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Shannon L. Carpenter, Thomas C. Abshire, James D. Anderst and the SECTION ON  
HEMATOLOGY/ONCOLOGY AND COMMITTEE ON CHILD ABUSE AND  
NEGLECT

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## TECHNICAL REPORT

# Evaluating for Suspected Child Abuse: Conditions That Predispose to Bleeding

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**KEY WORDS**

intracranial hemorrhage, inherited coagulation disorders, bruising, nonaccidental trauma

**ABBREVIATIONS**

AP— $\alpha$ -2 antiplasmin  
aPTT—activated partial thromboplastin time  
BSS—Bernard-Soulier syndrome  
CNS—central nervous system  
EDS—Ehlers-Danlos syndrome  
FFP—fresh-frozen plasma  
GT—Glanzmann thrombasthenia  
ICH—intracranial hemorrhage  
ITP—immune thrombocytopenia  
NARBDR—North American Rare Bleeding Disorders Registry  
OI—osteogenesis imperfecta  
PAI-1—plasminogen activator inhibitor type 1  
PFA-100—platelet function analyzer  
PT—prothrombin time  
VKDB—vitamin K deficiency bleeding  
VWAg—von Willebrand antigen  
VWD—von Willebrand disease  
VWF—von Willebrand factor

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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## abstract

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Child abuse might be suspected when children present with cutaneous bruising, intracranial hemorrhage, or other manifestations of bleeding. In these cases, it is necessary to consider medical conditions that predispose to easy bleeding/bruising. When evaluating for the possibility of bleeding disorders and other conditions that predispose to hemorrhage, the pediatrician must consider the child's presenting history, medical history, and physical examination findings before initiating a laboratory investigation. Many medical conditions can predispose to easy bleeding. Before ordering laboratory tests for a disease, it is useful to understand the biochemical basis and clinical presentation of the disorder, condition prevalence, and test characteristics. This technical report reviews the major medical conditions that predispose to bruising/bleeding and should be considered when evaluating for abusive injury. *Pediatrics* 2013;131:e1357–e1373

## INTRODUCTION

In the absence of known accidental mechanisms or medical causes, children with intracranial hemorrhage (ICH), cutaneous bruises, or other symptoms of bleeding might be suspected victims of child abuse. In such situations, physicians must often carefully evaluate for the possibility of a bleeding disorder or another medical condition as a possible cause. In addition, because of the legal proceedings associated with cases of potential abuse, physicians might feel compelled to rule out any theoretical possibility of a medical explanation for the child's findings despite clinical improbability. This can result in an expensive and, in the case of young children with limited total blood volume, potentially harmful laboratory investigation of diminished clinical value.

The list of congenital and acquired bleeding disorders that could potentially be confused with abusive injury is extensive: hemophilia, von Willebrand disease (VWD), disorders of fibrinogen, vitamin K deficiency, factor XIII and other factor deficiencies, thrombocytopenia, leukemia, aplastic anemia and other bone marrow infiltrative or failure syndromes, and platelet function abnormalities, among others. Most of these conditions can present with mucosal bleeding, such as epistaxis and cutaneous bruising, but some (especially factor deficiencies) have been noted to present with isolated ICH, or can increase susceptibility to severe ICH after minor trauma. Collagen disorders can also

predispose to easy bruising/bleeding in some circumstances. This report reviews the rationale for the consideration of bleeding disorders and collagen disorders as a cause of or as contributing to ICH, bruising, or bleeding when child abuse is suspected, and addresses several unsupported hypotheses related to these issues.

### **CLINICAL APPROACH TO THE EVALUATION OF CONDITIONS THAT PREDISPOSE TO BLEEDING IN THE SETTING OF POSSIBLE ABUSE**

In many children with bruising/bleeding concerning for abuse, the evaluation for medical conditions causing or contributing to the findings noted on the physical examination can be completed by assessing the child's presenting symptoms, trauma history, medical history, family history, and medications. Before engaging in a laboratory evaluation, physicians should consider the following:

1. The specific clinical characteristics of the child's findings, along with a previous history of bleeding or bruising. Family history of bleeding or bruising or a history of specific coagulopathies and other conditions should be addressed.
2. The known presentations and prevalence of the various bleeding disorders, collagen disorders, or other medical conditions under consideration.
3. The medical probability that a specific medical condition might cause or contribute to the child's bleeding or bruising.
4. The statistical characteristics of the proposed laboratory testing.
5. The history of the use of blood products or other factor replacement products that might alter test results.
6. The associated costs of testing, both financial and medical, such as the blood volume needed for testing.

7. The anticipated benefit of identifying conditions that might cause bleeding or bruising.

### **CLINICAL CHARACTERISTICS**

#### **Nonintracranial Bleeding**

The age and developmental capabilities of the child, history of trauma, and the location and pattern of bruising often provide significant evidence in determining the presence of abusive injury.<sup>1-5</sup> In many cases, the constellation of findings, taken in conjunction with the clinical history, can be so strongly consistent with abusive injury that a further laboratory investigation for medical conditions is not warranted. For instance, in a verbal child with a patterned slap mark who describes being hit with an open hand at the location of the slap mark, obtaining tests to rule out a bleeding disorder is unlikely to provide useful information. However, because few data exist comparing the specific clinical presentations of bleeding disorders and abuse, in some cases, a laboratory evaluation might be necessary to minimize the chances of a misdiagnosis. It also must be considered that the presence of a bleeding disorder or other medical condition does not rule out abuse as the etiology for bruising or bleeding.<sup>6</sup>

Other symptoms, such as hematemesis,<sup>7</sup> hematochezia,<sup>8</sup> and oronasal bleeding, can be caused by abuse or a bleeding disorder.<sup>9-13</sup> The relative frequencies of abuse or coagulopathies presenting with these symptoms should be considered, along with the patient's history and any other medical findings, such as fractures, neglect, and other manifestations of bleeding/bruising, before ordering laboratory tests. An increasing number of findings unrelated to bleeding disorders and consistent with abuse decrease the overall likelihood of

a coagulopathy or other medical condition contributing to or causing bleeding or bruising. However, it is prudent to evaluate for bleeding disorders or other medical causes in children who have presenting symptoms that are not typical of inflicted injury.

#### **ICH**

Multiple studies have assessed the roles of history,<sup>14</sup> clinical and radiographic findings,<sup>15-22</sup> and outcomes<sup>18,21,23,24</sup> in making the diagnosis of abusive head trauma. In a recent study of ICH in bleeding disorders, ICH was the presenting event in 19.2%.<sup>25</sup> However, no studies have addressed how to differentiate whether patients who present with ICH in the absence of trauma or with a history of minimal trauma have a bleeding disorder either causing or contributing to the clinical findings. No studies have systematically compared the presentation, clinical findings, patterns of ICH, or presence of retinal hemorrhages between bleeding disorders and/or collagen disorders and abusive head trauma. Therefore, for children presenting with ICH but without other findings strongly suggestive of abuse, such as fractures,<sup>26</sup> significant abdominal trauma, burns, or patterned bruising, an evaluation for other medical conditions causing or contributing to the findings is necessary. Additionally, physicians must recognize that although evidence of old inflicted injury, such as healing fractures, could support the diagnosis of abuse, healing injuries may be unrelated to recent bruising or ICH. Physicians must assess their own comfort in making and supporting the diagnosis of abuse in the absence of an extensive laboratory evaluation.

