Guideline for the diagnosis and management of the rare coagulation disorders

A United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology

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The objective of this document is to guide diagnosis and management of patients with rare coagulation disorders (RCD). This document replaces the 2004 UK Haemophilia Centre Doctors' Organization (UKHCDO) rare coagulation disorders guideline (Bolton-Maggs *et al*, 2004a).

The RCD are here defined as monogenic bleeding disorders caused by deficiency of a soluble coagulation factor or factors, other than von Willebrand disease (VWD), Haemophilia A or Haemophilia B. The RCD described in this document include heritable deficiencies of fibrinogen, prothrombin, factor (F) V, FVII, FX, FXI and FXIII, combined FV and FVIII deficiency and vitamin K-dependent coagulation factor deficiency. RCD are usually caused by recessive inheritance of unique or rare nucleotide variations in the genes encoding the coagulation factors or in proteins necessary for their post-translational processing. RCD are more common in ethnic groups in which consanguineous partnerships are common, because of the higher likelihood of homozygosity. Dysfibrinogenaemia and FXI deficiency may show autosomal dominant or recessive inheritance (Table I). Heterozygous carriers of variations in other classically 'recessive' RCDs sometimes display bleeding symptoms.

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Methods

The writing group was representative of UK experts in RCD. Evidence was gathered from primary English language publications identified in PubMed from 1990 using the disorder names and synonyms as index terms. Relevant reviews and other guidelines were also searched for informative primary publications. The writing group produced a draft guideline that was revised by consensus by the UKHCDO Advisory Group and the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH) and the BCSH Executive Committee. The guideline was then reviewed by a sounding board of 50 members of the British Society for Haematology (BSH) who have commented on its content and applicability in the UK setting. The strength of recommendations and quality of evidence are presented in GRADE format http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html.

Overview of the rare coagulation disorders

Published descriptions of the RCD have historically comprised case reports or short series. However, initiatives, such as the European Network of Rare Bleeding Disorders (EN-RBD; Peyvandi *et al*, 2012a), the North American Rare Bleeding Disorders Registry (Acharya *et al*, 2004) and several disease-specific registries (Herrmann *et al*, 2006, 2009; Ivaskevicius *et al*, 2007; Bernardi *et al*, 2009) have improved understanding of the RCD. This has enabled the EN-RBD, under the auspices of the International Society of Thrombosis and Haemostasis to propose laboratory criteria of disease severity for most RCD (Table I; Peyvandi *et al*, 2012a).

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Table I. Summary characteristics of the rare coagulation disorders. The laboratory criteria for definition of disease severity are as proposed by the European Network of Rare Bleeding Disorders (EN-RBD), which does not specify suggested upper limits of factor activity for the rare coagulation disorders (Peyvandi *et al*, 2012b).

Disorder	Worldwide prevalence	Gene(s) involved	EN-RBD disease severity			Clinical-laboratory correlation
			Severe	Moderate	Mild	
Fibrinogen deficiency (F1D)	1:1 million (AR) Unknown (AD)	*FGA*, *FGB*, *FGB*	Undetectable	0·1–1 g/l	>1 g/l	Strong
Prothrombin deficiency (F2D)	1:2 million	*F2*	Undetectable	≤0·1 iu/ml	>0·1 iu/ml	Strong
Factor V deficiency (F5D)	1:1 million	*F5*	Undetectable	<0·1 iu/ml	≥0·1 iu/ml	Weak
Factor VII deficiency (F7D)	1:0·5 million	*F7*	<0·1 iu/ml	0·1–0·2 iu/ml	>0·2 iu/ml	Weak
Factor X deficiency (F10D)	1:1 million	*F10*	<0·1 iu/ml	0·1–0·4 iu/ml	>0·4 iu/ml	Strong
Factor XI deficiency (F11D)	1:1 million (AR) 1:30 000 (AD)	*F11*	–	–	–	Very weak
Factor XIII deficiency (F13D)	1:2 million	*F13A*, *F13B*	Undetectable	0·3 iu/ml	≥0·3 iu/ml	Strong
Factor V + VIII deficiency (F5F8D)	1:1 million	*LMAN*, *MCDF2*	<0·2 iu/ml	0·1–0·4 iu/ml	>0·4 iu/ml	Weak
Vitamin K dependent coagulation factor deficiency (VKDCFD)	1:1 million	*GGCX*, *VKORC1*	–	–	–	Weak

AR, autosomal recessive; AD, autosomal dominant.

Despite this progress, the clinical characteristics of many RCD remain incompletely documented and management is informed by open label observational studies and not randomized controlled trials. Therefore, the quality of most evidence considered in this guideline is moderate (B) or low (C) and most recommendations are weak (2). This document is intended to guide factor replacement or other therapies for most clinical scenarios. However, clinicians are expected to modify treatment plans according to the severity of individual bleeds or procedures and to the background bleeding phenotype of each case. Further guidance about laboratory evaluation, selection of therapeutic products and the management of women with RCD, including regional anaesthesia, is provided in previous UKHCDO or BCSH guidelines (Lee *et al*, 2006; Keeling *et al*, 2008).

General recommendations for the rare coagulation disorders

In common with other heritable bleeding disorders, the treatment and prevention of bleeding in the RCD requires general measures, such as avoiding high bleeding risk activities, selecting invasive procedures with the minimum bleeding risk and ensuring adequate communication of treatment plans developed by haemophilia centres with appropriate expertise. Consideration should be given to adjunctive treatments, such as topical pro-haemostatic agents and endocrine therapy for heavy menstrual bleeding (HMB; Keeling *et al*, 2008; Peyvandi *et al*, 2013). Tranexamic acid or other antifibrinolytics may be sufficient for HMB and for minor bleeds, particularly at sites such as the oropharyngeal mucosa. Tranexamic acid may also be a useful adjunct to factor replacement, but is relatively contraindicated for renal tract bleeding and in cases with high thrombotic risk. For the prevention of surgical or obstetric bleeding, oral or intravenous tranexamic acid should be administered no later than 2 h before surgery or delivery to ensure peak plasma levels at the time of haemostatic challenge. Tranexamic acid should be used cautiously with prothrombin complex concentrate (PCC) or FXI concentrate because of thrombosis risk (Bolton-Maggs *et al*, 1994; Kohler, 1999), although more recent experience of tranexamic acid in combination with activated PCC in haemophilia inhibitor patients suggests that thrombosis risk may be low (Tran *et al*, 2014). Tranexamic acid is not licensed for use in children and should be used with caution in neonates.

Selection of therapeutic products

Replacement therapies for the RCD include recombinant factor concentrates of FXIII A-subunit and activated FVII (FVIIa) and plasma-derived factor concentrates of fibrinogen, FVII, FX, FXI and FXIII (Table II). If available, specific recombinant or virally inactivated plasma-derived factor concentrates should be used in preference to fresh frozen plasma (FFP) or cryoprecipitate.

PCC are plasma-derived concentrates that are available as 'four factor' products containing FII, FVII, FIX and FX and as 'three factor' products without FVII (Table III; Keeling *et al*, 2008). PCC may be useful in prothrombin deficiency, vitamin K-dependent clotting factor deficiency and in FX and FVII deficiency if a specific factor concentrate is unavailable. The potency of most PCC is expressed as FIX activity units, but the activities of the other constituent coagulation factors may vary between products and product batches (Table III). High or repeated doses of PCC have been associated with arterial and venous thrombosis, usually in cases with pre-existing risk factors (Kohler, 1999).

FFP is the only currently available replacement therapy for FV deficiency and combined deficiency of FV and FVIII, but

Table II. Selected recombinant and plasma-derived single factor concentrates for treatment of the rare coagulation disorders. Some products have licensed indications outside the treatment of rare coagulation disorders. Descriptions of other available concentrates are summarized in the World Federation Monograph registry of Clotting Factor Concentrates http://www1.wfh.org/publications/files/pdf-1227.pdf.

Product (manufacturer)	Product licence	Manufacture and purification	Vial sizes	Recovery	Plasma half life
Riastap (Fibrinogen) CSL Behring	Treatment of bleeding in congenital hypo- or afibrinogenaemia with bleeding tendency	Multiple adsorption by $Al(OH)_3$ and glycine precipitation from non-UK plasma. Pasteurization	1 g	0·017 g/l per mg/kg	3–4 d
NovoSeven (rFVIIa) NovoNordisk	Treatment and bleeding prevention of bleeding in surgery or invasive procedures in patients with congenital FVII deficiency	Recombinant, BEK cells, immunoaffinity and anionic exchange chromatography, nanometre filtration and solvent-detergent treatment	1, 2, 5, 8 mg	0·0044 iu/ml per iu/kg	2·8 h
Factor X (FX) Bioproducts laboratories (Elstree, UK)	No	Metal chelate affinity chromatography and ion-exchange chromatography of non-UK pooled plasma. Solvent detergent, virus-filtration and dry heat	250, 500 iu	0·02 iu/ml per iu/kg	30 h
Factor XI concentrate (FXI) Bioproducts laboratories	No	Affinity heparin-sepharose chromatography from non-UK sourced pooled plasma. Dry heat	1000 iu	0·021 iu/ml per iu/kg	48 h
Hemoleven (Factor XI) LFB (Les Ulis, France)	No	Depth filtration, ion exchange chromatography of non-UK pooled plasma. Solvent detergent and nanofiltration	1000 iu	0·019 iu/ml per iu/kg	46 h
NovoThirteen (rFXIII-A) NovoNordisk	Long term prophylaxis in adult and paediatric patients with congenital factor XIII A-subunit deficiency	Recombinant, yeast. No animal components, dual filtration	2500 iu	0·017 iu/ml per iu/kg	12 d
Fibrogammin (FXIII) CSL Behring	Congenital deficiency of FXIII and resultant haemorrhagic diathesis, haemorrhages and disturbances in wound healing (250 iu)	Precipitation and ion exchange chromatography from non-UK sourced plasma. Pasteurization and ultrafiltration	250, 1250 iu	Not reported	9 d

may be effective in other RCD in emergencies if a more specific replacement therapy is unavailable or if diagnosis is uncertain. Cryoprecipitate may be effective in fibrinogen or FXIII deficiency if a single factor concentrate is unavailable (O'Shaughnessy *et al*, 2004). Should FFP or cryoprecipitate be necessary, it is currently recommended that all cases with heritable bleeding disorders receive pathogen-reduced products (Keeling *et al*, 2008). This requires virus inactivation either by methylene blue and light (MB-FFP) or solvent detergent (SD-FFP) treatments during manufacture, which may reduce FV, FVIII, FXI and fibrinogen content (Table III; Williamson *et al*, 2003). Single donor MB-FFP supplied by UK NHS Blood and Transplant (NHS-BT) is currently quality controlled for FVIII activity (Williamson *et al*, 2003). The SD-FFP product Octaplas LG® (CSL Behring, Marburg, Germany) has mean FV, FVIII and FXI activities of 0·7–0·9 iu/ml and is quality controlled to ensure activities exceed 0·5 iu/ml (Table III). The activities of other coagulation factors in SD-FFP are 0·8–1·0 iu/ml. As SD-FFP is prepared from pooled plasma donations, there is less variation in factor activities compared to single donor MB-FFP. MB-cryoprecipitate supplied by NHS-BT has an average fibrinogen content of 250 mg/unit and a minimum of 140 mg/unit. There are limited data describing the pharmacokinetics of coagulation factors administered via FFP or cryoprecipitate (Inbal *et al*, 1993; Horowitz & Pehta, 1998). Achieving therapeutic levels of coagulation factors, particularly with FFP, may be practically difficult because of the low starting concentration of factors in this product.

