Approach to the adult with a suspected bleeding disorder

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INTRODUCTION

Evaluating a patient with a suspected bleeding disorder is one of the more challenging endeavors in hematology. Many features of the bleeding history are subjective, the family history may be unclear, and the extent of diagnostic testing is often highly individualized.

This topic discusses the diagnostic approach to a suspected bleeding disorder in an adult. The approach to a suspected bleeding disorder in children and adolescents is discussed separately. (See "Approach to the child with bleeding symptoms".)

Diagnostic testing for specific platelet and coagulation factor disorders and overviews of the hemostatic process and the uses of specific coagulation tests are presented separately.

- Hemostatic process – (See "Overview of hemostasis".)
- Coagulation tests – (See "Clinical use of coagulation tests".)
- Platelet disorders – (See "Inherited platelet function disorders (IPFDs)" and "Diagnostic approach to thrombocytopenia in adults".)
- Coagulation factor deficiencies – (See "Clinical manifestations and diagnosis of hemophilia" and "Factor XI (eleven) deficiency" and "Rare inherited coagulation disorders".)
- Fibrinogen disorders – (See "Disorders of fibrinogen".)
- Abnormal fibrinolysis – (See "Thrombotic and hemorrhagic disorders due to abnormal fibrinolysis".)

TERMINOLOGY

These terms are used to describe bleeding manifestations [1]:

- **Petechiae** – Petechiae are small, flat, red, discrete areas of skin bleeding, typically <2 mm in diameter (picture 1 and picture 2). They are nonblanching and nonpalpable. They typically occur in dependent areas of the body (lower legs in ambulatory individuals, sacral area in recumbent individuals). Petechiae can be seen in severe thrombocytopenia and with skin fragility or glucocorticoid use. (See "Immune thrombocytopenia (ITP) in adults: Clinical manifestations and diagnosis", section on 'Bleeding'.)

- **Purpura** – Purpura results from coalesced petechiae. Dry purpura describes purpura in the skin. Wet purpura describes hemorrhagic blisters in mucous membranes. Purpura due to thrombocytopenia is flat and nonblanching and is usually seen in dependent areas of the body. Purpura due to vasculitis is usually palpable and may be pruritic, and the distribution does not follow dependent areas. Wet purpura is the most predictive of serious bleeding in individuals with thrombocytopenia.

- **Bruise/ecchymosis** – A bruise (also called an ecchymosis) is a subcutaneous accumulation of extravasated blood. The skin is flat. The color evolves over time from purplish blue to reddish brown to greenish yellow, reflecting breakdown of hemoglobin to biliverdin and bilirubin. Bruises are generally considered significant when five or more are seen [2]. Bruises of the same age are consistent with a single traumatic event, whereas bruises of different ages are consistent with an ongoing process.

- **Hematoma** – A hematoma is a collection of blood in the extravascular space. A subcutaneous hematoma may raise the skin profile; hematomas in deep tissues (muscle, retroperitoneal) may be suspected due to pain, a drop in hemoglobin, or a fluid collection on imaging studies. Hematomas and hemarthroses (joint bleeding) are typical of coagulation factor deficiencies.

- **Bleeding challenge** – A bleeding challenge is an event that would normally cause bleeding, such as a dental extraction, surgery, delivery, or trauma.

- **Primary and secondary hemostasis** – Primary hemostasis refers to the initial steps in clot formation, which mostly rely on the integrity and elasticity of the vessel wall and interactions between the vessel wall, platelets, and von Willebrand factor (VWF). Secondary hemostasis refers to the subsequent formation of the fibrin-based clot, which mostly relies on coagulation factors. Disorders of primary hemostasis often present with

mucocutaneous bleeding or petechiae, whereas disorders of secondary hemostasis present with deep tissue hematomas or joint bleeding. von Willebrand disease (VWD) may have features of both. (See "Overview of hemostasis".)

- **Bleeding diathesis** – A bleeding diathesis (hemorrhagic diathesis, bleeding tendency, bleeding disorder) refers to an inherited or acquired disorder affecting primary or secondary hemostasis.

- **Major bleeding** – A variety of definitions have been used in clinical trials. Typically, major bleeding is defined as bleeding that results in death, affects a critical organ such as the brain or a large joint, causes a fall in hemoglobin level of 2 g/dL or more, or requires transfusion of two or more units of red blood cells [3]. Clinically relevant non-major bleeding (CRNMB) includes bleeding that is more than expected for the circumstances and that requires some intervention (hospitalization, medication, face-to-face discussion) but is not severe enough to constitute major bleeding [4].

- **Bleeding assessment tool (BAT)** – A BAT, also called a bleeding score, is used to quantify bleeding by site and severity as a means for predicting the likelihood of a bleeding disorder and/or to codify bleeding in clinical studies. (See 'Bleeding score' below.)

OVERVIEW OF THE EVALUATION

Actively bleeding patient — Individuals with active bleeding and a suspected (but not previously diagnosed) bleeding disorder are especially challenging to manage because they may require interventions for bleeding before a specific diagnosis is established.

- A search for an anatomic or surgical lesion responsible for the bleeding (tumor, nicked blood vessel) should be made, especially if the bleeding appears to be limited to a single site.

- A prothrombin time (PT) activated partial thromboplastin time (aPTT), platelet count, fibrinogen level, and blood smear are reviewed, with additional tests based on the clinical scenario. This may include evaluation for a platelet disorder with platelet function analyzer (PFA-100) and von Willebrand factor testing or testing for an acquired factor VIII inhibitor in individuals with no prior bleeding history who present with a prolonged aPTT. (See 'Clinical vignettes' below.)

Early involvement of the consulting hematologist should be sought for those with evidence of hemostatic perturbations, both to assist with the evaluation and determination of likely causes

as well as to help in obtaining and dosing hemostatic products if needed. (See 'Indications for hematologist referral' below.)

Interventions for bleeding during the evaluation — The following may also be appropriate:

- **Platelet transfusions** – Individuals with active bleeding and thrombocytopenia should receive platelet transfusions to raise the platelet count to at least 50,000/microL (100,000/microL for central nervous system bleeding or bleeding into a closed compartment). (See "Platelet transfusion: Indications, ordering, and associated risks", section on 'Actively bleeding patient'.)

  Platelet transfusions may also be appropriate if there is concern that impaired platelet function is contributing to bleeding (eg, use of antiplatelet medications, abnormal platelet morphology, uremia, diabetes mellitus, or certain other disorders). (See "Inherited platelet function disorders (IPFDs)".)

  There have been reports that certain disorders may be exacerbated by platelet transfusions (eg, thrombotic thrombocytopenic purpura [TTP], disseminated intravascular coagulation [DIC], heparin-induced thrombocytopenia [HIT]). Despite this, platelets should **not** be withheld for severe bleeding; in such cases, the risk of fatal bleeding outweighs the theoretical increased risk of thrombosis. (See "Platelet transfusion: Indications, ordering, and associated risks", section on 'TTP or HIT'.)

- **Fibrinogen or** vitamin K – Individuals with active bleeding and prolonged clotting times (PT and aPTT) may have vitamin K deficiency; a low fibrinogen level; or deficiency of factor II (prothrombin), X, or V. The thrombin time (TT) will be normal with factor II, X, or V deficiency and prolonged in individuals with a low fibrinogen level. The fibrinogen level should be checked (along with D-dimer if DIC is suspected) and vitamin K may be administered if deficiency is suspected. Fibrinogen concentrate (or cryoprecipitate) should be administered to actively bleeding individuals to maintain the fibrinogen level >100 mg/dL (>200 mg/dL during pregnancy). (See "Evaluation and management of disseminated intravascular coagulation (DIC) in adults", section on 'Prevention/treatment of bleeding' and "Disseminated intravascular coagulation (DIC) during pregnancy: Management and prognosis", section on 'Management of hemodynamically unstable patients'.)

- **Clotting factor products** – Clotting factor products such as a prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa) are generally reserved for specific indications such as reversal of warfarin anticoagulation for the former or treatment of hemophilia with an inhibitor with either product. However, in a potentially

fatal situation, these products may be administered. Some PCCs contain heparin and are contraindicated in individuals with HIT. Input from the consulting specialist is advised as some of these products are potentially thrombogenic. (See "Plasma derivatives and recombinant DNA-produced coagulation factors", section on 'Clotting factor products'.)

- **Antifibrinolytic agents** – Antifibrinolytic agents such as epsilon-aminocaproic acid (EACA) or tranexamic acid (TXA) have been used to treat mucosal bleeding in patients with congenital bleeding disorders. TXA is also licensed to treat heavy menstrual bleeding and has been shown to improve mortality when given early in trauma or in women with postpartum hemorrhage. These agents are contraindicated in individuals with upper pole urinary bleeding (due to the risk of ureteral blockage and hydronephrosis) and in individuals with DIC.

Acute bleeding can produce changes in the hemostatic system, and the full evaluation may need to be completed in the outpatient setting after the individual has recovered.

Patient not actively bleeding — The first step in an individual who is not actively bleeding is to determine whether the individual actually has a bleeding disorder. This may be challenging because the bleeding history is fraught with diagnostic uncertainty. Descriptions of bleeding severity can be subjective, not all individuals have been exposed to bleeding challenges, and clinical presentations may be quite variable even among individuals with the same bleeding disorder. Many individuals with inherited bleeding disorders report minimal bleeding; conversely, many individuals with normal hemostasis report exaggerated bleeding [5,6].

The variability in perceptions among different individuals and the lack of a uniform clinical measure of bleeding severity make the bleeding history even more important [7]. (See 'Patient history' below and 'Bleeding score' below.)

Once the bleeding history is obtained and quantified and the physical examination performed (see 'Targeted physical examination' below), screening laboratory testing is performed with subsequent testing based on the initial results. (See 'Laboratory evaluation' below and 'Subsequent testing based on initial clinical and laboratory features' below.)

PATIENT HISTORY

Underlying medical conditions — Several medical conditions predispose to bleeding, as discussed in separate topic reviews.

- **Cancer** – (See "Causes of anemia in patients with cancer".)

- **Excess alcohol use** – (See "Hematologic complications of alcohol use".)
- **Liver disease** – (See "Hemostatic abnormalities in patients with liver disease".)
- **Kidney disease** – (See "Uremic platelet dysfunction".)
- **Connective tissue disorders** – (See "Hematologic manifestations of systemic lupus erythematosus".)
- **Hypothyroidism** – (See "Acquired von Willebrand syndrome", section on 'Hypothyroidism'.)

A cohort study has suggested that tobacco smoking is associated with an increased risk of major bleeding (hazard ratio 1.49, 95% CI 1.38-1.61), with a higher magnitude of risk in current smokers than former smokers and a dose-response according to the number of cigarettes smoked per day [8]. However, causation was not addressed, the risk of surgical bleeding was not evaluated, and the mechanism remains unclear.

Bleeding history — Patients with a suspected bleeding disorder should have a dialogue with the clinician that incorporates a detailed personal bleeding history and family history. Typically this is done using a bleeding assessment tool (BAT; also called bleeding score). (See 'Bleeding score' below.)

The goal is to determine the likelihood that a bleeding disorder is present, and for those with a reasonably high likelihood of a bleeding disorder, to determine the most likely type of disorder (eg, associated with primary hemostasis [platelets] or secondary hemostasis [coagulation]) and whether the disorder is inherited or acquired.

Important questions focus on the following:

- The reason for the consultation.
- Prior bleeding events over time:
    - Bleeding during infancy (eg, umbilical stump bleeding) and childhood (eg, bleeding with loss of deciduous teeth).
    - Bleeding during adolescence and adulthood (additional questions below related to menstruation and pregnancy).
    - Any bleeds severe enough to require surgical intervention, nasal packing or cautery, a visit to the emergency department, or transfusion.
- History of iron deficiency or iron-responsive anemia.

