New developments in the management of congenital Factor XIII deficiency

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Abstract: Congenital Factor XIII (FXIII) deficiency is a rare, inherited, autosomal recessive coagulation disorder. Most mutations of this condition are found in the A-subunit with almost half these being missense mutations. Globally, approximately one in three million people suffer from this deficiency. Factor XIII deficiency is associated with severe life threatening bleeding, intracranial hemorrhage, impaired wound healing, and recurrent pregnancy losses. FXIII is known to have a potential role in mediating inflammatory processes, insulin resistance, bone metabolism, neoplasia, and angiogenesis. The algorithm provided for FXIII diagnosis and classification will enable prompt identification and early intervention for controlling potential life threatening complications. Prophylactic replacement therapy using blood products containing FXIII such as fresh frozen plasma, cryoprecipitate, or using FXIII concentrate remains the mainstay for the management of FXIII deficiency. In most parts of the world, cryoprecipitate and plasma transfusions are the only treatments available. Management developments have revealed the effectiveness and safety of recombinant FXIII concentrate for prophylaxis and treatment. The aim of this review is to provide an overview of advancements made in the management of FXIII deficiency from the time it was first detected, highlighting novel developments made in recent years. Greater research is warranted in identifying novel approaches to manage FXIII deficiency in light of its underlying pathophysiology.

Keywords: Factor XIII, Factor XIII deficiency, treatment, diagnosis, inherited coagulative disorders

Introduction

Approximately one in every three to five million people suffer from congenital Factor XIII (FXIII) deficiency globally. This coagulation blood disorder is inherited in an autosomal recessive manner. The incidence of the disease in the United Kingdom is known to be one in every two to five million people. The disease is so rare that, to date, a little over 300 cases have been reported worldwide. The greatest number of cases have been reported in Japan. This rare bleeding disorder affects people of all races and genders with a higher prevalence in families with FXIII deficient patients and consanguinity. In the case of nonconsanguineous families, a higher incidence of compound heterozygosity is observed. High rates of consanguineous marriages are seen in South Asia. A cross-section study conducted at a blood bank in Pakistan identified nine cases of Factor XIII through routine screening over a period of 7 years. A recent case-series report at a tertiary care hospital in the region identified ten cases of FXIII deficiency over a 10 year period with 80% of cases having a history of consanguineous marriages.
The clinical importance of FXIII came to light in the year 1960 when a boy in Switzerland was reported to have suffered from a severe bleeding diathesis 16 years after its discovery. The only bleeding abnormality described by Duckert et al was the solubility of his clots in 5Molar urea (concentration). Thirteen year later, the same patient was described as having a severe bleeding diathesis, and after another 16 years, it was discovered he had inherited FXIII-A deficiency. The patient died of a bleeding diathesis at age 70. It is now known that the clinical importance of FXIII-A deficiency is a result of FXIII-A subunit deficiency. The A subunit in the inherited deficiency is absent from plasma, platelets, and monocytes. Roughly 50% of molecular defects that cause a deficiency in the FXIII-A subunit are nonsense mutations. On the other hand, congenital deficiency in the FXIII-B subunit is a relatively rarer cause of FXIII deficiency. Plasma levels of the B subunit are usually reduced, and very rarely both A and B subunits are absent. Bleeding symptoms in patients with FXIII-B deficiencies are relatively mild compared to FXIII-A deficiencies. Severe clinical symptoms have been reported in fewer than ten cases.

### Molecular structure

FXIII in the plasma (pFXIII) is a precursor of transglutaminase and is a tetrameric complex (FXIII-A2B2) of two active A subunits (FXIIIA; molecular weight 83 kDa) and two carrier B subunits (FXIII-B; molecular weight 80 kDa). The gene coding for FXIII-A is located on chromosome 6p24-25, whereas the FXIII-B gene is located on chromosome 1 at 1q31-32. FXIII-A is synthesized in cells of bone marrow origin, whereas FXIII-B is produced by hepatocytes and the two types of subunits form a complex in the plasma. The cellular form of FXIII (cFXIII), a homodimer of FXIII-A (FXIII-A2), is found in the cytoplasm of platelets, monocytes, histiocytes, and tissue macrophages. FXIII-B is the protective unit of the tetramer that protects subunit A from proteolyis and under normal physiological conditions is found in excess in the serum as free FXIII-B.

