Rare Bleeding Disorders in Children: Identification and Primary Care Management

abstract

Bleeding symptoms are common in healthy children but occasionally may indicate an underlying congenital or acquired bleeding diathesis. The rare bleeding disorders (RBDs) comprise inherited deficiencies of coagulation factors I (congenital fibrinogen deficiencies), II, V, VII, X, XI, and XIII and combined factor deficiencies, most notably of factors V and VIII and of vitamin K–dependent factors. These disorders often manifest during childhood and may present with recurrent or even serious or life-threatening bleeding episodes, particularly during the neonatal period. Accordingly, primary care and other nonhematologist pediatric providers should be familiar with the clinical presentation and initial evaluation of these rare disorders. Bleeding manifestations generally vary within the same RBD and may be indistinguishable from 1 RBD to another or from other more common bleeding disorders. Serious bleeding events such as intracranial hemorrhage may be heralded by less serious bleeding symptoms. The results of initial coagulation studies, especially prothrombin time and activated partial thromboplastin time, are often helpful in narrowing down the potential factor deficiency, with factor XIII deficiency being an exception. Consultation with a hematologist is advised to facilitate accurate diagnosis and to ensure proper management and follow-up. The approach to bleeding episodes and invasive procedures is individualized and depends on the severity, frequency, and, in the case of procedures, likelihood of bleeding. Prophylaxis may be appropriate in children with recurrent serious bleeding and specifically after life-threatening bleeding episodes. When available, specific purified plasma-derived or recombinant factor concentrates, rather than fresh frozen plasma or cryoprecipitate, are the treatment of choice. Pediatrics 2013;132:882–892

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KEY WORDS
blood coagulation factor deficiencies, blood coagulation disorders, hemorrhage, pediatrics, blood coagulation tests

ABBREVIATIONS
APTT—activated partial thromboplastin time
AR—autosomal recessive
FFP—fresh frozen plasma
FI—fibrinogen
FII—factor II
FIX—factor IX
FV—factor V
FVII—factor VII
FVIII—factor VIII
FX—factor X
FIXI—factor XI
FXII—factor XII
FXIII—factor XIII
HA—hemophilia A
HB—hemophilia B
ICH—intracranial hemorrhage
PCC—prothrombin complex concentrate
PT—prothrombin time
RBD—rare bleeding disorder
VKCFD—vitamin K–dependent clotting factor deficiency

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Mild bleeding symptoms are fairly common in children and do not always indicate an underlying bleeding disorder. Epistaxis and easy bruising have been reported in 39% and 24% of children, respectively. Easy bruising may be related to "normal" childhood activity and varies in prevalence by motor developmental stage, with bruising reported in 61% to 90% of children aged 2 to 10 years. Other factors causing bleeding in children include anatomic abnormalities that contribute to serious bleeding events, such as intracranial, gastrointestinal, or genitourinary bleeds, and heavy menstrual bleeding in adolescent girls resulting from immaturity of the hypothalamic-pituitary-ovarian axis and anovulation. The pooled rate of bleeding after tonsillectomy, a common pediatric procedure, has been reported as 3.3% in patients without bleeding disorders.

The identification of the child with pathologic bleeding may therefore prove difficult, given the relative frequency of nonpathologic bleeding and similarities between pathologic and nonpathologic bleeding. Common bleeding sites (eg, skin and mucous membranes) are similar, and whereas bleeding often occurs spontaneously in the setting of bleeding disorders, affected individuals may initially present with bleeding only after trauma or surgery or, in girls, at menarche. Conversely, children with bleeding disorders may tolerate certain hemostatic challenges without seemingly excessive bleeding, only to present with pathologic bleeding later in life. Factors that may help in differentiating pathologic versus nonpathologic bleeding include age at first episode; frequency, extent, and duration of bleeding; personal history of recurrent spontaneous or procedure-related bleeding or heavy menstrual bleeding in girls, especially if accompanied by other bleeding; and family history of bleeding or known bleeding diatheses (Table 1). Nonaccidental trauma must also be considered in children with unexplained or excessive bleeding symptoms. Specifically, any bruising in a nonmobile child must be viewed as pathologic and may indicate either a bleeding disorder or nonaccidental trauma. In children who are mobile, bruising away from bony prominences, particularly on the face, head, or neck, is especially suggestive of nonaccidental trauma.

Pathologic bleeding occurs in the setting of congenital or acquired abnormalities in normal hemostasis, which consists of 3 basic processes: primary hemostasis, culminating in the formation of a platelet plug; secondary hemostasis, comprising the processes of coagulation (ie, fibrin formation) and clot stabilization; and fibrinolysis. Primary hemostatic disorders affecting children, namely quantitative and qualitative abnormalities of platelets and von Willebrand factor, are reviewed elsewhere. As are disorders of excessive fibrinolysis. Secondary hemostatic disorders encompass congenital or acquired deficiencies of clotting factors. Among those congenital disorders, hemophilia A (HA) and hemophilia B (HB) are the most common, resulting from deficiencies of factor VIII (FVIII) and factor IX (FIX), respectively. HA and HB are primarily inherited as X-linked recessive disorders and together affect ~1 in 5000 live male births per year in the United States, with HA accounting for ~80% of cases. The clinical hallmarks of HA and HB are musculoskeletal and soft tissue bleeding, the former of which may lead to debilitating arthropathy. In HA and HB, bleeding risk and phenotype correlate with plasma levels of the deficient factor in most cases.

