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THE RARE COAGULATION DISORDERS

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The Rare Coagulation Disorders

Paula HB Bolton-Maggs

Introduction

The rare coagulation disorders are inherited abnormalities of hemostasis that may present significant difficulties in diagnosis and management. The overall frequency of these disorders in the general population is low (with the exception of factor XI deficiency). Homozygous deficiency varies from 1 in 500,000 for factor VII deficiency to 1 in 2 million for prothrombin [2]. The prevalence of these disorders is strongly influenced by the racial mix in the population. Consequently, diagnosis and monitoring of affected individuals may require specialist phenotypic and molecular investigations that are not widely available. There may be considerable variation in bleeding pattern between affected individuals resulting at least in part from variability at the molecular level in the rare coagulation disorders.

All the disorders are autosomally inherited and, with the exception of factor XI deficiency, generally have no significant clinical manifestations in heterozygotes. Severe deficiencies are more likely to be found in populations where marriage between blood relatives is common, and in rare cases individuals may inherit more than one disorder [3]. Systematic reporting (case series) has been done from Iran for several disorders [4-12], although it is not clear how representative the clinical findings are for other populations and mutations.

Blood products available for each disorder are listed in Appendices 1 and 2.

Management of pregnancy in women with rare disorders

Pregnancy in women with severe rare disorders is best managed in an obstetric unit in a hospital that has a hemophilia centre. If this is not possible, close collaboration between the obstetric unit and hemophilia centre is required. Good communication between pediatricians, hematologists, and obstetricians is also important to ensure proper investigation and management of a potentially affected newborn, for example where the parents are related and already have one affected child or are known to be carriers for one of these disorders. Several of the severe disorders are associated with a significant risk of intracranial hemorrhage (ICH) in the first week of life.

Pediatricians and neonatologists need to be aware of the increased risk of the rare severe coagulation defects presenting in offspring of parents who are related. It is very important that newborns who present with unexpected bleeding be investigated urgently, and then the bleeding symptoms treated vigorously to raise the level of the missing coagulation factor. Inadequate or delayed treatment of ICH in a newborn leads to death or significant long-term disability. It is also important that appropriate normal ranges for factor levels are used for infants and children [13]. Many of the coagulation factors are low in newborns due to liver immaturity and/or vitamin K deficiency (which affects factors II, VII, IX, X, XI) so that where there is doubt, levels may need to be measured again after 6 months.

Laboratory tests

Laboratory tests used for investigation and diagnosis can be affected by methods of collection and processing, as well as by the choice and execution of the assays. A good venipuncture with free flowing blood is essential; blood should be drawn into anticoagulant (trisodium citrate 0.105-0.109M) taking care to fill the container correctly. Poor or difficult venipuncture may result in tissue activation in the sample, and false normal results, even in a severe coagulation disorder. Samples should be centrifuged as soon as possible and either analysed or frozen within 4 hours of collection. Frozen samples should be thawed for assay rapidly.

Table: Hemostatic level of the different factors and the half-life of the transfused factors

Factor	Hemostatic level U/dL		Half-life of transfused factor (h=hours, d=days)	
	(a)	(b)	(a)	(b)
Fibrinogen	10-20	50	4-6 d	2-4 d
Prothrombin	40	20-30	3 d	3-4 d
Factor V	10-15	15-20	80 h	36 h
Factor VII	5-10	15-20	4-6 h	4-6 h
Factor X	10-15	15-20	48h	40-60 h
Factor XI	?20-30	15-20	60-100 h	40-70h

Sources: Column (a) data from Rizza CR. Management of patients with inherited blood coagulation defects. Chapter 21 in Haemostasis and Thrombosis*, Eds. Bloom AL and Thomas DP, 1981, Churchill Livingstone, Edinburgh, page 371; column (b) data from Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders.* Blood *2004; 104:1243-52.*

Screening tests can vary considerably in sensitivity to factor deficiencies depending upon reagents and assay systems. It is therefore important that each laboratory establish a local normal range for each assay performed, and laboratories should participate in both internal and external quality assurance schemes. Test samples for factor assays should be measured in three dilutions to ensure that the test dose-response curve is parallel to the reference curve.

Defects of fibrinogen

Fibrinogen is a large molecule, made up of two identical halves, each half composed of three protein chains (A alpha, B beta, and gamma). The genes for these proteins are located on chromosome 4. Thrombin cleaves fibrinogen with the release of fibrinopeptides A and B, producing fibrin monomer which then polymerizes and is stabilized by the action of factor XIII. Fibrinogen also plays a role in normal platelet aggregation.

