

LEARNING OBJECTIVES

- Describe the clotting cascade, including the role of platelets and clotting factors
- Outline the natural inhibitors of clotting
- Discuss the workup of excessive bleeding and bruising, including initial screening tests
- Review the differential diagnosis of bleeding and bruising

Understanding and treating disorders of the clotting system

PAs must have a working knowledge of the intricate and complex clotting cascade in order to successfully diagnose and treat common bleeding disorders.

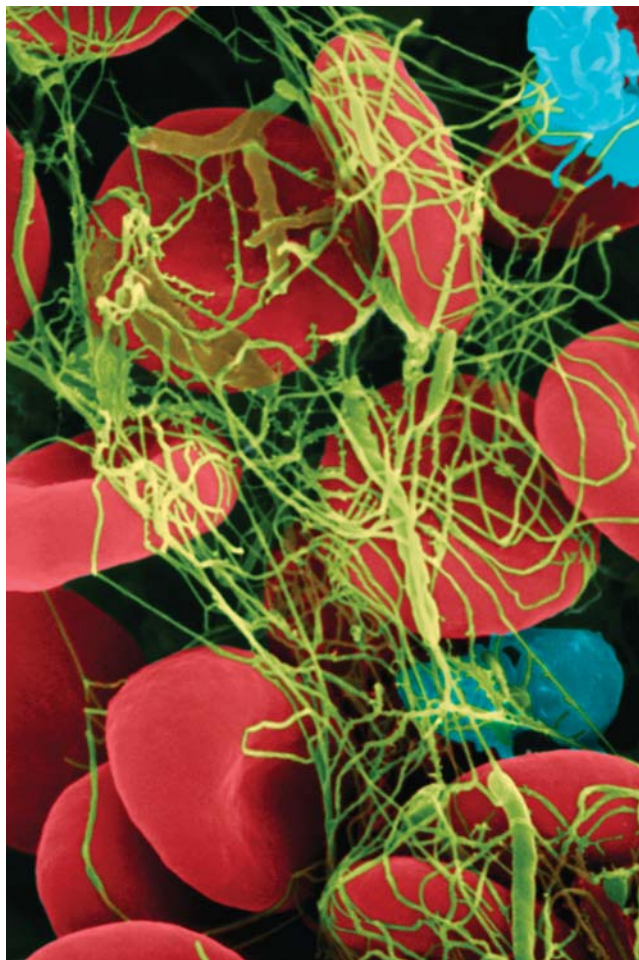
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Without the circulation of blood in the body, organ and tissue function ceases quickly and infarction begins to occur. The blood transports oxygen, glucose, proteins, vitamins, enzymes, and electrolytes to every living cell in the body through miles of intricate vessels: the arteries, veins, and capillaries. To keep the vessels intact, a clotting and repair system patches and repairs any damage that occurs. Anticlotting and clot lysis pathways keep this system in balance. When clotting occurs unnecessarily in vessels that do not need repair, blood flow is blocked and tissue infarction occurs. A malfunctioning clotting system can also cause excessive bleeding after surgical procedures, epistaxis, menorrhagia, GI bleeding, or stroke.

Clinicians must understand the pathophysiology, clinical workup, differential diagnosis, and treatment of common bleeding disorders. Twenty-six percent to 45% of healthy patients report a history of epistaxis, easy bruising, or gum bleeding.¹ As many as 10% to 15% of women report menorrhagia in their medical history.² During 2004, 45 million procedures were performed on hospital inpatients who required a working clotting system to prevent postprocedure bleeding.³ Seventeen thousand people in the United States have hemophilia, putting them at very high risk for bleeding complications and emergency department visits.⁴ PAs performing procedures or working in surgery or emergency medicine must identify patients at high risk for these and other conditions to prevent bleeding complications.

