 IU/dL and maintaining postoperative levels above 50 IU/dL until wound

healing [66]. The pdFX concentrate was safe and effective in 5 cases undergoing major and minor surgical procedures [69]. When this product is not available, for major surgery, PCC is advised at a dose of 20 to 30 IU/kg (FIX) in order to attain a target level of 20 IU/kg, with additional doses of 10 to 20 IU/kg at 24-hour intervals if required [8]. For minor bleeding and minor surgery, tranexamic acid (15-20 mg/kg or 1 g 4 times daily) is sufficient [8].

7.2 | Gynecologic and obstetrical management

Women with this deficiency may experience heavy menstrual bleeding and obstetrical complications. Although FX rises during pregnancy, severely deficient women are at risk because their plasma levels usually remain insufficient for hemostasis, and thus strict monitoring is required at delivery. Among 332 women, 25% had heavy menstrual bleeding and 64% required the administration of blood products [70]. Of 31 pregnancies, postpartum hemorrhage was observed in 22%, highlighting the importance of preventive peripartum hemostatic cover [70]. The occurrence of miscarriage seems to be similar to that in the general population [70]. The UKHCDO/Royal College of Obstetricians and Gynaecologists guidelines recommend that pregnant women with FX below 30 IU/dL and a history of bleeding as well as those who require cesarean section should receive PCC at a dose of 20 to 40 IU/kg (or of pdFX concentrate if available) with the goal of achieving levels above 40 IU/dL. Further dosages of 10 to 20 IU/kg once daily are required to maintain activity above 30 IU/dL for at least 3 days [8,30,70,71].

8 | FXI DEFICIENCY

FXI deficiency is characterized by both homozygous (1 in 10^6) and heterozygous (1 in 30,000) inheritance patterns [72,73]. Unprovoked bleeding is rare, and bleeding is more likely to occur after dental, oropharyngeal, or urogenital surgery, ie, in tissues with high fibrinolytic activity, but even individuals with low plasma FXI often remain asymptomatic, so regular prophylaxis is very seldom needed [73]. Available options for FXI replacement are FFP, SD-FFP, and pdFXI concentrates (2 are available in some European countries but not in the United States; Table 2), and antifibrinolytic agents are used as adjuvants [74]. FXI recovery in plasma is approximately 2 IU/dL per IU/kg, and a typical therapeutic dose is 15 to 20 IU/kg (Table 3) [74]. Because there have been cases of thrombosis following FXI concentrates in the postoperative period (pulmonary embolism and transient ischemic attacks), it is recommended not to exceed a dose of 30 IU/kg [8,74]. In the United States, FFP and SD-FFP are the only replacement products available [75]. SD-FFP offers an alternative to concentrates with a lower risk of thrombosis and contains a mean FXI activity of 70 to 90 IU/dL, so a typically prescribed amount is 15 to 25 mL/kg [8,75]. In patients with severe bleeding, FFP or SD-FFP at a dose of 1.5 L or more is required to reach factor activity levels of 30 IU/dL [74].

8.1 | Surgical management

The clinical history is the best predictor of the bleeding tendency and helps avoid unnecessary treatments [76]. Cases with FXI activity below 20 IU/dL sometimes develop surgical bleeding, particularly in sites rich in fibrinolytic activity [17]. In them, targeting a trough FXI level of 30 IU/dL for approximately 5 days is sufficient (Table 3). For minor bleeds and surgeries, tranexamic acid alone (15-20 mg/kg or 1 g 4 times daily for 5-7 days) suffices [8]. In the few major surgical operations associated with a risk of bleeding (in the oral cavity, nasal passages, and urinary tracts), FXI concentrates are initially administered at a dose of 10 to 15 IU/kg. Alternatively, a combination of FFP or SD-FFP (15-25 mL/kg) and tranexamic acid (15-20 mg/kg) may be considered (Table 3) [8]. Low-dose rFVIIa (15-20 μg/kg) is safe and effective for perioperative management of FXI-deficient patients who develop FXI inhibitory alloantibodies [72].

8.2 | Gynecologic and obstetrical management

Menorrhagia is common in FXI-deficient women [77], and inhibition of fibrinolysis with tranexamic acid (at a dose of 15-20 mg/kg or 1 g every 6 hours) is the preferred medication [8]. Obstetrical complications are more likely to occur in women with a history of bleeding. In those with more severe deficiency (FXI below 15 IU/dL), therapeutic regimens based upon FXI concentrate (dose, 10-15 IU/kg), FFP or SD-FFP (dose, 15-25 mg/kg), or tranexamic acid (dose, 15-20 mg/kg) are recommended at labor or before cesarean section [8,78]. For delivery in women with a history of bleeding, prophylactic tranexamic acid is recommended at a dosage of 15 mg/kg every 6 hours for more than 3 days [17]. The rate of miscarriage is comparable to that in the general population, but the risk of excessive bleeding following miscarriage is higher [78].

