

# Approach to the Diagnosis and Management of Common Bleeding Disorders

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Semin Thromb Hemost

## Abstract

### Keywords

- ▶ mucocutaneous bleeding
- ▶ bleeding scores
- ▶ bruising
- ▶ epistaxis
- ▶ menorrhagia
- ▶ von Willebrand disease
- ▶ hemophilia
- ▶ platelet function disorder

Mild mucocutaneous bleeding symptoms are common in the general population. Differentiating normal from pathological bleeding complaints begins with a detailed bleeding history that assesses: the pattern (primary versus secondary hemostasis), the severity, and the onset (congenital versus acquired) of bleeding. Bleeding assessment tools have been developed to aid in determining whether bleeding symptoms are outside of the normal range. Although the clinical pattern of bleeding and family history directs laboratory investigations, von Willebrand disease, the most common and best characterized of the primary hemostatic disorders, is often the first diagnosis to be considered. Clinical management focuses on the particular symptoms experienced by the patient. Medical interventions include replacement of the factor that is deficient or defective, or indirect treatments, such as antifibrinolytics (tranexamic acid), desmopressin, and hormone-based therapy (e.g., oral contraceptive pill for menorrhagia).

The evaluation of a patient presenting with bleeding symptoms is complicated by several challenges. Mild mucocutaneous bleeding symptoms are frequently reported by the normal population, and exhibit a great deal of overlap with those suffering from mild bleeding disorders.<sup>1-5</sup> Bleeding histories are subjective and significant symptoms may be interpreted as part of the spectrum of normal bleeding. The differential diagnosis is broad, ranging from defects in primary hemostasis (von Willebrand disease [VWD] or platelet function disorders [PFD]), coagulation deficiencies or dysfunction (e.g., mild hemophilia A [HA], hemophilia B [HB] or dysfibrinogenemia) as well as connective tissue disorders (Ehlers-Danlos Syndrome [EDS]). Many of the available laboratory investigations are not well standardized, and some can be difficult to interpret.<sup>6,7</sup> A significant portion of patients with clinically significant abnormal bleeding will not be categorizable into any specific diagnostic category after extensive investigation.<sup>8</sup> Awareness of these issues is of paramount importance in managing the investigation of a patient presenting with bleeding.

## Patient History

For each bleeding symptom, inciting factors, frequency, duration, severity, and the need for medical intervention should be elicited. In particular, it can be informative to learn if there was the presence or absence of excessive bleeding with past hemostatic challenges such as menses, invasive surgical procedures, dental extractions, injuries and childbirth. In children, relevant specific hemostatic challenges include postdelivery cephalohematoma, umbilical stump bleeding, excessive bleeding with heel pokes or venipuncture and/or bleeding at the time of circumcision. Characteristics that correlate with menorrhagia, which is defined as blood loss of > 80 mL include clots larger than ~1 inch, low serum ferritin, and the need to change a pad or tampon more than hourly.<sup>9</sup> Philipp et al developed a screening tool for women with menorrhagia for an underlying bleeding disorders with a sensitivity of 82%.<sup>10</sup> The screen is positive if the patient reports (1) duration of menses is greater than or equal to 7 days, "flooding" or impairment of daily activities with

**Issue Theme** Expert Approaches to Common Bleeding and Thrombotic Problems; Guest Editors, Catherine P.M. Hayward MD, PhD, FRCPC, and Kathryn E. Webert, MD, MSc, FRCPC.

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Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0032-1326783>.  
ISSN 0094-6176.

menses, (2) a history of treatment for anemia, (3) a family history of a diagnosed bleeding disorder, or (4) a history of excessive bleeding with tooth extraction, delivery or miscarriage, or surgery.

