Received: 20 October 2022 | Revised: 25 January 2023 | Accepted: 31 January 2023

DOI: 10.1111/ejh.13941

European Journal of Haematology WILEY

REVIEW

Management of rare inherited bleeding disorders: Proposals of the French Reference Centre on Haemophilia and Rare Coagulation Disorders

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Abstract

Introduction: The rare coagulation disorders may present significant difficulties in diagnosis and management. In addition, considerable inter-individual variation in bleeding phenotype is observed amongst affected individuals, making the bleeding risk difficult to assess in affected individuals. The last international recommendations on rare inherited bleeding disorders (RIBDs) were published by the United Kingdom Haemophilia Centre Doctors' Organisation in 2014. Since then, new drugs have been marketed, news studies on surgery management in patients with RIBD have been published, and new orphan diseases have been described.

Aim: Therefore, the two main objectives of this review, based on the recent recommendations published by the French Reference Centre on Haemophilia and Rare Bleeding Disorders, are: (i) to briefly describe RIBD (clinical presentation and diagnostic work-up) to help physicians in patient screening for the early detection of such disorders; and (ii) to focus on the current management of acute haemorrhages and long term prophylaxis, surgical interventions, and pregnancy/delivery in patients with RIBD.

KEYWORDS
acute haemorrhage, coagulation factor deficiency, pregnancy, prophylaxis, rare bleeding disorders, surgery

Novelty Statement

What is the new aspect of your work?

Guidelines for clinical management of the rare inherited factor deficiencies have not been updated since the last publication of the United Kingdom Haemophilia Centre Doctors' Organization guidelines in 2014. Since then, new drugs have been marketed, news studies on surgery management in patients with rare inherited bleeding disorder have been published, and new orphan diseases (e.g., thrombomodulin variants) have been described. This review includes the more recent therapies.

What could be the specific clinical relevance of your work?

This work can help physicians for the management of acute haemorrhages and long term prophylaxis, surgical interventions, and pregnancy/delivery in patients with rare inherited factor deficiencies.

What is the central finding of your work?

Optimal therapeutical management of rare factor deficiencies.

1 | INTRODUCTION

Haemostasis is a complex and highly regulated process that implicates many pro- and anti-coagulant proteins. Qualitative or quantitative defects in one or several of these proteins may affect this process. For each coagulation factor, there are inherited disorders in which the severity of haemorrhagic symptoms can greatly vary. This review article will focus on therapeutic management of rare inherited bleeding disorders (RIBD) (list in Table 1). Its objective is to summarise the recent recommendations by the French Reference Centre on Haemophilia and Rare Bleeding Disorders (FRCH) to optimise and harmonise their management.

2 | METHODS

As RIBD concern a small number of patients, it is almost impossible to design clinical studies with adequate sample size to generate results with high degree of evidence. Moreover, due to the bleeding risk, properly designed randomised studies against placebo cannot be performed. Therefore, the FRCH selected publications on RIBD to collect indirect evidences: previously published international guidelines, systematic reviews, longitudinal observational studies, registries (e.g., the French national rare bleeding disorders registry FranceCoag), meta-analyses on other inherited coagulation diseases. To this aim, they searched the NCBI database, World Federation of Hemophilia,

TABLE 1 Prevalence for severe factor deficiencies, correlation between factor levels measured in the laboratory and clinical manifestations, and inheritance mode of rare inherited bleeding disorders.

Coagulation factor	Prevalence[a]	Laboratory-clinical data correlation	Transmission mode
Fibrinogen (factor I): Afibrinogenaemia	1/1 000 000	Strong	Autosomal recessive
Factor II	1/2 000 000	Strong	Autosomal recessive
Factor V	1/1 000 000	Weak	Autosomal recessive
Combined factors V + VIII deficiency	1/1 000 000	Strong	Autosomal recessive[b]
Factor VII	1/500 000	Weak	Autosomal recessive
Factor X	1/1 000 000	Strong	Autosomal recessive
Factor XI	1/1 000 000	No	Recessive or dominant
Factor XIII	1/2 000 000	Strong	Autosomal recessive
Combined vitamin K- dependent factor deficiency	Not known	Weak	Autosomal recessive

[a]Approximative data. In some regions where consanguine marriages are frequent and in specific populations, prevalence is higher.
[b]In very rare cases, the factor VIII and FV defects can be transmitted separately by the parents.

Orphanet, Theriaque, French Haemophilia Association and the French rare inherited bleeding disorders network (MHEMO) websites using the key words given in Table S1 up to March 2021. They retained only articles in English and French. Expert-based consensus was used when published data were not available. The guideline was reviewed by a board of 34 members of the French Societies on Haemostasis and Thrombosis (GFHT and COMETH). The strength of recommendations is presented in GRADE format (https://www.has-sante.fr).

3 | MANAGEMENT PROPOSALS

Rare inherited bleeding disorder epidemiology is poorly known (Table 1). Although they are usually transmitted in an autosomal recessive manner, autosomal dominant inheritance has been described for some disorders. Clinically, RIBD are characterised by a wide range of bleeding symptom severity: from asymptomatic condition to major haemorrhagic symptoms (Table 2). The phenotypic profile varies also among patients with the same disorder, and sometimes within the same family.

Rare inherited bleeding disorder diagnosis may be fortuitous following the prescription of haemostasis tests, or after a bleeding event, or in the framework of a family investigation. The laboratory confirmation is often based on standard coagulation tests and the measurement of the activity of the implicated coagulation factor(s) (Table S2A). Gene sequencing may help to confirm the diagnosis by detecting a disease-causing gene variation (Table S2B). Upon identification of a gene variant, genetic counselling may be proposed to identify other family members with the same gene alteration.

After diagnosis, patients must be followed regularly by a multidisciplinary team:

- A physician (haematologist, paediatrician, internal medicine specialist, orthopaedic surgeon or other) in a comprehensive haemophilia care centre;
- Other hospital healthcare professionals (e.g., dentist, pharmacist, laboratory scientist, geneticist, specialised nurses, physiotherapist, psychologist, social assistant);
- Other healthcare professionals, particularly general practitioners.

The regular follow-up visit must be always the occasion to continue and update the patient's therapeutic education. Group sessions could be organised at the local, inter-regional or national level with the contribution of the different specialised centres and with the patients association's support.

Rare inherited bleeding disorder management is mainly based on expert consensus, but these recommendations have a low level of evidence due to the absence of controlled randomised trials.[1] Replacement therapy concerns only patients with proven bleeding phenotype and/or undergoing surgery procedures at high risk of bleeding, or following a major trauma.

This manuscript summarizes therapeutic management of acute bleeding episodes, surgical interventions, pregnancy and delivery in patients with RIBD, as well as the indications of long-term prophylaxis in these patients. Long term prophylaxis in RIBDs is usually recommended for patients with severe or recurrent spontaneous bleeding episodes, particularly intracranial haemorrhage or recurrent hemarthroses.[2,3]

Management of surgical interventions is one of the most challenging situations in patients with RIBD. A consultation in a specialised centre and a multidisciplinary approach must be proposed before any surgery and during pregnancy/delivery. The bleeding risk of each patient must be defined on the basis of several criteria:

- Bleeding history
- Surgery type and site (Table 4)
- RIBD severity
- Association with other haemostasis deficiencies
- Presence of neutralising inhibitors
- Thrombosis risk

In patients with RIBD undergoing surgery, replacement therapy dosage, target factor trough levels and treatment duration must be adapted in function of the basal factor level (Table 3), bleeding phenotype, and surgery type. The haemostatic thresholds should be defined for each coagulation factor. Two threshold types can be proposed: one to identify patients who will remain asymptomatic,[4,5] and one to protect patients against severe bleeding symptoms.[5] By taking into account the previously published thresholds and the experts' opinion, the FRCH suggests management proposals with revised haemostatic thresholds to guide the therapeutic decision in case of major bleeding accident/trauma, surgery, pregnancy and severe bleeding phenotype that requires long term prophylaxis in patients with RIBD (Table 3).

