Congenital Fibrinogen Disorders, Diagnosis, and Management

6

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6.1 Introduction

Congenital fibrinogen disorders encompass a large spectrum of fibrinogen anomalies [1]. The prevalence of congenital fibrinogen disorders is not known. Based on international databases, it has been estimated that they represent about 8% of the rare bleeding disorders [2]. The prevalence of afibrinogenemia is estimated to be 1 for 1,000,000 of person, and more frequent in countries with consanguinity [3, 4]. A recent study from the United States Hemophilia Treatment Centers Network reported a prevalence of 1.13 for 1,000,000 of persons, compared to 3.74 in the United Kingdom registry data and 0.70 in the World Federation of Hemophilia Global Survey [5]. However, this prevalence is probably underestimated since asymptomatic patients are often not included in such registries. In addition, national registries usually include patients with severe coagulation factors deficiencies, while dysfibrinogenemia and hypofibrinogenemic patients can have only moderate decreased fibrinogen levels.

In our previous chapter published in 2018 in "Congenital Bleeding Disorders" (Springer, Ed. A. Dorgalaleh), we summarized how to diagnosis a congenital fibrinogen disorders and reviewed the main clinical features [1]. In this update, we revise the classification, the diagnosis, the genetic, the clinical features, and the management of fibrinogen disorder focusing mainly on the last five-year publications.

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A. Dorgalaleh (ed.), *Congenital Bleeding Disorders*,
https://doi.org/10.1007/978-3-031-43156-2_6

6.2 Classification

Congenital fibrinogen disorders have historically been classified as quantitative (type I) or qualitative (type II) fibrinogen disorders [6]. Quantitative fibrinogen disorders include afibrinogenemia characterized by the complete absence of fibrinogen and hypofibrinogenemia characterized by proportionally decreased levels of functional and antigen fibrinogen levels [7]. On the other side, qualitative fibrinogen disorders include dysfibrinogenemia defined by normal levels of a dysfunctional fibrinogen molecule and hypodysfibrinogenemia characterized by decreased levels of a dysfunctional fibrinogen molecule [7]. The Fibrinogen and Factor XIII subcommittee of the International Society of Thrombosis and Hemostasis (ISTH) has proposed a new classification considering both the biological (fibrinogen levels and genotype) and the patient's clinical features [8]. Thus, afibrinogenemia is separated into type 1A (afibrinogenemia with bleeding symptoms) and 1B (afibrinogenemia with thrombotic phenotype). Hypofibrinogenemia is classified according to the functional fibrinogen level (<0.5 g/L severe, type 2A; 0.5– < 1 g/L moderate, type 2B; 1 g/L to the lower range of laboratory, mild, type 2C). A fourth sub-type is the fibrinogen storage disease (see session on genetics). Dysfibrinogenemia is classified in type 3A (asymptomatic, bleeding, or thrombotic phenotype) or 3B (thrombotic-related fibrinogen variant, see session on genetics). Hypodysfibrinogenemia is classified according to antigenic fibrinogen level (<0.5 g/L severe, 4A; 0.5– < 1 g/L moderate, 4B; 1 g/L to the lower range of laboratory, mild, 4C).

6.3 Diagnosis

An accurate diagnosis is essential to characterize the type and sub-type of fibrinogen disorder and drive the management. Diagnosis of can be made based on clinical presentations and appropriate laboratory assessment but even in well-equipped coagulation laboratory, sometimes, diagnosis of these disorders can be a sophisticated process especially for dysfibrinogenemia and hypodysfibrinogenemia [9–12]. Usually, a fibrinogen disorder is suspected according to the personal or familial history, but an acquired fibrinogen disorder should be excluded before to perform a complete fibrinogen work-up. Common causes of acquired fibrinogen disorders are summarized in Table 6.1 [13]. In case of suspicion of a congenital fibrinogen disorder, the first step is the assessment of the functional fibrinogen by the Clauss method [14]. The Clauss method is a modification of the thrombin time, in which citrated plasma is diluted and then excess thrombin, usually 100 U/ml (range 35–200 U/ml) is added, and time of clotting is measured. High concentration of thrombin is used to ensure that clotting time is independent of thrombin concentration [15–18]. The clotting time is inversely proportional to the amount of fibrinogen in the sample. For determination of the plasma fibrinogen level, a calibration curve with a serial dilution of reference plasma with known concentration of fibrinogen is provided. If the Clauss fibrinogen level is below the lower range of the laboratory, the screening should be completed with the assessment of the antigenic fibrinogen, which is