### **REVIEW OF BLEEDING DISORDERS**

This section describes the significant bleeding disorders that may require

further evaluation in cases of suspected abuse, including their common presentations, incidence of ICH, and the method of diagnosis (Table 1).

### Deficiency of Factor VIII or IX

Hemophilia A and B are attributable to deficiencies of factors VIII and IX, respectively. Factor VIII deficiency occurs in approximately 1 in 5000 live male births. Factor IX deficiency is rarer, occurring in 1 in 20 000 live male births. Because of the X-linked recessive inheritance pattern of these diseases, most patients affected with hemophilia are male. However, girls who are carriers can have low enough factor VIII or IX levels to present with bleeding as a result of homozygous mutations or extreme inactivation of the normal X chromosome. Rarely, a phenotypic female can have only 1 X chromosome and be affected with the disease (ie, testicular feminization, Turner syndrome).<sup>27,28</sup>

Major bleeding sequelae of hemophilia include bleeding into joints and soft tissues and ICH. The most common sites of the initial bleeding episode in one series were post-circumcision and intracranial.<sup>29</sup> ICH in a child with hemophilia can occur as a result of birth trauma, in response to mild head trauma, or spontaneously. ICH is estimated to occur in 5% to 12% of patients with hemophilia throughout their lives.<sup>25,30,31</sup> A review of 57 episodes of ICH in 52 patients with congenital factor deficiencies showed intraparenchymal and/or intraventricular bleeding in 39 patients, subdural in 15, subarachnoid in 2, and cerebellar in 1. Most of these patients (38) had severe hemophilia. The median age of presentation was 8 years (range, 1 month to 22 years). The overall prevalence of ICH in patients with hemophilia in this study was 9.1%.<sup>25</sup> The largest series to date of ICH in hemophilia reported a rate of

2.7% over 5 years in a cohort of 3629 patients with hemophilia, or 0.0054 cases per year. Most of the cases in this series were not the result of trauma (78.4%). Most (69%) occurred in patients with severe hemophilia, and 18% occurred in those with mild hemophilia. Sites of hemorrhage were intracerebral, subdural, subarachnoid, epidural, or unspecified. Trauma was implicated in all of the epidural hemorrhages, 36% of the subarachnoid hemorrhages, 10% of subdural hemorrhages, and 3% of intracerebral hemorrhages.<sup>31</sup> In a recent review of 97 patients with hemophilia who underwent a total of 295 computed tomography scans for head trauma, 9 (3%) were identified as having intracranial bleeding. The mean age of these patients was  $3.7 \pm 4.1$  years. Most of the bleeding in these patients was subdural, although in 2 patients, bleeding was intraparenchymal.<sup>32</sup> A recent study of hemophilia in the first 2 years of life revealed 19.0% of first bleeding episodes ( $n = 404$ ) were head bleeding, of which 36.4% were ICH. Seventy-five percent of the ICH occurred in infants younger than 1 month of age, and most of these were associated with delivery. In contrast to the aforementioned studies, the occurrence of ICH was distributed across all severities of the disease.<sup>29</sup>

Approximately two-thirds of patients who present with a diagnosis of hemophilia have a positive family history for the disease. The one-third of patients without a family history of hemophilia might represent new germ-line mutations.<sup>29,33</sup> Diagnosis of hemophilia requires measuring factor VIII or IX activity level. Hemophilia is categorized as severe if the factor level is  $<1\%$ , moderate if the factor level is between 1% and 5%, and mild if the factor level is  $\geq 5\%$ . Spontaneous bleeding is more common in

severe hemophilia. The activated partial thromboplastin time (aPTT) is prolonged in moderate and severe cases, but can be normal in patients with mild disease, depending on the laboratory's emphasis on detecting mild factor deficiencies. Factor VIII is also an acute phase reactant and can be elevated into the normal range in patients with mild disease in response to trauma or inflammation.<sup>34</sup>

### VWD

VWD is the most common heritable bleeding disorder, and typically presents with mild to moderate mucocutaneous bleeding. Low von Willebrand factor (VWF) levels may occur in up to 1% of the population, but fewer people may present with symptoms (0.01% to 0.1%). The current prevalence of VWD can be difficult to ascertain because recent changes in consensus have resulted in more specific diagnostic criteria. The new criteria for diagnosis requires VWF  $<30\%$  (normal range, 50% to 150%), resulting in fewer people with levels below the normal range meeting diagnostic criteria. Individuals with bleeding symptoms and VWF levels between 30% and 50% create a diagnostic dilemma.<sup>35</sup> In addition, because the bleeding symptoms of VWD are generally mild, there are likely to be patients who have not come to medical attention. On the basis of the number of symptomatic cases seen by hematology specialists, the prevalence has been estimated to be even lower than previously suggested (23 to 110 per million, or 0.0023% to 0.01%), meaning that many individuals with low VWF levels might never manifest bleeding symptoms.<sup>36</sup> The laboratory evaluation for, and common presentations of, the various types of VWD are variable (Tables 2 and 3). Type 1 VWD is the most common form (approximately 80%) and is characterized by a normally

**TABLE 1** Common Testing Strategies for Bleeding Disorders

Condition	Frequency	Inheritance	Screening Tests	Sn and Sp, %	PPV and NPV, %	Confirmatory Test
Factor abnormalities/deficiencies						
WVD type 1	1 per 1000	AD	PFA-100	Sn = 79–96 <sup>a</sup>	PPV = 93.3	VWAg <sup>b</sup> VWF activity VW multimer analysis
WVD type 2A	Uncommon	AD or AR	PFA-100	Sp = 88–96 <sup>a</sup>	NPV = 98.2	Factor VIII activity VWAg <sup>b</sup> VWF activity
WVD type 2B	Uncommon	AD	PFA-100	Sn = 94–100 <sup>a</sup>	PPV = 93.3	VW multimer analysis Factor VIII activity VWAg <sup>b</sup>
WVD type 2M	Uncommon	AD or AR	PFA-100	Sp = 88–96 <sup>a</sup>	NPV = 98.2	VWF activity VW multimer analysis Factor VIII activity VWAg <sup>b</sup>
WVD type 2N	Uncommon	AR, or compound heterozygote	aPTT	Sp = 88–96 <sup>a</sup>	NPV = 98.2	VWF activity VW multimer analysis Factor VIII activity VWF-Factor VIII binding assay
WVD type 3	1 per 300 000–1 000 000	AR, or compound heterozygote	PFA-100	Sn = 94–100 <sup>a</sup>	PPV = 93.3	VWAg <sup>b</sup> Ristocetin cofactor VWF multimer analysis
Factor II deficiency (prothrombin)	26 reported cases, estimated 1 per 1–2 million		aPTT, PT (may be normal)	Sn = variable	NA	Factor VIII activity Factor II activity +/- antigen levels
Factor V deficiency	1 per 1 million	AR	aPTT, PT	Sn = variable	NA	Factor V activity
Combined factor V/factor VIII deficiency	1 per 1 million	AR	aPTT>PT	Sn = variable	NA	Factor V and factor VIII activities
Factor VII deficiency	1 per 300 000–500 000	AR	PT	Sn = variable	NA	Factor VII activity
Factor VIII deficiency	1 per 5000 male births	X-linked	aPTT	Sn = variable	NA	Factor VIII activity
Factor IX deficiency	1 per 20 000 male births	X-linked	aPTT	Sn = variable	NA	Factor IX activity
Factor X deficiency	1 per 1 million	AR	aPTT, PT, RVV	Sn = variable	NA	Factor X activity
Factor XI deficiency	1 per 100 000	AR	aPTT	Sn = variable	NA	Factor XI activity
Factor XIII deficiency	1 per 2–5 million	AR	Clot solubility	Sn = variable	NA	Factor XIII activity
Fibrinolytic defects						
AP deficiency	~40 reported cases	AR	Euglobin lysis test	Sn = variable	NA	AP activity
PAI-1 deficiency	Very rare	AR		Sn = variable	NA	PAI-1 antigen and activity
Defects of fibrinogen						
Afibrinogenemia	1 per 500 000	AR	PT, aPTT	Sn = high	NA	Fibrinogen level
Hypofibrinogenemia	Less than afibrinogenemia		PT, aPTT	Sn = variable	NA	Thrombin time, fibrinogen activity
Dysfibrinogenemia	1 per million		Thrombin time, fibrinogen level	Sn = variable	NA	Thrombin time, fibrinogen antigen and activity level comparison, reptilase time
Platelet disorders						
ITP	Age-related	NA	CBC	Sn = high	NA	Antiplatelet Ab (rarely needed)

