# Clinical manifestations and diagnosis of hemophilia

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## INTRODUCTION

Hemophilia A and B are X-linked disorders that predominantly affect males, although females who are heterozygous carriers can also be affected and can have factor levels in the hemophilic range. Differentiation between hemophilia and other conditions, such as some types of von Willebrand disease, other rare coagulation factor deficiencies, or acquired factor inhibitors, and distinction between hemophilia A and B are crucial for appropriate management.

The clinical manifestations and diagnosis of hemophilia A and B will be reviewed here, along with a discussion of obstetric considerations. Other issues related to care for people with hemophilia are presented separately.

- **Routine care including prophylaxis** – (See "Hemophilia A and B: Routine management including prophylaxis".)
- **Treatment of bleeding and perioperative management** – (See "Acute treatment of bleeding and surgery in hemophilia A and B".)
- **Inhibitors** – (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication".)
- **Complications and comorbidities** – (See "Chronic complications and age-related comorbidities in people with hemophilia".)

- **Hemophilia C (factor XI deficiency)** – (See "Factor XI (eleven) deficiency".)

- **Genetics and biology** – (See "Genetics of hemophilia A and B" and "Biology and normal function of factor VIII and factor IX".)

An approach to the diagnostic evaluation of a patient with unexplained bleeding is also presented separately. (See "Easy bruising" and "Approach to the child with bleeding symptoms" and "Approach to the adult with a suspected bleeding disorder".)

## DEFINITIONS

Hemophilia typically refers to an inherited bleeding disorder caused by deficiency of coagulation factor VIII (hemophilia A), factor IX (hemophilia B), or factor XI (hemophilia C).

- **Hemophilia A** – Inherited deficiency of factor VIII (factor 8 [encoded by the *F8* gene]); an X-linked recessive disorder.

- **Hemophilia B** – Inherited deficiency of factor IX (factor 9 [encoded by the *F9* gene]); also called Christmas disease; an X-linked recessive disorder.

- **Hemophilia C** – Inherited deficiency of factor XI (factor 11); also called Rosenthal syndrome; an autosomal recessive disorder. Rarely, heterozygotes may have bleeding (autosomal dominant transmission, due to heterodimer binding). Hemophilia C is more common in Ashkenazi Jewish population (Jews from Eastern Europe). (See "Factor XI (eleven) deficiency".)

- **Acquired factor deficiencies** – Acquired coagulation factor deficiencies caused by an autoantibody (often to factor VIII) are sometimes referred to as acquired hemophilia. The terms "acquired factor inhibitor" or "acquired factor deficiency" are preferable to avoid potential mislabeling the patient as having hemophilia A or B. Management of these conditions is discussed separately. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)".)

- **Inhibitors** – In hemophilia, 'inhibitor' refers to an alloantibody that typically forms in response to infused factor. Inhibitors are most common in individuals with very low baseline factor levels and those with specific genetic variants. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication".)

- **Severity** – Hemophilia is characterized as mild, moderate, or severe, based on the residual or baseline factor activity level (also referred to as "factor level"); this is expressed as a

percent of normal or in international units (IU)/mL [1]. Factor levels typically correlate with the degree of bleeding symptoms [2,3].

Severity is defined as follows [1,4]:

- **Severe hemophilia** – Severe hemophilia is defined as <1 percent factor activity, which corresponds to <0.01 IU/mL.
- **Moderate hemophilia** – Moderate hemophilia is defined as a factor activity level ≥1 percent of normal and ≤5 percent of normal, corresponding to ≥0.01 and ≤0.05 IU/mL.
- **Mild hemophilia** – Mild hemophilia is defined as a factor activity level >5 percent of normal and <40 percent of normal (≥0.05 and <0.40 IU/mL). Individuals may also be classified as having mild hemophilia despite having a factor level of ≥40 percent if they share a genetic variant in the relevant factor gene (*F8* or *F9*) with a family member who has hemophilia [4].

- **Target joint** – A target joint is defined as a joint with ≥3 recurrent bleeding episodes in a six-month period. (See 'Joints and muscle' below.)

## EPIDEMIOLOGY

Hemophilia affects more than 1.2 million individuals (mostly males) worldwide [5]. Hemophilia A is more common than hemophilia B. Typically reported incidences are as follows [5,6]:

- **Hemophilia A** – Hemophilia A occurs in approximately 1 in 4000 to 1 in 5000 live male births. Approximately one-half to two-thirds have severe disease (factor VIII activity <1 percent of normal).
- **Hemophilia B** – Hemophilia B occurs in approximately 1 in 15,000 to 1 in 30,000 live male births. Approximately one-third to one-half have severe disease (factor IX activity <1 percent of normal).

Severe hemophilia is almost exclusively a disease of males, although females can be affected in some rare cases (eg, compound heterozygosity; skewed lyonization; X chromosome loss).

In contrast, mild hemophilia has been reported in up to one-quarter of female carriers who are heterozygous for the pathogenic variant in the factor gene (*F8* or *F9*). Mild hemophilia is an appropriate diagnosis in these individuals, rather than classification as 'symptomatic carriers' that has been used historically. (See 'Bleeding in females/carriers' below and 'Diagnosis' below.)

Most commonly, hemophilia is inherited (see "Genetics of hemophilia A and B"). However, sporadic disease (without a positive family history, presumed due to a de novo mutation) is also common. Studies have demonstrated that sporadic causes account for as much as 55 percent of cases of severe hemophilia A and 43 percent of cases of severe hemophilia B [7]. In moderate and mild hemophilia A and B, approximately 30 percent are sporadic cases.

Hemophilia occurs in all racial and ethnic groups and throughout the world. A publication from the World Federation of Haemophilia estimated that 43 percent of the world's hemophilia population lives in India, Bangladesh, Indonesia, and China, of which only 12 percent have been diagnosed [8]. Epidemiologic estimates may be skewed in other regions of the world by reduced diagnostic capabilities.

## CLINICAL MANIFESTATIONS

Clinical manifestations of hemophilia relate to bleeding from impaired hemostasis, sequelae from bleeding, or complications of coagulation factor infusion.

### Initial presentation

**Age at first bleeding** — Most infants with severe hemophilia present within the first year to one and a half years of life with easy bruising, hemarthrosis, bleeding due to oral injury, or after an invasive procedure.

- Average age of diagnosis based on life table analysis of 13,399 participants in a Centers for Disease Control (CDC) data collection project for severe, moderate, and mild hemophilia were 1 month, 8 months, and 36 months, respectively [9]. In another report from the CDC involving a cohort of 547 boys with hemophilia, 441 (81 percent) had at least one bleeding event during the first two years of life [10].

- In a survey of 140 boys from Sweden, the mean ages at diagnosis for severe disease and moderate disease were 9 and 22 months, respectively [11].

- In a report of 580 children diagnosed with hemophilia before age two, 75 percent were diagnosed within the first month of life, especially if there was a known family history of hemophilia or known carrier status of the mother [9]. These data did not include children diagnosed after age two, so they are likely to be biased towards inclusion of families with a known history of hemophilia.

Other reviews have reported similar mean age for first bleeding episode; however, the range of ages for first bleeding is large, with some children having severe bleeding at birth and others

not experiencing a bleeding episode until the age of four [12,13]. The majority of newborns with severe hemophilia undergo non-instrumented delivery without significant bleeding [14].