A congenital bleeding disorder is often suspected when there is a lifelong history of bleeding and a family history of a bleeding disorder and/or consanguinity. On the other hand, an acquired bleeding problem may be suspected when there are comorbidities such as renal disease, liver disease, and hypothyroidism. Acquired bleeding can also result from anticoagulant therapy and medications that inhibit platelet function. Some dietary supplements, such as the commonly used garlic, ginkgo, and ginseng, have been reported to impair platelet function and increase bleeding symptoms.<sup>11</sup>

Bleeding symptoms reported by patients with mild to moderate bleeding disorders overlap significantly with those reported by normal individuals. Studies comparing VWD to normal populations are summarized in ►Table 1. A positive family history of bleeding is sometimes reported among normal individuals: in a cohort study, parents and guardians reported a family history of bleeding in 44% of healthy children undergoing tonsillectomy.<sup>12</sup> A negative family history does not exclude a bleeding disorder.<sup>4,13</sup>

### Bleeding Assessment Tools

In recent years, attempts to standardize bleeding assessments have been made by the development of quantitative scoring systems, also known as BATs. A group of Italian investigators pioneered this work by developing and validating a BAT for the diagnosis of type 1 VWD in a primarily adult population.<sup>3</sup> Since this initial work, several adaptations have been developed and tested in both primary and tertiary care settings for VWD as well as PFD and other inherited bleeding disorders.

<sup>14–21</sup> The sensitivity and positive predictive value of the questionnaires vary depending on the setting and patient population enrolled, but the negative predictive value is  $> 0.99$ ,<sup>18,19,21</sup> meaning that a negative bleeding score nearly excludes a clinically significant inherited bleeding disorder. In an attempt to consolidate and standardize the BATs, the ISTH/SSC Joint VWF and Perinatal/Pediatric Hemostasis Subcommittees Working Group have established a revised BAT that is available online at [http://www.isth.org/default/assets/File/Bleeding\\_Type1\\_VWD.pdf](http://www.isth.org/default/assets/File/Bleeding_Type1_VWD.pdf).<sup>22</sup> Studies to establish validity and reliability of this new tool are ongoing.<sup>14</sup> A limitation of the current BATs is that they take into account the worst episode of bleeding within each category but do not account for the frequency of bleeding. In addition to the BATs derived from the Italian group's work, several other tools have been developed and published, including a comprehensive web-based system developed at Rockefeller University,<sup>23,24</sup> tools designed exclusively for the assessment of menorrhagia,<sup>10,25,26</sup> and a questionnaire specific for Quebec platelet disorder.<sup>27</sup>

### Physical Examination

Sequelae of bleeding include the presence of petechiae, ecchymoses and/or subcutaneous hematomas, evidence of arthropathy, hemarthrosis, and signs of anemia. Skin extensibility or widened atrophic scars may indicate a collagen defect. Joint hypermobility can be assessed using the Beighton scale<sup>28</sup> that involves five simple maneuvers, which are summarized in ►Table 2. In addition, if a secondary bleeding disorder is suspected, physical findings of potential secondary causes include cardiac murmurs, lymphadenopathy, splenomegaly, hepatomegaly, thyroid goiter, evidence of

**Table 1** Incidence (%) of bleeding symptoms in patients with VWD and in healthy individuals

Symptoms	Normals, <i>n</i> = 500, <sup>1</sup> <i>n</i> = 341, <sup>4a</sup> <i>n</i> = 215 <sup>3</sup>	All types VWD, <i>n</i> = 264 <sup>1</sup>	Type 1 VWD, <i>n</i> = 671 <sup>5</sup> <i>n</i> = 84 <sup>3</sup>	Type 2 VWD, <i>n</i> = 497 <sup>5</sup>	Type 3 VWD, <i>n</i> = 348, <sup>2</sup> <i>n</i> = 66 <sup>5</sup>
Epistaxis	5–11	63	54–61	63	66–77
Menorrhagia	17–44	60	32–67	32	56–69
Postdental extraction bleeding	5–11	52	31–72	39	53–77
Hematomas	12	49	13	14	33
Bleeding from minor wounds	0.2–5	36	36–46	40	50
Gum bleeding	7–37	35	31	35	56
Postsurgical bleeding	1–6	28	20–38	23	41
Postpartum bleeding	3–23	23	17–61	18	15–26
Gastrointestinal bleeding	1	14	5	8	19.2
Joint bleeding	6	8	3	4	37–45
Hematuria	1–8	7	2	5	1–12
Cerebral bleeding	NR	NR	1	2	9

Abbreviation: NR, not reported; VWD, von Willebrand disease.

