Approach to the child with bleeding symptoms

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INTRODUCTION

This topic reviews the approach to evaluating an infant, child, or adolescent presenting with either overt bruising or bleeding or with a history of increased bleeding.

Thrombocytopenia and specific bleeding disorders, including hemophilia and von Willebrand disease (VWD), are discussed in greater detail separately:

- Thrombocytopenia (see "Approach to the child with unexplained thrombocytopenia" and "Causes of thrombocytopenia in children" and "Neonatal thrombocytopenia: Etiology")
- Hemophilia A and B (see "Clinical manifestations and diagnosis of hemophilia" and "Hemophilia A and B: Routine management including prophylaxis" and "Treatment of bleeding and perioperative management in hemophilia A and B")
- VWD (see "Clinical presentation and diagnosis of von Willebrand disease" and "von Willebrand disease (VWD): Treatment of major bleeding and major surgery")

Specific sources of bleeding are also discussed in separate topics:

- Gastrointestinal bleeding (see "Approach to upper gastrointestinal bleeding in children" and "Lower gastrointestinal bleeding in children: Causes and diagnostic approach")
- Epistaxis (see "Evaluation of epistaxis in children" and "Causes of epistaxis in children" and "Management of epistaxis in children")
- Vaginal and/or abnormal uterine bleeding (see "Evaluation of vulvovaginal bleeding in children and adolescents" and "Abnormal uterine bleeding in adolescents: Evaluation

and approach to diagnosis" and "Abnormal uterine bleeding in adolescents: Management")

- Bruising that raises concerns for child abuse (see "Physical child abuse: Recognition" and "Physical child abuse: Diagnostic evaluation and management")

HISTORY

Clinical evaluation of a patient with bleeding symptoms begins with taking a careful history, including the child's age, sex, clinical presentation, personal and family medical history, and medications. Careful attention should be paid to the child's bleeding history, including number and severity of bleeding episodes and characterizing the type of bleeding (table 1 and table 2).

Bleeding questionnaires — Validated bleeding assessment tools (BATs) such as the Pediatric Bleeding Questionnaire (PBQ) and the International Society on Thrombosis and Haemostasis (ISTH) BAT allow for more objective quantification of bleeding symptoms in pediatric patients [1-3]. Both tools include a nearly identical panel of questions (table 2). They can be used as screening tools to identify patients who are more likely to have an underlying bleeding disorder (ie, those for whom laboratory evaluation may be appropriate). For pediatric patients, a score ≥3 (using either tool) is considered a positive screen. BATs have high negative predictive value in children undergoing investigation for von Willebrand disease (VWD; types 1 to 3) [4]. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Personal bleeding history and bleeding assessment tool (BAT)'.)

A self-administered version of the PBQ is available that uses lay language at a fourth grade reading level rather than medical terminology, making the tool more accessible in clinical practice [5-8]. It has been validated in patients as young as 8 to 12 years of age.

BATs do not perform as well in the preoperative setting (ie, to identify children at increased risk of surgical bleeding) [9-11]. Nevertheless, if the preoperative history raises concerns for a possible bleeding disorder, it is reasonable to use a BAT to objectively quantify the bleeding symptoms and help determine whether preoperative laboratory testing is warranted. Clinicians should be aware however, that a normal BAT score does not necessarily predict low risk of major bleeding during surgery, nor does an abnormal BAT score accurately predict increased risk of major surgical bleeding [10]. This issue is discussed in greater detail separately. (See "Preoperative assessment of bleeding risk", section on 'Determine bleeding risk'.)

Type of bleeding — Bleeding symptoms caused by platelet disorders are quite distinct from those associated with hemophilia or other disorders of coagulation proteins (table 1)

- Bleeding into the skin and mucous membranes is characteristic of disorders of platelets and their interaction with blood vessels and may be manifested as petechiae, ecchymoses, and/or mucosal bleeding (picture 1A-C). (See "Causes of thrombocytopenia in children" and "Congenital and acquired disorders of platelet function".)

- Bleeding into soft tissue, muscle, and joints suggests the presence of hemophilia or other disorders of coagulation proteins. (See "Clinical manifestations and diagnosis of hemophilia".)

Pathologic versus normal bleeding — One important goal of the medical history is to distinguish between a pathologic pattern of bleeding versus normal bleeding symptoms that commonly occur in healthy children.

- **Pathologic bleeding** – The possibility of an underlying bleeding disorder should be considered in children who experience bleeding symptoms that are:

  - Unusually frequent
  - Long-lasting, or
  - Severe

  In addition, an inherited bleeding disorder should be strongly considered when the onset of bleeding manifestations occurs in infancy or early childhood, particularly if associated with a positive family history.

  The following are examples of typical presentations suggestive of an underlying bleeding disorder:

  - A newborn with bleeding from the umbilical stump should be evaluated for coagulation protein defects, including factor XIII deficiency [12]. Intracranial hemorrhage in an infant without other risk factors should also prompt consideration of this diagnosis. (See "Rare inherited coagulation disorders".)

  - A male infant who is starting to walk and presents with a painful swollen joint after a fall is presumed to have hemophilia until proven otherwise. Similarly, an unusually prominent forehead hematoma ("goose-egg") in a male infant or young male is a common presentation of hemophilia [13], as is excess bleeding after circumcision. (See "Clinical manifestations and diagnosis of hemophilia", section on 'Initial presentation'.)

  - An otherwise healthy child who presents with petechiae and/or mucocutaneous purpura in the wake of a viral infection most likely has postinfectious immune thrombocytopenia [14-17]. (See "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis", section on 'Clinical features'.)

- An adolescent female who presents with excessive menstrual bleeding, recurrent nosebleeds, and pallor may have VWD, the most common inherited bleeding disorder [18]. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Clinical features'.)

Clinicians should be alert to the possibility that bruising or bleeding judged to be abnormal (eg, due to frequency, duration, or severity of episodes or lack of explanation for symptoms or physical findings) may be caused by a bleeding disorder or by nonaccidental injury (ie, child abuse). Furthermore, child abuse and bleeding disorders are not mutually exclusive. Therefore, the history should include complete details as to the type of bleeding, location, degree of symptoms, nature of provoking injuries, and whether such injuries are consistent with the child's development and level of activity [19]. (See "Physical child abuse: Recognition".)

- **Bleeding in healthy children** – Bleeding symptoms do occur in healthy children and may not necessarily suggest a generalized bleeding disorder. For example:

  - Epistaxis may be caused by rhinitis, trauma, superficial vessels, or dry air. However, evaluation for a bleeding disorder may be warranted for children with frequent recurrent nosebleeds, severe nosebleeds that are difficult to control, bilateral nosebleeds, and prior history of bleeding symptoms and/or positive family history [20]. (See "Evaluation of epistaxis in children" and "Causes of epistaxis in children".)

  - Abnormal postprocedural bleeding (eg, following tonsillectomy, circumcision, tooth extraction) may occur simply due to surgical trauma; however, it may also suggest the possibility of an underlying bleeding disorder, particularly if the child has had a prior history of bleeding symptoms and/or positive family history. (See "Tonsillectomy (with or without adenoidectomy) in children: Postoperative care and complications", section on 'Hemorrhage'.)

  - Bruising, particularly of the lower extremities, is common in active toddlers and young children. However, in children with abnormal bruising patterns (eg, bruises in a young, premobile infant; bruises that are unusually large; bruises in unusual locations such as the ear, neck, torso, or buttocks), the possibility of a bleeding disorder or nonaccidental trauma (child abuse) should be considered. (See "Physical child abuse: Recognition", section on 'Inflicted bruises'.)

    In a prospective study that followed 433 young children (58 with severe bleeding disorders, 47 with mild bleeding disorders, and 328 without bleeding disorders) over a period of 12 weeks, children with bleeding disorders had more and larger bruises compared with those without bleeding disorders, especially at premobile stages of development (ie, nonrolling/rolling over/sitting) [21]. Bruising was uncommon among premobile infants without bleeding disorders or with only mild bleeding disorders

(noted at 7 percent of assessments in both groups). By contrast, premobile infants with severe bleeding disorders were noted to have bruises at 52 percent of assessments. Among early mobile (crawling/cruising) and ambulatory children, bruising was common in all groups, noted in 50 to 80 percent of those without bleeding disorders and >90 percent of children with severe bleeding disorders.

- Abnormal uterine bleeding is commonly reported by adolescents and can be due to a variety of causes including immaturity of the hypothalamic-pituitary-ovarian axis, other causes of ovulatory dysfunction (eg, polycystic ovary syndrome, thyroid disease), pregnancy-related problems, medications, and infections. Features of abnormal uterine bleeding that are suggestive of an underlying bleeding disorder include heavy menses starting with menarche, presence of iron deficiency anemia, family history of bleeding, other symptoms of bleeding, or failure to respond to first-line treatment of heavy menses [22]. (See "Abnormal uterine bleeding in adolescents: Evaluation and approach to diagnosis".)

Family history — The family history is helpful in supporting a possible diagnosis of an inherited disorder of coagulation. The presence of bleeding manifestations only in male siblings and maternal uncles is suggestive of an X-linked recessive disorder, such as hemophilia A or B. However, a negative family history does not exclude an inherited coagulation disorder, as up to one-third of patients with hemophilia have a negative family history [23]. (See "Genetics of hemophilia A and B", section on 'Transmission'.)

In contrast, in autosomal dominant disorders such as hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease), an accurate pedigree will show affected individuals of both sexes for several generations [24]. Most instances of VWD are also transmitted in an autosomal dominant fashion. In autosomal recessive disorders, such as severe forms of the rarer coagulation factor deficiencies (eg, factor VII or factor XI deficiency), the family history may be negative; consanguinity increases the probability of such disorders [25]. (See "Clinical manifestations and diagnosis of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)" and "Rare inherited coagulation disorders".)

Medications — It is important to review any medications that the child is taking, particularly nonsteroidal antiinflammatory drugs (NSAIDs; eg, ibuprofen, naproxen), aspirin, or over-the-counter medications that contain NSAIDs or aspirin. Such drugs impair platelet function and may exacerbate an underlying coagulation disorder. It is important to ask about recent use (ie, within one to two weeks) of these agents even if they are not the suspected cause of the bruising or bleeding in the child because they may cause abnormalities in platelet function tests, which may lead to further unnecessary and expensive studies.

Less commonly, easy bruising may be attributable to selective serotonin reuptake inhibitors, stimulant medications used to treat attention deficit disorder (eg, as methylphenidate), and

oral or topical corticosteroids. All of these agents can lead to easy bruising. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Bleeding' and "Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents", section on 'Stimulant adverse effects' and "Major side effects of systemic glucocorticoids", section on 'Hematologic effects'.)

In addition, the clinician should inquire about use of herbal medicines that may contribute to abnormal bleeding (eg, ginger, feverfew, ginkgo biloba, large amounts of garlic) [26,27].

Accidental or intentional ingestion of warfarin or warfarin-containing rodenticides can also cause bleeding symptoms in children. (See "Overview of rodenticide poisoning", section on 'Anticoagulants (superwarfarins and warfarins)'.)

INITIAL LABORATORY EVALUATION

Approach to testing — The evaluation for bleeding disorders in children begins with general screening tests that assess hemostasis (table 3 and algorithm 1 and algorithm 2). Based upon the results of these tests and clinical suspicion, additional and more specific testing is performed to narrow the possibilities or make a definitive diagnosis. (See 'Diagnostic approach' below and 'Additional selective testing' below.)

For children with clinically significant bleeding symptoms (eg, a score ≥3 using a bleeding assessment tool [BAT] (table 2)) in whom the cause is not readily apparent based upon the history and physical examination, we suggest the following initial tests, which are discussed in the sections below:

- Complete blood count, including platelet count
- Examination of the peripheral blood smear
- Prothrombin time (PT)/international normalized ratio
- Activated partial thromboplastin time (aPTT)

At the author's center, we also commonly obtain the following tests as part of the initial evaluation; however, other centers may not include these in the initial testing:

- Fibrinogen activity level (see 'Fibrinogen' below)
- Testing for von Willebrand disease (VWD) (see 'von Willebrand disease testing' below)

In most cases, we initially obtain all of these screening tests; however, in certain circumstances, it may be appropriate to perform only limited testing. For example, in an otherwise well child who presents with mucocutaneous bleeding, a complete blood count with platelet count and examination of the peripheral blood smear are the most informative initial tests (algorithm 2).