In contrast to severe disease, mild hemophilia may go undetected for long periods of time. This is true in the absence of an informative family history as well as in individuals with a positive family history for whom the information is not communicated. Disease may only become apparent when there is a significant hemostatic challenge (trauma or surgery). In one report of 10 patients, the age of diagnosis of mild hemophilia ranged from 14 to 62 years [15]. Up to one-third of patients with mild hemophilia have no bleeding or very limited bleeding only associated with trauma or surgery [16].

The majority of patients with hemophilia present with a known family history. However, a significant number of individuals present with unexpected bleeding, most likely due to a de novo gene mutation transmitted from the mother [6]. In the survey of 140 boys with hemophilia (only some of whom had known carrier mothers), a bleeding episode preceded the diagnosis in one-fourth [11].

**Initial site of bleeding** — Bleeding may occur anywhere in the body in patients with hemophilia. Differences in disease severity and hemostatic challenges throughout life influence the initial site of bleeding.

- **Infants** – Common sites of bleeding in newborns include the central nervous system, extracranial sites such as cephalohematoma, and sites of medical interventions including circumcision, heel sticks, and venipunctures [10]. Approximately 3 to 5 percent of infants with severe hemophilia develop subgaleal or intracerebral hemorrhage in the perinatal period [17-22]. Approximately one-half have excessive bleeding with circumcision [23].

- **Children** – Bruising, joint bleeds, and other sites of musculoskeletal bleeding become more common once children become mobile (including crawling) [9]. Frenulum and oral injuries are also common sites in young toddlers. Forehead hematomas ("goose-eggs") were reported as a common presenting finding in a retrospective analysis of 324 children with hemophilia, in whom forehead hematoma was the initial site of bleeding in 84 (25 percent) and the only site of bleeding in 14 of these (17 percent) [24]. The ages of affected children ranged from six months to 11 years (mean, 3.4 years), and many had mild or moderate disease.

- **Older children and adults** – Common sites of bleeding in older children and adults include joints, muscles, central nervous system, and oral or gastrointestinal tract. (See 'Joints and muscle' below.)

Patients with bleeding will require hemostatic intervention, often including infusion of the appropriate coagulation factor, and they should be treated in consultation with a hemophilia treatment center. This and other management issues are discussed in detail separately. (See "Acute treatment of bleeding and surgery in hemophilia A and B".)

**Disease severity** — Patients with more severe hemophilia are more likely to have spontaneous bleeding, severe bleeding, and an earlier age of first bleeding episode, which can begin as early as birth [3,16]. (See 'Definitions' above.)

Immediate and delayed bleeding after trauma is common; it can be massive or may persist as continuous oozing for days or weeks. In contrast, excessive or prolonged bleeding from small cuts is uncommon. The overall frequency of bleeding has declined with greater use of prophylactic therapy, such that some patients with severe disease may not experience a severe bleeding event.

Rarely, patients with severe hemophilia have a milder-than-expected clinical course [25]. The following examples illustrate potential mechanisms for the attenuation of disease severity:

- **Hemophilia B Leyden** – The hemophilia B Leyden phenotype is characterized by severe hemophilia B in childhood that becomes progressively milder after puberty. Mutations in these individuals occur in the factor IX promoter, affecting expression of the gene, rather than the factor IX coding region. The increase in factor IX expression is seen as a child ages, often thought to occur by or during puberty, likely due to hormonal changes and testosterone sensitivity. (See "Genetics of hemophilia A and B", section on 'Leyden phenotype'.)

- **Coinheritance of thrombophilia** – The factor V Leiden mutation or other thrombophilic conditions can co-occur with hemophilia [26,27]. These prothrombotic conditions may potentially ameliorate the bleeding phenotype of hemophilia, resulting in fewer bleeding episodes and a later onset of first bleeding [12,27,28]. (See "Factor V Leiden and activated protein C resistance" and 'Initial presentation' above.)

Patients with moderate hemophilia often bleed in response to intercurrent injury and invasive procedures. Bleeding is less frequent than in severe hemophilia and typically occurs four to six times yearly. However, more frequent bleeding may occur if a target joint (a joint with ≥3 recurrent bleeding episodes in six months) develops. Some patients with moderate hemophilia may express a more severe phenotype requiring the use of prophylactic treatment regimens. (See 'Hemophilic arthropathy' below.)

In contrast, individuals with mild hemophilia generally only have bleeding in response to injury/trauma or surgery, and bleeding may not become clinically apparent until later in life [3,16]. Delayed bleeding can occur after minor surgical procedures such as dental extraction, even in patients with mild disease. (See 'Age at first bleeding' above.)

Heterozygous females have variable factor levels. Those with a factor activity level above 50 percent of normal are not expected to experience excessive bleeding, and, in these cases, carrier status is primarily important for the potential reproductive implications (risk to male children). Other female carriers may have factor activity levels less than 50 percent of normal and may have greater bleeding than unaffected relatives or matched controls [29]. It may be challenging to obtain a true baseline factor activity level, especially in hemophilia A carriers, due to the stress response, use of hormonal regulation for birth control or menses, or during pregnancy; these may elevate factor VIII levels. Clinical observation and close attention to management are required in these cases, especially if only a single factor activity level measurement is available. (See 'Bleeding in females/carriers' below.)

**Sites of bleeding**

**Intracranial bleeding** — Intracranial hemorrhage (ICH) is relatively rare compared with other sites of bleeding, but it is one of the most dangerous and life-threatening events in individuals with hemophilia [30]. ICH can occur in individuals of all ages, spontaneously or after trauma [31,32].

The overall incidence of ICH in people with hemophilia is approximately 3 to 4 percent at birth [10,18,21,31-34].

- In a meta-analysis from 2021 that included over 54,000 people with hemophilia, the pooled ICH incidence was 2.3 per 1000 person-years (95% CI 1.2-4.8), equivalent to 0.23 per 100 person-years [35]. ICH was spontaneous in 35 to 58 percent. Mortality was 0.8 per 1000 person-years (95% CI 0.5-1.2).

  The pooled incidence according to age group was as follows:

  - Neonates – ICH: 2.1 percent (95% CI 1.5-2.8); mortality 0.2 percent (95% CI 0.0-1.2)
  - Children and young adults – ICH: 7.4 per 1000 person-years (95% CI 4.9-11.1); mortality 0.5 (95% CI 0.3-0.9)

- A 2016 cohort study of 547 babies with hemophilia reported an annual ICH prevalence of approximately 4 percent per year [10]. In this cohort, 46 episodes of ICH occurred in the first two years of life, and of these, 18 (39 percent) were spontaneous, occurring in

approximately 3 percent of patients overall; 14 (30 percent) were associated with delivery, occurring in 2.5 percent overall; and 11 (24 percent) were traumatic, occurring in 2 percent overall; the remainder were of unknown cause.

Risk factors for ICH include trauma (especially related to delivery with trauma or requiring instrumentation), severe factor deficiency (activity <1 percent), presence of an inhibitor, age over 50 years, hypertension, and in some cases human immunodeficiency virus (HIV) infection; prophylaxis is associated with reduction of ICH risk [33,36].

The incidence of ICH has declined since the 1960s, likely due to earlier diagnosis and greater use of prophylactic factor administration [34,37]. The mortality rate for ICH has also declined to approximately 20 percent, compared with reports from the 1960s in which ICH carried a mortality rate of 70 percent [31].

Risk factors for ICH during birth include lack of awareness of the hemophilia diagnosis, severity of factor deficiency, nulliparity, prolonged second stage of labor, and use of forceps or vacuum devices for assisted delivery. ICH related to delivery can present at the time of birth or up to one month later.

- **Spontaneous** – Spontaneous ICH occurs in infants as well as adults. Importantly, many neonates with spontaneous ICH do not have a known family history of hemophilia.

