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REVIEW ARTICLE

Occurrence and management of severe bleeding episodes in patients with hereditary factor X deficiency

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Abstract

Vitamin K–dependent factor X (FX) plays an important role in thrombin formation, and a deficiency in FX can cause impaired coagulation, the severity of which is usually correlated with the degree of deficiency. Due to the critical role that FX plays in the coagulation cascade, FX deficiency is associated with a higher risk of bleeding than deficiencies in other coagulation factors. Patients with the hereditary autosomal-recessive homozygous form of FX deficiency, which occurs in approximately 1:1,000,000 individuals worldwide, are often diagnosed when they present with spontaneous life-threatening haemorrhage (most often intracranial haemorrhage) during the first month of life. In addition to central nervous system bleeds, other severe bleeding types experienced by such patients may include umbilical cord bleeding, gastrointestinal or pulmonary haemorrhage, intramuscular haematomas and/or haemarthrosis. Delayed treatment or inadequate replacement of FX may result in developmental delays, musculoskeletal disabilities or death. The high risk of recurrent severe bleeding necessitates prophylactic replacement therapy for many individuals with severe FX deficiency. Available products for replacement therapy include plasma-derived FX concentrate and prothrombin complex concentrates. Fresh-frozen plasma may be used when concentrates are not available but is a less efficient means of FX replacement. This article reviews the literature on severe bleeding in individuals with hereditary FX deficiency and discusses current treatment options.

KEYWORDS
factor X deficiency, intracranial haemorrhage, plasma-derived factor X, prothrombin complex concentrate, rare blood disorder, severe bleeding episode

1 | INTRODUCTION

The vitamin K–dependent plasma protein factor X (FX) is essential throughout the coagulation process, and a deficiency in FX causes a haemorrhagic phenotype, the severity of which is directly related to the degree of deficiency.[1,2] Severe homozygous FX deficiency is an autosomal-recessive disorder that occurs in approximately 1 in 1,000,000 individuals worldwide (whereas approximately 1 in 500 individuals have heterozygous mutations), though the incidence of homozygous FX deficiency is higher in regions in which consanguineous marriage is common.[3,4]

Rare bleeding disorders such as FX deficiency are classified as mild, moderate or severe depending on the residual proportion of missing factor. Classification of coagulation factor deficiencies has traditionally paralleled that of the less rare haemophilias, with factor activity levels <1% classified as severe deficiency, levels of 1%–5%

classified as moderate deficiency and levels >5% classified as mild deficiency.[5] However, bleeding patterns vary among the factor deficiencies, and homozygous FX deficiency is associated with a more severe bleeding tendency than deficiencies in other coagulation factors.[6–8] In a study of the association between bleeding severity and coagulation factor activity level, the European Network of Rare Bleeding Disorders (EN-RBD) found that, among the nine coagulation factor deficiencies studied, fibrinogen, FX and factor XIII (FXIII) activity levels were most strongly correlated with bleeding severity.[9] In addition, patients with hereditary FX deficiency often present with severe or even life-threatening bleeding—for example intracerebral haemorrhage (ICH) or umbilical stump bleeding—within the first months of life, when FX activity (FX:C) levels have not yet reached adult levels.[10] The combination of symptom severity and early-life presentation pattern distinguishes FX deficiency from most other factor deficiencies, in which patients may be identified later in childhood following minor bleeding episodes or post-surgical bleeding.[4] As a result, in 2012 the European Network of Rare Bleeding Disorders (EN-RBD) proposed an expanded classification scale of FX:C < 10% (severe), 10%–40% (moderate) and >40% (mild). This scale was based on the reported bleeding tendency and severity for patients in its database, in whom FX:C levels <10% were associated with high risk of major spontaneous bleeding, FX:C of 10%–40% with minor spontaneous bleeding and FX:C > 40% with low bleeding risk.[5,11] Recent reports have suggested that even patients with heterozygous mutations may have mild bleeding phenotypes with FX:C levels of 40%–60%.[3,12] This article will review reports in the literature of severe bleeds in patients with FX deficiency and discuss current treatment options.

2 | MATERIALS AND METHODS

2.1 | Literature search

Literature searches were performed to identify reports published on or before 6 June 2018 of severe bleeding episodes in patients with FX deficiency. An updated search was conducted in September 2019 to include publications between 1 June 2018 and 1 September 2019. Formal searches were conducted in the MEDLINE (https://www.ncbi.nlm.nih.gov/pubmed) and Embase (www.embase.com) electronic databases using the search string '((factor X) OR (Stuart-Prower)) AND deficiency AND (hereditary OR congenital) AND (hemorrhage OR haemorrhage OR bleeding)'. Search results were limited to 'human' and 'English language'.