- Outcome of bleeding challenges:
  - Trauma, including severity of bleeding, need for surgical intervention, and need for transfusions.
  - Surgical procedures, including timing and location, comments of the surgeon regarding the character of the bleeding (eg, diffuse oozing versus bleeding from a specific source), and need for transfusions.
  - Dental procedures (eg, extractions), including timing, duration, and need for packing or additional interventions.
  - If a woman has bled with some procedures but not others, she should be asked if she was taking oral contraceptives or hormone therapy during procedures in which she had good hemostasis, since these hormones can increase levels of von Willebrand factor (VWF) and normalize hemostasis.
  - History of poor wound healing.
- Menstrual history, especially the presence of nighttime "flooding," passage of clots larger than approximately 2.5 cm (size of a quarter [United States coin]), duration of menses longer than eight days, development of iron deficiency, and/or heavy menstrual bleeding (previously called menorrhagia) leading to hysterectomy at a young age [9]. Measures such as number of pads or tampons used can be imprecise because they depend on the fastidiousness of the individual, and the volume of blood lost is nearly impossible to determine if pads or tampons are used. Scoring systems have been devised that use pictures of pads or tampons with varying degrees of saturation; a high score correlated well with the presence of heavy menstrual bleeding in some studies [10]. Endometriosis and hemorrhagic ovarian cysts are seen with increased frequency in women with von Willebrand disease (VWD) [11].
- Pregnancy history, including bleeding with delivery or postpartum and early pregnancy loss (seen with some rare coagulation factor disorders). In VWD, postpartum bleeding (24 to 28 hours after delivery) is more common than bleeding during pregnancy because higher estrogen levels in the second and third trimesters promote increased VWF production. Pro-hemostatic changes during pregnancy may also reduce bleeding due to other disorders. (See "Maternal adaptations to pregnancy: Hematologic changes", section on 'Coagulation and fibrinolysis' and "Pathophysiology of von Willebrand disease", section on 'Clearance and control of plasma VWF levels'.)

- Antibiotic use or malabsorption syndromes that could cause vitamin K deficiency. (See 'Underlying medical conditions' above.)

Bruising — Individuals with an isolated history of easy bruising should be asked about their personal bleeding history and family history, as described above. (See 'Bleeding history' above.)

The distribution of the bruises and other associated features may also be relevant:

- Certain patterns of bruising may prompt questions about the possibility of intimate partner violence or elder abuse. (See "Intimate partner violence: Diagnosis and screening" and "Elder abuse, self-neglect, and related phenomena".)

- If bruises are due to frequent falls, it may be appropriate to ask about and examine changes in the individual's balance or strength that might lead to frequent falling. (See "Falls in older persons: Risk factors and patient evaluation".)

- If bruising only occurs on the hands and forearms, especially in an older individual, this may suggest solar purpura (also called senile purpura). (See "Photoaging", section on 'Photoaging in individuals with phototypes I to IV'.)

Interpretation of the bleeding history — A history of bleeding severe enough to require surgical interventions, transfusions, or iron replacement supports the suspicion of an underlying bleeding disorder. Conversely, a history of surgical procedures, dental extractions, and/or significant trauma that did not require transfusions or other nonstandard interventions is evidence against the presence of an inherited bleeding disorder (or, if the individual currently has abnormal bleeding, supports the possibility of an acquired bleeding disorder).

In contrast, a history of easy bruising, which is commonly reported, lacks sensitivity and specificity and may be a sign of trauma or skin fragility rather than a true bleeding disorder.

The sites and character of bleeding may help distinguish disorders of primary hemostasis (platelet function) from secondary hemostasis (coagulation factor function), as illustrated in the table (table 1). Examples include the following:

- Excessive menstrual bleeding has many causes (eg, an anatomic lesion, hormonal factors, or impaired hemostasis). A bleeding disorder is found in as many as 10 to 30 percent of women with excessive menstrual bleeding in some settings [9,12-15]. (See "Abnormal uterine bleeding in nonpregnant reproductive-age patients: Terminology, evaluation, and approach to diagnosis" and "Abnormal uterine bleeding in adolescents: Evaluation and approach to diagnosis".)

- Platelet and vascular disorders are generally characterized by mucosal bleeding (eg, mouth, nose, urinary tract, gastrointestinal tract) and immediate bleeding upon a bleeding challenge. Epistaxis may be a presenting finding in VWD or hereditary hemorrhagic telangiectasia (HHT). New-onset bruising may herald a new thrombocytopenic disorder (eg, immune thrombocytopenia [ITP], acute leukemia) or an acquired coagulation disorder such as acquired hemophilia or disseminated intravascular coagulation (DIC).

- Coagulation factor disorders are generally characterized by bleeding into muscles and joints and delayed bleeding after a bleeding challenge. Bleeding with circumcision is characteristic of severe hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency). Exceptions are factor XI deficiency, which tends to have more mucosal bleeding, and factor XIII deficiency, which tends to show delayed bleeding after trauma or surgery. Umbilical stump bleeding is characteristic of factor XIII deficiency.

- Disorders of fibrinolysis tend to show delayed bleeding after trauma or surgery.

- Inherited disorders tend to present in childhood if severe but frequently present in adulthood or only after a bleeding challenge if mild. Some inherited disorders have additional syndromic features.

- Some acquired disorders are associated with an underlying condition such as pregnancy, cancer, or connective tissue diseases.

The presence of one of these bleeding patterns or of other clinical features may help to narrow or expand the evaluation; however, it is rarely sufficient to provide a specific diagnosis.

Family history — A family history of bleeding should be obtained to help determine the likelihood of an inherited condition. The figure summarizes diagnostic approach to a suspected heritable disorder (algorithm 1).

Some individuals may be aware of a specific diagnosis in a first- or second-degree relative; others may report a family history of severe bleeding requiring medical interventions (surgery, transfusions).

While a positive family history increases the likelihood of an inherited bleeding disorder, lack of a family history does not eliminate the possibility.

- As many as 30 to 40 percent of individuals with hemophilia A have a de novo germline mutation and thus have a negative family history.

- Certain autosomal recessive conditions (eg, rare coagulation factor deficiencies, Glanzmann thrombasthenia, type 2N VWD) do not manifest in either parent.

The transmission pattern may suggest a specific set of disorders. Hemophilia A and B are X-linked (transmitted from carrier mothers to affected sons and from affected fathers to carrier daughters), whereas VWD and other factor deficiencies are autosomally transmitted. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Patient and family history' and "Clinical presentation and diagnosis of von Willebrand disease" and "Rare inherited coagulation disorders".)

Medication use — Review of medications, including over-the-counter medications, is essential to identify agents that impair hemostasis (nonsteroidal antiinflammatory agents [NSAIDs], anticoagulants, long-term glucocorticoids).

Bleeding risk may also be increased with herbal preparations and dietary supplements that interfere with primary or secondary hemostasis (table 2). In individuals with milder bleeding disorders, use of these agents may exacerbate the bleeding tendency and cause clinically obvious bleeding.

It is important to ask specifically about over-the-counter medications because some individuals do not include these on their medication list and/or do not consider them relevant because they are not prescribed. Aspirin or an NSAID may be taken intermittently and may be included in over-the-counter remedies for colds or flu with names that do not suggest the presence of an antiplatelet ingredient. In the southeastern United States, aspirin is present in remedies such as "Goody powders" or "BC powders" used for migraine headaches or minor aches and pains.

While fish oil has been cited as a cause of increased bleeding, several meta-analyses have not found an increased risk of bleeding or surgical blood loss [16-18]. (See "Fish oil: Physiologic effects and administration", section on 'Safety'.)

Before laboratory testing, it is advisable to discontinue over-the-counter medications and herbs because they may contain unknown ingredients that could interfere with test results. Cessation of bleeding upon discontinuation is also suggestive of a role of the drug.

BLEEDING SCORE

It may be helpful to use a standardized bleeding assessment tool (BAT) in the evaluation of a patient with a suspected bleeding disorder in order to codify the bleeding history [19,20]. We

routinely use a BAT, as do many specialized hemostasis centers, in order to quantify our clinical impression of the likelihood of a bleeding disorder.

- A low BAT score is very good at predicting the absence of a bleeding disorder and can help in limiting the amount of laboratory testing in an individual with a low likelihood of an abnormal finding.

- An elevated BAT score may predict an increased risk of subsequent bleeding [21].

The first BATs were validated for von Willebrand disease (VWD) (eg, the Molecular and Clinical Markers for the Diagnosis and Management of type 1 VWD [MCMDM-1 VWD]) [22-24]. Subsequently, a condensed score was devised (the condensed MCMDM-1 VWD BAT) that incorporated more details about interventions required for bleeding (eg, packing, surgery, medications) [20,25]. The International Society on Thrombosis and Haemostasis (ISTH) has made a version of this BAT available online at bleedingscore.certe.nl [2,19,26,27].

This score has subsequently been validated in several populations:

- **VWD** – In a 2008 study involving 259 individuals with known or unknown VWD status, use of the score with a cutoff score of ≥4 points had a sensitivity of 100 percent, specificity of 87 percent, positive predictive value (PPV) of 0.20, and negative predictive value (NPV) of 1 for the diagnosis of VWD [25]. A subsequent meta-analysis that evaluated several BATs for VWD screening found an overall sensitivity of 75 percent (95% CI, 66 to 83 percent) and an overall specificity of 54 percent (95% CI, 29 to 77 percent); performance characteristics of individual BATs were also reported [28].

- **General bleeding evaluation** – In a 2011 study involving 215 individuals referred for a bleeding evaluation, use of the score with a cutoff of >3 points had a sensitivity of 25 to 47 percent (depending on the reason for referral) and a specificity of 81 to 98 percent [20]. A series of PPV and NPV values were derived based on the baseline prevalence of bleeding disorders in the groups tested (eg, individuals with bleeding symptoms, abnormal coagulation testing, or an affected family member). Addition of the activated partial thromboplastin time (aPTT) test to the BAT score further improved sensitivity and specificity (PPV 0.71 to 0.78).

- **Heavy menstrual bleeding** – In a 2012 study involving 30 females with heavy menstrual bleeding for whom anatomic, hormonal, and medication-related causes had been excluded, use of the score with a cutoff of 3.5 points had a sensitivity of 85 percent, specificity of 90 percent, PPV of 0.89, and NPV of 0.86 [29]. A bleeding disorder was diagnosed in 20 of the 30, most commonly VWD or Glanzmann thrombasthenia. In a 2020

prospective evaluation of 200 adolescents with heavy menstrual bleeding, an ISTH-BAT score of >4 (instead of the established cut-off of >3 or >2 in children) was highly specific in predicting a bleeding disorder [30].

- **Platelet disorders** – The International Society on Thrombosis and Haemostasis Scientific and Standardization Committee (ISTH/SSC) BAT was validated for inherited platelet disorders in a 2020 study of a large cohort of patients with inherited platelet function disorders (IPFD) [31]. Individuals with IPFDs had significantly higher bleeding scores (BS; median 9) than individuals with type 1 VWD (median 5), a higher number of hemorrhagic symptoms (4 versus 3), and higher likelihood of clinically relevant symptoms (score >2). The ISTH-BAT showed excellent discrimination power between individuals with IPFDs and healthy controls.

Higher BAT scores have been associated with increased risk of bleeding in various populations:

- **Platelet function disorders** – A higher BAT score quartile has associated with future bleeding events in patients with inherited platelet disorders [32]. (See "Inherited platelet function disorders (IPFDs)".)

- **Factor XIII deficiency** – A higher BAT score was correlated with bleeding symptoms in patients with factor XIII deficiency [33]. (See "Rare inherited coagulation disorders", section on 'Factor XIII deficiency (F13D)'.)

- **BDUC and mild bleeding disorders** – In patients enrolled in the Vienna Bleeding Biobank, most of whom had a bleeding disorder of unknown cause (BDUC), a high BAT score was correlated with a risk of future bleeding events [21].

TARGETED PHYSICAL EXAMINATION

The physical examination is targeted to potential findings that might support the presence of a bleeding disorder and suggest an underlying diagnosis.

- **Cutaneous findings**

  - **Petechiae** – Petechiae (picture 1 and picture 2 and picture 3), especially if present in dependent areas (legs, sacrum), may indicate thrombocytopenia. (See "Diagnostic approach to thrombocytopenia in adults", section on 'Skin and other sites of bleeding'.)

Petechiae, purpura, ecchymosis, and scarring on the arms may indicate solar purpura, which is a common finding related to aging and is generally not considered a bleeding disorder. (See "Photoaging", section on 'Photoaging in individuals with phototypes I to IV'.)

- **Telangiectasias** – Telangiectasias around the lips or on the fingertips may indicate hereditary hemorrhagic telangiectasia (HHT). (See "Clinical manifestations and diagnosis of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)".)