THE CLOTTING SYSTEM

Clotting To prevent blood loss, the body requires an intact and functional blood vessel endothelium, the proper number



RBCs and activated platelets trapped in a fibrin blood clot

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of working platelets, enough von Willebrand factor (vWF) to adhere platelets to broken blood vessel walls, and the proper amount of protein clotting factors. When a blood vessel is broken or penetrated, the smooth muscle in the vessel wall contracts to minimize the opening. With the aid of vWF, circulating platelets adhere to exposed collagen in the broken vessel walls. These platelets become activated, changing from a round to a flat and pointed shape. They degranulate, releasing several substances to attract more platelets, cause vasoconstriction, and activate clotting factors in the blood.^{5,6}

Soluble clotting factors circulating in the area are changed from inactive to activated in a dual sequence known as the *clotting cascade*. The main result of these chemical reactions is to convert the soluble protein fibrinogen into insoluble fibrin strands, trapping and binding together platelets and RBCs. The adhered platelets contract with the protein actomyosin inside, forcing out plasma and closing the blood vessel hole with a firm, organized clot.^{5,6}

Platelets These are small discoid fragments of bone marrow megakaryocytes. They have a 9-day average life span and are stored and recycled in the spleen. Granules containing adenosine diphosphate (ADP), ATP serotonin, calcium, fibrinogen, platelet factor 4, clotting factor V, platelet-derived growth factor (PDGF), thrombospondin, and vWF are released when the platelet is activated. Platelet production in the bone marrow is regulated by thrombopoietin, a hormone made in the liver and bound to circulating platelets. The lower the platelet count, the more free thrombopoietin is circulating to stimulate new platelet production.⁷

Platelets flow in the bloodstream until they are exposed to thrombin, collagen, ADP, or vWF from damaged endothelium or other activated platelets.⁸ The platelets adhere to the damaged site with the help of vWF, where they enlarge, flatten, become pointed, and degranulate, releasing all the stored mediators that attract other platelets, cause vasoconstriction, and activate the clotting cascade to form an organized clot. Platelets stick together using fibrinogen bound to the glycoprotein IIb–IIIa receptors on the platelet surface.⁹

Activated platelets produce thromboxane A₂, a vasoconstrictor and platelet attractor, from arachidonic acid using the cyclo-oxygenase (COX) pathway. Negatively charged phospholipids appear on the platelet's surface, causing the intrinsic

clotting pathway to activate. Clotting factor V is released from the platelet to supply the clotting cascade-forming fibrin threads surrounding the activated platelets. Platelet actinomyosin finally contracts, pulling the clot into a tight plug.¹⁰

Growth factors such as PDGF, which stimulates proliferation of smooth muscle cells and mediates tissue repair, are released. PDGF may also contribute to the development of atherosclerosis and reocclusion after coronary angioplasty.⁷

von Willebrand factor This is the “superglue” of platelets, adhering them to damaged blood vessel walls and allowing them to resist the shear stress of flowing blood. vWF is made and stored in endothelial cells and in the platelets. Deficiency

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of vWF will cause bleeding because the platelet can not adhere to the damaged vessel wall and activate. vWF is also the plasma carrier for clotting factor VIII, prolonging its half-life in circulation. A decrease in vWF causes decreased circulating factor VIII.¹¹

Clotting factors Several inactive protein-clotting factors in the blood circulation activate via two pathways to change soluble fibrinogen to fibrin strands (see Figure 1). The *intrinsic pathway* is the most complicated, requiring negatively charged collagen inside the damaged endothelium to activate factor XII, which activates XI, then IX, then VIII, and then the common pathway.^{9,12} The intrinsic pathway is best assessed by measuring the activated partial thromboplastin time (aPTT).^{12,13} The second cascade is the *extrinsic pathway*, which is initiated when factor VII contacts tissue factor released into the circulation from injured endothelium. This starts the *common pathway* cascade, activating X with factor V present, then factor II (prothrombin to thrombin), and finally factor I (fibrinogen to fibrin).^{6,14} The extrinsic pathway is best evaluated by measuring the prothrombin time

KEY POINTS

- PAs should be able to identify patients at high risk for coagulation disorders in order to prevent bleeding complications.
- A history of bleeding, as well as prolonged bleeding during surgery, a dental procedure, pregnancy, or trauma, should prompt a diagnostic workup.
- A thorough history and physical examination can provide clues to the cause of excessive bleeding or bruising.
- Important laboratory tests include a CBC with cell morphology, chemistry profile, urinalysis, and measures of coagulation.
- The mnemonic CALF DIPS is an easy way to remember the differential diagnosis of increased bleeding and bruising.