Table 6.1 Causes of acquired fibrinogen deficiency

Cause	Potential physiopathologic mechanism
Liver disease	Increased sialylation of Bβ and γ chains [93]
Malignancy (renal carcinoma, hepatoma)	Paraneoplastic synthesis of abnormal fibrinogen [94]
Plasma cells disorders	Paraproteinemia binding fibrinogen [95]
Systemic lupus erythematosus and rheumatoid arthritis	Autoantibody against fibrinogen [96]
Disseminated intravascular coagulation	Consumption of clotting factors [97]
Hemophagocytic lymphohistiocytosis	Induced fibrinolysis or histiocytes binding fibrinogen [50]
Medications (isoniazid, asparaginase, thrombolytic drugs, valproic acid, tigecycline)	Impaired hepatic synthesis, fibrinolysis or unknown [98]
Plasma exchange	Apheresis without plasma as replacement fluid [99]

Causes mainly associated with qualitative fibrinogen disorder are indicated in italic type

mandatory to distinguish between hypofibrinogenemia, dysfibrinogenemia, and hypodysfibrinogenemia. Several immunological assays are available to evaluate the fibrinogen concentration but unfortunately, only a minority of routine laboratory are equipped with. A good alternative is the indirect fibrinogen evaluation from the prothrombin time (PT) curve. In this method, the PT is performed on plasma dilutions with known amount of fibrinogen, and a curve is drawn based on optical changes against different fibrinogen concentrations. By this graph, an optical change in plasma with known amount of fibrinogen is converted to fibrinogen level [15, 19]. The PT-derived fibrinogen overestimates the functional fibrinogen in dysfibrinogenemia [19] but provides an excellent correlation with the antigenic fibrinogen (r = 0.898) [20]. In a study including 66 patients with dysfibrinogemia and 54 patients with hypofibrinogenemia, a cut-off >1.7 for the ratio PT-derived fibrinogen/Clauss fibrinogen gave a 100% of specificity and sensitivity for the diagnosis of dysfibrinogenemia [21]. As indicated in Fig. 6.1, the type of fibrinogen disorder is defined by the functional and antigen fibrinogen level. In afibrinogenemia, all tests based on fibrin clot as endpoint are infinitely prolonged. Fibrinogen functional and antigen are undetectable. In hypofibrinogenemia, a proportional reduction of activity and antigen fibrinogen level is observed. The prolongation of standard coagulation assays and of thrombin and reptilase time depends on the fibrinogen levels. Distinguishing severe hypofibrinogenemia from afibrinogenemia can be difficult and depends on the limit detection of the fibrinogen assay. In such cases, additional methods, such as mass spectrometry, can be useful [22]. Dysfibrinogenemia is suspected in case of discrepancy between functional and antigenic fibrinogen levels. A ratio activity/antigen below 0.7 is historically used to diagnose dysfibrinogenemia, although this cut-off has never been validated [16, 23]. Hypodysfibrinogenemia is defined by low level of dysfunctional fibrinogen. It is suspected in case of discrepancy between decreased activity and decreased antigen fibrinogen levels. Since