  Risk factors for spontaneous ICH include disease severity and the presence of an inhibitor [31]. In adults, additional risk factors such as hypertension may play a role. Presenting symptoms include headache, vomiting, and lethargy; however, some ICH are silent and only detected by imaging [32]. (See "Spontaneous intracerebral hemorrhage: Pathogenesis, clinical features, and diagnosis".)

- **Post-traumatic** – ICH can occur immediately after trauma or as a delayed complication days to weeks later. Importantly, delayed ICH can occur up to three to four weeks **after** trauma, and also up to one month following birth. Thus, patients should receive immediate factor replacement for all head and neck injuries except those that are clearly insignificant. Patients who are not hospitalized (and their family members/caregivers) should be instructed regarding potential neurologic signs and symptoms that may occur and have a clear plan for early intervention. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Serious, life-threatening bleeding and head trauma'.)

The specific sites of ICH were evaluated in a cohort of 3269 males with hemophilia followed over a five-year period [36]. There were 88 episodes of ICH (2.7 percent); of these, approximately one-third were intracerebral, one-third subdural, and the remainder subarachnoid, epidural, or

unspecified. ICH usually presents with headache, vomiting, and lethargy; seizures are also common. However, some episodes are clinically silent and detected incidentally on brain imaging [32].

Persistent neurologic sequelae of ICH are common. In a multicenter review that included 29 children with ICH, psychomotor impairment and cerebral palsy were reported in 17 and 13 (59 and 45 percent), respectively [18]. Only one-fourth had no neurologic sequelae; older children had better neurologic outcomes than neonates. All children who have experienced an ICH should have neuropsychiatric testing to detect subtle sequelae. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Serious, life-threatening bleeding and head trauma'.)

In cases of suspected ICH, neuroimaging is appropriate; however, infusion of factor should occur immediately if ICH is suspected and should not be delayed while awaiting neuroimaging. Infusion of factor in ICH is discussed separately. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Acute therapy for bleeding'.)

**Joints and muscle** — Hemarthrosis (hemorrhage into a joint) is the most common site for bleeding in ambulatory patients, representing up to 80 percent of hemorrhages [38,39]. Spontaneous hemarthroses are characteristic of severe disease.

Bleeding into the joint space originates from the synovial vessels. Bleeding episodes often affect a variety of joints but are most common in the index joints (elbows, ankles, and knees). One joint is usually affected at a time, but multiple bleeding sites are not uncommon. The ankles are most commonly affected in children, and the knees, elbows, and ankles in adolescents and adults [38].

Hemarthrosis is painful and can be physically debilitating, as distension of the synovial space and associated muscle spasm lead to markedly increased intrasynovial pressure. The clinical presentation varies by age:

- In infants, early signs of bleeding include irritability and decreased use of the affected limb.
- In older children and adults, hemarthrosis is manifested by prodromal stiffness and, in some patients, by a characteristic warm sensation, which is followed by acute pain and swelling.

The diagnosis of hemarthrosis is made clinically, based on pain, reduced mobility, and/or findings on physical examination. Imaging may be done in complicated cases where a target

joint has developed and it is more challenging to determine whether pain and swelling are related to recent/acute bleeding, or possibly related to joint damage from prior bleeding events (known as 'hemophilic arthropathy'). (See 'Hemophilic arthropathy' below.)

Joint aspiration is generally not done in individuals with hemophilia, although some advocate joint aspiration in complicated cases or with initial joint bleeding. (See "Acute treatment of bleeding and surgery in hemophilia A and B".)

Point-of-care musculoskeletal ultrasound (POC-MSKUS) is a useful emerging modality for identifying hemorrhage as well as viewing soft tissue and bony changes over time; it is noninvasive, does not require sedation, and is less time-consuming and relatively less expensive than other modalities such as magnetic resonance imaging [40,41]. The use of this imaging technique largely depends on local expertise [42-45].

Once joint damage and inflammation occur, a joint can develop increased susceptibility to further bleeding and become a target joint. Chronic synovitis and permanent disability may develop. (See 'Hemophilic arthropathy' below.)

Prevention, early diagnosis, and prompt treatment of hemarthroses may preserve the joints or delay progression of hemophilic arthropathy [11,13]. However, even if early prophylaxis is used, some individuals may develop joint disease that may not have been associated with a recognizable bleeding event [46]. These management issues are discussed in detail separately. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Hemarthroses' and "Hemophilia A and B: Routine management including prophylaxis", section on 'Prophylaxis versus on-demand therapy' and "Chronic complications and age-related comorbidities in people with hemophilia", section on 'Arthropathy'.)

Bleeding into muscles with hematoma formation is common. Most often this affects large muscle groups such as muscles in the leg (quadriceps), hip (iliopsoas), and arm. Muscle bleeding may be extensive and may compromise neurovascular structures and produce a compartment syndrome (increased pressures in a muscle compartment), especially in the lower leg and forearm [47].

Untreated or inadequately treated hemorrhage may lead to the formation of a pseudotumor with hematoma surrounded by a fibrous membrane. Pseudotumors can occur with bleeding of any severity, may increase bleeding risk, and may make bleeding more challenging to treat. MRI may be useful for diagnosis and therapeutic decision making [48]. Recurrent hemorrhage is common.

**Epistaxis, oral, gastrointestinal bleeding** — Bleeding can occur from numerous oropharyngeal sites such as the nose, oral mucosa, gingiva, and frenulum; sometimes this type of bleeding follows minor trauma or dental procedures. In addition, coughing or vomiting can produce bleeding into the posterior pharynx or floor of the mouth; bleeding can dissect into the neck, which can lead to airway compromise or airway obstruction [49].

A variety of lesions in the gastrointestinal tract, such as esophagitis, gastritis, polyps, diverticuli, and swallowed blood from epistaxis, can present with blood in the stool or hematemesis. In addition, bleeding into the abdominal wall can produce severe pain that often is misdiagnosed as an acute abdomen [50]. Computed tomography (CT) may be required to distinguish an intraabdominal hematoma from other conditions.

Hematomas of the bowel wall can also occur, producing symptoms that mimic acute appendicitis or produce obstruction or intussusception. The diagnosis of "pseudo-appendicitis" usually can be made with CT scan, but occasionally surgery is required to confirm the diagnosis [51]. Bleeding into the retroperitoneal space can also occur.

**Genitourinary tract** — Hematuria is a frequent manifestation of severe hemophilia; usually, it is benign and not associated with progressive loss of renal function [52,53]. The bleeding can arise from the kidneys or bladder and may persist for days or weeks. Ureteral obstruction with colic may occur when clots form within the ureter.

Other etiologies should be excluded if a particular episode is associated with pain or fever, if bleeding is not responsive to therapeutic intervention, or if recurrent episodes are frequent.

**Bleeding in females/carriers** — Female carriers of hemophilia are heterozygous for the relevant gene variant (they have one unaffected allele and one allele with the variant in the gene that encodes the relevant factor). Thus, overall, they are expected to have approximately 50 percent of normal factor activity, which is generally sufficient to prevent clinical bleeding.

However, some hemophilia carriers have symptoms similar to affected males with mild hemophilia [54-58]. The range of factor levels in carriers was illustrated by a survey of 274 hemophilia A or B carriers [59]. Factor levels ranged from 0.05 to 2.19 international units (IU)/mL (median: 0.60 IU/mL), compared with levels between 0.45 and 3.28 IU/mL (median: 1.02 IU/mL) in non-carrier controls [59]. Twenty-eight percent of carriers met the definition for mild hemophilia (factor level below 0.40 IU/mL, corresponding to <40 percent of normal activity). Bleeding was more prevalent in carriers than non-carriers, and factor levels from 0.05 to 0.60 IU (5 to 60 percent of normal activity) were more likely to be associated with bleeding than factor levels >0.60 IU.