Fibrinogen deficiency

Description

Fibrinogen deficiency (F1D; MIM #202400) is an autosomal recessive or dominant disorder in which quantitative (afibrinogenaemia or hypofibrinogenaemia) or qualitative (dysfibrinogenaemia) defects in the fibrinogen Aα, Bβ or γ protein chains lead to reduced functional fibrinogen. Hypodysfibrinogenaemia describes F1D with both quantitative and qualitative fibrinogen defects. Afibrinogenaemia has an estimated prevalence of one in 1 000 000 (Mannucci *et al*,

Table III. Summary of selected UK prothrombin complex concentrate and unfractionated plasma products for the treatment of rare coagulation disorders.

Product (manufacturer)	Product licence	Manufacture and purification	Unit sizes	Factor content (iu)		Recovery (iu/ml per iu/kg)	Plasma half- life (h)
Beriplex P/N PCC (FII, VII, IX and X) CSL Behring	Treatment and perioperative prophylaxis in congenital deficiency of any vitamin K-dependent clotting factor when purified specific products are unavailable	Fractionation of non-UK plasma by cryoprecipitation, subsequent adsorption of vitamin K-dependent coagulation factors. Pasteurization and nanofiltration	250, 500, 1000 iu	Factor II Factor VII Factor IX Factor X	400–960 iu* 200–500 iu* 400–620 iu* 440–1200 iu*	0·022 0·024 0·016 0·02	60 4 17 31
Octaplex PCC (FII, VII, IX and X) Octapharma	Bleeding and perioperative prophylaxis in congenital deficiency of coagulation factors II and X when purified specific coagulation factor product is not available	Ion exchange chromatography, solvent detergent and nanofiltration purification of non-UK plasma	500 FIX units	Factor II Factor VII Factor IX Factor X	280–760 iu 180–480 iu 500 iu 360–600 iu	0·02 NK NK 0·017	48–60 1·5–6 20–24 24–48
Standard fresh frozen plasma NHS Blood and Transplant (Watford, UK)	No	Plasmaphaeresis of UK plasma from single whole blood donations	180–400 ml (adult)	FV FVIII Others	0·8–1·0 iu/ml 0·6–1·0 iu/ml 0·8–1·0 iu/ml	NK NK NK	NK NK NK
OctaplasLG Pathogen-reduced plasma Octapharma	Substitution in coagulation factor deficiencies when a specific coagulation factor concentrate is unavailable or in emergency situations when a precise laboratory diagnosis is not possible	Solvent detergent and ligand gel purification of non-UK pooled plasma donations	200 ml	FV, FVIII, FIX Others	0·76–0·88 iu/ml (min 0·5 iu/ml) 0·8–1·0 iu/ml	NK NK	NK NK
Pathogen reduced cryoprecipitate NHS Blood and Transplant	No	Cryoglobulin fractionation of methylene-blue treated non-UK plasma	25–50 ml per single donor	Fibrinogen	250 mg/unit (>140 mg/unit)	NK	NK

PCC, prothrombin complex concentrate; NK, not known.

*Per 500 (FIX) iu vial Beriplex, Descriptions of other available concentrates are summarized in the 2012 World Federation Monograph registry of Clotting Factor Concentrates- http://www1.wfh.org/publications/files/pdf-1227.pdf.

2004). There are no reliable estimates of the prevalence of dysfibrinogenaemia.

Pathogenesis

Fibrinogen is a complex glycoprotein comprising pairs of Aα, Bβ and γ chains and is the major ligand for the platelet αIIBβ3 integrin during platelet aggregation. Partial proteolysis of fibrinogen by thrombin enables polymerization to form fibrin clot (Weisel & Litvinov, 2013). Fibrinogen also has an anticoagulant effect, possibly by sequestering free thrombin, and contributes to fetal implantation and wound healing.

Afibrinogenaemia is caused by variations in the *FGA*, *FGB* and *FGG* genes, which encode the fibrinogen Aα, Bβ and γ chains, respectively. Afibrinogenaemia is associated with homozygous or compound heterozygous mutations and hypofibrinogenaemia is usually linked with heterozygous mutations (de Moerloose *et al*, 2013). Dysfibrinogenaemia is usually associated with heterozygous mutations in *FGA*, *FGB* or *FGG*, clustered within specific functional domains (Haverkate & Samama, 1995; Miesbach *et al*, 2010; Shapiro *et al*, 2013). Some *FGA* variations cause hereditary renal amyloidosis, which is not associated with abnormal haemostasis (Gillmore *et al*, 2009).

Afibrinogenaemia and hypofibrinogenaemia

Clinical features. In 106 cases with afibrinogenaemia or hypofibrinogenaemia in US, Iranian and Indian registries, the most common symptoms were mucocutaneous, soft-tissue, joint, genitourinary, traumatic and surgical bleeding and HMB (Peyvandi & Mannucci, 1999; Acharya *et al*, 2004; Viswabandya *et al*, 2012). Intracranial bleeding was reported in 5% of registry cases. Similar symptoms and frequent umbilical bleeding were reported in 65 cases in Iranian and Palestinian case series (Fried & Kaufman, 1980; Lak *et al*, 1999) and in an international survey of 100 cases (Peyvandi *et al*, 2006). Arterial and venous thrombosis, poor wound healing and splenic rupture are rare features of afibrinogenaemia and hypofibrinogenaemia (de Moerloose *et al*, 2013). Some types of hypofibrinogenaemia are associated with liver disease because of retention of abnormal fibrinogen in hepatocytes (Brennan *et al*, 2000).

In 26 cases with afibrinogenaemia or hypofibrinogenaemia in the EN-RBD registry, cases with severe bleeding had fibrinogen activity <0·9 g/l and asymptomatic cases had fibrinogen activity 0·2–2·0 g/l determined by the Clauss assay (Peyvandi *et al*, 2012a).

Laboratory features and diagnosis. Afibrinogenaemia and usually hypofibrinogenaemia manifest as prolonged prothrombin (PT), activated partial thromboplastin (APTT) and thrombin clotting (TCT) times and absent or reduced fibrinogen activity determined by the Clauss assay. There is a concordant reduction in fibrinogen antigen determined by immunoassay, gravimetric assays or by measurement of dry clot weight (Cunningham *et al*, 2002; Mackie *et al*, 2003). Assays that measure total clottable fibrinogen are an alternative that may assist diagnosis of F1D subtypes (Mackie *et al*, 2003). Acquired hypofibrinogenaemia is a feature of many acquired coagulopathies and can usually be distinguished from F1D on clinical grounds.

Management. Fibrinogen replacement with plasma-derived fibrinogen concentrate (Table II) may be required to treat or prevent bleeding in F1D. In afibrinogenaemia, the recovery of fibrinogen activity after infusion of fibrinogen concentrate was 0·018 g/l per mg/kg and the half-life was 80 h, but it was shorter in children aged <16 years (Manco-Johnson *et al*, 2009). Therefore, a typical dose of fibrinogen concentrate of 4–6 g is expected to increase plasma fibrinogen activity by 1·0–1·5 g/l in a 70 kg adult. In a review of case reports (Bornikova *et al*, 2011) and in a questionnaire survey of physicians treating F1D (Peyvandi *et al*, 2006), fibrinogen concentrate 50–100 mg/kg every 2–4 d, to achieve fibrinogen activity >1·0–1·5 g/l was usually sufficient to treat or prevent spontaneous or surgical bleeding. Higher and more frequent dosing was required in children and in cases with severe bleeds or having major surgery (Peyvandi *et al*, 2006; Bornikova *et al*, 2011). Venous or arterial thrombosis occurred in 30% of cases in the case report series, most with afibrinogenaemia (Bornikova *et al*, 2011). In an open label prospective study, fibrinogen concentrate was effective in 26 bleeds and 11 surgical procedures in 12 cases with F1D. Venous thrombosis occurred in one case with other thrombotic risk factors (Kreuz *et al*, 2005). Fibrinogen isoantibody formation has not been reported in F1D.

Pathogen-reduced cryoprecipitate has greater variation in fibrinogen content than fibrinogen concentrate and may be associated with transfusion reactions or volume overload (Table III: O'Shaughnessy *et al*, 2004). A typical dose of 10–20 units (500–1000 ml) of MB-cryoprecipitate is expected to increase fibrinogen activity by 0·6–1·2 g/l in a 70 kg adult. The efficacy of cryoprecipitate is similar to that of fibrinogen concentrate (Peyvandi *et al*, 2006).

Paediatric care. Afibrinogenaemia may present with intracranial haemorrhage and umbilical bleeding (Lak *et al*, 1999; Peyvandi & Mannucci, 1999). Fibrinogen activity determined by the Clauss assay was reduced and the TCT prolonged in the healthy newborn compared to adults in some (Reverdiau-Moalic *et al*, 1996) but not other (Andrew *et al*, 1987) studies. This may be because the high sialic acid content of fetal fibrinogen affects some fibrinogen activity and TCT tests (Barr, 1978; Ignjatovic *et al*, 2011). Although diagnosis of afibrinogenaemia is straightforward on cord or neonatal blood samples, diagnosis of hypofibrinogenaemia requires comparison of test results with neonatal reference intervals and on re-testing at 3–6 months.