In addition to the management of delivery and neuraxial anesthesia in pregnant women with RIBD, management of new-borns from parents with RIBD requires some basic knowledge on rare inherited disorders. It is worthy to emphasize that the children of women with RIBD characterised by autosomal recessive transmission are usually heterozygous and thus asymptomatic. Nevertheless, it is important to confirm that the partner is not consanguineous, does not carry a variant on the same gene and has normal factor level. In case of consanguinity, the risk for the foetus depends on the parents' gene mutational status. It is better to avoid instrumental vaginal delivery, invasive foetal monitoring and the coagulation factor level can be quantified in umbilical cord blood.

4 | FIBRINOGEN DISORDERS

Congenital fibrinogen disorders include quantitative (afibrinogenaemia, hypofibrinogenaemia) and qualitative (dysfibrinogenaemia and hypodysfibrinogenaemia) disorders. Quantitative fibrinogen deficiencies are associated with bleeding symptoms and poor wound healing, whilst half of patients with dysfibrinogenemia are asymptomatic, 20%–25% present venous or arterial thrombosis and 25% exhibit bleeding symptoms.

TABLE 2 Summary of the clinical presentation of rare inherited bleeding disorders.

Disease	Bleeding severity	First bleeding episode	Spontaneous or post-trauma/post-surgery bleeding	Intracranial bleeding	Gastro-intestinal bleeding	Muscle/joint bleeding	Ecchymosis	Mucosal bleeding (epistaxis/gum)	Menorrhagia	Other symptoms
Fibrinogen deficiencies (see also Table 4)	Variable	From birth (neonatal intracranial haemorrhage or umbilical cord) for afibrinogenemia	Both, in function of the defect severity	Afibrinogenemia	Rare	Yes	Yes	Yes	Yes, often severe	Miscarriages (afibrinogenemia) Post-partum bleeding Arterial and venous thrombosis
FII deficiency	Variable		Both, but rare post-surgery	Rare	Rare	Yes	Yes	Yes	Yes	Bleeding risk during delivery (severe deficiency)
FV deficiency	Variable	Rare from birth	Both	Rare	Rare	Less frequent		Yes Gum: 23%–48% Epistaxis: 25%–68% of patients	Yes 8%–50% of patients	
FVII deficiency	Variable		Both	If FVII <1%–2%	Yes (severe forms)	Yes	Yes	Yes	Yes 50%–69% of patients	Arterial and venous thrombosis Bleeding risk during pregnancy/delivery
FX deficiency	Variable	All ages; from birth in severe cases	Both	Yes in severe forms	Yes	Yes (recurrent in severe forms)	Yes	Rare	Yes 50% of patients	Bleeding risk during delivery
FXI deficiency	Variable	Usually late diagnosis	Most often post-trauma/surgery	Rare	Rare		Yes	Rare	Yes	Bleeding risk during delivery
FXII deficiency	Asymptomatic even in patients with severe deficiency									
FXIII deficiency	Variable	From birth in severe forms (80%): neonatal intracranial haemorrhage or umbilical cord	Both	Yes	Yes (when FXIII <10%)	Yes (when FXIII <10%)	Yes (when FXIII 0%–24%)	Yes	Yes (when FXIII 0%–24%)	Abnormal and late wound healing, miscarriages
Combined FV + FVIII deficiency	Variable, but often moderate/minor	All ages (51% before 5 years of age)	Often post-trauma/post-surgery (33%–92%)	Very rare; cephalhematoma ($n = 1$)	Rare	Rare	29%–44% of patients	Yes	Yes 33%–100% of patients	Bleeding during ovulation (rare); haemorrhagic ovarian cysts (rare)
Combined vitamin K-dependent factor deficiency	Variable	From birth in severe forms	Both	Yes	Yes, mostly after antibiotics	Yes	Yes	Yes		Developmental abnormalities, early osteoporosis, reduced hearing, pseudoxanthoma elasticum, valvular heart disease, midfacial hypoplasia

TABLE 2 (Continued)

Disease	Bleeding severity	First bleeding episode	Spontaneous or post-trauma/post-surgery bleeding	Intracranial bleeding	Gastro-intestinal bleeding	Muscle/joint bleeding	Ecchymosis	Mucosal bleeding (epistaxis/gum)	Menorrhagia	Other symptoms
Combined FVII + FX deficiency	Asymptomatic-minor	All ages	Often post-trauma/post-surgery	Rare	Rare	Rare	Rare	Rare	Rare	Heart, genitourinary, gastrointestinal, musculoskeletal symptoms caused by the 13q deletion or distal monosomy 13q.
Alpha2-antiplasmine deficiency	Severe if homozygous[a], to asymptomatic if heterozygous	From birth (if severe)	Post-trauma/post-surgery (late appearance)	Rare	Rare	Rare	Yes	Yes	Yes	N/A
PAI-1 deficiency	From severe for homozygotes to asymptomatic for heterozygotes	From infancy	Rare spontaneous bleeding/post-surgery /post-trauma	Rare	Rare	Rare	Yes	Yes	Yes	Early spontaneous abortion, early delivery. Vaginal and post-partum bleeding.
Thrombomodulin deficiency	Moderate to severe bleeding	All ages	Only post-trauma/post-surgery							

[a]Spontaneous or post-traumatic long-bone diaphyseal hematoma typical of homozygotes.

TABLE 3 Coagulation factor thresholds for bleeding risk proposed by Mannucci et al,[4] Peyvandi et al,[5] UK Guidelines Mumford et al[1] and FRCH (this review).

		Coagulation factor threshold				
			Peyvandi et al. 2012			
Coagulation factor concerned	Half life	Mannucci et al. 2004	Threshold to "remain asymptomatic"	Threshold to "avoid severe bleeding"	UK Guidelines Mumford A et al. 2014	FRCH proposals 2021
Fibrinogen	80 h	0.5 g/L	1 g/L	"Detectable"	1–1.5[a] g/L	0.5 g/L
Factor II	100 h	20–30 IU/dL	—	—	20 IU/dL	30 IU/dL[b]
Factor V	25 h	15–20 IU/dL	12 IU/dL	15 IU/dL	15–20 IU/dL	20 IU/dL
Factor VII	4–6 h	15–20 IU/dL	25 IU/dL	8 IU/dL	10–20[a] IU/dL	20 IU/dL
Factor X	40–60 h	15–20 IU/dL	56 IU/dL	10 IU/dL	20 IU/dL	20 IU/dL
Factor XI	50 h	15–20 IU/dL	26 IU/dL	25 IU/dL	20 IU/dL	15–30 IU/dL[c]
Factor XIII	150 h	2–5 IU/dL	3 IU/dL	15 IU/dL	10–20 IU/dL	20 IU/dL
Factor V + Factor VIII	FV 25 h and FVIII 12 h	15–20 IU/dL	43 IU/dL	8 IU/dL	FV: 15 IU/dL and FVIII: 50 IU/dL	FV: 20 IU/dL and FVIII: 50 IU/dL

[a]For delivery in pregnant women.
[b]For FII deficiency, no data available. A FII level >30% is very likely to ensure normal haemostasis that allows normal loco-regional anaesthesia.
[c]In rare patients with FXI levels up to 30%, abnormal bleeding may occur. Therefore, their personal and family history is very important.