- **Bruises** – New bruises are deeply purple and older bruises are yellow or green. Bruises that occur only on areas reachable by the patient's hands (arms, thighs, chest) may suggest self-inflicted injury, whereas bruises in locations the patient cannot reach may suggest injury by another person or a fall, depending on the site and pattern. Bruises that are all of the same age may suggest a single traumatic episode, whereas bruises of different ages may suggest a more chronic condition.

- **Hair follicle changes** – Perifollicular hemorrhages (picture 4 and picture 5) and "corkscrew hairs" are seen in scurvy (vitamin C deficiency). (See "Overview of water-soluble vitamins", section on 'Vitamin C (ascorbic acid)'.)

- **Albinism** – Oculocutaneous albinism is associated with certain platelet disorders (Hermansky-Pudlak and Chediak-Higashi syndromes). (See "Hermansky-Pudlak syndrome" and "Chediak-Higashi syndrome".)

- **Other findings**

  - **Splenomegaly** – Splenomegaly may indicate underlying liver disease, lymphoma, or a myeloproliferative neoplasm. Related findings for liver disease include jaundice, spider angiomata, gynecomastia, and asterixis. Related findings for hematologic malignancies include pallor and lymphadenopathy. (See "Hemostatic abnormalities in patients with liver disease" and "Evaluation of peripheral lymphadenopathy in adults".)

  - **Joint laxity** – Joint hypermobility and skin hyperelasticity may be seen in some Ehlers-Danlos syndromes (EDS). Vascular EDS may lead to bleeding due to arterial rupture. (See "Clinical manifestations and diagnosis of Ehlers-Danlos syndromes".)

  - **Cardiac findings** – A harsh systolic murmur may indicate aortic stenosis, a cause of acquired von Willebrand syndrome (AVWS), which may be associated with bleeding from gastrointestinal arteriovenous malformations (AVMs). This and other causes of

AVWS are discussed separately. (See "Acquired von Willebrand syndrome", section on 'Associated diseases'.)

- **Macroglossia and organ infiltration** – Macroglossia and other signs of organ infiltration (carpal tunnel syndrome and periorbital purpura (picture 6)) may indicate amyloidosis, which can cause a number of acquired clotting factor deficiencies (factors X and V, von Willebrand factor [VWF], alpha-2-antiplasmin, and plasminogen activator inhibitor-1 [PAI-1]). (See "Overview of amyloidosis", section on 'Hematologic abnormalities'.)

- **Syndromic findings** – Certain disorders have skeletal findings (eg, thrombocytopenia-absent radius syndrome). (See "Inherited platelet function disorders (IPFDs)", section on 'Specific disorders'.)

LABORATORY EVALUATION

General approach to laboratory testing — Laboratory confirmation is required for a precise diagnosis and treatment in all individuals with a bleeding disorder. However, the extent and sequence of testing are tailored to the likelihood of a bleeding disorder, its seriousness, and its likely cause(s). The following discussion reflects initial testing by the primary hematologist; individuals sent to a tertiary referral center may have already had extensive testing and if they remain undiagnosed may be more likely to have rare conditions that require specialized investigations.

There is no single laboratory test that is adequate for screening the entirety of hemostasis or that can reliably exclude or confirm the presence of a bleeding disorder. A typical evaluation begins with:

- Complete blood count (CBC) that includes platelet count
- Morphology
- Screening tests of coagulation
  - Prothrombin time (PT)
  - Activated partial thromboplastin time (aPTT)

If the patient presents with mucocutaneous bleeding or other reasons to suspect a disorder of primary hemostasis (see 'Interpretation of the bleeding history' above):

- Platelet function analyzer (PFA-100)

- von Willebrand factor (VWF) antigen and activity and factor VIII activity (see 'VWD testing' below)

Depending on the results, additional testing is done to obtain a precise diagnosis.

An exception may be an individual with a negative history for excessive bleeding, especially if:

- They are otherwise healthy.
- They have undergone bleeding challenges (eg, surgery, dental extractions) without excessive bleeding.
- Their family history is negative for bleeding disorders.
- Their only abnormality on history or examination is bruising along distal extremities, especially associated with trauma.

Such individuals may be followed clinically with a plan to perform laboratory testing if they require an invasive procedure and/or if their clinical status changes. However, individuals with heavy bruising who have never been hemostatically challenged may have a mild bleeding disorder and thus may warrant laboratory evaluation prior to an invasive procedure.

Rarely, an individual or family may have multiple abnormalities in their hemostatic system (eg, VWD plus hemophilia) [34]. Thus, if a single abnormality is found that does not fully explain the clinical or laboratory findings, the evaluation should continue until all of the findings are explained.

Summary of available tests — Tests of platelet and coagulation factor function are summarized here briefly and discussed in greater detail separately. (See "Clinical use of coagulation tests" and "Diagnostic approach to thrombocytopenia in adults", section on 'Peripheral blood smear' and "Platelet function testing".)

Results may be affected by pre-analytic variables (incompletely filled tubes, use of a small-gauge needle, high temperatures during transport) and certain medical conditions (eg, hematocrit >55 percent), as discussed separately (see "Clinical use of coagulation tests", section on 'Ensuring accuracy'). Repeat testing with attention to these variables may be appropriate, especially if the result is unexpected.

- **Secondary hemostasis** – Tests for secondary hemostatic defects include the following:

  - **PT and aPTT** – The PT and aPTT are standard initial tests that measure the time it takes for plasma to clot by generating thrombin. Prolongation usually indicates a deficiency or an inhibitor (usually an autoantibody) of one or more clotting factors (figure 1).

There are exceptions, such as prolongation of the aPTT due to antiphospholipid antibodies, which rarely cause bleeding. (See 'Initial testing (all patients)' below.)

The international normalized ratio (INR) is used to normalize the PT result across all testing laboratories. If the PT is elevated, the INR will be elevated, but the INR was developed and validated for monitoring anticoagulation with warfarin or other vitamin K-dependent antagonists rather than to evaluate bleeding disorders.

Mixing studies are PT or aPTT assays in which patient plasma is mixed 1:1 with normal plasma. This can distinguish between a deficiency (which is corrected by mixing because 50 percent of normal factor activity is sufficient for a normal clotting time) and an inhibitor (which typically cannot be overcome by mixing). Nuances and interpretation are discussed separately. (See "Clinical use of coagulation tests", section on 'Use of mixing studies'.)

- **Thrombin time and reptilase time** – The thrombin time (TT) and reptilase time (RT) both measure the final step in the clotting cascade (cleavage of fibrinogen to fibrin). These tests may be done if an anticoagulant or fibrinogen disorder (deficiency, dysfunction, or paraproteins that interfere with polymerization) is suspected as the cause of a prolonged aPTT. The TT is sensitive to thrombin inhibitor anticoagulants (heparin, dabigatran, argatroban) and to fibrinogen abnormalities; the RT is sensitive to fibrinogen disorders but not to heparin. (See "Clinical use of coagulation tests", section on 'Thrombin time (TT)' and "Disorders of fibrinogen".)

- **Specific clotting factor assays** – Assays for individual clotting factors are typically performed if one or more of the screening tests are abnormal. These assays are typically done using a type of mixing study in which patient plasma is mixed with a reference plasma that is deficient in a single clotting factor, so that the only source of that factor will be the patient's plasma.

  Factor XIII, when activated by thrombin, crosslinks fibrin monomers, leading to a more stable clot. Factor XIII deficiency can cause a severe bleeding disorder, often with delayed bleeding, as well as delayed wound healing and early pregnancy loss. (See "Rare inherited coagulation disorders", section on 'Factor XIII deficiency (F13D)'.)

  Standard clot-based tests (PT, aPTT, TT) are normal because these tests only assay clot formation, not crosslinking. (See 'Tests for defects in fibrin crosslinking or fibrinolysis' below.)

- **Primary hemostasis** – Tests for primary hemostasis (platelet and vascular function defects) include:
  - **Testing for VWD** – This includes von Willebrand factor (VWF) antigen, tests for VWF function, and factor VIII activity. (See 'VWD testing' below and "Clinical presentation and diagnosis of von Willebrand disease".)
  - **Testing for platelet function disorders** – The platelet count and platelet morphology should be reviewed from the complete blood count (CBC). Additional testing can be done using platelet aggregation studies or the PFA-100. (See 'Platelet function testing' below.)
- **Tests for individuals with normal clotting times** – Testing for VWD, platelet function abnormalities, vascular and connective tissue disorders, and/or disorders of fibrinolysis may be appropriate in an individual with a suspected bleeding disorder who has a normal PT, aPTT, and platelet count. These tests are discussed below. (See 'VWD testing' below and 'Platelet function testing' below.)

Tests for increased fibrinolysis may be especially relevant in individuals with delayed bleeding. (See 'Tests for defects in fibrin crosslinking or fibrinolysis' below.)

Initial testing (all patients) — Virtually all patients with a suggestive bleeding history (and many concerned about bleeding who have no personal bleeding history [eg, those with a positive family history]) will be tested for the following:

- CBC with platelet count and review of platelet morphology
- PT and aPTT

For those with active bleeding, the fibrinogen activity level (and in some cases D-dimer) is often included in the initial screen. For those with mucocutaneous bleeding, a PFA-100 and evaluation for VWD is warranted. (See 'Actively bleeding patient' above.)

Interpretation of the results is outlined in the table (table 3).

SUBSEQUENT TESTING BASED ON INITIAL CLINICAL AND LABORATORY FEATURES

Positive bleeding history and abnormal screening tests

Thrombocytopenia — Evaluation is presented separately. (See "Diagnostic approach to thrombocytopenia in adults".)

PT and aPTT both prolonged — Prolongation of both the prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests suggests a deficiency (or inhibitor) in a common pathway factor (eg, factor X, V, II [prothrombin], or fibrinogen) or a combination of deficiencies (or inhibitors) affecting both the intrinsic and extrinsic pathways (figure 2). (See "Overview of hemostasis", section on 'Clotting cascade and propagation of the clot'.)

Causes may include the following (table 4):

- Congenital deficiency of one or more common pathway factors. These conditions are autosomal recessive and rare; they are discussed in detail separately. (See "Rare inherited coagulation disorders", section on 'Laboratory findings' and "Disorders of fibrinogen", section on 'Heritable (genetic) disorders'.)
- Acquired factor X deficiency due to amyloidosis. (See "Overview of amyloidosis", section on 'Hematologic abnormalities'.)
- Acquired factor inhibitor of factor X, V, II, or fibrinogen. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)".)
  - Acquired inhibitors may be associated with pregnancy, malignancy, or connective tissue disorder; in some cases, no such condition is present.
  - Antibodies to factor II (prothrombin) may accompany a lupus anticoagulant that increases clearance of factor II; thus, mixing studies will show correction of the PT.
  - Repeated vascular or cardiac surgery using bovine thrombin was previously associated with development of antibodies to thrombin (factor IIa); this occurs less commonly with use of human thrombin.
- Vitamin K deficiency. (See "Overview of vitamin K", section on 'Vitamin K deficiency'.)
- Liver disease. (See "Hemostatic abnormalities in patients with liver disease".)
- Disseminated intravascular coagulation (DIC). (See "Evaluation and management of disseminated intravascular coagulation (DIC) in adults".)
- Anticoagulants such as heparin, warfarin, argatroban, dabigatran, or the factor Xa inhibitors (apixaban, rivaroxaban, edoxaban), especially when given in excess.

- Poisoning by a vitamin K antagonist, which may occur by ingestion of rat poison or by use of synthetic cannabinoids contaminated with an anticoagulant rodenticide. (See "Anticoagulant rodenticide poisoning: Clinical manifestations and diagnostic evaluation".)

In many cases, the clinical scenario will guide the direction, sequence, and extent of testing. Examples are presented below. (See 'Clinical vignettes' below.)

If the clinical scenario does not point to a likely diagnosis, several tests may be performed, including a mixing study, thrombin time (TT), fibrinogen level, and/or liver function tests. The first test is typically a mixing study to distinguish between a factor deficiency and a factor inhibitor. If mixing normalizes the clotting time (ie, if there is no inhibitor), then a TT and fibrinogen level is appropriate; if these tests are unrevealing, then individual factor levels can be obtained. Deficiencies that prolong both the PT and aPTT include factors X, V, and II (prothrombin), as well as fibrinogen.

- In an inpatient, we would be more likely to order a fibrinogen level due to concerns about an acute medical illness such as DIC or liver disease.