FXIII is the last factor in the coagulation cascade. It is a protransglutaminase, which is activated by thrombin to transglutaminase in presence of calcium ions. Fibrin, along with optimal serum calcium levels, also functions as an important cofactor in the activation process and accelerates the activation rate manifold. Activated FXIII converts loose fibrin polymers into an organized structure by cross linking the peptide-bound glutamyl and lysine residues of fibrinogen chains through an isopeptide bond, thereby releasing ammonia. This stable fibrin clot that is formed as a result adheres firmly to the underlying wound and is not easily degraded by sheer stress and the fibrinolytic system. Plasma concentrations of FXIII and age of the clot are the two most important determinants of a clot’s resistance to degradation by the fibrinolytic system. The average plasma concentration of the A2B2 heterotetramer is approximately 22 μg/mL and its half-life is 9–14 days.

A study conducted using two separate lines of FXIII-A knockout mice with prolonged bleeding times indicated impaired clot retraction in FXIII-A deficient mice in the presence of normal platelet aggregation induced by collagen and adenosine diphosphate.

In recent years, developments in DNA technology have facilitated genetic studies in families with inherited deficiencies as well as in normal individuals. The nucleotide substitutions leading to nonsense mutations, missense mutations, and splice defects do not appear to be clustered in specific regions on the gene, but are spread over the entire FXIII-A gene along with its messenger RNA. Studies focusing on the structural and functional consequences of these mutations and normal polymorphisms in the gene have translated into a better understanding of FXIII function. These mutations predict the severity of the disease in patients deficient in FXIII.

### Classifying FXIII deficiency

Formerly, FXIII deficiency was categorized as either type 1 or type 2. Type 1 deficiency was described as a combined deficiency of FXIII-A and FXIII-B, whereas type II was defined as FXIII-A deficiency only. However, this classification is outdated as it was later learnt that patients assumed to have type I combined deficiency are in fact defective in the FXIII-B gene and that the lower FXIII-A level is due to increased clearance from the circulation in the absence of protective FXIII-B. Nevertheless, for the purpose of classification (Figure 1), FXIII-A2B2 antigen in the plasma is first determined, and if decreased, further measurement of the individual subunits is recommended in the plasma and FXIII-A in platelet lysate.

Inherited FXIII deficiency is now classified as FXIII-A and FXIII-B. FXIII-A can further be sub-classified as type 1 or type 2 defects where type 1 represents a quantitative defect, whereas type 2 represents a qualitative defect. Although recognized as a hereditary disorder, with research advancements, it is now known that FXIII-A deficiency is due to mutations in gene coding the catalytic A subunit (FXIII-A) located on Chromosome 6. A little over 104 mutations have been associated with this deficiency and the majority are a result of missense and nonsense mutations, frameshifts, and splice defects. These mutations leading to nonsense mutations, missense mutations, and splice defects do not appear to be clustered in specific regions on the gene, but are spread over the entire FXIII-A gene along with its messenger RNA. Studies focusing on the structural and functional consequences of these mutations and normal polymorphisms in the gene have translated into a better understanding of FXIII function. These mutations predict the severity of the disease in patients deficient in FXIII.
Clinical manifestations

Congenital FXIII deficiency can manifest as a severe bleeding condition as early as a few days after birth in the form of umbilical stump bleeding. The bleeding in FXIII deficient individuals is more severe as compared to other coagulative disorders. Intracutaneous bleeding (57%), umbilical stump bleeds (56%), intramuscular bleeding (49%), and intracranial hemorrhage (34%) are the most common clinical manifestations in these individuals as determined by International Registry of Factor XIII deficiency. 1,3,7-9 The rates of umbilical bleeding and intracranial hemorrhage are much higher compared to Hemophilia and Type III von Willebrand factor deficiency. 10

Most patients with congenital FXIII deficiency suffer from life-long crippling bleeding diathesis with a very high risk of early mortality. Nearly 80% of deaths are attributed to intracranial hemorrhage. 7 Clinical manifestations vary in patients and are unpredictable whereby long periods of mild symptoms may follow severe bleeding complications. 22