2.2 | Selection criteria

Search results were included regardless of publication format (eg, abstract of conference presentation, letter to the editor or full-length article). Publications were included if they described a severe bleeding episode for ≥1 individual diagnosed with hereditary FX deficiency. Severe bleeding episodes were defined as spontaneous or life-threatening major bleeds, as described by the EN-RBD.[9] Major bleeds included intramuscular haematomas requiring hospitalization, haemarthrosis, central nervous system (CNS) bleeding (including intracranial haemorrhage), pulmonary haemorrhage, life-threatening gastrointestinal (GI) haemorrhage and umbilical cord bleeding. Other types of bleeding episodes were included if they were described as life-threatening or as severely affecting the patient's quality of life or ability to function. Studies were also included if they reported the occurrence of severe bleeding episodes in a larger study group even without defining or describing the term 'severe' within the publication. Titles and abstracts of the search results were reviewed, and all publications that focused solely on the biology or genetics of FX deficiency or on other coagulation factor deficiencies were excluded. When duplicate reports of a study or case were identified, only the most recent publication was included. Journal articles were retained in the final search results if the full text was available.

3 | RESULTS

3.1 | Literature search results

Fifty-two publications, including 18 congress abstracts and 34 journal articles, were identified from the literature screening as relevant to the review. The full text was available for 33 of the 34 journal articles. The 50 publications included in the final results comprised 36 case reports or series, eight retrospective studies, five prospective studies and one systematic review.

3.2 | Occurrence of severe bleeds

Spontaneous CNS bleeds were the most commonly reported type of severe haemorrhage for patients with hereditary FX deficiency, described in all prospective studies, seven of eight retrospective studies and 28 of 36 case reports (Table 1). Reports included a total of 220 patients. Among the 197 patients included in publications that listed the specific number of patients with each type of bleed, CNS bleeds were most common (n = 82; 42%), followed by haemarthrosis (n = 51; 26%), GI bleeds (n = 31; 16%), umbilical bleeds (n = 23; 12%) and intramuscular bleeds (n = 17; 9%). Some patients exhibited more than one type of bleed. With the exception of 12 women with severe obstetric bleeding[13] and four other adult patients—one each with subdural haematoma, spinal haematoma, GI and intramuscular bleed, and ovarian cyst rupture[14–17]—all of the severe bleeds were reported as occurring in infants and children aged <2 years.

The majority of prospective and retrospective studies included patients with other bleeding disorders and provided only basic information about those with FX deficiency. However, a prospective international study of individuals with hereditary FX deficiency reported spontaneous (but not necessarily severe) bleeding symptoms in 42 of 102 patients. ICH occurred in nine of 42 symptomatic

TABLE 1 Publications reporting on severe bleeds in patients with FX deficiency.

Reference	Type of bleed	Patients with severe bleeds, *n*	Patient age	Initial treatment	Prophylactic treatment	Outcome
Garg et al 2019[44]	ICH	1	8 months	NS	FFP biweekly	Prophylactic treatment was irregular, and FX levels remained <1%. Patient died of spontaneous ICH 10 months after initial episode
Grottke et al 2019[37]	ICH	1	4 months	Initially: 50 IU/kg PCC, 150 ml FFP, 100 mg tranexamic acid, 150 ml red blood cells, 4 mg vitamin K Day 5: 250 IU pdFX daily, followed by twice daily and then every 18 h	250 IU pdFX 3 times/week	Patient discharged at week 7 in good condition with prophylactic treatment; no signs of rebleeding
Soker et al 2019[63]	ICH	3	70 months[a]	NS	Administered, but type NS	Prophylactic treatment administered and no subsequent ICH events occurred
Spiliopoulos et al 2019[13]b	Ovulatory bleed requiring surgery (*n* = 6) Miscarriage (*n* = 3) Neonatal death (*n* = 2) Postpartum haemorrhage requiring hysterectomy (*n* = 1)	12	20–43 years	FFP, PCC, transfusions, red blood cells and/or hysterectomy	Administered to some patients, but specific cases NS	NS
Borhany et al 2018[42]	Case 1: 2 umbilical bleeds, haemarthrosis Case 2: umbilical bleed, ICH, haemarthrosis, haemoptysis Case 3: umbilical bleed, ICH, haematoma	3	Case 1: 15 days Case 2: 8 days Case 3: 10 days	FFP and antifibrinolytics	Case 1: No Case 2: FFP weekly and antifibrinolytic Case 3: FFP weekly and antifibrinolytic	Case 1: No subsequent severe bleed Case 2: Vegetative state, mental retardation Case 3: No subsequent severe bleed
Samia et al 2018[64]	ICH	1	1 month	FFP, 5 mg IV vitamin K 3 times/week, 5 mg oral vitamin K daily	NS	Favourable clinical and biological progress
Albayrak et al 2017[45]	ICH	3	<1 month	FFP and activated PCC	50 IU/kg PCC twice weekly	No subsequent bleeds during prophylaxis

(Continues)