TABLE 1 Continued

Condition	Frequency	Inheritance	Screening Tests	Sn and Sp, %	PPV and NPV, %	Confirmatory Test
GT	Very rare	AR	PFA-100	Sn = 97–100	NA	Platelet aggregation testing Flow cytometry
BSS	Rare	AR	PFA-100	Sn = 100	NA	Platelet aggregation testing Flow cytometry
Platelet release/ storage disorders	Unknown, more common than other platelet function disorders	variable	PFA-100	Sn = 27–50	NA	Platelet aggregation and secretion Electron microscopy Molecular and cytogenetic testing

AD, autosomal dominant; AR, autosomal recessive; CBC, complete blood cell (count); NA, not available or not applicable; NPV, negative predictive value; PPV, positive predictive value; RVV, Russell viper venom (test); Sn, sensitivity; Sp, specificity; VW, von Willebrand; Ab, antibody.

<sup>a</sup> Values derived from data before 2008 National Institutes of Health Consensus guidelines. Sn and Sp using current diagnostic cutoffs unknown but would be expected to have higher Sp with lower Sn.

<sup>b</sup> May be reasonable to proceed directly to diagnostic testing depending on availability. See accompanying technical report for detailed discussion.<sup>25</sup>

functioning but decreased von Willebrand antigen (VWAg), resulting in low levels of both VWAg and VWF activity. Type 1 VWD has a wide range of bleeding severity and variable penetration among members of the same family. Type 2 VWD subtypes are characterized by abnormally functioning von Willebrand molecules and variable bleeding severity. Type 3 VWD presents with absence of VWF and a very low but detectable factor VIII level. The bleeding in type 3 VWD can be quite severe and can also include hemarthroses resulting from low factor VIII levels (Table 3).<sup>35</sup>

ICH has very rarely been reported in association with VWD. A single case series detailed 4 episodes of ICH thought to have occurred spontaneously in patients with no previous history of VWD. Patient ages ranged from 18 to 65 years of age.<sup>37</sup> There was an additional report of ICH in a newborn child with type 3 VWD and simultaneous sinovenous thrombosis.<sup>38</sup> One case report implicated type 1 VWD as a possible cause of subdural hematoma and retinal hemorrhages<sup>39</sup>; however, the laboratory findings in that case report did not meet the diagnostic criteria for definitive VWD,<sup>40</sup> and child abuse was not completely investigated, because no repeat skeletal survey was performed. Large mass-effect ICH associated with minor trauma in children with VWD outside of the typical age range for abusive head injury has been reported.<sup>41,42</sup> The extreme rarity of this presentation and the questions surrounding the validity of VWD causing ICH in some cases, indicate that VWD is not a typical cause of ICH.

The platelet function analyzer (PFA-100 [Siemens Healthcare Diagnostics, Tarrytown, NY]) has been proposed as a screening test for VWD, and results are often abnormal in patients who are known to have the disorder and have

VWF levels <30%. It is superior to the bleeding time because of ease of testing but does not test for blood vessel integrity and is affected by medications, platelet count, and hematocrit. The bleeding time is not recommended for bleeding disorder screening because of poor test characteristics and the invasive nature of the test.<sup>43</sup> The utility of the PFA-100 as a screening tool for VWD has not been established with population studies. It can be a useful tool as a preliminary screen for VWD or a platelet function defect, but if the result is normal and clinical suspicion remains high, other specific testing for these disorders should be obtained. Abnormal results of the PFA-100 test should also prompt further testing as well.<sup>35,40,44,45</sup> It is important to realize that the PFA-100 is not a diagnostic test for bleeding disorders but rather acts as a quick screen in situations in which more specific testing is unavailable or will be delayed. If access to specific testing is available, it might be rational to skip the PFA-100. Specific testing consists of VWAg, VW activity (also referred to as ristocetin cofactor by some laboratories), factor VIII activity, and often, von Willebrand multimer analysis. Some practitioners also include ristocetin-induced platelet agglutination and/or a collagen-binding assay. Contributing to the difficulty of diagnosis, particularly for type 1 VWD, VWF levels increase in response to stress, pregnancy, and inflammation and exhibit significant variability within an individual. In addition, some patients' test results will fall below the lower limits of normal but above the current upper diagnostic cutoff (31% to 50%), creating a diagnostic dilemma.<sup>35</sup> Because of these issues and the lack of a single diagnostic test, the diagnosis of VWD might require repeated testing and is best accomplished by a pediatric hematologist.

**TABLE 2** VWD Variants

Test	Type 1	Type 2A	Type 2B	PT-VWD	Type 2N	Type 2M	Type 3
VWF:Ag	Low	Low	Low	Low	Low	Low	Absent
VWF:Act	Low	VWF:Act/VWF:Ag <0.5	Low	Low	Low	VWF:Act/VWF:Ag <0.5	Absent
FVIII	Low	NI	NI	NI	Low	NI	Absent
RIPA	NI	Low	NI	NI	NI	Low	Absent
RIPA-LD	Absent	Absent	Increased	Increased	Absent	Absent	Absent
Frequency	70%–80%	10%–12%	3%–5%	0%–1%	1%–2%	1%–2%	1%–3%
Multimers	NI	Small	Small	Small	NI	NI	Absent

FVIII, factor VIII activity; NI, normal; PT-VWD, platelet-type pseudo VWD; RIPA, ristocetin-induced platelet aggregation; RIPA-LD, low-dose ristocetin-induced platelet aggregation; VWF:Act, VWF activity; VWF:Ag, VWF antigen. Reprinted with permission from Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Reports (USA). *Haemophilia*. 2008;14(2):191.