Inherited deficiencies of other coagulation factors that may manifest with bleeding occur much less commonly and are thus collectively referred to as “rare” bleeding disorders (RBDs). The RBDs consist of inherited quantitative or functional deficiencies of factors I (ie, fibrinogen [F1]), II (FII), V (FV), VII (FVII), X (FX), XI (F XI), and XIII (FXIII) and combined factor deficiencies, most notably of FV and FVIII and of vitamin K–dependent factors. Given the congenital nature of these conditions, they may present with bleeding in infancy or

**TABLE 1 Initial Features Suggestive of Pathologic Bleeding in Children**

<table>
<thead>
<tr>
<th>Age-related</th>
<th>Bleeding (eg, umbilical stump bleeding, ICH, excessive and prolonged bleeding postcircumcision or after heel stick or intramuscular injection) during neonatal period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable and multiple bruises in infants and older children who are not independently mobile</td>
<td>Persistent palpatble bruising in an older mobile child</td>
</tr>
<tr>
<td>Spontaneous bleeding in the absence of anatomic causes</td>
<td></td>
</tr>
<tr>
<td>Personal history of</td>
<td></td>
</tr>
<tr>
<td>Recurrent (especially excessive and spontaneous) mucocutaneous bleeding</td>
<td></td>
</tr>
<tr>
<td>Atypical bleeds (eg, hemarthroses, retroperitoneal bleeding), whether spontaneous or provoked</td>
<td></td>
</tr>
<tr>
<td>Excessive or prolonged bleeding after hemostatic challenges (ie, trauma, dental procedures, or surgery)</td>
<td></td>
</tr>
<tr>
<td>Menorrhagia in adolescent girls: menstrual bleeding for &gt;7 d or &gt;80 mL blood loss per menstrual cycle (as evidenced by soaking through a pad or tampon within 1 h or change of pads or tampons every hour, or passage of large [&gt;1.1-inch diameter] clots)</td>
<td></td>
</tr>
<tr>
<td>Traumatic bleeding that is out of proportion to or inconsistent with reported injury (consider nonaccidental trauma)</td>
<td></td>
</tr>
<tr>
<td>Family history of</td>
<td></td>
</tr>
<tr>
<td>Recurrent bleeding symptoms</td>
<td></td>
</tr>
<tr>
<td>Excessive or prolonged bleeding after trauma or invasive procedures</td>
<td></td>
</tr>
<tr>
<td>Known or suspected bleeding diatheses</td>
<td></td>
</tr>
<tr>
<td>Physical findings</td>
<td></td>
</tr>
<tr>
<td>Multiple bleeding stigmata</td>
<td></td>
</tr>
<tr>
<td>Physical findings suggestive of specific underlying causes (eg, petechiae in platelet disorders, jaundice in liver disease, hypermobility, vascular malformations, musculoskeletal abnormalities)</td>
<td></td>
</tr>
<tr>
<td>Pallor/anemia</td>
<td></td>
</tr>
</tbody>
</table>
childhood. Although severe RBDs may initially present with serious bleeding complications such as intracranial hemorrhage (ICH), such events may be occasionally heralded by less serious bleeding symptoms. Recognizing the historical and laboratory features that suggest the presence of an RBD is paramount, to optimize prompt consultation with a hematologist for definitive diagnosis, treatment, and long-term follow-up of affected infants and children. However, identification of these disorders is challenged by their rarity, their variable and often indistinguishable clinical presentations, and a frequent lack of family history to suggest an inherited bleeding disorder. Whereas much is known (and written) about the clinical presentation and management of HA and HB in children, similar information pertaining to RBDs is relatively limited in general as well as in the pediatric literature, largely due to the small numbers of identified children with these disorders. This review summarizes the clinical presentations, diagnosis, and basic management of RBDs in children for the nonhematologist pediatric provider, with an emphasis on a primary care approach.

**Epidemiology and Clinical Presentation**

Features that distinguish RBDs from the most common inherited bleeding disorders, HA and HB, are summarized in Table 2. RBDs encompass 3% to 5% of all inherited coagulation disorders overall and, specifically, in children. With a prevalence of 1 symptomatic person per 500,000 population, FVII deficiency is the most common RBD, constituting 30% to 50% of various RBDs included in published series. Followed by FXI deficiency, which accounts for 23% to 39% of RBDs in various multinational registries. The least common RBDs are FII and FXIII deficiencies, with a prevalence of ~1 per 2 million each, and vitamin K–dependent clotting factor deficiency (VKCFD), of which <30 cases were reported as of 2008.