Data are summarized from references<sup>1–5</sup>.

<sup>a</sup>341 controls were sent a questionnaire. Exact number of respondents in the studies cited was not reported.

**Table 2** Beighton score

Maneuver	Points
Passive dorsiflexion of the little (5th) finger > 90°	1 point for each hand
Passive apposition of the thumbs to the flexor aspects of the forearm	1 point for each hand
Hyperextension of the elbows beyond 10°	1 point for each elbow
Hyperextension of the knees beyond 10°	1 point for each knee
Forward flexion of the trunk with knees fully extended so that palms of the hands rest flat on the floor	1 point

Adapted from reference<sup>28</sup>.

A score greater or equal to 5 indicates joint hypermobility and raises the possibility of an underlying connective tissue disorder.

cirrhosis, and findings associated with Cushing syndrome (moon facies, central obesity, striae, etc.).

### Clinical Manifestations of Bleeding Disorders

No single bleeding symptom is pathognomonic for a specific bleeding disorder and significant overlap exists among the clinical manifestations of all the bleeding disorders. However, the symptoms that are characteristic of bleeding disorder categories are summarized in **Table 3**. Defects of primary hemostasis (PFD and VWD) are characterized by excessive mucocutaneous bleeding. Hemarthrosis, muscular hematomas, and bleeding into the central nervous system or gastrointestinal tract can occur in moderate to severe VWD and PFD.<sup>29</sup> Severe defects of secondary hemostasis (deficiencies in coagulation factors) manifest deep tissue bleeding such as large palpable ecchymoses, deep soft tissue hematomas,

intramuscular hematomas, and hemarthrosis. Abnormalities of connective tissue/collagen, such as EDS can result in spontaneous bruising, which often recur in the same areas causing a characteristic discoloration of the skin from hemosiderin deposition.<sup>30</sup> Defects in fibrinolysis are associated with mild to moderate, delayed bleeding often after injury, or surgery (e.g., in the case of plasminogen activator inhibitor-1 [PAI-1] deficiency)<sup>31</sup> or severe spontaneous bleeding symptoms reminiscent of severe hemophilia (e.g., in the case of severe  $\alpha_2$ -antiplasmin deficiency).<sup>32</sup> The rare complication of intramedullary hemorrhage into the diaphyses of the long bones has been described in severe  $\alpha_2$ -antiplasmin deficiency.<sup>32</sup> Acquired bleeding disorders can affect any of the components of hemostasis: platelets, coagulation factors, and even the vessel wall. Therefore, the pattern of bleeding will depend on the underlying pathological process.

**Table 3** Clinical manifestations of bleeding disorder categories

Symptom	PFD/VWD	Clotting factor deficiencies	Connective tissue disorders
Location of bleeding symptoms	Mucocutaneous bleeding: epistaxis, oral cavity, GI and GU bleeding	Deep tissue bleeding: joints and muscles	Mucocutaneous bleeding
Ecchymoses	Common, superficial, can be associated with small subcutaneous hematomas	Large subcutaneous and soft tissue hematomas	Common and may be associated with subcutaneous hematomas
Petechiae	Common	Uncommon	Common
Bleeding after minor cuts	Common	Uncommon	Common with abnormal healing and scar formation
Deep tissue bleeding (joint and muscle bleeds)	Uncommon	Spontaneous in severe factor deficiencies; provoked in moderate to mild deficiencies	Uncommon
Bleeding with invasive procedures	Immediate	Delayed	Immediate
Manifestations other than bleeding	Rare subtypes of PFD can be associated with hearing loss, mental retardation, albinism	Dysfibrinogenemia has an increased risk of thrombosis; FXIII deficiency is marked by poor wound healing; both are associated with recurrent miscarriages	Skin hyperextensibility; delayed wound healing; atrophic scarring; joint hypermobility

Abbreviations: F, factor; GI, gastrointestinal; GU, genitourinary; PFD, platelet function disorder; VWD, von Willebrand disease.