9 | FXIII DEFICIENCY

It is inherited as an autosomal recessive trait, and its prevalence is ~1 in 3×10^6, ie, one of the rarest RICDs [79]. The European Network of Rare Bleeding Disorders showed in general an association between FXIII activity and bleeding severity but a varied bleeding tendency in patients with plasma levels ranging from unmeasurable to 30 IU/dL. Patients with levels between 5 and 30 IU/dL experienced not only spontaneous minor or posttraumatic bleeding but also excessive menstruation and CNS, gastrointestinal, and umbilical cord bleeding [3]. This high degree of heterogeneity led Menegatti et al. [80] to indicate a cutoff of 15 IU/dL to prevent all spontaneous major bleeding. A prophylactic regimen in cases with a personal or family history of bleeding and those with severe deficiency is recommended to maintain trough levels of 10 to 20 IU/dL (Table 3) [8]. A wide range of medications is available to manage FXIII deficiency, including FFP, SD-FFP, cryoprecipitate, and a pdFXIII concentrate. However, recombinant FXIII (rFXIII-A2) is preferred when available in cases with FXIII A-subunit defects (95% of all deficient cases) owing to the small infusion volume, low risk of transfusion-associated

adverse events, and more precise dosing [81,82]. Based on the MENTOR 2 study, a prospective multi-center observational study, a recommended prophylactic dosage of rFXIII every 4 weeks is 35 IU/kg [83]. An alternative is to increase this dosage and further increase the duration between the infusion intervals [84].

9.1 | Surgical management

For minor surgery, tranexamic acid (15-20 mg/kg or 1 g 4 times daily) has been recommended. In major surgery, a concentrate dosage of 10 to 40 IU/kg has been recommended depending on the severity of bleeding (Table 3) [8]. FFP, SD-FFP, and cryoprecipitate should only be used if the pd product is not available. There is no guide for the use of rFXIII in surgery in order to prevent perioperative bleeding. In the MENTOR 2 trial, elective surgery was successfully performed with rFXIII-A2 prophylaxis at a dosage of 35 IU/kg every 4 weeks [85].

9.2 | Gynecologic and obstetrical management

Deficient women often have menorrhagia and are at risk for recurrent miscarriage (70% in FXIII-A2 defects; 15% in FXIII-B2 defects), and postpartum bleeding has been reported in 25% of pregnancies [8,17,86]. Due to the decrease of FXIII during pregnancy, the UKHCDO guidelines recommend prophylaxis to maintain plasma levels above 20 IU/dL [8,87]. Only a couple of cases employed rFXIII during pregnancy. A woman was treated with 2500 IU monthly and although she had some obstetrical complications, she delivered a healthy baby; in another case, the same dose was administered every 3 weeks with the goal of maintaining FXIII at a level of at least 10 IU/dL, was associated with a favorable course without complications [88,89]. In pregnant women on prophylaxis, infusion frequency should be increased to every 14 to 21 days in order to maintain FXIII above 20 IU/dL [8]. The pdFXIII concentrate at a single dose of 10 to 40 IU/kg is considered during labor or before cesarean section, with dosage adjustments based on the time since the last prophylactic treatment in order to prevent postpartum hemorrhage [8,17].

10 | CONCLUSIVE REMARKS AND PERSPECTIVES

This report indicates that RICDs are generating a growing interest in caregivers, advocacy organizations, and learned scientific societies, as well as in drug manufacturers. The spectrum of availability of single-factor products did increase, spanning from those employed for afibrinogenemia to FVII, FX, FXI, and FXIII deficiencies, even though no single factor is available for FV deficiency and the extremely rare FII deficiency. Moreover, for FVII and FXIII deficiencies, the early availability of pd single-factor concentrates has evolved toward their manufacturing by recombinant DNA technology. Recombinant products are no more clinically efficacious than those derived from plasma and were thus presumably developed in order to avoid hepatitis and other viral blood-borne infections, notwithstanding the reduction of this risk for pd agents through the adoption of multiple viral inactivation methods (mainly heating, pasteurization, nanofiltration, and SD; Table 2).