Normal values of coagulation tests may vary with age and among different laboratories (table 4). In particular, normal PTs and aPTTs should be based upon an individual clinical laboratory's reference ranges [28]; published ranges should not be used to conclusively ascertain whether an individual result is normal or abnormal.

Proper collection of the blood sample is essential for interpreting the results of coagulation tests. Blood for coagulation tests should not be drawn from an existing heparinized indwelling line. A cleanly drawn venipuncture sample without air bubbles or tissue fluid contamination is the most appropriate sample for coagulation tests. Coagulation tests are performed on blood anticoagulated with a solution of sodium citrate in a ratio of nine parts of blood to one part of citrate. When the hematocrit is high (eg, newborns and children with cyanotic cardiac disease), the amount of citrate must be adjusted (reduced) to provide the proper ratio [29]. (See "Clinical use of coagulation tests", section on 'Sample collection and handling'.)

Platelet count and the peripheral smear — The platelet count is typically performed with an automated cell counter. (See "Automated hematology instrumentation".)

Platelets may also be counted directly on the blood smear. Examination of the peripheral blood smear is essential in patients with low platelet counts in order to exclude the presence of pseudothrombocytopenia caused by platelet aggregation after using ethylenediaminetetraacetic acid (EDTA) as an in vitro anticoagulant (picture 2) [30]. Platelet aggregation causes falsely low platelet counts by the automated cell counter, but the platelet clumps are obvious on examination of the smear. Alternative anticoagulants (eg, trisodium citrate or heparin) may circumvent in vitro EDTA-associated platelet aggregation [31]. Platelet clumping on the smear of a patient with bleeding symptoms may also suggest type 2B VWD or pseudo (platelet type)-VWD (algorithm 2). (See "Approach to the child with unexplained thrombocytopenia", section on 'Verification of thrombocytopenia'.)

Examination of the peripheral smear is important as it may reveal findings that point to an underlying etiology (eg, peripheral blasts (picture 3 and picture 4), schistocytes (picture 5)). In addition, it permits assessment of platelet size and granularity, which helps to narrow the diagnostic possibilities in a patient with thrombocytopenia (table 5). (See "Causes of thrombocytopenia in children".)

Prothrombin time (PT) — The production of fibrin via the extrinsic pathway and the final common pathway requires tissue thromboplastin (tissue factor); factors VII, X, and V; prothrombin (factor II); and fibrinogen. The functioning of these pathways is measured by the PT (figure 1). This test bypasses the intrinsic pathway and uses "complete" thromboplastins (ie, tissue factor) capable of activating the extrinsic pathway.

The PT is sensitive to alterations in the vitamin K-dependent coagulation factors, especially factors II, VII, and X. (See "Clinical use of coagulation tests", section on 'Prothrombin time (PT)

and INR'.)

Activated partial thromboplastin time (aPTT) — The aPTT measures the intrinsic and common pathways of coagulation (figure 1). It is called "partial" because clotting is initiated in vitro with agents that are only partial thromboplastins (ie, they are incapable of activating the extrinsic pathway). (See "Clinical use of coagulation tests", section on 'Activated partial thromboplastin time (aPTT)'.)

The aPTT is sensitive to deficiencies of factors XII, XI, IX, and VIII and to inhibitors such as heparin (figure 1). It is less sensitive than the PT to deficiencies within the common pathway (eg, factors X and V, prothrombin, and fibrinogen) and is unaffected by alterations in factors VII and XIII.

Fibrinogen — We routinely obtain fibrinogen levels in addition to the PT and aPTT because the three tests together are more sensitive than the PT/aPTT alone for detecting fibrinogen disorders. Mild hypofibrinogenemia (fibrinogen levels between 100 to 150 mg/dL) may not cause prolongation in the PT/aPTT. However, in most cases of severe fibrinogen disorders, the PT and aPTT are both prolonged. Thus, some centers do not routinely obtain fibrinogen levels if the PT and aPTT are normal. (See "Disorders of fibrinogen".)

The functional fibrinogen concentration is typically measured using a sensitized modification of the thrombin time (TT), whereas fibrinogen protein levels are measured using immunologic assays. Immunologic and functional assays of fibrinogen may be discordant in patients with an inherited dysfibrinogenemia (generally with a significantly higher protein level than activity level). Fibrinogen levels reported by most clinical coagulation labs represent functional fibrinogen concentrations.

von Willebrand disease testing — Initial testing for VWD involves three screening tests that assess the quantity and function of von Willebrand factor (VWF). These tests can usually establish whether or not the patient has VWD (algorithm 3):

- VWF antigen – Quantitative measurement of VWF protein level.
- VWF activity – Functional assays of VWF binding to platelets or collagen. Though the VWF:RCo assay has been the "gold standard" for the platelet binding activity of VWF, newer activity tests such as the VWF:GPIbM are generally more reproducible and are becoming widely used.
- Factor VIII activity.

The rationale for these tests and the details of their interpretation are summarized in the table (table 6) and discussed in greater detail separately. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Laboratory testing'.)

DIAGNOSTIC APPROACH

Results of the initial laboratory testing allow the clinician to narrow the diagnostic possibilities in the child with a bleeding disorder (table 3 and algorithm 1 and algorithm 2).

Abnormal blood count

Pancytopenia — Two important diagnostic considerations in a child with mucocutaneous bleeding and pancytopenia include:

- **Leukemia** – Other concerning findings that may point to this diagnosis include organomegaly, lymphadenopathy, and/or bone pain. Examination of the peripheral blood smear may reveal the presence of leukemic blasts (picture 3 and picture 4), an observation that should be confirmed with a bone marrow examination. (See "Evaluation of the peripheral blood smear", section on 'Worrisome findings'.)

- **Aplastic anemia** – Children with aplastic anemia present with varying combinations of symptomatic anemia, bleeding, and infection, depending upon the severity of the pancytopenia. Single or multiple skeletal anomalies may be present in children with the congenital forms of aplastic anemia. (See "Aplastic anemia: Pathogenesis, clinical manifestations, and diagnosis".)

Thrombocytopenia — Causes of thrombocytopenia in pediatric patients are summarized in the table (table 7). The approach to evaluating children with thrombocytopenia is discussed in detail separately. (See "Approach to the child with unexplained thrombocytopenia" and "Neonatal thrombocytopenia: Etiology" and "Causes of thrombocytopenia in children".)

Abnormal coagulation tests — The results of coagulation studies (prothrombin time [PT], international normalized ratio, activated partial thromboplastin time [aPTT]) may help narrow the diagnostic possibilities (algorithm 1 and table 3).

aPTT prolonged/PT normal — An isolated prolonged aPTT can be seen in the following conditions (algorithm 1):

- **Hemophilia A or B** – Hemophilia A (factor VIII deficiency) is the most common inherited disorder yielding a significantly prolonged aPTT. The reported incidence is 1 in 5000 males [23]. Hemophilia B (factor IX deficiency) occurs less often: 1 in 20,000 males. Both disorders have an X-linked recessive transmission and demonstrate a range of presentations depending on severity of the phenotype, ranging from prolonged bleeding after surgery or other trauma to spontaneous soft tissue and joint hemorrhages. Mucocutaneous bleeding (eg, excessive bruising, prolonged oozing from oral wounds) can also occur. Hemophilia carriers may have symptoms similar to affected

males with mild hemophilia and are at increased risk for reproductive bleeding. (See "Clinical manifestations and diagnosis of hemophilia".)

- **Factor XI deficiency** – Factor XI deficiency is seen more commonly in Ashkenazi Jews and presents with a variable history of bleeding, often mucocutaneous in nature [32]. (See "Factor XI (eleven) deficiency".)

- **Lupus anticoagulants** – Lupus anticoagulants are acquired inhibitors (autoantibodies) directed against phospholipid-protein complexes that produce a prolonged aPTT. They are commonly seen in children, frequently associated with recent infections (particularly viral infections), and usually transient. Lupus anticoagulants are **not** associated with bleeding symptoms but rather an increased risk of thrombosis. However, children with transient viral-triggered lupus anticoagulants are generally not at risk for thrombotic complications. (See 'Antiphospholipid antibodies' below.)

- **Deficiencies of factor XII, high molecular weight kininogen, and prekallikrein** – These disorders are typically asymptomatic and not associated with clinical bleeding. Patients with these deficiencies are often discovered when an asymptomatic child demonstrates a significantly prolonged aPTT on routine preoperative screening. Although such a deficiency may hold little clinical consequence, it can be important to identify since it provides an explanation for an otherwise puzzling prolonged aPTT.

- **Heparin contamination** – Blood drawn from heparin-containing intravascular lines is another cause of isolated aPTT prolongation. This possibility can generally be excluded by obtaining a fresh blood sample from a venipuncture stick. Heparin contamination can also be confirmed by measuring the thrombin time (TT) and reptilase time (RT; the former will be prolonged, while the latter will be normal); however, this is not commonly done in clinical practice. (See 'Thrombin time and reptilase time' below.)

PT prolonged/aPTT normal — An isolated prolonged PT is characteristic of (figure 1 and algorithm 1):

- **Inherited factor VII deficiency**, which displays phenotypic and molecular heterogeneity (see "Rare inherited coagulation disorders")

- **Acquired factor VII inhibitors**, which are very rare occurrences during childhood [33] (see "Acquired hemophilia A (and other acquired coagulation factor inhibitors)")

PT and aPTT both prolonged

Well child — Prolongation of both PT and aPTT in a child with bleeding symptoms but who is otherwise well indicates an inherited disorder within the common pathway or an acquired disorder involving multiple pathways (figure 1 and algorithm 1).

Inherited deficiencies in this category include deficiency of factors X, V, and II; (prothrombin); or fibrinogen. These deficiencies are rare. (See "Rare inherited coagulation disorders".)

Inherited disorders of fibrinogen (hypo- or afibrinogenemia) are autosomal recessive disorders, and bleeding associated with these disorders is treatable with cryoprecipitate or fibrinogen concentrates. Dysfibrinogenemia, an autosomal dominant disorder, may be associated with either bleeding or excessive clotting. (See "Disorders of fibrinogen".)

Sick child — In a sick child with prolongation of both PT and aPTT, disorders to consider are disseminated intravascular coagulation (DIC; eg, due to sepsis or other systemic illness), severe liver disease, or severe vitamin K deficiency (algorithm 1). The factor V level can be used to distinguish between vitamin K deficiency and liver disease or DIC (it is normal in the former and decreased in the latter two conditions). (See "Disseminated intravascular coagulation in infants and children".)

Other rare causes of prolonged PT and aPTT in an ill-appearing child include major vessel thrombosis, as well as consumption coagulopathy in certain vascular lesions.

Accidental or intentional ingestion of warfarin or warfarin-containing rodenticides sufficient to cause bleeding usually results in a prolongation of the PT and aPTT because the vitamin K-dependent factors that are inhibited by warfarin are present in the extrinsic (factor VII), intrinsic (factor IX), and common pathways (factors II and X) (figure 1) [34]. Hemorrhage under such circumstances may be life-threatening and requires immediate treatment with combinations of intravenous vitamin K, fresh frozen plasma, and/or prothrombin complex concentrates (which contain all of the vitamin K-dependent coagulation factors). (See "Management of warfarin-associated bleeding or supratherapeutic INR", section on 'Treatment of bleeding' and "Overview of rodenticide poisoning", section on 'Anticoagulants (superwarfarins and warfarins)'.)

There have been rare case reports of acquired inhibitors to prothrombin, factor V, and factor X. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)".)

Abnormal von Willebrand disease testing — von Willebrand disease (VWD) is the most common inherited bleeding disorder. There are three major types of VWD. Types 1 and 3 are quantitative deficiencies of von Willebrand factor (VWF), whereas type 2 is a qualitative disorder. (See "Clinical presentation and diagnosis of von Willebrand disease".)

Laboratory tests for VWD include VWF antigen, VWF activity, and factor VIII activity (algorithm 3). The platelet count may be low in some patients with type 2B VWD. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Laboratory testing'.)