**Table 4** Suggested approach to investigations for bleeding disorders

<b>First line</b> – Includes: screening tests and causes/consequences of bleeding disorders	<ul style="list-style-type: none"> <li>• CBC, PBS, APTT, PT, TT, fibrinogen</li> <li>• Ferritin, renal and liver function tests, TSH</li> <li>• Consider PFA-100</li> </ul>
<b>Second line</b> – In the presence of normal screening tests, this line of investigations will identify the two most common causes of mild to moderate bleeding disorders	<ul style="list-style-type: none"> <li>• VWF:Ag, VWF:RCo, FVIII</li> <li>• Platelet function testing (LTA and EM)</li> </ul>
<b>Third line</b> – Performance of the following tests should be based on abnormal screening tests or in the presence of severe bleeding symptoms with unremarkable testing thus far	<ul style="list-style-type: none"> <li>• Mixing studies</li> <li>• Factor assays (e.g., II, V, VII, XI, XIII)</li> <li>• Inhibitor assays</li> <li>• Urea clot stability or Euglobulin clot lysis time</li> <li>• <math>\alpha_2</math>-antiplasmin level and PAI-I activity</li> <li>• Reptilase time</li> </ul>

Abbreviations: APTT, activated partial thromboplastin time; BT, bleeding time; CBC, complete blood count; EM, electron microscopy; F, factor; LTA, light transmission aggregometry; PAI-1, plasminogen activator inhibitor-1; PBS, peripheral blood smear; PT, prothrombin time; TSH, thyroid-stimulating hormone; TT, thrombin time; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity. Only those with a high clinical index of suspicion should be investigated. If the history clearly indicates a particular disorder, the appropriate investigations should be done at first-line testing.

### Laboratory Testing

The approach to the investigation of a bleeding disorder is outlined in **Table 4**.

#### Screening Tests

Screening tests include complete blood count (CBC), peripheral blood smear (PBS), activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), and fibrinogen concentration. **Table 5** outlines the differential diagnosis of abnormal coagulation tests.<sup>33</sup> PFA-100, which measures primary hemostasis under conditions of high shear is a simple, rapid noninvasive test that does not require specialized training. PFA-100 is abnormal in patients with severe VWD but lacks sensitivity in persons with mild type 1 VWD (VWF level > 0.30 IU/mL) where reported sensitivities

range from 61.5 to 71%.<sup>33-35</sup> Similarly, a review of the evidence on PFA-100 measurement in congenital platelet disorders demonstrated sensitivities that range from 24 to 80% and low specificity with PFA-100 measurement being highly dependent on several factors including hematocrit, platelet count, and VWF levels.<sup>36</sup> Thus, the role of PFA-100 in the algorithm for screening of disorders of primary hemostasis is not clear. Common causes of acquired bleeding disorders such as renal, liver, and thyroid disease should be excluded at the time of screening.

#### Second-Line Tests

Unless the screening tests suggest an alternate diagnosis, tests for VWD and PFD should be performed. VWD testing includes measuring VWF:Ag, VWF:RCo (ristocetin cofactor activity),

**Table 5** Differential diagnosis of abnormal screening tests and further investigations

PT	APTT	TT	Fibrinogen	Interpretation – check for
N	N	N	N	Normal results can be seen with mild factor deficiencies, mild VWD, PFD, FXIII deficiency, PAI-1 deficiency, $\alpha_2$ -antiplasmin deficiency, and connective tissue disorders
↓	N	N	N	FVII deficiency, warfarin therapy, early liver failure, early DIC
N	↓	N	N	Deficiencies of FVIII, FIX, FXI, FXII VWD if FVIII is significantly decreased
↓	↓	N	N	Multiple factor deficiencies Single factor deficiencies affecting factors FII, FV or FX Warfarin Direct Xa inhibitors (e.g., rivaroxaban) <sup>72</sup>
↓	↓	↓	↓	Dys-, hypo-, or afibrinogenemia Late DIC or liver failure Direct thrombin inhibitors (e.g., dabigatran) <sup>72</sup>
↓	↓	↓	N	Large amounts of heparin (reptilase time will be normal)
N	N	↓	↓	Mild cases of dysfibrinogenemia or hypofibrinogenemia
N	↓	↓	N	Heparin