**Inheritance**

Most RBDs are considered autosomal recessive (AR); however, in all but VKCFD and combined FV/FVIII deficiency, heterozygotes (who number 1 per every 350 to 700 individuals) may have varying degrees of corresponding factor deficiency that render an unpredictable propensity for bleeding, especially in FVII and FXI deficiencies. Whereas the occurrence of symptomatic heterozygotes contradicts an AR pattern of inheritance, the prevalence of most of these RBDs is increased where consanguinity is commonplace, similar to other AR conditions. In addition, a family history of bleeding is often lacking. Combined FV/FVIII deficiency and VKCFD, which are caused by mutations in genes outside those encoding the coagulation factors themselves, are true AR disorders in that heterozygotes have normal factor levels and are thus asymptomatic. Strictly non-AR RBDs include FXI deficiency (autosomal with variable penetrance) and dysfibrinogénemia (autosomal dominant).

There are no inherent race- or ethnicity-based propensities for specific RBDs, with the exception of FXI deficiency, which is especially prevalent among Ashkenazi Jews: 1 of every 450 is affected and 8% are heterozygotes, accounting for a higher incidence of severe disease, in particular, in this group. In addition, F1I deficiency was found to disproportionately affect Latinos in a survey of 58 North American hemophilia treatment centers.

**Clinical Manifestations of RBDs**

**Common Bleeding Symptoms**

Bleeding propensity varies widely among individuals affected by RBDs, from no symptoms (45.8% of 489 people with RBDs in a European series) to life-threatening bleeding. However, when accounting for patients across all ages and genotypes, the most common bleeding manifestation of RBDs overall is mucocutaneous bleeding. This characteristic may make it difficult to clinically distinguish RBDs from platelet disorders or von Willebrand disease or from nonpathologic bleeding. That said, in contrast to nonpathologic bleeding, RBD-related bleeding is often spontaneous. Alternatively, RBDs may present with excessive bleeding after a hemostatic challenge. For example, bleeding after procedures such as circumcision or heel stick in the neonatal period and dental extractions later in childhood is a symptom common to all RBDs, although the historical absence of bleeding after these challenges does not necessarily exclude an RBD.

**Site-Specific Bleeding Symptoms**

The presentation of individual RBDs may be diverse. In general, serious bleeding (eg, ICH or musculoskeletal or umbilical cord bleeding) is rare in FV and FXI deficiencies, as is spontaneous bleeding in FXI deficiency. Bleeding phenotype is widely heterogeneous in FV, FVII, and FXI deficiencies and, in contrast to HA and HB, correlates poorly with factor activity level. Specifically, a recent review documented a poor correlation between clinical severity and coagulant activity in FV and FXI deficiencies, and no correlation between clinical severity and coagulant activity in FXI deficiency, even at undetectable or moderately reduced (<20%) levels. In particular, severe FVII deficiency may be asymptomatic or, in contrast, may present with serious bleeding events (eg, ICH) in infancy. In deficiencies of F, FI, FX, and FXIII, clinical severity strongly correlates with factor levels. The bleeding phenotype in FI deficiency (afibrinogénemia) may be similar to that in moderate or severe HA or HB, however, umbilical cord bleeding and mucosal bleeding are among the most common bleeding.
symptoms.41 Severe FII deficiency presents early in life with mucosal and musculoskeletal bleeding and ICH.42 Serious bleeding events such as umbilical cord bleeding, ovulatory hemoperitoneum, and hemarthrosis are relatively common in FII deficiency relative to other RBDs.36 Similarly, FX and FXIII deficiencies are generally characterized by early onset of serious or life-threatening bleeding episodes, such as ICH or umbilical cord bleeding.22,26 The latter is virtually pathognomonic of FXIII deficiency and is often delayed, given the role of FXIII in stabilizing clots.

Although more common in certain RBDs, serious bleeding events may occur in virtually any RBD and may therefore not always distinguish 1 RBD from another or from other bleeding disorders, for that matter. For example, umbilical cord bleeding may occur in conditions other than FX and FXIII deficiencies, including HA, HB, and other RBDs.22,25,35,36,45,44 Likewise, ICH has been described in the neonatal period in severe deficiencies of FII, FV, and FVII and in VKCFD,31,42,45,46 although ICH is especially common in FX and FXIII deficiencies; ICH has been reported in as many as 20% of individuals with FX deficiency44,47,48 and as many as 30% of those with FXIII deficiency,49–51 in which ICH is the main cause of death and disability.23,48 Other life- and limb-threatening bleeding events, such as ovulatory hemoperitoneum and hemarthroses, have been reported, most frequently in FII, FX, and FXIII deficiencies.36,57 FX deficiency has been associated with various non-coagulation-related abnormalities, including thrombocytopenia-absent radius syndrome, mitral valve prolapse, hypertrophic cardiomyopathy, and hypercholesterolemia.52 FV deficiency is sometimes confused with FV Leiden. FV deficiency is an inherited disorder characterized by low levels of FV due to mutations in the FV gene, which preclude the synthesis of this procoagulant protein. Therefore, individuals with FV deficiency have an increased risk of excessive bleeding. FV Leiden, on the other hand, is a genetic thrombophilia wherein a defect in the FV gene makes FV resistant to inactivation by anticoagulant protein C, thus increasing the risk of clotting events such as deep vein thrombosis, pulmonary embolus, and miscarriages.