TABLE 1 (Continued)

Reference	Type of bleed	Patients with severe bleeds, *n*	Patient age	Initial treatment	Prophylactic treatment	Outcome
Antmen et al 2017[36]	ICH	4	NS	PCC and FFP	No	No bleeding was seen after surgery for ICH
Aydogan et al 2017[65]	ICH (*n* = 4) Intramuscular bleed (*n* = 4) Haemarthrosis (*n* = 2)	10	NS	PCC	PCC for 1 patient with ICH and recurrent haemarthrosis	NS
Kavakli et al 2017[14]	ICH	1	20 years	15 IU/kg pdFX, followed by 31–62 IU/kg/day in ICU for 1 week	25 IU/kg pdFX every 1–2 week	Headache subsided after 1 day of treatment. Patient remained in ICU for 1 week, then began prophylactic treatment with pdFX for 5 months (0 bleeds reported), on-demand treatment for 10 months (6 bleeds reported), and now receives pdFX prophylaxis (0 bleeds)
Matsuo et al 2017[47]	Umbilical bleed	1	5 days	20 ml/kg FFP	PCC weekly	Normal growth and development at 2.5 years of age
Salciogliu et al 2017[66]	Haemarthrosis	3	NS[c]	NS[c]	NS[c]	Recurrent haemarthrosis in 1 patient
Della Valle et al 2016[27]	CNS	1	2 days	3-factor PCC (100 IU/kg, followed by 30 IU/kg every 3 days) to maintain FX:C > 10%	Weekly infusions of beginning at week 4, with PCC Behring (100 IU/kg)	No bleeding episode during first year of life. No FX inhibitor development.
Corsini et al 2015[25]	CNS	1	1 day	10 ml/kg FFP, 10 ml/kg packed red blood cells, and sodium bicarbonate, followed by 100 IU/day PCC for 54 days	30 IU/kg PCC every other day, extended over time to weekly dosing intervals of 20 IU/kg (frequency increased following traumatic events)	6-year-old child maintains trough FX:C of approximately 1% via weekly prophylactic treatment

(Continues)

TABLE 1 (Continued)

Reference	Type of bleed	Patients with severe bleeds, *n*	Patient age	Initial treatment	Prophylactic treatment	Outcome
Lin et al 2015[15]	Spinal haematoma	1	48 years	Pre-surgery: 15 U/kg PCC and then 15 ml/kg FFP Post-surgery: 15 ml/kg/day FFP and then PCC 5–10 U/kg/day	No	Successful removal of spinal haematoma; no bleeding-related post-surgical complications
Ozdemir et al 2015[67]	ICH	2	1 week and 2.5 months	NS	NS	1 patient was receiving FX prophylaxis when second trauma-related ICH events occurred
Salcioglu et al 2015[20]	CNS (46.7%) Haemarthrosis (26.7%) Haematuria (13.3%)	12	2 weeks–24 years	FFP, PCC, tranexamic acid	Four patients received PCC	No evidence of inhibitor development allergy or thrombosis
Tugcu et al 2015[8]	NS	8	NS	NS	1 of 8 patients received prophylactic treatment	No evidence of inhibitor development; no deaths
Tuysuz et al 2015[19]	Umbilical bleed (*n* = 1) GI bleed (*n* = 2) Intramuscular haematoma (*n* = 2) Recurrent haemarthrosis (*n* = 1)	6	Neonates (*n* = 3) 4 months–8 years (*n* = 3)	FFP before 2013; PCC after 2013	PCC (dosage not specified)	No thrombosis due to PCC. Prophylactic treatment decreased bleeding frequency for the 3 patients who received it
Vinod et al 2015[17]	Life-threatening ovarian cyst rupture	1	25 years	FFP, packed red blood cells	NS	Patient discharged after 1 week of treatment
Madhusoodhan et al 2014[31]	ICH	1	2 days	FFP twice daily, switched to 40 U/kg PCC daily for 14 days	75 U/kg PCC twice weekly	No bleeding symptoms after initial FFP treatment; prophylaxis maintained trough FX:C at 3%–5%
Shetty et al 2014[7]	Umbilical bleed (*n* = 1) GI bleed (*n* = 5) Intramuscular haematoma (*n* = 7) Haemarthrosis (*n* = 6) ICH (*n* = 12)	29	NS	FFP or whole blood	NS	NS
Abdelwahab et al 2013[57]	ICH	5	NS	Replacement therapy given but not specified	No	NS
Naderi et al 2013[68]	ICH	37.5% of all events	NS[c]	NS[c]	NS[c]	NS[c]

(Continues)

TABLE 1 (Continued)