Abbreviations: ↓, decreased; ↑, increased; DIC, disseminated intravascular coagulation; F, factor; N, within normal range, PAI-1, plasminogen activator inhibitor-1; PFD, platelet function disorder; VWD, von Willebrand disease.

and factor VIII (FVIII):C. Intra-patient variations in VWF studies are influenced by physiological factors such as stress and hormones. Also, several analytical issues (e.g., the high degree of assay variability) and pre-analytical issues can complicate the diagnostic workup of VWD.<sup>6</sup> In cases of borderline abnormal results, at least two sets of tests using appropriately handled samples are needed to confirm or refute the diagnosis of VWD with testing being avoided in stressed, ill, or pregnant patients.

Platelet function disorder testing includes light transmission aggregometry (LTA) assessments of platelet function and electron microscopy to assess for dense granule deficiency. In a prospective cohort of individuals referred for bleeding disorder assessments, abnormal aggregation results by LTA were associated with bleeding disorders (OR 32, 95% CI, 4.3 to 245).<sup>37</sup> These tests are time-consuming, time-sensitive, and subject to significant pre-analytical and analytical variables. Efforts to standardize LTA methods are ongoing.<sup>38</sup> Abnormal results should be confirmed with repeat testing on another sample. Low numbers of dense granules per platelet by electron microscopy are diagnostic of dense granule deficiency (OR estimated as infinite, 95% CI, 1.12 to infinity)<sup>37</sup> that can be associated with normal aggregation findings.<sup>39</sup> North American consensus guidelines provide recommendations on how to further investigate LTA abnormalities that suggest specific diagnoses.<sup>38</sup>

### Third Line Tests

The follow-up of a prolonged PT or APTT can include a mixing study, to aid in the differentiation of a factor deficiency versus an inhibitor, both of which then need to be confirmed with appropriate factor assays or inhibitor studies. This test has no clinical utility if the baseline APTT or PT is not prolonged. Coagulation screening tests can be normal with mild deficiencies. Factor assays are helpful to determine if there is a deficiency in FVIII or FIX, as mild hemophilias, represent a common inherited factor deficiency. Other factor deficiencies are rare, but should be considered in specific populations, such as FXI deficiency in the Ashkenazi Jewish population and consanguineous families.<sup>40</sup> If first and second-line investigations have not yet yielded a diagnosis, there is a possibility of obtaining a diagnosis by tests for factor XIII (FXIII) deficiency (clot stability and quantitative assays)<sup>41</sup> and the fibrinolytic defects,  $\alpha_2$ -antiplasmin deficiency ( $\alpha_2$ -antiplasmin assays),<sup>32</sup> and PAI-1 deficiency (euglobulin clot lysis time and PAI-1 activity assays).<sup>31</sup>

## Differential Diagnosis

### von Willebrand Disease

von Willebrand factor (VWF) is an adhesive multimeric plasma glycoprotein that performs two functions in hemostasis: it mediates platelet adhesion to injured subendothelium via glycoprotein Ib-IX-V, and it binds and stabilizes FVIII in the circulation. VWD is caused by defective or deficient plasma VWF and it represents the most common inherited bleeding disorder, affecting as much as 0.1 to 1% of the population.<sup>42-44</sup> Bleeding symptoms associated with VWD

reflect the defect in primary hemostasis, unless the deficiency of VWF is severe, which can cause additional, hemophilia-like symptoms. In severe VWD, FVIII levels may be sufficiently decreased to prolong the APTT.