Successful long-term prophylaxis with cryoprecipitate (Rodriguez *et al*, 1988; Peyvandi *et al*, 2006) or fibrinogen concentrate (Parameswaran *et al*, 2000; Kreuz *et al*, 2005; Peyvandi *et al*, 2006) has been reported in cases with afibrinogenaemia associated with intracranial bleeding. Typical regimens comprised fibrinogen concentrate 18–120 mg/kg, once per week to give trough fibrinogen activity of 0·5–1·0 g/l (Parameswaran *et al*, 2000; Peyvandi *et al*, 2006).

Obstetric management. Fibrinogen activity increases during normal pregnancy (Stirling *et al*, 1984). However, this does not prevent potential complications such as venous thrombosis, pregnancy loss, ante-partum haemorrhage (APH) and post-partum haemorrhage (PPH) in women with afibrinogenaemia and hypofibrinogenaemia (Goodwin, 1989; Dupuy *et al*, 2001; Roque *et al*, 2004; Kadir *et al*, 2009).

Fibrinogen replacement helps maintain pregnancy and reduces bleeding. However, reports indicate that fibrinogen concentrate 5–30 g per week in 2–3 divided doses to maintain fibrinogen activity >0·6–1·0 and >1·5 g/l at delivery and post-partum does not prevent all pregnancy complications (Bornikova *et al*, 2011), possibly because these trough levels are inadequate. Higher doses of fibrinogen concentrate are required to maintain fibrinogen activity as pregnancy progresses (Roque *et al*, 2004).

Dysfibrinogenaemia

Clinical features. In a review of 250 reported cases with dysfibrinogenaemia, 53% were asymptomatic and 26% had bleeding that was typically mucocutaneous, traumatic or surgical (Haverkate & Samama, 1995). The remaining 21% of cases had venous or arterial thrombosis (Haverkate & Samama, 1995). Similar symptoms were reported in a series of 93 cases with dysfibrinogenaemia in which incidental diagnosis after routine coagulation tests or thrombophilia screens was also common (Miesbach *et al*, 2010; Shapiro *et al*, 2013). Thrombosis and bleeding may co-exist in the same case (Haverkate & Samama, 1995).

Laboratory features and diagnosis. Dysfibrinogenaemia may manifest as a prolonged PT and/or APTT depending on test reagent and methodology. The TCT and reptilase time are usually prolonged and there is a reduction in the Clauss fibrinogen activity, typically to 0·1–0·8 g/l. Some rare variants are associated with a shortened TCT (Cunningham *et al*, 2002; Mackie *et al*, 2003). As dysfibrinogenaemia is associated with a selective functional defect in fibrinogen activity, fibrinogen antigen or total clottable fibrinogen are not reduced. There is no association between fibrinogen activity and clinical phenotype in dysfibrinogenaemia, but some genotypes correlate with either bleeding or thrombosis (Haverkate & Samama, 1995). The PT-derived fibrinogen assay is not suitable for evaluation of dysfibrinogenaemia (Mackie *et al*, 2003).

Management. There are individual reports of cases with haemorrhagic dysfibrinogenaemia receiving fibrinogen concentrate (Kreuz *et al*, 2005). Thrombotic dysfibrinogenaemia has been managed with low molecular weight heparin for thromboprophylaxis and with coumarin anticoagulation for long-term prevention of thrombosis. Fibrinogen concentrate may have an anti-thrombotic effect by increasing the proportion of normal circulating fibrinogen molecules compared to endogenous thrombotic variant molecules. However, any therapeutic effect may be offset by the increased absolute fibrinogen concentration after concentrate infusion. There are no available data to guide optimum dosing of fibrinogen concentrate in thrombotic dysfibrinogenaemia. Women with dysfibrinogenaemia experience similar pregnancy complications to women with hypofibrinogenaemia. There are isolated case reports suggesting that these may be prevented by fibrinogen replacement throughout pregnancy (Yamanaka *et al*, 2003).

Recommendations

1 **For mild bleeding or minor surgery in afibrinogenaemia, hypofibrinogenaemia or haemorrhagic dysfibrinogenaemia, consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone (2C).**
2 **For severe bleeding or major surgery in afibrinogenaemia, hypofibrinogenaemia or haemorrhagic dysfibrinogenaemia, consider fibrinogen concentrate 50–100 mg/kg, with smaller doses repeated if necessary at 2–4 d intervals to maintain fibrinogen activity >1·0 g/l (2C).**
3 **Consider long-term prophylaxis in cases with a personal or family history of severe bleeding or with fibrinogen activity <0·1 g/l using fibrinogen concentrate initially 50–100 mg/kg once per week, adjusted to maintain trough fibrinogen activity >0·5 g/l (2C).**
4 **For women with fibrinogen activity <0·5 g/l or with previous adverse pregnancy outcomes, consider prophylaxis throughout pregnancy with fibrinogen concentrate initially 50–100 mg/kg twice per week, adjusted to maintain trough fibrinogen activity >1 g/l. Consider additional fibrinogen concentrate at established labour to ensure fibrinogen activity >1·5 g/l for at least 3 d (2C).**
5 **For pregnant women with thrombotic dysfibrinogenaemia or with afibrinogenaemia or hypofibrinogenaemia and other risk factors for venous thrombosis, consider thromboprophylaxis with low molecular weight heparin (2C).**
6 **Consider pathogen-reduced cryoprecipitate 15–20 ml/kg if fibrinogen concentrate is unavailable (2C).**
7 **For cases with a dysfibrinogenaemia variant not previously associated with bleeding or thrombosis and with no personal or family history of bleeding or thrombosis, consider routine thromboprophylaxis after surgery and delivery and fibrinogen replacement only if there is abnormal bleeding (2C).**

Prothrombin deficiency

Description

Prothrombin (FII) deficiency (F2D; MIM #613679) is an autosomal recessive disorder in which reduced plasma prothrombin activity is caused by quantitative (hypoprothrominaemia) or qualitative (dysprothrombinaemia) defects in the FII protein. F2D has an estimated prevalence of one in 2 000 000 (Mannucci *et al*, 2004).

Pathogenesis

FII is activated to the serine protease thrombin by activated FX in the initiation phase of coagulation, and by the prothrombinase complex in the amplification phase. Thrombin back-activates other coagulation factors and platelets and enables fibrin generation (Roberts *et al*, 2006). F2D is caused by variations in the *F2* gene which encodes FII. There is a poor association between *F2* genotype and clinical phenotype (Lancellotti *et al*, 2013).

Clinical features

In 43 cases with F2D in the US, Iranian and Indian registries, the most common symptoms were mucocutaneous, soft tissue, joint and surgical bleeding and HMB. Less common symptoms were gastrointestinal, urinary, obstetric and umbilical bleeding. Intracranial haemorrhage was reported in 7% of registry cases (Peyvandi & Mannucci, 1999; Acharya *et al*, 2004). Similar symptoms were reported in a survey of 26 case reports (Girolami *et al*, 1998).

Bleeding caused by F2D in hypoprothrombinaemia was more severe in cases with FII activity <0·1 iu/ml than in those with FII activity >0·1 iu/ml who typically experienced mild mucocutaneous bleeding (Acharya *et al*, 2004). In dysprothrombinaemia there is a poor association between clinical and laboratory phenotypes (Akhavan *et al*, 2000). Heterozygous F2D carriers have FII activities of 0·4–75 iu/ml and are typically asymptomatic (Girolami *et al*, 1998).

Laboratory features and diagnosis

F2D manifests as prolongation of the PT and APTT and reduced FII activity determined by one-stage PT-based assay, although test results may vary by reagent. Plasma FII antigen, determined by immunoassay, is necessary to distinguish hypo- and dysprothrombinaemia (Girolami *et al*, 1998; Akhavan *et al*, 2000). Clotting endpoint assays that utilize *Echis carinatus*, Taipan and textrarin snake venoms may differentiate some dysprothrombinaemia variants (Dumont *et al*, 1987).

Acquired FII deficiency may occur in lupus anticoagulant-hypoprothrombinaemia syndrome which is distinguished from F2D on clinical grounds, PT and APTT mixing studies and the presence of antiphospholipid antibodies (Mazodier *et al*, 2012).

Management

FII replacement with PCC may be required to treat or prevent bleeding in F2D. PCC contain approximately equivalent FIX and FII activities and show FII activity recovery of 0·02 iu/ml per iu/kg and a half-life of 60 h (Table I; Ostermann *et al*, 2007). Therefore, a typical therapeutic dose of PCC 20–30 (FIX) iu/kg is expected to increase plasma FII activity by 0·4–0·6 iu/ml. Similar doses at 2–3 d intervals may be necessary for sustained treatment (Lechler, 1999). If PCC is unavailable, pathogen-reduced FFP 15–25 ml/kg is expected to increase plasma FII activity by 0·3–0·4 iu/dl. FII alloantibodies have not been reported in F2D.

Paediatric care

Intracranial and umbilical bleeding may be presenting features of F2D (Strijks *et al*, 1999; Akhavan *et al*, 2000). FII activity is 0·26–0·70 iu/ml in healthy term neonates and reaches adult values at 6 months (Andrew *et al*, 1987). Therefore, diagnosis of F2D at delivery requires comparison of test results with neonatal reference intervals or testing after routine administration of vitamin K_1 and at re-testing when 6 months old. There is limited experience of long term prophylaxis in F2D. PCC 20–40 (FIX) iu/kg every 5–7 d has been reported as effective in case reports (Todd & Perry, 2010).

Obstetric care

FII activity does not change significantly during normal pregnancy (Stirling *et al*, 1984), and usually remains insufficient for delivery in women with severe F2D. APH, pregnancy loss and PPH were identified in two case series of 22 pregnancies in women with F2D (Catanzarite *et al*, 1997; Peyvandi & Mannucci, 1999). Management had comprised PCC 20–40 iu/kg during labour (Catanzarite *et al*, 1997).

Recommendations

1 **For mild bleeding or minor surgery in F2D consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone (2C).**
2 **For severe bleeding or major surgery in F2D, consider PCC 20–40 (FIX) iu/kg with further PCC 10–20 (FIX) iu/kg at 48-h intervals if required, to maintain FII activity >0·2 iu/ml (2C).**
3 **Consider long-term prophylaxis for cases with personal or family history of severe bleeding or with FII activity <0·01 iu/ml using PCC 20–40 iu/kg once a week, adjusted to maintain trough FII activity >0·1 iu/ml (2C).**

4 **For delivery in women with FII activity <0·2 iu/ml in the third trimester, consider PCC 20–40 iu/kg once in established labour or before caesarean section to achieve FII activity 0·2–0·4 iu/ml. Consider further PCC 10–20 iu/kg at 48 h to maintain FII activity >0·2 iu/ml for at least 3 d (2C).**
5 **SD-FFP 15–25 ml/kg is an alternative if PCC is unavailable (2C).**

Factor V deficiency

Description

Factor V (FV) deficiency (F5D; MIM 227400#) is an autosomal recessive disorder in which reduced plasma FV activity is caused by quantitative or, very rarely, qualitative defects in the FV protein. F5D has an estimated prevalence of one in 1 000 000 (Mannucci *et al*, 2004).