The laboratory diagnosis of VWD in pediatric patients is complicated by VWF assay variability and stress-induced elevations in VWF levels. Patients with a high suspicion of VWD who have borderline initial laboratory results should undergo repeat testing. In a retrospective cohort of 811 patients undergoing evaluation for a suspected bleeding disorder, 22 percent were ultimately diagnosed with VWD, of whom approximately 30 percent required repeat testing to make the diagnosis [35]. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Repeat testing in individuals with borderline or discordant clinical and laboratory findings'.)

Normal initial testing — In children with bleeding symptoms and a normal initial laboratory screen, possible diagnoses include some cases of hemophilia, factor XIII deficiency, platelet function disorders, vascular anomalies, connective tissue disorders, and fibrinolytic disorders. In addition, some patients with VWD may have equivocal or borderline results on initial testing, as discussed above. (See 'Abnormal von Willebrand disease testing' above.)

Some cases of hemophilia — Mild cases of hemophilia B, in which factor IX activity is in the 6 to 40 percent range, may not reliably result in prolongation of the aPTT on initial hemostatic screening, due to relative insensitivity of aPTT reagents to mild factor IX deficiency. In addition, there exist uncommon forms of hemophilia A in which factor VIII deficiency may be undetectable on the typical, one-stage, aPTT-based assay used in the majority of laboratories worldwide [36]. In such cases, a mild "discrepant" form of hemophilia A may only be recognized with use of special two-stage or chromogenic assays of factor VIII activity [37]. When there is a high clinical suspicion for an underlying bleeding disorder but the initial coagulation tests are normal, these diagnoses can be ruled out by specific testing of factor IX activity and a two-stage or chromogenic assay of factor VIII activity, respectively. (See 'Specific factor deficiencies and inhibitors' below.)

Factor XIII deficiency and other fibrinolytic disorders — Activated factor XIII is responsible for clot stabilization and crosslinking of fibrin polymer (figure 1). Factor XIII deficiency is not detected by prolongation of either PT or aPTT since neither assay measures the mechanical strength or stability of the fibrin clot.

Inherited factor XIII deficiency is an autosomal recessive disorder characterized by reduced clot stability and abnormal bleeding. One of the characteristic abnormalities of factor XIII deficiency is delayed separation of the umbilical cord and delayed bleeding from the umbilical stump. In the neonatal period, intracranial hemorrhage with little or no trauma and poor wound healing also are associated with the deficiency. Evaluation and management of factor XIII deficiency are discussed in detail separately. (See "Rare inherited coagulation disorders", section on 'Factor XIII deficiency (F13D)'.)

If factor XIII deficiency is suspected, the quantitative assay should be performed [12]. (See 'Clot solubility in urea and factor XIII activity testing' below.)

Deficiencies of alpha-2-antiplasmin and plasminogen activator inhibitor have also been associated with an increased bleeding tendency. (See "Thrombotic and hemorrhagic disorders due to abnormal fibrinolysis", section on 'Alpha-2-antiplasmin deficiency' and "Thrombotic and hemorrhagic disorders due to abnormal fibrinolysis", section on 'PAI-1 deficiency' and "Thrombotic and hemorrhagic disorders due to abnormal fibrinolysis", section on 'Alpha-2-antiplasmin'.)

Platelet function disorders — Studies to confirm the presence of qualitative disorders of platelet function include evaluation of platelet morphology on the peripheral blood smear, tests of platelet aggregation, and other tests of platelet function [38,39]. (See "Platelet function testing".)

Acquired causes of abnormal platelet function are much more common than inherited causes and include use of certain medications (eg, aspirin, nonsteroidal antiinflammatory drugs [NSAIDS]), uremia, and the myeloproliferative and myelodysplastic syndromes. As noted above, it is critical to ascertain a history of ingestion of NSAIDs or other platelet inhibitors in any patient with a bleeding disorder. In addition, if platelet function tests are to be performed (eg, platelet function analyzer [PFA]-100, platelet aggregation studies), the subject must refrain from taking these drugs prior to testing. (See "Platelet function testing", section on 'Caveats with testing'.)

Classic inherited disorders of platelet function are relatively rare and include (table 8) (see "Congenital and acquired disorders of platelet function"):

- Glanzmann thrombasthenia – Characterized by a defect in the platelet glycoprotein IIb/IIIa complex that normally upon platelet activation functions as the fibrinogen receptor, mediating platelet aggregation by enabling crosslinking between platelets and fibrinogen. Affected children present with significant mucocutaneous bleeding and a normal platelet count but highly abnormal platelet aggregation (absent or decreased aggregation to adenosine phosphate, epinephrine, collagen, and thrombin but normal aggregation to ristocetin) [40]. (See "Congenital and acquired disorders of platelet function".)

- Bernard-Soulier syndrome – Characterized by a defect in one of the components of the platelet glycoprotein Ib-IX-V complex, giant platelets, and bleeding that is greater than expected for the degree of thrombocytopenia [41]. (See "Congenital and acquired disorders of platelet function".)

- Storage pool diseases – Hermansky-Pudlak syndrome and Chediak-Higashi syndrome are characterized by deficiency of delta-granule platelet storage pools. Milder and less specific forms of platelet storage pool disorders, such as alpha-granule deficiency (gray platelet syndrome), are more common than these two rare syndromes [42]. These are readily identifiable by specific platelet morphologic changes on the peripheral blood

smear. (See "Hermansky-Pudlak syndrome" and "Chediak-Higashi syndrome" and "Congenital and acquired disorders of platelet function".)

- Other platelet function disorders – Platelet function testing in patients undergoing evaluation of mucocutaneous bleeding frequently identifies abnormalities that are less well characterized than for the classic disorders described above. These observations lead some experts to conclude that platelet function defects are actually quite common and should be tested for concurrent with or soon after testing for VWD [38,39].

Vascular purpuras — Screening tests usually are normal in patients with bleeding disorders related to vascular abnormalities.

These include:

- Structural vascular abnormalities (eg, hereditary hemorrhagic telangiectasia) (see "Clinical manifestations and diagnosis of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)")
- Hereditary disorders of connective tissue (eg, Ehlers-Danlos disease and osteogenesis imperfecta) (see "Clinical manifestations and diagnosis of Ehlers-Danlos syndromes" and "Osteogenesis imperfecta: An overview")
- Acquired connective tissue disorders (eg, scurvy, steroid-induced purpura) (see "Major side effects of systemic glucocorticoids", section on 'Dermatologic effects and appearance')
- Small vessel vasculitis (eosinophilic granulomatosis with polyangiitis [Churg-Strauss], immunoglobulin A vasculitis [Henoch-Schönlein purpura], microscopic polyangiitis, or granulomatosis with polyangiitis) (see "Vasculitis in children: Incidence and classification")
- Psychogenic purpura (see "Psychogenic purpura (Gardner-Diamond syndrome)")
- Purpura associated with the presence of paraproteins

Bleeding of unknown cause — A subset of patients with mild to moderate bleeding tendencies have no abnormalities in clinically available laboratory assays [43]. The term "bleeding of unknown cause" is often used as a diagnosis for such patients. Studies in which extensive specialized testing was performed for patients in this category have demonstrated impairments in thrombin-generating potential, clot formation, and clot lysis [43,44].

Physical abuse of the child should be considered in such cases. (See "Physical child abuse: Diagnostic evaluation and management".)

ADDITIONAL SELECTIVE TESTING

Based upon the results of the initial tests, additional testing may be performed to narrow the possibilities or make a definitive diagnosis. The approach to the diagnostic evaluation is reviewed above. (See 'Diagnostic approach' above.)

Specific factor deficiencies and inhibitors — An abnormally prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT) can be due to the absence or reduced concentration of a coagulation factor or the presence of an inhibitor to one of the coagulation factors:

- A factor deficiency should be correctable by the addition of normal plasma ("mixing study"). This normally is performed by repeating the abnormal PT or aPTT with a 1:1 mixture of patient and normal plasma. If the 1:1 mixture corrects the abnormal test, a deficiency of a coagulation factor is likely to be present. (See "Clinical use of coagulation tests", section on 'Evaluation of abnormal results'.)

- The presence of a factor inhibitor is suspected when the abnormal test does not correct, or only partially corrects, after immediate assay of a 1:1 mixture of patient and normal plasma. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)".)

Deficiencies of specific factors may be determined by assessing the PT or aPTT in mixtures of patient plasma with commercially available plasma deficient in known factors. Factor levels can be assessed functionally by comparing test results with standard curves generated by mixtures of serially diluted normal plasma and factor-deficient plasma. Immunologic assays also can be used to measure factor protein levels. Immunologic and functional assays should give equivalent results when a quantitative factor deficiency is present (generally referred to as "type 1 deficiency"). Reduction in a functional assay with a normal immunologic assay suggests the presence of a functionally abnormal factor ("type 2 deficiency").

Platelet function testing — In addition to the evaluation of platelet count and morphology by examination of the peripheral blood smear, different tests are available that evaluate platelet function (table 9). Testing is challenging because some tests are highly operator-dependent, many tests are poorly standardized and poorly reproducible, and no test assesses all aspects of platelet function. When platelet function testing is performed, it generally should be carried out in consultation with a hematologist. Platelet aggregation testing should be performed in specialized laboratories with expertise in their methods and interpretation.

The following sections briefly summarize a few of the available platelet function tests. These and other platelet function tests are discussed in greater detail separately (see "Platelet function testing"):

- **Platelet function analyzer (PFA-100)** – The PFA-100 is a simple, rapid test that can be performed at the point of care to measure global platelet function. Because of its simplicity, it is sometimes used as a screening tool for platelet function defects and von Willebrand disease (VWD) in children [45,46]. However, it is neither sensitive nor specific for any particular disorder and its optimal use in clinical practice remains uncertain. The PFA-100 is discussed in greater detail separately. (See "Platelet function testing", section on 'PFA-100'.)

- **Platelet aggregation** – Traditional platelet aggregation assays measure platelet activation and aggregation in vitro in response to various known platelet agonists (eg, adenosine diphosphate [ADP], arachidonic acid, collagen, epinephrine, thrombin, and ristocetin). Either whole blood or platelet-rich plasma is used depending on the technique. Since many common medications can affect platelet function, care must be taken to avoid their use in patients prior to testing. Expected aggregation results with specific platelet disorders are summarized in the table (table 8). (See "Platelet function testing", section on 'Platelet aggregometry'.)

- **Thromboelastography (TEG) and rotational thromboelastometry (ROTEM)** – TEG and ROTEM assess platelet-mediated thrombin formation. These tests are uncommonly used in pediatric patents. They are discussed separately. (See "Platelet function testing", section on 'Viscoelastic testing (TEG and ROTEM)'.)

- **Bleeding time** – The bleeding time is **not** performed routinely as a screening test in children (or adults), because it is poorly reproducible, invasive, insensitive, and time consuming. A normal bleeding time does not predict the safety of surgical procedures, nor does an abnormal bleeding time predict for excessive surgical bleeding. It is not recommended as a preoperative screening test. (See "Platelet function testing", section on 'Tests not commonly used'.)

Antiphospholipid antibodies — Antiphospholipid antibodies (aPL) are not typically associated with bleeding symptoms (to the contrary, they are associated with increased thrombotic risk). However, they can be associated with prolongation of the aPTT that is not correctable by the addition of normal plasma. Thus, testing for aPL can be helpful in patients with a prolonged aPTT that is not otherwise explained. The effect of aPL on the aPTT can be partially overcome by adding excess platelet phospholipid or by assessing the diluted Russell viper venom time [47]. (See "Clinical use of coagulation tests", section on 'dRVVT' and "Diagnosis of antiphospholipid syndrome", section on 'Antiphospholipid antibody testing'.)

Thrombin time and reptilase time — The thrombin time (TT) and reptilase time (RT) measure the final step of coagulation: the conversion of fibrinogen to fibrin (figure 1). The TT is performed by incubating citrated plasma in the presence of dilute thrombin, measuring

the time to clot formation. Reptilase, a thrombin-like enzyme obtained from snake venom, differs from thrombin in that it resists inhibition by heparin via antithrombin III.