TABLE 4 Classification of the bleeding risk of surgical procedures in patients with bleeding disorders according Solimeno et al.[91]

Bleeding risk	General surgery	Orthopaedic surgery	Others
Major	• Procedures "…-ectomy" • Procedures "…-otomy" • Resection of haemophilic pseudotumours	• Osteotomy/arthrodesis • Joint replacement /arthroplasty • Synovectomy (including arthroscopic) • Fracture reduction • Amputation • Arthroscopy	• Extraction of at least 3 teeth (including wisdom teeth) • Polypectomies/mucosectomies and biopsies associated with digestive endoscopy
Minor	• Placing/removing a central venous catheter	• Chemical/radioisotopic synoviorthesis	• Extraction of <3 teeth (other than wisdom teeth) • Cataract (insertion or removal) • Wound debridement

4.1 | Management of acute haemorrhages

The objective of replacement therapy with fibrinogen concentrate is to reach a fibrinogen level >1 g/L for minor bleedings and >1.5 g/L for major bleedings (Grade 2C).[6] If the fibrinogen level is unknown, an initial dose may be administered (50–70 mg/kg) in emergency situations. In afibrinogenemia, 50–70 mg/kg of fibrinogen increases plasma fibrinogen level to ~1 g/L. Doses and injection frequency after the first fibrinogen infusion is in general 2–4 days but must be adapted in function of the clinical situation and laboratory results. The in vivo half-life of fibrinogen is estimated to be about 3–4 days. In children weighing <40 kg, the fibrinogen dose must be increased by ~20 mg/kg compared with adults.[6–8] For minor bleeding tranexamic acid 1 g three to four times per day can be used (Grade 2C).

In patients with dysfibrinogenaemia, replacement therapy with fibrinogen concentrates should be discussed in patients with personal and/or family history of bleeding[6] (Grade 2C), since only 25% of patients with dysfibrinogenaemia exhibit bleeding symptoms and the majority of them have high risk of thrombosis (Table 4).

4.2 | Management of surgical procedures

Some non-comparative studies confirmed fibrinogen concentrate efficacy and safety for prophylaxis before surgery.[9] In function of the surgery type and haemorrhagic risk, a fibrinogen trough level of at least 1–1.5 g/L until wound healing seems adapted to most situations. For major surgery or severe bleeding, fibrinogen (50–100 mg/kg)

may be used on day 1 to reach a fibrinogen target level >1.5 g/L (Grade 2C); dosage may then be adapted to maintain a trough level of 1.0–1.5 g/L until wound healing (Table 5).

Tranexamic acid usually given alone for minor bleeding/surgery can also be used as an adjunct treatment for major bleeding/surgery, particularly in mucosal based injuries. Antithrombotic prophylaxis may be discussed for patients receiving replacement therapy with fibrinogen.

Postoperative thromboprophylaxis by low molecular weight heparin is recommended in all patients with dysfibrinogenemia and replacement therapy is used only in case of surgery induced bleeding and in patients with personal history of bleeding symptoms (Grade 2C).

4.3 | Management of pregnancy and delivery

Fibrinogen plays a key role in placenta development and maintenance. In pregnant women with afibrinogenemia, substitutive treatment with fibrinogen must be started in the first trimester (Grade 2C).[10] Fibrinogen dosage must be progressively increased due to the physiological increase of its requirement and clearance during pregnancy.[11–14] Although the expert opinions diverge concerning the fibrinogen target level during pregnancy, a level >1 g/L in the first trimester and 1.5–2 g/L in the second and third trimester may be adequate (Grade 2C) (Table 5). Pregnant women with low fibrinogen activity are at risk of placental abruption and/or vaginal bleeding.[12] In women with qualitative defects, the risk of miscarriage is increased,[13] particularly in patients with a variant known to increase the thrombotic risk. Some experts think that in the case of repeated miscarriages, the administration of fibrinogen may facilitate pregnancy maintenance, particularly by diluting the abnormal fibrinogen.[14] In patients with known thrombotic risk and on prophylaxis, thromboprophylaxis should be considered at least during the post-partum period. In women with dysfibrinogenemia, in the absence of bleeding phenotype, specific genetic mutation may be helpful to decide whether replacement therapy is needed for peripartum management.

During delivery, fibrinogen concentrate should be administered to reach a fibrinogen level >1.5 g/L for at least 3 days (Grade 2C) (Table 5). The risk of post-partum haemorrhages and of venous thrombosis is increased in women with any inherited fibrinogen variant.[13]

4.4 | Long-term prophylaxis

Currently, there is no specific recommendation for primary or secondary prophylaxis in patients with afibrinogenaemia. However, the interest of prophylaxis should be assessed, particularly following a severe bleeding episode, notably intracranial haemorrhage.[8] A fibrinogen trough level >0.5 g/L is recommended during prophylaxis (Grade 2C).[8] Prophylaxis may be started with a weekly frequency. If adaptations are needed, it would be better to increase the administration frequency rather than the dose. Prophylaxis is very rarely needed for patients with hyperfibrinogenaemia or dysfibrinogenemia.

5 | FACTOR (F) II DEFICIENCY

Prothrombin deficiency is very rare bleeding disorder. Bleeding symptoms are more severe in patients with plasma FII activity below 10 IU/dL compared to others with higher FII activity.

5.1 | Management of acute haemorrhages

In patients with severe FII deficiency, replacement therapy may be justified (in vivo half-life: 3–4 days). For acute bleedings, the European Network of Rare Bleeding Disorders (EN-RBD) retrospective registry suggests one dose of 20–40 IU/kg of prothrombin complex concentrate (PCC) to reach a target FII between 20 and 40 IU/dL (Grade 2).[15] The FII trough level required to avoid spontaneous bleedings must be at least >20 IU/dL. For minor bleeding tranexamic acid 1 g three to four times per day can be considered (Grade 2C).

5.2 | Management of surgical procedures

A pre-operative PCC dose of 20–40 IU/kg to reach a target FII level between 20 and 40 IU/dL is recommended (Grade 2).[16] The FII trough level required to avoid postoperative bleeding must be >20 IU/dL (Table 5). Tranexamic acid usually given alone for minor bleeding/surgery can also be used as an adjunct treatment for major bleeding/surgery, particularly in mucosal based injuries.

5.3 | Management of pregnancy and delivery

On the basis of two retrospective studies on 22 women, one injection of 20–40 IU/kg of PCC should be considered, from the beginning of labour, to prevent bleeding (Grade 2C)[17] (Table 5).

5.4 | Long-term prophylaxis

Long term prophylaxis is recommended for patients with severe or recurrent spontaneous bleeding episodes. For prophylaxis, the recommended PCC dose ranges from 20 to 40 IU/kg once per week to maintain the FII trough level ≥10 IU/dL (Grade 2C).[1]

6 | FV DEFICIENCY

The majority of FV deficiencies are quantitative. In addition to plasma FV, 20% of the total FV are localized in platelet alfa-granules. There is

TABLE 5 Summary of management of surgical procedures and pregnancy/delivery in patients with rare inherited bleeding disorders.