Another early manifestation of FXIII deficiency is post-operative bleeding, which usually occurs as a result of disruption of an unstable clot. 44 Circumcision in deficient individuals 24 hours after birth has resulted in severe bleeding. 7 Other characteristic symptoms include ecchymosis, intramuscular and subcutaneous hematomas, oral cavity, mouth and gingival bleeding, and prolonged bleeding following trauma. 22 Hemarthrosis occurs in a number of patients, 42 with joint-associated bleeding usually occurring periarticular rather than into the joint cavity. 7,43 A rare case of subdural and epidural hematoma has also been reported in the literature deeming it necessary to screen a patient with a bleed with no identifiable cause. 44 Studies have shown that many patients recover if managed with adequate replacement therapy alone. 45 Surgery has been reserved for worsening neurological conditions where prompt intervention has had life-saving outcomes, especially for subdural bleeds. 46

Besides its role in hemostatic function, FXIII deficiency is also associated with poor wound healing and angiogenesis. 14,41 Evidence from studies suggests FXIII-A2 facilitates Fcc and complement receptor mediated phagocytosis. Deficient patients have been shown to have impaired function in these activities. 37 Murine wound healing models also support the important role of intracellular FXIII-A2 in leukocyte and tissue remodeling and repair. Studies on myocardial repair following infarction induced in FXIII knockout mice demonstrated a reduction in leukocyte recruitment, phagocytosis, and protease activity in injured myocardial tissue. 48 Factor XIII is known to play a role in maintaining pregnancy. 49 The rate of miscarriage in FXIII deficient females can be as high as 80%. 51 The production of FXIII-A2 in the placenta, confirms its role in maintaining the integrity of placental attachment in the uterus. 50 A study assessing FXIII...
plasma activity in pregnancy has shown that low maternal plasma activity of FXIII leads to a low concentration of subunit A at the placental bed resulting in the formation of an insufficient and inadequate cytotrophoblastic shell and increased risk of miscarriage. Recurrent fetal losses with a normal miscarriage workup and a family history negative for bleeding disorders needs to be evaluated for FXIII deficiency.

Molecular research focusing on the implications of FXIII deficiency in adults identified a lower prevalence of myocardial infarction in subjects without a factor XIII Val 34 Leu mutation. A relatively higher incidence of primary intracerebral hemorrhage was seen in patients with factor XIII Val 34 Leu mutation. However, the precise role of fibrin in causing cerebrovascular disease is unknown. Nevertheless, the formation of cross-linked fibrin from fibrin monomer is vital for the development and maintenance of a stable clot, and abnormalities of fibrin structure and architecture are associated with premature myocardial infarction in males.

New developments reveal the role of FXIII for functions other than coagulation and cardiovascular disease, maintaining pregnancy, and wound healing. FXIII is known to play a role in osteoblast matrix secretion and deposition where FXIII-A and its cross-linking activity are localized with plasma membrane-associated tubulin. The cross-linking activity is aimed at stabilizing the interaction of microtubules with the plasma membrane, demonstrating that transglutaminase activity can affect protein secretion and matrix deposition in osteoblasts.

Expression of FXIII may potentially be considered as a leukemia-associated immunophenotype. FXIII assays may be used for diagnosis or for monitoring disease progress.

Diagnosis

It is important to screen patients born with a bleeding diathesis, or with a family history of bleeding disorders in order to start prophylactic therapy to lower the risk of spontaneous or acquired intracranial bleeding and its complications. Diagnosis might be delayed in situations where a family history of bleeding disorders is not revealed. Lack of awareness of this condition in emergency units has also been associated with delayed diagnosis.

Standard hemostasis assays, including prothrombin time, activated partial thromboplastin time, fibrinogen level, platelet count, and platelet function testing, are normal in individuals with FXIII deficiency as FXIII acts when fibrin has already been formed. These assays have proven to be effective for diagnoses of bleeding disorders, such as congenital or acquired hemophilia, where there is a deficiency in factor VIII or factor IX. However, none of these tests are capable of detecting a deficiency in FXIII.