COMPETENCIES

●●●● Medical knowledge

●●● Interpersonal & communication skills

●●● Patient care

● Professionalism

● Practice-based learning and improvement

● Systems-based practice

(PT).^{10,14} Activated factor XIII is needed to crosslink the fibrin strands to form a mesh over trapped platelets.

All clotting factors are made in the liver. The vitamin K-dependent factors are prothrombin, factor VII, factor IX, and factor X. These factors are best assessed by the PT and are blocked by warfarin (Coumadin) therapy.^{12,13}

Natural inhibitors of clotting The body has an anticlotting system to keep things in balance. Antithrombin III, protein C, protein S, and tissue factor pathway inhibitor (TFPI) block the clotting cascade at different sites. Endothelial cell-manufactured prostacyclin and nitric oxide cause vasodilation and inhibit platelet activation. Ecto-ADPase inhibits platelet attraction and aggregation. TFPI, also made in the endothelium, binds to and inhibits activated factor X. The endothelial cells generate heparin, which increases the activity of antithrombin III to block thrombin production. Heparin also blocks factors XII, XI, and IX in the intrinsic pathway. Thrombomodulin increases activation of the anticoagulant protein C.^{6,9,10,14} Tissue plasminogen activator and urokinase convert plasminogen to plasmin that binds to fibrin and cuts the strands into fibrin split products and D-dimers.

THE WORKUP OF EXCESSIVE BLEEDING AND BRUISING

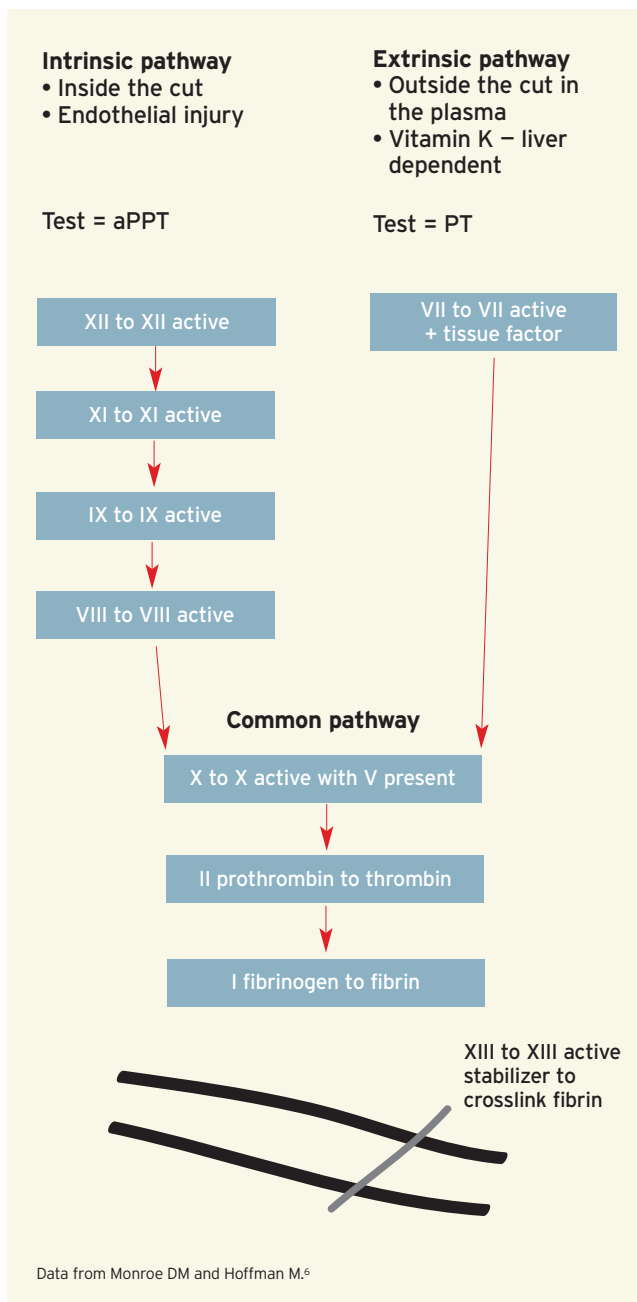
A history of bleeding from two distinct sites such as the skin (bleeding manifests as bruising and petechiae), nose, gums, vagina, GI tract, or GU tract, as well as prolonged bleeding during surgery, a dental procedure, pregnancy, or trauma, should prompt a diagnostic workup. Bleeding is significant if a transfusion of RBCs is required. This section describes questions to ask, clues to look for in the physical examination, and laboratory tests to order for the patient with excessive bleeding.¹⁵