- For an outpatient who is currently well, we test for liver disease, DIC, and deficiency of factors in the common pathway (X, V, II, and fibrinogen).

PT prolonged (aPTT normal) — Prolongation of the prothrombin time (PT) with a normal activated partial thromboplastin time (aPTT) suggests a deficiency or inhibitor in the extrinsic pathway (eg, factor VII) (table 4). A mixing study can be used to distinguish between a deficiency and an inhibitor; mixing studies often have a short turnaround time and may inform further testing and management while awaiting specific factor activity levels.

- Congenital factor VII deficiency and acquired factor VII inhibitors are both rare. (See "Rare inherited coagulation disorders" and "Acquired hemophilia A (and other acquired coagulation factor inhibitors)".)

- Occasionally, an evolving systemic defect in coagulation such as DIC, vitamin K deficiency, warfarin use, or liver disease can present with an isolated prolongation of the PT because factor VII has the shortest half-life of the coagulation factors. (See "Biology of warfarin and modulators of INR control", section on 'PT/INR prolongation' and "Hemostatic abnormalities in patients with liver disease", section on 'Laboratory abnormalities'.)

- Paraproteins and dysfunctional fibrinogens can also prolong the PT out of proportion to the aPTT. In these cases, the thrombin time (TT) may also be prolonged. (See "Clinical use of coagulation tests", section on 'Clotting times'.)

aPTT prolonged (PT normal) — Prolongation of the activated partial thromboplastin time (aPTT) with a normal prothrombin time (PT) suggests a deficiency or inhibitor in the intrinsic pathway (eg, factor VIII, IX, or XI) (table 4).

- Von Willebrand disease (VWD) is the most common inherited bleeding disorder and generally is associated with a normal aPTT. However, when VWD is more severe, the low factor VIII level that results from low von Willebrand factor (VWF) levels may be enough to slightly prolong the aPTT. Acquired von Willebrand syndrome (AVWS) can result from a condition that leads to decreased production, sequestration, or increased destruction of VWF. Most individuals with VWD or AVWS have normal platelet counts and normal PT and aPTT values; however, in severe disease or type 2N VWD, the factor VIII level may be low enough to result in slight prolongation of the aPTT. (See 'VWD testing' below and "Clinical presentation and diagnosis of von Willebrand disease" and "Acquired von Willebrand syndrome".)

- Hemophilia A (congenital factor VIII deficiency) is the most common inherited factor deficiency, followed by hemophilia B (congenital factor IX deficiency). These disorders are both X-linked, but up to one-third of cases of hemophilia A occur as de novo mutations. (See "Clinical manifestations and diagnosis of hemophilia".)

- Congenital factor XI deficiency is an autosomal dominant disorder seen with increased frequency in individuals of Ashkenazi Jewish ancestry. Factor XI deficiency produces a mucocutaneous bleeding pattern (eg, easy bruising and epistaxis rather than joint or muscle bleeding), and bleeding is more variable relative to the absolute factor XI level than in hemophilia A and B. (See "Factor XI (eleven) deficiency", section on 'Bleeding'.)

- Acquired inhibitors (antibodies) of intrinsic pathway factors may be seen with pregnancy, malignancy, connective tissue disorders, or in otherwise healthy individuals. Acquired inhibitors to factor VIII are most common. The initial presentation may be with severe bleeding, often out of proportion to factor VIII levels, in cutaneous, deep tissue, and multifocal sites; hemarthroses are rare. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)" and "Clinical use of coagulation tests", section on 'Use of mixing studies'.)

- Heparin and direct thrombin inhibitor anticoagulants (argatroban, dabigatran) can prolong the aPTT, as can direct factor Xa inhibitors, though less reliably. (See "Clinical use of coagulation tests", section on 'Causes of prolonged aPTT'.)

- Certain malignancies such as plasma cell disorders can produce a heparin-like substance (also called heparin-like anticoagulant [HLAC]) that causes similar laboratory findings to

heparin (prolonged aPTT, prolonged TT, and normal reptilase time [RT]) [35].

If the aPTT is prolonged and the PT is normal, we do a mixing study. If the mixing study corrects, then we perform assays for factors XII, XI, IX, and VIII. Even though factor XII deficiency is not associated with bleeding, it may explain a prolonged aPTT that corrects with mixing. If the mixing study fails to correct, we test for the presence of a lupus anticoagulant and factor VIII activity (the latter to detect a rare patient with acquired hemophilia A).

Positive bleeding history and normal initial testing — Individuals with a positive bleeding history and/or high score on a bleeding assessment tool (BAT) such as the International Society on Thrombosis and Haemostasis (ISTH) BAT who have normal PT, aPTT, and platelet count are evaluated for other bleeding disorders such as von Willebrand disease (VWD), platelet function disorders, and vascular and connective tissue disorders.

Even after more extensive testing such as fibrinogen, von Willebrand factor (VWF) analysis, clotting factor levels, and platelet aggregation testing, up to 30 to 60 percent of patients sent to tertiary centers for a bleeding evaluation will have a positive history of bleeding (some with quite elevated BAT scores) and a negative hemostatic evaluation. These patients are predominantly female and often have mucocutaneous bleeding, similar to individuals with VWD or platelet function disorders, referred to as having a bleeding disorder of unknown cause (BDUC).

VWD testing — Von Willebrand disease (VWD) is the most common inherited bleeding disorder, with low VWF levels in approximately 1 percent of the general population. Only a fraction of these individuals come to medical attention for concern about a bleeding disorder. Inheritance is autosomal. Bleeding severity is variable. Typical findings are mucocutaneous and post-surgical bleeding and easy bruising; women may also report heavy menstrual periods, endometriosis, and postpartum hemorrhage. Diagnosis is often significantly delayed.

Acquired von Willebrand syndrome (AVWS) may be due to reduced production, sequestration, or increased destruction of VWF.

The aPTT may be prolonged in severe cases of VWD or AVWS and normal in mild cases (especially if the factor VIII activity level is above 40 to 50 percent). We use the platelet function analyzer (PFA-100) in conjunction with VWF activity and antigen levels in evaluating patients with mucocutaneous bleeding. In the rare type 2N VWD, factor VIII levels may be very low and patients may be misdiagnosed as having hemophilia A; in these patients, the PFA-100 is normal; in type 2B VWD, many patients have varying degrees of thrombocytopenia (platelet count 50,000 to 149,000/microL).

Testing for VWF function typically includes the following (table 5):

- Plasma VWF antigen (VWF:Ag)
- Plasma VWF activity (ristocetin cofactor [VWF:RCo] and collagen binding [VWF:CB])
- Plasma factor VIII activity

Analysis of multimers should be done if there is low VWF antigen or activity or if the ratio of VWF:Rco to VWF:Ag is <0.7, suggesting the presence of a dysfunctional VWF.

Levels of VWF fluctuate in response to estrogens, stress, exercise, inflammation, and bleeding; repeated assays may be required to make the diagnosis. Additional details of interpretation of the test results, testing to determine the type of VWD, and testing to determine appropriate therapy are presented separately. (See "Acquired von Willebrand syndrome" and "Clinical presentation and diagnosis of von Willebrand disease", section on 'Laboratory testing'.)

Platelet function testing — There are a number of congenital and acquired disorders affecting platelet number, platelet function, or both. Testing is challenging because some tests are highly operator-dependent, many tests are poorly standardized and poorly reproducible, and no test is able to assay all aspects of platelet function [36]. (See "Platelet function testing", section on 'Overview'.)

If a drug-induced cause is suspected based on the history (see 'Medication use' above), it may be appropriate to substitute another agent that does not affect platelet function or to discontinue the drug and observe for resolution of the bleeding manifestations.

If uremia, a myeloproliferative disorder, or cardiopulmonary bypass is suspected as a cause of platelet dysfunction, it may be appropriate to treat the underlying disorder and re-evaluate. (See "Overview of the myeloproliferative neoplasms", section on 'Thrombosis and bleeding' and "Early noncardiac complications of coronary artery bypass graft surgery", section on 'Bleeding' and "Uremic platelet dysfunction", section on 'Treatment of bleeding'.)

When platelet function testing is indicated, it is generally performed by the hematology consultant and/or in specialized laboratories with expertise in their methods and interpretation:

- **Platelet aggregation studies** – Platelet aggregation studies measure platelet-platelet cohesion as induced by various known platelet agonists (eg, thrombin, collagen, epinephrine, ADP) (see "Overview of hemostasis", section on 'Platelet aggregation'). Aggregation causes platelets to come out of solution, which increases light transmission in a spectrophotometer-based assay.

- In Glanzmann thrombasthenia (GT; defect in platelet GPIIb-IIIa complex), platelets will not aggregate to any agonists but will agglutinate in response to ristocetin.
- In Bernard-Soulier syndrome (BSS; defect in platelet GPIb-IX complex), platelets will aggregate in response to thrombin, collagen, epinephrine, and ADP but not to ristocetin.
- In some granule disorders, platelets may show an abnormal aggregation tracing (loss of the second wave of aggregation in response to weaker platelet agonists).

Aggregometry is considered the gold standard for platelet function testing. Lumiaggregometry is a variation in which ADP released from dense granules is converted to ATP, which reacts with a bioluminescent compound (luciferin). These tests are discussed in more detail separately. (See "Platelet function testing", section on 'Platelet aggregometry'.)

- **PFA-100** – The platelet function analyzer (PFA-100) measures the time it takes for blood flow to stop under shear stress in a capillary tube containing a membrane impregnated with collagen and epinephrine (Col/Epi) or collagen and ADP (Col/ADP) and then exposed to shear stress. The test's sensitivity for bleeding disorders is low, and different centers have different conventions for its use. We find it a useful adjunct in evaluating patients with mucocutaneous bleeding. (See "Platelet function testing", section on 'PFA-100'.)
- **Genetic testing** – Genetic testing for known platelet function disorders (eg, using a gene panel) is becoming more widely available and may be reasonable in certain individuals with a suspected platelet disorder of genetic origin [37]. (See "Inherited platelet function disorders (IPFDs)", section on 'Specific disorders'.)
- **Electron microscopy** – Electron microscopy (EM) to examine the ultrastructure of platelets is typically ordered by specialized referral centers. Transmission EM may be used to image the ultrastructure of platelet granules in individuals with suspected platelet storage pool diseases (SPDs; eg, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome) who have a normal platelet aggregometry and PFA-100. EM can also be used to diagnose the nonmuscle myosin heavy chain 9 (*MYH9*)-related disorders (previously referred to a May-Hegglin anomaly, Fechtner syndrome, Epstein syndrome, and Sebastian syndrome). (See "Causes of thrombocytopenia in children", section on 'Large or giant platelets' and "Inherited platelet function disorders (IPFDs)", section on 'Specific disorders'.)

The bleeding time (BT) is no longer commonly used (and has largely been replaced by PFA-100). The BT is performed at the bedside by inflating a blood pressure cuff on the upper arm to 40

mmHg, creating a cut of standard size and depth on the forearm using an automated device, and measuring the time until bleeding stops. The BT is typically prolonged in platelet disorders, VWD, thrombocytopenia, and disorders of vascular contractility. However, the test is insensitive and operator-dependent.

Other tests of platelet function have been developed, but they are not especially good at screening for bleeding disorders or predicting surgical bleeding and are not widely available. (See "Platelet function testing", section on 'Tests not commonly used'.)

Tests for defects in fibrin crosslinking or fibrinolysis — Factor XIII crosslinks fibrin to stabilize clots. Factor XIII deficiency is a rare autosomal disorder that presents with severe bleeding (eg, umbilical stump, intracranial hemorrhage). Rare cases of factor XIII inhibitors have also been reported. Diagnostic testing is with qualitative or quantitative factor XIII levels.

Fibrinolysis (clot breakdown) is a normal hemostatic process. Disorders of fibrinolysis often show delayed bleeding. The cause may be inherited (eg, congenital deficiencies of fibrinolytic inhibitors such as alpha-2-antiplasmin or plasminogen activator inhibitor-1) or acquired (eg, hyperfibrinolysis associated with envenomations, acute promyelocytic leukemia, overdoses of fibrinolytic agents, prostate cancer, or DIC). Laboratory testing involves measurement of fibrinogen levels and D-dimer (a fibrin degradation product) or related tests (table 6). The euglobulin clot lysis test (ECLT) may also be used. (See "Thrombotic and hemorrhagic disorders due to abnormal fibrinolysis".)