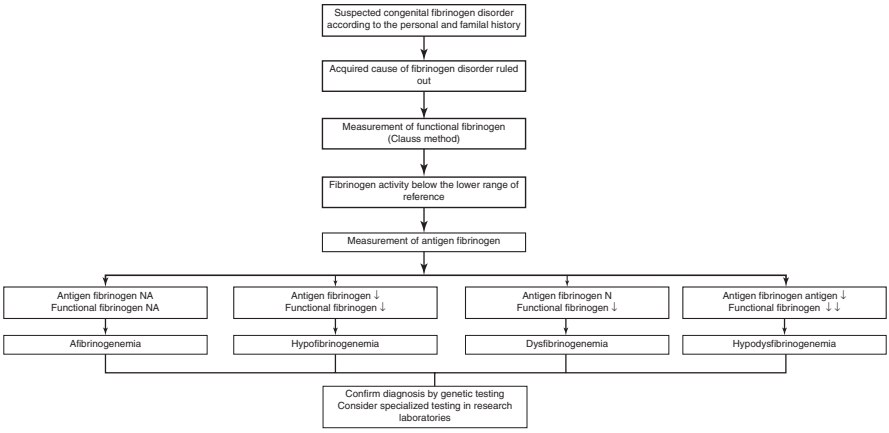

Fig. 6.1 Algorithm for diagnosis of fibrinogen disorders, adapted from [62]. *NA* not available as in afibrinogenemia both the antigen and the functional fibrinogen are not measurable. *N* in the normal range. ↓: below the lower range of reference. ↓↓: discordance between the antigen and functional fibrinogen

hypodysfibrinogenemia shares some features with both hypofibrinogenemia and dysfibrinogenemia, misdiagnosis is an important issue in this disorder. Distinguishing it from hypofibrinogenemia is difficult, especially in case with very low fibrinogen levels [24]. In systematic review of literature, the functional/antigenic fibrinogen ratio of <0.7 showed a poor sensitivity (86%) with a mean functional/antigenic fibrinogen ratio of 0.46 (0.07–1.25) observed in 32 cases [25].

When suspecting a fibrinogen disorder, it is important to underline two points. The first is that in some clinical situations as pregnancy, inflammatory disease, acute infection and active neoplasm, functional fibrinogen levels could be increased up to the normal levels. In such settings, if the suspicion of fibrinogen disorder is high, the assessment of the antigenic fibrinogen and eventually of the genotype is indicated even if the functional fibrinogen level is in the normal range. The second point is related to the diagnosis of dysfibrinogenemia. In dysfibrinogenemia, the sensitivity of the Clauss and PT-derived fibrinogen is dependent on the reagents, the assays, and the fibrinogen variant [17]. In an international study involving several European laboratories ($n = 86$), 39% of centers reported a normal or raised fibrinogen level for the Fibrinogen Longmont. The particularity of this fibrinogen variant is to form a translucent clot that can better be detected by a mechanical rather than a spectrophotometric clot assay [26]. Marked differences in Clauss fibrinogen results with different reagents were also noted for hotspot mutations (median 1.01 g/L vs 5.10 g/L for the two mostly widely used reagents) [27]. The thrombin origin (human or bovine) and the method for the detection of the fibrin clot (mechanical or optical endpoint) explain part of the variability observed in measurement of fibrinogen levels in dysfibrinogenemia [18, 28]. Recently, it has been reported that the clot waveform analysis (CWA) in the Clauss fibrinogen assay could be useful to detect functional fibrinogen abnormalities with no additional measurement of antigenic fibrinogen

[29, 30]. Of note, the thrombin time can be used when the fibrinogen Clauss is not available, even though the specificity and sensitivity of this assay are poor in fibrinogen disorders [31]. For the thrombin time measurement, a standard amount of thrombin is added to the patient's citrated plasma and then clotting time is measured. Thrombin cleaves both molecules of FpA and FpB to mediate fibrin formation. For the reptilase time, reptilase is used instead of thrombin to initiate the fibrin formation. In contrast to thrombin, reptilase induces fibrin formation only by cleavage of FpA. Thrombin time is prolonged in presence of unfractionated heparin or direct thrombin inhibitors in patient's plasma, while RT is not affected in this situation [14].

To better determine the patient's clinical phenotype, global hemostasis assays and an assessment of the fibrin clot properties are performed in research laboratories [11]. Point-of-care viscoelastic tests (i.e., rotational thromboelastometry or thromboelastography) can help to guide the hemostatic management in high bleeding risk surgeries [32, 33]. However, they have a limited sensitivity to certain changes in fibrinogen molecule structure and function, reducing their utility only to patients with hypofibrinogenemia [34, 35]. Similarly, in a small series of patients with dysfibrinogenemia, thrombin generation measurement seems not able to distinguish between specific clinical phenotypes [34].