These tests may be used in the following settings (see "Clinical use of coagulation tests", section on 'Thrombin time (TT)'):

- To evaluate patients with otherwise unexplained prolonged PT and aPTT. (See 'PT and aPTT both prolonged' above.)
- To detect heparin in a sample – Simultaneous measurement of TT and RT is useful in this setting since heparin prolongs the former but not the latter.
- To evaluate for an inherited fibrinogen disorder. (See "Disorders of fibrinogen", section on 'Heritable (genetic) disorders'.)

While the TT is also abnormal in disseminated intravascular coagulation (DIC), this test is not routinely used in the evaluation for DIC. (See "Disseminated intravascular coagulation in infants and children".)

Clot solubility in urea and factor XIII activity testing — The initial immature fibrin clot, held together by noncovalent bonds, is soluble in urea. Subsequent transglutamination within the clot by activated factor XIIIa covalently crosslinks overlapping fibrin strands, which then are resistant to solubilization by urea (figure 1). The ability of urea to solubilize the mature clot reflects a severe deficiency of factor XIII [12]. However, the clot solubility assay is sensitive only at very low levels (factor XIII 1 to 3 percent) and may miss the diagnosis in less severe cases. Therefore, if factor XIII deficiency is suspected, specific quantitative assays are recommended. (See "Rare inherited coagulation disorders", section on 'Diagnostic evaluation'.)

Tests for fibrinolysis — Fibrin and fibrinogen degradation products are protein fragments resulting from the action of plasmin on fibrin or fibrinogen, respectively (figure 2). Elevated levels are seen in states of fibrinolysis such as DIC. (See "Overview of hemostasis", section on 'Clot dissolution and fibrinolysis' and "Disseminated intravascular coagulation in infants and children".)

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".)

SUMMARY AND RECOMMENDATIONS

- **History** – The evaluation of a child with abnormal bleeding begins with a focused history, including the clinical presentation, medical history, family history, and medications. (See 'History' above.)
  - Bleeding questionnaires (eg, the International Society on Thrombosis and Haemostasis bleeding assessment tool [ISTH BAT]) can be useful for assessing the bleeding history (table 2). (See 'Bleeding questionnaires' above.)
  - Mucocutaneous bleeding into the skin and mucous membranes is characteristic of platelet disorders, while muscle, joint, and soft tissue bleeding is characteristic of coagulation disorders (table 1). (See 'Type of bleeding' above.)
  - The nature and extent of the injuries producing bleeding symptoms should be noted. Clinicians should be alert to the possibility of child abuse as a potential cause of abnormal bruising or bleeding. (See "Physical child abuse: Recognition".)
- **Initial laboratory evaluation** – We suggest the following initial laboratory evaluation for children with clinically significant bleeding symptoms (eg, a score of ≥3 on the ISTH BAT (table 2)) when the cause is not readily apparent based upon the history and physical examination (see 'Initial laboratory evaluation' above):
  - Complete blood count (including platelet count)
  - Examination of the peripheral blood smear
  - Prothrombin time (PT)
  - Activated partial thromboplastin time (aPTT)
  - Fibrinogen level
  - Screening tests for von Willebrand disease (VWD), including von Willebrand factor (VWF) antigen, VWF activity, and factor VIII activity (algorithm 3)

  Normal values for coagulation assays may vary with age and among different laboratories (table 4).
- **Diagnostic approach** – The results of the initial testing help differentiate among the different diagnostic possibilities, as summarized in the table and algorithms (table 3 and algorithm 1 and algorithm 2) and discussed in detail above. (See 'Diagnostic approach' above.)
- **Additional testing** – Based upon the results of the initial tests, additional testing may be performed to narrow the possibilities or make a definitive diagnosis. Depending on the clinical circumstances, such testing may include tests for specific factor deficiencies,

platelet function tests, testing for antiphospholipid antibodies (aPL), thrombin time (TT), factor XIII activity, and tests for fibrinolysis. (See 'Additional selective testing' above.)

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REFERENCES

1. Bowman M, Riddel J, Rand ML, et al. Evaluation of the diagnostic utility for von Willebrand disease of a pediatric bleeding questionnaire. J Thromb Haemost 2009; 7:1418.
2. Biss TT, Blanchette VS, Clark DS, et al. Quantitation of bleeding symptoms in children with von Willebrand disease: use of a standardized pediatric bleeding questionnaire. J Thromb Haemost 2010; 8:950.
3. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. J Thromb Haemost 2010; 8:2063.
4. Moenen FCJI, Nelemans PJ, Schols SEM, et al. The diagnostic accuracy of bleeding assessment tools for the identification of patients with mild bleeding disorders: A systematic review. Haemophilia 2018; 24:525.
5. Deforest M, Grabell J, Albert S, et al. Generation and optimization of the self-administered bleeding assessment tool and its validation as a screening test for von Willebrand disease. Haemophilia 2015; 21:e384.
6. Casey LJ, Tuttle A, Grabell J, et al. Generation and optimization of the self-administered pediatric bleeding questionnaire and its validation as a screening tool for von Willebrand disease. Pediatr Blood Cancer 2017; 64.
7. Bui J, Martyres D, James PD, et al. Validation of the school age self-administered pediatric bleeding questionnaire (Self-PBQ) in children aged 8-12 years. Pediatr Blood Cancer 2019; 66:e27709.
8. Kaur D, Kerlin BA, Stanek JR, O'Brien SH. Use of electronic self-administered bleeding assessment tool in diagnosis of paediatric bleeding disorders. Haemophilia 2021; 27:710.
9. Ambaglio C, Zane F, Russo MC, et al. Preoperative bleeding risk assessment with ISTH-BAT and laboratory tests in patients undergoing elective surgery: A prospective cohort study. Haemophilia 2021; 27:717.

10. Sim AY, Bowman M, Hopman W, et al. Predicting operative bleeding in elective pediatric surgeries using the Pediatric Bleeding Questionnaire (PBQ). J Pediatr Hematol Oncol 2014; 36:e246.
11. Guay J, Faraoni D, Bonhomme F, et al. Ability of hemostatic assessment to detect bleeding disorders and to predict abnormal surgical blood loss in children: a systematic review and meta-analysis. Paediatr Anaesth 2015; 25:1216.
12. Hsieh L, Nugent D. Factor XIII deficiency. Haemophilia 2008; 14:1190.
13. Plummer ES, Crary SE, Buchanan GR. Prominent forehead hematomas ("goose-eggs") as an initial manifestation of hemophilia. J Pediatr 2013; 163:1781.
14. Despotovic JM, Grimes AB. Pediatric ITP: is it different from adult ITP? Hematology Am Soc Hematol Educ Program 2018; 2018:405.
15. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011; 117:4190.
16. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010; 115:168.
17. Blanchette V, Bolton-Maggs P. Childhood immune thrombocytopenic purpura: diagnosis and management. Hematol Oncol Clin North Am 2010; 24:249.
18. O'Brien SH, Saini S. von Willebrand Disease in Pediatrics: Evaluation and Management. Hematol Oncol Clin North Am 2019; 33:425.
19. Khair K, Liesner R. Bruising and bleeding in infants and children--a practical approach. Br J Haematol 2006; 133:221.
20. Stokhuijzen E, Segbefia CI, Biss TT, et al. Severity and Features of Epistaxis in Children with a Mucocutaneous Bleeding Disorder. J Pediatr 2018; 193:183.
21. Collins PW, Hamilton M, Dunstan FD, et al. Patterns of bruising in preschool children with inherited bleeding disorders: a longitudinal study. Arch Dis Child 2017; 102:1110.
22. James AH, Kouides PA, Abdul-Kadir R, et al. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. Am J Obstet Gynecol 2009; 201:12.e1.
23. Bertamino M, Riccardi F, Banov L, et al. Hemophilia Care in the Pediatric Age. J Clin Med 2017; 6.
24. Kühnel T, Wirsching K, Wohlgemuth W, et al. Hereditary Hemorrhagic Telangiectasia. Otolaryngol Clin North Am 2018; 51:237.
25. Napolitano M, Siragusa S, Mariani G. Factor VII Deficiency: Clinical Phenotype, Genotype and Therapy. J Clin Med 2017; 6.
26. Ghauri AJ, Abbott J, Shah P, Gardiner P. Bleeding risks associated with herbal medicine in children. Glob Adv Health Med 2014; 3:5.

27. Schulman S. World Federation of Hemophilia. Drugs that can cause bleeding. 2010. Availa ble at: www.wfh.org/en/page.aspx?pid=639 (Accessed on August 26, 2019).
28. Monagle P, Barnes C, Ignjatovic V, et al. Developmental haemostasis. Impact for clinical haemostasis laboratories. Thromb Haemost 2006; 95:362.
29. Marlar RA, Potts RM, Marlar AA. Effect on routine and special coagulation testing values of citrate anticoagulant adjustment in patients with high hematocrit values. Am J Clin Pathol 2006; 126:400.
30. Payne BA, Pierre RV. Pseudothrombocytopenia: a laboratory artifact with potentially serious consequences. Mayo Clin Proc 1984; 59:123.
31. Lippi U, Schinella M, Nicoli M, et al. EDTA-induced platelet aggregation can be avoided by a new anticoagulant also suitable for automated complete blood count. Haematologica 1990; 75:38.
32. Gomez K, Bolton-Maggs P. Factor XI deficiency. Haemophilia 2008; 14:1183.
33. Perry DJ. Factor VII Deficiency. Br J Haematol 2002; 118:689.
34. Chua JD, Friedenberg WR. Superwarfarin poisoning. Arch Intern Med 1998; 158:1929.
35. Doshi BS, Rogers RS, Whitworth HB, et al. Utility of repeat testing in the evaluation for von Willebrand disease in pediatric patients. J Thromb Haemost 2019; 17:1838.
36. Park CH, Seo JY, Kim HJ, et al. A diagnostic challenge: mild hemophilia B with normal activated partial thromboplastin time. Blood Coagul Fibrinolysis 2010; 21:368.
37. Duncan EM, Rodgers SE, McRae SJ. Diagnostic testing for mild hemophilia a in patients with discrepant one-stage, two-stage, and chromogenic factor VIII:C assays. Semin Thromb Hemost 2013; 39:272.
38. Hayward CP. Diagnostic approach to platelet function disorders. Transfus Apher Sci 2008; 38:65.
39. Israels SJ, Kahr WH, Blanchette VS, et al. Platelet disorders in children: A diagnostic approach. Pediatr Blood Cancer 2011; 56:975.
40. Poon MC, Di Minno G, d'Oiron R, Zotz R. New Insights Into the Treatment of Glanzmann Thrombasthenia. Transfus Med Rev 2016; 30:92.
41. Andrews RK, Berndt MC. Bernard-Soulier syndrome: an update. Semin Thromb Hemost 2013; 39:656.
42. Nurden P, Nurden AT. Congenital disorders associated with platelet dysfunctions. Thromb Haemost 2008; 99:253.
43. Gebhart J, Hofer S, Panzer S, et al. High proportion of patients with bleeding of unknown cause in persons with a mild-to-moderate bleeding tendency: Results from the Vienna Bleeding Biobank (VIBB). Haemophilia 2018; 24:405.

44. Hofer S, Ay C, Rejtö J, et al. Thrombin-generating potential, plasma clot formation, and clot lysis are impaired in patients with bleeding of unknown cause. J Thromb Haemost 2019; 17:1478.

45. Ardillon L, Ternisien C, Fouassier M, et al. Platelet function analyser (PFA-100) results and von Willebrand factor deficiency: a 16-year 'real-world' experience. Haemophilia 2015; 21:646.

46. Podda GM, Bucciarelli P, Lussana F, et al. Usefulness of PFA-100 testing in the diagnostic screening of patients with suspected abnormalities of hemostasis: comparison with the bleeding time. J Thromb Haemost 2007; 5:2393.