Since the discovery of the first case of FXIII in 1960 through standard clot solubility testing, labs have used this test for the diagnosis of FXIII deficiency. The test involves using a small volume of the patient’s plasma which is incubated at room temperature with a buffer and a solution of calcium ± thrombin. Incubation is continued for approximately 1-hour to allow for clot stabilization. The clot is then suspended in a freshly prepared solution of 1% monochloroacetic acid or in a solution of 5Molar urea. Under normal conditions, rapid dissolution of the clot should occur anywhere between a few minutes to 1-hour. The clot solubility test is a qualitative test and is only positive if FXIII activity is zero or close to zero. Adding a small amount of normal plasma to the system elevates FXIII activity to 1% ± 3% of normal, rendering the clot insoluble.

However, this test is poorly standardized and detects only very severe deficiencies in FXIII activity. FXIII < 1 Udl⁻¹ has been associated with a severe bleeding risk, whereas levels of between 1 and 4 Udl⁻¹ indicate moderate disease. Even with an accurate measure of FXIII levels, the phenotype does not always correlate with levels obtained, as those with levels > 5 Udl⁻¹ have also suffered bleeding complications. However, although this test is no longer found to be a reliable screening tool, it is still used by most routine laboratories because of its simplicity and the lack of availability of quantitative screening tools.

If the diagnosis of FXIII deficiency is suggested by the solubility test, other quantitative tests can be undertaken. Mild to moderate deficiencies in FXIII are better diagnosed through the use of a quantitative assay, such as amine incorporation and ammonia release assays, which measure the transglutaminase activity of FXIII. The screening test, which establishes the diagnosis of FXIII deficiency, should
be a FXIII activity assay. FXIII activity assays are based on: (i) measuring the ammonia released during the transglutaminase reaction by the nicotinamide adenine dinucleotide phosphate (NAD[P])H-dependent glutamate dehydrogenase reaction spectrophotometrically at 340 nm, and (ii) measuring the amount of a small molecular weight labeled amine substrate covalently linked to a protein. In the latter case, the free and bound radiolabeled, fluorescent, or biotinylated amine should be separated and the protein-linked fraction is quantitatively measured. Amine incorporation methods are known to have a high sensitivity, are automated, resulting in quick kinetic testing. However, they are more time consuming than the ammonia release assays, difficult to standardize, and the separation step makes it difficult to design a true kinetic assay.

On the other hand, disadvantages of the ammonia test include its relatively low sensitivity. The assay may give overestimated results in low FXIII concentrations as high ammonia levels in the test plasma compromise accuracy. Mixing studies with normal plasma can avoid this complication. Levels below 15% should be closely evaluated as they may contain either traces of FXIII or no FXIII at all. Enzyme-linked immunosorbent assay (ELISA) has been recommended to account for the aforementioned drawbacks of traditional testing. ELISA has been used to determine FXIII or antigen levels to diagnose or monitor therapy for FXIII deficiency. The test directly measures FXIII A-subunit or FXIII B-subunit proteins using specific antibodies. ELISA is a sensitive technique, thus making it reliable for low range FXIII levels. Table 1 shows the expected levels in different subtypes.

The diagnostic tools used for the classification of FXIII deficiencies include FXIII-A2B2, FXIII-A, and FXIII-B antigen determinations from the plasma, FXIII activity, and FXIII-A antigen measurement from the platelet lysate produced using a nonionic detergent. Study of fibrin cross-linking by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE) analysis of washed plasma clot is a useful addition in a series of tests to confirm diagnoses.

It has become highly desirable to also study the type of mutations causing the defect to fully characterize the patient and contribute to our understanding of disease mechanisms. PCR has been shown to play a role in the diagnosis of FXIII deficiency. With over 100 mutations having been identified in the gene coding for FXIII and the type of mutation affecting the presentation and disease course, genetic testing has a significant role in the diagnosis of FXIII deficiency.

Once the mutation has been identified it can aid in family counseling, prenatal screening, and further characterization of specific bleeding risk.