The history If the patient has a history of alcohol abuse, jaundice, or hepatitis, consider liver disease as a cause of excessive bleeding or bruising. A family history of a bleeding disorder should raise suspicion of hemophilia or von Willebrand disease (vWD). If the patient reports weight loss, the differential diagnosis includes cancer, HIV infection, rheumatoid arthritis, lupus erythematosus, thyroid disease, or renal disease. Patients who have had prolonged bleeding after dental extractions, menorrhagia, epistaxis, gum bleeding, or easy bruising may have low or dysfunctional platelets or vWD. A history of bleeding into the joints suggests hemophilia. Finally, consider platelet dysfunction in patients who report use of aspirin or NSAIDs.¹²

Physical examination Pallor in the conjunctiva, nails, or palmar creases suggests anemia. Splinter hemorrhages in the nails may be a sign of subacute bacterial endocarditis (SBE). The skin may reveal clues to the presence of hypothyroidism, lupus, low or dysfunctional platelets, vWD, or renal failure. Weight loss may be due to cancer, HIV infection, or a chronic disease process; weight gain suggests hypothyroidism. Tachycardia may be the result of increased cardiac output in anemia. Orthostatic hypotension may be a sign of volume depletion or acute bleeding. Patients with infection or drug or transfusion reactions may have a fever; body tem-

perature may be low in hypothyroidism. Jaundice suggests hemolysis, as does pallor in the palpebral conjunctiva. Bleeding gums or epistaxis may be clues to low platelets or vWD. The neck may reveal thyroid enlargement, thyroid nodules, or lymphadenopathy. High cardiac output or signs of heart failure suggest anemia; a murmur may indicate SBE. Lung crackles may be heard in patients with uremia. In the abdominal examination, check the size of the liver and spleen, and palpate for masses or tenderness; be alert for sur-

FIGURE 1. The clotting cascade



gical scars. A fecal occult blood test should be performed, as should pelvic and breast examinations looking for uterine abnormalities, pregnancy, a postpartum state, or breast nodules. Palpate the lymph nodes, considering lymphoma, leukemia, infection, and connective tissue disease.

Laboratory tests In addition to PT and aPTT, as listed in Table 1, the following laboratory tests are recommended:^{5,16}

- CBC with cell morphology. There should be 8 to 12 platelets per high-power field (at ×1,000 magnification), corresponding to a normal platelet count of 150,000 to 300,000/μL. Bleeding can occur if the platelet count is less than 50,000/μL. The smear also shows platelet granularity and whether megathrombocytes are present. Pancytopenia (low RBC, WBC, and platelet counts) indicates bone marrow production failure. The vitamin B₁₂ level should be checked, and bone marrow biopsy may be needed to identify the cause.
- Chemistry profile. Total bilirubin is assessed by adding the level of indirect bilirubin (preliver) to the level of direct bilirubin (liver). The indirect bilirubin is increased in hemolysis. The direct bilirubin is increased in liver disease. Lactate dehydrogenase is rich in red cells, and the level is increased in hemolysis. Measures of ALT, AST, and alkaline phosphatase all are increased in liver dysfunction. BUN and creatinine levels are increased in renal failure.
- Urinalysis. Protein may be higher than 2+ in patients with renal failure. Urinary bilirubin may be increased in hemolysis or liver disease. Hemoglobinuria may indicate hemolysis. Hematuria suggests bleeding from the kidney, ureter, or bladder.
- Measures of coagulation. To evaluate increased bleeding or bruising or as part of a preoperative evaluation, PT and aPTT should be evaluated. A PT of 11 to 16 seconds indi-

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cates that the extrinsic coagulation system is functioning normally. Factors I, II, V, VII, and X can be assessed using the international normalized ratio, where 1 is normal and 2 to 3 is therapeutic for patients receiving warfarin therapy. An aPTT of 33 to 45 seconds indicates that the intrinsic coagulation system is functioning normally. This measures factors XII, XI, X, IX, VIII, V, and prothrombin and is used to monitor patients receiving heparin therapy.