Reference	Type of bleed	Patients with severe bleeds, *n*	Patient age	Initial treatment	Prophylactic treatment	Outcome
Shim et al 2013[34]	CNS	1	18 and 22 months	18 months: 20 ml/kg FFP and 80 IU/kg during 2 separate surgeries 22 months: 80 IU/kg FEIBA	74 IU/kg FEIBA weekly for 11 months	43 minor trauma-related bleeds occurred during prophylaxis; all resolved spontaneously. FX:C remained >1.0 IU/dl. Patient developed normally with no additional ICH episodes
Pena Siado et al 2012[43]	ICH 3 CNS bleeds	1	39 days	NS	Initially, FFP twice weekly. Due to allergic reaction, switched to 30 IU/kg/day activated PCC 3 times weekly	No subsequent bleeding episodes on activated PPC. Patient has normal neurodevelopment after 4 years on prophylaxis
Peyvandi et al 2012[9]	Haematomas Haemarthrosis CNS GI bleed Umbilical bleed	11	NS[c]	NS[c]	NS[c]	NS[c]
Wetzel et al 2012[41]	CNS	1	1 day	FFP, packed red blood cells, sodium bicarbonate, calcium gluconate, FIX complex	PCC (dose not specified)	At discharge (following FIX complex infusions), FX:C > 60% and FII:C = 145%
Kavanagh et al 2011[46]	GI bleed (*n* = 2) Umbilical bleed (*n* = 1) ICH (*n* = 2)	5	1–4 days	NS	Begun in first week of life; 25–60 IU/kg PCC 1–2 times/week	No spontaneous life- or function-threatening bleeding episodes while on prophylaxis
Rauch et al 2011[32]	Umbilical bleed ICH	1	Neonate and 14 weeks	FFP (umbilical stump bleed), PCC (ICH)	60 IU/kg PCC 3 times/week	'Almost complete' recovery from ICH treatment. No outcome described for prophylactic treatment
Senturk et al 2010[58]	Recurrent ICH	1	6–7 months	FFP	No	No subsequent ICH or bleeding symptoms for 1 year after surgery
Sriram et al 2010[69]	Intramuscular haematomas ICH	1	20–50 days	10 ml/kg FFP ×2	Transfusions	NS
Bowles et al 2009[24]	Case 1: ICH Case 2: umbilical bleed, intramuscular haematoma Case 3: umbilical bleed, GI bleed	3	Case 1: 14 weeks Case 2: 1 and 25 days Case 3: 6 days	Case 1: NS Case 2: FFP and vitamin K (day 1); FFP and PCC (day 25) Case 3: FFP daily	Case 1: 20 U/kg PCC every 3 days Case 2: 28 U/kg PCC every 72 h Case 3: 30 U/kg PCC every 72 h	Case 1: No additional bleeds at 3.5 years of age, but does have residual left arm weakness and developmental delay Case 2: No further bleeds at 4 years of age Case 3: No further bleeds at 3 years of age

(Continues)

TABLE 1 (Continued)

Reference	Type of bleed	Patients with severe bleeds, *n*	Patient age	Initial treatment	Prophylactic treatment	Outcome
Hainmann et al 2009[29]	Haemarthrosis GI bleed Intramuscular haemorrhage	1	15 months–5 years	25–40 U/kg plasma-derived FX-containing FIX preparation	NS	NS
Karimi et al 2009[70]	ICH	2	NS[c]	NS[c]	NS[c]	NS[c]
Mishra et al 2008[6]	ICH	5	<6 months	FFP	FFP every 3 weeks	1 patient died during presentation. For other patients, bleeding episodes decreased in severity and frequency once the patient was on prophylactic FFP despite FX:C levels <1%. No recurrent ICH episodes
Herrmann et al 2006[18]	ICH (*n* = 9) GI bleed (*n* = 5) Haemarthrosis (*n* = 14)	28	ICH and GI bleed: 1–27 days Haemarthrosis: NS	NS	NS	NS
Thachil et al 2006[49]	ICH	1	15 week	Repeated doses of 10 ml/kg FFP and 2 mg vitamin K	FIX concentrate twice weekly	No bleeds rand no neurological deficit reported 1 year after surgery for ICH
Todd et al 2006[35]	ICH	1	1 days	PCC to maintain FX levels 20 IU/dl	40 IU/kg PCC every 3 days	No further bleeds at 2.25 years and normal neurologic development. Trough FX levels are 7–10 IU/dl; trough FIX levels are ≤200 IU/dl (reference range, 50–150 IU/dl)
Ermis et al 2004[40]	ICH	2	2.6 months	Case 1: FFP and vitamin K Case 2: NS	Case 1: No Case 2: Yes, but not specified	Case 1: Died on day 1 due to ICH Case 2: ICH recurred despite prophylaxis, followed by hydrocephalus
McMahon et al 2002[48]	Case 1: umbilical bleed Case 2: umbilical bleed, haematemesis Case 3: umbilical bleed, intraperitoneal haemorrhage Case 4: umbilical bleed, haematemesis	4	Neonates	Case 1: FFP Case 2: NS Case 3: FFP and PCC Case 4: FFP and PCC	Case 1: 70 IU/kg PCC Case 2: PCC (40–80 IU/kg, at varyingfrequencies) Case 3: 70 IU/kg PCC weekly Case 4: 70 IU/kg PCC (frequency not specified)	Case 1: 1 joint bleed since beginning prophylaxis Case 2: Initial prophylaxis dose adjusted due to bruising; 2 joint bleeds occurred following subsequent dose reductions in prophylaxis; no further bleeds since last dose increase; no development of FX inhibitors Case 3: One joint bleed since beginning prophylaxis Case 4: Two joint bleeds during prophylaxis: 1 traumatic tongue bleed (treated with 70 IU/kg PCC) and 1 joint bleed due to prophylaxis dose omission