Chromogenic factor VIII assays — Most testing for factor VIII activity in the United States is done using a one-stage aPTT-based assay, but 40 percent of individuals with mild hemophilia A have a factor VIII molecule that shows discrepant values in the one-stage factor VIII assay versus the factor VIII activity measured using a chromogenic assay [38]. Some women who are lyonized carriers of these types of factor VIII variants might show a normal aPTT and a normal one-stage factor VIII assay but a low factor VIII activity in a chromogenic factor VIII assay. An example of the use of this testing is described below. (See 'Clinical vignettes' below.)

Vascular and connective tissue disorders — Disorders that affect vascular function (some of which are referred to as vascular purpuras) include the following:

- **HHT** – Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder associated with telangiectasias and arteriovenous malformations (AVMs) of the small vessels in skin, oropharynx, lungs, gastrointestinal tract, and other tissues. Common findings include epistaxis, gastrointestinal bleeding, telangiectasias on the lips and fingertips, and iron deficiency anemia. Bleeding may begin in childhood; by age 16, the

majority of patients will experience hemorrhagic symptoms. (See "Clinical manifestations and diagnosis of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)".)

- **Scurvy** – Scurvy is caused by vitamin C deficiency. Symptoms are thought to be due to impaired collagen synthesis and disordered connective tissue; these generally occur when the vitamin C level is <0.2 mg/dL (<11 micromol/L). Recent vitamin C intake can falsely normalize levels. (See "Overview of water-soluble vitamins", section on 'Vitamin C (ascorbic acid)'.)

- **Ehlers-Danlos syndrome** – Ehlers-Danlos syndrome (EDS) refers to a group of collagen disorders characterized by easy bruising and hemorrhage from ruptured blood vessels; there are several genes involved [39].

  - The classical EDS causing joint hypermotility and hyperextensibility of the skin may cause bruising but is not likely to result in massive bleeding.

  - The vascular type IV EDS is due to pathogenic variants in t*he COL3A1* gene; bruising can be very extensive, and vascular rupture can be fatal. The skin may be thin and wrinkled, but joint hyperextensibility is rare.

  In a cohort of 52 individuals with various types of EDS (classical, hypermobile, vascular) who were evaluated with the ISTH-BAT, the mean score was 9.1, well over the threshold for bleeding disorders [40]. An abnormally high ISTH-BAT score was seen in 32 of 52 individuals with EDS (62 percent), versus none of the 52 controls without EDS. Common bleeding histories in the EDS patients were not limited to individuals with a specific EDS subtype and included bruising, epistaxis, oral and dental, muscle hematomas, and heavy menstrual bleeding. Life-threatening menstrual bleeding occurred in 7 of 50 females (14 percent). (See 'Bleeding score' above.)

  Tests of platelet and clotting function are normal in EDS syndromes. Diagnosis requires thorough clinical assessment and demonstration of the genetic abnormality or of abnormal type III collagen. (See "Clinical manifestations and diagnosis of Ehlers-Danlos syndromes" and "Gene test interpretation: *COL3A1* (vascular Ehlers-Danlos syndrome gene)".)

- **Osteogenesis imperfecta** – Osteogenesis imperfecta (OI) is a connective tissue disorder that primarily affects bone but can also be associated with bleeding due to capillary fragility [41]. (See "Osteogenesis imperfecta: An overview".)

Isolated laboratory abnormalities with negative bleeding history — Some individuals may be referred for evaluation if they have isolated laboratory abnormalities, without a personal or family history of abnormal bleeding. Many individuals with mild bleeding disorders will be in this category because they have not experienced sufficient bleeding challenges.

In most of these cases, the evaluation of the abnormality is similar to that for individuals with a bleeding history because it is possible that such an individual has not had a significant bleeding challenge or that an acquired disorder has developed that has not yet manifested bleeding. This is especially true if surgery is planned. The approach is discussed in detail in a separate topic review. (See "Clinical use of coagulation tests", section on 'Prolonged PT and/or aPTT without bleeding or thrombosis'.)

Certain coagulation factor abnormalities will affect the coagulation studies but are not associated with clinical bleeding. These include deficiencies of high molecular weight kininogen, prekallikrein, and factor XII, many dysfibrinogenemias, as well as certain mutations in the factor VII molecule that affect its interaction with bovine but not human thromboplastin (this occurs if the laboratory is using bovine thromboplastin as the tissue factor reagent in the PT assay). Some individuals with other factor deficiencies may not have bleeding (eg, certain individuals with factor XI deficiency or mild factor VII deficiency). (See "Overview of the causes of venous thrombosis", section on 'Factor XII deficiency'.)

Isolated family history of a bleeding disorder — Individuals who have a family history of a bleeding disorder may request an evaluation for the disorder even if they have not had bleeding (eg, prior to surgery or to assist with preconception counseling). In such individuals, it is reasonable to review the family member's diagnosis to determine if it is in fact a heritable condition. If so, it is reasonable to test the individual, especially prior to surgery. Often this will entail a screening test plus specific testing (eg, for hemophilia, aPTT plus factor VIII level). (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Screening family members' and "Clinical manifestations and diagnosis of hemophilia", section on 'Patient and family history'.)

INDICATIONS FOR HEMATOLOGIST REFERRAL

Hematologist referral is appropriate for individuals who are concerned about a bleeding disorder based on any of the following:

- Active bleeding that requires administration of hemostatic products

- Abnormal initial testing that cannot be easily explained (eg, by presence of an anticoagulant) and/or that persists upon retesting
- Test results consistent with a specific hematologic disorder (eg, von Willebrand disease [VWD], immune thrombocytopenia [ITP])
- Concern about a bleeding disorder based on personal or family history, with normal initial testing
- Concern that a previous diagnosis may be inaccurate (eg, individual with borderline von Willebrand factor [VWF] levels told they have VWD)
- Concern about a bleeding disorder and upcoming surgery
- Question about whether anticoagulant or antiplatelet medications can be used in an individual with a mild bleeding disorder
- Family history of a bleeding disorder with upcoming surgery, delivery, or desire for prenatal counseling

CLINICAL VIGNETTES

The following vignettes illustrate some of the concepts discussed above:

- **Positive personal and family history of bleeding** – A 42-year-old woman with a longstanding personal and family history of mucocutaneous bleeding was seen prior to surgery for infiltrating ductal carcinoma of the breast. Her International Society on Thrombosis and Haemostasis (ISTH) bleeding score was 14, strongly indicative of an underlying bleeding disorder. She had been told she had von Willebrand disease (VWD). Her breast biopsy was complicated by hemorrhage; her entire breast turned hard and purple, and she developed purple discoloration down to the level of her umbilicus. Coagulation testing revealed a normal prothrombin time (PT) and activated partial thromboplastin time (aPTT). Platelet function analyzer (PFA-100) showed closure times of >300 seconds in both the collagen/epinephrine and collagen/ADP cartridges. Von Willebrand factor (VWF) antigen and activity were both >100 percent. Platelet lumiaggregation testing showed a secretion defect in response to collagen, ADP, epinephrine, and arachidonic acid. She had a defect in the secondary wave in response to epinephrine and low-dose ADP. She thus did not have VWD, but rather a qualitative platelet defect (storage pool disorder). Electron microscopy (EM) could be used in this case to distinguish between specific types of storage pool disorders. (See "Inherited platelet function disorders (IPFDs)", section on 'Specific disorders'.)

- **Positive family history and initial bleeding challenge in adulthood** – A 55-year-old woman presented with post-surgical bleeding after a face lift. She was known to have a

father and son with hemophilia A and thus was an obligate carrier. Laboratory evaluation revealed that her aPTT was mildly prolonged and her factor VIII activity level was 50 percent in a one-stage assay but 22 percent in a chromogenic factor VIII activity assay. This case emphasizes the importance of the family history and the possibility of bleeding in females who are heterozygous for a hemophilia mutation. Appropriate preoperative testing and management of these individuals is discussed separately. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Bleeding in females/carriers'.)

- **New onset bleeding in an adult** – A 65-year-old man with no prior personal or family history of bleeding presented with massive gastrointestinal bleeding following polypectomy. Laboratory evaluation showed a normal PT and an abnormally prolonged aPTT of 102 seconds (reference range, 25 to 35 seconds). A mixing study showed an aPTT of 40 seconds (partial correction). The factor VIII level was <1 percent. In this case, the mixing study failed to show complete correction, which is indicative of an inhibitor. The patient thus had acquired hemophilia A (an acquired factor VIII inhibitor) and could be treated with either rFVIIa, the humanized bispecific antibody emicizumab, a factor VIII bypassing agent (eg, FEIBA), or recombinant porcine factor VIII. Management of bleeding and other aspects of care are discussed separately. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)", section on 'Management'.)

DIFFERENTIAL DIAGNOSIS

In some cases, bleeding or purpura may have a cause other than a bleeding disorder.

- **Trauma** – Trauma from frequent falls or other injuries (eg, due to loss of balance, self-injury, or physical abuse) can produce ecchymoses and/or internal bleeding. Like bleeding disorders, the history may be vague or unrevealing, especially if the individual fears the outcomes of such disclosure (eg, loss of independence or need for a walker with reduced balance, retaliation from an abuser). Unlike bleeding disorders, these individuals do not have excessive bleeding with true bleeding challenges, and their laboratory testing for bleeding disorders is normal. (See "Falls in older persons: Risk factors and patient evaluation" and "Intimate partner violence: Diagnosis and screening" and "Elder abuse, self-neglect, and related phenomena".)

- **Vasculitis** – Some vasculitides (especially small-vessel) produce palpable purpura. Unlike purpura from thrombocytopenia, purpura associated with vasculitis is palpable and the platelet count is typically normal. (See "Overview of and approach to the vasculitides in adults", section on 'Small-vessel vasculitis'.)

- **Psychogenic purpura** – Psychogenic purpura refers to purpura or bleeding in an unusual pattern that often resembles religious stigmata; it is a diagnosis of exclusion. The cause is not well understood, and psychiatric factors are often implicated. (See "Psychogenic purpura (Gardner-Diamond syndrome)".)

- **Dysproteinemias** – Bleeding due to dysproteinemias such as seen in plasma cell dyscrasias is discussed separately. (See "Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis", section on 'Systemic presentations' and "Epidemiology, pathogenesis, clinical manifestations, and diagnosis of Waldenström macroglobulinemia", section on 'Platelet function and blood coagulation' and "Acquired von Willebrand syndrome".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hemophilia A and B" and "Society guideline links: von Willebrand disease" and "Society guideline links: Rare inherited bleeding disorders" and "Society guideline links: Acquired bleeding disorders".)

PATIENT PERSPECTIVE TOPIC

Patient perspectives are provided for selected disorders to help clinicians better understand the patient experience and patient concerns. These narratives may offer insights into patient values and preferences not included in other UpToDate topics. (See "Patient perspective: von Willebrand disease".)

SUMMARY AND RECOMMENDATIONS

- **History** – The first step in evaluating a suspected bleeding disorder is to determine whether a disorder is present. We start with a thorough history that includes underlying medical conditions, spontaneous bleeding, response to bleeding challenges, family history, and medication use, including over-the-counter medications and herbal preparations (table 2). The history also helps to determine if a disorder is likely inherited or acquired and likely due to platelet/vascular abnormalities or coagulation factor dysfunction (table 1). The bleeding score is used to quantify the personal bleeding history. (See 'Patient history' above and 'Bleeding score' above.)

- **Examination** – We perform a targeted physical examination focused on skin and other relevant findings that would help establish and narrow the diagnosis. (See 'Targeted physical examination' above.)

- **Initial laboratory testing** – Laboratory confirmation is required for a precise diagnosis and treatment in all individuals with a bleeding disorder. The extent and sequence of testing are tailored to the urgency and likely cause(s). A typical evaluation begins with platelet count and morphology review, prothrombin time (PT), and activated partial thromboplastin time (aPTT). For those with a bleeding history that suggests a disorder of primary hemostasis (eg, mucocutaneous bleeding), an evaluation for VWD and platelet function is warranted. (See 'Overview of the evaluation' above and 'Laboratory evaluation' above and "Platelet function testing".)

- **Specialized testing in selected cases** – Depending on the results of the initial testing, additional specialized testing is done to obtain a precise diagnosis. Often this involves input from the consulting hematologist. (See 'Indications for hematologist referral' above.)