**Bleeding in Women With RBDs**

Menorrhagia is the most common bleeding symptom in women with bleeding disorders, including RBDs.53 Approximately 50% of women affected by all RBDs report menorrhagia.25 Menarche may be the first significant hemostatic challenge encountered by girls with RBDs, but data regarding the prevalence of RBDs among adolescent girls with menorrhagia are limited.53 Menorrhagia is likely underreported in adolescents on the whole5 and constitutes a “hidden” source of bleeding, making it difficult to identify without disclosure by the patient or explicit questioning by clinicians. Factors suggestive of menorrhagia are presented in Table 1.3–5 The presence of structural lesions (eg, leiomyomata) may compound menorrhagia in women with RBDs and may even lead to life-threatening bleeding.54 Women with RBDs are also at increased risk of developing hemorrhagic ovarian cysts, which are a less common but perhaps more specific manifestation of an underlying bleeding disorder than menorrhagia.53,55 A ruptured follicle may lead to hemoperitoneum in women with RBDs, as previously described.57 Women with RBDs may experience obstetric complications as well, including postpartum hemorrhage56 and recurrent miscarriages due to the roles that deficient factors (namely FXIII and FII) play in placental implantation and pregnancy maintenance.45,57–59

**Combined Factor Deficiencies**

Even rarer than isolated deficiencies are combined factor deficiencies. Combined FV/FVIII deficiency exists due to a common molecular defect affecting intracellular processing of both proteins, rather than coincident defects in the genes for both factors.60 This condition is associated with a mild bleeding phenotype, without any apparent cumulative effect of the combined deficiencies.60 In contrast, VKCFD is often associated with significant bleeding.31 VKCFD results from inherited defects in activation (γ-carboxylation) of the vitamin K–dependent factors (FII, FVII, FIX, and FX).31 Affected children often present in infancy or in early childhood with serious bleeding events, including ICH. Skeletal abnormalities have also been reported, possibly due to defective γ-carboxylation of bone matrix proteins.31

**DIAGNOSTIC EVALUATION AND CONSIDERATIONS**

After obtaining thorough personal and family histories, the initial laboratory evaluation of a child with suspected pathologic bleeding should consist of a complete blood count and routine coagulation studies (prothrombin time [PT], activated partial thromboplastin time [APTT], FI, and thrombin time). The results of routine coagulation studies can be used to narrow down the possible disorders (Fig 1, Table 3).51–65 In isolation, the PT and APTT, respectively, assess the integrity of the extrinsic and intrinsic pathways of the coagulation cascade.65 Together, PT and APTT assess the integrity of the final common pathway of the coagulation cascade.65 Likewise, PT and APTT are simultaneously prolonged in conditions that involve deficiencies spanning all 3 pathways, such as VKCFD.31,64 Because fibrin generation is not affected in FXIII deficiency, PT and APTT are normal in this RBD.61 Consultation with a hematologist is recommended to assist with interpretation.
of laboratory results, facilitate further definitive testing, and ensure that confirmatory laboratory assays are performed properly. If readily available, a mixing study combining normal pooled plasma and patient plasma in a 1:1 ratio may be performed to determine the cause of an abnormal PT or APTT (Fig 1). In quantitative factor deficiencies such as RBDs, the addition of normal plasma replaces the deficient factor(s), thereby correcting the abnormal PT or APTT. Conversely, a lack of or partial correction in a mixing study suggests the presence of a specific coagulation factor inhibitor (inhibitor). Nonspecific inhibitors include lupus anticoagulants, which may occur transiently in children (eg, after viral illness), are typically asymptomatic, and tend to be the most common cause of a prolonged APTT in non-bleeding children. Speciﬁc coagulation factor inhibitors are far less common in children, even less common than most RBDs. Therefore, when a prolonged APTT or simultaneously prolonged APTT and PT fail to correct in a mixing study, consideration should first be given to further investigation for a lupus anticoagulant. This investigation is

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**TABLE 2** Distinguishing Epidemiologic, Genetic, Clinical, and Laboratory Features of the Hemophilias and RBDs