Pathogenesis

FV is synthesized in hepatocytes and circulates approximately 80% in plasma and 20% in platelet α-granules. FV is activated by thrombin or activated FX to form a non-enzymatic cofactor for activated FX in the prothrombinase complex (Roberts *et al*, 2006). F5D is associated with variations in the *F5* gene that encodes FV, which usually abolish FV expression (Thalji & Camire, 2013). There is a poor correlation between *F5* genotype and the clinical phenotype of F5D.

Clinical features

In 105 cases with F5D in the US, Iranian and Indian registries, the most common symptoms were mucocutaneous, soft-tissue, surgical and traumatic bleeding and HMB. Less common symptoms were joint, muscle, genitourinary, gastrointestinal and umbilical bleeding (Lak *et al*, 1998; Peyvandi & Mannucci, 1999; Acharya *et al*, 2004; Viswabandya *et al*, 2012). Similar symptoms were reported in two series of 38 cases (Delev *et al*, 2009; Chapla *et al*, 2011). Intracranial bleeding occurred in 8% of registry cases and may be a presenting feature of F5D (Salooja *et al*, 2000; Mathias *et al*, 2013).

Bleeding caused by F5D was more severe in registry cases with FV activity <0·1 iu/ml than in those with FV activity >0·1 iu/ml who were typically asymptomatic or had mild mucocutaneous, surgical bleeding and HMB (Acharya *et al*, 2004; Delev *et al*, 2009; Viswabandya *et al*, 2012). In 50 cases with F5D in the EN-RBD registry, cases with severe bleeding had FV activity 0–0·19 iu/ml and asymptomatic cases had FV activity 0–0·34 iu/ml (Peyvandi *et al*, 2012b). There are reports of haemarthrosis and intracranial bleeding in cases with FV activity >0·1 iu/ml (Lak *et al*, 1998; Delev *et al*, 2009), indicating a poor association between clinical and laboratory phenotypes. Heterozygous F5D carriers have FV activity of 0·2–0·6 iu/ml and are typically asymptomatic (Acharya *et al*, 2004).

Laboratory features and diagnosis

F5D manifests as prolongation of the PT and APTT and reduced FV activity determined by one stage PT-based assay. Plasma FV antigen determined by immunoassay is required to distinguish qualitative from quantitative F5D (Murray *et al*, 1995). FV inhibitors have been reported after FFP treatment in F5D (Salooja *et al*, 2000; Lee *et al*, 2001) and after exposure to bovine FV in topical thrombin in cases without F5D (Franchini & Lippi, 2011). Acquired FV deficiency may be distinguished from F5D by PT and APTT mixing studies (Ortel, 1999).

Management

As there is currently no FV concentrate, FV replacement with FFP may be required to treat or prevent bleeding in F5D. Pathogen-reduced FFP has been recommended previously for replacement therapy in F5D, although FV activity may be lower than standard FFP (Keeling *et al*, 2008). SD-FFP (Octaplas LG®; Octapharma, Lachen, Switzerland) has FV activity of 0·7–0·9 iu/ml and less variation than single donor MB-FFP (Table III). In an open label study of 41 treatment episodes in F5D, SD-FFP 15 ml/kg increased FV activity by 0·15 iu/ml and was effective for the treatment of spontaneous or traumatic bleeds and the prevention of surgical bleeds (Horowitz & Pehta, 1998). The half-life of FV activity after FFP infusion was 16–36 h (Bowie *et al*, 1967; Thalji & Camire, 2013).

Platelet concentrates are an alternative source of FV that have been used previously in combination with SD-FFP when SD-FFP alone was ineffective (Di Paola *et al*, 2001). Off-label recombinant factor VIIa (rFVIIa) was effective in cases with allergy to FFP (Gonzalez-Boullosa *et al*, 2005; Coppola *et al*, 2010), with FV inhibitors (Divanon *et al*, 2002) or to avoid volume overload (Petros *et al*, 2008). Symptomatic FV inhibitors in F5D have been neutralized using large volumes of FFP (Di Paola *et al*, 2001) or intravenous immunoglobulin (Nesheim *et al*, 1986). Platelet transfusion was effective in acquired FV deficiency not related to F5D (Chediak *et al*, 1980). A specific FV concentrate (Kedrion Bipharma, Barga, Italy) is currently in clinical development.

Paediatric care

Intracranial bleeding is reported in neonates with F5D, usually with FV activity <0·1 iu/ml (Mathias *et al*, 2013). FV activity has a broad range of 0·36–1·08 in healthy term neonates which increases within 1 week (Andrew *et al*, 1987). Diagnosis of F5D at delivery requires comparison of test results with neonatal reference intervals and confirmation at re-testing at 6 months.

Long-term prophylaxis with SD-FFP has been reported in neonates with intracerebral bleeding or FV activity <0·01 iu/ml with FFP 20–30 ml/kg twice weekly (Salooja *et al*, 2000; Frotscher *et al*, 2012). FV prophylaxis is practically difficult and may be limited by allergy and fluid overload, particularly in neonates. In cases with severe F5D, it is seldom possible to maintain measurable trough FV activity using SD-FFP.

Obstetric care

FV activity does not change significantly during normal pregnancy (Stirling *et al*, 1984), and is usually insufficient for delivery in women with severe F5D. F5D was associated with PPH in an Iranian case series (Lak *et al*, 1998) and in a review of 25 pregnancies in women with F5D (Noia *et al*, 1997). Infusions of FFP twice daily for 3 d to maintain FV activity 0·2–0·3 iu/ml and rFVIIa have been reported as effective in preventing bleeding at caesarean delivery in women with F5D (Girolami *et al*, 2005; Coppola *et al*, 2010).

Recommendations

1 **For mild bleeding or minor surgery in F5D consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone (2C).**
2 **For severe bleeding or major surgery in F5D, consider SD-FFP 15–25 ml/kg with further SD-FFP 10 ml/kg at 12-h intervals if required, adjusted to maintain FV activity >0·15–0·20 iu/ml. Consider additional platelet transfusion for severe bleeding or major surgery (2C).**
3 **Consider short-term or long-term prophylaxis for cases with a personal or family history of severe bleeding and FV activity <0·05 iu/ml. Prophylaxis should be with SD-FFP 20 ml/kg at least twice weekly adjusted to maintain clinical response (2C).**
4 **For delivery in women with FV activity <0·2 iu/ml, consider SD-FFP 15–25 ml/kg once in established labour or before caesarean section, to achieve FV activity 0·2–0·4 iu/ml. Consider further SD-FFP 10 ml/kg at 12-h intervals to maintain FV activity >0·2 iu/ml for at least 3 d (2C).**

Factor VII deficiency

Description

Factor VII (FVII) deficiency (F7D; MIM #227500) is an autosomal recessive disorder in which reduced plasma FVII activity is caused by quantitative or qualitative defects in the FVII protein. F7D has an estimated worldwide prevalence of one in 500 000 (Mannucci *et al*, 2004).

Pathogenesis

Approximately 99% of FVII circulates as inactive zymogen and 1% as activated FVII (FVIIa), which binds tissue factor (TF) at sites of blood vessel injury. TF-FVIIa then generates further FVIIa from FVII zymogen and activates FX and FIX to enable low level thrombin generation in the initiation phase of coagulation (Roberts *et al*, 2006). F7D is caused by rare variations in the *F7* gene that encodes FVII (Herrmann *et al*, 2009). Common variations in the *F7* promoter, intron 7 and exon 8 occur in 30% of some populations and influence baseline FVII activity (Bernardi *et al*, 1997). These may cause clinical and laboratory variability in the phenotype of patients with F7D, but alone, are insufficient to reduce FVII activity to levels associated with bleeding.

Clinical features

In 217 symptomatic cases in the Greifswald F7D registry, the most common symptoms were mucocutaneous, soft tissue, joint and gastrointestinal bleeding and HMB. Intracranial bleeding was reported in 1% of symptomatic cases (Bernardi *et al*, 2009; Herrmann *et al*, 2009). Similar symptoms were reported in 225 cases with F7D in US, Iranian and Indian registries, although intracranial bleeding was reported in 3–17% (Peyvandi & Mannucci, 1999; Acharya *et al*, 2004; Viswabandya *et al*, 2012). Approximately 60% of cases in the US and Greifswald F7D registries were asymptomatic and were identified after an abnormal PT test (Acharya *et al*, 2004; Herrmann *et al*, 2009). Reports of venous thrombosis in F7D have uncertain significance (Giansily-Blaizot *et al*, 2012).

Severe bleeding was more likely in registry cases with FVII activity <0·01 iu/ml than those with FVII activity >0·01 iu/ml who typically had mild mucocutaneous bleeding or were asymptomatic (Bernardi *et al*, 2009; Viswabandya *et al*, 2012). In 203 cases with F7D in the EN-RBD registry, cases with severe bleeding had FVII activity 0–0·21 iu/ml and asymptomatic cases had FVII activity 0·15–0·35 iu/ml (Peyvandi *et al*, 2012a). However, severe bleeding is reported in some rare cases with FVII activity >0·2 iu/ml, indicating a weak association between clinical and laboratory phenotype (Peyvandi & Mannucci, 1999; Acharya *et al*, 2004; Bernardi *et al*, 2009; Peyvandi *et al*, 2012b). Amongst 626 cases with F7D in the Seven Treatment Evaluation registry, those who presented with bleeding had a higher likelihood of further bleeding than cases who presented with an abnormal laboratory test result (Di Minno *et al*, 2013). Heterozygous F7D carriers have FVII activity 0·4–0·6 iu/ml and are typically asymptomatic (Mariani *et al*, 2005; Herrmann *et al*, 2009).

Laboratory features and diagnosis

F7D manifests as a prolonged PT, normal APTT and reduced FVII activity by one stage PT-based assay. The choice of thromboplastin may influence PT and FVII activity test results (Girolami *et al*, 2012). Measurement of plasma FVII antigen by immunoassay is necessary to distinguish qualitative from quantitative F7D. Acquired FVII deficiency is very

rare disorder that is usually immune mediated and may be distinguished from F7D using PT mixing studies (Mullighan *et al*, 2004; Granger & Gidvani, 2009).