  - **Active bleeding** – In individuals with active bleeding, obtain a fibrinogen activity level and other testing appropriate to the clinical setting; an acquired factor VIII inhibitor may be suspected in an individual with no prior bleeding history and a prolonged aPTT. For severe bleeding, it may be appropriate to administer platelets, fibrinogen, or a hemostatic agent while performing the diagnostic evaluation. (See 'Actively bleeding patient' above.)

  - **Abnormal coagulation studies or platelet count** – Individuals with isolated laboratory abnormalities and/or a prior bleeding history have subsequent testing based on the results of the platelet count, PT, aPTT, and in some cases von Willebrand disease (VWD) testing (table 5) and/or platelet function testing (table 4). (See 'Isolated laboratory abnormalities with negative bleeding history' above and 'Positive bleeding history and abnormal screening tests' above.)

  - **Normal initial testing but positive bleeding history** – Additional bleeding disorders that may not be apparent with the initial screening test may be evaluated for VWD, disorders of fibrin crosslinking and fibrinolysis (table 6), and/or vascular disorders such as hereditary hemorrhagic telangiectasia (HHT), scurvy, and Ehlers-Danlos syndrome (EDS). (See 'Positive bleeding history and normal initial testing' above.)

- **Testing details** – Details of available tests are summarized briefly above and discussed in more detail separately. (See 'Summary of available tests' above and "Clinical use of coagulation tests".)

- **Differential diagnosis** – The differential diagnosis of bleeding disorders includes trauma (due to loss of balance, self-injury, or physical abuse), vasculitis (especially small-vessel vasculitides, which may cause palpable purpura), and dysproteinemias such as seen in plasma cell dyscrasias. (See 'Differential diagnosis' above.)

- **Related topics** – An overview of the hemostatic process, preoperative assessment of hemostasis, and an approach to a suspected bleeding disorder in infants and children are discussed separately. (See "Overview of hemostasis" and "Preoperative assessment of bleeding risk" and "Approach to the child with bleeding symptoms".)

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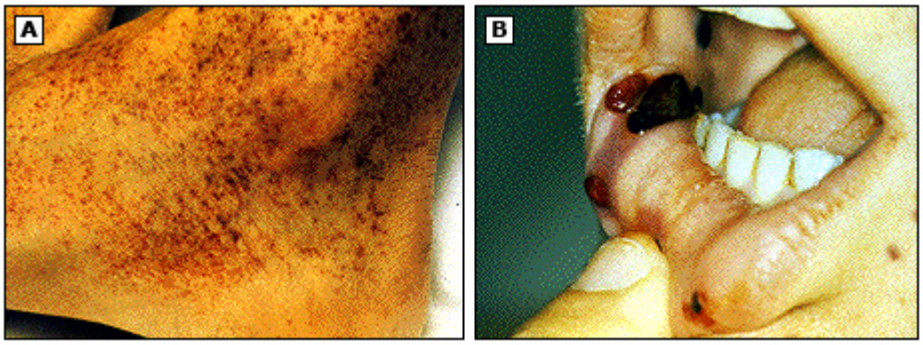
Topic 1367 Version 50.0

GRAPHICS

Petechiae in immune thrombocytopenia (ITP)



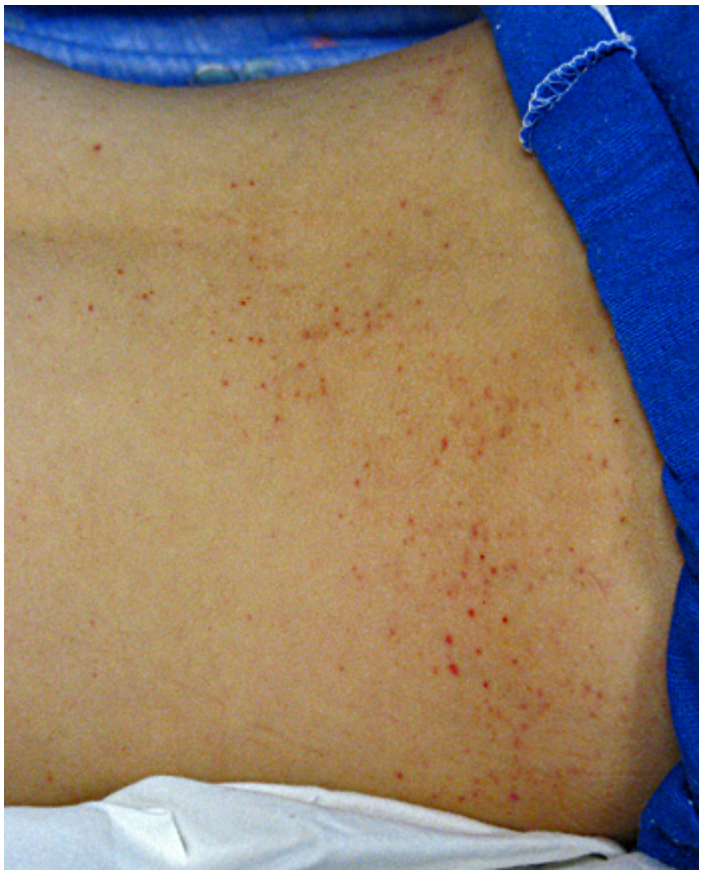
Petechiae in a man with immune thrombocytopenia (ITP).

(A) Dense, cutaneous petechiae on the foot and ankle. There are no petechiae on the sole of his foot, a site at which the vessels are protected by the strong subcutaneous tissue.

(B) Occasional petechiae on the patient's face and large, bullous hemorrhages on the buccal mucosa, which are related to the lack of vessel protection by the submucosal tissue. Similar petechiae and hemorrhagic bullae can be seen in patients with thrombocytopenia of any cause.

Graphic 71480 Version 8.0

Petechiae



Courtesy of Leslie Raffini, MD.

Graphic 73905 Version 2.0

Clinical features of bleeding disorders

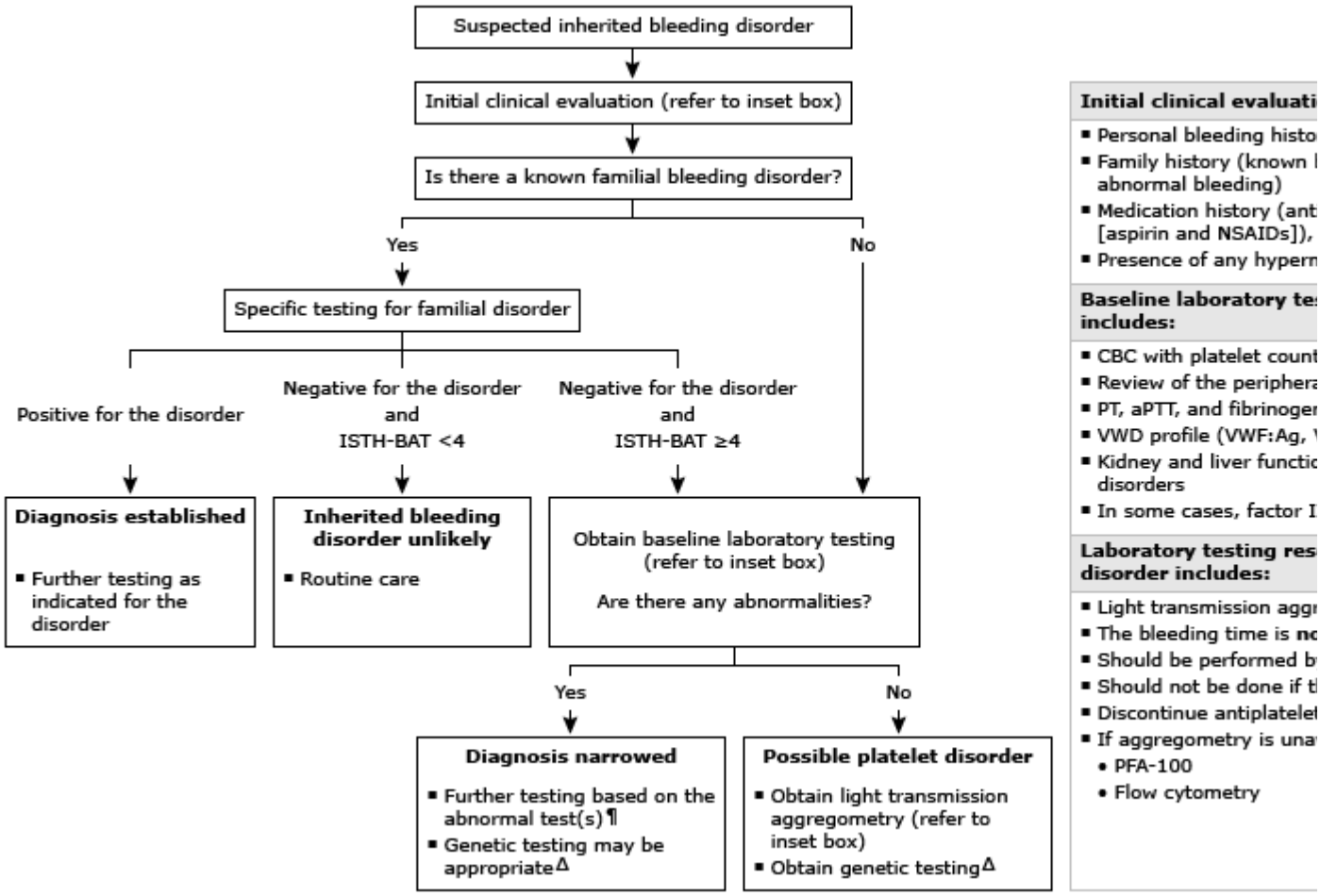
Bleeding characteristics	Type of bleeding disorder	
	Thrombocytopenia or platelet function disorders	**Clotting factor deficiencies or inhibitors**
Major sites of bleeding	Mucocutaneous (mouth, nose, gastrointestinal tract, urinary tract, menorrhagia)	Deep tissue (joints, muscles) or soft tissue hematomas
Petechiae	Common	Uncommon
Ecchymoses	Generally small and superficial. May be significant, depending upon the degree of thrombocytopenia.	May develop large ecchymoses
Excessive bleeding after minor cuts	Yes	Not usually
Excessive bleeding with surgery or invasive procedures	Often immediate; severity is variable (no excess bleeding with mild thrombocytopenia, severe bleeding with certain platelet function disorders such as GT)	Often during the procedure. Individuals with factor XIII deficiency may experience delayed bleeding.

Individuals with mild disorders may not report significant bleeding. Refer to UpToDate for details of the evaluation of a suspected bleeding disorder and for diagnostic testing for specific disorders.

GT: Glanzmann thrombasthenia.

Graphic 77834 Version 13.0

Evaluation of an inherited bleeding disorder



Reasons to suspect an inherited bleeding disorder may include a positive family history, a personal history of increased bleeding, an abnormality of a laboratory test (coagulation test, platelet count, platelet morphology), or other reasonable patient concern. A carefully performed bleeding history is the best initial assessment for a bleeding disorder. Information from the clinical evaluation may guide subsequent workup, such as evaluation for a connective tissue disorder in an individual with joint hypermobility and increased bleeding. The medication history is important to identify possible causes of bleeding as well as to determine medications that may need to be discontinued prior to obtaining platelet aggregometry. Optimal evaluation is done by a hemostasis expert with access to specialist assays including platelet aggregometry testing.

CBC: complete blood count; PT: prothrombin time; aPTT: activated partial thromboplastin time; NSAID: nonsteroidal antiinflammatory drug; SSRI: selective serotonin reuptake inhibitor; VWD: von Willebrand disease.

* The ISTH-BAT delineates and quantifies personal bleeding history and responses to bleeding challenges. A calculator is available at bleedingscore.certe.nl. Cutoffs vary by age and sex, since bleeding challenges are more common in older individuals (surgery, dental procedures) and females (menses and pregnancy). A score ≥4 suggests a possible bleeding disorder; often individuals with bleeding disorders have scores of ≥10.

¶ The aPTT can be normal with mild factor IX or factor XI deficiency. Factor IX and XI activity testing is most relevant in individuals with a positive family history of bleeding (for factor IX, especially in males; for factor XI, especially for those with Ashkenazi Jewish ancestry) and a very high ISTH-BAT score and/or joint and soft tissue bleeding; it may be omitted in individuals with less-severe bleeding history or those in whom other diagnoses seem more likely. Refer to UpToDate topics on bleeding disorders and coagulation testing for details of the likely diagnoses and subsequent testing.