Fibrinogen abnormalities may be:
1. Absence of fibrinogen – afibrinogenemia;
2. A decreased level of fibrinogen with normal structure – hypofibrinogenemia;
3. A structurally abnormal fibrinogen – dysfibrinogenemia.

In practice it may be difficult to distinguish between hypo- and dysfibrinogenemia. Mild forms are probably underdiagnosed. Fibrinogen disorders with severe bleeding manifestations are uncommon. Two large case series, one from Iran [10] and the other from Israel [14], describe umbilical bleeding and mucosal hemorrhage as the most common bleeding problems. Musculoskeletal bleeding was not infrequent, and cerebral bleeding was reported. There is some evidence of impaired wound healing. Bleeding is less severe in hypofibrinogenemia but may occur following invasive procedures.

Women with either afibrinogenemia or hypofibrinogenemia have an increased risk of miscarriage, which suggests that fibrinogen has a role in implantation. Prophylaxis with fibrinogen concentrate during pregnancy may improve the outcome and prevent postpartum hemorrhage [15].

Paradoxically, thrombosis is also reported in some people with afibrinogenemia, unrelated to replacement therapy – the mechanism is not clear. There is little literature on

dysfibrinogenemia and what there is mainly consists of case reports or molecular analyses. The clinical picture is very variable; a compilation of 250 cases reported hemorrhage in 26%, thrombosis in 21% and no symptoms in 53%. An analysis of patients with dysfibrinogenemia and thrombosis demonstrated an unequivocal association of thrombosis with 26 different mutations [16].

Laboratory investigation

Coagulation tests will be prolonged in proportion to the reduced fibrinogen. It is important to exclude acquired causes of hypofibrinogenemia. Family studies are often helpful. The thrombin time is the most sensitive test for dysfibrinogenemia. Diagnosis depends upon documenting a difference between functional and antigenic fibrinogen assays. In patients with thrombosis, other causes of thrombophilia should be excluded by a thrombophilia screen. Genetic testing can be performed in some research laboratories. A database of mutations can be viewed at http://www.geht.org/databaseang/fibrinogen/.

Treatment

Fibrinogen concentrates are detailed in recent UK treatment guidelines [17]. The half-life of infused fibrinogen is 3-5 days (based on adult data). Cryoprecipitate is a good source of fibrinogen but has the major disadvantage of not being treated to inactivate blood-borne viruses.

Replacement therapy is recommended before surgery in people with afibrinogenemia (post-operative hemorrhage occurred in 40% of those untreated in one series [10]) and should be sufficient to produce a rise of fibrinogen to at least 1 g/L to ensure hemostasis. Further doses will depend upon clinical and laboratory monitoring, and should aim to achieve a trough level of >0.5 g/L. It is not clear whether infants diagnosed with afibrinogenemia require primary prophylaxis, but the occurrence of ICH in newborns may be an indication. The management of dysfibrinogenemia is less clear [18] and the issues are discussed in the UK guidelines for the management of rare coagulation disorders [1]. In individuals with thrombotic risk, anticoagulant prophylaxis may be indicated in addition to replacement therapy, depending upon the clinical circumstances.

Prothrombin deficiency

Factor II (FII) is a vitamin K-dependent carboxylase synthesized in the liver. It is a single chain glycoprotein with four domains. Factor Xa (FXa) activates it on the surface of platelets releasing an activation peptide (fragment 1.2) on cleavage. FII deficiency is very rare, estimated to be 1 in 2 million of the general population. Deficiency may be hypoprothrombinemia (reduced level of a normal molecule, Type 1) or dysprothrombinemia (activity reduced but antigen normal, Type 2). A complete deficiency may be incompatible with life (lethal in knockout mice). Only a small number of cases are reported worldwide [19], and the largest series (14 patients) is from Iran [6]. Severe deficiency was associated with levels of 4-10% and the most common bleeding manifestations were hemarthrosis and muscle hematomata. Life-threatening umbilical bleeding occurred in two patients, and intracranial hemorrhage (ICH) in one. Five other cases of ICH are found in the literature. The clinical picture in dysprothrombinemia is more variable.

Laboratory investigation

Both the prothrombin time (PT) and the activated partial thromboplastin time (APTT) will be prolonged but this may be minimal and is reagent dependent. FII assays may be performed by a variety of methods and particular caution is required in infants [1].