Management

Treatment or prevention of bleeding in F7D may require rFVIIa (NovoSeven®; NovoNordisk, Bagsvaerd, Denmark; Table II), which has replaced the historical alternatives of FVII concentrate, PCC or FFP. Data describing the efficacy and safety of rFVIIa from the NovoSeven Compassionate and Emergency use programmes and from independent reports were reviewed in 2006 (Mariani *et al*, 2006). More recently, in a prospective survey of 41 surgical procedures in F7D, there were three bleeds after rFVIIa treatment, but all in cases given low treatment doses. A minimum dose of rFVIIa 13 μg/kg before, and at least twice after surgery consistently prevented bleeding (Mariani *et al*, 2011). A prospective study of 79 spontaneous or traumatic bleeds in F7D showed that most bleeds resolved with a single dose of rFVIIa 60 μg/kg (Mariani *et al*, 2013). Thrombosis was not reported in these studies, but FVII inhibitors were identified in three cases.

rFVIIa infusion shortens the PT and markedly increases FVII activity by one-stage PT assay (Mariani *et al*, 2011). However, the PT and FVII activity assays do not directly reflect the haemostatic activity of rFVIIa and have limited value in monitoring treatment. The plasma half-life of rFVIIa has been estimated as 2·8 h (Berrettini *et al*, 2001), although the biological effect may be longer because of extravascular redistribution of rFVIIa (Mathijssen *et al*, 2013). FVII replacement with plasma-derived FVII concentrate 10–40 iu/kg at 4- to 6-h intervals has been reported for the treatment and prevention of bleeding in F7D. FVII concentrate has similar efficacy to rFVIIa and may be monitored using the FVII activity assay (Ferster *et al*, 1993; Mariani *et al*, 2013).

Paediatric care

Intracranial or umbilical bleeding may be the presenting feature of F7D although other bleeding in neonates is uncommon (Herrmann *et al*, 2009; Di Minno *et al*, 2013). FVII activity has a broad range of 0·28–1·04 iu/ml in healthy term neonates and increases over the first 6 months (Andrew *et al*, 1987). Therefore, diagnosis of F7D at delivery requires comparison of test results with neonatal reference intervals or testing after routine administration of vitamin K_1 or at 6 months of age.

There are reports of long-term prophylaxis in F7D using rFVIIa or FVII concentrate, mostly in cases with FVII activity <0·1 iu/ml and severe bleeding (Dike *et al*, 1980; Mariani *et al*, 2006). In 34 cases with F7D, prophylaxis with rFVIIa 30 μg/kg three times a week was more effective that less intense regimens (Napolitano *et al*, 2013).

Obstetric care

As FVII activity increases in normal pregnancy (Stirling *et al*, 1984), women with mild F7D may achieve haemostatic FVII activity by the time of delivery. However, this is unlikely in women with severe F7D (Kulkarni *et al*, 2006).

APH and pregnancy loss have been reported in F7D (Fadel & Krauss, 1989; Kulkarni *et al*, 2006) but less commonly than PPH (Kadir *et al*, 2009). In a review of case reports describing 94 live births in women with F7D, FVII replacement usually with rFVIIa, was used before 32% of deliveries especially before caesarean delivery (Baumann Kreuziger *et al*, 2013). PPH occurred in 13% of deliveries without FVII replacement, but also in 10% of deliveries with FVII replacement. Women with no history of bleeding did not experience PPH (Baumann Kreuziger *et al*, 2013).

Recommendations

1 **Cases with F7D should be identified as at a higher risk of bleeding if the FVII activity is <0·1 iu/ml or if there is another coagulopathy or a personal history of bleeding (2C).**
2 **For mild bleeding or minor surgery in higher bleeding risk cases, and for all bleeds and surgery in low bleeding risk cases, consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone (2C).**
3 **For severe bleeding or major surgery in higher bleeding risk cases, consider rFVIIa 15–30 μg/kg repeated if required every 4–6 h, usually for a minimum of three doses (2B).**
4 **Consider long-term prophylaxis for cases with a personal or family history of severe bleeding or with FVII activity <0·01 iu/ml using rFVIIa 20–40 μg/kg three times a week, adjusted to maintain clinical response (2B).**
5 **Consider short-term prophylaxis for neonates without a personal or family history of severe bleeding but who have FVII activity 0·01–0·05 iu/ml, up to 6–12 months of age (2C).**
6 **For delivery in women with FVII activity <0·2 iu/ml in the third trimester, who require caesarean delivery or who have a history of bleeding, consider rFVIIa 15–30 μg/kg every 4–6 h for at least 3 d. For all other women with F7D, consider rFVIIa 15–30 μg/kg only in response to abnormal bleeding (2C).**
7 **Plasma derived FVII concentrate 10–40 iu/kg is an alternative if rFVIIa is not available (2C).**

Factor X deficiency

Description

Factor X (FX) deficiency (F10D; MIM #227600) is an autosomal recessive disorder in which reduced plasma FX activity is

caused by quantitative or qualitative defects in the FX protein. F10D has an estimated worldwide prevalence of one in 1 000 000 (Mannucci *et al*, 2004).

Pathogenesis

FX is activated during the initiation phase of coagulation by TF-FVIIa and during the amplification phase by the tenase complex. Activated FX and its co-factor, activated FV, contribute to the prothrombinase complex (Roberts *et al*, 2006). F10D is caused by variations in the *F10* gene that encodes FX (Mannucci *et al*, 2004; Herrmann *et al*, 2006).

Clinical features

In 42 symptomatic cases in the Griefswald registry of F10D, the most common symptoms were mucocutaneous, soft tissue, joint and gastrointestinal bleeding and HMB. Intracranial bleeding was reported in 21% of the symptomatic cases (Herrmann *et al*, 2006). Similar symptoms were reported in cases with F10D in the US, Iranian and Indian registries (Peyvandi & Mannucci, 1999; Acharya *et al*, 2004; Viswabandya *et al*, 2012) and in an Iranian series of 32 cases (Peyvandi *et al*, 1998a).

Bleeding was more likely to be severe in registry cases with FX activity <0·1 iu/ml than in those with FX activity >0·1 iu/ml, who typically had mild mucocutaneous or surgical bleeding or were asymptomatic (Peyvandi *et al*, 1998a; Acharya *et al*, 2004; Herrmann *et al*, 2006; Viswabandya *et al*, 2012). In the Griefswald registry (Herrmann *et al*, 2006) and in a review of case reports (Herrmann *et al*, 2006; Rauch *et al*, 2011), intracranial, gastrointestinal and joint bleeding only occurred in cases with FX activity ≤0·02 iu/ml. In 34 cases with F10D in the EN-RBD registry, cases with severe bleeding had FX activity 0–0·39 iu/ml and asymptomatic cases had FX activity 0·29–0·83 iu/ml (Peyvandi *et al*, 2012b). Heterozygous FXD carriers have FX activities of approximately 0·5 iu/ml and are typically asymptomatic (Herrmann *et al*, 2006).

Laboratory features

F10D typically manifests as prolonged PT and APTT and reduced FX activity determined by one stage PT-based assay. The choice of thromboplastin may influence PT and FX activity test results. FX activity may also be determined using APTT and Russell viper venom activators with either clotting or chromogenic endpoints, either of which may be essential to demonstrate some rare F10D variants (Girolami *et al*, 2011). Measurement of FX antigen by immunoassay is necessary to distinguish qualitative from quantitative F10D (Girolami *et al*, 2009).

Acquired FX deficiency is reported in 9–14% of cases with AL-amyloidosis, after infection, drug exposure and in malignancy (Uprichard & Perry, 2002). In the rare immune-mediated cases, acquired FX deficiency may be distinguished from F10D using PT or APTT mixing studies. However, in AL-amyloidosis and most other settings, acquired FX deficiency is consumptive and must be distinguished from F10D on clinical grounds.

Management

FX replacement therapy with PCC or FX concentrate may be required to treat or prevent bleeding in F10D. Most PCC contain approximately equivalent FIX and FX activities and show recoveries of FX activity of approximately 0·02 iu/ml per iu/kg and a half-life of approximately 30 h (Table III; Ostermann *et al*, 2007). Therefore, a typical therapeutic dose of PCC 20–30 (FIX) iu/kg is expected to increase plasma FX activity by 0·4–0·6 iu/ml. Further infusions at 1- to 2-d intervals may be required if sustained treatment is necessary (Lechler, 1999; van Veen *et al*, 2007).

A high purity FX concentrate (Table II) is an alternative source of FX for replacement therapy, which achieved good haemostatic response after a dose of 25 iu/kg per day in a patient with F10D and shoulder haemarthrosis (Alvarez *et al*, 2010). This concentrate has recently been evaluated in an open label observational cohort study. Pathogen-reduced FFP 15–25 ml/kg is an alternative source of FX replacement if PCC is unavailable (Lechler, 1999; Brown & Kouides, 2008). FX isoantibody formation has not been reported in F10D.

Paediatric care

Intracranial bleeding and umbilical bleeding may be a presenting feature of F10D (Peyvandi & Mannucci, 1999; Acharya *et al*, 2004; Herrmann *et al*, 2006). FX activity has a broad range of 0·12–0·68 iu/ml in healthy term neonates and increases over the next 6 months (Andrew *et al*, 1987). Therefore, diagnosis of F10D at delivery requires comparison of test results with neonatal reference intervals or testing after routine administration of vitamin K_1, and confirmation at re-testing at 6 months of age.

Prophylaxis has been reported in <40 children and some adults with F10D, usually with severe bleeding and FX activity <0·05 iu/ml (Todd & Perry, 2010; Karimi *et al*, 2012). Regimens such as PCC 15–40 (FIX) iu/ml administered two or three times per week, are reported as more effective than PCC 20–70 (FIX) iu/ml, once per week (Kouides & Kulzer, 2001; McMahon *et al*, 2002; Bowles *et al*, 2009). Alternative approaches have included FX concentrate 20 iu/kg once weekly (Karimi *et al*, 2012).