Disease	Minor surgery	Major surgery	Pregnancy and Delivery
Fibrinogen disorders	For all deficiencies: tranexamic acid alone (1) *Intravenous administration*: Adults: 1–4 g (1 mL/min) 4 times/day in case of local fibrinolysis; 1 g (1 mL/min) every 6–8 h in case of systemic fibrinolysis. Children: 15–20 mg/kg/day from 1 year (few data); dose adaptation in case of kidney disease, contraindication in case of severe kidney disease. (2) *Per os* (*tablets or vials*): Adults: 2–4 g in 24 h Children: 20 mg/kg/day from 1 year (few data); dose adaptation if kidney disease. For oral bleeding, kept in the mouth for 2–3 min before swallowing (local + systemic effect). In infants, the vial content can be put on a compress and used to dab the bleeding site.	*Pre-surgery treatment*: • Dose: 50–100 mg fibrinogen/kg • Target fibrinogen level: >1.5 g/L *Post-surgery treatment*: • Dose: to be adapted • Target fibrinogen level: 1.0–1.5 g/L *Treatment duration*: Up to wound healing *Median drug half-life*: In function of the chosen fibrinogen concentrate (for example CLOTTAFACT®: 66.7 ± 19 h; FIBRYGA®: 75.9 ± 23.8 h; RIASTAP®: 77.1 h).	*Pregnancy*: • Prophylaxis to obtain fibrinogen level >1 g/L in the first trimester and 2 g/L afterwards. • To obtain a fibrinogen level >1.5–2 g/L, treatment for at least 3 days. *Delivery*: Fibrinogen for at least 3 days to obtain a fibrinogen level >1.5–2 g/L.
FII deficiency		*Pre-surgery treatment*: • Dose: 20–40 IU/kg PCC every 24–48 h • Target FII level: 20%–40% *Post-surgery treatment*: • Dose: ~20–40 IU/kg PCC every 24–48 h • Target FII level: FII >20% *Treatment duration*: Up to wound healing PCC half-life: 48–60 h FFP (~20 mL/kg) as alternative when PCC unavailable.	*Pregnancy*: not needed. *Delivery*: • Dose: 20–40 IU/kg PCC from first contractions or before caesarean section • Target FII level: 20%–40% Additional PCC injections to maintain FII >20% for at least 3 days.
FV deficiency		*Pre- and post-surgery treatment*: • Dose: 15–25 mL/kg FFP every 12 h if needed • Target FV level >25% *Treatment duration*: Up to wound healing If clinically ineffective, platelet concentrates with FFP may be discussed.	*Pregnancy*: Not needed. *Delivery*: • Dose: 15–25 mL FFP/kg from first contractions or before caesarean section • Target FV level: >25%. Then, 10 mL/kg FFP every 12 h for at least 3 days.
FVII deficiency		*Pre- and post-surgery treatment*: • Dose: 15–30 µg/kg eptocog alfa (NovoSeven®) to be repeated, if needed, every 4–6 h. *Treatment duration*: Up to wound healing Exceptional use if FVII >20%.	*Pregnancy*: not needed. *Delivery*: 15–30 µg/kg eptocog alfa (NovoSeven®) every 4–6 h for at least 3 days if FVII level <20% and symptomatic disease, especially in case of caesarean section; only in case of complications in the other cases.
FX deficiency		*Pre- and post-surgery treatment*: • Dose: (i) 20–30 IU/kg PCC (up to 60 IU/kg before surgery if major bleeding risk) every 24 h • (ii) Max 60 IU/kg/day COAGADEX® (plasma-derived FX concentrate) • *Target FX level*: FX >20%. *Treatment duration*: up to wound healing Median COAGADEX® half-life: 48–60 h; recovery: 2% (>12 years) FFP (15–25 mL/kg), if PCC or COAGADEX® unavailable.	*Pregnancy*: not needed. *Delivery*: • Dose: (i) 20–40 IU/kg PCC from first contractions or before caesarean section to obtain a FX level > 20% for at least 3 days • (ii) max 60 IU/kg/day COAGADEX® (plasma-derived FX concentrate) • (iii) 15–25 mL/kg FFP if PCC or COAGADEX® not available

TABLE 5 (Continued)

Disease	Minor surgery	Major surgery	Pregnancy and Delivery
FXI deficiency		*Pre- and post-surgery treatment*: • Dose: 10–15 IU/kg HEMOLEVEN® (plasma derived FXI concentrate) • Target FXI level: >30% *Treatment duration*: up to wound healing Tranexamic acid to be avoided when using HEMOLEVEN®. FFP (15–25 mL/kg), possibly associated with tranexamic acid, if HEMOLEVEN® not available.	*Pregnancy*: not needed. *Delivery*: If FXI <15% at pregnancy end and no surgery/trauma-induced bleeding history, tranexamic acid; HEMOLEVEN® (human FXI; 10–15 IU/kg) only if abnormal bleeding. If FXI >15% at pregnancy end, tranexamic acid and HEMOLEVEN® only in case of abnormal bleeding.
FXIII deficiency		*Pre-surgery treatment*: • Dose: 20–40 IU/kg FIBROGAMMIN® (plasma derived FXIII concentrate), NovoThirteen® (recombinant FXIII) • Target FXIII level: >20% *Treatment duration*: up to wound healing *Half-life*: 9 days (FIBROGAMMIN®) and 11.8 days (NovoThirteen®) *Recovery*: 1.7% (FIBROGAMMIN® and NovoThirteen®)	*Pregnancy*: prophylaxis with FXIII (FIBROGAMMIN®, NovoThirteen®) to maintain FXIII level >10%–20% in the first two trimesters and FXIII >30% afterwards. *Delivery*: Additional injection of 10–40 IU/kg FIBROGAMMIN® from first contractions or before caesarean section.
FV + FVIII deficiency		*Pre-surgery treatment*: • Dose: (i) 15–25 mL/kg FFP • (ii) 20–40 IU/kg FVIII or 0.3 μg/kg desmopressin • Target factor levels: FV >15% and FVIII >50% *Treatment duration*: up to wound healing	*Pregnancy*: not needed. *Delivery*: if FV <20% at pregnancy end, 15–25 mL/kg FFP from first contractions or before caesarean section to reach FV >25%. Then, 10 mL/kg FFP to maintain FV >20% for at least 3 days. FVIII may be used to maintain FVIII >50% for at least 5 days.
Combined vitamin K-dependent factor deficiency		*Pre-surgery treatment*: • Dose: 20–40 IU/kg PCC + 20 mg vitamin K1; FFP (~20 mL/kg) as an alternative if PCC not available.	*Pregnancy*: not needed. *Delivery*: 20–40 IU/kg PCC + 20 mg vitamin K1
FVII + FX deficiency		*Pre-surgery treatment*: • Dose: 20–40 IU/kg PCC • Target factor levels: FX >20% *Treatment duration*: up to wound healing	*Pregnancy*: not needed. *Delivery*: 20–40 IU/kg PCC
alpha2-antiplasmine deficiency		*Pre-surgery treatment*: • Dose: 5–10 mg/kg tranexamic acid per os every 6 h starting 3 h before surgery, or 20 mg/kg (iv) before surgery *Treatment duration*: to be continued for 7 days in total[298]	Pregnancy: not needed. Delivery: not needed
PAI-1 deficiency		Anti-fibrinolytic agents	*Pregnancy*: Not needed. *Delivery*: Not needed
Contact phase factor deficiency	Not needed because asymptomatic	Not needed because asymptomatic	*Pregnancy*: Not needed. *Delivery*: Not needed
Thrombomodulin variants	Tranexamic acid	PCC or activated PCC	*Delivery*: PCC or activated PCC

a weak correlation between the laboratory FV results and the clinical bleeding phenotype of patients.[18,19]

6.1 | Management of acute haemorrhages

For acute bleeding episodes, in patients with FV < 20 IU/dL, 15–25 mL/kg of fresh frozen plasma (FFP) is recommended (Grade 2C). In patients with major bleeding risk, the treatment can be continued with FFP, 10 mL/kg every 12 h.[20,21] FV trough level at ~15–25 IU/dL is recommended until resolution. The treatment duration must be adapted to the FV deficiency severity, the bleeding phenotype and the bleeding accident type (in vivo half-life of FV: 36 h). In the presence of anti-FV alloantibodies (inhibitors), replacement therapy is not efficient,[22] thus the infusion of platelet concentrates and/or activated recombinant FVII (rFVIIa) may be considered (Grade 2C).