Treatment

There are no products licensed for use in prothrombin deficiency but several factor concentrates contain FII [17]. In the absence of these, viral-inactivated fresh frozen plasma (FFP) is a potential source of FII.

Factor V deficiency

Factor V (FV) is a large glycoprotein with 40% sequence homology to factor VIII (FVIII) in the A and C domains and a similar overall structure. FV is encoded on chromosome 1 and produced in hepatocytes and megakaryocytes. Platelets contain about 20% of circulating FV. Both quantitative and qualitative defects are reported. FV deficiency is rare, occurring in 1 in 1 million of the general population. Severely deficient individuals have FV levels from <1 to 10 IU/dL

(normal range 71-125 IU/dL), and have a moderately severe bleeding tendency which presents in childhood with easy bruising and mucous membrane bleeding, especially epistaxis. Joint and muscle bleeding may also occur but usually less than in hemophilia A. ICH has been reported in infancy and several of the cases in the literature have been complicated by the development of inhibitors after treatment with plasma.

Laboratory investigation

Both the PT and APTT are prolonged, and the diagnosis is confirmed by performing a FV assay. A FVIII assay should also be performed to exclude combined deficiency (see below).

Treatment

There are no FV-containing concentrates. FFP, preferably viral inactivated, is the treatment of choice [20]. The minimum hemostatic level has been reported as 15 IU/dL [6]. Large volumes of plasma may be required [20]. Platelet transfusions (with FV in the granules) may be of benefit. Neonates with ICH have been reported; it is therefore prudent to watch infants with care and perform a cranial ultrasound within the first few days of life.

Combined deficiency of factors V and VIII

The combined deficiency of FV and FVIII is of particular interest as it is the first coagulation disorder attributable to gene defects outside the coagulation factor genes themselves, as inheritance patterns had suggested. The disorder is caused by abnormal transport through the endoplasmic reticulum due to a defect in ERGIC-53 coded on chromosome 18 [21,22]. The factor levels are not usually below 1 IU/dL so spontaneous bleeding is rare. Bleeding occurs after surgery and dental extractions; women may have menorrhagia and postpartum hemorrhage.

Laboratory investigation

Both PT and APTT are prolonged with the latter being disproportionately long. FV and FVIII levels are generally between 5 and 20 IU/dL.

Treatment

Both FV and FVIII levels must be corrected, using FFP for FV to achieve a level of >25 IU/dL, and FVIII concentrate as a source of FVIII to raise the level to 25 IU/dL for minor procedures and >50 IU/dL for major procedures or bleeding episodes. Neonatal ICH has not been reported.

Factor VII deficiency

Factor VII (FVII) is one of the vitamin K-dependent glycoproteins and is encoded on chromosome 13. A mutation database can be viewed at http://www.193.60.222.13/index.htm. FVII deficiency is the commonest of the rare coagulation disorders excluding factor XI deficiency (severe FVII deficiency occurs in 1 in 500,000 of the general population), but diagnosis of the heterozygous state is complicated by the considerable variation of levels in the normal population, due to both inherited (F7 gene polymorphisms [23]) and acquired (dietary fat, age, obesity, etc.) causes. In addition, reagent (thromboplastin source) can markedly affect the assay result. There is a relatively poor correlation between FVII level and the wide variety of bleeding manifestations [7]. Mucous membrane bleeding, including epistaxis and menorrhagia, is common. Some patients with severe deficiency have suffered ICH, often in the neonatal period, or joint bleeding. Occasionally patients have paradoxical thrombosis, which is not understood [23].

Laboratory investigation

The PT is prolonged but all other screening tests are normal. FVII is assayed in a one-stage prothrombin-based assay. Human thromboplastin may give a better reflection of *in vivo* levels than animal thromboplastins. Blood samples should not be stored on ice before the assay is done as this may induce cold activation of FVII and cause an overestimate of the level.

Treatment

People with heterozygous deficiency do not have an abnormal bleeding risk. Viral-inactivated plasma-derived FVII concentrates have been available and are effective (see [1] and Appendix 1). Factor IX (FIX) and prothrombin complex concentrates containing FVII have also been used, but carry a risk of thrombosis and are

no longer recommended. Recombinant factor VIIa (FVIIa) is the treatment of choice [17], and is now licensed for use in this condition [1]. The dose required is much lower than that used for patients with FVIII inhibitors; 15-30 ug/kg seems to be effective. The half-life of FVII is short, and treatment needs to be given every 2-4 hours. The hemostatic level is probably 10-15 IU/dL. For treatment strategies, please see the UKHCDO guidelines [1].