<table>
<thead>
<tr>
<th>HA and HB</th>
<th>RBDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Together with VWD, account for &gt;90% of all inherited bleeding disorders</td>
<td>Account for 3% to 5% of all inherited coagulation disorders; autosomal inheritance, so both boys and girls affected; most are AR (except for FXI deficiency [AV] and dysfibrinogenemia [AD]); however, heterozygotes variably symptomatic, especially in FVII and FXI deficiencies</td>
</tr>
<tr>
<td>XR inheritance; therefore, majority of affected individuals are male</td>
<td>Autosomal inheritance, so both boys and girls affected; most are AR (except for FXI deficiency [AV] and dysfibrinogenemia [AD]); however, heterozygotes variably symptomatic, especially in FVII and FXI deficiencies</td>
</tr>
<tr>
<td>Family history of disease in brothers or in maternal male relatives; may be absent in up to one-third of patients</td>
<td>Family history often lacking; most RBDs more prevalent where consanguinity is commonplace</td>
</tr>
<tr>
<td>Clinical course predominated by soft tissue and musculoskeletal bleeding, especially in older children; postcircumcision/post-heal stick and CNS bleeding most common bleeding events in newborns</td>
<td>Clinical presentation variable within and among individual RBDs; mucocutaneous bleeding is most common symptom overall; serious bleeding (eg, ICH) characteristic of FX and FXIII deficiencies in particular but can occur in virtually any of the RBDs</td>
</tr>
<tr>
<td>Initial laboratory evaluation remarkable for isolated prolonged APTT that corrects in a mixing study</td>
<td>Both PT and APTT prolonged in most RBDs (see Fig 1); PT/APTT abnormalities correct in a mixing study; quantitative functional FXIII activity assay should be used to screen for FXIII deficiency, in which PT/APTT are normal</td>
</tr>
<tr>
<td>Clinical severity correlates with coagulant activity</td>
<td>Poor association between clinical severity and coagulant activity in FV and FXI deficiencies; no association between clinical severity and coagulant activity, both when undetectable or moderately reduced (&lt;20%), in FXI deficiency</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AV, autosomal variable penetrance; CNS, central nervous system; VWD, von Willebrand disease; XR, X-linked recessive.

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FIGURE 1
Basic process for evaluating coagulation profile abnormalities. If available, a mixing study should be performed to differentiate a coagulation factor deficiency from an inhibitor. The possible factors involved may then be narrowed down on the basis of which coagulation study or studies are abnormal. Note: PT and APTT are normal in FXII deficiency. H/LMWK, high-/low-molecular-weight kininogen.
first accomplished by demonstrating phospholipid-dependence of the inhibitor, given that lupus anticoagulants fall into this category.\(^6\) Correction of APTT or of another phospholipid-based screening test, the dilute Russell viper-venom time, after the addition of a phospholipid-rich source (eg, platelets in the platelet neutralization procedure) confirms the presence of a lupus anticoagulant.\(^63\) \(^66\) If testing for a coagulation factor inhibitor is indicated based on clinical grounds or negative lupus anticoagulant testing, the coagulation factors of interest can be narrowed down on the basis of the uncorrected coagulation study (Fig 1).

RBDs are generally confirmed by reduced activity of the respective factor(s) in a functional activity assay, which is the assay commonly used when a factor level is ordered. Because routine coagulation studies are normal in FXIII deficiency, alternative “screening” tests must be used when there is suspicion of (or to rule out) this deficiency. Currently, a quantitative functional FXIII activity assay (ammonia-release or amine-incorporation) is recommended for screening instead of the traditionally used clot solubility test, which is sensitive at only low FXIII levels (<0.5% to 5%) and may thus miss more moderate deficiencies.\(^23\) \(^67\) \(^68\) FXIII deficiency is then confirmed by quantification of FXIII-A2B2 antigen by enzyme-linked immunosorbent assay, followed by quantification of the A- and B-subunit antigens if FXIII-A2B2 antigen is reduced.\(^23\) \(^67\) \(^69\) There are several important considerations in the laboratory evaluation for RBDs in children. First, reference values for full-term and preterm infants in the first 6 months of life (and beyond, in some cases) differ from those in adults, particularly for APTT and all coagulation factor levels except for FVIII.\(^70\) \(^72\) Because the levels of many factors increase over the first month of life, milder or equivocal deficiencies may need to be confirmed once a child is older or by screening both parents.\(^35\) As always, several things may artifactually affect coagulation study results, including heparin contamination of the sample,\(^55\) \(^73\) and failure to collect the specified amount of blood within the collection tube (for an optimal plasma-to-citrate ratio).\(^53\) Immediate gentle mixing of the sample with anticoagulant is recommended to avoid activation of coagulation.\(^55\) Samples should ideally be analyzed within 4 hours of collection or, alternatively, frozen immediately for future use.\(^35\) If originally drawn after empirical administration of fresh frozen plasma (FFP) to treat active bleeding, coagulation tests should be repeated before interpreting the results and concluding whether a patient has an RBD. The timing for rechecking coagulation studies to rule out RBDs (or other bleeding disorders) will depend on the half-lives of the potentially affected coagulation factors (ie, FXI in an isolated APTT abnormality; FVII when only the PT is abnormal; FI, FII, FV, or FX when both APTT and PT are abnormal; and FXIII when both APTT and PT are normal; Fig 1, Table 4). Individual factor levels may likewise be affected by previous administration of FFP and may thus need to be rechecked after an appropriate amount of time has elapsed (again, based on half-life, Table 4). In general, relevant coagulation studies or factor levels should be rechecked after 5 elimination half-lives of the suspected deficient factor(s) have elapsed if aiming to make a diagnosis of an RBD after administration of FFP to treat an initial bleeding episode. Ideally, samples for hematologic testing should be collected into $\geq 2$ blue-top tubes (which contain sodium citrate as the anticoagulant) before administering FFP or any other factor replacement products when the presence of a bleeding disorder is possible or suspected.