### Table 1 Laboratory Diagnosis/Classification of factor XIII deficiency

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Plasma FXIII activity</th>
<th>Plasma FXIII-A_B² antigen</th>
<th>Plasma FXIII-A antigen</th>
<th>Plasma FXIII-B antigen</th>
<th>Platelet FXIII activity</th>
<th>Platelet FXIII-A antigen</th>
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<td>Inherited</td>
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<td>FXIII-A deficiency</td>
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<tr>
<td>Type I</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>&gt;30%</td>
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<tr>
<td>Type II</td>
<td>↓↓↓</td>
<td>↓-N</td>
<td>↓-N</td>
<td>&gt;30%</td>
<td>↓↓↓</td>
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<td>FXIII-B deficiency</td>
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<td>Autoantibody against FXIII</td>
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<td>Neutralizing</td>
<td>↓↓↓</td>
<td>↓-N</td>
<td>↓-N</td>
<td>&gt;30%</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Non-neutralizing</td>
<td>↓↓↓</td>
<td>↓-N</td>
<td>↓-N</td>
<td>&gt;30%</td>
<td>N</td>
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<tr>
<td>Anti-FXIII-B</td>
<td>↓↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>N</td>
<td>N</td>
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<td>Other acquired deficiencies</td>
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<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
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Notes: ↓↓↓, highly decreased activity/concentration usually below 3%; ↓↓, considerably decreased activity/concentration, usually 5%–10%; ↓, slightly decreased activity, usually 20%–70%.


**Abbreviations:** FXIII, factor XIII; N, normal; NA, non-applicable.
1–4 U/dL are also prone to moderate to severe spontaneous bleeding episodes and prophylactic replacement therapy should also be considered in this subset of deficient individuals. Serum FXIII levels > 5 U/dL are desirable but do not rule out the possibility of spontaneous bleeds that may occur in a small percentage of patients.

Despite the rarity of the disease, studies have focused on long term effects of prophylactic treatment. Two prospective studies demonstrated that prophylactic treatment successfully kept a check on bleeding episodes, without any significant toxicity or transmission of infection.

Evidence from the literature suggests that FXIII levels of 3%–10% of the normal population mean (0.03–0.1 IU/mL) are sufficient to prevent spontaneous bleeds. A recent data analysis concluded that a plasma concentration of 10% is needed to significantly prevent episodes of any spontaneous hemorrhages. However, there may still remain a chance of cutaneous bleeds in 10% of patients.

Even though plasma derived sources of FXIII, namely, whole blood, fresh frozen plasma, and cryoprecipitate have been widely used for decades due to the ease of availability, they carry a high risk for allergic reaction and infections with blood-borne pathogens, including hepatitis and human immunodeficiency virus (HIV). Highly purified and heat treated FXIII concentrate from plasma is the treatment of choice for long term prophylaxis as it contains adequate and reliable concentrations of FXIII in optimal volume with fewer contaminations and is virally inactivated. FXIII concentrate has the longest plasma half-life (11–14 days) of all clotting factors. Primary prophylaxis is practical and feasible in cases of FXIII deficiency as the concentrate has a long half-life and only a low plasma concentration of 10% is needed to significantly reduce bleeding episodes.

Since placenta derived FXIII was withdrawn from the market in 1994, plasma derived pasteurized concentrate of FXIII marketed under the name of Fibrogammin P has been widely used for prophylaxis. It is licensed for use in several countries in Asia, South America, Europe while phase II/III trials are still ongoing in United States to assess its efficacy and safety profile. Fibrogammin P is derived from HIV negative pooled human plasma screened for common viruses (hepatitis B surface antigen, anti-hepatitis C virus, anti-HIV-1, and anti-HIV-2). It is available in pharmacies as a 250 IU pack for IV administration for £106.58 (£0.42/Unit) and is equally efficacious in all forms of congenital FXIII deficiency (A and B). An ongoing investigational new drug study in the United States, evaluating the prophylactic efficacy and long-term safety of Fibrogammin P has 61 enrolled subjects (Male 44, Female 17; Mean age 12.7); representing approximately two-thirds of patients with FXIII deficiency nationwide. Response to therapy with a 9-year follow up has been good to excellent, without any evidence of FXIII inhibitor development or seroconversion. No major intracranial or life-threatening bleeds have been reported in these patients. The half-life of the concentrate in serum is comparable to that of patients who receive cryoprecipitate or fresh frozen plasma.

For patients with congenital factor XIII deficiency that undergo any major surgery, it is required that a higher dose of 20–30 U/kg/day be administered instead of the prophylactic dose (10–20 U/kg every 4–6 weeks), to maintain a plasma concentration of higher than 5%. Replacement therapy should ideally be administered immediately prior to surgery and should be continued until complete recovery is made. A dose of 10–20 U/kg/day for 2–3 days should be sufficient for minor surgeries.