In families where both parents are known to have heterozygous deficiency, preparation for the delivery of a potentially affected newborn includes making a careful management plan with the obstetrician and pediatrician, and avoidance of instrumental delivery. A severely affected newborn is at risk for ICH in the neonatal period.

Factor X deficiency

Factor X (FX) is a vitamin K-dependent protease and has a key role in the coagulation pathway, being the first enzyme in the common pathway and the most important activator of prothrombin. In association with factor Va and phospholipid membranes, FXa accelerates the conversion of prothrombin to thrombin 280,000-fold. The gene is located on chromosome 13 near the FVII gene to which it is closely related. FX is synthesized in the liver. The overall frequency of severe deficiency is estimated to be 1 in 1 million of the general population. Although most heterozygotes do not have any symptoms, some have a significant bleeding tendency.

Severe FX deficiency (FX <1 IU/dL) is generally a severe bleeding disorder [8]. It carries a particular risk of ICH in the neonatal period, therefore, where both parents are known to be heterozygous a delivery management plan should be prepared and the infant watched closely for evidence of ICH. Epistaxis is particularly common, and menorrhagia occurs in 50% of women. Joint bleeding can result in severe arthropathy. Prophylactic treatment for severe FX deficiency should be considered.

Mild FX deficiency is defined as 6-10 IU/dL and may be discovered incidentally. Individuals with more than 10 IU/dL and no bleeding history despite hemostatic challenge may not require replacement therapy.

Laboratory investigation

The PT and APTT are both prolonged, and the deficiency confirmed by FX assay. Several different assay methods are available (PT- or APTT-based, chromogenic, immunological). The results may vary depending upon the source of thromboplastin used, and chromogenic assays may give normal results in some dysfunctional FX variants.

Treatment

The hemostatic level for FX post-operatively is thought to be 10-20 IU/dL, and the half-life of infused FX is 60 hours. There is no FX concentrate but prothrombin complex concentrates contain FX and are effective. 1 IU/kg of FX raises the FX level by 1.5%. These concentrates are associated with a thrombotic risk and should be used with caution in those patients with additional risk factors [24]. Children with repeated joint bleeds may benefit from prophylaxis once or twice a week. FFP, preferably viral inactivated, is an alternative. As the half-life *in vivo* varies in different individuals, regular treatment and post-operative dosing should always be guided by measurement of levels.

Deficiency of vitamin K-dependent factors (II, VII, IX, X)

FII, FVII, FIX, and FX require a critical gamma-carboxylation step during synthesis to become activated. Defects in the carboxylation steps, caused by enzyme deficiencies, can produce combined deficiency of these four factors. Gene defects have been reported in gamma glutamyl carboxylase and the vitamin K epoxide reductase complex [25,26]. The defect is rare, and is inherited as an autosomal recessive disorder. It has been reported in only about 20 kindreds with variable severity between them. Severe deficiency is associated with levels of <5 IU/dL, and may present in the neonatal period (with umbilical cord bleeding or even ICH) at which time it must be distinguished from vitamin K deficiency. Milder types may present with mucocutaneous or post-surgical bleeding.

The defect also affects the other vitamin K-dependent factors, which are protein C and S, matrix Gla protein and osteocalcin. Thus, severely deficient children may also have other clinical features similar to warfarin embryopathy, such as nasal hypoplasia, distal digital hypoplasia, epiphyseal stippling, and mild conductive hearing loss.

Laboratory investigation
The PT and APTT are prolonged and the four factor levels reduced. Vitamin K deficiency and coumarin exposure must be excluded.

Treatment
Oral vitamin K therapy produces a significant improvement in many individuals, but severely affected people may require replacement therapy prior to surgery with prothrombin complex concentrates, bearing in mind the prothrombotic risks. FFP, preferably viral inactivated, has also been used for some acute bleeds.

Factor XI deficiency

Factor XI (FXI) is a dimeric serine protease whose function in coagulation is to recruit the intrinsic factor pathway after the tissue factor pathway has generated thrombin. Bleeding tendency may depend upon the levels of other coagulation factors such as FVIII:C and von Willebrand factor (vWF). The gene is on chromosome 4.