In situations in which nonaccidental trauma is suspected, clinicians are often rightly concerned about missing an

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**Table 3** Findings of Initial Laboratory Studies in RBDs

<table>
<thead>
<tr>
<th>RBD</th>
<th>PT</th>
<th>APTT</th>
<th>FI$^a$</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FII deficiency$^{46}$</td>
<td>Prolonged$^a$</td>
<td>Prolonged$^a$</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>FV deficiency$^{31,45}$</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>FXI deficiency$^{28,47}$</td>
<td>Prolonged$^a$</td>
<td>Prolonged$^a$</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>FXI deficiency$^{42,64}$</td>
<td>Normal</td>
<td>Prolonged$^a$</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>FXIII deficiency$^{23}$</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>FI deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affibrinogenemia$^{43}$</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>&lt;1 g/L</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Hypoaffibrinogenemia$^{43}$</td>
<td>Normal/prolonged$^a$</td>
<td>Normal/prolonged$^a$</td>
<td>1–1.5 g/L</td>
<td>Mildly prolonged</td>
</tr>
<tr>
<td>Dysaffibrinogenemia$^{31,45}$</td>
<td>Normal/prolonged</td>
<td>Normal/prolonged</td>
<td>Normal/slightly reduced</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Combined FV/FVIII deficiency$^{31,45}$</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Table 4** Half-lives of Coagulation Factors

<table>
<thead>
<tr>
<th>Coagulation Factor</th>
<th>Plasma Half-life, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI (fibrinogen)</td>
<td>90</td>
</tr>
<tr>
<td>FII</td>
<td>65</td>
</tr>
<tr>
<td>FV</td>
<td>15</td>
</tr>
<tr>
<td>FVII</td>
<td>5</td>
</tr>
<tr>
<td>FXIII</td>
<td>10</td>
</tr>
<tr>
<td>FIX</td>
<td>25</td>
</tr>
<tr>
<td>FX</td>
<td>40</td>
</tr>
<tr>
<td>FII</td>
<td>45</td>
</tr>
<tr>
<td>FXIII</td>
<td>200</td>
</tr>
</tbody>
</table>

Hoffbrand and Moss (74).

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Footnotes:

1. Normal range = 1.5–3.5 g/L.
2. May be only minimally prolonged depending on reagents used; results may also be within normal range.
3. Congenital variants with normal PT and APTT have been reported.
4. Normal APTT does not exclude a diagnosis of mild FXI deficiency, particularly if FVIII levels are elevated.\(^35\)
5. PT or APTT may be normal or prolonged in hypoaffibrinogenemia, depending on how low the FI level is; PT and APTT are typically normal when FI level exceeds 1 g/L.\(^41\)
6. Normal range = 1.5–3.5 g/L.
7. May be only minimally prolonged depending on reagents used; results may also be within normal range.
8. Congenital variants with normal PT and APTT have been reported.
9. Normal APTT does not exclude a diagnosis of mild FXI deficiency, particularly if FVIII levels are elevated.\(^35\)
10. PT or APTT may be normal or prolonged in hypoaffibrinogenemia, depending on how low the FI level is; PT and APTT are typically normal when FI level exceeds 1 g/L.\(^41\)
11. Normal range = 1.5–3.5 g/L.
12. May be only minimally prolonged depending on reagents used; results may also be within normal range.
13. Congenital variants with normal PT and APTT have been reported.
14. Normal APTT does not exclude a diagnosis of mild FXI deficiency, particularly if FVIII levels are elevated.\(^35\)
15. PT or APTT may be normal or prolonged in hypoaffibrinogenemia, depending on how low the FI level is; PT and APTT are typically normal when FI level exceeds 1 g/L.\(^41\)
16. Normal range = 1.5–3.5 g/L.
17. May be only minimally prolonged depending on reagents used; results may also be within normal range.
18. Congenital variants with normal PT and APTT have been reported.
19. Normal APTT does not exclude a diagnosis of mild FXI deficiency, particularly if FVIII levels are elevated.\(^35\)
20. PT or APTT may be normal or prolonged in hypoaffibrinogenemia, depending on how low the FI level is; PT and APTT are typically normal when FI level exceeds 1 g/L.\(^41\)
underlying bleeding diathesis. Although subdural hematomas in children <2 years of age are most often caused by non-accidental trauma,76 particularly if associated with retinal hemorrhages,76 there are anecdotal reports of patients in whom this combination of findings was attributed to a bleeding diathesis, including vitamin K–deficiency bleeding in the newborn (also known as late hemorrhagic disease of the newborn),77,78 HA,77 von Willebrand disease type 1,79 and Hermansky-Pudlak syndrome.76 Bleeding disorders have only rarely been reported to be the cause of isolated retinal hemorrhages in neonates.80 Multiple fractures of differing ages (especially posterior rib fractures in infants with subdural hematoma) or inconsistencies between the reported mechanism and the pattern or extent of injuries suggest nonaccidental trauma, especially when there is a delay in seeking medical attention.81 Conversely, consideration should be given to RBDs in children from consanguineous parents or with a personal or family history of bleeding, particularly in the absence of other features suggesting nonaccidental trauma. Recommendations for consideration of various bleeding disorders, including RBDs, in the setting of possible nonaccidental trauma were recently summarized in a technical report from the American Academy of Pediatrics.82 The presence of a bleeding disorder and nonaccidental trauma are not mutually exclusive, so the possibility of the latter must always be kept in mind, especially if any of the aforementioned features suggestive of nonaccidental trauma apply.