Obstetric care

Although FX activity increases during normal pregnancy (Condie, 1976), levels usually remain insufficient for haemostasis at delivery in women with severe FXD (Konje *et al*, 1994; Bofill *et al*, 1996). APH, pregnancy loss and PPH were

common in reviews of 25 pregnancies in women with F10D (Girolami *et al*, 2006; Nance *et al*, 2012). There are reports of FX replacement with PCC during pregnancy in women with previous adverse pregnancy outcomes (Kumar & Mehta, 1994; Beksac *et al*, 2010) and FX replacement during labour with PCC or FFP, but with highly variable regimens (Nance *et al*, 2012).

Recommendations

1 **For mild bleeding or minor surgery in FXD consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone (2C).**
2 **For severe bleeding or major surgery in F10D, consider PCC 20–30 (FIX) iu/kg with further PCC 10–20 (FIX) iu/kg at 24-h intervals if required, adjusted to maintain FX activity >0·2 iu/ml (2C).**
3 **SD-FFP 15–25 ml/kg is an alternative if PCC is unavailable. There is insufficient evidence at present to recommend FX concentrate (2C).**
4 **Consider long-term prophylaxis for cases with a personal or family history of severe bleeding or with FX activity <0·02 iu/ml using PCC 20–30 iu/kg twice or three times a week, adjusted to maintain trough FX activity >0·01 and >0·02 iu/ml in children (2C).**
5 **For delivery in women with FX activity <0·3 iu/ml in the third trimester who have a history of bleeding and all those who require caesarean section, consider PCC 20–40 iu/kg to achieve FX activity >0·4 iu/ml. Consider further PCC 10–20 iu/kg once daily to maintain FX activity >0·3 iu/ml for at least 3 d (2C).**

Factor XI deficiency

Description

Factor XI (FXI) deficiency (F11D; MIM #612416) is an autosomal recessive or dominant disorder in which reduced plasma FXI activity is caused by quantitative or, very rarely, by qualitative defects in the FXI protein. Previous sources have estimated the prevalence of 'autosomal recessive' F11D as one in 1 000 000 and 'autosomal dominant' F11D as one in 30 000 worldwide (Mannucci *et al*, 2004). These terms should be considered with caution in F11D because of the occurrence of dominant negative variants with laboratory and clinical phenotypes in heterozygotes. The prevalence of F11D is higher in Jewish and some other populations (Shpilberg *et al*, 1995; Zivelin *et al*, 2002; Bolton-Maggs *et al*, 2004b; Gueguen *et al*, 2012; Kim *et al*, 2012).

Pathogenesis

Zymogen FXI circulates as a homodimer that is activated on the platelet surface by thrombin during the initiation phase of coagulation. Activated FXI then enhances FIX activation to enable sustained thrombin generation (Roberts *et al*, 2006). FXI also enables thrombin generation after clot formation, leading to activation of the anti-fibrinolytic thrombin-activatable fibrinolysis inhibitor (TAFI) (von dem Borne *et al*, 1997).

F11D is cause by variations in the *F11* gene that encodes FXI (Berber, 2011). In the Askenazi Jewish population, one in 11 individuals are heterozygous (FXI activity 0·5–0·7 iu/ml) and one in 450 are homozygous or compound heterozygous (FXI activity <0·1 iu/ml) for two common *F11* variations that reduce FXI protein expression (Asakai *et al*, 1991). Some *F11* variations are dominant negative because they cause intracellular retention of FXI dimers (Kravtsov *et al*, 2005). Heterozygous carriers of these variations may show FXI activity <0·25 iu/ml and may have mild bleeding.

Clinical features

In two UK series of 128 cases with F11D, approximately 65% were asymptomatic. In the remainder, the most common symptoms were bleeding after surgery and trauma (Bolton-Maggs *et al*, 1988, 1995). Bleeding was more likely after dental, oropharyngeal or urogenital surgery compared to musculoskeletal or gastrointestinal surgery (Salomon *et al*, 2006) but there is conflicting evidence about circumcision (Bolton-Maggs *et al*, 1988; Salomon *et al*, 2006). HMB and post-partum haemorrhage are common in women with F11D (Bolton-Maggs *et al*, 1995; Kadir *et al*, 1999; Salomon *et al*, 2005). Spontaneous bleeding and intracranial bleeding are very uncommon.

The likelihood of surgical bleeding in F11D is greatest with FXI activity <0·2 iu/ml. However, some cases with FXI activity <0·2 iu/ml never bleed excessively after surgery (Bolton-Maggs *et al*, 1995), and others experience surgical bleeding despite higher FXI activity (Ragni *et al*, 1985). In 125 cases with F11D in the EN-RBD registry, cases with severe bleeding had FXI activity 0·09–0·41 iu/ml and asymptomatic cases had FXI activity 0·14–0·39 iu/ml (Peyvandi *et al*, 2012b), confirming a weak correlation between FXI activity and clinical phenotype. Some phenotypic variation in F11D may be caused by co-inheritance of VWD (Tavori *et al*, 1990) or platelet disorders (Winter *et al*, 1983).

Laboratory features and diagnosis

F11D typically manifests as a prolongation of the APTT and reduced FXI activity determined by one-stage APTT assay. However, some APTT reagents may be insensitive to FXI activities 0·5–0·7 iu/ml, which is associated with bleeding in some cases. Therefore, consider FXI activity assay even if the APTT is normal in patients with bleeding. Measurement of FXI antigen by immunoassay is necessary to distinguish qualitative from quantitative F11D (Ragni *et al*, 1985).

Management

As spontaneous bleeding is uncommon in F11D, management usually comprises treatment of traumatic bleeds and prevention of surgical or obstetric bleeding. Although FXI activity is a weak predictor of bleeding, other predictors include additional coagulopathy, bleeding and dental, oropharyngeal or urogenital surgery (Collins *et al*, 1995; Brenner *et al*, 1997; Salomon *et al*, 2006; Myers *et al*, 2007).

There are two unlicensed FXI concentrates (Table II; Bolton-Maggs *et al*, 1992; Burnouf-Radosevich & Burnouf, 1992) that are available in some countries on a named case basis. The approximate recovery of FXI activity from FXI concentrate is 0·02 iu/ml per iu/kg and the plasma half-life is 50 h (Bolton-Maggs *et al*, 1992). Therefore, a typical therapeutic dose of FXI concentrate, 10–20 iu/kg, is expected to increase FXI activity by 20–40 iu/ml, which is sufficient for haemostasis for most procedures without the need for repeat infusion. Early reports of thrombosis with FXI concentrate (Bolton-Maggs *et al*, 1994; Mannucci *et al*, 1994; Briggs *et al*, 1996; Aledort *et al*, 2005) were addressed by including heparin and antithrombin in FXI concentrate formulations and by recommendations that individual doses should not exceed 30 iu/kg, give peak FXI activity >0·7 iu/ml or be used with anti-fibrinolytic drugs (Bolton-Maggs *et al*, 2004a). In subsequent UK case series of 134 surgical procedures managed with FXI concentrate, there were only two reports of thrombosis (O'Connell *et al*, 2002a; Batty *et al*, 2013). However, a more recent report suggests that these measures were insufficient to eliminate all thrombotic complications (Bolton-Maggs *et al*, 2014), suggesting that FXI concentrate should be considered at more conservative doses and only in scenarios of high bleeding risk where other approaches are likely to be insufficient. Pathogen-reduced FFP is an alternative FXI concentrate in F11D that is not associated with thrombosis (Bolton-Maggs *et al*, 2004a; Keeling *et al*, 2008). The commercially available pooled SD-FFP has less variation in FXI content than single donor MB-FFP and has a mean FXI activity 0·7–0·9 iu/ml (Table III).

Tranexamic acid is usually sufficient to prevent bleeding in minor procedures (Berliner *et al*, 1992) or for HMB (Lee *et al*, 2006) in F11D, but should not be co-administered with FXI concentrate because of thrombosis risk. Off-label rFVIIa was effective in several reported cases (Lawler *et al*, 2002; O'Connell *et al*, 2002b; Brown, 2005; Schulman & Nemeth, 2006) but has been associated with thrombosis (O'Connell *et al*, 2002b; Kenet *et al*, 2009).

FXI inhibitors

FXI inhibitors after FXI replacement are described in case reports (Ginsberg *et al*, 1993; Teruya & Styler, 2000) and were identified in seven of 188 surveyed cases with F11D (Salomon *et al*, 2003), all homozygous for the *F11* Glu 135* variation that is common in Ashkenazi Jews. FXI inhibitors may increase surgical bleeding and reduce responses to FXI replacement, may be detected using APTT mixing studies and quantified using a modified Bethesda assay (Salomon *et al*, 2003). Reported interventions include immunosuppression (Teruya & Styler, 2000), plasma exchange (Teruya & Styler, 2000). rFVIIa 15–30 μg/kg in combination with tranexamic acid prevented bleeding in major surgery in cases with FXI inhibitors, without venous thrombosis (Kenet *et al*, 2009; Livnat *et al*, 2009).

Paediatric care

FXI activity in healthy term neonates has a broad range of 0·1–0·68 iu/ml and increases over 6 months (Andrew *et al*, 1987). Therefore, diagnosis of F11D at delivery requires comparison of test results with neonatal reference intervals and confirmation at re-testing at 6 months of age.

Spontaneous bleeding is not reported in the newborn with F11D. However, religious circumcision is usually performed on male Jewish infants at 8 d of age and has been associated with bleeding, sometimes severe, in 19% of infants in a UK series (Collins *et al*, 1995) and in <2% in an Israeli series (Salomon *et al*, 2006). Treatment with tranexamic acid alone is sufficient to prevent severe bleeding in most infants after day-8 circumcision, although in some centres it is the practice to avoid tranexamic acid in this age group and use FFP alone as an alternative.

Obstetric care

There is poor consensus about whether FXI activity changes in normal pregnancy (Kadir *et al*, 2009). In two case series of 133 pregnancies in women with F11D, PPH occurred in 15% of women (Kadir *et al*, 1998; Myers *et al*, 2007). Obstetric bleeding correlated poorly with baseline FXI activity but was more common in women with a history of bleeding (Myers *et al*, 2007). A detailed review of bleeding risk and management is provided in a previous UKHCDO guideline (Lee *et al*, 2006).

