Bleeding and Bruising: A Diagnostic Work-up

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Primary care physicians are often asked about easy bruising, excessive bleeding, or risk of bleeding before surgery. A thorough history, including a family history, will guide the appropriate work-up, and a physical examination may provide clues to diagnosis. A standardized bleeding score system can help physicians to organize the patient's bleeding history and to avoid overlooking the most common inherited bleeding disorder, von Willebrand's disease. In cases of suspected bleeding disorders, initial laboratory evaluations should include a complete blood count with platelet count, peripheral blood smear, prothrombin time, and partial thromboplastin time. More specialized yet relatively simple tests, such as the Platelet Function Analyzer-100, mixing studies, and inhibitor assays, may also be helpful. These tests can help diagnose platelet function disorders, quantitative platelet disorders, factor deficiencies, and factor inhibitors. (*Am Fam Physician*. 2008;77(8):1117-1124. Copyright © 2008 American Academy of Family Physicians.)

Numerous disorders can cause abnormal bleeding and bruising, including platelet function disorders, quantitative platelet disorders, factor deficiencies, and factor inhibitors. Additionally, there are diseases that affect the connective tissue and integrity of the blood vessel, making the skin bruise more easily and vessels more prone to bleed. *Table 1* lists the differential diagnosis of bleeding and bruising disorders. *Table 2*[1,2] shows the diagnostic work-up, which begins with a focused history.

Illustrated Case Studies

CASE ONE

A 52-year-old man gave a lifelong history of easy bruising and excessive bleeding following tooth extractions. After taking aspirin, he developed severe nosebleeds. Family history was remarkable for heavy vaginal bleeding in his mother and sister.

CASE TWO

A 35-year-old woman presents with bruising of the upper thighs. She denies menorrhagia or other bleeding symptoms. She reports two vaginal deliveries, an appendectomy, and a tubal ligation, all without excessive bleeding. Her family history does not suggest a bleeding disorder and, except for the simple bruising, her physical examination is unremarkable.

CASE THREE

A 43-year-old woman was admitted to the hospital with a large hematoma in the right thigh. She had no history of trauma or spontaneous bleeding and had tolerated minor surgical procedures in the past without bleeding. Her family history was negative and she had not been on any medications associated with increased bleeding risk.

History and Physical Examination

Taking a personal history starts with a list of screening questions based on a bleeding score system *(Table 3)*.[3] This bleeding score system is a clinical decision rule to screen for von Willebrand's disease, the most common inherited bleeding disorder. This disease results from a quantitative or qualitative defect in von Willebrand's factor, which is required for platelet aggregation. Although the bleeding score system is intended for the diagnosis of von Willebrand's disease, it lists criteria necessary to diagnose other bleeding disorders as well.[4-9] A history of bleeding that requires surgical intervention, blood transfusion, or replacement therapy is a significant red flag for a bleeding disorder and, therefore, receives a high number of points. More information on the bleeding score can be found at http://www.euvwd.group.shef.ac.uk/bleed_score.htm. *Table 4*[3] indicates the probability of von Willebrand's disease based on the bleeding score.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Because a positive family history increases the risk of a bleeding disorder, family history should be obtained in patients with a suspected bleeding disorder.	C	5-8, 11
The use of bleeding time to assess platelet function is discouraged; the Platelet Function Analyzer-100 is preferred.	C	1, 17-24

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1063 or http://www.aafp.org/afpsort.xml.