MANAGEMENT

Overall, there is relatively little information regarding the management of individuals with RBDs,25 although guidelines for the management of bleeding episodes, surgery, and pregnancy (including care of the potentially affected newborn)35 have been proposed on the basis of existing literature and clinical experience. Nevertheless, given the rarity of RBDs and the complex, often costly nature of treatment, affected children should be followed at a hemophilia treatment center at least biannually to guarantee not only appropriate care but also ready access to therapies that may not be immediately available elsewhere.29,83 The hemophilia treatment center should be consulted regarding management of any bleeding as well as hemostatic coverage and precautions for invasive procedures. Not all bleeding events require treatment. In general, the need for hemostatic coverage for surgery or other invasive procedures is based on the general risk of bleeding attributable to the respective factor deficiency and procedure itself and on personal and family history of bleeding with previous hemostatic challenges, including surgery.

Replacement Products

Replacement products available in the United States for treatment or prevention of bleeding in RBDs, when indicated, are summarized in Table 5.31,35,84–86 When available, specific, single-factor concentrates are the treatment of choice. In the United States, single-factor concentrates are available for all deficient factors encompassed by the RBDs except for FII, FV, FX, (concentrate in clinical development), and FXI (concentrate available only in Europe). For deficiencies of FII and FX, prothrombin complex concentrates (PCCs) are recommended. PCCs are highly purified concentrates of specific coagulation factors obtained from pooled normal plasma,87 namely FII, FIX, FX, and FVII in varying amounts depending on the product.84 PCCs contain known amounts of the factors therein and are submitted to a process of viral inactivation, making them preferable to FFP and cryoprecipitate when aiming to replace FII or FX.

FFP is often used as an alternative source of factor replacement in RBDs and is a mainstay of treatment for FV deficiency, absent any other products containing this factor. FFP may also be used when hemostatic treatment or coverage is indicated in FXI deficiency in the United States.62 Cryoprecipitate, a byproduct of FFP obtained after thawing a single-donor volume of FFP at 4°C, is rich in von Willebrand factor, FVIII, FXIII, and FI and is most often used for replacement of FI and FXIII, although more recently, purified plasma-derived products have become available to treat these latter 2 deficiencies.49,84,88 Although widely available and relatively inexpensive,26 FFP and cryoprecipitate have potential disadvantages compared with single-factor concentrates and PCCs in that they are not subjected to a viral inactivation process in the United States (although donors and plasma are comprehensively screened) and, given the relatively small amounts of individual factors therein, are often required in large volumes to replace a single factor, potentially putting recipients at risk for fluid overload.35 Hemostatic treatment or coverage in combined FV/FVIII deficiency consists of replacement of both factors using FFP to replace FV and plasma-derived or recombinant FVIII concentrates to replace FVIII (Table 5). Based primarily on experience with reversing warfarin anticoagulation, FFP or PCCs are recommended for treatment of bleeding or for surgical coverage in VKCFD, in addition to maintenance oral vitamin K.31

Ancillary Therapies

Ancillary therapies that may be used as alternatives or adjuncts to factor replacement include systemic antifibrinolytics (ie, tranexamic acid and e-aminocaproic acid), topical hemostatic agents (eg, fibrin glue), and, in the setting of combined FV/FVIII deficiency,65 desmopressin to boost FVIII levels. In
Cryoprecipitate is generally preferred over FFP as a second-line option for FI replacement.

### Table 5: Factor Replacement Products Currently Available in the United States for Treatment or Prevention of Bleeding in RBDs