With the current abundance of efficacious and safe replacement products, are there still unmet needs for RICDs? In the most clinically severe cases, the treatment regimen of choice should be prophylaxis instead of episodic treatment at the time of bleeding or invasive procedures. For instance, clinical experience has shown that prophylaxis should be implemented in order to avoid the risk of CNS bleeding in most patients with severe FXIII deficiency and afibrinogenemia and also, but less frequently, in FVII and FX deficiencies. The establishment by Peyvandi et al. [3] of the minimum plasma levels needed for each RICD to avoid unprovoked bleeding offers a target for the rational implementation of prophylaxis (Table 3). However, in some RICDs, prophylaxis is less practically feasible than in the hemophilias, owing to the need for repeated intravenous injections due to the short plasma half-life of deficient coagulation factors. This snag is particularly cogent for FVII deficiency, but also so for FX and the still orphan FV deficiency: the latter not only for the relatively short half-life of FV but also because prophylaxis is made difficult by the risk of circulatory overload associated with repeated doses of plasma.

Tremendous progress took place in the last few years for prophylaxis in both the hemophilias, first with extended half-life coagulation FVIII and FIX, emicizumab, and more recently with nonfactor therapeutic agents based upon the inhibition of naturally occurring anticoagulant proteins (such as fitusiran for antithrombin, concizumab and marstacimab for tissue factor pathway inhibitor, and serpin protein C for activated protein C). These agents offer the possibility to exploit in RICDs their enhanced thrombin formation, which is the common mechanism of the hemostatic efficacy of all rebalancing products (Table 4). Rebalancing agents, currently still unlicensed but in the advanced phase of clinical development for both the hemophilias, have the blatant advantages of being administered subcutaneously and of a very prolonged plasma half-life that permits subcutaneous injections at intervals as spaced as daily for concizumab, fortnightly for marstacimab, and monthly for fitusiran and serpin protein C. Obviously, these nonfactor products could also potentially remedy the current lack of therapeutic agents for FV and FII deficiency.

At the moment, none of them is licensed or available for prophylaxis, except off-label for compassionate individual use. However, their potential use in RICDs is being contemplated, as shown by the availability of a few experimental studies. Marstacimab has been evaluated for its capacity to enhance thrombin generation in plasma from patients with FV, FVII, and FXI deficiency; positive results were obtained for FXI deficiency [90]. *In silico* modeling has been employed to simulate the impact of antithrombin reduction by fitusiran on thrombin generation in FV, FVII, and FX deficiencies, with the prediction that lowering antithrombin to 20% increased thrombin generation in all these deficiencies [91]. An *in vitro* study showed that the combination of reducing plasma antithrombin together with partially replacing FV, FVII, and FXI levels to 1 to 10 IU/dL increased thrombin

TABLE 4 Rebalancing agents for potential use in rare inherited coagulation disorders.

Parameters	Fitusiran	Concizumab/marstacimab	Serpin protein C
Targeted inhibitor of blood coagulation	AT	TFPI FXa	APC
Targeted clotting factor(s)	FXa and thrombin	FXa and FVIIa	FVa and FVIIa
Target	Liver cells	Circulating TFPI	Circulating APC
Mechanism of action	Reduced liver synthesis. Silencing RNA	Direct inhibition. Antibody	Direct inhibition. Enzyme inhibitor
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous
Monitoring	AT levels	TFPI levels	-
Frequency	Once-monthly	Concizumab: Once-dailyMarstacimab: Once-weekly	Once/2 weeks

APC, activated protein C; AT, antithrombin; FVIIa, activated factor VII; FXa, activated factor Xa; TFPI, tissue factor pathway inhibitor.

generation to normal values [92]. A study carried out in mice that were made completely deficient in FX demonstrated that the infusion of fitusiran markedly increased thrombin generation and, at the same time, stopped provoked bleeding [93]. Of course, these experimental studies remain to be validated with the administration of these rebalancing agents to patients with RICDs. An obvious obstacle to the licensing of these products is the rarity of the diseases, so drug regulatory agencies should accept protocols of safety and efficacy less demanding in terms of case size than those requested for the hemophilias. These protocols may be based on real-world registers, retrospective analyses, and self-controlled study designs in which patients may be their own control. An example that has already materialized is that of the tissue factor pathway inhibitor concizumab, approved by Health Canada in March 2023 for persons with hemophilia B complicated by neutralizing alloantibodies, a very rare coagulation disorder. On the whole, we envisage that the tremendous progress that materialized in the last 10 to 15 years for prophylaxis of the hemophilias will soon carry benefits also for the much rarer inherited coagulation deficiencies.

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AUTHOR CONTRIBUTIONS

All the authors jointly wrote, read, and approved the manuscript.

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P.M.M. has received from Bayer, Roche, Takeda, and Werfen honoraria for lectures at educational symposia; F.P. has received from CSL Behring, BioMarin, Roche, Sanofi, and Sobi honoraria as a member of advisory committees and from Takeda and Spark honoraria for educational symposia; S.M. and M.M. have no conflict of interest.

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