6.4 Genetics

Since the identification of the first causative mutation of dysfibrinogenemia in 1968 [36] and of afibrinogenemia in 1999 [37], hundreds of mutations have been reported. Mutations are scattered throughout the three fibrinogen genes (i.e., *FGA*, *FGB*, *FGG*). Some hotspot mutations have been identified but number of new fibrinogen variants are still reported to date. Hotspot mutations are found worldwide, and some mutational clusters have been reported in some countries. List all the variants is out of the scope of this chapter, and we refer the reader to on-line database (https://site.geht.org/base-fibrinogene/, last accessed 20 June 2022) and to recent reviews that provide an exhaustive list of fibrinogen variants [33, 38–40]. The type and the localization of the mutation differ according to the fibrinogen disorder. Patients with afibrinogenemia are mostly either homozygous or compound heterozygous for null mutations (e.g., large deletions, frameshift mutations, early truncation, non-sense mutations, splice-site mutations). Overall, these molecular anomalies affect the fibrinogen assembly, stability, or secretion [37, 41–47]. Although traditionally afibrinogenemia and hypofibrinogenemia were considered as two completely separated clinical entities, in fact, they are the phenotypic expression of the heterozygote and homozygote allelic status for a given fibrinogen mutation. Two recurrent mutations have been identified in quantitative fibrinogen disorders; both localize in FGA. The IVS4 + 1G > T splice-site mutation results in an early α-chain truncation. The 11-kb deletion leads to the absence of the Aα chain.

Most dysfibrinogenemia cases are inherited in an autosomal dominant manner caused by heterozygote missense mutation in one of the three fibrinogen genes; although, rarely homozygotes or compound heterozygote have been reported. Dysfibrinogenemia is usually heterozygous for missense mutations, especially located in the thrombin cleavage site in the exon 2 of *FGA* (Arg35-Gly36), in knob A (Gly36, Pro37, and Arg38) and in residues Arg301 of exon 8 of *FGG* [38]. Two missense mutations (i.e., hotspot mutations) are frequent. The residue Arg35 of exon 2 of *FGA* (c.103C > T or c.104G > A) can be mutated in histidine or cysteine resulting in a defective thrombin binding and an abnormal release of FpA [8, 48–50]. The residue Arg301 of exon 8 of *FGG* (c.901C > T or c.902GA) can also be mutated in histidine or cysteine affecting the D:D interactions, causing a defect in the early stage of fibrin polymerisation [7]. Considering hotspot mutations and the surrounding residues in exon 2 of *FGA* and exon 8 of FGG, about 85% of dysfibrinogenemia can be identified.

Other mutations observed in both quantitative and qualitative fibrinogen disorders are clustered in the αC-region (composed by the αC-domain and connector, α221–α610) [51]. Interestingly, missense mutations in the C-terminal region of the γ chain lead to qualitative fibrinogen disorder demonstrating that this domain can tolerate structural change, at least for the assembly and secretion of fibrinogen [38]. On the contrary, mutations in the C-terminal domain of the β-chain result in quantitative fibrinogen disorders suggesting that this domain does not tolerate structural changes [52].

In hypodysfibrinogenemia, a total of 32 causative mutations, mainly missense, non-sense, and frameshift, have been identified [25]. The “hypo” phenotype of hypodysfibrinogenemia is due to impaired assembly of fibrinogen molecule, decreased secretion, or increased fibrinogen clearance, while the “dysf” phenotype is often due to defective fibrin polymerization or abnormal binding of calcium or tissue plasminogen activator. Several molecular mechanisms explain these phenotypes. On one hand, a single mutation can lead to production of an abnormal fibrinogen chain that is less effectively secreted. On the other hand, two distinct heterozygous mutations can cause the qualitative defect and the quantitative one, respectively [25, 53–56].