In acute and severe bleeding conditions, a FXIII concentrate can be administered at a dose of 20 U/kg. Further treatment depends on serum FXIII levels achieved after administering the initial dose. FXIII infusion should continue until bleeding stops. In case a patient develops intracranial hemorrhage, FXIII levels need to be monitored closely and maintained at a normal range for a minimum of 2 weeks before reverting to therapy at the prophylactic dosage. Such aggressive management will require replacement therapy on alternate days. If, for any reason, FXIII concentrate or plasma is not available in hemorrhagic emergencies, platelet transfusion can be used as an alternative means of providing hemodynamic stability as FXIII is contained in platelets.

Neonates with severe FXIII deficiency (<3 U/dL) are at a high risk of life threatening umbilical bleeding, cephalohematoma, and intracranial bleeding. Aggressive management is recommended with 10 U/kg prophylactic therapy given at 4 weekly intervals. Subsequent dosages and frequency of doses depends upon pretreatment (<3 U/dL) and 1-hour post treatment (>60 U/dL) plasma FXIII levels. Assuming young children are active and more prone to injury, 4 weekly FXIII replacements have been recommended to achieve a constant serum concentration of at least 10% of mean serum FXIII concentration in the normal population. Six weekly replacements usually results in a serum FXIII level of 3%–5% towards the end of the period.

Approximately half of pregnant women with severe congenital FXIII deficiency can end up with spontaneous abortions and recurrent pregnancy losses, without proper replacement therapy. There is a scarcity of data on
adequate replacement therapy for pregnancy. A plasma FXIII level of greater than 10% has been reported to be adequate to carry a pregnancy to term in deficient individuals. Asahina et al reported that a replacement therapy with 250 IU per week was found to be sufficient to maintain a plasma level above 10%. The study recommended increasing the dose to 500 IU per week from the 23rd week of gestation to maintain pregnancy. A booster dose of 1000 IU can be given at the onset of labor to achieve plasma levels of over 30% to prevent severe hemorrhagic obstetric complications during labor.

Recently, ZymoGenetics Inc (Seattle, WA, USA) developed a novel recombinant FXIII-A2 (rFXIII-A2) that is free of human or mammalian products. rFXIII-A combines with free endogenous FXIII-B in plasma to form a functional tetramer with a half-life of 10–14 days, similar to the endogenous form. However, in patients with congenital deficiency of FXIII-B, the plasma half-life of the functional tetramer becomes significantly shorter. A phase 1 escalating dose trial conducted to evaluate the safety and efficacy of the novel recombinant rFXIII-A for long term prophylaxis concluded that the new product had a good safety profile, without any threatening adverse events or development of specific autoantibodies. The study recommended monthly prophylaxis with rFXIII-A for the treatment of congenital FXIII deficiency. Inbal et al’s phase III trial of 2012 involving 41 patients with congenital FXIII deficiency reported five trauma-induced bleeding episodes in four patients treated with rFXIII-A2. Biochemical tests revealed transient, non-neutralizing, low volume antibody titers in the sera of four patients, but none of them developed any allergic or anaphylactic reactions, nor did they have any severe bleeding that required urgent intervention. Although the antibodies developed in this study were clinically insignificant, in case of inhibitor development, the management typically involves immunosuppressive therapies including prednisone, cyclophosphamide, plasma exchange, intravenous immunoglobulin, and rituximab.

Conclusion
Congenital FXIII deficiency is a rare autosomal recessive disorder occurring in only one in three to five million people that remains underdiagnosed despite advances in the diagnostic modalities. Early recognition of this deficiency and adequate prophylactic therapy is crucial in order to save patients from life-threatening bleeding episodes and subsequent neurological morbidities and mortality. In this review, we have attempted to touch upon the recent advancements in the diagnosis and management of this congenital deficiency.

Although standard prophylaxis therapy includes FXIII concentrates, recombinant FXIII may be available in the future. Further studies are still needed to fully understand the varying functions of FXIII and how they impact clinical practice.

Disclosure
The authors report no conflicts of interest in this work.

References