47. Pengo V, Tripodi A, Reber G, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2009; 7:1737.

Topic 5936 Version 36.0

GRAPHICS

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

International Society on Thrombosis and Haemostasis bleeding assessment tool (ISTH BAT)

Type of bleeding	Score			
	0	1	2	3
Epistaxis	None or trivial	>5 episodes per year or episode(s) lasting >10 minutes	Consultation only*	Required packing cauterization, or antifibrinolytic therapy
Cutaneous (eg, bruising, ecchymoses, purpura)	None or trivial	≥5 (>1 cm) in exposed areas	Consultation only*	Extensive
Bleeding from minor wounds	None or trivial	>5 episodes per year or episode(s) lasting >10 minutes	Consultation only*	Required surgica hemostasis
Oral cavity	None or trivial	Present	Consultation only*	Required surgica hemostasis or antifibrinolytic therapy
Gastrointestinal bleeding	None or trivial	Present (not associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia)	Consultation only*	Required surgica hemostasis or antifibrinolytic therapy
Hematuria	None or trivial	Present (macroscopic)	Consultation only*	Required surgica hemostasis or irr therapy
Bleeding after tooth extraction	None, trivial, or no prior extractions	Reported in ≤25% of all procedures, did not require intervention[Δ]	Reported in >25% of all procedures, did not require intervention[Δ]	Required resutur or packing
Surgical bleeding	None, trivial, or no prior surgeries	Reported in ≤25% of all procedures, did not require intervention[Δ]	Reported in >25% of all procedures, did not require intervention[Δ]	Required surgica hemostasis or antifibrinolytic

Menorrhagia	None or trivial	Any of the following: ▪ Changing pads more frequently than every 2 hours ▪ Clot and flooding ▪ Consultation* without intervention	Required any of the following: ▪ Time off work/school >2 times per year ▪ Antifibrinolytic therapy ▪ Hormonal therapy ▪ Iron therapy	Either of the following: ▪ Present sin menarche a has been ongoing fo months ▪ Required combined treatment v antifibrinol and hormo therapy
Postpartum hemorrhage	No/trivial or no deliveries	Any of the following: ▪ Use of oxytocin ▪ Lochia (postpartum shedding of blood and decidua) lasting >6 weeks ▪ Consultation* without intervention	Required iron or antifibrinolytic therapy	Either of the following: ▪ Required bl transfusion replacemer therapy¶, c desmopres ▪ Required examinatio under anaesthesi and/or the of uterine balloon/pa to tampona the uterus
Muscle hematomas	Never	Post-traumatic, not requiring treatment	Spontaneous, not requiring treatment	Spontaneous or traumatic, requi desmopressin or replacement therapy¶
Hemarthrosis	Never	Post-traumatic, not requiring treatment	Spontaneous, not requiring treatment	Spontaneous or traumatic, requi desmopressin or replacement therapy¶
Intracranial hemorrhage	Never	N/A	N/A	Subdural

Other: ▪ Umbilical stump bleeding◇ ▪ Cephalohematoma◇ ▪ Cheek hematoma (caused by sucking during breast/bottle feeding)◇ ▪ Conjunctival hemorrhage ▪ Excessive bleeding following circumcision◇ ▪ Excessive bleeding following venipuncture	None or trivial	More than trivial but did not require medical evaluation	Consultation only*	Required surgica hemostasis or antifibrinolytic therapy

The ISTH BAT is used to screen for the likelihood of a bleeding disorder (particularly VWD) in children with bleeding symptoms. In children, a score of ≥2 points is considered a positive screen. For additional details, refer to UpToDate topics on VWD and evaluation of bleeding symptoms in children.

ISTH BAT: International Society on Thrombosis and Haemostasis bleeding assessment tool; D&C: dilatation & curettage; VWD: von Willebrand disease.

* Consultation only means that the patient sought medical evaluation and was either referred to a specialist or offered laboratory investigation but did not require hemostatic therapy or transfusion.

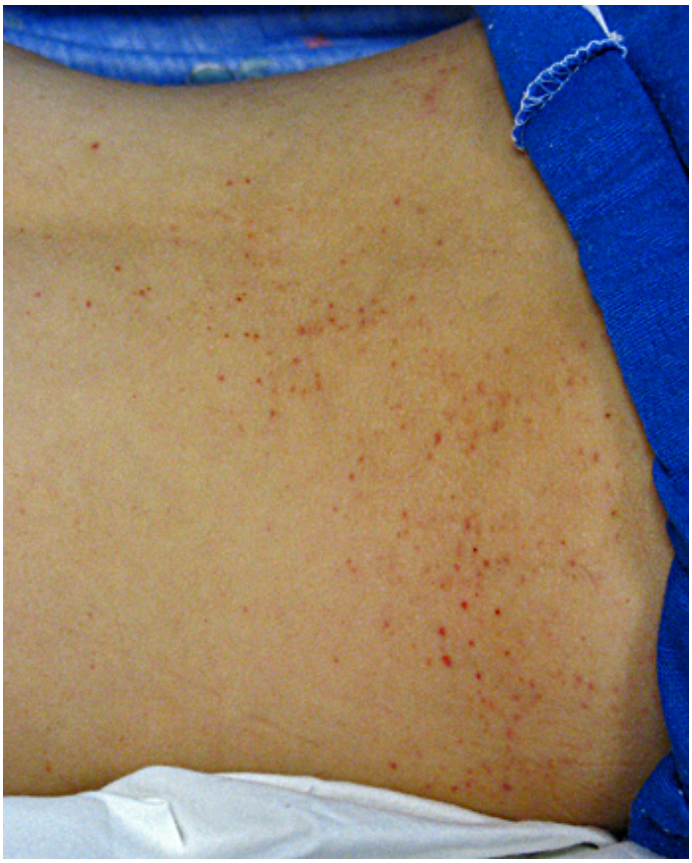
¶ Replacement therapy includes use of hemostatic blood components and/or recombinant factor VIIa.

Δ For example, if the patient had ≥4 prior extractions/surgeries and experienced more than trivial bleeding only once without need for intervention, a score of 1 should be assigned. If the patient had ≤3 prior extractions/surgeries and experienced more than trivial bleeding in any of them (not requiring intervention), a score of 2 should be assigned. If the patient experienced bleeding that required intervention, the score to be assigned is a 3 or 4 depending on the type of intervention (as detailed in the table above).

◇ For these categories, the presence of more than trial bleeding in infancy requires detailed investigation independently from the overall score.

Graphic 134983 Version 2.0

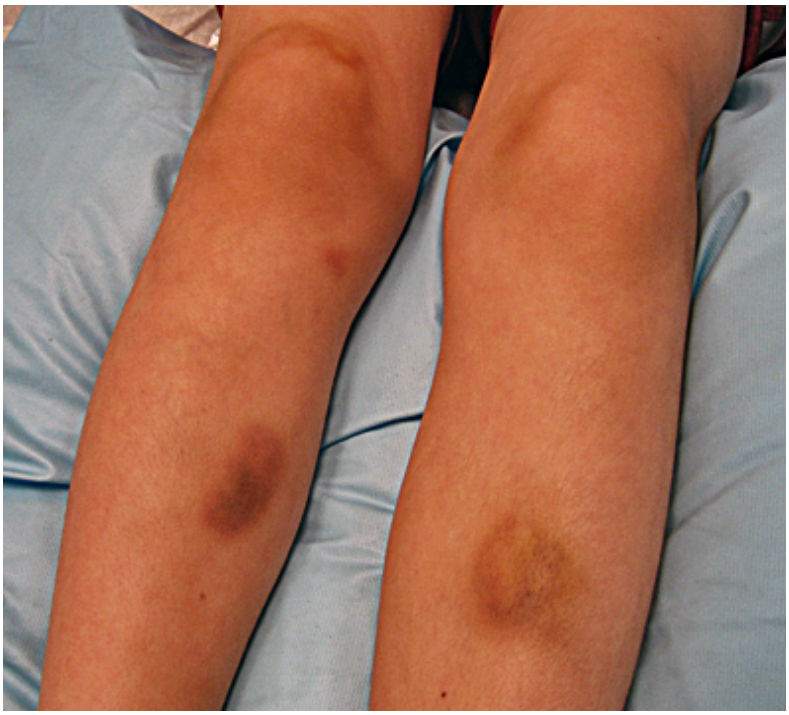
Petechiae



Courtesy of Leslie Raffini, MD.

Graphic 73905 Version 2.0

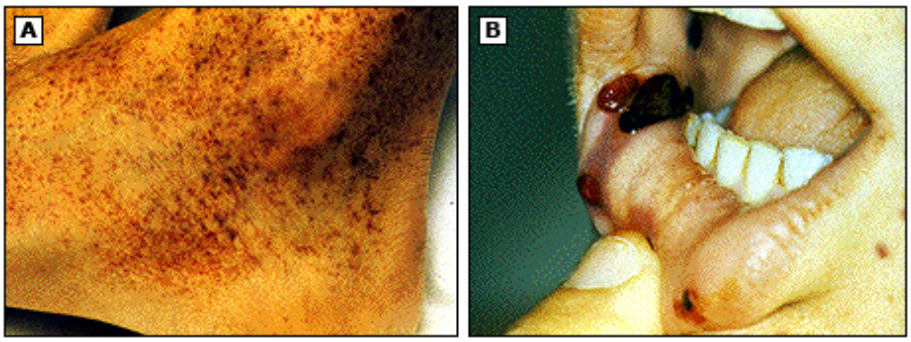
Ecchymoses



Courtesy of Leslie Raffini, MD.

Graphic 59402 Version 1.0

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.

Reproduced with permission from: Stein JH, Internal Medicine, 5th ed, Mosby, St. Louis, 1998.

Graphic 71480 Version 8.0

Expected results of tests for hemostatic function in representative hemorrhagic disorders

Disorder	Platelet count	PT	aPTT	Fibrinogen
Vasculopathies, connective tissue diseases, or collagen disorders affecting skin	normal	normal	normal	normal or increased*
Thrombocytopenia	low	normal	normal	normal
Qualitative platelet abnormalities	normal or low¶	normal	normal	normal
Hemophilia A (factor VIII deficiency)	normal	normal	long	normal
von Willebrand disease	normalΔ	normal	normal or long◇	normal
Disseminated intravascular coagulation	low	long	long	low

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

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

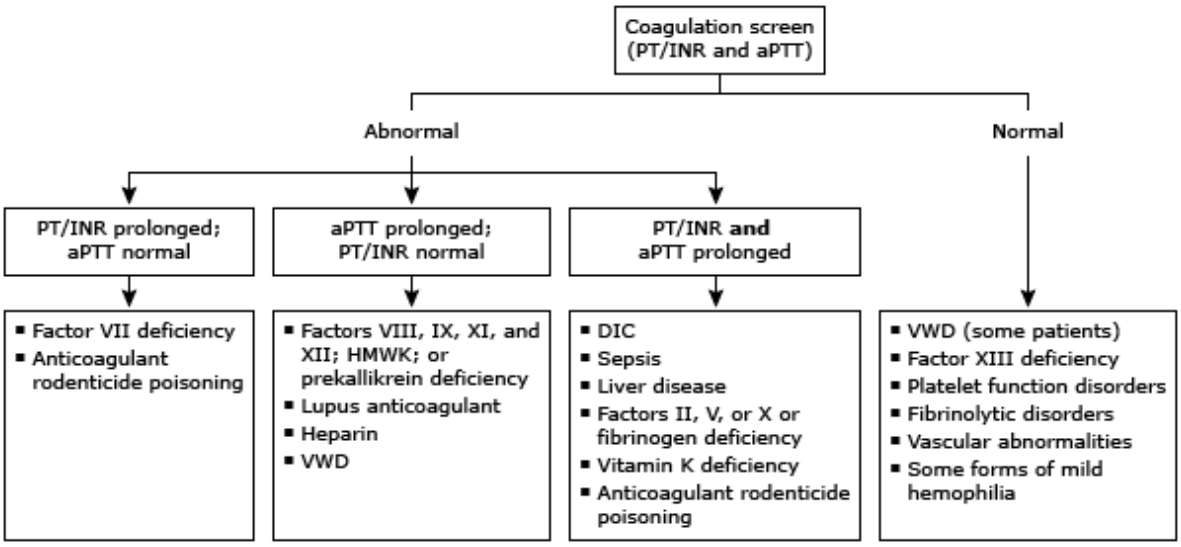
¶ The platelet count in myeloproliferative disorders is usually high (eg, essential thrombocythemia) and platelets may also be qualitatively abnormal, predisposing to hemorrhagic and thrombotic diatheses.