VWD classification comprises three main subtypes.<sup>45</sup> Type 1 VWD is a partial quantitative deficiency of VWF, type 2 VWD a qualitative defective VWF that is further divided into four subtypes based on specific functional and structural defects in the VWF protein, and type 3 VWD is a complete deficiency of VWF. The two main treatments for VWD are desmopressin (1-deamino-8-D-arginine vasopressin or DDAVP), which raises plasma levels of VWF and FVIII, and VWF concentrates. Other treatment options include antifibrinolytic drugs (tranexamic acid and amino caproic acid) and hormone therapy (oral contraceptive pill, OCP).

### Ehlers–Danlos Syndrome

EDS comprises a heterogeneous group of connective tissue diseases that affect the skin, ligaments, joints, blood vessels, and internal organs. Most subtypes are caused by mutations in structural collagen genes or in genes encoding enzymes that are involved in collagen posttranslational modification. Prevalence is ~1/5,000 births, with no racial predisposition. No specific therapy exists for EDS. Interventions for bleeding/bruising may include supplementation of ascorbic acid (a cofactor for cross-linking of collagen fibrils, which can improve bruising symptoms), and DDAVP perioperatively.<sup>46,47</sup>

### Thrombocytopenia

The mean platelet volume, platelet size and morphology, as well as additional abnormalities in the other cells lines may be helpful in narrowing the differential diagnosis. There are several congenital platelet disorders in which thrombocytopenia and platelet dysfunction coexist.<sup>48</sup> In such a case, the bleeding phenotype will appear more severe than expected from the thrombocytopenia alone.

### Platelet Function Disorders

PFD comprise a heterogeneous group of disorders. The prevalence of PFD is unknown, but this group of disorders may be as prevalent as VWD. Prospective studies of individuals presenting with mucocutaneous symptoms indicate that approximately one-fifth of patients will be diagnosed with a mild PFD.<sup>8,37</sup> The well-described inherited disorders of platelet function, such as Bernard Soulier syndrome, or Glanzmann thrombasthenia, are rare and it is the incompletely characterized platelet secretion and signal transduction defects that are the most frequently diagnosed inherited PFD.

### Inherited Coagulation Disorders

#### Hemophilia

Hemophilia A (FVIII) and B (FIX) are the two most common inherited coagulation disorders with an incidence of 1:10,000 and 1:60,000, respectively.<sup>49</sup> They are X-linked recessive disorders, and thus predominately affect males. Females may be affected with low levels of coagulation factor and a

bleeding diathesis in the case of extreme lyonization, chromosomal abnormalities or homozygosity for the *F8* or *F9* gene mutations.<sup>50</sup> The clinical manifestations of HA or HB are dependent on the level of coagulant activity. Severe hemophilia, defined by a factor level < 0.01 IU/mL, is marked by recurrent spontaneous hemarthrosis and deep tissue bleeding. Mild and moderate hemophilia, which are respectively defined by factor levels greater than 0.05 IU/mL, and between 0.01 to 0.05 IU/mL, respectively, are associated with increased and delayed bleeding with injury or postoperatively. Treatment generally includes indirect therapies such as tranexamic acid, and DDAVP (in the case of mild HA), as well as direct therapies such as replacement of the factor with recombinant products.

### Recessively Inherited Coagulation Disorders

The remaining coagulation disorders of factors II, V, VII, X, XI, XII, or XIII are rare, autosomal recessive diseases that are more common in consanguineous families.<sup>51</sup> The PT and APTT will detect the majority of significant factor deficiencies with the exception of FXIII. However, heterozygous individuals will have only mild to moderate reductions to the factor levels that will result in prolongation of the PT or APTT and up to 40% of these patients may be symptomatic.<sup>52</sup> The associated bleeding symptoms do not always correlate with plasma levels, particularly with factor XI deficiency. Clinical manifestations not only overlap with those of hemophilia, with musculoskeletal bleeding and excessive bleeding after injury, but also include mucocutaneous bleeding.

### Defects in Fibrinolysis

The PT and APTT will detect the majority of moderate or severe factor deficiencies but may fail to detect mild factor deficiencies and deficiencies of FXIII,  $\alpha_2$ -antiplasmin and PAI-1.  $\alpha_2$ -antiplasmin deficiency<sup>32</sup> and PAI-1<sup>31</sup> deficiency are extremely rare and testing should only be considered when a bleeding diathesis, with features of delayed bleeding, is present and testing has otherwise been negative.