Causes of severe hemophilia in females include the following:

- Inheritance of disease-causing variants from both parents (an affected male and a female carrier)
- Extreme degrees of X chromosome inactivation (lyonization)
- Loss of part or all of the X chromosome that contains the normal factor VIII or IX allele (as in Turner syndrome) [55]

Based on these observations, we measure factor activity levels in all hemophilia carriers, so that the risk of bleeding can be appropriately assessed and managed during hemostatic challenges such as surgery, regardless of whether they are clinically symptomatic. It is especially important to have an appropriate baseline factor level because factor VIII increases with stress and pregnancy; factor IX is lower in infancy. Often it is useful to obtain more than one measurement to confirm that the baseline value is accurate and to use this baseline when making treatment decisions.

We manage female hemophilia carriers with mild bleeding symptoms and/or reduced factor activity levels similarly to males with mild hemophilia. (See "Acute treatment of bleeding and surgery in hemophilia A and B".)

**Laboratory findings** — Hemophilia is characterized by a prolonged activated partial thromboplastin time (aPTT). However, the aPTT may be normal in individuals with milder factor deficiencies (eg, factor activity level >15 percent), especially in hemophilia B (factor IX deficiency), where even individuals with moderate and mild disease may have a normal aPTT. In some individuals with hemophilia A, factor VIII levels may increase with stress, leading to a normalization of the aPTT or mis-categorization of factor levels and disease severity.

In patients with hemophilia, the aPTT corrects in mixing studies, unless an inhibitor is present, which only applies to individuals who have received factor infusions or who have an autoantibody such as a lupus anticoagulant or an acquired factor inhibitor. Mixing studies that do not show correction of a prolonged aPTT suggest an alternative diagnosis such as an acquired factor inhibitor. (See 'Differential diagnosis' below.)

The platelet count and prothrombin time (PT) are normal in hemophilia. Thrombocytopenia and/or prolonged PT suggest another diagnosis instead of (or in addition to) hemophilia.

Measurement of the factor activity level (factor VIII in hemophilia A; factor IX in hemophilia B) shows a reduced level compared with controls (generally <40 percent). One exception is an individual with mild hemophilia A who undergoes testing when stressed, affected by an inflammatory condition, or pregnant and has a falsely elevated factor level. If this is suspected,

factor activity testing should be repeated under conditions of low stress and/or after the inflammatory condition has resolved.

The plasma von Willebrand factor antigen (VWF:Ag) is normal in hemophilia. If VWF:Ag is reduced, this suggests the possibility of von Willebrand disease (VWD) rather than (or in addition to) hemophilia. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Laboratory testing'.)

Urinalysis is not done routinely, but if performed it may sometimes (but not always) show microscopic or macroscopic hematuria.

## LATE COMPLICATIONS

Important late complications of bleeding events include neurologic sequelae of intracranial hemorrhage and sequelae from repetitive hemarthrosis, including joint destruction, muscular atrophy and contraction, nerve damage from compartment syndrome, and bone mineral density loss with increased risk of fracture. (See 'Hemophilic arthropathy' below.)

Rarely, a pseudotumor may develop.

Complications from factor infusion include infections transmitted from plasma-derived factor products (typically viral) and development of antibodies to factor (termed inhibitors); inhibitors typically develop following factor infusions in patients with severe disease but can also occur in moderate and mild disease, especially in hemophilia A. (See 'Infection from plasma-derived products' below and 'Development of inhibitors' below.)

**Hemophilic arthropathy** — Hemophilic arthropathy (also called hemophilic arthritis) refers to persistent joint disease caused by hemarthrosis in a joint; this complication occurs in up to one-half of patients with severe hemophilia and over one-half of patients who have hemarthroses [39,60]. Sequelae can include [41]:

- Muscular atrophy and contraction
- Nerve damage and loss of function from compartment syndrome
- Loss of bone mineral density with increased risk of fracture
- Chronic pain and diminished quality of life
- Need for joint replacement

In a study that compared the frequency of joint bleeding in several cohorts of men with severe hemophilia from the 1950s through the 1990s, the proportion with frequent joint bleeds declined gradually over time, but even in the 1990s, one-half had two or fewer joint bleeds in

the prior six months, and one third had five or more joint bleeds in the prior six months [61]. Joints affected by frequent hemarthrosis are most likely to progress to arthropathy, especially the knee, ankle, and elbow.

Arthropathy typically develops over time with recurrent hemarthroses, with more advanced arthropathy generally developing in late adolescence [62]. By adulthood, arthropathy may represent a major cause of morbidity and interfere with numerous activities and quality of life.

The mechanism of hemophilic arthropathy is multifactorial and includes chronic or episodic synovitis, with loss of cartilage, subchondral cyst formation, bone cysts, erosion, and joint space narrowing [62,63]. Deposition of iron may contribute to synovial inflammation, and dense fibrosis of the joint can lead to contractures, pain, and limitation of motion [39,62,64,65].

Prevention and management are discussed separately. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Hemarthroses' and "Hemophilia A and B: Routine management including prophylaxis", section on 'Prophylaxis versus on-demand therapy' and "Chronic complications and age-related comorbidities in people with hemophilia", section on 'Arthropathy'.)

**Infection from plasma-derived products** — Available clotting factor products derived from human plasma undergo several procedures to reduce the risk of transmission of infectious organisms, including thorough predonation screening, plasma testing, viral reduction and inactivation processes, and other treatments directed at eliminating human immunodeficiency virus (HIV) and hepatitis B and C viruses (HBC and HCV). (See "Blood donor screening: Laboratory testing" and "Pathogen inactivation of blood products".)

These procedures, as well as the use of recombinant factor products that are produced in cell culture, have led to a generation of products that have an extremely low risk of viral transmission. No documented HIV transmissions from factor concentrates have been reported since the implementation of improved viral inactivation procedures for plasma derivatives in the mid-1980s. These procedures kill HIV, even if it is present in high concentrations [66].

However, patients treated with factor concentrates produced in the late 1970s and early 1980s were at high risk for infection with HIV, HCV, and other hepatitis viruses (eg, A, B, D [delta]) [67-72]. Patients treated with blood products and concentrates before this time were at higher risk of hepatitis viruses as well. One study reported that the prevalence of antibodies to HCV was 83 percent in patients infused for the first time before 1985 compared with 6 percent in patients infused for the first time between 1985 and 1991 [73]. The incidence of HIV infection peaked in 1982, at 22 infections per 100 person-years at risk [70]. HIV infection occurred in approximately

one-half of patients overall, and HCV infection occurred in most patients; thus, many were co-infected with both HCV and HIV [68-70,74].

Coinfection with HCV and HIV is clinically significant, as it may result in accelerated development of liver disease that may not respond well to treatment [75]. Increased risk for hepatocellular carcinoma is also a concern [74]. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection" and "Epidemiology and risk factors for hepatocellular carcinoma".)

Other potential infectious risks from plasma-derived products include the following:

- Parvovirus B19 is a non-lipid envelope virus that causes fifth disease, arthropathy, and transient aplastic crisis. Parvovirus is not eliminated by some methods of viral inactivation of plasma products [76]. Parvovirus has also been transmitted in factor concentrates despite solvent-detergent treatment, since these treatments target the viral lipid envelope, which parvovirus lacks [77,78]. (See "Clinical manifestations and diagnosis of parvovirus B19 infection" and "Pathogen inactivation of blood products".)