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 percent.

Graphic 80791 Version 5.0

Algorithm for identifying causes of bleeding symptoms in children based on results of coagulation screen

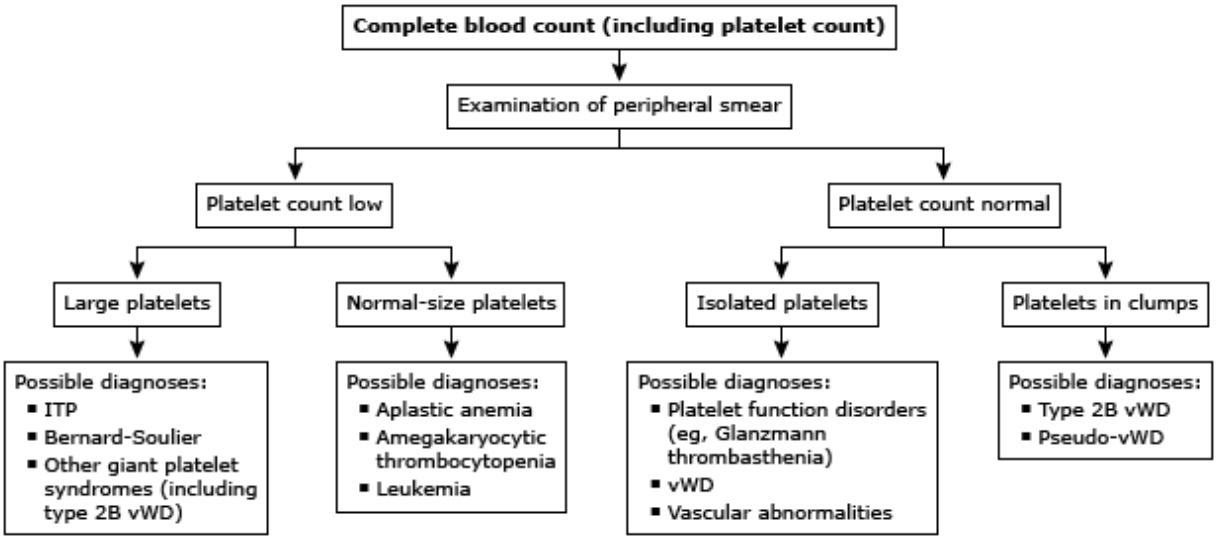


Refer to UpToDate topic on the evaluation of bleeding symptoms in children for additional details.

PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; VWD: von Willebrand disease; HMWK: high molecular weight kininogen; DIC: disseminated intravascular coagulation.

Graphic 60745 Version 12.0

Diagnostic approach to a child with mucocutaneous bleeding (purpuric disorders) based on platelet count and platelet appearance on peripheral smear*



ITP: immune thrombocytopenia (previously known as idiopathic thrombocytopenic purpura); vWD: von Willebrand disease.

* Mucocutaneous bleeding in children is characteristic of disorders that cause abnormal platelet number and/or function. However, mucocutaneous bleeding can also occur in patients with abnormal coagulation (eg, hemophilia, disseminated intravascular coagulation). The diagnostic approach presented here represents a simplified approach based solely on platelet count and the appearance of the platelets on peripheral smear. In many cases, additional evaluation is warranted. Refer to UpToDate topic on the evaluation of bleeding symptoms in children for additional details.

Graphic 82633 Version 6.0

Normal range for coagulation tests by age

Coagulation tests	Age					
	Day 1 of life Mean (boundary)	Day 3 of life Mean (boundary)	1 to 12 months Mean (boundary)	1 to 5 years Mean (boundary)	6 to 10 years Mean (boundary)	11 to 1 years Mean (boundary)
PT(s)*	15.6 (14.4-16.4)¶	14.9 (13.5-16.4)¶	13.1 (11.5-15.3)	13.3 (12.1-14.5)¶	13.4 (11.7-15.1)¶	13.8 (12.1-16.1)¶
INR	1.26 (1.15-1.35)¶	1.2 (1.05-1.35)¶	1 (0.86-1.22)	1.03 (0.92-1.14)¶	1.04 (0.87-1.2)¶	1.08 (0.9-1.3)¶
aPTT(s)*	38.7 (34.3-44.8)¶	36.3 (29.5-42.2)¶	39.3 (35.1-46.3)¶	37.7 (33.6-46.3)¶	37.3 (31.8-43.7)¶	39.5 (33.-46.1)¶
Fibrinogen (g/L)	2.8 (1.92-3.74)	3.3 (2.83-4.01)	2.42 (0.82-3.83)¶	2.82 (1.62-4.01)¶	3.04 (1.99-4.09)	3.15 (2.1-4.33)
Factor II (U/mL)	0.54 (0.41-0.69)¶	0.62 (0.5-0.73)¶	0.9 (0.62-1.03)¶	0.89 (0.7-1.09)¶	0.89 (0.67-1.1)¶	0.9 (0.61-1.07)¶
Factor V (U/mL)	0.81 (0.64-1.03)¶	1.22 (0.92-1.54)	1.13 (0.94-1.41)	0.97 (0.67-1.27)¶	0.99 (0.56-1.41)¶	0.89 (0.6-1.41)¶
Factor VII (U/mL)	0.7 (0.52-0.88)¶	0.86 (0.67-1.07)¶	1.28 (0.83-1.6)	1.11 (0.72-1.5)¶	1.13 (0.7-1.56)¶	1.18 (0.6
Factor VIII (U/mL)	1.82 (1.05-3.29)	1.59 (0.83-2.74)	0.94 (0.54-1.45)¶	1.1 (0.36-1.85)¶	1.17 (0.52-1.82)¶	1.2 (0.59
vWF (U/mL)	n/a	n/a	n/a	0.82 (0.6-1.2)	0.95 (0.44-1.44)	1 (0.46-1
Factor IX (U/mL)	0.48 (0.35-0.56)¶	0.72 (0.44-0.97)¶	0.71 (0.43-1.21)¶	0.85 (0.44-1.27)¶	0.96 (0.48-1.45)¶	1.11 (0.6-2.16)¶
Factor X (U/mL)	0.55 (0.46-0.67)¶	0.6 (0.46-0.75)¶	0.95 (0.77-1.22)¶	0.98 (0.72-1.25)¶	0.97 (0.68-1.25)¶	0.91 (0.5-1.22)¶
Factor XI (U/mL)	0.3 (0.7-0.41)¶	0.57 (0.24-0.79)¶	0.89 (0.62-1.25)¶	1.13 (0.65-1.62)	1.13 (0.65-1.62)	1.11 (0.6-1.39)
Factor XII (U/mL)	0.58 (0.43-0.8)¶	0.53 (0.14-0.8)¶	0.79 (0.2-1.35)¶	0.85 (0.36-1.35)¶	0.81 (0.26-1.37)¶	0.75 (0.1-1.17)¶
XIIIa (U/mL)	n/a	n/a	n/a	1.08 (0.72-1.43)¶	1.09 (0.65-1.51)¶	0.99 (0.5-1.4)
XIIIs (U/mL)	n/a	n/a	n/a	1.13 (0.69-1.56)¶	1.16 (0.77-1.54)¶	1.02 (0.6-1.43)

All factors except fibrinogen are expressed as units per milliliter, where pooled plasma contains 1.0 U/mL. All data are expressed as the mean, followed by the upper and lower boundary

encompassing 95% of the population. Between 20 and 67 samples were assayed for each value for each age group. Some measurements were skewed due to a disproportionate number of high values. The lower limit, which excludes the lower 2.5% of the population, is given.

PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; VIII: factor VIII procoagulant; vWF: von Willebrand factor; n/a: data not available.

* Normal range for PT and aPTT should be based upon the standards set by individual clinical laboratories.

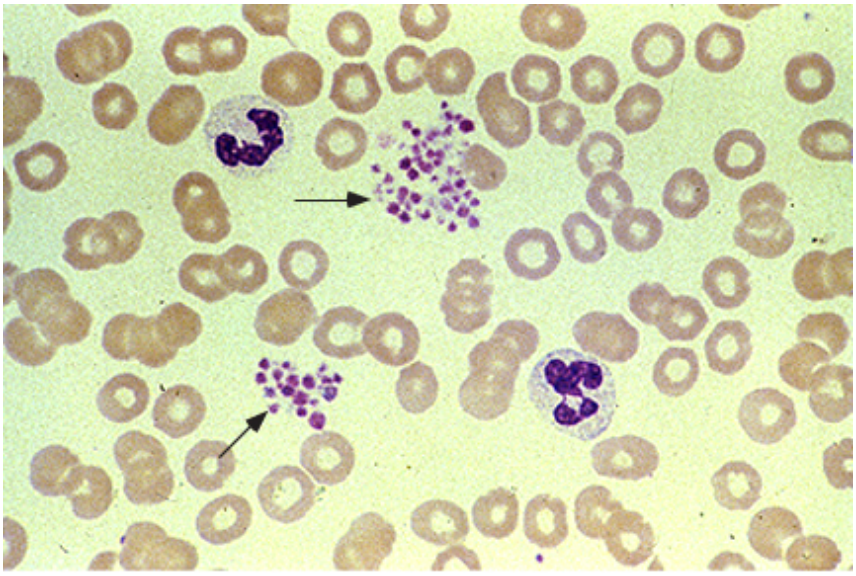
¶ Denotes values that are significantly different from adults.

Data on vWF, XIIIa and XIIIs from: Andrew M, Vegh P, Johnston M, et al. Maturation of the Hemostatic System During Childhood. Blood 1992; 80:1999.

Remaining data from: Monagle P, Barnes C, Ignjatovic V, et al. Developmental Haemostasis. Thrombosis and Haemostasis 2006; 95:362.

Graphic 66999 Version 6.0

Pseudothrombocytopenia due to platelet clumping in EDTA



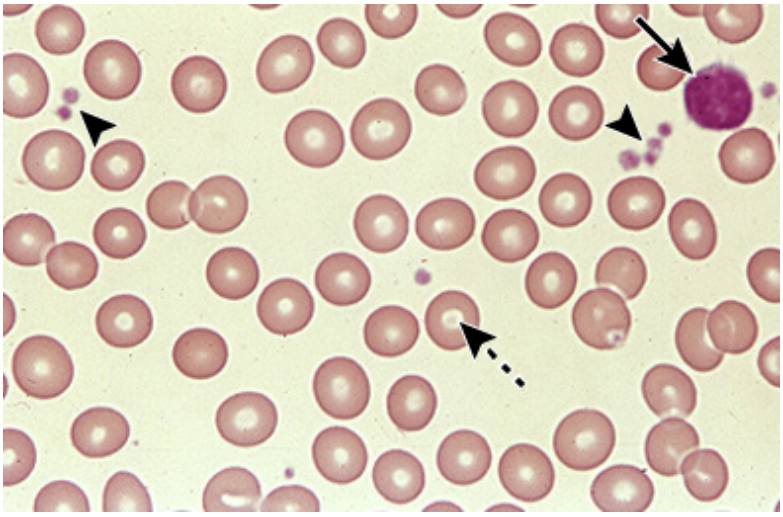
This peripheral blood smear shows platelet clumping (arrows) in an EDTA-anticoagulated blood sample. This patient had an EDTA-dependent platelet agglutinin that caused in vitro platelet clumping, resulting in an artifactually low platelet count (ie, "pseudothrombocytopenia"). No platelet clumping was seen, and the platelet count was normal, in a blood sample from this patient anticoagulated with sodium citrate.

EDTA: ethylenediaminetetraacetic acid.

Reproduced with permission from Beutler, E, Lichtman, MA, Coller, BS, et al, Hematology, 5th ed, McGraw-Hill, New York, 1995.