Recommendations

1 **Cases with F11D should be identified as at a higher risk of bleeding if the FXI activity is <0·1 iu/ml or if there is another coagulopathy, a personal history of bleeding or if surgery comprises dental extraction or involves the oropharyngeal or genitourinary mucosa (2C).**
2 **Cases with FXI activity <0·1 iu/ml should be screened for FXI inhibitors before surgery or childbirth, if they have had previous FXI replacement therapy (2B).**
3 **For minor bleeds or minor surgery in higher bleeding risk cases, and for all bleeds or surgery in low bleeding risk cases, consider tranexamic acid 15–20 mg/kg or 1 g four times daily for 5–7 d (2C).**
4 **For severe bleeds or major surgery in high bleeding risk cases, consider an initial dose of FXI concentrate**

10–15 iu/kg, without additional tranexamic acid. A combination of SD-FFP 15–25 ml/kg and tranexamic acid 15–20 mg/kg or 1 g four times daily is an alternative to FXI concentrate (2C).

5 **For delivery in all women with factor XI activity <0·15 iu/ml in the third trimester, consider FXI concentrate 10–15 iu/kg or SD-FFP 15–25 ml/kg and tranexamic acid 15–20 mg/kg at established labour or before caesarean section (2C).**

6 **For delivery in women with FXI activity 0·15–0·7 iu/ml in the third trimester and a history of bleeding or no previous haemostatic challenges, consider tranexamic acid 15 mg/kg or 1 g four times a day continued for at least 3 d (2C).**

7 **For delivery in women with FXI activity 0·15–0·7 iu/ml in the third trimester and no bleeding despite haemostatic challenges, only consider FXI concentrate or antifibrinolytics if abnormal bleeding occurs (2C).**

Factor XIII deficiency

Description

Factor XIII (FXIII) deficiency (F13D; MIM#613225 and 613235) is an autosomal recessive disorder in which reduced plasma FXIII activity is caused by quantitative or, rarely, by qualitative defects in the FXIII A-subunit protein. Much less commonly, F13D is caused by quantitative defects in the FXIII B-subunit protein. F13D has an estimated worldwide prevalence of one in 2 000 000 (Mannucci *et al*, 2004).

Pathogenesis

FXIII circulates in plasma as a heterotetramer comprising two catalytic A subunits and two carrier B-subunits and in platelets and monocytes as A-subunit homodimers. FXIII is activated by thrombin to form free activated A subunits which covalently crosslink fibrin chains, increasing clot strength, and crosslink fibrin to α2-antiplasmin, reducing fibrinolysis. Activated FXIII also contributes to tissue repair and embryonic implantation (Schroeder & Kohler, 2013a). F13D is caused by variations in the *F13A* gene that encodes the FXIII A-subunit (Schroeder & Kohler, 2013b) or in *F13B,* which encodes the FXIII B-subunit (Ivaskevicius *et al*, 2010a). There is a poor correlation between *F13A* or *F13B* genotype and the clinical phenotype of each disorder (Ivaskevicius *et al*, 2007).

Clinical features

In an international registry of 104 cases with FXIII-A subunit deficiency, the most common symptoms were soft tissue, umbilical, surgical, joint and intracranial bleeding which occurred in 34% of cases. Less common symptoms included oral, genitourinary and gastrointestinal bleeding. Only 3% of cases were asymptomatic (Ivaskevicius *et al*, 2007). Similar symptoms were identified in other registries (Acharya *et al*, 2004; Viswabandya *et al*, 2012) and in a case series (Lak *et al*, 2003). HMB and intra-abdominal bleeding at first ovulation are common in women with F13D (Ivaskevicius *et al*, 2007; Sharief & Kadir, 2013). Cases with F13D may also have poor wound healing (Ivaskevicius *et al*, 2007). F13D caused by FXIII B-subunit deficiency is associated with mild mucocutaneous or surgical bleeding (Ivaskevicius *et al*, 2007, 2010a).

In 33 cases with F13D in the EN-RBD registry, cases with severe bleeding had plasma FXIII activity 0–0·11 iu/ml and asymptomatic cases had FXIII activity 0·11–0·51 iu/ml (Peyvandi *et al*, 2012a). Heterozygous F13D carriers have plasma FXIII activity 0·2–0·7 iu/ml and sometimes display mild bleeding symptoms (Ivaskevicius *et al*, 2010b) although the significance of this has been questioned (Mannucci, 2010). Acquired F13D has been reported in patients with cardiac surgery, inflammatory bowel disease and Henoch-Schonlein purpura and is rarely associated with *de novo* FXIII inhibitors (Boehlen *et al*, 2013).

Laboratory features and diagnosis

F13D manifests as normal PT, APTT and TCT but reduced plasma FXIII activity, determined using ammonia release or amine incorporation assays (Kohler *et al*, 2011). Both activity assays have a lower limit of detection of FXIII activity of 0·03–0·05 iu/ml (Kohler *et al*, 2011). The ammonia release assay may overestimate FXIII activity in plasma, unless there is subtraction of a plasma blank (Ajzner & Muszbek, 2004).

An immunoassay for the FXIII-A subunit is an alternative initial test to detect F13D. Immunoassays for both FXIII subunits are required to differentiate FXIII A-subunit from B-subunit deficiency and to identify qualitative FXIII A-subunit deficiency variants (Ajzner & Muszbek, 2004). Detection of low FXIII activity in plasma, but not in platelet lysates, supports a diagnosis of FXIII B-subunit deficiency. Clot solubility FXIII assays are poorly standardized, may be sensitive only to severe F13D and are not recommended (Kohler *et al*, 2011).

F13D can usually be distinguished from acquired FXIII deficiency on clinical grounds. Autoimmune acquired FXIII deficiency may be detected using mixing studies and by showing preserved FXIII activity in platelet lysates (Ajzner & Muszbek, 2004).

Management

Given that intracranial bleeding is common in F13D and may be a presenting feature later in childhood, most cases receive long-term prophylaxis with FXIII concentrate. This has been shown in registry and observational studies to be a highly effective means of preventing intracranial and other life threatening bleeds.

The plasma-derived FXIII concentrate (pdFXIII; Fibrogammin®/Corifact™; CSL Behring; Table II) has a half-life in plasma of 7 d, enabling haemostatic FXIII activity to be maintained with prophylaxis every 28 d. In a prospective, open label study of 41 cases with F13D, pdFXIII, initially at 40 iu/kg every month adjusted to maintain FXIII activity >0·05–0·2 iu/ml, abolished spontaneous bleeding including intracranial haemorrhage, and was associated with no significant adverse events (Nugent, 2012). The European and North American manufacturers' recommended doses for prophylaxis with pdFXIII are 10 and 40 iu/kg respectively, every 28 d.

Recombinant FXIII concentrate (rFXIII; NovoThirteen®; NovoNordisk; Table II) is a recombinant human FXIII A-subunit that increases plasma FXIII activity with similar pharmacokinetics to pdFXIII in cases with FXIII A-subunit deficiency (Lovejoy *et al*, 2006). In a prospective, open label, phase 3 prophylaxis trial in 41 cases with FXIII A-subunit deficiency, rFXIII 35 iu/kg per month abolished spontaneous bleeds and was associated with no significant adverse events (Inbal *et al*, 2012). The manufacturer's recommended dose for prophylaxis is rFXIIIa is 35 iu/kg every 28 d. rFXIII concentrate is unsuitable for prophylaxis in F13D B-subunit deficiency. Standard and pathogen-reduced FFP, cryoprecipitate and platelet concentrates are alternative sources of FXIII (O'Shaughnessy *et al*, 2004) that may be clinically useful for emergency replacement therapy if a FXIII concentrate is unavailable.

Paediatric care

FXIII activity in healthy term neonates has a broad range of 0·27–1·31 iu/ml and increases in the first week of life (Andrew *et al*, 1987). Therefore, diagnosis of F13D is straightforward in cord or neonatal blood samples using an assay sensitive to FXIII activity <0·1 iu/ml. As F13D may present with intracranial bleeding in neonates or older children (Ivaskevicius *et al*, 2007), there is a strong indication for prophylaxis from the point of diagnosis.

Obstetric care

Rates of pregnancy loss in women with F13D were reported previously as >90% (Burrows *et al*, 2000). However, with prophylaxis there are now numerous reports of successful term pregnancies (Sharief & Kadir, 2013). FXIII activity decreases during normal pregnancy (Sharief *et al*, 2013). In pregnant women with F13D, increased prophylaxis is required to maintain FXIII activity to ensure haemostasis and maintain pregnancy (Asahina *et al*, 2007). Additional FXIII replacement therapy is usually required in women at the start of labour to prevent PPH (Asahina *et al*, 2007; Sharief & Kadir, 2013). There is no evidence to inform target FXIII activities during delivery.

Recommendations

1 Diagnosis and monitoring of F13D requires a FXIII activity assay that enables accurate measurement of FXIII activity <0·1 iu/ml (2C).

2 We recommend long-term prophylaxis with FXIII concentrate in all cases with F13D and a personal or family history of bleeding and those with plasma FXIII activity <0·1 iu/ml. Prophylaxis should start with FXIII concentrate 20–40 iu/kg every 28 d, adjusted to maintain trough FXIII activity 0·1–0·2 iu/ml (2B).

3 Consider prophylaxis with rFXIII concentrate rather than pdFXIII in cases with FXIII A-subunit deficiencies that have not previously been exposed to plasma products (2C).

4 For mild bleeding or minor surgery in F13D consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone (2C).

5 For severe bleeding or major surgery in F13D, consider additional FXIII concentrate 10–40 iu/kg depending on the interval since last prophylaxis and severity of bleeding (2C).

6 We recommend that women with F13D on prophylaxis with FXIII concentrate are monitored closely throughout pregnancy and that prophylaxis is increased in frequency to every 14–21 d to maintain FXIII activity >0·2 iu/ml. For delivery, consider additional FXIII concentrate 10–40 iu/kg once in established labour or before caesarean section, depending on the interval since last prophylaxis (2C).

Combined factor V and factor VIII deficiency

Description

Combined Factor V and VIII deficiency (F5F8D; MIM #227300 and #61362522) is an autosomal recessive disorder in which reduced activity of both FV and FVIII is caused by defects in lectin mannose-binding protein 1 (*LMAN1*) or multiple coagulation factor deficiency protein 2 (*MCFD2*). F5F8D has an estimated prevalence of one in 2 000 000 (Mannucci *et al*, 2004).

Pathogenesis

Intracellular transport of FV and FVIII during synthesis requires a vesicular receptor that comprises LMAN1 and MCFD2 (Zheng *et al*, 2010). F5F8D is caused by variations in the *LMAN1 or MCFD2* genes, which encode LMAN1 and MCFD2, respectively. *MCFD2* mutations are associated with lower FV and FVIII activities than *LMAN1* variations, but are associated with a similar clinical phenotype (Zhang *et al*, 2008).