- Viral inactivation procedures do not fully eliminate hepatitis A virus; however, all individuals with hemophilia should be vaccinated against hepatitis A and thus should have a fair degree of protection. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Immunizations' and "Pathogen inactivation of blood products", section on 'Technologies'.)

- Some infectious agents, such as prion diseases, lack a screening test or methods for removal or inactivation. Examples include the agents responsible for Creutzfeldt-Jakob disease (CJD) and new variant CJD (vCJD). While there is some concern regarding these agents, there have been only rare case reports in the United Kingdom of vCJD from blood transfusions; transmission from factor concentrates has not been reported. (See "Creutzfeldt-Jakob disease" and "Variant Creutzfeldt-Jakob disease".)

**Development of inhibitors** — An important complication in patients with severe hemophilia is the development of alloantibodies (inhibitors) that block the activity of the relevant factor. Inhibitors can also develop in individuals with moderate and mild hemophilia, especially with certain hemophilia A genotypes. (See 'Definitions' above.)

These inhibitory antibodies develop in response to exogenous factor; they occur in approximately 30 percent of patients with severe hemophilia A and 5 to 15 percent with severe hemophilia B [79,80]. Inhibitors are much less common in patients with mild or moderate disease, presumably because the infused factor is not as likely to be recognized as a foreign protein in these individuals. Inhibitors complicate bleeding episodes because they decrease

responsiveness to factor infusions; in addition, anaphylactoid reactions can occur with factor IX inhibitors.

In addition to the increased risk for bleeding, inhibitors may be associated with other complications. As an example, maturational delays were reported in a study of 333 children and adolescents with hemophilia who were followed at six-month intervals for seven years; all were HIV-negative [81]. When compared with those without inhibitors, patients with inhibitors had delayed bone age and Tanner stage transition, lower maximum growth velocity, and lower serum testosterone levels.

The evaluation and management of inhibitors, and additional data on prevalence, risk factors, and mechanisms, are discussed in detail separately. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication" and "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Inhibitors'.)

**Cardiovascular disease** — An emerging issue is the prevalence of cardiovascular disease (CVD) in individuals with hemophilia. This is discussed separately. (See "Acute treatment of bleeding and surgery in hemophilia A and B".)

## DIAGNOSTIC EVALUATION

Hemophilia may be suspected in any individual with bleeding. Severe hemophilia is more common in males because the factor VIII and IX genes are on the X chromosome (hemophilia A and B are both X-linked). While a positive family history is supportive, a negative family history cannot be used as evidence against the diagnosis, since many cases are sporadic. (See 'Epidemiology' above.)

The diagnostic evaluation in cases of suspected hemophilia typically begins with a thorough review of the patient's personal bleeding history and family history. Screening tests are then performed and the diagnosis is confirmed with a specific clotting factor activity measurement(s) and/or genetic testing.

### Patient and family history

- **Symptoms** – Prior bleeding symptoms should be assessed in patients even if asymptomatic at the time of the evaluation, to evaluate the severity of bleeding. For infants and children, this includes the method of delivery, the length of the second stage of labor, the use of forceps or vacuum extraction, and any bleeding with delivery and/or umbilical cord separation. Bruising and/or bleeding with procedures (eg, immunizations,

circumcision), and minor trauma, as well as spontaneous bleeding are also important to ascertain.

Adults should be asked about all potential hemostatic challenges including menstrual cycles, dental extractions, trauma, and surgical interventions.

Bleeding Assessment Tools (BATs) such as the International Society of Thrombosis and Haemostasis (ISTH) BAT are helpful to guide systematic inquiry regarding bleeding symptoms and provide a framework for discussing specific anatomic locations of bleeding (eg, epistaxis, cutaneous) and quantification of bleeding based on severity of symptoms and/or intervention required with bleeding episodes. (See "Approach to the adult with a suspected bleeding disorder", section on 'Bleeding score'.)

However, the BAT score cannot be used to exclude a diagnosis of hemophilia, especially in individuals with a positive family history and/or those who are younger and have not experienced bleeding challenges.

- **Family history** – Patients should have a thorough family history that includes bleeding and prior evaluations of family members for hemophilia and other bleeding disorders. It is worthwhile to verify that the correct testing was performed, as occasional testing errors due to the transposition or misreading of Roman numerals have occurred (eg, testing factor VII rather than factor VIII; testing factor XI rather than factor IX) [82]. It is important to review the pedigree and identify individuals who may have mild disease and have not yet been tested.

  Hemophilia A and B are both transmitted in an X-linked recessive pattern ( figure 1). Transmission is from female carriers to male children; approximately one-half of male children of a female carrier will be affected. Female children of affected males are obligate carriers and should be evaluated with testing of factor activity level of the relevant factor (VIII or IX). Father to son transmission does not occur. (See "Inheritance patterns of monogenic disorders (Mendelian and non-Mendelian)", section on 'Sex-linked patterns'.)

  Males within a family who inherit the familial mutation will all have approximately the same degree of factor deficiency and similar severity of disease because they share the same genetic variant.

As noted above, a large proportion of affected individuals have a negative family history, and a negative family history cannot be used to exclude the possibility of hemophilia. A negative family history is typically explained by a de novo hemophilia mutation in the mother [83,84]. Less commonly, the family history may be negative due to neonatal deaths or the passage of

the trait through a succession of female carriers (a pedigree that lacks evaluable males); or the family history may be unknown due to lack of available medical information (eg, adopted child, poor communication). In some cases, the family history may be negative when the disease is mild and prior bleeding events were not identified or investigated. (See "Genetics of hemophilia A and B".)

**Laboratory testing** — Laboratory testing is similar for the majority of patients with hemophilia. Initial testing includes screening tests of hemostasis, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count (see 'Screening tests' below). Mixing studies for the aPTT assay are performed if the aPTT is prolonged. If mixing studies show correction, consistent with a factor deficiency rather than an inhibitor, factor activity levels are then measured (see 'Factor activity levels' below). An exception is diagnosis in a male neonate with a positive family history or a known-carrier mother. For these males, factor levels are often measured directly on cord blood. (See 'Neonatal diagnosis' below.)

In patients with factor VIII deficiency, it is important to exclude von Willebrand disease (VWD) by von Willebrand factor (VWF) antigen testing (VWF:Ag); this testing is discussed separately. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'VWD screening tests'.)

In addition, genetic testing is often performed to identify a familial variant if it has not been identified or to confirm the presence of a known familial gene mutation. (See 'Genetic testing' below.)

In contrast to patients with suspected hemophilia, suspected female carriers should have genetic testing considered as first-line evaluation, with measurement of factor levels in identified carriers. However, if a potential female carrier has not undergone genetic confirmation and requires an invasive procedure, factor activity level should be measured prior to the procedure so that appropriate planning and management can be assured. (See 'Carrier detection' below.)

**Screening tests** — Screening tests of hemostasis, including the PT, aPTT, thrombin time (TT), and platelet count, are appropriate for all patients with suspected hemophilia. In hemophilia the PT and platelet count are normal and the aPTT is prolonged in moderate and severe disease ( table 1). Patients with mild hemophilia may have a normal aPTT because the aPTT can be normal with factor levels above 15 percent, depending on the sensitivity of the aPTT assay used. Other conditions that can normalize the aPTT in individuals with hemophilia are discussed above. (See 'Laboratory findings' above.)