### Acquired Bleeding Disorders

Acquired disorders affecting coagulation factors or platelet function are generally obvious after a thorough history, physical examination, and screening blood work. A review of acquired bleeding disorders is outside the scope of this manuscript. However, two acquired disorders warrant special mention: acquired coagulation inhibitors and acquired von Willebrand syndrome (AVWS).

### Acquired Coagulation Inhibitors

Acquired inhibitors against coagulation proteins present with severe and acute bleeding. Although inhibitors to FV, IX, X, XI, XIII have been described, the most common acquired inhibitors affect FVIII, with an incidence of 1 to 4 per million per year.<sup>53</sup> Prompt diagnosis and treatment is important as up to 90% of patients with acquired factor deficiencies will experience a severe bleed into muscles, soft tissue, and mucous membranes and mortality rates range from 8 to 22%.<sup>53</sup> The incidence of acquired inhibitors increases with age, with most

cases occurring between the ages of 68 to 80 years. There is a small peak in the age distribution for women during child-bearing years who are at increased risks of developing an inhibitor during the postpartum period. Up to 50% of acquired factor deficiencies are idiopathic. With acquired FVIII deficiency, inhibitor development can be associated with autoimmune disease, underlying hematologic or solid tumor malignancy, infections, or medications. The laboratory findings for acquired coagulation inhibitors can include prolongation of APTT and/or PT, depending on which factor is affected and if the inhibitor is rapid acting, a mixing study may fail to correct. With acquired FVIII inhibitors, the inhibitor may be time and temperature dependent. Specific factor assays will identify reductions in the affected factor and the inhibitor activity will be confirmed by an inhibitor assay. Treatment of active bleeding warranting therapy involves the infusion of large amounts of factor, or bypassing agents such as activated prothrombin complex concentrates and recombinant activated FVII (rFVIIa). Eradication of the inhibitor may involve the use of prednisone, cyclophosphamide, intravenous immunoglobulin, and/or rituximab.

### Acquired von Willebrand Syndrome

This acquired mild to moderate bleeding disorder results in deficient or defective VWF. The prevalence is difficult to estimate and depends on the patient population. For example, AVWS has been reported in ~10% of patients with hematological disorders,<sup>54</sup> 79% with aortic stenosis,<sup>55</sup> and up to 100% of patients with left ventricular assist devices.<sup>56,57</sup> The median age of diagnosis is 62 years but may occur in any age group (range 2 to 96 years).<sup>58</sup> AVWS has diverse pathology that includes autoantibodies (systemic lupus erythematosus or lymphoproliferative disorders) sequestration of the larger VWF multimers (essential thrombocytopenia or Wilms tumor), proteolytic cleavage of VWF after shear stress-induced unfolding (aortic valvular stenosis and ventricular septal defect), or decreased synthesis (hypothyroidism and valproic acid). The agents used in the treatment of active bleeding or in peri-surgical prophylaxis settings include DDAVP or VWF-containing concentrates, rFVIIa, antifibrinolytics, IVIG, or plasmapheresis for AVWS associated with IgG-monoclonal gammopathy of uncertain significance.<sup>59</sup> Whenever possible, treatment of the underlying disorder should be considered.

## Treatment

### Initial Evaluation and Education of the Patient

The patient should be screened for hepatitis B and C as well as human immunodeficiency virus if the individual received blood products or plasma-derived clotting factor concentrates before 1985. This screening should be followed by vaccinations for hepatitis A and B.<sup>60</sup> Women with menorrhagia require a complete gynecological evaluation.<sup>61</sup> Patients should be instructed to avoid medications that may exacerbate bleeding tendencies, such as aspirin and nonsteroidal anti-inflammatories and certain complimentary and alternative medications.

### Localized Measures

The importance of direct pressure to a site of bleeding should not be understated. For the management of nosebleeds, some patients may benefit from a stepwise action plan that escalates from initial direct pressure, to packing after a certain time period, and includes guidelines on how long to wait before seeking medical attention. In selected cases, nasal cautery may be required for prolonged or excessive epistaxis, if localized lesions can be identified on examination.