(Continues)

TABLE 1 (Continued)

Reference	Type of bleed	Patients with severe bleeds, *n*	Patient age	Initial treatment	Prophylactic treatment	Outcome
Citak et al 2001[39]	ICH	1	3 months	FFP and vitamin K	No	Patient discharged with FX:C 5% and FVII:C 40%; described as 'well and neurologically normal'
Mukhopadhyay et al 2001[16]	GI bleed Intramuscular haematoma	1	21 years	FFP and PCC	1–2 units FFP/week and 400–600 mg/day danazol	Danazol treatment was tapered and stopped several times, but symptoms reappeared within 6 months each time. Patient remains on 400 mg dose of danazol with FX:C 30%
Fujimoto et al 1999[28]	ICH	1	40 days	IVH: Treatment not specified Epidural haematoma: PCC + 15 ml/kg red blood cells + craniectomy	70 U/kg PCC or 15 ml/kg FFP	10 days after operation, epidural haematoma increased in size but physical and neurologic condition remained stable
Peyvandi et al 1998[2]	Haemarthrosis (*n* = 22) GI bleed (*n* = 12) Umbilical bleed (*n* = 9) Haematuria (*n* = 8) CNS (*n* = 3)	32	5–72 years	NS[c]	NS[c]	NS[c]
el Kalla et al 1991[55,71]	ICH	2	Neonates	Case 1: 40 U/kg PCC every 3 days (*n* = 1) Case 2: NS	Case 1: No Case 2: FX replacement	Case 1: Died due to ICH Cases 2–3: Subsequent ICH episode in infancy
de Sousa et al 1988[26]	Antenatal CNS bleed Postnatal GI bleed ICH	1	Antenatal and then 4–7 months	FFP and PCC	PCC (dosage not specified)	Prophylactic PCC begun at 2 months of age; did not maintain FX:C 'more than a few percent for much of the time', but no major bleeds occurred until 7 months, when patient died from ICH
Sumer et al 1986[38]	ICH	1	3 months and 7 months	FFP	15 ml/kg FFP weekly, increased to every 4 days	Patient sustained severe psychomotor retardation and cortical amblyopia at 27 months of age
Machin et al 1980[30]	Haematomas ICH	1	4 months	10 ml PCC including 250 U FX:C, plus 75 ml red blood cells	10 ml PCC weekly	4 occasions of spontaneous bruising over 3 months; death at 4 months due to ICH, despite regular prophylaxis[d]

Abbreviations: CNS, central nervous system; FEIBA, factor VIII inhibitor bypass activity; FFP, fresh-frozen plasma; FII:C, factor II activity; FIX, factor IX; FVII:C, factor VII activity; FX, factor X; FX:C, FX activity; GI, gastrointestinal; ICH, intracerebral haemorrhage; ICU, intensive care unit; IV, intravenous; IVH, intraventricular haemorrhage; NS, not specified; PCC, prothrombin complex concentrate; pdFX, plasma-derived factor X concentrate.

[a]Median age for all patients in study who experienced ICH, including 7 with other coagulation factor deficiencies.

[b]Spiliopoulos et al describe a systematic literature review. Results are reported here for cases not described elsewhere in the table.

[c]Treatment and outcomes are not specified.

[d]Patient received prophylactic treatment following uncontrolled bleeding from heel prick sites at age 1 day; death from ICH occurred at 4 months despite regular prophylaxis.

patients (21%) and GI haemorrhage in five of 42 symptomatic patients (12%).[18] Whereas the 42 symptomatic patients overall had a mean age of 26 years and a median FX:C level of 13.3% (range, <1%–70%), all of those in whom ICH or GI bleeds occurred were <1 month old (median 9.7 days old) and had FX:C levels <2%.[19]