Table 1. Differential Diagnosis of Bleeding and Bruising Disorders

Disorder	*Findings or clues to diagnosis*
Bleeding	
Platelet disorders (quantitative)	Bleeding, bruising, petechia, or purpura Consider idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, malignancy, viral disease
Platelet disorders (functional)	Consider in a patient with a lifelong history of bleeding despite negative laboratory work-up Consider glycoprotein disorders (Bernard-Soulier syndrome, Glanzmann thrombasthenia), storage pool disease, von Willebrand's disease If platelets are abnormally shaped, consider May-Hegglin anomaly, Wiskott-Aldrich syndrome
Hemophilia type A or B (factor VIII or IX deficiency) or other factor deficiencies	Classically presents with joint or soft-tissue bleeding; family history of bleeding in men (skipped generations)
Factor inhibitors	Presentation similar to hemophilia, but onset is typically sudden with no patient or family history of bleeding
Hereditary hemorrhagic telangiectasia	Telangiectasias over lips, tongue, nasal cavity, and skin; epistaxis
Vasculitis or cryoglobulinemia	Neuropathy; pulmonary-renal involvement; purpura
Leukemia	Abnormal complete blood count or peripheral blood smear
Disseminated intravascular coagulation	Bleeding from multiple sites; prolonged prothrombin time and partial thromboplastin time
Vitamin K deficiency	More common causes include malabsorption (bacterial overgrowth, celiac disease, chronic pancreatitis, inflammatory bowel disease, short-gut syndrome), poor diet (alcoholism, total parenteral nutrition) or drugs that bind vitamin K (cholestyramine [Questran]).
Bruising	
Purpura simplex (easy bruising)	Typically found in women on the upper thighs and arms
Alcohol abuse	Social history
Abuse (including child abuse)	Atypical pattern of bruising or bleeding; bruises that pattern after objects; bruises in children who are not yet mobile; history that is inconsistent with the patient's injuries
Senile purpura	Dark ecchymosis in aged, thin skin; typically over extensor surfaces of forearms
Cushing's disease	Facial plethora; hirsutism; hyperglycemia; hypertension; poor wound healing; stria
Marfan's syndrome	Enlarged aortic root; eye involvement; mitral valve prolapse; scoliosis; pectus excavatum; stretch marks; tall and slim, with long limbs and digits
Vitamin C deficiency (scurvy)	Dietary history
Ehlers-Danlos syndrome or connective tissue diseases	Atrophic scarring or joint dislocations; hypermobile joints; skin hyperextensibility

NOTE: *Disorders are categorized as predominantly bleeding or bruising and are in order of relative frequency.*

Table 2. Evaluation of Bleeding Disorders

Prothrombin time	*Partial thromboplastin time*	*Further evaluation*	*Next step*
Normal	Normal	Platelet Function Analyzer-100, which checks the amount of time it takes platelets to aggregate onto an aperture coated with a collagen/epinephrine membrane and a collagen/adenosine diphosphate membrane	Is there a prolonged aggregation time with both membranes? • Yes: Evaluate for von Willebrand's disease • No: If prolonged aggregation time is found only with the collagen/epinephrine membrane, look for drug effect, such as from aspirin. If neither are prolonged, further evaluation is warranted, based on clinical suspicion
Normal	Abnormal	Partial thromboplastin time mixing study	Does partial thromboplastin time correct (normalize)? • Yes: Factor VIII, IX, and XI assays. If factor VIII low, work-up for von Willebrand's disease • No: Screen for inhibitors (lupus anticoagulant and factor VIII inhibitor)
Abnormal	Normal	Determine if the patient is malnourished or if there is clinical suspicion for vitamin K deficiency	Does prothrombin time correct or normalize with administration of vitamin K? • Yes: Replace vitamin K as needed • No: Factor assay for factor VII
Abnormal	Abnormal	Consider disseminated intravascular coagulopathy Verify no use of warfarin (Coumadin) or heparin Verify no liver disease	Consider factor assays for factor deficiencies

Information from references 1 and 2.

A positive family history increases the risk of a bleeding disorder and is reason to initiate a work-up,[10,11] especially in women with menorrhagia.[12] Many bleeding disorders have an inheritance pattern, including the X-linked recessive hemophilias. Family history is especially important in children because they may not have had the opportunity to experience a hemostatic challenge (e.g., surgery, delivery, tooth extraction). In a study of children referred to a tertiary care center with either a personal or family history of bleeding, a positive family history was significantly associated with a diagnosis of a bleeding disorder.[10]

The patient in case study one who had a history of bruising and bleeding after tooth extraction would have a bleeding score of at least 4 (epistaxis: 1; bruising: 1; and tooth extraction: 2). This score, coupled with his family history of menorrhagia in the mother and sister, creates a high index of suspicion for a bleeding disorder, even before any laboratory testing is obtained.

The bleeding score system assigns a negative number if there is no significant bleeding after a hemostatic challenge. The importance of the "negative history" is illustrated by the woman in case study two who had bruising on her upper thigh