Δ Genetic testing can be done simultaneously with other testing or sequentially, depending on clinical situation and local practices. A hemostasis genetic panel is often used. Refer to UpToDate topics on heritable platelet disorders for listings of specific disorders and genes.

Graphic 138359 Version 1.0

Medications and other substances that may increase the risk of bleeding or bruising

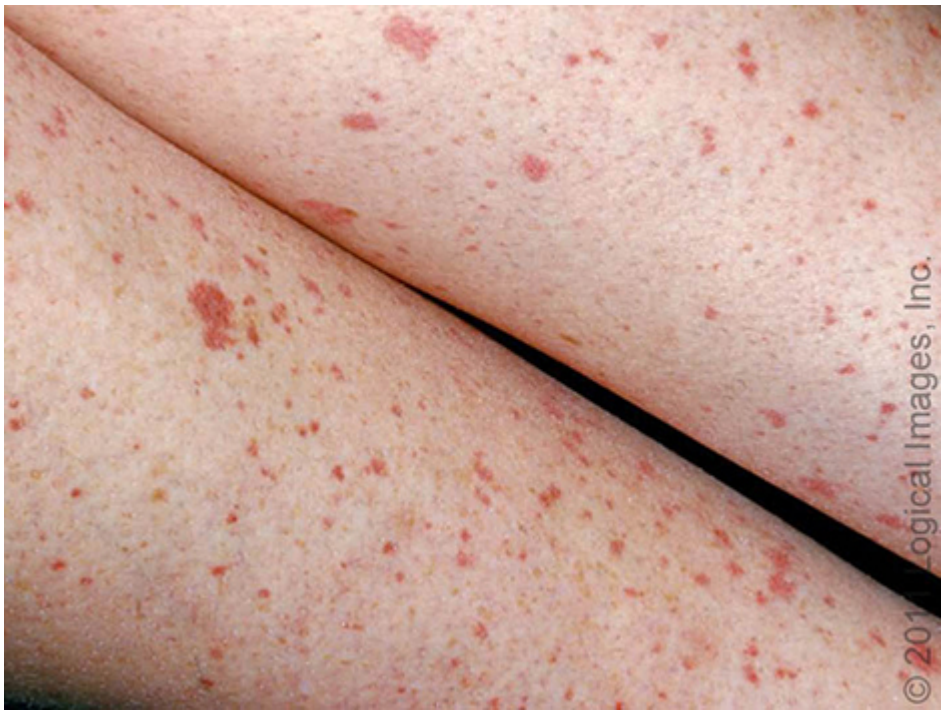
Drug class or substance	Mechanism
Anticoagulants	Interfere with clot formation (secondary hemostasis)
Antiplatelet agents, including NSAIDs	Interfere with platelet function (primary hemostasis)
Glucocorticoids	Interfere with vascular integrity
Antibiotics	Cause vitamin K deficiency, especially with longer use Some interfere with platelet function
SSRIs	Interfere with platelet function (primary hemostasis)
Alcohol	Complications of liver disease may affect clot formation and may cause thrombocytopenia May cause thrombocytopenia due to direct marrow toxicity
Vitamin E	Interferes with vitamin K metabolism in some individuals
Garlic	Interferes with platelet function in some individuals
Gingko biloba	Unknown

This is a partial list that does not include drugs used for cancer therapy or drugs that alter the metabolism of anticoagulants. The magnitude of increased bleeding risk depends on many factors including the patient's other bleeding risk factors and the specific drug, dose, and duration of use. Fish oil is often cited, but bleeding risk does not appear to be increased. Refer to drug information monographs and UpToDate topics for further information.

NSAIDs: nonsteroidal antiinflammatory drugs; SSRIs: selective serotonin reuptake inhibitors.

Graphic 120264 Version 2.0

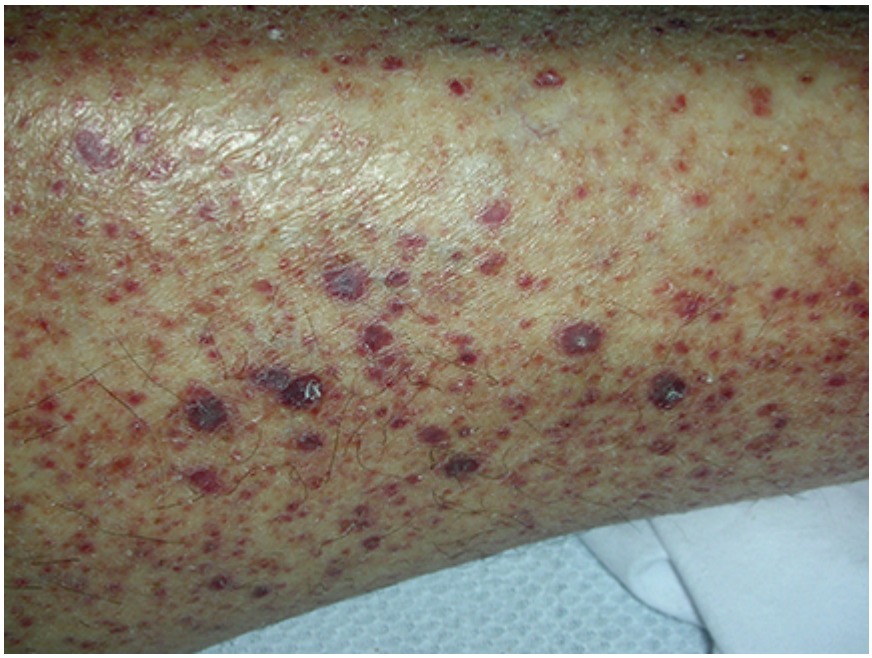
Immune thrombocytopenia (ITP)



Petechiae and scattered purpura on the legs of a patient with ITP.

Graphic 76671 Version 7.0

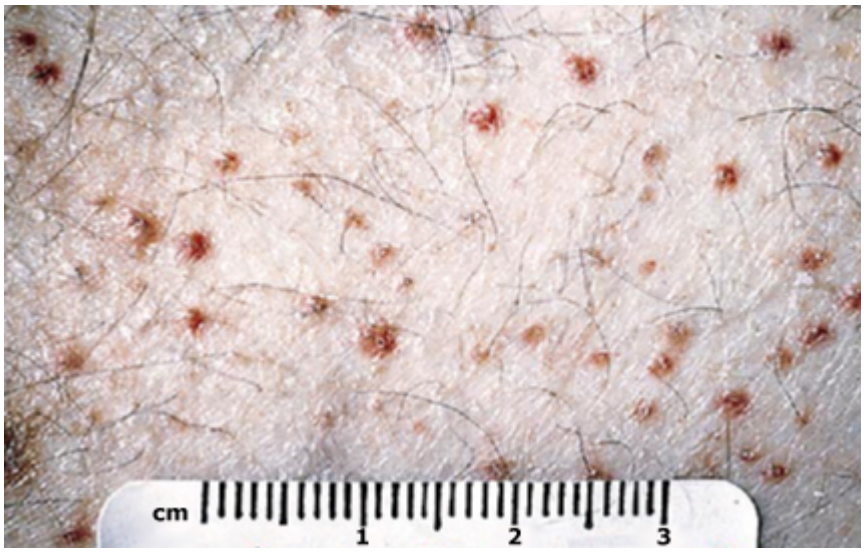
Scurvy



Perifollicular, purpuric macules are present in this patient with scurvy.

Graphic 51219 Version 2.0

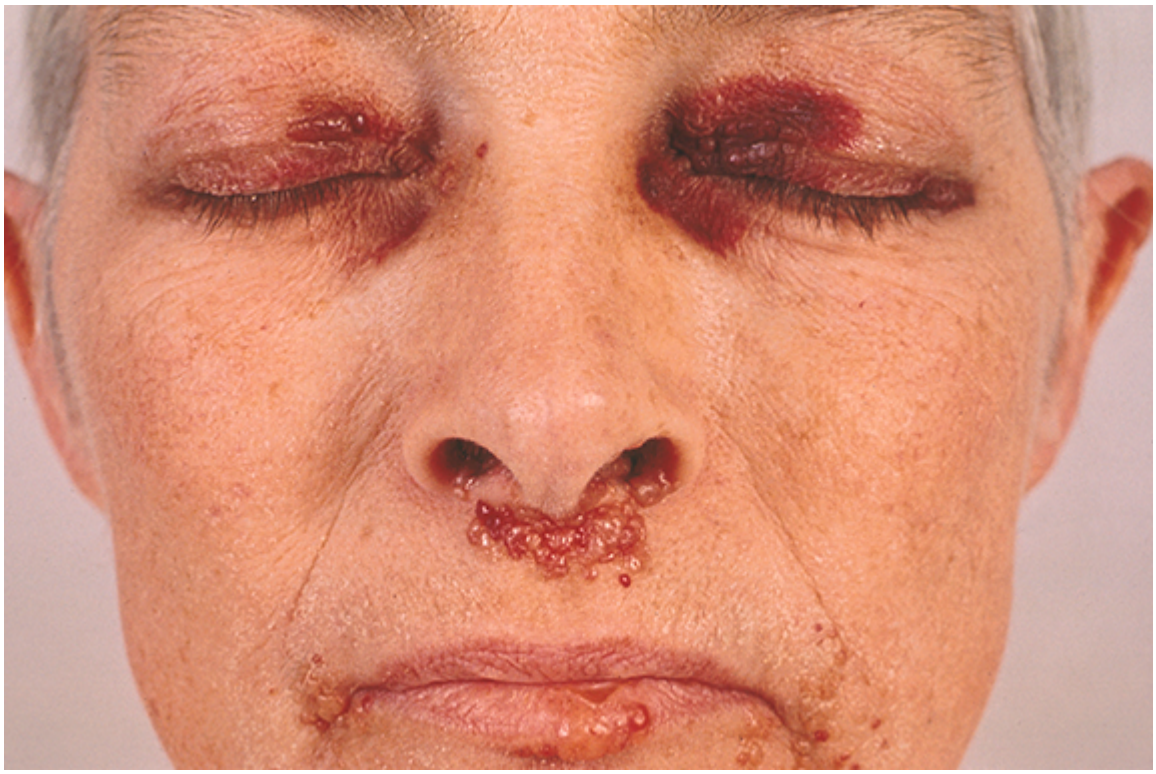
Perifollicular abnormalities in scurvy



In this example, the perifollicular hyperkeratotic papules are quite prominent, with surrounding hemorrhage. These lesions have been misinterpreted as "palpable purpura," leading to the mistaken clinical diagnosis of vasculitis.

Graphic 64172 Version 2.0

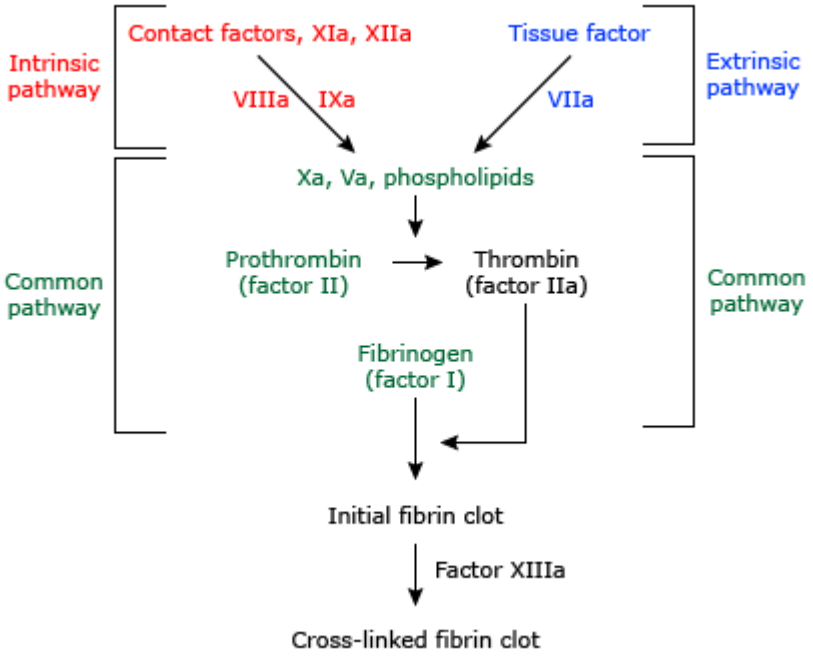
AL amyloidosis affecting facial skin and eyelids



In this patient with AL amyloidosis, amyloid deposits are seen below the nose, around the lips, and on the eyelids. These lesions are waxy and raised, and they show characteristic hemorrhage. This patient also had severe amyloid arthritis and eventually developed a malignant plasma cell dyscrasia.