<table>
<thead>
<tr>
<th>Product</th>
<th>Content</th>
<th>Virally inactivated?</th>
<th>Therapeutic Option for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoprecipitate</td>
<td>Rich in FVIII, FI, VWF, and FXIII</td>
<td>No</td>
<td>Fl deficiency, FXII deficiency</td>
</tr>
<tr>
<td>Single-factor concentrates</td>
<td>rFVIIa</td>
<td>N/A</td>
<td>FVII deficiency</td>
</tr>
<tr>
<td>NovoSeven</td>
<td>pd-FXIII</td>
<td>Yes</td>
<td>FXIII deficiency</td>
</tr>
<tr>
<td>RiaSTAP</td>
<td>pd-FI</td>
<td>Yes</td>
<td>FI deficiency</td>
</tr>
<tr>
<td>FVIII (numerous options)</td>
<td>rFVIII or pd-FVIII</td>
<td>N/A (rFVIII), yes (pd-FVIII)</td>
<td>FV/FVIII deficiency</td>
</tr>
<tr>
<td>PCCs</td>
<td>FIL, FIX, FX, and FVIII</td>
<td>Yes</td>
<td>FIL deficiency</td>
</tr>
<tr>
<td>Profilnine</td>
<td>FIL, FIX, FX, and FVIII</td>
<td>Yes</td>
<td>FX deficiency, VKCFD</td>
</tr>
<tr>
<td>Bebulin</td>
<td>FIL, FIX, FX, and FVIII</td>
<td>Yes</td>
<td>FIL deficiency, VKCFD</td>
</tr>
<tr>
<td>FFP</td>
<td>All coagulation factors</td>
<td>No</td>
<td>FV deficiency, FXI deficiency, VKCFD</td>
</tr>
</tbody>
</table>

N/A, not applicable; pd-, plasma-derived; rFVIIa, recombinant activated FVII; rFVIII, recombinant FVIII; VWF, von Willebrand factor.

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some cases, antifibrinolytics may be exclusively used for mucosal bleeding or minor (eg, dental) procedures to avoid using pooled blood products. For RBD-related menorrhagia, hormonal therapies and antifibrinolytics are often effective and considered first-line therapies, as they are in women without bleeding disorders.7,89

**Prophylactic Replacement Therapy**

In some cases, ongoing prophylactic hemostatic therapy may be warranted, either primarily (initiated before any bleeding occurs) or secondarily (initiated after a bleeding event, to prevent recurrence). Primary prophylaxis has been effectively used in boys with severe HA to reduce joint damage from recurrent hemarthroses.80 However, data regarding any benefit of primary prophylaxis in RBDs are sparse. The only RBD for which prophylaxis is routinely recommended is severe FXIII deficiency, in which prophylaxis is recommended from the time of diagnosis because of the risk for serious, even life-threatening, bleeding events such as ICH.91 Secondary prophylaxis may be considered after musculoskeletal bleeding or life-threatening hemorrhage to prevent recurrent bleeding, particularly in deficiencies of FXIII, FX, and FVII and in severe cases of FI and FV deficiencies.25

**Perinatal Recommendations**

Delivery of a potentially affected neonate should ideally take place in a specialized center with advance planning to limit the risk of bleeding in both mother and infant.35 Fetal scalp monitoring and forceps- or vacuum-assisted delivery should be discouraged. Communication among the hemophilia treatment center, obstetrician, and pediatrician or neonatologist is key to prevent serious consequences such as ICH in the potentially affected newborn and for ongoing management thereafter. After delivery, a thorough diagnostic evaluation of the neonate is indicated; cord blood may be sent if there is a known family history of an RBD, given ease of collection and to avoid venipuncture-related soft tissue bleeding. Hemostatic challenges (eg, circumcision, arterial sticks) should be avoided until the results are obtained. A cranial ultrasound is recommended during the first week of life in neonates with known severe RBDs to exclude the presence of ICH.35

**Additional Pediatric Recommendations**

In the neonatal period and beyond, consideration should be given to subcutaneous (rather than intramuscular) administration of medications (including vitamin K in the newborn) and immunizations, when possible. In particular,
hepatitis A and B vaccines should be given as recommended for all children by the US Centers for Disease Control and Prevention. Routine preventive dental care should be encouraged and facilitated via consultation with the hemophilia treatment center regarding the necessity of prophylaxis and other hemostatic measures. Parents should avoid giving children with RBDs analgesics/antipyretics that may affect platelet function (ie, nonsteroidal antiinflammatory drugs). Providers and parents may consult existing resources (eg, from the National Hemophilia Foundation and the World Federation of Hemophilia Web site at www.wfh.org) and the hemophilia treatment center for guidance pertaining to physical activity and other aspects of care in children and adolescents with RBDs. Finally, genetic counseling and screening should be offered to the entire family to identify potential carriers at risk for affected progeny, especially in countries where the incidence of consanguinity is high or when a specific genetic mutation has been identified in the family.

CONCLUSIONS

Early identification of RBDs in children is critical to ensure optimal treatment of any bleeding events and to mitigate any risk for future bleeding. Bleeding may be severe, even life-threatening, and given the congenital nature of these disorders, symptoms may begin during the neonatal period or early childhood. Serious bleeding episodes, including ICH, may be preceded by relatively minor bleeding events, providing an opportunity for diagnosis before the former occur. Primary care and other nonhematologist pediatric providers must be familiar with the variable clinical presentation and initial diagnostic evaluation of these rare disorders. RBDs should be considered, in particular, when there is consanguinity. Consultation with a hematologist who is ideally affiliated with a hemophilia treatment center will facilitate efficient diagnosis and appropriate ongoing management.

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