Factor XI deficiency is the commonest of the rare disorders. The deficiency is particularly common in Ashkenazi Jews where the carrier rate is 8-9%. In this population most individuals have one or both of two particular mutations, a stop codon in exon 5 (type II) and a missense mutation in exon 9 (type III) leading to reduced secretion of the molecule. In other populations the mutations are more variable, but founder mutations have been noted in the English (in as many as 1-2% of the population) and Basques.

Heterozygotes with FXI often have a bleeding risk that is not well predicted by the FXI:C level [27]. Women may have menorrhagia and bleeding after childbirth. Severely deficient individuals (FXI <10 IU/dL) have a mild bleeding tendency after surgery, especially in areas with high fibrinolytic potential such as the mouth and nose and the genitor-urinary tract. Spontaneous bleeding is rare, and hemarthroses are not a feature. The disorder rarely presents in the neonatal period. ICH has not been reported, but bleeding may occur after circumcision.

Laboratory investigation
The APTT is prolonged (reagent dependent) and the diagnosis established by FXI assay. The lower limit of the normal range is in the region of 60-70 IU/dL, therefore, the defect may be missed by the APTT. However, caution is required since heterozygotes may bleed excessively after surgery and childbirth.

Treatment
Treatment is not straightforward partly because of the variable bleeding tendency and the risks associated with the currently available FXI concentrates. These have been associated with a risk of thrombosis mainly in older patients with other risk factors. FFP, preferably viral inactivated, is an alternative but large volumes may be required. It is not clear what the hemostatic level is, although a level of 30 IU/dL is probably adequate for surgery in severe deficiency. For those with mild deficiency who have a bleeding history at baseline levels above this, it is reasonable to aim at a level of 70 IU/dL. Optimal management will, therefore, vary with individual circumstances. Another alternative treatment is rVIIa, but in a pilot study thrombotic events were also reported [28]. Dental extractions can be managed with oral tranexamic acid alone, even in those with severe deficiency. FXI concentrate is the appropriate therapy for severely deficient women during labour.

Circumcision should be delayed in infants with FXI:C <10 IU/dL at birth and the level checked at 6 months. If it is still <10 IU/dL the procedure should be performed in hospital with appropriate cover, co-ordinating with the Mohel if necessary.

Factor XII deficiency

Factor XII (FXII) deficiency does not give rise to a bleeding disorder. FXII deficiency (heterozygous) is common in the general Caucasian population (2.3% of blood donors

[29]) and is the commonest cause of an unexpected prolongation of the APTT in pre-surgical screening. Severe FXII deficiency is most common in Asians where it is usually completely asymptomatic. There is the possibility that FXII deficiency is related to thrombotic events, but recent analysis suggests that there is no association [30,31].

Factor XIII deficiency

FXIII deficiency is rare, estimated at 1 per million of the general population. As with the other rare disorders, heterozygotes are asymptomatic. Factor XIII (FXIII) is a tetramer with two 'a' chains (containing the thrombin cleavage site and a calcium binding site) and two 'b' chains which are cleaved away when FXIII is activated, in other words the 'b' unit is a carrier for the activatable 'a' unit. The activated molecule then stabilizes fibrin by cross-linking the gamma and alpha chains by the formation of lysine-glutamine links. Alpha2-plasmin inhibitor is also linked to the 'a' chains of fibrin by XIIIa. Interestingly, the subunits have different sites of synthesis and location. The 'a' subunits are located in platelets and megakaryocytes, placenta, uterus, and macrophages whereas the 'b' units are synthesized in the liver. Thus liver transplantation changes the 'b' subunit to that of the donor, leaving the 'a' unit unchanged and bone marrow transplantation does the reverse. The FXIII subunit 'a' gene is located on chromosome 6, and the 'b' gene on chromosome 1. The majority of mutations associated with FXIII deficiency have been described for the 'a' unit. [32].

The disorder shows considerable molecular heterogeneity and therefore variable clinical severity, which is discussed by Anwar et al. [32]. Affected individuals tend to bleed excessively from the umbilical stump and are at risk for ICH, which may occur in the neonatal period. Extensive skin bruising and bleeding is also common and patients may suffer muscle and joint bleeding. Pregnancy is often associated with miscarriage unless prophylaxis is given.