6.2 | Management of surgical procedures

Replacement therapy with FFP is not always needed during surgery. TxAc alone is often enough. For major surgery in patients with severe FV deficiency, FFP should be used at 15–25 mL/kg initially, and then at 10 mL/kg every 12 h (Grade 2C).[19] FV trough level should be maintained at ~15–25 IU/dL until wound healing[19] (Table 5).

No study has evaluated the interest of anti-thrombotic prophylaxis. This should be discussed in function of the patient's bleeding and thrombotic risks and surgery type.

6.3 | Management of pregnancy and delivery

FV remains stable during pregnancy. During delivery, FFP is recommended to maintain FV level >25 IU/dL for at least 3 days (Grade 2C).[23] In case of caesarean delivery, FFP should be continued until wound healing (Table 5).

6.4 | Long-term prophylaxis

Most patients with symptomatic FV deficiency need on-demand treatment. However, in the rare patients with a severe form, bleedings may start early in life and prophylaxis may be required (suggested dose: 20 mL/kg of FFP twice per week) (Grade 2C).[19]

7 | FVII DEFICIENCY

Severe bleeding is usually observed in patients with FVII <10 IU/dL while patients with a plasma FVII >20 IU/dL are usually asymptomatic.[24] Recombinant activated FVII (rFVIIa) is the treatment of choice[25] which replaced plasma derived FVII concentrates.

7.1 | Management of acute haemorrhages

For minor bleeding in patients at high bleeding risk, and for all bleeding episodes in patients with low bleeding risk, tranexamic acid (TxAc; 15–20 mg/kg or 1 g every 6 h) is suggested (Grade 2C).[1]

For major bleedings in patients with FVII <20 IU/dL, rFVIIa, 15–30 µg/kg, may be repeated every 4–6 h on day 1 (Grade 2B), and then every 8–12 h. At least three injections are recommended to control bleeding (Grade 2B).[26,27] FVII and rFVIIa concentrates can also considered with target FVII levels between 20 and 50 IU/dL depending on the severity and intensity of the bleeding.

Occurrence of anti-FVII alloantibodies (inhibitors) is a rare but serious therapeutic challenge. It is seen only in severe FVII deficiency <10 IU/dL.[28,29] Patients were not responsive to rFVIIa. Controversial experiences were reported with activated prothrombin complex concentrate (aPCC).[28] An immune tolerance induction (ITI) regimen with plasma derived-FVII concentrate was successfully used to eradicate inhibitors and post-inhibitor treatment with aPCC was associated with excellent clinical response.[28]

7.2 | Management of surgical procedures

Surgery-related bleeding episodes are frequently reported in the literature.[24,30] The FVII threshold level to avoid surgery-related haemorrhages has not been clearly defined.[30,31] The recommendations for bleeding prevention in patients undergoing surgery are based on case reports and registries. The patient's history (particularly previous surgical interventions) is crucial to determine the need of replacement therapy that remains exceptional when FVII >20 IU/dL (Table 5).

- Minor surgery: TxAc alone may be considered for patients at high risk (20 mg/kg in children and 1 g/6–8 h in adults) (Grade 2C). The administration of FVII or rFVIIa may be discussed for patients with severe FVII deficiency (same dosage as for major surgery).
- Major surgery: in patients at high bleeding risk, FVII or rFVIIa should be considered (15–30 µg/kg to be repeated every 4–6 h if needed, at least three injections) (Grade 2B).[1,30,31]
  In patients at low bleeding risk, TxAc is the treatment of choice; in case of very high risk surgery (i.e. neurosurgery), rFVIIa can be considered.

When using rFVIIa, the treatment duration can vary from 24 h to several days (i.e. until wound healing for major surgery, and 1–3 days for minor surgery).

7.3 | Management of pregnancy and delivery

FVII level usually increases during pregnancy, particularly from the second trimester, in patients with mild and moderate FVII deficiency, but not with severe forms.[31,32] No substitutive treatment is required during pregnancy, and on-demand treatment in patients with severe

FVII deficiency is rarely needed in case of bleeding.[32–34] During delivery, in women with personal history of bleeding and/or factor levels below 20%, FVII concentrate (15–30 μg/kg) can be administered 30–60 min before a caesarean section or when the cervix is fully dilated for vaginal delivery (Grade 2C)[32] (Table 5). In the absence of clinical bleeding tendency, no replacement therapy is needed if FVII level >20 IU/dL.

7.4 | Long-term prophylaxis

Patients with a clinically severe FVII deficiency (10% of all patients with FVII deficiency) often present early symptoms, and very low FVII levels. For them prophylaxis seems a good option. However, as the half-lives of FVII and FVIIa are <3 h, long-term prophylaxis is challenging. On the basis of case reports and the Seven Treatment Evaluation Registry, the following prophylaxis modalities have been proposed[35]: plasma-derived FVII concentrate (10–30 IU/kg) or rFVIIa (20–30 μg/kg) two or three times per week. Heavy menstrual bleeding may be an indication for "prophylaxis" on the first days of the menses to reduce bleeding.[36]

The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) recommends long-term prophylaxis in patients with severe familial or personal bleeding history or with FVII level <1 IU/dL, and short-term (6–12 months) prophylaxis in new-borns without personal or familial history of bleeding but with FVII level between 1 and 5 IU/dL (Grade 2B).[1]

8 | FX DEFICIENCY

Severe bleeding is frequent in patients with FX <10 IU/dL with 20% of intracranial haemorrhages reported in symptomatic patients.[37] Treatment of severe FX deficiency has been recently improved with the development of a plasma derived FX concentrate.

8.1 | Management of acute haemorrhages

Plasma FX activity does not mirror exactly the bleeding risk.[38,39] Therefore, the bleeding severity is the main criterion to guide management. Circulating levels of 20–25 IU/dL usually are sufficient to ensure efficient haemostasis, including in surgical settings.[1,39] Three therapeutic strategies are available:

8.1.1 | Prothrombin complex concentrate

Prothrombin complex concentrate is the most widely prescribed treatment for FX deficiency; 1 IU/kg of FX usually increases the plasma FX activity by 1.8 IU/dL. In practice, PCC doses of 10–15 IU/kg are sufficient to correct haemostasis in patients with FX deficiency (Grade 2C).[1,37–39] Nevertheless, in function of the bleeding severity, higher doses (25–60 IU/kg) may be required.[38] Then, treatment is adapted to maintain a FX trough level between 10 and 20 IU/dL until recovery.

8.1.2 | Plasma-derived FX concentrate (Coagadex®; BioProducts)

Coagadex® is a plasma-derived FX concentrate with a half-life of 29.4 h. Phase III clinical trials showed its efficacy and safety at 25 IU/kg for on-demand treatment and short-term prophylaxis. For bleeding episodes, 25 IU/kg of Coagadex® should be injected at the first signs and then every 24 h until resolution (Grade 2C).[40–43] In patients with severe FX deficiency requiring prophylaxis, the recommended dose is 25 IU/kg once-twice per week and up to 60 IU/kg in 24 h.[41]

8.1.3 | Fresh frozen plasma

The recommended initial dose is 10–20 mL/kg, followed by 3–6 mL/kg every 12–24 h with the objective of a FX trough level between 10 and 20 IU/dL (Grade 2C).[39]

8.2 | Management of surgical procedures

Prothrombin complex concentrate 10–25 IU/kg, administered preoperatively is often enough to avoid bleeding complications.[1,44] In case of non-elective emergency surgery, if the patient is on long-term prophylaxis, PCC pre-surgery dosage must be adapted in function of the last prophylactic injection. Nevertheless, according to the intervention bleeding risk, a higher PCC dose (25–60 IU/kg) may be discussed[44,45] (Table 5).