Thus, while a prolonged aPTT is consistent with hemophilia, a normal aPTT does not exclude the possibility of mild hemophilia, especially hemophilia B (factor IX deficiency). Thus, specific factor analysis is performed regardless of the aPTT result.

If the aPTT is prolonged, mixing studies are done to determine whether the patient has a factor deficiency or an inhibitor. This approach is discussed in more detail separately. (See "Approach to the child with bleeding symptoms" and "Approach to the adult with a suspected bleeding disorder" and "Clinical use of coagulation tests".)

Individuals with an isolated prolonged aPTT that corrects in mixing studies, and those with normal PT, aPTT, TT, and platelet count who have a clinical history compatible with hemophilia or a known family history of hemophilia, should have factor activity levels measured. (See 'Factor activity levels' below.)

**Factor activity levels** — Factor activity levels (also called factor levels) should be measured in the following settings:

- Male patients **with** a known family history of hemophilia.
    - In patients with a prolonged aPTT, factor levels are important for management because they help in predicting bleeding risk and the likelihood of inhibitor development.
    - If the family history is known to be accurate, affected males have severe disease, and the patient's aPTT is normal, hemophilia is extremely unlikely. We test the factor activity level to confirm this.
- Patients **without** a known familial variant who are suspected to have hemophilia based on clinical history and/or a prolonged aPTT that corrects in mixing studies.
- Females identified as carriers by genetic testing, or females who potentially may be carriers for whom genetic testing is not available.

Factor activity levels are measured for the relevant factor (factor VIII, IX, or XI) if the familial variant is known, and for all of these factors in new cases.

Factor activity level is generally measured in an aPTT-based assay (a functional assay) [6]. Normal ranges for activity are determined from reference plasma. The normal range is generally considered to be from approximately 55 percent to 150 percent of the normal value; this range may also depend on the laboratory performing the testing and the age of the patient. A factor activity level of 100 percent corresponds to 1 IU/mL. Chromogenic assays, in

which the readout is based on release of a colored product, are increasingly being used; these assays have less variability and measure the activity of the specific factor rather than the entire coagulation cascade.

Some assays are performed as automated, one-stage assays that compare coagulation time of patient plasma to reference plasmas (normal and factor-deficient), using serial dilution to determine the factor activity level. Less commonly, a two-stage aPTT-based assay is used. In the first step of a two-stage assay, patient plasma is depleted of some factors (II, VII, IX, and X), and then factors are added that allow coagulation to progress to the formation of factor Xa but not further ( figure 2). In the second step, normal plasma is added to allow coagulation to progress to clot formation. The coagulation time can be measured by release of a chromogenic end product or by optical density [85]. Two-stage methods are more difficult to perform but are less subject to other variables (eg, variation in the levels of other coagulation factors, presence of a lupus anticoagulant) [86,87]. Two-stage and chromogenic assays are more sensitive for identifying mild hemophilia. Highly specific assays using immunoradiometric methods and enzyme-linked immunoabsorbent techniques (ELISA) also have been developed [88].

Two-stage and chromogenic assays are especially useful for patients with borderline values. Several reports have described hemophilia mutations for which a two-stage assay demonstrated lower factor activity than a one-stage assay; a hemophilia diagnosis may have been missed if only the one-stage method had been used [86,87,89,90].

Some forms of von Willebrand disease (VWD; type 2N or 3) have decreased factor VIII activity levels because von Willebrand factor (VWF) stabilizes circulating factor VIII. All patients with reduced factor VIII activity levels should have testing for VWF antigen (VWF:Ag) to eliminate the possibility of type 3 VWD. To evaluate for Type 2N VWD, a factor VIII/von Willebrand factor binding assay can be performed. (See 'Differential diagnosis' below and "Clinical presentation and diagnosis of von Willebrand disease", section on 'VWD screening tests'.)

Conditions that can interfere with factor activity testing include the following:

- Factor VIII is an acute phase reactant. Thus, a patient with mild hemophilia and an intercurrent illness or stress may have a transient elevation of the factor VIII level. If mild hemophilia is suspected, the factor VIII level can be repeated after the intercurrent illness/stress resolves or to verify the level obtained [82].

- Healthy newborns have lower levels of factor IX because synthesis of vitamin K-dependent factors (eg, II, VII, IX, X) requires the gamma carboxylase system, which does not fully mature until later in infancy [6].

- A lupus anticoagulant can interfere with coagulation in vitro, as measured by optical density. This can be addressed using serial dilution and/or colorimetric substrates, which measure enzymatic activity of coagulation factors rather than formation of a clot. The dilute Russell's viper venom time (dRVVT) is also useful in the setting of a lupus anticoagulant causing a baseline prolonged aPTT. (See "Clinical use of coagulation tests", section on 'dRVVT'.)

- Factor inhibitors may cause depletion of a specific factor; distinction of an acquired inhibitor from an inherited deficiency due to factor mutation is done with an inhibitor assay. This typically applies to adults in an appropriate clinical setting such as malignancy, rheumatologic disease, or postpartum. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)", section on 'Evaluation'.)

**Genetic testing** — Genetic testing (also called molecular testing) is appropriate in most patients. This information helps predict the risk of inhibitor formation in the patient and facilitates carrier identification in female family members [91-93]. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication" and 'Carrier detection' below.)

Genetic testing was also offered for a period of time at no cost to individuals in the United States with hemophilia and to potential carrier females through participating Hemophilia Treatment Centers by the My Life, Our Future initiative [94,95]. Laboratories that provide genetic testing are listed on the Genetic Testing Registry website [96].

The specific genetic test(s) performed (eg, testing for specific mutations or inversions, versus whole gene sequencing) differs according to the individual laboratory and takes into account the severity of hemophilia and the gene affected (*F8* or *F9*).

- Hemophilia A families with mild to moderate disease are more likely to have a point mutation in the *F8* gene (approximately 90 percent of the time); thus, if genetic testing is indicated, we perform gene sequencing in families with mild to moderate disease [97].

- Hemophilia A families with severe disease have an inversion in intron 22 approximately 40 to 50 percent of the time and an intron 1 mutation 2 to 5 percent of the time [92,98-102]. Thus, if genetic testing is indicated we perform gene analysis for intron 22 and intron 1 inversion first, followed by DNA sequencing if intron 22 and 1 analysis is uninformative. Some labs will reflexively test for DNA mutations, deletions, and duplications if the initial testing for inversions is uninformative. If the causative familial *F8* variant is known, targeted testing of potentially affected family members is often performed instead of whole gene sequencing.

- Hemophilia B families have a variety of *F9* gene mutations. If genetic testing is indicated, we perform *F9* gene sequencing. If the causative familial *F9* variant is known, targeted testing of potentially affected relatives is often performed instead of whole gene sequencing.

**Carrier detection** — The preferred method for carrier detection is genetic testing for a hemophilia mutation that has been identified in an affected family member [91-93]. In some cases, this is not needed, if a mutation is identified that is known to be deleterious. (See 'Genetic testing' above.)

All potential hemophilia carriers should have genetic testing because confirming or excluding carrier status is important for managing the carrier herself, counseling for delivery, and determining whether her children need to be tested.

- Hemophilia A and B are X-linked. A son or daughter of a mother who is a carrier has an approximately 50 percent chance of being a carrier. Daughters of a father with hemophilia will be carriers of the familial *F8* or *F9* variant and are referred to as obligate carriers. Sons of fathers with hemophilia A or B cannot be carriers because the *F8* and *F9* genes are located on the X chromosome.