Table 3. Bleeding Score System for Evaluation of Bleeding History

	Score			
Symptom	*–1*	*0*	*1*	*2*
Epistaxis	—	No or trivial (< 5 episodes per year)	> 5 episodes per year or lasts > 10 minutes	Consultation only*
Cutaneous (bruises, petechia, subcutaneous hematoma)	—	No or trivial (< 1 cm)	> 1 cm and no trauma	Consultation only*
Bleeding minor wounds	—	No or trivial (< 5 episodes per year)	> 5 episodes per year or lasts > 5 minutes	Consultation only*
Oral cavity (bleeding gums [spontaneous or with brushing], bites to lip and tongue, tooth eruption)	—	No	Bleeding noted at least once	Consultation only*
Gastrointestinal bleeding (hematemesis, hematochezia, melena)	—	No	Associated with angiodysplasia, hemorrhoids, portal hypertension, ulcer	Spontaneous
Tooth extraction	No bleeding in at least two extractions	None performed or no bleed in one extraction	Bleeding noted in < 25% of all procedures	Bleeding noted in > 25% of all procedures, but no intervention
Surgery	No bleeding in at least two surgeries	None performed or no bleeding in one surgery	Bleeding noted in < 25% of all procedures	Bleeding noted in > 25% of all procedures, but no intervention
Menorrhagia	—	No	Consultation only*	Antifibrinolytics, pill use
Postpartum hemorrhage	No bleeding in at least two deliveries	No deliveries or no bleeding in one delivery	Consultation only*	Dilatation and curettage, iron therapy, antifibrinolytics
Muscle hematomas	—	Never	Post-trauma, no therapy	Spontaneous, no therapy
Hemarthrosis	—	Never	Post-trauma, no therapy	Spontaneous, no therapy
Central nervous system bleeding	—	Never	—	—

NOTE: *This bleeding score system has not been prospectively validated.*

**—Implies that a referral was made to a specialist for bleeding, but that no treatment was administered.*

Adapted with permission from Tosetto A, Rodeghiero F, Castaman G, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results for a multicenter European study (MCMDM-1 VWD). J Thromb Haemost. *2006;4(4):768.*

	3	4
	Packing, cauterization, or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin (DDAVP)
	—	—
	Surgical hemostasis	Blood transfusion, replacement therapy, or desmopressin
	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, or antifibrinolytic	—
	Resuturing or packing	Blood transfusion, replacement therapy, or desmopressin
	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy, or desmopressin
	Dilatation and curettage, iron therapy	Blood transfusion, replacement therapy, desmopressin, or hysterectomy
	Blood transfusion, replacement therapy, or desmopressin	Hysterectomy
	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
	Subdural, any intervention	Intracerebral, any intervention

Table 4. Diagnosis of von Willebrand's Disease Using the Bleeding Score

Bleeding score	*Likelihood ratio**	*Post-test probability (%)*
-3	0.00	0.0
-2	0.04	0.2
-1	0.10	0.5
0	0.13	0.7
1	1.60	8.0
2	2.20	10.0
3	3.00	13.0
4	16.00	43.0

NOTE: *This table is based on a 5 percent pretest probability.*

**—Likelihood ratio with a 95% confidence interval.*

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(score: 1); an appendectomy and tubal ligation without a significant bleed (score: –1); two vaginal deliveries without a significant bleed (score: –1); and no other bleeding symptoms (score: 0). This gives her a total bleeding score of –1.

As illustrated in case study three, a patient may have a low bleeding score and a negative family history, but still present with physical examination findings suggestive of a bleeding disorder. Pertinent physical examination findings of bleeding and bruising disorders are listed in the second column of *Table 1.*

Table 5[4-6] lists medications that cause bleeding or bruising. The physician should not rule out a bleeding disorder just because a patient is receiving one of these medications, especially if the patient has a high bleeding score. Medications may cause the disease to manifest itself with bleeding symptoms, as illustrated in case study one.

Initial Laboratory Evaluation

Understanding of the complexity of hemostasis has greatly increased since it was originally described in 1964.[13,14] Interactions of basic "ingredients" are required for a clot to form, and a qualitative or quantitative defect of any "ingredient" can result in a bleeding or bruising disorder. Knowledge of basic clot

Table 5. Medications That Cause Bleeding and Bruising

Common
Aspirin
Clopidogrel (Plavix)
Heparin
Nonsteroidal anti-inflammatory drugs
Warfarin (Coumadin)
Rare
Cephalosporins
Ginkgo biloba
Gold
Interferon
Metaxalone (Skelaxin)
Penicillins
Propothiouricil
Selective serotonin reuptake inhibitors
Testosterone replacement
Tricyclic antidepressants

Information from references 4 through 6.

formation can help the physician to understand these disorders and their initial laboratory work-up, which includes complete blood count with platelet count, peripheral blood smear, prothrombin time (PT), and partial thromboplastin time (PTT).

COMPLETE BLOOD COUNT AND PERIPHERAL BLOOD SMEAR

A shortage of platelets (thrombocytopenia) can be detected on complete blood count. A peripheral blood smear can help to rule out pseudothrombocytopenia and to look for abnormally shaped platelets.