In a retrospective study of patients with FX deficiency, 16 of 20 patients (80%) reported bleeding episodes, of whom 12 (75%) experienced severe bleeds. FX:C levels were <1% for six of 20 patients (30%), 1%–5% for six of 20 patients (30%) and >5% for eight of 20 patients (40%). CNS bleed (generally ICH) was the first bleeding episode in six of 16 cases (37.5%) and occurred in eight of 16 patients (50%) aged <3 months, in two of 16 patients (12.5%) aged 3 months to 1 year and in six of 16 patients (37.5%) aged >1 year. Serious CNS bleeds occurred in 46.7% of the overall study population, haemarthrosis in 26.7%, and iliopsoas bleeds and haematuria each in 13.3%, respectively.[20]

Another retrospective study of seven children with FX deficiency (six with FX:C levels <10%) reported recurrent haemarthrosis in a patient with FX:C of 1.7%, muscle haematoma in a patient with FX:C of 1.0% and GI bleed in a patient with FX:C of 1.8%. Muscle haematoma after vaccination, umbilical bleeding and spontaneous intra-abdominal bleeding occurred in neonates; otherwise, patients were between 4 months and 8 years old when bleeding episodes occurred.[19]

In a retrospective study of 192 patients with rare bleeding disorders (RBDs), 15 patients (8%) had FX deficiency, nine with FX:C levels <5%. Nine episodes of severe bleeds were recorded in eight patients aged <5 years, including five CNS bleeds, three haemarthroses and one iliopsoas bleed. Of the 13 symptomatic patients, seven (54%) had experienced their first bleed before 3 months of age, four (31%) between 3 months and 1 year of age, and two (15%) at 1–5 years of age.[8]

In another retrospective study of RBDs, 50 of 321 individuals (16%) had FX deficiency. The precise severity of FX deficiency is unknown, as all patients with FX:C < 10 IU/dl were simply categorized as having 'severe' deficiency. However, 96% of patients with FX deficiency had activity levels below this threshold, and 12 of 50 patients (24%) had experienced ICH, with muscle haematomas (n = 7), joint bleeds (n = 6), GI bleeds (n = 5) and umbilical bleed (n = 1) the other severe bleeds reported.[7]

In a retrospective study of 52 patients with a hereditary factor deficiency (severe haemophilia, von Willebrand disease, or FXIII, factor V, or FX deficiency) who had experienced ICH, five patients had FX deficiency, in all cases diagnosed when the patient presented with ICH at 1–5 months of age. By contrast, the overall study population presented with ICH at a median age of 8 years.[6]

3.3 | Treatment of severe bleeds

Treatment for initial bleeding episodes was reported in 38 of 50 publications (76%). Many of these reports were published prior to the approval of FX concentrate in the United States (2015) and European Union (2016),[21,22] when fresh-frozen plasma (FFP) and prothrombin complex concentrate (PCC) were the primary treatments available, or in countries where FFP and PCC remain the only available treatments (Table 1). PCC products contain three or four coagulation factors, including factor IX (FIX), FX and factor II in three-factor products along with factor VII in four-factor products, and are dosed according to FIX activity units, with levels of the other factors varying among products and product batches.[3,23] The precise amount of FX administered in a specific PCC dose is therefore unknown. Because FFP and PCC supply other plasma components in addition to the one in which the patient is deficient, administration of either compound increases levels of coagulation factors in which the patient is not deficient, and high or repeated dosing is thus associated with risk of thrombosis.[3]

For treatment of bleeds related to FX deficiency, 33 case reports and studies mentioned the use of FFP, and 23 mentioned treatment with PCC,[15,16,19,20,24–36] with some patients receiving both FFP and PCC. The single-factor plasma-derived FX (pdFX) product was used to treat two patients.[14,37] Treatment with danazol was attempted in a few instances with limited efficacy.[16,38] Whole blood or red blood cell transfusions and vitamin K were also used, in some instances even after a diagnosis of FX deficiency was made, suggesting that the physicians may have been unfamiliar with the pathophysiology of the disorder or had limited access to appropriate agents for FX repletion.[7,24,25,39–41]

Prophylactic treatment of hereditary FX deficiency was reported in 33 publications and included FFP (mentioned in seven publications),[6,16,28,38,42–44] PCC (19 publications)[19,24-28,30–35,41,43,45–49] and/or pdFX (two publications),[14,37] with some publications not specifying the therapy or reporting more than one therapy.

In nearly all cases, patients with FX deficiency who had received prophylactic treatment did not experience severe bleeding episodes after beginning prophylaxis. One exception was a case report of two siblings with FX deficiency in which the older sibling (FX:C < 1%) experienced a fatal intracranial haemorrhage despite treatment with FFP. Several years later, his 18-day-old sister was admitted to the hospital with ICH and FX:C < 0.5%. The bleeding resolved with treatment but then recurred despite an unspecified type of prophylactic therapy.[40] An additional case report described a patient who experienced a fatal ICH at age 2.5 years despite weekly infusions of PCC.[30]