- Hemophilia C (factor XI deficiency) is autosomal. Both sons and daughters of mothers and/or fathers with hemophilia C are carriers. (See "Factor XI (eleven) deficiency".)

Compared with genetic testing, measurement of factor activity levels is significantly less accurate for determination of carrier status because factor levels vary and normal ranges are wide, resulting in significant overlap between hemophilia carriers and the unaffected population [29,103]. A finding of factor levels approximately 50 percent of normal or lower is strongly suggestive of carrier status, but levels in the normal range do not exclude carrier status and genetic testing is still required.

In contrast to the avoidance of factor levels as a means of carrier detection, measurement of factor activity levels in known carriers is extremely useful for management, by allowing individuals with low factor levels to be managed more intensively during hemostatic challenges such as surgery, trauma, or at the time of delivery. (See "Acute treatment of bleeding and surgery in hemophilia A and B".)

**Diagnosis**

- **Hemophilia A** – The diagnosis of hemophilia A (inherited factor VIII [F8] deficiency) requires confirmation of a factor VIII activity level below 40 percent of normal (below 0.40

international units [IU]/mL), or, in some circumstances where the factor VIII activity level is ≥40 percent, a pathogenic variant in the *F8* gene. A normal VWF antigen (VWF:Ag) should also be documented to eliminate of the possibility of some forms of VWD.

- **Hemophilia B** – The diagnosis of hemophilia B (inherited factor IX [F9] deficiency) requires confirmation of a factor IX activity level below 40 percent of normal, or, in some circumstances where the factor IX activity level is ≥40 percent, a pathogenic variant in the *F9* gene. Newborns have a lower normal range of factor IX activity; the normal newborn range should be used as a reference when evaluating factor levels in newborns. It may be challenging to discern mild factor IX deficiency from the lower end of the normal range in a newborn, so caution should be used and testing repeated later in infancy.

- **Hemophilia carrier** – The diagnosis of hemophilia carrier status requires identification of a causative variant in the relevant clotting factor gene (*F8* or *F9*). Factor levels are important for managing carriers but are not optimal for determining or eliminating the diagnosis of a hemophilia carrier. (See 'Carrier detection' above.)

## OBSTETRIC CONSIDERATIONS

**Reproductive counseling and testing** — Known carriers of hemophilia and potential carriers who do not know their status should have the opportunity to receive genetic counseling, optimally from a genetic counselor with specific expertise in this area or from a hematologist with expertise in hemophilia care. This includes the risk of having an affected fetus, timing of diagnosis (prenatal versus at birth), and potential issues with delivery (such as potential risks from vaginal delivery if the child has hemophilia). Female carriers of hemophilia do not appear to have an increased risk of miscarriage. (See "The preconception office visit" and "Genetic testing".)

If carrier status is unknown, this should be determined so that appropriate information can be provided. (See 'Carrier detection' above.)

Hemophilia carriers can have a range of factor activity levels (see 'Bleeding in females/carriers' above). Thus, if factor activity level was not determined previously, this should be done at least once during the pregnancy, and repeated if low (eg, <40 percent). Factor VIII levels usually increase during pregnancy; whereas levels of factor IX typically remain fairly consistent. Factor VIII activity levels should be reassessed during the pregnancy, especially in the third trimester to aid in delivery planning, in women with low levels on previous measurements to determine

the need for treatment [104]. (See "Maternal adaptations to pregnancy: Hematologic changes", section on 'Coagulation and fibrinolysis'.)

Individuals with a low factor activity level may be at increased risk for bleeding with procedures during pregnancy and/or delivery, including neuraxial anesthesia. Plans should be made to manage the pregnancy and delivery in a setting in which there is access to diagnostic testing (eg, factor activity levels), replacement factor, and expertise in hemophilia management. (See 'Method of delivery and anesthesia' below.)

**Prenatal evaluation** — Pregnant hemophilia carriers should undergo evaluation of fetal sex using a non-invasive method, such as ultrasound, as male children are potentially affected. Methods such as detection of Y chromosome sequences from maternal blood may also be available. (See "Prenatal screening for common aneuploidies using cell-free DNA".)

Hemophilia A and B are X-linked recessive disorders; approximately one-half of male children of carrier females will inherit the hemophilic variant ( figure 1). Thus, pregnancy with a male child is generally managed as if the child had hemophilia (eg, avoidance of invasive fetal procedures and forceps/vacuum assisted delivery), unless hemophilia has been excluded. Early involvement of a hemophilia treatment center or a clinician with expertise in the management of obstetric considerations in hemophilia is advised. (See 'Method of delivery and anesthesia' below.)

For most patients, prenatal diagnosis of an affected fetus does not alter pregnancy management or method of delivery. Invasive diagnostic testing, such as amniocentesis or chorionic villus sampling, is often not chosen; and commonly, diagnosis of the infant is deferred until delivery or testing for fetal cells in maternal blood is used in order to avoid risks of these procedures. In rare cases, prenatal testing may be recommended when an invasive fetal procedure is required/planned and management would change if hemophilia were diagnosed or excluded. (See "Prenatal screening for common aneuploidies using cell-free DNA".)

**Method of delivery and anesthesia** — Management of delivery involves multidisciplinary planning. Maternal issues include the risks of bleeding with vaginal delivery versus planned cesarean delivery, and the safety of neuraxial anesthesia. Fetal issues include the lack of a definitive diagnosis at the time of delivery in most cases, and the potential risks of bleeding during or after delivery, especially intracranial bleeding and cephalohematoma.

The optimal method of delivery (vaginal versus cesarean) remains a subject of debate, although the majority of neonates with hemophilia can be delivered safely with either method. There are no data from randomized trials to allow comparison of risks.

- Proponents of scheduled cesarean delivery cite the potential increased risks of intracerebral hemorrhage associated with a trial of labor, especially in the setting of labor abnormalities. In addition, a delivery that occurs when there is no immediate access to factor replacement and the expertise to administer it may lead to potentially serious complications [105].

- Proponents of vaginal delivery note the low overall risk of bleeding with vaginal delivery in a neonate with severe hemophilia (in the range of 2 to 4 percent), especially with appropriate planning and conversion to cesarean delivery if labor does not progress normally; and the potential benefits of vaginal delivery [106]. (See "Cesarean birth on patient request", section on 'Potential disadvantages and risks of planned cesarean birth'.)

There is agreement that operative vaginal delivery (eg, use of forceps, vacuum extraction) should be avoided due to the increased risk of cephalohematoma and intracerebral bleeding from these interventions. Use of scalp electrodes for fetal heart rate monitoring should be used only if adequate information cannot be obtained from an external monitor.

Data from several large observational studies have illustrated the risks of intracerebral or intracranial hemorrhage in neonates with hemophilia.

A very large series of deliveries in the general population (583,340 deliveries of individuals without hemophilia) compared various risks with different delivery methods [107]. The risk of subdural or cerebral hemorrhage with spontaneous vaginal delivery, vacuum, or forceps delivery was 2.9, 8.0, or 9.8 per 10,000, respectively. With vacuum plus forceps, the risk was 21.3 per 10,000. This compared with a risk of 4.1 per 10,000 who underwent planned cesarean delivery; rates with cesarean delivery following attempted labor were higher.

Data specific to patients with hemophilia have confirmed a higher rate of intracranial hemorrhage with operative versus spontaneous vaginal delivery; most cases of intracranial hemorrhage were associated with instrumentation [108]. In the Centers for Disease Control (CDC) data collection project series of 580 male infants with hemophilia, intracranial hemorrhage occurred in 16 of 385 vaginal deliveries (4 percent), all of which involved operative interventions (12 vacuum extraction and four forceps); versus 1 of 184 delivered by cesarean delivery (0.5 percent) [109].