### Indirect Therapies

Fibrinolytic inhibitors (i.e., tranexamic acid) inhibit the conversion of plasminogen to plasmin and have been shown to be useful in a wide range of clinical situations, including HA,<sup>62</sup> VWD,<sup>63</sup> and acquired bleeding from warfarin therapy<sup>64</sup> and uremia.<sup>65</sup> Tranexamic acid is contraindicated in disseminated intravascular coagulation and bleeding from the upper urinary tract, where it may lead to urinary tract obstruction secondary to large clots.

Hormonal treatments (i.e., OCP) are effective for the treatment of menorrhagia. Nonmedical treatments including the levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena [levonorgestrel] IUD) or endometrial ablation may be useful in selected patients. A consensus document on the management of abnormal gynecological or obstetrical bleeding in women with bleeding disorders was recently published.<sup>61</sup>

DDAVP induces secretion of VWF from endothelial cells, and results in an increase of VWF and FVIII. The best defined indications for DDAVP are VWD<sup>66</sup> and HA,<sup>67</sup> where in mild to moderate disease, DDAVP raises levels 3 to 10 fold, thereby providing adequate hemostatic coverage for many invasive procedures. A test dose of DDAVP, followed by measurements of VWF:RCO and/or FVIII at baseline, 1 hour and 2 to 4 hours after administration, is recommended before its clinical use. This ensures DDAVP responsiveness and evaluates for shortened survival, which may be missed if a 4-hour sample is not collected.<sup>63</sup> DDAVP is also clinically useful in several other mild bleeding disorders, including but not limited to PFDs,<sup>68</sup> FXI deficiency,<sup>69</sup> bleeding secondary to connective tissue disease,<sup>30</sup> and uremia.<sup>65</sup> Severe hyponatremia and seizures can develop following its use if fluid intake is not restricted to limit the risks for water intoxication; patients must be counseled about restricting fluid intake following administration. Desmopressin should be avoided in individuals at high risk for arteriovascular disease as myocardial infarction after treatment with DDAVP has been reported.<sup>63</sup> Finally, DDAVP should be avoided in  $\alpha_2$ -antiplasmin deficiency where its effect of increasing plasma levels of tissue plasminogen activator (tPA) may exacerbate the enhanced fibrinolysis.<sup>32</sup>

### Direct/Replacement Therapies

For details regarding the indications, dosing and side-effects of these replacement products, the reader should reference the appropriate disease-specific guidelines or reviews.<sup>51,62,68</sup> In the case of refractory bleeding or an inhibitor, bypassing agents may be considered and include rFVIIa and FEIBA (factor eight bypassing agent) that is an activated prothrombin complex concentrate.

### Bleeding of Unknown Cause

In two prospective cohort studies of individuals referred for bleeding disorder assessment, 28 to 60% of patients were found to have bleeding of unknown cause (BUC) despite extensive laboratory testing.<sup>8,37</sup> In a cohort of 280 individuals, Quiroga et al found that those with BUC were indistinguishable clinically from patients with known bleeding disorders as per a bleeding score criteria.<sup>8</sup> Although, the approach to patients with BUC is controversial and there is a general lack of evidence, tranexamic acid and DDAVP may be useful in treating bleeding symptoms in this population.<sup>70,71</sup> If bleeding is refractory to these agents, then second-line interventions may include a trial of platelet transfusion.

### Conclusion

A thorough clinical history with the aid of tools such as the BATs are necessary to determine if bleeding symptoms are outside of the normal range and warrant investigations. The treatment of bleeding symptoms will depend on the specific bleeding disorder. Referral to a specialized center may be useful for initial investigations to establish the diagnosis, to outline an approach to the patient's bleeding symptoms and for longitudinal care. Despite extensive investigations, many patients will not have a diagnosis made, which illustrates that the causes of pathological bleeding are not well understood and highlights the need for ongoing research.

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