Laboratory investigation

All standard coagulation tests give normal results. Clot solubility is increased after coagulation with thrombin and suspension in 2% acetic acid, which is more sensitive than urea solubility. Various methods for measurement of FXIII are commercially available but the rarity of this disorder means that laboratories are unfamiliar with this test and it may be advisable to send samples to a specialist laboratory for confirmation.

Treatment

Because of the high risk of ICH, people with severe deficiency should be offered prophylaxis. FXIII concentrate is available and due to the long half-life of FXIII this only needs to be given every 4-6 weeks. Other sources of FXIII are FFP, cryoprecipitate, and stored plasma. Because of the difficulty of measuring FXIII levels it is hard to make recommendations about trough levels or hemostatic levels for surgery [1].

Conclusion

The clinical expression of the rare coagulation disorders is more variable than hemophilia and may present challenges in both diagnosis and management. Awareness of the increased risk of these disorders in appropriate population groups will prompt a higher index of suspicion and thus earlier diagnosis of severely affected infants who are at risk of serious bleeding, particularly ICH.

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Appendix 1: Clotting factor concentrates for rare bleeding disorders

BRAND	COMPANY	SITE OF MANUFACTURE	PLASMA SOURCE	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	COMMENTS
Clottagen (fibrinogen)	LFB	France	Western Europe, unpaid	Both	Cryoprecipitate, adsorption on aluminum hydroxide gel, anion exchange chromatography	TNBP/ polysorbate 80	
Fibrinogen HT	Benesis	Osaka, Japan	Japan: unpaid	Domestic	Ethanol fractionation, glycine precipitaion	TNBP / polysorbate 80; dry heat, 60° C, 72 hr; 35 nm nanofiltation	No albumin added
Fibrinogen	SNBTS	Edinburgh, Scotland	United States & Germany, unpaid	Both	Multiple precipitation, ion exchange chromatography	TNBP/ polysorbate 80; Dry heat, 80° C, 72 hr	No albumin added
FIBRORAAS (fibrinogen)	Shanghai RAAS	Shanghai, China	China: paid & unpaid apheresis	Both	Multiple fractionation	TNBP/ polysorbate 80	
Haemocomplettan P = Haemocomplettan HS (fibrinogen)	ZLB Behring	Marburg, Germany	United States, Austria, Germany; paid & unpaid	Both	Multiple precipitation	Pasteurization at 60° C, 20 hr	Albumin added
Factor VII*	Baxter BioScience	Vienna, Austria	United States, Austria, Czech Republic, Germany, Sweden: mostly paid apheresis	Both	Aluminum hydroxide absorption	Vapor heat, 60° C, 10 hr at 190 mbar then 80° C, 1 hr at 375 mbar	
Factor VII*	Bio Products	Elstree, England,	United States: paid apheresis	Both	Ion exchange chromatography	Dry heat, 80° C, 72 hr	S.A. 1.5 – 2 U/ mg protein
FACTEUR VII*	LFB	France	France: unpaid recovered & apheresis	Both	DEAE adsorption, anion exchange chromatography	TNBP/ polysorbate 80	SA 1-2 U/ mg protein; no albumin added
Factor XI	Bio Products	Elstree, England, UK	United States: paid apheresis	Both	Affinity heparin sepharose chromatography	Dry heat, 80° C, 72 hr	Heparin, Anti-thrombin III added, S.A. 3- >5 U/ mg protein
HEMOLEVEN (Factor XI)	LFB	France	Western Europe, unpaid	Both	Dialysis, cation exchange chromatography	Solvent/ detergent, 15 nm nanofiltration	Heparin, Anti-thrombin III added, C-1 esterase inhibitor added
NovoSeven = Niastase (in Canada)	Novo Nordisk	Copenhagen, Denmark	None	Both	Recombinant Factor VIIa	None	Also licensed for use in congenital deficiency of factor VII, in United States
Fibrogammin P = Fibrogammin HS (Factor XIII)	ZLB Behring	Marburg, Germany	United States, Austria, Germany: paid & unpaid	Both	Multiple precipitation	Pasteurization at 60° C, 10 hr	Albumin added

Source: Reprinted from Kasper C and Brooker M. *Registry of Clotting Factor Concentrates*, seventh edition. Montreal: Canada, WFH, 2006.

* Author's note: The three companies manufacturing plasma-derived FVII concentrates are stopping production as rFVIIa is licensed for FVII deficiency.