PT AND PTT

The PT measures the factors of the extrinsic and common pathways. Deficiencies of these factors (most notably factor VII) will prolong the PT. Vitamin K is required for the synthesis of the critical factors of these pathways; therefore, patients with vitamin K deficient conditions may have a prolonged PT.[15]

The PTT measures the factors of the intrinsic and common pathways. Deficiencies of these factors, including factor VIII (hemophilia A) and factor IX (hemophilia B), will prolong the PTT. Factor VIII levels may be low in patients with von Willebrand's disease; therefore, these patients could present with a prolonged PTT.[1]

Inhibitors, autoantibodies that attach to a factor and render it useless for clot formation, can also prolong the PTT. The most common inhibitors are the factor VIII inhibitors and the lupus anticoagulant ("lupus anticoagulant" is incorrectly named and typically presents more often as thrombosis than as bleeding). A factor VIII inhibitor should be suspected in anyone who has no history of bleeding, but develops significant bleeding (such as the woman with the large spontaneous hematoma in case study three) and has a prolonged PTT.[16]

Specialized Laboratory Tests

PLATELET FUNCTION ACTIVITY

Traditionally, the test of choice for evaluation of platelet function was bleeding time; however, the use of bleeding time to predict surgical bleeding has been questioned[17,18] and its use has been discouraged or eliminated at some institutions.[1,19] The Platelet Function Analyzer (PFA)-100 has been shown to be superior to bleeding time in detecting von Willebrand's disease.[20-22]

The PFA-100 simulates the formation of the platelet plug in vivo by passing the patient's blood through an aperture coated with collagen/epinephrine and collagen/adenosine diphosphate. In patients with von Willebrand's disease and other platelet function disorders, the amount of time required for the platelets to aggregate from both collagen/epinephrine and collagen/adenosine diphosphate is prolonged. A prolonged time to clot to just collagen/epinephrine usually indicates a drug effect, such as from aspirin.

The reported sensitivity of the PFA-100 for diagnosing von Willebrand's disease and other platelet function disorders is 88 to 90 percent with a specificity of 86 to 94 percent.[23,24] Studies have concluded that the PFA-100 is a useful screening test,[23,24] but this conclusion is still being debated.[24-28] Although the PFA-100 is more sensitive than bleeding time, a negative result should not preclude further testing for von Willebrand's

disease or other platelet function disorders. If the PFA-100 is negative, the physician should review the initial history to determine if further testing should be performed.

MIXING STUDIES AND INHIBITOR AND FACTOR ASSAYS

A mixing study determines if the patient has a clotting factor deficiency or an inhibitor to a factor. When one part of the patient's blood is mixed with one part of normal blood, the inhibitor in the patient's blood disables the factor in the normal blood. The PTT stays prolonged and does not "correct." Inhibitor assays are then performed to identify which inhibitor is present. When the blood from a patient with a factor VIII deficiency is mixed with normal blood, the PTT should normalize or correct. Factor assays are then performed to identify which factor is deficient.

The sensitivity of the mixing study to detect a lupus anticoagulant is 95 percent with a specificity of 60 percent.[29] In a study of 42 laboratories asked to analyze known samples,[30] 97.5 percent correctly identified the sample with a lupus anticoagulant and 90.2 percent correctly reported the negative serum sample as negative. However, 53.6 percent did not correctly identify the factor VIII inhibitor and many did poorly with contaminated specimens. Therefore, knowledge of a laboratory's limitations, especially when trying to identify an inhibitor that is not a lupus anticoagulant, is helpful when interpreting the results.

Referral

If the laboratory work-up does not diagnose a bleeding disorder, but there is still high suspicion based on personal and family history, the patient should be referred to a hematologist. If von Willebrand's disease, a factor VIII inhibitor, or factor deficiencies are discovered, referral is based on the diagnosis and severity, as well as the comfort level of the physician. If the history, physical examination, or the routine laboratory studies are abnormal in the preoperative assessment, surgery should be delayed until a cause can be determined with a work-up or by referral.

RESOLUTION OF CASE STUDIES

Case One. Laboratory testing included a normal blood count and platelet count. A PFA-100 test was abnormal to collagen/epinephrine and collagen/adenosine diphosphate. Further testing was diagnostic for von Willebrand's disease.

Case Two. A complete blood count, PT, PTT, and PFA-100 were normal. The patient was reassured that with a low bleeding score, a negative family history, and an unremarkable physical examination, she most likely has purpura simplex (easy bruising). She was told to follow up if her symptoms got worse or if she had any new symptoms.

Case Three. Laboratory evaluation included a hemoglobin count of 7 g per dL (70 g per L), a platelet count of 400×10^3 per µL (400×10^9 per L), a PT of 12 seconds, and a PTT of 100 seconds. A mixing study did not return the PTT to normal. Measurement of factor VIII showed a level of 1 percent, and an assay for the presence of a factor VIII inhibitor showed a high-titer inhibitor.

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