- Minor surgery or moderate bleeding symptoms: TxAc alone may be considered.
- Major surgery or severe bleeding history: PCC (usually 20–30 IU/kg, and up to 60 IU/kg before surgery if the bleeding risk is very high) every 24 h, if needed, to maintain FX level >20 IU/dL.

Coagadex® (plasma-derived human FX concentrate), available in many countries, can be used (up to 60 IU/kg/day) to increase the plasma FX level to 20–50 IU/dL (according to the surgery bleeding risk) (Grade 2C) (Table 5).[43–45] FFP (15–25 mL/kg) may be an alternative, if PCC is not available.

After surgery, a FX trough level >20 IU/dL is recommended until the surgery-linked bleeding risk disappears, and then of 10–20 IU/dL until wound healing.

8.3 | Management of pregnancy and delivery

Before delivery, in women with severe FX deficiency, PCC (20–40 IU/kg) is often used to avoid bleeding complications (Grade 2C)[1,46,47]

(Table 5). FFP (15–25 mL/kg) may be an alternative if PCC is not available. Coagadex® (plasma-derived FX concentrate) can be used to increase the plasma FX level to 20–50 IU/dL.[48]

8.4 | Long-term prophylaxis

No clear recommendation exists for regular prophylaxis (modalities, agent, dose and target trough level) in patients with severe FX deficiency. Most studies concern prophylaxis with PCC.[49] The injection frequency (1–3 times/week) and PCC dose (18–50.8 IU/kg) vary in function of the patient (Grade 2C).[40] Twice-per-week or every-three-day frequencies seem more effective than once per week to maintain FX levels >10 IU/dL in adults and >20 IU/dL in children.[1]

Clinical data are limited on long-term prophylaxis with Coagadex® in adults. Initial doses of 25 IU/kg and 40 IU/kg twice per week are recommended for prophylaxis in >12-year-old and in <12-year-old patients, respectively (Grade 2C). Dosage may be adjusted in function of the clinical response and to maintain a minimum FX trough level >5 IU/dL.[41] Prophylaxis with FX is the choice option in adults with thrombotic or cardiovascular disease risk due to the thrombotic accidents reported with PCC in this population.

9 | FXI DEFICIENCY

FXI deficiency is more frequently found in communities with high consanguinity rates like Ashkenazi Jews, some populations from Middle-East and Arabic countries. The majority of patients with FXI deficiency are asymptomatic and others exhibit trauma- and/or surgery-induced bleeding.

9.1 | Management of acute haemorrhages

There is a poor correlation between plasma level of FXI and the bleeding risk, however a plasma FXI concentration <15 IU/dL may be associated with bleeding complications whereas haemorrhages are rarer with FXI concentrations >15 IU/dL[50] Post-traumatic bleeds rarely require substitutive treatment. If needed, TxAc alone may be considered, especially in case of haemorrhage in high fibrinolytic activity tissues (Grade 2C).

In patients with severe bleeding, plasma FXI concentrate or FFP, 15–20 mL/kg, may be used to reach a FXI level of ~30–40 IU/dL in function of the bleeding severity (Grade 2C). FXI concentrate should not be combined with TxAc due to the thrombotic risk, and must be reserved for patients with severe bleeding phenotype and without cardiovascular risks.[51] Due to its long half-life and thrombotic risk, FXI concentrate should not be re-injected before 24 h.

A severe complication of replacement therapy in congenital FXI deficiency is the development of inhibitor to infused FXI. When the titer of inhibitor is low, the use of FXI concentrate may be sufficient. Successful use of low dose rFVIIa 15–30 µg/kg with TxAc was reported without thrombotic adverse event.[52]

9.2 | Management of surgical procedures

Surgical procedures at low bleeding risk generally do not require replacement therapy and are performed without preventive treatment or only with TxAc when surgery concerns high fibrinolytic activity tissues. The benefit–risk balance of replacement therapy must always been evaluated, particularly when using plasma FXI concentrate. Treatment, including in patients with severe deficiency, is not systematic, particularly for interventions at high thrombotic risk.[52] Thromboprophylaxis is recommended when replacement therapy is prescribed.

Haemostatic treatment is usually considered for patients with FXI level <15 IU/dL (Table 5).

- Minor surgery or moderate bleeding symptoms: TxAc alone.
- Major surgery or severe bleeding symptoms: FXI concentrate (10–15 IU/kg)[50,52] to maintain the FXI level >30 IU/dL. FXI concentrate should not be combined with TxAc. FFP (15–25 mL/kg), possibly combined with TxAc, can be an alternative if FXI concentrate is not available or in patients at high risk of thrombosis (Grade 2C).

9.3 | Management of pregnancy and delivery

Data on FXI levels during pregnancy are contradictory: increase, decrease, or no change. Nevertheless, FXI levels should be monitored at the end of pregnancy in women with a known deficit, and a FXI defect detected at pregnancy end must be confirmed.[53,54] Haemorrhages during delivery are exceptional.[53] The few studies on the bleeding risk related to epidural anaesthesia did not find any increased risk of bleeding in pregnant women with FXI deficiency, but they have several methodological limitations. A recent study reported that in women with known FXI deficiency, epidural anaesthesia, was systematically refused when FXI levels were <30 IU/dL.[55] Replacement therapy for delivery is not systematic, even for women with severe FXI deficiency, and only in function of their bleeding history (Grade 2C) (Table 5). Thromboprophylaxis is needed if a substitutive treatment is prescribed.

9.4 | Long-term prophylaxis

Long-term prophylaxis is not justified. Combined oral contraceptives and/or TxAc may be proposed in patients with menorrhagia.[56]

9.5 | Contact phase factor (FXII, Plasma Prekallikrein, high molecular weight kininogen) Deficiency

Due to the absence of bleeding risk, no specific treatment is recommended for these patients.[57]

10 | FXIII DEFICIENCY

Intracranial haemorrhage is frequent complication in patients with FXIII <10 IU/dL and who are not on long-term prophylaxis.[58,59] Soft tissue and umbilical cord bleed, poor wound healing, foetal losses are other frequent symptoms associated with FXIII deficiency.[60–64]

10.1 | Management of acute haemorrhages

Besides long-term prophylaxis, in moderate or severe acute (particularly intracerebral) haemorrhages, the initial recommended plasma derived or recombinant FXIII dose is 20–40 IU/kg (Grade 2C). For patient on prophylaxis, the dose should be adapted[58] For minor bleedings, TxAc should be considered as first-line treatment, particularly in patients on prophylaxis (Grade 2C). The recommended dose is 20 mg/kg/day in children and 2–4 g/day in adults, in 2–4 doses.[1]

In the absence of recombinant or plasma derived-FXIII concentrate, FFP could be considered for patients with life-threating haemorrhages. However, physicians should be aware of its very low content of FXIII that is usually insufficient to achieve haemostasis.[64]

10.2 | Management of surgical procedures

Preoperative administration of FXIII concentrate (20–40 IU/kg) is sufficient to prevent bleeding (Grade 2C). Dosage should be adapted in patients on long-term prophylaxis (Table 5).

- Minor surgery or moderate bleeding symptoms: TxAc alone, particularly in patients on long-term prophylaxis.[1,58]
- Major surgery or severe bleeding symptoms: FXIII concentrate (20–40 IU/kg) before surgery to maintain FXIII level >20 IU/dL (Grade 2C).[59] One preoperative infusion is usually sufficient due to its long half-life (9–12 days).