**TABLE 3** Common Bleeding Symptoms of Healthy Individuals and Patients With VWD

Symptoms	Healthy Individuals ( <i>n</i> = 500; <i>n</i> = 341; <i>n</i> = 88; <i>n</i> = 60), %	All Types of VWD ( <i>n</i> = 264; <i>n</i> = 1885), %	Type 1 VWD ( <i>n</i> = 42; <i>n</i> = 671), %	Type 2 VWD ( <i>n</i> = 497), %	Type 3 VWD ( <i>n</i> = 66; <i>n</i> = 385), %
Epistaxis	4.6–22.7	38.1–62.5	53–61	63	66–77
Menorrhagia	23.0–68.4	47–60	32	32	56–69
Bleeding after dental extraction	4.8–41.9	28.6–51.5	17–31	39	53–70
Ecchymoses	11.8–50.0	49.2–50.4	50	NR	NR
Bleeding from minor cuts and abrasions	0.2–33.3	36	36	40	50
Gingival bleeding	7.4–47.1	26.1–34.8	29–31	35	56
Postoperative bleeding	1.4–28.2	19.5–28	20–47	23	41
Hemarthrosis	0–14.9	6.3–8.3	2–3	4	37–45
Gastrointestinal tract bleeding	0.6–27.7	14	5	8	20

NR, not reported. Reprinted with permission from Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Reports (USA). *Haemophilia*. 2008;14(2):186.

Acquired von Willebrand syndrome is a rare phenomenon in pediatrics that can be associated with a number of clinical disorders, such as vascular anomalies, Wilms tumor and other cancers, cardiovascular lesions, hypothyroidism, lymphoproliferative or myeloproliferative disorders, storage disorders, autoimmune illnesses, monoclonal gammopathies, and certain medications. It has been estimated to occur at a prevalence of 0.04% to 0.13% in the general population, although the rate in pediatrics may be lower.<sup>46</sup> It is usually caused by autoimmune clearance or inhibition of VWF, increased shear stress causing consumption of VWF, or adsorption of VWF to cell surfaces. Laboratory tests used to diagnose acquired VWD are the same as those used to diagnose the congenital disorder. The addition of the von Willebrand propeptide can help to distinguish between the 2 entities.<sup>46</sup>

### Factor VII Deficiency

Factor VII deficiency is the only plasma coagulation factor deficiency in which the prothrombin time (PT) alone is prolonged. The incidence is estimated as 1 in 300 000 to 1 in 500 000. To date, more than 150 cases have been reported. A quantitative factor VII determination by standard factor assay methods provides a definitive diagnosis. Homozygous patients usually have less than 10 U/dL of factor VII. Heterozygous patients have factor VII levels between 40 and 60 U/dL and might represent single or double heterozygous abnormalities. It is very important to use age and gestational-related normal ranges, because factor VII is naturally low at birth.<sup>47</sup>

ICH has been reported in 4.0% to 6.5% of patients with factor VII deficiency and usually occurs in those with severe disease (<1% factor activity), both spontaneously and as a result of

trauma.<sup>48,49</sup> Central nervous system (CNS) bleeding was reported in 4.4% of factor VII-deficient patients as a presenting symptom in 1 registry and was found to occur in subjects younger than 6 months.<sup>49</sup> Bleeding symptoms can be extremely variable, and individuals can have minimal bleeding despite very low levels of factor VII. Using the most recent severity grading system, all patients with CNS bleeding have severe disease by definition.<sup>50</sup> Intracranial bleeding in these patients has been recorded as intraparenchymal, intraventricular, subdural, and tentorial, often accompanied with overlying cephalohematoma and usually occurring soon after birth.<sup>48,51,52</sup>

It is also important to rule out acquired factor VII deficiency as a result of vitamin K deficiency, liver disease, or consumptive coagulopathy. Although in these conditions, one would expect

more extensive coagulopathy, prolongation of the PT is often the only finding in the early stages of these disorders because of the short half-life of factor VII.

### Factor XI Deficiency

Factor XI deficiency (also termed hemophilia C) has an estimated frequency in the general population of 1 in 100 000.<sup>53,54</sup> Factor XI deficiency occurs more frequently in the Ashkenazi Jewish population; approximately 0.2% of Ashkenazi Jewish people are homozygous and 11.0% are heterozygous for this disorder.<sup>55</sup>

Bleeding in factor XI deficiency tends to be mild and associated with trauma or surgery. Bleeding symptoms often cannot be predicted by the factor level. Serious spontaneous hemorrhage is uncommon, even in individuals with very low factor levels.<sup>56</sup> There was 1 report of subarachnoid hemorrhage in a 53-year-old man with previously undiagnosed factor XI deficiency. This patient was also found to have cerebral aneurysms.<sup>57</sup>

Laboratory screening tests reveal a prolonged aPTT and normal PT, though the aPTT can be normal in heterozygous patients with mild deficiency. Other screening test results are normal. The specific assay for factor XI is the definitive test for this deficiency. In homozygous individuals, factor XI activity ranges from <1 U/dL up to 10 U/dL. Severe deficiency is defined as <15 U/dL.<sup>58</sup> It is important to compare results with age-matched norms, because healthy ranges in infants are lower than those in adults.<sup>59</sup>

### Factor XIII Deficiency

Factor XIII acts to covalently cross-link and stabilize fibrin. Because the PT and aPTT measure the production of fibrin from fibrinogen and the action of factor XIII is subsequent to the

formation of fibrin, these tests are normal in factor XIII deficiency and therefore cannot be used to screen for this disorder. The clot solubility test, which is the most commonly used test to screen for factor XIII deficiency, is abnormal only in very severe deficiencies of factor XIII, typically with factor XIII activities <3% of normal. This is the level most experts believe is necessary to cause spontaneous bleeding. A quantitative test for factor XIII exists.<sup>60,61</sup>

Deficiency of factor XIII is rare, occurring in only approximately 1 in 2 to 5 million people. However, intracranial bleeding is a common manifestation of this disorder, occurring in up to one-third of those with the deficiency.<sup>60,62</sup> Bleeding has been reported in subdural, intraparenchymal, and epidural locations, although because most registries and case reports have not specified the location of ICH, it is likely that it has occurred in more disparate sites. ICH has been reported to occur occasionally in patients with factor levels >3%, and therefore, the diagnosis can be missed if only the clot solubility test is used.<sup>63–65</sup> Other manifestations of factor XIII deficiency are umbilical cord bleeding, muscle hematomas, and postoperative bleeding.<sup>62</sup>

### Other Factor Deficiencies (Factors II, V, Combined V and VIII, and X)

#### *Prothrombin (Factor II) Deficiency*

Homozygous prothrombin deficiency occurs at an estimated prevalence of 1 in 1 to 2 million. The most common bleeding presentation in homozygous and heterozygous patients is bleeding involving the skin and mucous membranes. In the North American Rare Bleeding Disorders Registry (NARBDR), 11% of the subjects with factor II deficiency suffered a CNS complication (which included both ICH and ischemic stroke). In subjects with factor II levels <0.01 U/mL, the rate of ICH was 20%.<sup>66</sup>

Little description of these hemorrhages exists, although case reports have described subdural and epidural hematomas.<sup>67–69</sup> Homozygous patients can also present with surgical or trauma-induced bleeding.<sup>70</sup> Hemarthroses occurred in 42%, and gastrointestinal bleeding in 12% of homozygous subjects in one registry.<sup>71</sup> Acquired prothrombin deficiency can occur with vitamin K deficiency, liver disease, warfarin therapy, or overdose or in the setting of connective tissue disorders with accompanying lupus anticoagulant.<sup>70</sup>

The degree to which the PT and aPTT are prolonged varies from patient to patient, from a few seconds in some patients to more than 60 seconds in others, and occasionally, these screening results can be in the normal range.<sup>47,71</sup> The diagnosis is established with a factor assay for functional prothrombin (FII), along with immunologic tests for antigen levels if necessary.