In most cases, when severe bleeding does occur following treatment, it is due to decreased FX levels. One case report described a neonate with ICH in whom FX deficiency was identified (FX:C < 1%), who was initially treated with 15 ml/kg FFP. Treatment increased FX:C to 70%, but all subsequent measurements of FX:C were <1%. Whether the patient was tested for neutralizing alloantibodies was not noted in the report. The patient was rehospitalized at 1 month of age for rectal bleeding and again at 4 months of age for ICH (both times treated with FFP). Following discharge at 4 months, he received 3 months of weekly prophylactic treatment with 15 ml/kg FFP, but he was readmitted 6 days after one such FFP treatment for convulsions secondary to ICH. Cortical blindness and psychomotor retardation subsequently developed and were sustained at 27 months. The patient was maintained on prophylaxis of 15 ml/kg FFP every 4 days.[38]

A third case report described four patients, all of whom experienced joint bleeds while receiving varying doses of PCC as prophylactic treatment. In at least two of the four, the bleeds appeared to be due to reduced or omitted doses.[48] One patient was diagnosed when he was 1 day old and presented with umbilical cord bleeding, ICH and FX <1 IU/dl. He was initially treated with FFP and then given prophylaxis of 70 IU/kg PCC weekly. At 15 years of age, he had experienced only one joint bleed since beginning prophylaxis. The younger sister of the first case had umbilical cord bleeding and haematemesis at 1 day of age. She continued to experience bruising when she was given the same prophylactic PCC dosage as her brother; adjusting the dosage to 40–80 IU/kg every other day increased her FX levels to >50 IU/dl. Subsequent attempts to decrease treatment resulted in joint bleeds, but these issues were resolved when the dose was increased. A relative of the first two children was diagnosed with FX deficiency (FX <1 IU/dl) at 3 days of age with umbilical cord and intraperitoneal bleeding. He was also prescribed PCC prophylaxis after initial treatment with FFP and PCC (dosages not specified), with one report of a bleed in the right foot. The fourth child was diagnosed with FX deficiency (FX <1 IU/dl) at 3 days of age with umbilical cord bleeding, which was treated with FFP; however, this patient did not begin prophylaxis (70 IU/kg PCC) until an episode of severe haematemesis occurred 17 days later. During prophylaxis, the patient experienced a traumatic tongue bleed and a joint bleed temporally related to treatment omission.

During a phase 3 prospective study of pdFX efficacy as on-demand treatment of bleeding episodes, one 20-year-old male experienced a subdural haematoma, which was treated with 15 IU/kg pdFX, followed by an additional 46 IU/kg.[14] Symptoms resolved after the first day of treatment, and the patient received daily doses of 31–62 IU/kg pdFX for 1 week in the intensive care unit. Following discharge, he began weekly prophylactic treatment (25 IU/kg) with pdFX for 5 months. When no bleeding episodes occurred, he began receiving pdFX on-demand to treat bleeds, but he experienced six bleeding episodes over 10 months. Prophylactic treatment was then resumed at approximately 25 IU/kg every 2 weeks, with no subsequent bleeds reported.

4 | DISCUSSION

The case reports, prospective studies and retrospective studies consistently show that CNS bleeds, in particular ICH, are the most common type of severe bleed in individuals with hereditary FX deficiency and that patients appear to be at the highest risk of ICH during the first few months of life. In most cases, CNS bleeds were successfully treated medically with PCC, FFP or FX replacement along with surgery. Many patients were prescribed long-term prophylactic treatment after the first bleeding episode; others received prophylaxis after a subsequent severe bleed or recurrent spontaneous bleeds.

For all patients with bleeding disorders, rapid and sufficient replacement of the deficient coagulation factor is essential to treat severe bleeds.[3] However, restoration of FX:C to haemostatic levels[1,50] is particularly important for patients with FX deficiency given the key role that FX plays in the thrombin formation pathway.[1,51] The goal is to return trough FX:C to 10%–20%, ideally increasing FX:C to >40%, at which point patients are usually asymptomatic.[5,52] The consequences of insufficient treatment are evident in the literature reviewed here.

The importance of adequate replacement therapy is underscored by a retrospective study in which investigators attributed seven of 15 deaths of haemophilia patients to underdosing or delayed treatment.[6] Several studies have identified mortality rates of 20%–30% for haemophilia patients with ICH, which the investigators also attributed to delayed treatment.[53,54] However, severe bleeding incompatible with survival is often the cause of death: in the retrospective study cited above, the remaining eight of 15 deaths were due to the severity and type of bleed, including one untreated patient <6 months old who died during presentation due to intraparenchymal bleeding.[6]

The use of prophylaxis to reduce bleeding risk is essential for patients with FX deficiency given the risk of spontaneous and/or life-threatening bleeds. Patients who receive treatment are at a relatively low risk of mortality, particularly after the first year of life. Of the 125 patients with FX deficiency for whom treatment is described in the literature, only five deaths were reported (all at <15 months of age, with four due to ICH and one to hydrocephalus).[6,26,30,40,55,56]