- Other tests. A platelet function analysis (PFA) screens for vWD or platelet dysfunction. If this test is not available, consider measuring bleeding time.¹⁷ Normal bleeding time (3 to 8 minutes) is a measure of platelet function, vWF, and an intact coagulation cascade. If the PFA or bleeding time is abnormal and use of aspirin, NSAIDs, or anti-platelet drugs is not an issue, consider tests that measure von Willebrand antigen, ristocetin cofactor activity (von Willebrand activity), factor VIII, and von Willebrand multimer analysis. If vWF activity is normal, platelet aggregation testing may be warranted. Finally, a normal fibrinogen level is 100 to 300 mg/dL. Causes of an abnormally low fibrinogen level include disseminated intravascular coagulation (DIC), hereditary dysfibrinogenemia, and hepatic failure.

TABLE 1. Measures of coagulation

Prothrombin time	Activated partial thromboplastin time	Differential diagnosis
Prolonged	Normal	Factor VII deficiency, vitamin K deficiency, liver disease, warfarin therapy
Normal	Prolonged	Factor VIII, IX, XI, XII deficiency; von Willebrand disease; lupus anticoagulant; heparin therapy
Prolonged	Prolonged	Prothrombin, fibrinogen, factor V or X deficiency; liver disease; disseminated intravascular coagulation; combined heparin and warfarin therapy

Data from James AH et al.²

THE DIFFERENTIAL DIAGNOSIS OF BLEEDING OR BRUISING

The mnemonic *CALF DIPS* is an easy way to remember the differential diagnosis of increased bleeding and bruising.

C—cirrhosis, liver disease The liver manufactures the vitamin K-dependent clotting factors: factor II (prothrombin), factor VII, factor IX, and factor X. The liver also manufactures fibrinogen and a host of other proteins necessary for coagulation. Signs and symptoms of liver dysfunction may be present, and screening tests may demonstrate a prolonged PT and aPTT as well as an elevated direct bilirubin level. Treatment with fresh frozen plasma transfusions may correct the coagulation disorder for a limited time.¹⁸

Warfarin interferes with the vitamin K-dependent clotting factors, producing the same clinical picture as vitamin K deficiency. This will prolong the PT, which is used to monitor therapy. The problem can be corrected with administration of fresh frozen plasma or vitamin K.¹⁹

A—aspirin and other NSAIDs Aspirin acts to decrease platelet aggregation by blocking oxidation of arachidonic acid by irreversibly inhibiting COX-1 for the life of the platelet. Other NSAIDs reversibly block this pathway, so that it can return to normal function if the medication is stopped.

COX-2 NSAIDs and acetaminophen do not block the COX-1 pathway.¹⁵

L-leukemia Leukemic cells in the bone marrow displace platelet-producing megakaryocytes. The diagnostic features include a very high WBC count, hepatosplenomegaly, lymphadenopathy, and bone pain. The marrow invasion causes thrombocytopenia.²⁰

F-factor VIII or IX dysfunction For the 10-year period 1982 to 1991, the average incidence of hemophilia A and B in six surveillance states (Colorado, Georgia, Louisiana, Massachusetts, New York, and Oklahoma) was estimated to be 1 in 5,032 live male births.⁴ This translates into an estimated national population of 13,320 cases of hemophilia A and 3,640 cases of hemophilia B.⁴

Persons with factor VIII dysfunction have hemophilia A, a sex-linked genetic disorder that affects males only. Clinical manifestations are excessive bleeding with or without trauma, or bleeding into joints. Laboratory findings include a prolonged aPTT with a normal PT, bleeding time, and platelet count. Factor VIII can be measured and will be low. The treatment goal is to raise the plasma factor VIII level to 0.3 to 0.5 U/mL during any bleeding episode.²¹

Persons with factor IX dysfunction have hemophilia B, or Christmas disease. This is a less common male-linked disorder that will manifest with the same laboratory and physical findings as does hemophilia A. Factor IX will be low when measured. Treatment is replacement factor IX.²¹

D-disseminated intravascular coagulation This condition involves an activation of the coagulation system, causing abnormal thrombin formation and depletion of clotting factors. Causes include pregnancy, surgical complications, sepsis, hemolytic transfusion reactions, metastatic cancers, drug reactions, and snake bites. Laboratory findings include decreased platelets, prolonged PT and aPTT, decreased fibrinogen, and increased fibrin split products. Treatment includes fresh frozen plasma, platelet transfusions, and resolving the precipitating cause.²²