Graphic 68949 Version 4.0

Normal peripheral blood smear

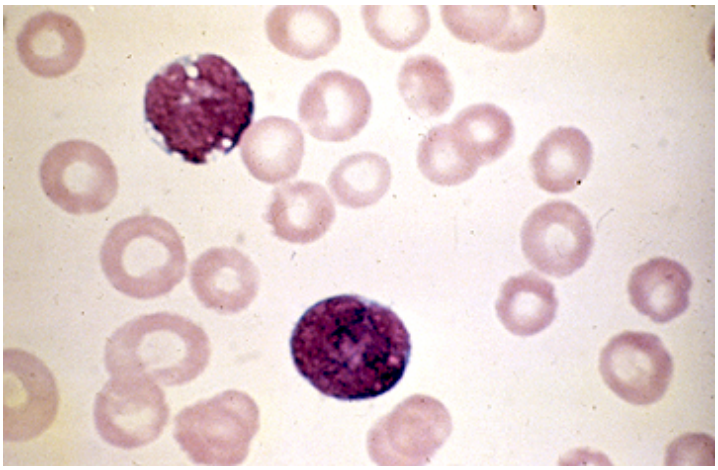


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Lymphoblasts in acute lymphoblastic leukemia

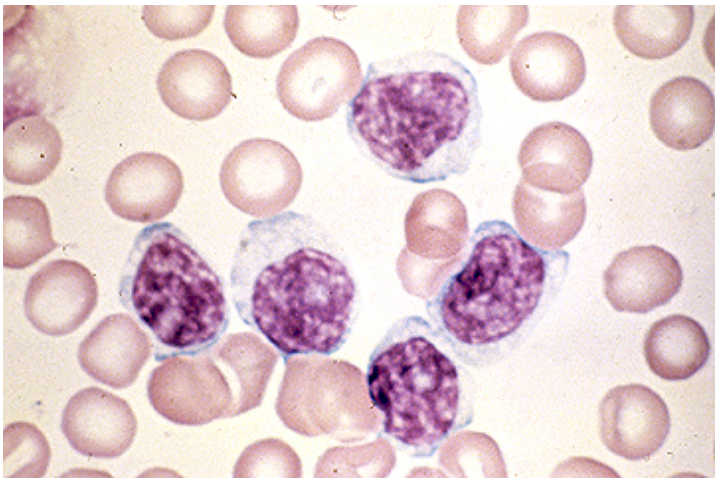


Blood smear showing small lymphoblasts with rare nucleoli and vacuoles, as seen in acute lymphocytic leukemia.

Courtesy of Robert Baehner, MD.

Graphic 57831 Version 5.0

Lymphoblasts in acute lymphoblastic leukemia

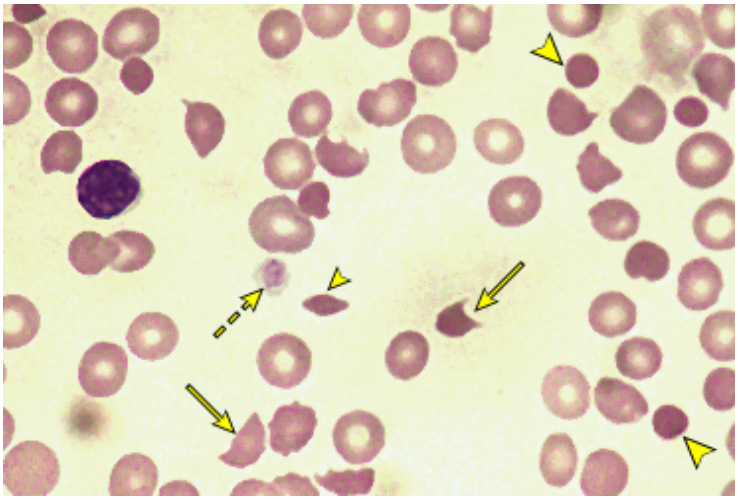


Blood smear showing large lymphoblasts with prominent nucleoli and light blue cytoplasm, as seen in acute lymphoblastic leukemia of the World Health Organization classification. (Wright-Giemsa stain)

Courtesy of Robert Baehner, MD.

Graphic 65474 Version 4.0

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

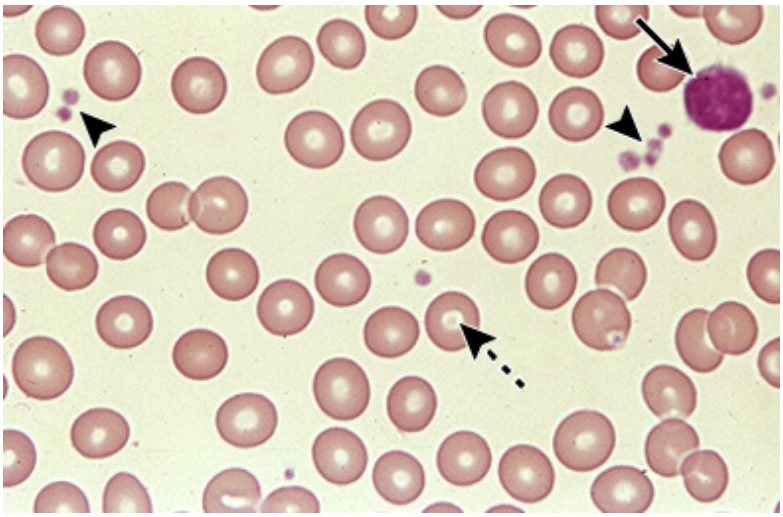


Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (arrows) and other fragmented red cells (small arrowhead); microspherocytes are also seen (large arrowheads). The platelet number is reduced; the large platelet in the center (dashed arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70851 Version 8.0

Normal peripheral blood smear



High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of

the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Classification of inherited thrombocytopenias by platelet size

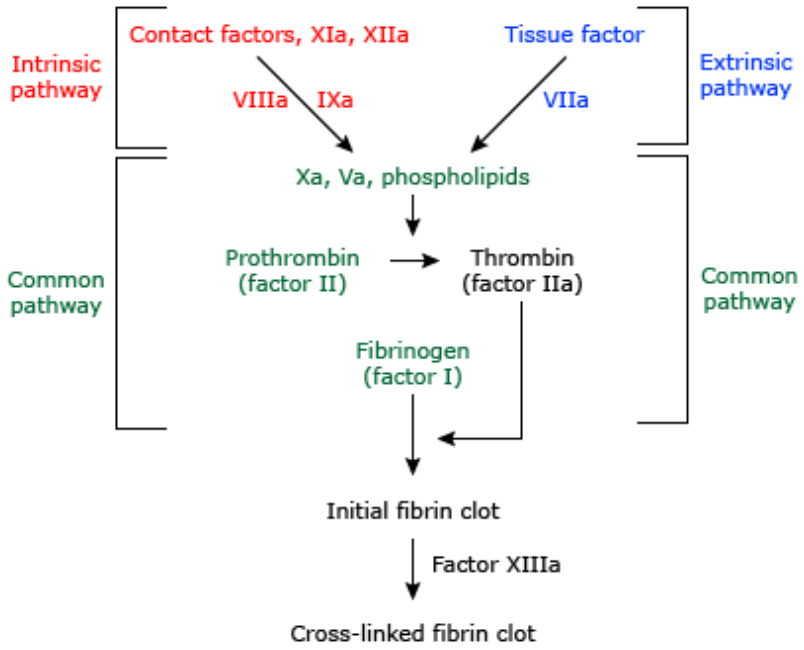
Small platelets (MPV <7 fL)	Normal-sized platelets (MPV 7 to 11 fL)	Large platelets (MPV >11 fL)
Wiskott-Aldrich syndrome	Inherited bone marrow failure syndromes: ▪ Fanconi anemia ▪ Dyskeratosis congenita ▪ Shwachman-Diamond syndrome ▪ Congenital amegakaryocytic thrombocytopenia	Bernard-Soulier syndrome
X-linked thrombocytopenia	Thrombocytopenia-absent radius (TAR) syndrome	DiGeorge syndrome
	Amegakaryocytic thrombocytopenia with radioulnar synostosis	MYH9-related disorders
	Familial platelet disorders with predisposition to myeloid malignancy: ▪ Thrombocytopenia 2 (*ANKRD26* mutation) ▪ Thrombocytopenia 5 (*ETV6* mutation)	Paris-Trousseau syndrome
		Gray platelet syndrome
		X-linked thrombocytopenia with dyserythropoiesis/thalassemia
		Autosomal dominant deafness with thrombocytopenia (*DIAPH1* mutation)
		Sitosterolemia
		ACTN1-related macrothrombocytopenia

MPV: mean platelet volume; MYH9: non-muscle myosin heavy chain.

Original figure modified for this publication. Kumar R, Kahr W. Congenital thrombocytopenia: Clinical manifestations, laboratory abnormalities, and molecular defects of a heterogeneous group of conditions. Hematol Oncol Clin North Am 2013; 27:465. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 89962 Version 4.0

Intrinsic, extrinsic, and common coagulation pathways

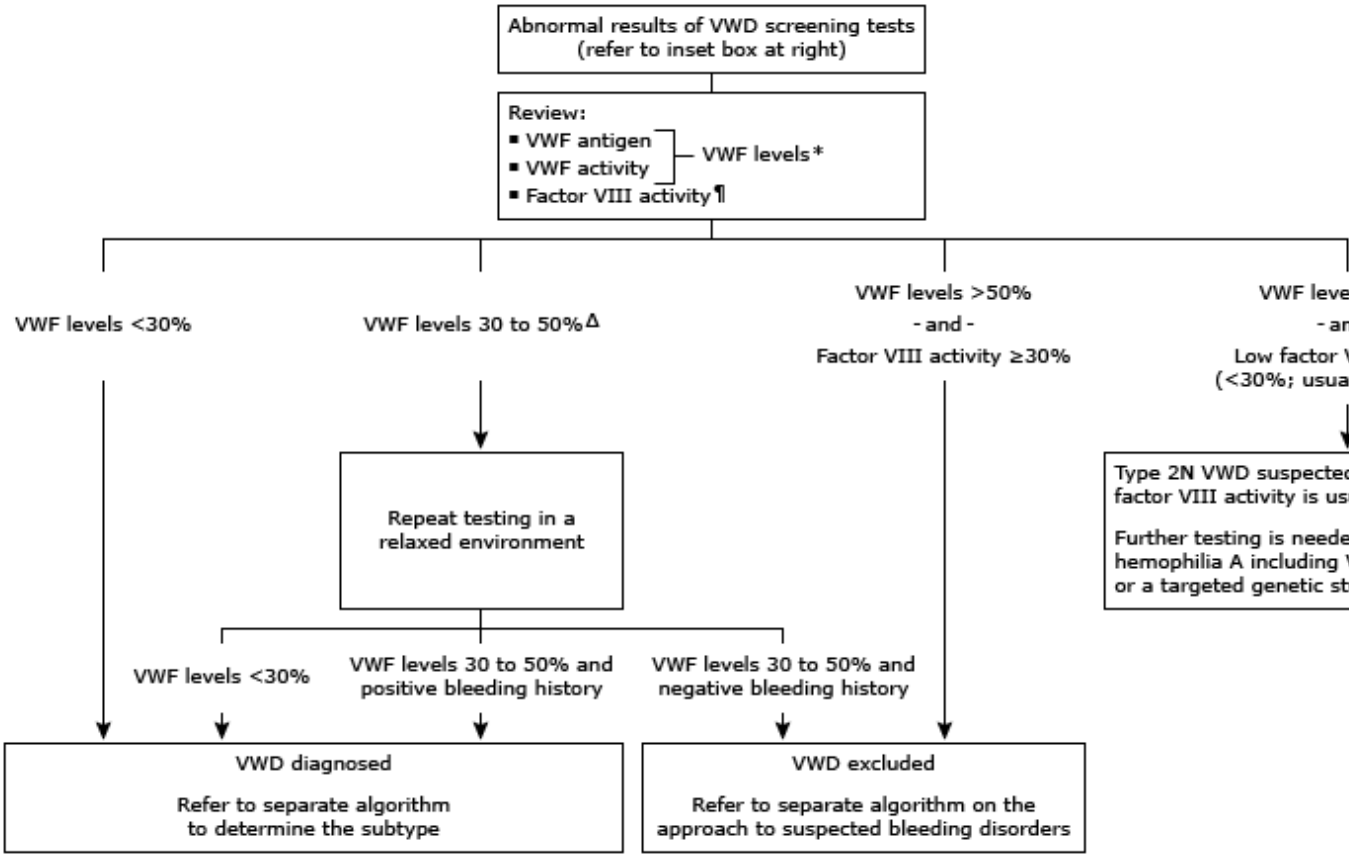


Schematic representation of the intrinsic (red), extrinsic (blue), and common (green) coagulation pathways. Contact factors include prekallikrein and HMWK. In the clinical laboratory, the intrinsic (and common) pathway is assessed by the aPTT and the extrinsic (and common) pathway by the PT. The TT assesses 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

Approach to VWD initial diagnosis



Diagnosis of VWD includes both clinical and laboratory features. The evaluation first determines whether
the subtype, which has implications for management (refer to separate algorithm in UpToDate). Screening
hematologist. Secondary testing is generally done by the consulting hematologist or clinician with experti

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VWD: von Willebrand disease; VWF: von Willebrand factor; ELISA: enzyme-linked immunosorbent assay; G

* "VWF Levels" includes VWF antigen (VWF:Ag) and/or VWF activity (VWF:Act). Concordant reductions in VW
undetectable or extremely low, type 3 VWD; discordant reductions (VWF:Act lower than VWF:Ag) suggest t

¶ Factor VIII activity can be low in VWD because VWF is a carrier for factor VIII. Factor VIII activity is typica
and 2M VWD. Factor VIII activity can be low in type 2N and type 3; in these cases, it is important to disting
and, for type 2N, using additional testing listed in the box above.