In general, ICH in patients with bleeding disorders is often the result of trauma.[6] In patients with FX deficiency, ICH is likely to be spontaneous, to occur at an early age and to recur.[3,6,57,58] Patients are at a particularly high risk of ICH in the first 6 months of life, when FX:C levels remain low.[10]

One report further describing six neonates with ICH related to FX deficiency included in the analysis above[56] described multiple additional symptoms, including GI bleeds, epistaxis, gingival haemorrhage, easy bruising, haematomas and haematuria.[56] One patient died at 15 months due to hydrocephalus, and four later developed neurological delays or physical or learning disabilities. The only patient who survived with no severe problems received early treatment with PCC, which the authors suggested was not the case for the others. Another publication described five patients with FX deficiency, all of whom had a history of multiple bleeds, including three patients who experienced severe bleeding (ICH, umbilical bleeds, haemarthrosis and/or haematoma) before 1 month of age. Two of these patients were given prophylaxis with FFP and an antifibrinolytic, but one patient remained in a vegetative state with mental retardation on follow-up.[42] As demonstrated in the numerous case reports, patients with homozygous FX deficiency often experience their first severe bleed during the first few months of life, and this is generally when the disorder is diagnosed (unless a genetic mutation was previously identified in a family member).

The ideal treatment for RBDs is a single-factor concentrate that supplies only the necessary component to achieve sufficient factor activity levels for coagulation.[23] Single-factor FX concentrate is currently considered the standard of care for both on-demand and

prophylactic treatment of patients with hereditary FX deficiency, but PCC products may be used where FX concentrate is not available.[3] Because of the increased risk of thrombosis associated with PCCs, careful monitoring of levels of other coagulation factors is essential. Although FFP was used more frequently than other treatments in the publications reviewed here, experts now recommend it as a secondary alternative if FX concentrate or PCC is not available.[3] The use of FFP is associated with inhibitor development in some patients with RBDs, though this appears to be a greater risk with deficiencies of factors other than FX. None of the publications in this review reported patients developing neutralizing antibodies to FX.[3]

Most patients described in these case reports and studies were treated before a specific replacement factor for FX deficiency became available. However, pdFX, a high-purity, high-potency concentrate, is now available for on-demand and prophylactic treatment of patients with hereditary FX deficiency as well as perioperative management of bleeding in patients with mild or moderate hereditary FX deficiency.[21,22] Clinical trials published to date have demonstrated a favourable efficacy profile for pdFX.[59,60] All clinical studies of pdFX, including on-demand, prophylactic and/or perisurgical treatment, have reported that patients show no evidence of developing inhibitors to pdFX.[59–61] Recently, a case series was published describing 4 neonates and infants with hereditary FX deficiency who exhibited ICH.[62] pdFX was used for both management of acute bleeding and prophylaxis. No breakthrough bleeding episodes were reported over a median of more than 2 years of follow-up.

5 | CONCLUSION

Despite the rarity of hereditary FX deficiency, it is important that clinicians be prepared to recognize and treat this disorder given the suddenness and severity with which complications may manifest. Many patients with hereditary FX deficiency present with a severe bleeding episode within the first few months of life. This is particularly true for those with severe FX deficiency, in whom such episodes are more likely to occur spontaneously. Delayed treatment or insufficient FX replacement prolongs bleeding and increases the risk of complications such as developmental delays (in the case of CNS bleeds), joint damage (in the case of joint bleeds) and death. Treatments such as PCC and FFP are available and widely used, but their risks include thrombosis, volume overload and inhibitor development (particularly in the case of FFP). Based on the publications identified here, FFP remains the most frequently used treatment for severe bleeding episodes in patients with FX deficiency. However, many of these case reports and studies were published before specific FX concentrate, which is now the recommended treatment for such symptoms, became available.[23] When neither FX concentrate nor PCC is available, FFP may be used. FX concentrate has not been associated with the same level of risk as FFP (eg, allergic reactions and transfusion-associated lung injury) and PCC (eg, thrombosis),[1] and it has been shown to be safe and effective in patients with hereditary FX deficiency.[59,61]

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DISCLOSURES

Dr. Micheal Tarantino is the Chief Executive Officer and Chief Medical officer of the Bleeding and Clotting disorders institute and the President of Michael D. Tarantino, MD, SC, private practice. He has acted as a paid consultant to Amgen, BioMarin, Dova, Genentech, Octapharma, Principia, Sobi, Spark Therapeutics, Takeda, and UCB Pharmaceuticals. He has served on the Speakers Bureaus for Amgen, Dova, Octapharma, Sobi, Takeda, and UCB Pharmaceuticals. He is a clinical trial PI for Dova, Pfizer, Principia, Spark Therapeutics, Takeda, and UCB Pharmaceuticals.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data were generated or analyzed in this study.

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