#### *Factor V Deficiency*

Factor V deficiency is estimated to occur in 1 in 1 million people. Both homozygous and heterozygous patients with factor V deficiency typically have bleeding symptoms. Bleeding in homozygous patients tends to be spontaneous and occurs in the skin and mucous membranes, joints and muscles, genitourinary tract, gastrointestinal tract, and CNS. In the NARBDR, 8% of homozygous patients presented with intracranial bleeding.<sup>66</sup> Intrauterine subdural hematomas have been reported, as have spontaneous intraparenchymal hemorrhages.<sup>72,73</sup> Fifty-percent of heterozygous patients also had bleeding. Skin and mucous membrane bleeding were the most common manifestations, and none experienced ICH.<sup>66</sup>

Factor V can also be low in some platelet disorders, because it is also



present in platelet  $\alpha$  granules. In addition, acquired factor V deficiency can occur in patients with rheumatologic disorders or malignancies, patients using antimicrobial agents, or patients using topical bovine thrombin because of antibodies to factor V.<sup>74</sup>

In factor V deficiency, the PT and aPTT are both prolonged. Abnormal bleeding time or positive PFA-100 result is reported in approximately one-third of patients, perhaps related to a deficiency of factor V in platelet  $\alpha$  granules.<sup>53</sup> Other screening test results are normal. Definitive diagnosis requires a factor V assay.

#### *Combined Factor V and Factor VIII Deficiency*

Combined deficiency of factor V and factor VIII is rare, occurring in 1 in 1 million people, with higher frequency in populations in which consanguinity is more common. In this syndrome, factor V and factor VIII levels (both antigen and activity) range from 5% to 30% of normal.<sup>47,75</sup> Bleeding is usually mild to moderate. Patients typically have easy bruising, epistaxis, and gum bleeding, as well as bleeding after trauma or surgery. Menorrhagia and postpartum bleeding in affected women have also been reported. Hemarthrosis can also occur. Intracranial bleeding is rare but has been reported in 1 patient of 46 reported in the 2 largest registries of this disorder (27 and 19 subjects, respectively).<sup>76,77</sup>

Combined deficiency of factor V and factor VIII is passed down in an autosomal-recessive fashion and is attributable to a mutation of a protein of the endoplasmic reticulum–Golgi intermediate compartment (ERGIC 53) encoded by the *LMAN1* gene. This protein has been shown to be important in facilitating protein transport from the endoplasmic reticulum to

the Golgi apparatus. The decrease in factors V and VIII is, thus, attributable to defective intracellular transport and secretion unique to these 2 coagulation factors.<sup>47</sup> The PT and aPTT are prolonged in this disorder, with the prolongation of aPTT out of proportion to that of the PT.

#### *Factor X Deficiency*

The prevalence of factor X deficiency is 1 in 1 million in the general population and more common in populations with higher rates of consanguinity.<sup>47</sup> It is passed down in an autosomal-recessive pattern. As many as 1 in 500 people might be carriers of the disorder.<sup>78</sup> More severe deficiency would be expected to present earlier in life. Heterozygous cases might be identified incidentally by laboratory tests performed preoperatively or for another purpose.<sup>79</sup>

In the NARBDR, most bleeding symptoms in factor X deficiency were mucocutaneous, including easy bruising, followed by musculoskeletal bleeding. Intracranial bleeding occurred in 15% of the homozygous cohort, of which 54% had a factor X level  $<0.01$  U/mL. This cohort had the highest rate of ICH in the study, compared with other rare bleeding disorders. No heterozygous subjects experienced ICH.<sup>66</sup> Severely affected patients also present in the neonatal period with bleeding at circumcision, umbilical stump bleeding, or gastrointestinal hemorrhage.<sup>78</sup> The Greifswald factor X deficiency registry, which enrolls patients from Europe and Latin America, showed ICH in 21% of its cohort. ICH was reported only in patients who were homozygous and compound heterozygous.<sup>80</sup>

Severe liver disease can result in deficiency of all liver-produced factors, including factor X. Acquired factor X deficiency can also occur with amyloidosis, cancer, myeloma, infection,

and use of sodium valproate. Acquired inhibitors to factor X have also been reported in association with upper respiratory infections and burns and usually present with active bleeding from multiple body sites.<sup>78,80</sup> Because of the frequency of the associated diseases, acquired factor X deficiency is actually fairly common. Although the overall rate is unknown, this disorder has been reported in up to 5% of patients with amyloidosis.<sup>78</sup> Therefore, diagnosis of inherited factor X deficiency in the face of concomitant medical diagnoses should be made carefully and ideally with the assistance of a pediatric hematologist.

Both the PT and aPTT are usually prolonged and correct with a 1:1 mix with normal plasma; however, with 2 types of mutations, the PT is prolonged and the aPTT is normal, whereas the opposite is true in another variant.<sup>81</sup> The Russell viper venom test is usually prolonged, although it can be normal in some variants.<sup>53</sup> A factor X assay is the definitive test, although it is important to compare results with normal levels for age and exclude vitamin K deficiency before confirming the diagnosis.

#### **Vitamin K Deficiency**

Vitamin K is required to complete the posttranslational alteration of factors II, VII, IX, and X and proteins C and S. In the absence of vitamin K, precursor proteins are synthesized by hepatic cells, but because  $\gamma$ -carboxyglutamic acid residues are absent, the calcium-binding sites are nonfunctional. Deficiency of vitamin K results in induced functional deficiencies of all of these proteins. If the level of functional proteins falls below 30 U/dL, bleeding symptoms can result, and the PT and/or the aPTT will be prolonged.<sup>82</sup>

Vitamin K deficiency bleeding (VKDB) is most often seen in newborn infants in the first days of life (in infants who do

not receive vitamin K at birth). Because their livers are still immature, synthesis of the vitamin K–dependent factors in newborn infants is 30% to 50% of adult levels. Almost all neonates are vitamin K deficient as a result of poor placental transmission of maternal vitamin K and the lack of colonization of the colon by vitamin K–producing bacteria in the neonate, although not all infants will go on to have VKDB without prophylaxis.

VKDB is divided into 3 subtypes: early, classic, and late. Early VKDB occurs primarily in infants of mothers who have been on a vitamin K–blocking medication, such as anticonvulsants, and usually occurs within hours to the first week of life. Classic-onset VKDB occurs between the first week and first month of life and is largely prevented by prophylactic vitamin K administration at birth. Late VKDB occurs from the first month to 3 months after birth.<sup>83</sup> This deficiency is more prevalent in breastfed babies, because human milk contains less vitamin K than does cow milk. It can be precipitated by acquired or inherited gastrointestinal tract disease. Infants with liver disease might also be susceptible.