Next-generation sequencing technologies allow sequencing of the coding region of the genome at low cost and are of undeniable value for investigation of fibrinogen disorder [57, 58], especially in the setting of complex mutations [59]. Moreover, a whole exome sequencing can provide information on fibrinogen polymorphisms acting as genetic modifiers that could explain the phenotype variability in dysfibrinogenemia [60]. Genotype helps to determine the correct diagnosis of fibrinogen disorder, allows the familial and prenatal screening, and correlates to the clinical phenotype. Indeed, some fibrinogen variants are strongly associated with a thrombotic risk (type 3B in the ISTH classification) [61]. These variants are observed in multiple structural domains of the fibrinogen molecule [62]. Several mechanisms, often overlapping, lead to hypercoagulability such as defective binding of thrombin, hypofibrinolysis, defective clot retraction, and abnormal viscoelastic properties of the fibrin clot [63]. Other variants, clustered in the C-terminal part of the γ chain, are

associated with the fibrinogen storage disease [64]. The fibrinogen storage disease is a disorder characterized by protein aggregation in the endoplasmic reticulum, hypofibrinogenemia, and liver disease of variable severity [65].

6.5 Clinical Features

Bleeding is the main symptom of quantitative fibrinogen disorder and depends on the fibrinogen concentration [66]. Recently, a cross-sectional international multicentric study including 204 patients with afibrinogenemia has provided new insights on the bleeding phenotype of such patients [67]. The median ISTH bleeding assessment tool score was of 14 points. Most of patients reported at least one bleeding episodes per month and about half of patients suffered from muscle hematoma, hemarthrosis, and peri-operative bleeding. As previously observed [68], cerebral bleeding was frequent, occurring in 23% of patients in both adults and children group. Of note, the bleeding phenotype impacted the health-related quality of life, especially in women. Miscellaneous symptoms are typical complications of afibrinogenemia. In the aforementioned study, spontaneous spleen rupture and bone cysts were reported in 11 (5.4%) and 36 (17.6%) patients, respectively [67]. Thrombosis is a paradoxical complication of afibrinogenemia. In the cohort of 204 patients, a total of 37 (18.1%) patients experienced a thrombotic event in venous, arterial, or both territories. Venous thromboses occurred in young patients with a mean age at first event of 27 years. Arterial thromboses were also observed in young patients with a mean age at first event of 36 years. Thrombotic recurrence was reported in 15 (40.5%) patients [67]. Several mechanisms may explain the clinical conundrum of thrombosis in the absence of fibrin(ogen): the increased thrombin generation due to the lack of the antithrombin-like effect of fibrin and the tendency to embolism of platelets clots made in the absence of fibrinogen [69]. A potential link between fibrinogen infusion and thrombotic events has been often reported, even though no causality has been established, and pharmacovigilance data suggest that this risk, if any, is extremely low [70, 71]. In a recent study including 20 patients with afibrinogenemia, the thrombin generation analyzed by a calibrated automated thrombography after a single standard dose of fibrinogen concentrate increased but did not reach the levels measured in controls [71]. Pregnancy is a high-risk clinical situation in women with afibrinogenemia. Fibrinogen replacement should be started early in gestation to prevent miscarriage and kept throughout the pregnancy to reduce the risk of vaginal bleeding and fetal loss [72]. Patients with mild or moderate hypofibrinogenemia are more often asymptomatic. The bleeding risk is essentially related to trauma or surgeries [73].

Bleeding symptoms reported in dysfibrinogenemia are usually mild (Table 6.2). Recent and older series of patients indicated that most of patients suffer from cutaneous and mucosal bleeding. Heavy menstrual bleeding and post-surgical bleeding are more frequent. Of note, clinical data are often limited to the time of inclusion or diagnosis, but the clinical course of dysfibrinogenemia can be complicated by spontaneous or traumatic major bleeding [48, 74]. Post-partum hemorrhage is frequent

Table 6.2 Bleeding pattern from recent large series of patients with dysfibrinogenemia