Δ Individuals with 30 to 50% VWF levels require repeat testing, especially after recovery from an acute stre
contraceptives or pregnancy). Diagnosis of VWD in individuals with VWF levels of 30 to 50% is based on th

◇ A VWF:Ag to factor VIII activity ratio >3 is expected; if this does not occur, initial VWD screening should b

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Graphic 131037 Version 2.0

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

Major causes of thrombocytopenia in children

Destructive thrombocytopenias
Immune-mediated
Immune thrombocytopenia (ITP)
Drug-induced thrombocytopenia
Systemic autoimmune disorders and immune dysregulation syndromes (secondary ITP)
Systemic lupus erythematosus
Autoimmune lymphoproliferative syndrome
Antiphospholipid antibody syndrome
Common variable immunodeficiency
DiGeorge syndrome
Platelet activation and consumption
Microangiopathic disorders
Hemolytic-uremic syndrome
Thrombotic thrombocytopenic purpura
Disseminated intravascular coagulation
Major surgery or trauma
Kasabach-Merritt syndrome
Mechanical destruction
Extracorporeal therapies (eg, cardiopulmonary bypass)
Sequestration and trapping
Hypersplenism
Type 2B or platelet-type von Willebrand disease

Decreased platelet production
Infection (Epstein-Barr virus, cytomegalovirus, parvovirus, varicella, rickettsia, bacterial sepsis)
Nutritional deficiencies (folate, B12, iron)
Acquired bone marrow failure
Aplastic anemia
Myelodysplastic syndromes
Medications (eg, chemotherapy)
Radiation
Infiltrative bone marrow diseases
Leukemias
Lymphomas
Metastatic cancers
Infectious granulomas
Storage diseases
Genetic causes of impaired thrombopoiesis*
Wiskott-Aldrich syndrome/X-linked thrombocytopenia
Inherited bone marrow failure syndromes
Fanconi anemia
Dyskeratosis congenita
Shwachman-Diamond syndrome
Congenital amegakaryocytic thrombocytopenia
Thrombocytopenia with absent radii syndrome
Amegakaryocytic thrombocytopenia with radioulnar synostosis
Familial platelet disorder with predisposition to hematologic malignancy
Bernard-Soulier syndrome

MYH9-related disorders
Paris-Trousseau syndrome
X-linked thrombocytopenia with dyserythropoiesis

MYH9: nonmuscle myosin heavy chain gene.

* This is a partial list. For further details, refer to UpToDate topics on causes of thrombocytopenia in children and disorders of platelet function.

Graphic 61163 Version 14.0

Patterns of platelet aggregation in selected disorders of platelet function and VWD

Disorder	Aggregation response				Other features
	Primary ADP	Secondary ADP	Collagen	Ristocetin	
VWD	++++	++++	++++	Highly variable	Platelet morphology normal; VWD panel is usually abnormal
Bernard-Soulier syndrome	++++	++++	++++	0	Giant platelets, thrombocytopenia; VWD panel is normal
Glanzmann thrombasthenia	0	0	0	+++	Normal platelet morphology
Storage pool disease	++++	0 to ++	++	++	Platelet morphology normal (except in gray platelet subgroup); electron microscopy is abnormal
Secretion defect	++++	0 to ++	++	++	Normal morphology by light and electron microscopy

Expected aggregation responses in various disorders are illustrated. Refer to UpToDate for details. For inherited COX-1 defects or acquired interference with COX-1 function (eg, aspirin), testing can be done using arachidonic acid as the agonist. Results will show absent aggregation response to arachidonic acid as well as reduced secondary aggregation to ADP. Thromboxane receptor defects can be tested for using U-46619 in conjunction with this.

VWD: von Willebrand disease; ADP: adenosine diphosphate; COX-1: cyclooxygenase 1; ++++: normal response; +++: slightly reduced response; ++: reduced response; +: markedly reduced response; 0: no response.

Graphic 69518 Version 4.0

Selected platelet function tests in clinical use

	Test	What it measures	Methodology	Caveats
Commonly used	Aggregometry	▪ Ability of platelets to aggregate in response to several agonists	▪ Clinical laboratory ▪ Whole blood or PRP	▪ Labor intensive and requires technical expertise ▪ Not widely available outside a tertiary center ▪ May be inaccurate in individuals with moderate to severe thrombocytopenia (platelet count <80,000/microL) ▪ May be insensitive to secretion disorders
	Platelet function analyzer (PFA-100 or PFA-200)	▪ Closure of a small aperture in the cartridge as a method of assessing platelet function	▪ Clinical laboratory ▪ Cartridge-based system ▪ Whole blood only	▪ Lack of specificity for a platelet function disorder (abnormalities may be caused by other hemostatic disorders) ▪ Affected by a number of factors including platelet count, hemoglobin, and VWF levels
	VerifyNow	▪ Ability of platelets to aggregate in response to several agonists (a type of automated aggregometry using fibrinogen-coated beads)	▪ Point-of-care test ▪ Cartridge-based system ▪ Whole blood only	▪ Intended for monitoring anti-platelet drugs ▪ Lacking evidence/not validated for identifying platelet function disorders

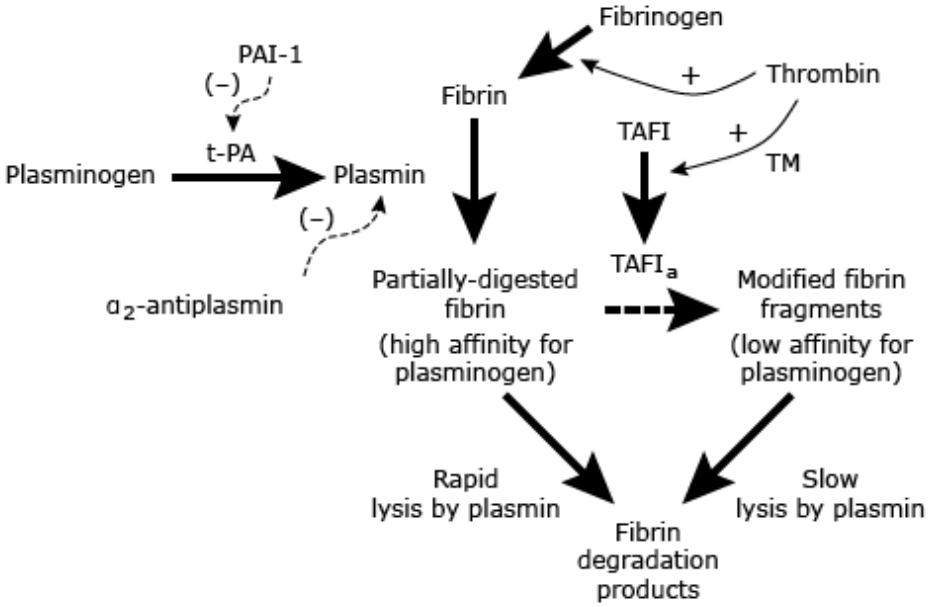
Reserved for special cases or research	Viscoelastic testing, including thromboelastography (TEG) and rotational thromboelastography (ROTEM)	▪ Global hemostasis, from clot formation, physical properties of the clot, and fibrinolysis	▪ Point-of-care test ▪ Whole blood or PRP	▪ Lack of specificity for a platelet function disorder (may be caused by other hemostatic disorders) ▪ Affected by a number of factors including platelet count and fibrinogen level
	Flow cytometry	▪ Appearance of platelet activation markers after exposure to platelet agonists ▪ Can also use granule binding dyes to detect granule disorders	▪ Specialized laboratory ▪ Basal or in response to an agonist ▪ Whole blood or PRP	▪ Sensitive ▪ Quality of samples is important (must be taken without undue activation, may be affected by transportation)
	Genetic testing	▪ Pathogenic variants in specific platelet function genes	▪ Clinical laboratory ▪ DNA from cheek swab cells or WBCs from a blood sample ▪ Single gene or a panel of genes	▪ Determines genotype, not function ▪ May not detect some platelet function disorders
	Electron microscopy	▪ Ultrastructure of platelet granules and other organelles	▪ Specialized research laboratory ▪ Platelets from whole blood or PRP	▪ Labor intensive and time-consuming
	Microfluidic devices such as the Total thrombus formation analysis system (T-TAS)	▪ Thrombus formation in whole blood	▪ Clinical laboratory ▪ Whole blood	▪ Limited experience to date

Aggregometry is the gold standard test for diagnosing platelet function disorders. The bleeding time is no longer routinely used. Consultation with a hemostasis expert is advised when using platelet function tests to evaluate a potential bleeding disorder.

PRP: platelet-rich plasma; VWF: von Willebrand factor; DNA: deoxyribonucleic acid; WBCs: white blood cells.

Graphic 138645 Version 1.0

Regulation of fibrinolysis by plasminogen activator inhibitor-1 (PAI-1), α2-antiplasmin, and thrombin-activatable fibrinolysis inhibitor (TAFI)



PAI-1 inhibits plasmin formation by inhibiting t-PA. α_2-antiplasmin inhibits the activity of plasmin, thereby inhibiting fibrinolysis. TAFI circulates in plasma as a zymogen. It is activated by thrombin when thrombin is bound on to its endothelial cofactor TM, and therefore represents a link between blood coagulation and fibrinolysis. During fibrinolysis, plasmin cleaves intact fibrin at lysine residues, initially yielding large, insoluble fibrin fragments with lysine residues at their carboxyl termini. Plasminogen binds avidly to C-terminal lysine residues within the partially degraded fibrin clot and assumes a conformation that is susceptible to activation by t-PA, thereby promoting plasmin formation, continued fibrinolysis ("rapid fibrinolysis"), and generation of smaller, soluble fibrin fragments that are dispersed by flowing blood. Activated TAFI ($TAFI_a$) is a carboxypeptidase that removes lysine residues from the C-termini of partially degraded fibrin fragments. By removing C-terminal lysine residues from large fibrin fragments in the partially degraded clot, TAFI inhibits recruitment of plasminogen to the clot, thereby slowing fibrinolysis ("slow fibrinolysis").

PAI-1: plasminogen activator inhibitor-1; t-PA: tissue-type plasminogen activator; TAFI: thrombin-activatable fibrinolysis inhibitor; $TAFI_a$: activated form of TAFI; TM: thrombomodulin.

Diagram supplied by William P Fay, MD.

Graphic 81428 Version 8.0

Contributor Disclosures

Sarah O'Brien, MD, MSc Grant/Research/Clinical Trial Support: Bristol Myers Squibb [Anticoagulation]. Consultant/Advisory Boards: AstraZeneca [Reversal agent for anticoagulation]; Bristol Myers Squibb [Anticoagulation]; Pharmacosmos [Intravenous iron]. All of the relevant financial relationships listed have been mitigated. **Lawrence LK Leung, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Carrie Armsby, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.

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