Manifestations of VKDB are bleeding in the skin or from mucosal surfaces, bleeding from circumcision, generalized ecchymoses, large intramuscular hemorrhages, and ICH. Although VKDB is rare in countries that provide prophylaxis, more than 50% of infants with late VKDB will present with ICH.<sup>82</sup> VKDB is prevented in the United States by encouraging administration of vitamin K to all newborn infants. Although most states have laws that require administration, some do not. Administration of oral vitamin K prophylaxis reduces the incidence of late VKDB from 4.4 to 10.5/100 000 live births to 1.5 to 6.4/100 000 live births.<sup>83</sup> Intramuscular vitamin K prophylaxis

prevents almost all cases of late VKDB; however, these can still occur, particularly if there is an unrecognized underlying cause of vitamin K deficiency. Secondary VKDB can occur in the setting of hepatobiliary disease, antimicrobial therapy, coumarol poisoning/rat poison ingestion, biliary atresia, and chronic diarrhea. ICH in this setting is rare but does occur.<sup>84</sup>

Diagnosis of VKDB is the same regardless of underlying cause. Laboratory tests show prolonged PT and possibly aPTT for age. Specific factor assays for factors II, VII, IX, and X are markedly decreased. In patients who have already received vitamin K as treatment or transfusion of plasma, measurement of proteins induced by vitamin K absence can confirm the diagnosis.<sup>82,84</sup>

Inherited combined deficiencies of vitamin K–dependent proteins occur when there is a mutation in the  $\gamma$ -glutamyl carboxylase gene or the vitamin K epoxide reductase complex. Fewer than 30 cases have been reported. Bleeding symptoms range from mild to severe, and ICH has been reported. Some patients also have dysmorphic features or skeletal defects.<sup>85</sup>

### Defects of Fibrinogen

Abnormalities of fibrinogen can result in complete lack of the protein (afibrinogenemia), decreased levels (hypofibrinogenemia), or an abnormally functioning molecule (dysfibrinogenemia). Clinical presentations range from mild to severe bleeding, and some patients have an increased risk of thrombosis as well, depending on the causative mutation.<sup>86,87</sup> Fibrinogen deficiencies can also be acquired in other medical disorders, such as liver disease or consumptive coagulopathy.<sup>87</sup>

Severe disorders of fibrinogen result in prolongation of PT and aPTT, but

milder disorders might be missed by these screening tests. Thrombin time tests conversion of fibrinogen to fibrin and is more sensitive to both deficiencies and abnormalities of fibrinogen than are PT and aPTT. Reptilase time is similar to thrombin time, except that it is not affected by heparin and might help distinguish hypofibrinogenemia from dysfibrinogenemia because of its slightly different mechanism of action. One can also measure the amount of fibrinogen antigen through a variety of methods.<sup>87</sup> Most patients with dysfibrinogenemia are asymptomatic. Bleeding, when it is present, is typically mild and triggered by surgery or trauma, and thrombosis can occur. The presence of a bleeding or thrombotic phenotype is dependent on the underlying mutation.<sup>88</sup> One case report of ICH and cephalhematomas in a child with suspected dysfibrinogenemia has been published. The case in that report was unique in that the patient had a long history of bleeding and almost undetectable fibrinogen levels. In addition, the patient appeared to inherit his disease in a double heterozygous-recessive manner from consanguineous parents, in contrast to most cases, which are autosomal dominant in nature.<sup>89</sup>

Overall, bleeding symptoms in afibrinogenemia are variable and can range from mild to life threatening. ICH has been reported in patients with afibrinogenemia (5% to 10% of patients).<sup>90,91</sup> Up to 85% of patients present in the neonatal period with umbilical cord bleeding.<sup>92</sup>

### Defects of Fibrinolysis

Fibrinolysis refers to the breakdown of the fibrin clot and is directed by plasmin. Plasmin is generated from plasminogen by the actions of plasminogen activators. The inhibitors of this action are  $\alpha$ -2 antiplasmin (AP, also known as  $\alpha$ -2 plasmin inhibitor

and plasmin inhibitor), thrombin-activatable fibrinolysis inhibitor, and plasminogen activator inhibitor type 1 (PAI-1). Deficiencies in AP and PAI-1 have been described, although both are rare.<sup>93,94</sup>

Patients with PAI-1 deficiency have been described as having mild to moderate bleeding symptoms, such as epistaxis, menorrhagia, and delayed bleeding after surgery or trauma. Spontaneous bleeding is rare. Diagnosis of PAI-1 deficiency can be problematic in that the laboratory assay used for diagnosis is inaccurate at low levels. Normal ranges often are reported beginning at 0, creating a large crossover between those patients with an abnormality in PAI-1 and healthy individuals. Only 2 of the reported deficiencies of PAI-1 have been correlated with an underlying genetic defect.<sup>94</sup> In 1 large kindred in whom a null mutation was identified, ICH and bleeding into joints were reported after mild trauma.<sup>95</sup> ICH has been reported in 2 adults in whom the only underlying coagulation abnormality identified was a low PAI-1 level. One adult also had osteogenesis imperfecta (OI).<sup>96,97</sup>

There have been approximately 40 cases of AP deficiency reported in the literature. AP deficiency is inherited in an autosomal-recessive pattern, although heterozygous patients can also present with bleeding. Acquired deficiency has also been reported in patients with liver disease, disseminated intravascular coagulation, and acute promyelocytic leukemia. Homozygous patients tend to have severe bleeding similar to that seen in factor XIII deficiency, although ICH has not been reported. Heterozygous patients can have bleeding in response to trauma, surgery, or dental procedures or can be asymptomatic.<sup>93,98</sup> Intramedullary hematomas of long bones, which can occur without a history of

trauma, are an unusual feature of homozygous AP deficiency.<sup>99,100</sup> Similar lesions have been seen in patients with afibrinogenemia. A shortened euglobulin lysis time can be used as a screening test for AP deficiency. Definitive diagnosis requires measurement of AP antigen and activity.<sup>101</sup>

### **Congenital Platelet Abnormalities**

Platelets interact with VWF to adhere to sites of vessel wall injury. Subsequent activation and aggregation of platelets, which includes the release of granular contents, leads to formation of a platelet plug. Congenital platelet disorders can result in fewer platelets, abnormal function of platelets, or a combination of the two. There is a wide range in the presenting symptoms of these disorders, from mild mucocutaneous bleeding to severe life-threatening hemorrhage.<sup>102</sup>

The most severe and best-characterized platelet function disorders are also the rarest. These are the autosomal recessive disorders Bernard-Soulier syndrome (BSS) and Glanzmann thrombasthenia (GT). BSS results from absence or abnormal function of the GP Ib-IX-V receptor, which is responsible for platelet adhesion to VWF. Patients with BSS also commonly have mild thrombocytopenia with enlarged platelet size. In GT, the  $\alpha$ IIb $\beta$ 3 platelet integrin is abnormal or missing, leading to impaired platelet aggregation, but the platelet count is normal. In both of these disorders, significant mucocutaneous bleeding and ICH have been reported, although ICH is rare, occurring in only 0.3% to 2.0% of patients with GT and even less in those with BSS.<sup>103,104</sup> The PFA-100 is a fairly reliable screening mechanism for these diagnoses (Table 1).<sup>102,103</sup>