Appendix 2: Prothrombin complex concentrates ("PCC"; concentrates of prothrombin and factors VII, IX and X)

BRAND	COMPANY	SITE OF MANUFACTURE	PLASMA SOURCE	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	SA: F. IX, IU/ mg	COMMENTS
Proplex – T	Baxter BioScience	Los Angeles, CA, USA	United States: paid apheresis	Both	Tricalcium phosphate absorption, PEG fractionation	Exposure to 20% ethanol; dry heat, 60° C, 144 hr	> 8	Heparin added; maximum 3.5 U factor VII per IU factor IX
Prothroraas	Shanghai RAAS	Shanghai, China	China, paid/unpaid apheresis	Both	PEG precipitation, DEAE sephadex	Solvent/ detergent, nanofiltration		
Beriplex P/N	ZLB Behring	Marburg, Germany	United States, Austria, Germany paid/unpaid	Both	DEAE-sephadex	Pasteurization at 60° C, 10 hr, & nanofiltration	3.5 – 5	Contains protein C 700-900 IU per 500 IU factor IX; anti-thrombin III, heparin & albumin added
Faktor IX HS Behring	ZLB Behring	Marburg, Germany	United States, Austria, Germany; paid/unpaid	Both	DEAE-sephadex and precipitations	Pasteurization at 60° C, 10 hr	15	Contains high amount of factor X; antithrombin III and heparin added, no albumin added
Haemosolvex Factor IX	National Bioproducts	Durban, South Africa	South Africa: unpaid	Both	DEAE-sephadex	TNBP/polysorbate 80	1.5	No albumin added; heparin added
Profilnine SD	Grifols	Los Angeles, CA, USA	United States: paid pheresis	Both	Double DEAE cellulose chromatography	Solvent/detergent	4	No albumin, heparin or antithrombin III added
Prothrombinex- HT	CSL Bioplasma	Melbourne, Australia	Australia, New Zealand, Hong Kong, Malaysia, unpaid	Both	DEAE cellulose absorption	Dry heat, 80° C, 72 hr	1 – 5	No albumin added
Prothromplex-T	Baxter BioScience	Vienna, Austria	United States, Austria, Czech Republic, Germany, Sweden: mostly paid apheresis	Both	Ion exchange adsorption	Vapor heat, 60° C for 10 hr at 190 mbar, then 80° C for 1 hr at 375 mbar		Anti-thrombin III & heparin added
Bebulin VH	Baxter BioScience	Vienna, Austria	United States: paid apheresis	Export to USA	Same as above	Same as above		Heparin added
HT DEFIX	SNBTS	Edinburgh, Scotland	United States & Germany: unpaid	Both	Ion exchange chromatography	Dry heat, 80° C, 72 hr	2	Anti-thrombin III added

BRAND	COMPANY	SITE OF MANUFACTURE	PLASMA SOURCE	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	SA: F. IX, IU/ mg	COMMENTS
Octaplex	Octapharma	Vienna, Austria & Lingolsheim, France	Sweden, Austria, Germany & United States	Both	Ion exchange chromatography	TNBP/ polysorbate 80 & nanofiltration	1 or more	Heparin added, no anti-thrombin or albumin added, low factor VIIa content
Facnyne	Greencross Corp	Seoul, Korea	Korea: unpaid	Domestic	Ion exchange chromatography	TNBP/ polysorbate 80	@ 6 – 7	No albumin added
Cofact	Sanquin	Amsterdam, Netherlands	Netherlands : unpaid	Domestic	DEAE ion exchange chromatography	TNBP/polysorbate 80 & 15 nm nanofiltration		Anti-thrombin III added
PPSB-human SD/Nano 300/600	German Red Cross NSTOB	Springe, Germany	Germany: unpaid	Domestic	DEAE-sephadex, ion exchange chromatography	TNBP/ polysorbate 80 & Two nanofiltration steps, 50 nm & 15-19 nm	1	Anti-thrombin III & heparin added; no albumin added
UMAN Complex D.I.	Kedrion	Italy	Europe & United States, unpaid & paid	Both	Anion exchange: DEAE-sephadex/ sepharose chromatography	TNBP/ polysorbate 80 & Dry heat, 100^{o} C, 30 min	< 1.6	Anti-thrombin III & heparin added; no albumin added; factor II & factor X titration
KASKADIL	LFB	France	Western Europe, unpaid	Both	DEAE-sephadex absorption, anion exchange chromatography	TNBP/ polysorbate 80	0.6	

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