Clinical features

F5F8D is typically a mild or moderate bleeding disorder associated with mucocutaneous, traumatic and surgical

bleeding and HMB (Seligsohn *et al*, 1982; Peyvandi & Mannucci, 1999; Mansouritorgabeh *et al*, 2004; Viswabandya *et al*, 2012). Spontaneous muscle and joint bleeds are rare in most case series. Intracranial, gastrointestinal and umbilical bleeding are very rare (Seligsohn *et al*, 1982; Peyvandi *et al*, 1998b; Viswabandya *et al*, 2010). In 18 cases with F5F8D in the EN-RBD registry, cases with severe bleeding had FV and FVIII activities of 0–0·37 iu/ml and asymptomatic cases had FV and FVIII activities 0·25–0·62 iu/ml (Peyvandi *et al*, 2012b), indicating a poor correlation between clinical and laboratory phenotypes. The bleeding phenotype of heterozygous F5F8D carriers is not reported.

Laboratory features and diagnosis

F5F8D typically manifests as prolongation of both the PT and APTT and an approximately concordant reduction in FV and FVIII activities, typically 0·05–0·2 iu/ml (Zhang *et al*, 2008) and rarely <0·05 iu/ml (Peyvandi *et al*, 1998b).

Management

Replacement therapy F5F8D is usually only required to treat traumatic bleeding or to prevent surgical or obstetric bleeding. Available therapies include SD-FFP which contains FV and FVIII activities of 0·7–0·9 iu/ml. Therefore infusion of a typical dose of 15–25 ml/kg FFP is expected to achieve haemostatic FV activity in most cases, but may be insufficient for FVIII activity (Horowitz & Pehta, 1998). The plasma half-life of FVIII is also approximately 10–14 h compared with 16–36 h for FV (Bowie *et al*, 1967; Thalji & Camire, 2013). Therefore, SD-FFP should be administered with an additional source of FVIII to achieve and maintain haemostatic FVIII activity (Bolton-Maggs *et al*, 2004a; Mannucci *et al*, 2004; Spreafico & Peyvandi, 2008). Previous approaches have included recombinant FVIII (rFVIII) concentrate (Ueno *et al*, 1991; Mansouritorghabeh *et al*, 2009; Oukkache *et al*, 2012) and desmopressin (Bauduer *et al*, 2004; Guglielmone *et al*, 2009). rFVIIa has been reported as effective for bleeding when FFP was either ineffective (Di Marzio *et al*, 2011) or was associated with severe allergy (Lechner *et al*, 2010).

Transient low level FV and FVIII inhibitors have been reported as common in some cases with F5F8D and may respond to high dose FFP or intravenous immunoglobulin (Spreafico & Peyvandi, 2008).

Paediatric care

F5F8D very rarely presents with bleeding in neonates (Abdullah *et al*, 2013). FV and FVIII activities in healthy term neonates are 0·36–1·08 and 0·61–1·39 iu/ml, respectively, with FV activity increasing further within 1 week (Andrew *et al*, 1987). Therefore, diagnosis of F5F8D is straightforward in cord or neonatal blood samples. There are no reports of prophylaxis in F5F8D.

Obstetric care

During normal pregnancy FV remains unchanged but FVIII increases progressively (Stirling *et al*, 1984). In women with F5F8D, this may restore FVIII activity, but FV activity usually remains insufficient for haemostasis at delivery (Oukkache *et al*, 2012). F5F8D has been associated with PPH (Seligsohn *et al*, 1982; Peyvandi *et al*, 1998b) that has been managed with FFP, rFVIII concentrate and desmopressin (Oukkache *et al*, 2012) or rFVIII concentrate alone (Hoffmann *et al*, 2013).

Recommendations

1 **For mild bleeding or low risk surgery in F5F8D, consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone (2C).**
2 **For severe bleeding or high risk surgery in F5F8D, consider FV and FVIII replacement with SD-FFP 15–25 ml/kg with supplementary FVIII replacement with rFVIII 20–40 iu/kg or desmopressin 0·3 μg/kg and further treatment at 12-h intervals, adjusted to maintain FV activity >0·15 iu/ml and FVIII activity >0·5 iu/ml (2C).**
3 **For delivery in women with FV activity <0·2 iu/ml in the third trimester, consider SD-FFP 15–25 ml/kg once in established labour or before caesarean section to achieve FV activity 0·2–0·4 iu/ml. Consider further SD-FFP 10 ml/kg once every 12 h to maintain FV activity >0·2 iu/ml for at least 3 d. Consider additional rFVIII if the FVIII activity is <0·5 iu/ml in the third trimester (2C).**

Vitamin K-dependent coagulation factor deficiency

Description

Vitamin K-dependent coagulation factor deficiency (VKDCFD; MIM #277450 and #607473) is an autosomal recessive disorder in which reduced activities of FII, FVII, FIX, FX and other vitamin K-dependent proteins is caused by defects in the γ-glutamyl carboxylase (GGCX; type I VKDCFD) protein or in subunit 1 of vitamin K epoxide reductase protein (VKORC1: type II VKDCFD). VKDCFD has been reported in less than 30 families worldwide.

Pathogenesis

During synthesis, the vitamin K-dependent coagulation factors undergo γ-carboxylation by GGCX and the cofactor vitamin K hydroquinone (KH_2), which is oxidized to vitamin K 2,3 epoxide (KO) during γ-carboxylation. KO then undergoes reciprocal de-epoxidation by VKOR to restore KH_2 (Presnell & Stafford, 2002).

VKCDFD is caused by variations in the *GGCX* and *VKORC1* genes, which encode GGCX and subunit 1 of the VKOR complex, respectively (Brenner *et al*, 1998; Rost *et al*, 2004a). These result in loss of carboxylase activity and the synthesis of FII, FVII, FIX and FX and other vitamin K dependent-proteins, with reduced function. Other heterozygous nucleotide variations in *VKORC1* are associated with heritable coumarin resistance (OMIM #122700) (Rost *et al*, 2004a).

Clinical features

VKDCFD may present at birth with intracranial or umbilical bleeding (Oldenburg *et al*, 2000; Spronk *et al*, 2000) or in infancy or childhood with joint, mucocutaneous, soft tissue or gastrointestinal bleeding (Brenner *et al*, 1998). Less commonly, VKDCFD presents with bleeding in early adulthood (Lunghi *et al*, 2011) or is an incidental laboratory finding (Rost *et al*, 2004b). The VKDCFD phenotype may be modified by vitamin K intake or absorption (Brenner *et al*, 1998). There is no close correlation between clinical phenotype and the activities of FII, FVII, FIX and FX.

VKCDFD may also be associated with nasal hypoplasia, brachydactyly and conductive hearing loss, which are similar to warfarin embryopathy (Pauli *et al*, 1987) or with a pseudoxanthoma elasticum-like phenotype (Vanakker *et al*, 2007). These features may be caused by defective γ-carboxylation of osteocalcin and matrix-Gla (Pauli *et al*, 1987).

Laboratory features and diagnosis

VKCDFD typically manifests as prolongation of the PT and APTT and approximately parallel reductions in the activities of FII, FVII, FIX and FX. Factor activities may be <0·1 iu/ml at presentation (Brenner *et al*, 1998; Spronk *et al*, 2000) but more typically are 0·2–0·6 iu/ml (Oldenburg *et al*, 2000; Rost *et al*, 2004b; Lunghi *et al*, 2011).

VKCDFD may be distinguished from acquired vitamin K deficiency or exposure to coumarin anticoagulants by demonstrating normal fasting serum KH_2 concentration. Circulating KO is normally undetectable in VKCDFD type I at baseline, and after vitamin K supplementation. However, in VKCDFD type II, vitamin K supplementation causes a marked elevation in KO (Oldenburg *et al*, 2000).

Management

Most reported cases with VKDCFD show partial or complete long term restoration of coagulation factor activities with oral (Oldenburg *et al*, 2000; Spronk *et al*, 2000; Rost *et al*, 2004b) or parenteral (Brenner *et al*, 1998; McMahon & James, 2001; Marchetti *et al*, 2008) vitamin K_1 (phytomenadione). In a minority of cases, vitamin K_1 was ineffective (Lunghi *et al*, 2011). FFP and three-factor PCC with FVII concentrate are reported as effective for the treatment or short-term prevention of bleeding (Brenner *et al*, 1998; McMahon & James, 2001).

Paediatric care

VKDCFD may cause intracranial bleeding in neonates but may be difficult to distinguish from vitamin K deficiency bleeding. The lower limit of the reference intervals for FII, FVII, FIX and FX activities are 0·12–0·28 iu/ml in healthy term neonates and increase over 6 months (Andrew *et al*, 1987). Therefore, diagnosis at birth requires comparison of test results with neonatal reference intervals and confirmation at re-testing at 6 months old.

Infants and children receiving long term vitamin K_1 prophylaxis, who have partially restored coagulation factor levels, may experience worsening coagulopathy and bleeding during treatment with antibiotics or anticonvulsants because of impaired vitamin K absorption or metabolism (Brenner *et al*, 1998).

Obstetric care

The activities of FVII and FX usually increase and FII and FIX remain unchanged in normal pregnancy (Kadir *et al*, 2009). There is a single report of pregnancy in an individual with VKDCFD type II who displayed a partial restoration of coagulation factor activities with vitamin K_1 15 mg/d throughout pregnancy (McMahon & James, 2001). There are no previous reports of factor replacement therapy before delivery in women with VKDCFD.

Recommendations

1 **Long term prevention of bleeding should start at diagnosis of VKDCFD with oral vitamin K_1 (phytomenadione) 5–20 mg/d. In poor responders, consider parenteral vitamin K_1 5–20 mg/week (2C).**
2 **For mild bleeding or minor surgery in VKDCFD, consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone (2C).**
3 **For severe bleeding or major surgery in VKDCFD, consider four-factor PCC 20–30 (FIX) iu/kg with vitamin K_1 5–20 mg. FFP 15–25 ml/kg is an alternative if four-factor PCC is unavailable (2C).**
4 **For delivery in women with activities of any of the VKDCFD <20 iu/ml in the third trimester, consider four-factor PCC 20–30 (FIX) iu/kg once in established labour or before caesarean section, for at least 3 d (2C).**

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Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BCSH current guidelines website (http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html) if it becomes obsolete. If new recommendations are made an addendum will be published on the BCSH guidelines website. If minor changes are required due to changes in level of evidence or significant additional evidence supporting current recommendations, a new version of the current guidance will be issued on the BCSH website (http://www.bcshguidelines.com/).

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