Graphic 51684 Version 27.0

Intrinsic, extrinsic, and common coagulation pathways



Schematic representation of the intrinsic (red), extrinsic (blue), and common (green) coagulation pathways. Contact factors include prekallikrein and HMWK. In the clinical laboratory, the intrinsic (and common) pathway is assessed by the aPTT and the extrinsic (and common) pathway by the PT. The TT assesses the final step in the common pathway, the conversion of fibrinogen to fibrin, following the addition of exogenous thrombin. Fibrin is crosslinked through the action of factor XIII, making the final fibrin clot insoluble in 5 Molar urea or monochloroacetic acid. This latter function is not tested by the PT, aPTT, or TT.

HMWK: high molecular weight kininogen; aPTT: activated partial thromboplastin time; PT: prothrombin time; TT: thrombin time.

Graphic 79998 Version 6.0

Expected results of tests for hemostatic function in representative bleeding disorders

Disorder	Platelet count	PT	aPTT	TT	Fibrinogen level
Vasculopathies, connective tissue diseases, or collagen disorders affecting skin	Normal	Normal	Normal	Normal	Normal or increased*
Thrombocytopenia	Decreased	Normal	Normal	Normal	Normal
Qualitative platelet abnormalities	Normal or decreased¶	Normal	Normal	Normal	Normal
Hemophilia A or B (factor VIII or IX deficiency)	Normal	Normal	Prolonged	Normal	Normal
von Willebrand disease	NormalΔ	Normal	Normal or prolonged◇	Normal	Normal
Disseminated intravascular coagulation	Decreased	Prolonged	Prolonged	Prolonged	Decreased

Refer to UpToDate topics on the evaluation of unexplained bleeding or bruising for a discussion of these findings and our approach to the evaluation.

PT: prothrombin time; aPTT: activated partial thromboplastin time; TT: thrombin time.

* Fibrinogen may be elevated as an acute phase reactant in disorders of inflammation.

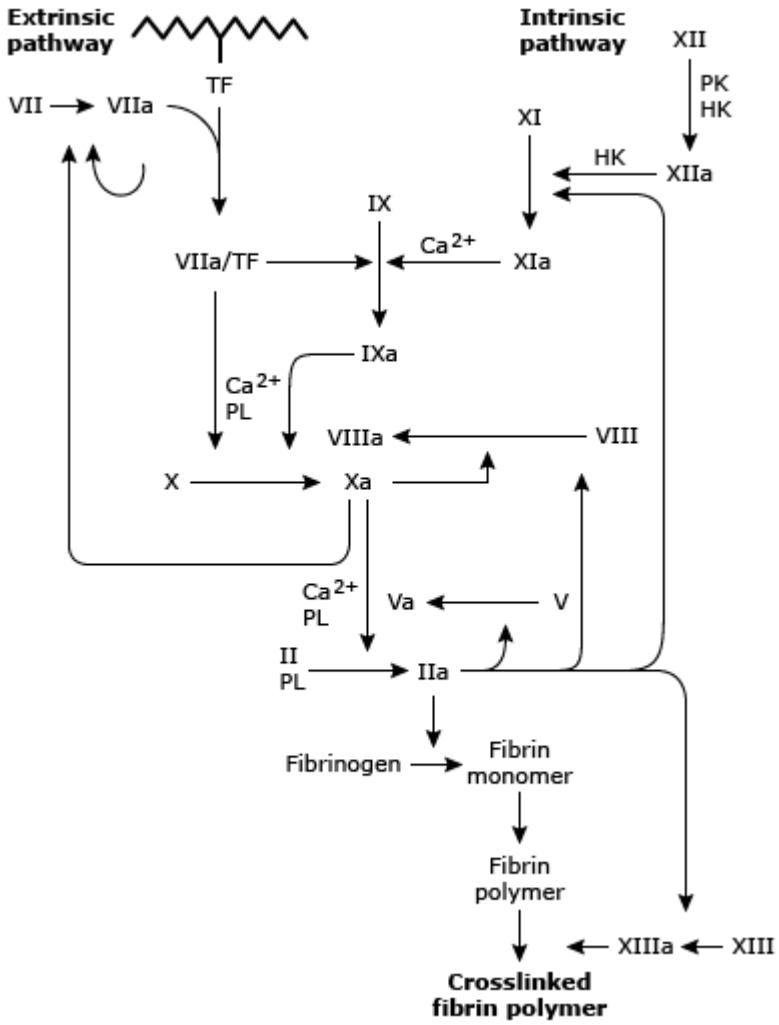
¶ The platelet count in myeloproliferative disorders is usually high (eg, essential thrombocythemia) and platelets may also be qualitatively abnormal, predisposing to hemorrhagic and thrombotic diatheses.

Δ The platelet count may be low in some patients with type 2B von Willebrand disease.

◇ The aPTT may be normal in those with factor VIII activity >40%.

Graphic 67121 Version 14.0

Coagulation cascade detailed/traditional view



Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting, interactions between pathways, and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors. Factor II is prothrombin, and factor IIa is thrombin.

PK: prekallikrein; HK: high molecular weight kininogen; PL: phospholipid.

Adapted from: Ferguson JD, Banning AP. Spontaneous intramural aortic haematoma: incidence, prognosis and complications. Eur Heart J 1998; Suppl 19:8.

Graphic 69920 Version 11.0

Causes of a prolonged prothrombin time (PT) and/or a prolonged activated partial thromboplastin time (aPTT)

Test result		Causes of test result pattern
PT	**aPTT**	
Prolonged	Normal	**Inherited**
		Factor VII deficiency
		Acquired
		Mild vitamin K deficiency
		Liver disease
		Warfarin*
		Acute DIC¶
Normal	Prolonged	**Inherited**
		Deficiency of factor VIII, IX, or XI
		Deficiency of factor XII, prekallikrein, or HMW kininogen (not associated with a bleeding diathesis)
		von Willebrand disease (variable)
		Acquired
		Heparin, dabigatran, argatroban, direct factor Xa inhibitors (variable)*
		Acquired inhibitor of factor VIII, IX, XI, or XII
		Acquired von Willebrand syndrome
		Lupus anticoagulant (more likely to be associated with thrombosis than bleeding)
Prolonged	Prolonged	**Inherited**
		Deficiency of prothrombin, fibrinogen, factor V, or factor X
		Combined factor deficiencies
		Acquired
		Liver disease
		Acute DIC¶
		Severe vitamin K deficiency
		Anticoagulants (warfarin, direct thrombin inhibitors, others)*
		Acquired inhibitor of prothrombin, fibrinogen, factor V, or factor X

		Amyloidosis-associated factor X deficiency
		Anticoagulant rodenticide poisoning

Refer to UpToDate topics on use of coagulation tests and on evaluation of patients with bleeding or specific inherited and acquired conditions for additional details.

PT: prothrombin time; aPTT: activated partial thromboplastin time; DIC: disseminated intravascular coagulation; HMW: high molecular weight.

* In principle, many anticoagulants affect common pathway factors and can prolong both the PT and the aPTT if present at high enough levels. As examples:

- Warfarin typically prolongs the PT alone, with some reagents, both the PT and aPTT can be prolonged.
- Heparin typically prolongs the aPTT alone (because PT reagents contain heparin-binding agents that block heparin effect), but at high levels heparin can prolong both tests.
- Direct thrombin inhibitors (argatroban, dabigatran) typically prolong both tests, but at low levels dabigatran may not prolong the PT.
- Direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) can prolong the PT and aPTT, although these effects are variable.

¶ In chronic DIC (also called compensated DIC) both the PT and aPTT may be normal.

Graphic 79969 Version 11.0

Assays used for diagnosing von Willebrand disease (VWD)

Assay name	What it measures	Method
VWF activity		
VWF activity: Platelet binding	Ability of VWF to bind to:	Quantitate binding of plasma VWF to:
VWF:RCo (ristocetin cofactor activity)	Fixed normal platelets in the presence of ristocetin	Platelets; assess agglutination using dilutions of plasma to quantitate VWF
VWF:GPIbR (binding to platelet glycoprotein Ib)	Recombinant GPIb in the presence of ristocetin	Recombinant GPIb using an ELISA plate or latex or magnetic beads
VWF:GPIbM (binding to a platelet glycoprotein Ib mutant)	Recombinant mutated "gain-of-function" GPIb (GPIbM) in the absence of ristocetin	Recombinant GPIbM using an ELISA plate or latex or magnetic beads
Binding to a monoclonal antibody to the GPIb site)	Binding of a specific monoclonal antibody to the VWF binding site for GPIb	Antibody that is specific for the GPIb binding site in VWF
VWF activity: Collagen binding (VWF:CB)	VWF binding to collagen	Binding of patient plasma VWF to collagen-coated plates in an ELISA assay (usually type I or type III collagen)
VWF antigen (VWF:Ag)	VWF protein concentration measured by immunologic assays (does not imply functional activity)	Immunologic assay using ELISA, RIA, or latex beads
VWF multimer analysis	Distribution of VWF multimers as visualized in gels	Electrophoresis in low concentration agarose gel and visualization using a monospecific antibody to VWF
Ristocetin-induced platelet aggregation (RIPA)	Ability of patient's VWF to bind to platelets in the presence of suboptimal concentrations of ristocetin	Platelet aggregation using patient's platelet-rich plasma and low concentrations of ristocetin (less than required in VWF:RCo)
VWF activity:VWF antigen ratio (VWF:Act/VWF:Ag)	Comparison of functional activity of VWF with its protein concentration	Ratio of measured levels of VWF:Act to VWF:Ag (a ratio of <0.7 suggests type 2A, 2B, or 2M)
Factor VIII activity:VWF:Ag ratio (FVIII/VWF:Ag)	Comparison of factor VIII activity to VWF antigen	Ratio of measured levels of FVIII to VWF:Ag (a low level suggests

		type 2N)

von Willebrand factor is a multimeric glycoprotein that promotes platelet adhesion to collagen and platelet aggregation. VWF also acts as a carrier protein for coagulation factor VIII in plasma. Ristocetin is an antibiotic (no longer in clinical use) that induces VWF binding to platelet glycoprotein Ib (GPIb), which in turn causes platelets to aggregate. Refer to UpToDate for information on how these tests are used and interpreted in the patient evaluation.

VWD: von Willebrand disease; VWF: von Willebrand factor; ELISA: enzyme-linked immunosorbent assay; RIA: radioimmunoassay.

Adapted from: The National Heart, Lung, and Blood Institute. The Diagnosis, Evaluation, and Management of Von Willebrand Disease. Bethesda, MD: National Institutes of Health Publication 08-5832, December 2007.

Graphic 73391 Version 5.0

Laboratory diagnosis of abnormal fibrinolysis

Test	Primary hyperfibrinolysis	DIC	TTP
CBC and blood smear	Normal	Thrombocytopenia, MAHA	Thrombocytopenia, MAHA
PT and aPTT	Normal or prolonged	Prolonged	Normal
Fibrinogen	Decreased	Decreased	Normal
D-dimer or FDP*	Increased	Increased	Normal
Antithrombin	Normal	Decreased	Normal
Euglobulin clot lysis time	Shortened	Shortened	Normal
ADAMTS13 activity	Normal	Normal or mildly reduced¶	Severely deficient (usually <10%)Δ

Refer to UpToDate topics on disorders of fibrinolysis, DIC, and TTP for additional details.

DIC: disseminated intravascular coagulation; TTP: thrombotic thrombocytopenic purpura; CBC: complete blood count; MAHA: microangiopathic hemolytic anemia, characterized by anemia, laboratory markers of hemolysis, and schistocytes on the blood smear; PT: prothrombin time; aPTT: activated partial thromboplastin time; FDP: fibrinogen degradation products; ADAMTS13: von Willebrand factor-cleaving protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).

* FDP is not routinely measured.

¶ ADAMTS13 activity may be mildly reduced (activity, 20 to 60%) in the setting of acute illness.

Δ Refer to UpToDate for a discussion of the role of ADAMTS13 activity testing in the diagnosis of TTP.

Graphic 78455 Version 9.0