Less well characterized but more common, the disorders of platelet signaling and secretion result from

a variety of defects. Platelet activation leads to a conformational change in the platelet and normally results in secretion of platelet granule contents, which recruits other platelets to the site of injury. Without this response, platelets are unable to recruit other platelets. This group of disorders includes Quebec platelet disorder, the MYH9-related disorders, Scott syndrome, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, and Wiskott-Aldrich syndrome. Most bleeding with these disorders is mild and manifests as excessive bruising or menorrhagia. The PFA-100 does not reliably screen for these disorders.<sup>105</sup> More specific platelet aggregation and secretion testing is required, and occasionally, electron microscopic examination or genetic mutation testing is necessary to confirm the diagnosis.<sup>102</sup> All forms of genetic inheritance have been reported. Most patients with these disorders present with mucocutaneous bleeding manifestations or bleeding after surgery or trauma. Bleeding symptoms are variable and dependent on the specific defect. Joint bleeding can occur in some disorders. ICH has been reported after childbirth in neonates and trauma in older individuals. Some platelet function disorders are part of syndromes with associated physical findings. Individual review of these entities is outside of the scope of this report.<sup>106,107</sup> Of note, a variety of medications can lead to platelet dysfunction (eg, nonsteroidal antiinflammatory drugs, sodium valproate); therefore, a careful medication history should be obtained before diagnosing a congenital platelet abnormality.<sup>108</sup> Acquired thrombocytopenia, whether from medication, immune thrombocytopenia (ITP), maternal ITP, or neonatal alloimmune thrombocytopenia, should be readily diagnosed on the basis of a complete

blood cell count. The rate of ICH in patients with idiopathic ITP is <1%.<sup>109</sup>

### Vascular Disorders

Certain vascular disorders can present with bruising or bleeding. Two disorders that might be confused for abuse are outlined. Discussion of all vascular disorders is outside of the scope of this report but can be found elsewhere.<sup>110</sup>

#### *Ehlers-Danlos*

Ehlers-Danlos syndrome (EDS) consists of a group of genetically and clinically heterogeneous connective tissue diseases that might be mistaken for child abuse.<sup>111,112</sup> The exact prevalence of EDS is unknown but is estimated to be 1 in 5000.<sup>113</sup> There are 6 genetic subtypes, which differ in the underlying biochemical defect, inheritance pattern, and clinical symptoms<sup>114</sup>; however, prominent bruising and bleeding are seen in all subtypes.<sup>115</sup> Mutations in collagen type I, type III, type V, or the genes involved in processing type I collagen result in most EDS subtypes. The tendency to bleed and/or bruise in EDS is caused by an abnormal capillary structure with deficiency of normal perivascular collagen. Cutaneous blood vessels are poorly supported and can rupture when subject to shearing forces. Tests for bleeding disorders are generally normal, except for the Hess test, which can be abnormal, indicating capillary fragility.<sup>115</sup> Clinically, the disorder manifests itself with easy bruising, bleeding gums, prolonged bleeding after surgical procedures, and menorrhagia. When evaluating children with possible abusive findings, pediatricians should assess for the typical signs of EDS. Skin hyperextensibility describes skin that extends easily and snaps back after release and is best tested at the volar surface of the forearm.<sup>115</sup> Widened, thin scarring often occurs at knees,

shins, elbows, and the forehead.<sup>115</sup> Joint hypermobility is also often seen. The vascular type of EDS, also known as EDS type IV, particularly might be confused with child abuse.<sup>111</sup> The precise prevalence is not known but has been estimated to be 1 in 250 000.<sup>116,117</sup> Both autosomal-recessive and -dominant inheritance patterns, as well as sporadic mutations, have been described.<sup>118</sup> The clinical diagnosis is made on the basis of 4 criteria: easy bruising; skin with visible veins; characteristic facial features; and rupture of arteries, uterus, or intestines.<sup>114</sup> The diagnosis is confirmed by the demonstration that cultured fibroblasts synthesize abnormal type III procollagen molecules or by the identification of a mutation in the gene for type III procollagen (*COL3A1*).<sup>119</sup> Excessive bruising is the most common presentation, but other severe complications, such as spontaneous rupture of the bowel and hemorrhagic pneumothorax, can occur. Vascular ruptures, including renal or splenic arteries, aneurysmal rupture, or stroke can also occur. ICH, including subdural hemorrhage, has only very rarely been described, and findings would likely not be confused with those commonly seen in inflicted head injury.<sup>118,120</sup> Severe complications are rare in childhood.<sup>116</sup> Joint hypermobility is often limited to the small joints of the hands. Skin hypermobility is typically not present, but the skin is often translucent, showing a visible venous pattern.<sup>121,122</sup> The characteristic facial appearance includes prominent eyes, pinched nose, small lips, hollow cheeks, and lobeless ears.<sup>117,121</sup>

If clinical suspicion exists, the diagnosis of most subtypes of EDS can be evaluated with biochemical and molecular analysis. Cultured skin fibroblasts can be used for gel electrophoresis of collagen types I, III,

and V. For the vascular subtype (EDS type IV), biochemical analysis of type III procollagen identifies more than 95% of patients, whereas molecular screening of the *COL3A1* gene identifies up to 99% of mutations.<sup>117,119</sup>

#### *OI*

OI is a heterogeneous group of diseases characterized by bone fragility, dentinogenesis imperfecta, and adult hearing loss.<sup>123</sup> OI has been associated with easy bruising and ICH after minimal or no trauma.<sup>124,125</sup> Bleeding diathesis in OI is thought to occur as a result of platelet dysfunction and capillary fragility.<sup>126,127</sup>

Inheritance is generally autosomal-dominant, but autosomal-recessive inheritance and new mutations are known to occur. Most cases are the result of mutations in *COL1A1* and *COL1A2*. At least 8 types of OI are known to exist, and the prevalence is approximated at 1 in 15 000 to 1 in 20 000.<sup>128,129</sup>

Testing for OI by using DNA sequencing or collagen analysis is available. Sensitivities and specificities vary depending on the type of OI, but approximately 90% of individuals with OI types I, II, III, and IV (but none with OI types V, VI, VII, or VIII) have an identifiable mutation in either *COL1A1* or *COL1A2*.<sup>125</sup> Rare case reports have attributed multiple varieties of ICH, including subdural hematomas in children, to OI.<sup>130–134</sup> Additionally, 3 cases of relatively minor retinal hemorrhages coupled with subdural hematomas have been reported after trivial trauma in patients with OI type 1.<sup>124</sup> Despite these case reports, OI is a rare condition, and the occurrence of subdural hematomas and/or retinal hemorrhages attributable to OI is exceedingly rare.

Despite the reported associations of OI with easy bruising, no large-scale studies have characterized the

frequency and nature of bruising in children with OI or compared these patterns to nonabused children without OI or abused children. In children with bruises only, in the absence of other clinical indicators of OI, such as short stature, blue sclera, wormian or demineralized bones, or family history, it is generally not necessary to rule out OI via collagen or DNA testing.

### Unsupported Hypotheses

Many alternative hypotheses have been proposed to explain bruising or bleeding concerning for abuse that are not supported by scientific evidence. It is outside of the scope of this report to discuss all hypotheses of this nature. Two of the more common are intracranial findings concerning for abuse caused by the effects of vaccines or by intracranial thrombosis.

#### *Vaccines Mimicking Abusive Head Trauma*

Some have proposed that vaccines cause findings that might be confused with abusive head trauma.<sup>135–137</sup> The hypothesized mechanism is a combination of ascorbate (vitamin C) depletion and foreign protein in vaccines causing a high histamine level, which then leads to capillary fragility and venous bleeding. No scientific evidence exists to support the hypothesis that immunizations cause findings that might be confused with inflicted trauma.