The occurrence of anti-factor FXIII inhibitors is a very rare and serious complication, as by-passing agents are not efficient in FXIII deficiency. The use of high dose FXIII concentrates and immune desensitization protocols (immune tolerance induction and immunoadsorption) were described.[65]

10.3 | Management of pregnancy and delivery

Prophylactic treatment can prevent early miscarriage in women with severe deficiency; however, the dosage and target trough FXIII levels are still discussed. In 2018, a review proposed to maintain a FXIII trough level >10–20 IU/dL up to the 22nd gestational week with monthly infusions, and then to increase the frequency (every 2–3 weeks) to maintain a trough level >30 IU/dL.[58] Other authors suggested 250 IU/week until the 23rd week of amenorrhea, and then 500 IU/week until term, and a dose of 1000 IU at delivery with the objective of FXIII trough levels of 12 IU/dL during pregnancy and 35 IU/dL during delivery.[64] A recent retrospective series (13 pregnancies in 9 women) reported no bleeding complication during pregnancy on prophylaxis (400–1250 IU every 2–4 weeks) and during delivery (5 vaginal and 6 caesarean deliveries) with one injection of FXIII concentrate (1250 IU)[66] (Table 5).

10.4 | Long-term prophylaxis

There is no international consensus on the practical aspects of prophylaxis (e.g., when to start, the best schema) in FXIII deficiency. However, given the high risk of intracranial haemorrhages, primary long-term prophylaxis should be considered for patients with severe FXIII deficiency. A FXIII dose of 10–40 IU/kg is usually recommended (from 10 IU/kg every 2–6 weeks to 40 IU/kg every 4 weeks) (Grade 2B).[67,68]

11 | COMBINED FV AND FVIII DEFICIENCY

Combined FV and FVIII deficiency is caused by genetic variations of two molecular chaperones involved in their intracellular transport: lectin mannose-binding protein 1 (LMAN 1) and multiple coagulation factor deficiency protein (MCFD 2).[69]

11.1 | Management of acute haemorrhages

For minor bleedings, TxAc (15–20 mg/kg or 1 g, 3–4 times/day) should be considered.[1] For serious bleeding episodes that require replacement therapy, FFP (15–25 mL/kg)[70] should be considered with FVIII concentrate (20–40 IU/kg) or desmopressin (0.3 μg/kg) for "good responders"[71,72] (Grade 2C). Treatments should be repeated after 12 h (FFP 10 mL/kg), if needed. Dose and injection frequency must be adapted to maintain FV and FVIII trough levels >15 and >50 IU/dL, respectively.[1] The treatment duration depends on the trauma severity, clinical course, and estimated wound healing time. If the clinical response is insufficient for FV, infusion of platelet concentrate may be considered due to the FV contained in platelet α-granules. It has been reported that rFVIIa (90 μg/kg every 2–3 h) can be effective in some patients showing resistance to the previously described treatments or allergy towards FFP.[70]

In patients with minor bleeding, desmopressin alone may correct the FVIII deficiency.[69]

11.2 | Management of surgical procedures

There are very few case reports on surgery. Most interventions were performed in patients who received FFP and in whom FVIII levels were corrected with FVIII concentrate or desmopressin (Table 5). Recently, a group described a patient who underwent abdominal surgery without substitutive treatment with basal FV and FVIII levels of 9.6 and 24.8 IU/dL, respectively.[72]

- Minor surgery or moderated bleeding risk: TxAc alone (15–20 mg/kg for children or 1 g, 4 times per day, for adults).[1]
- Major surgery or severe bleeding risk: FFP (15–25 mL/kg) to maintain FV level >15 IU/dL and FVIII concentrate (20–40 IU/kg) or desmopressin (0.3 μg/kg)[72] may be considered before surgery to correct and maintain FVIII level > 50 IU/dL until wound healing (Grade 2C).[71] TxAc may be added when the intervention concerns mucosal tissues.

If the FV correction is insufficient, a transfusion of platelet concentrate may be recommended due to the FV contained in α-granules.

It has been reported that NovoSeven® (rFVIIa, 90 μg/kg every 2–3 h) may be an alternative to FFP in patients with allergy to plasma products.[70]

Thromboprophylaxis can be discussed in patients at high risk of thrombosis and/or for procedures with high thrombosis risk.

11.3 | Management of pregnancy and delivery

During pregnancy, FV level remains stable, whereas FVIII level increases progressively. At pregnancy end, FVIII level may be enough to ensure proper haemostasis during delivery. Conversely, FV is usually insufficient. A review found abnormal post-partum bleeding in 32% of the 19 included deliveries that required a red blood cell transfusion in one-third of patients.[73] Perinatal management is based on TxAc, the correction of the FV and FVIII levels with FFP, injection of FVIII or administration of desmopressin[51] (Table 5). FV and FVIII levels must be monitored during the third trimester of pregnancy.

The UK recommendations include a substitutive treatment for women with FV <20 IU/dL and/or FVIII <50 IU/dL in the third trimester.[1,74] It is suggested to perform an FFP infusion (15–25 mL/kg) at delivery start to obtain FV levels between 20 and 40 IU/dL and to repeat (10 mL/kg/12 h) to maintain FV level >20 IU/dL for at least 3 days (Grade 2C). If needed, recombinant FVIII may be considered to reach a FVIII level >50 IU/dL.[1,74,75] Desmopressin also seems effective at delivery[3,72] TxAc (15–20 mg/kg or 1 g, 3–4 times per day) after delivery may be discussed in patients with abnormal lochia (Grade 2C).

11.4 | Long-term prophylaxis

Prophylaxis may be considered in patients with severe deficiency (very rare) and recurrent spontaneous bleeding episodes such as recurrent joint bleeds.[73]

12 | COMBINED VITAMIN K-DEPENDENT FACTOR DEFICIENCY

Combined vitamin K-dependent factor deficiency is caused by variations of VKORC1 or GGCX genes which are involved in post-translational gamma carboxylation of vitamin K-dependent proteins.[76]

12.1 | Management of acute haemorrhages

Vitamin K is the first-line treatment, but with a relatively heterogeneous clinical response. In most patients, vitamin K (10 mg per os, 2–3 times per week) allows limiting skin/mucosal bleedings and preventing major haemorrhages (Grade 2C). The target factor concentrations are still poorly known. Moreover, administration of vitamin K at important doses does not always lead to the complete correction of FII, FVII, FIX and FX activity, suggesting incomplete carboxylation. Therefore, the dosage must be adapted in function of the patient's clinical symptoms.[76] In case of severe deficiency, the use of prothrombin complex concentrates (PCCs) can be discussed (Grade 2C). Antibiotics must be used with caution because vitamin K-dependent coagulation dysfunction might be induced by long-term use of antibiotics, especially cephalosporins.[77]

12.2 | Management of surgical procedures

For major surgery or major bleeding risk, FFP (15–20 mL/kg) has been often used, but repeated infusions may be needed before observing a clinical effect. The use of PCC is less documented for surgery,[78] but its greater efficacy compared to FFP has been proven in patients taking vitamin K antagonists, in whom PCC is the treatment of choice (Table 5).

- Minor surgery or moderate bleeding symptoms: TxAc alone
- Major surgery or severe bleeding symptoms: PCC (∼20–40 IU/kg of FIX) combined with vitamin K1 (20 mg) before surgery (Grade 2C).[79] FFP (∼20 mL/kg) may be an alternative if PCC is not available (Grade 2C).

12.3 | Management of pregnancy and delivery

Same management as for surgery (Table 5).