Author, year	Number of patients, n	Bleeding, n (%)	Cutaneous and minor wound, n (%)	Heavy menstrual bleeding, n (%)	Epistaxis and oral cavity, n (%)	Post-surgery, n (%)	Major,[a] n (%)
Casini (2015) [48]	101	53 (52)	28 (27.7)	20 (29.4)	15 (14.9)	9 (8.9)	13 (12.9)
Zhou (2015) [100]	102	28 (27.5)	13 (12.7)	3 (6.1)	9 (8.8)	6 (5.9)	11 (10.8)
Smith (2018) [101]	13	7 (53.8)	1 (7.7)	ND	1 (7.7)	2 (15.3)	3 (23)
Castaman (2019) [102]	50	15[b] [30]	ND	2 (10)	NA	2 (4)	3 (6)
Wypasek (2019) [73]	14	6 (42.9)	2 (14)	3 (27.3)	2 (14)	2 (14)	ND
Simurda (2020) [103]	31	13 (42)	3 (9.6)	6 (31)	ND	1 (3.2)	1 (3.2)
Zhou (2020) [104]	15	5 (33.3)	2 (13.3)	1 (6.7)	1 (6.7)	ND	1 (6.7)
Mohsenian (2021) [105]	10	9 (90)	8 (80)	5 (71)	2 (20)	1 (10)	ND

[a]Bleeding requiring a blood transfusion, a surgical hemostasis or in a critical site (cerebral, hemarthrosis, muscle hematoma, retro-peritoneal bleeding)
[b]Indicated only patients requiring a treatment; *ND* no data

in dysfibrinogenemia. In a recent systematic literature review, 6/32 (18%) pregnancies were complicated by post-partum hemorrhage requiring a fibrinogen infusion [75]. Women with a bleeding phenotype seem particularly at risk of obstetrical complications [48, 76]. As previously mentioned, dysfibrinogenemia is also associated with a thrombotic risk and should be considered as a mild thrombophilia [62]. Patients with hypodysfibrinogenemia are more prone to bleeding symptoms due to lower levels of a dysfunctional fibrinogen [77].

6.6 Management

General recommendations according to specific clinical settings are reported in Table 6.3. Fibrinogen replacement is the main step in prevention and treatment of bleeding in fibrinogen disorders. Fresh-frozen plasma, cryoprecipitates, and fibrinogen concentrate can be administered to increase fibrinogen levels [70]. The latter has the advantages to be purified, to be virus-inactivated, to contain a defined fibrinogen concentration, and to be rapidly infused with relatively small volumes [78].

Table 6.3 Recommendation for management of congenital fibrinogen disorders in selected clinical settings adapted from [62, 108]

General
In quantitative fibrinogen disorders, all new symptoms should be considered as bleeding and treated accordingly until additional investigations are performed
In afibrinogenemia and severe bleeding phenotype, all invasive procedure (including venipuncture) should be avoided and performed only upon approval of hematologist
Anti-inflammatory drugs should be avoided in patients with a bleeding phenotype
Hormonal contraception should be suggested in women with heavy menstrual bleeding
Annual visit to a hemophilia center should be organized for all patients with fibrinogen disorders
Surgical procedure and pregnancy management should be performed under the guidance of specialized centers dealing with bleeding disorders
Thrombosis
Screening for dysfibrinogenemia should be considered as second-line investigation in the absence of more common causes of thrombophilia
The same recommendations as for the general population should be proposed, favoring a limited duration of anticoagulation (except for type 3B dysfibrinogenemia)
Anticoagulation with a direct anticoagulant is the first choice
A mechanical or pharmacological thromboprophylaxis should always be considered taking into account the bleeding risk
Pregnancy
A preconception counseling is mandatory with a multidisciplinary team
In afibrinogenemia and severe hypofibrinogenemia, fibrinogen replacement should be started as early in gestation as possible targeting at least >1 g/L
A quarterly assessment of fibrinogen level and a systematic monitoring of fetal growth should be proposed
Fibrinogen replacement to allow neuroaxial anesthesia targeting >1.5 g/L
Avoid invasive fetal procedures
Early fibrinogen replacement and tranexamic acid in case of post-partum hemorrhage
Consider thromboprophylaxis

Three fibrinogen concentrates are marketed and several other are in the process of authorization. However, they are still inaccessible in many areas of the world. In the aforementioned large cohort on afibrinogenemia, some patients from Asia (7.5%) and Africa (18%) had no access to fibrinogen supplementation [67].