#### *Intracranial Venous Thrombosis Mimicking Abusive Head Trauma*

The incidence of intracranial venous thrombosis in children is estimated to be 0.67 cases per 100 000 children per year.<sup>138</sup> Of these, approximately 28% involve hemorrhagic venous infarction; thus, the incidence of hemorrhagic venous infarction is 0.19 cases per 100 000 children per year.<sup>138</sup> Common congenital associations include factor V Leiden, prothrombin gene mutation, protein C or S

deficiency, and antithrombin deficiency. Other causes include infections (eg, otitis media, mastoiditis, sinusitis), dehydration, and trauma. Affected infants typically present with seizures and diffuse neurologic signs.<sup>138</sup> No studies have systematically compared characteristics of ICH resulting from intracranial thrombosis with characteristics of ICH resulting from trauma. A single study evaluating nontraumatic intracranial venous thrombosis detected no subdural hematoma in the study population ( $n = 36$ ).<sup>139</sup> Additionally, bleeding from intracranial thrombosis has a typical appearance on magnetic resonance imaging, including localized bleeding near the thrombus, typically in an intraparenchymal distribution. This appearance is in contrast to the typical presenting features of deceleration head trauma, including thin-film subdural hemorrhages involving the interhemispheric region and the cerebral convexities.<sup>22</sup> If there is concern for intracranial thrombosis, magnetic resonance venography is the test of choice. Given the significant difference in appearance of ICH as a result of intracranial venous thrombosis in comparison with ICH from deceleration trauma, confusion between the 2 conditions should not exist.

### INTERPRETATION OF TESTS

It should be noted that aPTT can be falsely prolonged in certain conditions, such as in the presence of a lupus anticoagulant, or can be prolonged and not indicate a true bleeding disorder, such as in factor XII deficiency or other contact factor deficiencies. In addition, patients who suffer a traumatic brain injury often have a transient coagulopathy that does not reflect an underlying congenital disorder.<sup>140,141</sup> It should also be noted that coagulation tests are very sensitive to specimen handling and should be performed in

laboratories experienced with these assays. Inappropriate handling commonly leads to false-positive results.

Patients who have sustained significant trauma also might receive transfusions of blood products. Fresh-frozen plasma (FFP) is prepared by separating the liquid portion of blood from the cellular portion after the collection of whole blood or by collecting the liquid portion of blood by using apheresis technique. By definition, each milliliter of FFP contains 1 unit of all normal coagulation factors and inhibitors of coagulation, but in general, 10 to 20 mL/kg will raise factor levels only by 15% to 25%.<sup>142</sup>

Cryoprecipitate is prepared by thawing FFP and refreezing the precipitate. It contains high concentrations of fibrinogen, factor VIII, VWF, and factor XIII. Each coagulation factor has a different half-life (Table 4). Therefore, the administration of FFP or cryoprecipitate will affect the investigation for a coagulation factor deficiency differently depending on the factor being measured.

### FREQUENCY OF THE CONDITION AND MEDICAL PROBABILITY

Specific data regarding the prevalence of bleeding disorders within the population of children with ICH or subdural hemorrhage are not available; however, there are data on the frequency of ICH as a result of specific bleeding disorders. If the prevalence of a condition and the frequency of a particular presentation of that condition are known, a physician can construct the probability of that specific condition (bleeding disorder) resulting in the specific presentation (ICH):

$$P(B) = \text{Prev}(A) \times \text{Prev}(B|A),$$

where B is ICH attributable to condition A, P is probability, and Prev is prevalence. For example, factor XIII deficiency is extremely rare, occurring at an

**TABLE 4** Half-Lives of Coagulation Factors

Factor	Half-Life Postinfusion, h
Fibrinogen	96–150
II	60
V	24
VII	4–6
VIII	11–12
IX	22
X	35
XI	60
XIII	144–300
VWF	8–12

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upper limit estimated population prevalence of 1 in 2 million; however, it can present with isolated intracranial bleeding in up to one-third of cases.<sup>59</sup> The estimated probability that factor XIII deficiency will cause an ICH in a person in the population at large is:

$$\begin{aligned} & (\text{Prevalence of factor XIII deficiency}) \\ & \times (\text{Prevalence of ICH in factor XIII deficiency}) \\ & (1/2 \text{ million}) \times (1/3) = 1/6 \text{ million} \end{aligned}$$

Table 5 contains probabilities for congenital bleeding disorders to cause ICHs in the population at large.

**TABLE 5** Probabilities for Congenital Coagulopathies to Cause ICH<sup>a</sup>

Condition	Prevalence of Condition, Upper Limits	Prevalence of ICH, Upper Limits	Probability <sup>b</sup>
VWD	1/1000	Extremely rare	Low
Factor II deficiency	1/1 million	11%	1/10 million
Factor V deficiency	1/1 million	8% of homozygotes	1/10 million homozygotes
Combined factors V and VIII deficiency	1/1 million	2%	1/50 million
Factor VII deficiency	1/300 000	4%–6.5%	1/5 million
Factor VIII deficiency	1/5000 males	5%–12%	1/50 000 males
Factor IX deficiency	1/20 000 males	5%–12%	1/200 000 males
Factor X deficiency	1/1 million	21%	1/5 million
Factor XI deficiency	1/100 000	Extremely rare	Low
Factor XIII deficiency	1/2 million	33%	1/6 million
AP deficiency	40 cases reported	Not reported	Low
PAI-1 deficiency	Extremely rare	Common	Low
Afibrinogenemia	1/500 000	10%	1/5 million
Dysfibrinogenemia	1/1 million	Single case report	Low

<sup>a</sup> The probability of having a specific bleeding disorder increases in the setting of a family history of that specific named bleeding disorder or if the patient is from an ethnicity in which a specific bleeding disorder is more common (eg, Ashkenazi Jewish people and factor XI deficiency).

<sup>b</sup> "Probability" indicates the probability that an individual in the general population would have the following specific coagulopathy causing an ICH.

No calculation was made in situations in which no reliable estimates of prevalence of the condition or frequency of ICH exist. The most liberal prevalence and frequency numbers were used, so as to provide the upper limits of probability.

## CONCLUSIONS

In cases of suspected abuse involving bruising and/or bleeding, physicians must consider the possibility of coagulopathies causing or contributing to the findings. In many cases, the possible coagulopathies can be effectively evaluated by a thorough history and physical examination, and possibly by the specific nature of the child's findings; however, in some cases, a laboratory evaluation for coagulopathies might be necessary. The diagnosis of a bleeding disorder does not automatically rule out the presence of nonaccidental trauma. Because of the chronic nature of their disease, children with bleeding disorders may be at higher risk of abuse.<sup>143</sup>

Limited evidence exists comparing bruising and bleeding in children with

coagulopathies with child victims of abuse. Conducting such studies would be difficult, given the overall rarity of coagulopathies; however, large databases exist for rare hematologic conditions, and modification of these databases to include factors, such as location of bruising or location/character of ICH, which would assist in discriminating between bleeding disorders and abuse, would be beneficial. In the absence of such data, physicians must use existing data, including epidemiologic and clinical factors, in their decision-making process.

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