Deficiency of vitamin K, a fat-soluble vitamin responsible for the hepatic production of coagulation factors II (prothrombin), VII, IX, and X, may also cause increased bleeding and bruising. Normal body levels are obtained by eating green leafy vegetables and vegetable oils and from production in the gut via the normal intestinal bacteria. Any use of antibiotics that alter the gut flora can cause deficiency in 48 hours. Impaired absorption occurs when bile salts are absent or in steatorrhea. The PT will be prolonged because of decreased factor VII. Treatment is administration of vitamin K, 15 mg SC, or, in cases of serious bleeding, 5 to 10 mg IV administered very slowly. IM injection should be avoided because of the risk of hematoma.²³

I-idiopathic thrombocytopenic purpura (ITP) This autoimmune IgG antibody attack on platelets causes a low platelet count. Treatment is indicated in patients with platelet counts less than 20,000 to 30,000/ μ L and in those with platelet counts less than 50,000/ μ L who have significant mucosal bleeding or risk factors for bleeding. ITP is usually treated

with prednisone and, in emergencies, platelet transfusions. Splenectomy may also improve platelet counts.²⁴

P-platelet deficiency (decreased production or hypersplenism) Platelet counts less than 100,000/ μ L may be caused by marrow infiltration, marrow hypoplasia from radiation, chemicals, insecticides, drugs like heparin (heparin-induced thrombocytopenia), viruses, alcohol abuse, and megaloblastic anemias. Increased destruction of platelets occurs in hypersplenism, hemolytic-uremic syndrome, bypass surgery, severe vitamin B₁₂ deficiency (pancytopenia), DIC, and thrombotic thrombocytopenic purpura.²⁵ The *HELLP syndrome* refers to a disorder that occurs during pregnancy and is characterized by hemolysis, elevated levels of liver enzymes, and a low platelet count. It probably represents an extremely severe form of posttransfusion, drug-induced preeclampsia. Treatment includes recombinant thrombopoietin to stimulate platelet production, platelet transfusion, and a correction of the underlying cause.²⁶

Platelet dysfunction can be caused by vWD, the most frequent bleeding disorder, with an estimated prevalence in the general population of 1%.²⁷ This disease affects both males and females, and it results in poor platelet adhesion to vascular walls and deficient factor VIII availability. The bleeding severity can be major to minor and is usually evident after dental, obstetric, or surgical procedures or trauma. Joint hemorrhage is rare. Patients have a prolonged bleeding time, a low vWF, low factor VIII procoagulant levels, and decreased platelet aggregation when ristocetin is added to the plasma.

“To enhance clotting, patients should stop taking aspirin and NSAIDs 1 week before any scheduled surgery or procedures.”

There are three major types of vWD: 1, 2, and 3; with four subtypes in type 2 vWD: 2A, 2B, 2M, and 2N. The type is determined by multimer analysis. Type 1 vWD accounts for 60% to 80% of cases.²⁷ Treatment and risk of bleeding differ, depending on type and subtype. Consultation with hematologists and genetics experts should be part of the treatment plan. Treatment and prevention of bleeding complications may include desmopressin acetate, cryoprecipitate, fresh frozen plasma, and/or factor VIII concentrate.^{27,29}

Uremia is the most common systemic disorder causing platelet dysfunction because of increased nitric oxide, a platelet activation inhibitor.¹⁵

S-scurvy Vitamin C is needed for collagen synthesis. When vitamin C is deficient, blood loss occurs through the endothelium of small blood vessels. Scurvy is very rare in most parts of the world where a varied diet is available. The condition is treated by administration of oral vitamin C, 1 g daily.³⁰

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THERAPY

The problem-specific therapies for coagulation disorders are discussed earlier in this article. To enhance clotting, patients should stop taking aspirin and NSAIDs 1 week before any scheduled surgery or procedures. Acetaminophen is an alternative analgesic that will not interfere with platelet function. In crisis situations, platelet transfusions and fresh frozen plasma may provide temporary clotting support. Finally, PAs should know to consult with hematologists and genetics experts when inherited clotting factor deficiencies or hereditary vWD is discovered. [JAAPA](#)

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