13 | COMBINED FVII AND FX DEFICIENCY

The F7 and F10 genes are located on the long arm of chromosome 13 and are only 2.8 kb apart. Combined FVII and FX deficiency can be caused by different mechanisms i.e. coincidental inheritance of separate coagulation factor deficiencies or a common cause as large deletions comprising both gene loci or complex chromosomal translocations.[80]

13.1 | Management of acute haemorrhages

Curative or prophylactic treatment should be considered in function of the FVII and FX levels associated with increased bleeding risk (15–20 IU/dL) in the single factor deficiency.[80] PCC is the first-line

treatment for abnormal bleeding or as prophylaxis before any surgery in patients with FVII or FX levels lower than the safety level, at the same dose recommended for FX deficiency alone (Grade 2C). If PCC is unavailable, FFP may be administered in life-threatening situations. In patients with severe FVII deficiency and bleeding symptoms, the use of rFVIIa may be discussed.

13.2 | Management of surgical procedures

Before surgery and when FVII or FX are below the safety level, PCC (same dose as for FX deficiency) is recommended (Grade 2C). If not available, FFP can be considered in emergency situations. In patients with severe FVII deficiency and bleeding symptoms, rFVIIa may be discussed (Table 5).

13.3 | Management of pregnancy and delivery

Same management as for surgery (Table 5).

14 | ALPHA2-ANTIPLASMINE DEFICIENCY

14.1 | Management of acute haemorrhages

Bleeding episodes are usually managed with anti-fibrinolytic agents, such as TxAc (Grade 2C). Desmopressin must be avoided because it can induce the liberation of plasminogen activators that may promote fibrinolysis.[81,82]

14.2 | Management of surgical procedures

Surgery-induced bleeding can be avoided by oral or intravenous administration of TxAc (5–10 mg/kg per os before and every 6 h after surgery or 20 mg/kg IV before surgery). It is recommended to continue the treatment for 7 days (Grade 2C).[83]

15 | MANAGEMENT OF PREGNANCY AND DELIVERY

Same management as for surgery (Table 5).

16 | PAI-1 DEFICIENCY

16.1 | Management of acute haemorrhages

Bleeding accidents are managed with anti-fibrinolytic agents (e.g., TxAc). FFP (10–15 mL/kg) may be considered in an emergency, while waiting for the anti-fibrinolytic agent effect.[84]

16.2 | Management of surgical procedures

Before surgery, anti-fibrinolytic agents may be considered (intravenous, per os) (Grade 2C).[85]

16.3 | Management of pregnancy and delivery

Same management as for surgery (Table 5).

16.4 | Long-term prophylaxis

Continuous or intermittent prophylaxis with an anti-fibrinolytic agent associated or not with combined oral contraceptives may be proposed to women with menorrhagia.

17 | THROMBOMODULIN VARIANTS

Thrombomodulin (TM) variants are very rare congenital bleeding disorders. Some variants are associated with excessive concentrations of soluble TM responsible for dramatically decreased thrombin generation and bleeding symptoms[86–88]; and other variants are associated with reduced expression of TM on the endothelial cell membrane, responsible for disseminated intravascular coagulation-like symptoms.[89] There is no specific treatment. In patients with bleedings, treatment is symptomatic. PCC and aPCC may be discussed in patients presenting TM p.Cys537Stop mutation.[90]

18 | CONCLUSION

Rare inherited bleeding disorders are rare diseases with highly heterogeneous clinical manifestations. Therefore, guidance is limited concerning the best agent and dosage for long-term prophylaxis to reduce bleeding frequency, for on-demand treatment to control bleeding episodes, and for the management of the pregnancy/delivery and peri-operative bleeding risk. The present French guidelines on RIBD management are the result of the synthesis of the available literature data analysed by expert haematologists. However, more research is needed regarding heterozygotes and risk for bleeding with major surgery or trauma and also to precisely identify the factor level thresholds to define each deficit severity and to determine the minimum amount of factor activity required to achieve haemostasis. This will allow proposing robust, evidence-based guidelines to improve the management of patients with severe and moderate RIBD. Until larger studies and high level evidence-based guidelines are available, management of major surgeries or trauma in patients with RIBD should be addressed on a case-by-case basis at multidisciplinary meetings. Although many open questions on RIBD management still need to be addressed, the authors hope that these guidelines may help physicians who are involved in the care of patients with RIBD.

AUTHOR CONTRIBUTIONS

Trossaert Marc, Chamouard Valerie, Biron-Andreani Christine, Casini Alessandro, De Mazancourt Philippe, De Raucourt Emmanuelle, Drillaud Nicolas, Frotscher Birgit, Guillet Benoit, Lebreton Aurelien, Lucia Rugeri and Dargaud Yesim made literature search, analysed selected publications, wrote the manuscript, edited and gave final approval.

ACKNOWLEDGEMENTS

The authors are thankful Claire BERGER (Saint-Etienne), Fanny BONHOMME (Genève), Géraldine BOUREILLE (Nantes), Christophe CANEVET (Lille), Sabine CASTET (Bordeaux), Dominique DESPREZ (Strasbourg), Marc FOUASSIER (Nantes), Muriel GIANSILY-BLAIZOT (Montpellier), Benjamin GILLET (Paris), Nicolas GIRAUD (Paris), Anne GODIER (Paris), Audrey HOCHARD (Lille), Michel HANSS (Lyon), Annie HARROCHE (Paris), Yohann JOURDY (Lyon), Cécile LANGLOIS (Nantes), Sandra LE QUELLEC (Lyon), Anne LIENHART (Lyon), Sandrine MEUNIER (Lyon), Claude NEGRIER (Lyon), Sylvie ODENT (Rennes), Caroline OUDOT (Limoges), Florence QUELIN (Paris), Brigitte PAN-PETESCH (Brest), Alain RAMASSAMY (Poitiers), Pascale RICHARD (Paris), Catherine Ternisien (Nantes), Christine Vinciguerra (Lyon), Fabienne Volot (Dijon), Benedicte Wibaut (Lille) for their valuable contribution to the work.

CONFLICT OF INTEREST STATEMENT

Trossaert Marc has received grants and research support from NovoNordisk, CSL Behring and Octapharma. Chamouard Valerie has received grant/research support from Roche. Biron-Andreani Christine: none. Casini Alessandro acted as a speaker at satellite symposia organized by LFB, performed consulting for LFB and Pentapharma, participated at advisory board of LFB, Octapharma, Takeda and received unrestricted grant from NovoNordisk and CSL Behring. De Mazancourt Philippe: none. De Raucourt Emmanuelle has received funding from CSL Behring for research support, and from CSL Behring, Takeda and LFB for reimbursement for attending symposia and consultant work. Drillaud Nicolas has received educational grant from NovoNordisk and honoraria from CSL Behring, Sobi, Takeda and Octapharma. Frotscher Birgit: none. Guillet Benoit has been consultant for Baxter/Baxalta/Shire/Takeda, CSL Behring, LFB, NovoNordisk, Octapharma, Roche Chugai, Sobi. Lebreton Aurelien: none. Lucia Rugeri has received speaker fees from NovoNordisk, CSL Behring, LFB, Octapharma. Dargaud Yesim has received grants/research support from Bayer, Baxter, Baxalta, Novo Nordisk, CSL Behring, LFB, Pfizer, LeoPharma, Octapharma and Stago; an educational grant from Takeda and honoraria from Bayer, Baxter, NovoNordisk, CSL Behring, Sobi and Octapharma.

DATA AVAILABILITY STATEMENT

Not applicable as this review article is based on published evidence and clinical experience reported in the literature. There is no original data set except references indicated at the end of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Trossaert M, Chamouard V, Biron-Andreani C, et al. Management of rare inherited bleeding disorders: Proposals of the French Reference Centre on Haemophilia and Rare Coagulation Disorders. *Eur J Haematol*. 2023;1-18. doi:10.1111/ejh.13941