Pharmacokinetics properties are similar among the fibrinogen concentrates even though slight differences in the half-lives and the recovery times have been observed (Table 6.4). In view of interindividual variations, an individual pharmacokinetics study should be proposed to each patient under fibrinogen prophylaxis [79–81]. Currently, there are no evidence-based data to drive the management of patients with fibrinogen disorders [82]. Conventionally, patients with quantitative fibrinogen disorders are treated "on-demand", although secondary prophylaxis regimens should be proposed after life-threatening bleeding. Long-term prophylaxis should be proposed as primary prophylaxis in patients with afibrinogenemia to decrease the risk of cerebral bleeding [69]. In case of primary or secondary prophylaxis, the target trough fibrinogen level should be more than 0.5 g/L. The long half-life of fibrinogen usually allows an administration every 5-7 to 14 days [70, 83, 84]. To determine

Table 6.4 Pharmacokinetic parameters for median (minimal–maximum) fibrinogen activity of three fibrinogen concentrates

		Manco-Johnson et al. [106]	Djambas-Khayat et al. [81]	Ross et al. [107]
Primary PK parameters	Clearance (ml/h/kg)	0.55 [0.45–0.86]	0.57 [0.38–0.77]	0.63 [0.40–1.17]
	Volume of distribution (ml/kg)	52.7 [36.22–67.67]	53.5 [36.3–60.4]	61.04 [36.89–149.11]
Secondary PK parameters	C_{max} (g/L)	1.3 [1.00–2.10]	1.34 [1.06–2.19]	1.24 [0.75–1.96]
	AUC $_{0\text{-}\infty}$ (g h/L)	126.8 [81.7–156.4]	105 [78.2–167]	111.14 [59.7–175.5]
	Half-life $t_{1/2}$ (h)	77.1 [55.73–117.26]	67.9 [51.0–99.9]	72.85 [40.03–156.96]
In vivo recovery	Incremental recovery (mg/dl mg/kg)	1.7 [1.30–2.73]	2.22 [1.77–3.65]	1.77 [1.08–2.62]
	According to the plasmatic volume (%)	61.8 [52.45–97.43]	89.0 [69.5–133.0]	64.83 [40.89–88.13]

PK pharmacokinetics, C_{max} maximum plasma concentration, *AUC* area under the plasma concentration-time curve from the start of infusion (time 0)

the required dose of fibrinogen, the following formula can be used: Amount of fibrinogen to be administered (g/L) = [target fibrinogen level (g/L) – basal fibrinogen level (g/L)] × 1/incremental recovery time (mg/dl mg/kg) × weight (kg). The optimal target of fibrinogen activity in cases of acute bleeding or to prevent bleeding during surgery is unknown and is mainly extrapolated from non-randomized clinical trials [81, 85, 86]. Recent expert's guidelines suggest raising peak fibrinogen levels to 1.5 g/L for most major or clinically relevant nonmajor bleeding events or high-risk bleeding surgeries [62]. Subsequent doses should be based on the clinical evolution and the patient's trough fibrinogen activity level, aiming at least 0.5 g/L throughout wound healing [87]. Keeping a minimal level of fibrin(ogen) is essential to maintaining an optimal activation of factor XIII and thus helping in wound healing and angiogenesis [49]. Tranexamic acid can be added in cases with bleeding involving mucous membranes [88]. In case of thrombosis, the same recommendations as for the general population are usually adopted. Increasing data support the utilization of direct oral anticoagulant [60, 89–92]. The overall management of patients with qualitative fibrinogen disorders should always consider the personal and familial history of bleeding and thrombosis as well as the genotype [62]. In case of bleeding, the same recommendations for quantitative fibrinogen disorder are valuable. Fibrinogen replacement prophylaxis before surgery is usually necessary only in case of a bleeding phenotype or in case of major surgery [62]. Most often, the fibrinogen replacement is required only in case of complications. Patients should receive an accurate thromboprophylaxis in high thrombotic risk situation.

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