For a female hemophilia carrier delivering a male child, the maternal and fetal risks of vaginal delivery versus planned cesarean delivery should be discussed, and the option of a planned cesarean delivery should be provided.

The need for factor replacement for the mother and use of neuraxial anesthesia should be addressed prior to delivery based on maternal factor levels.

Other considerations besides the methods of delivery and anesthesia and the need for fetal or maternal factor replacement include the following:

- Factor concentrates and expertise in their use should be available if needed for managing a potentially affected male child.
- Fetal scalp electrodes and venous sampling should be avoided if possible unless a diagnosis of hemophilia has been eliminated.
- Scheduled cesarean delivery should be used for a breech fetus at risk of hemophilia.
- In patients undergoing a trial of labor with a potentially affected fetus, there should be a low threshold for converting to cesarean delivery for second stage protraction or arrest of labor. (See "Labor: Overview of normal and abnormal progression", section on 'Overview of protraction and arrest disorders'.)
- Clinical signs of hemorrhage in the neonate should be addressed immediately. Appropriate interventions and diagnostic testing are determined according to the clinical setting (eg, intracranial imaging with magnetic resonance imaging for an affected neonate with suspected intracerebral bleeding). Factor is administered before imaging for clinically significant bleeding. (See "Acute treatment of bleeding and surgery in hemophilia A and B", section on 'Acute therapy for bleeding'.)
- Intramuscular vitamin K can be administered using a small needle with pressure following the injection.
- Heel stick for standard neonatal screening can be performed by experienced staff, with pressure held for longer than done with an unaffected neonate.
- Circumcision of male neonates should be deferred until a hemophilia diagnosis is confirmed or excluded. (See 'Neonatal diagnosis' below.)
- Some centers routinely obtain imaging for intracerebral hemorrhage (eg, ultrasound) prior to discharge from the hospital in neonates with moderate to severe hemophilia.
- Female neonates have a low risk of bleeding and are managed according to routine obstetric/neonatal practices. However, any clinical suspicion of bleeding in a female

neonate should be investigated promptly with appropriate imaging and measurement of factor levels.

- In hemophilia A, the mother's factor VIII level generally decreases after delivery; the risk of postpartum bleeding is more of a concern for a carrier with a low baseline factor VIII level. Thus, maternal factor levels should be monitored postpartum. Management is individualized based on the woman's baseline factor VIII level, her factor VIII level at the time of delivery, the delivery method, and clinical symptoms.

- Prophylactic factor replacement therapy is not administered to neonates in the absence of bleeding or an invasive procedure. Initiation of prophylactic factor administration to young children (ideally, before the first joint bleed) is discussed separately. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Prophylaxis versus on-demand therapy'.)

These recommendations are largely consistent with guidelines from the National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) in the United States and the United Kingdom Haemophilia Centre Doctors' Organization [108,109].

**Neonatal diagnosis** — At birth, diagnosis can be made using cord blood or a venous blood sample; arterial blood sampling should be avoided. Cord blood testing is preferred if possible to avoid the risk of bleeding with venipuncture [110]. Cord blood is tested for factor activity level of the appropriate factor. Values must be compared with age-appropriate normal ranges because healthy newborns have lower levels of factor IX than older children. Results of cord blood testing may not be accurate in newborns with mild hemophilia, and it is prudent in later infancy to retest those who appear to be unaffected when tested as a newborn.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hemophilia includes other inherited bleeding disorders and other causes of an isolated prolongation of the activated partial thromboplastin time (aPTT). Usually these conditions can be readily differentiated by measurement of the appropriate factor level.

- **von Willebrand disease** – Like hemophilia, von Willebrand disease (VWD) is an inherited bleeding disorder that may be associated with a normal or prolonged aPTT; some patients with VWD will also have reductions in factor VIII levels. Unlike hemophilia, VWD transmission is autosomal. Thus, VWD is equally common in male and female patients, and disease severity is similar in both sexes. Most types of VWD present with a different bleeding pattern from hemophilia (eg, mucosal bleeding seen in VWD; joint bleeding seen

in hemophilia) ( table 2). However, some types of VWD (eg, type 2N, type 3) have bleeding patterns similar to hemophilia. Details of diagnostic testing to differentiate VWD from hemophilia are presented separately. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Laboratory testing'.)

- **Inherited platelet disorders** – A variety of inherited platelet disorders can cause clinical bleeding symptoms. Like hemophilia, some of these may be associated with normal platelet counts. Unlike hemophilia, inherited platelet disorders should have normal coagulation testing, and most of these disorders are autosomal rather than X-linked. Inherited platelet disorders may be characterized by thrombocytopenia, abnormal platelet function, and/or abnormal platelet morphology ( table 3). (See "Causes of thrombocytopenia in children", section on 'Inherited platelet disorders' and "Inherited platelet function disorders (IPFDs)", section on 'Specific disorders'.)

- **Factor XI deficiency** – Factor XI deficiency (also called Rosenthal syndrome; hemophilia C) is an inherited bleeding disorder. Like hemophilia A and B, factor XI deficiency is characterized by a prolonged aPTT. Unlike hemophilia A and B, patients with factor XI deficiency tend to exhibit provoked bleeding (eg, bleeding in response to trauma) rather than spontaneous bleeding. Factor XI deficiency is more prevalent in Ashkenazi Jews (Jews from Eastern Europe). Diagnostic testing for factor XI deficiency will reveal low factor XI levels and normal factor VIII and factor IX levels. (See "Factor XI (eleven) deficiency".)

- **Factor XIII deficiency** – Factor XIII is involved in stabilizing the fibrin clot and protecting it from fibrinolysis. Factor XIII deficiency is an inherited bleeding disorder that can produce severe bleeding in homozygotes or compound heterozygotes, and milder bleeding in heterozygotes. Like hemophilia, factor XIII deficiency can present with intracranial hemorrhage around the time of birth or bleeding associated with umbilical cord separation. Unlike hemophilia, the typical presentation is delayed bleeding after initial hemostasis; impaired wound healing and pregnancy loss may also be seen. Unlike hemophilia, factor XIII deficiency is characterized by a normal aPTT and PT, and normal activity levels of factor VIII, IX, and XI. (See "Rare inherited coagulation disorders", section on 'Factor XIII deficiency (F13D)'.)

- **Other factor deficiencies with prolonged aPTT** – Other inherited conditions such as deficiencies of factor XII, prekallikrein, or high molecular weight kininogen can cause an isolated prolongation of the aPTT, with a normal prothrombin time (PT). Unlike hemophilia, these deficiencies are not associated with clinical bleeding. Diagnostic testing will reveal the specific deficiency, with normal factor VIII, IX, and XI levels. (See "Rare inherited coagulation disorders".)

Very rarely, a patient may have combined factor VIII and factor V deficiency due to a variant in a gene affecting cellular transport rather than in a coagulation factor gene. Unlike hemophilia, however, these patients will have a prolonged PT as well as aPTT. Finding of prolonged PT and aPTT or if the inheritance pattern includes females or multiple male and female siblings, should prompt additional testing such as mixing studies for the PT test and specific factor assays if coagulation testing shows correction with mixing studies. (See "Rare inherited coagulation disorders", section on 'Factor V and VIII combined deficiency (F5F8D)'.)

- **Acquired factor inhibitors (acquired hemophilia)** – Acquired inhibitors are autoantibodies that can interfere with the normal activity of coagulation factors. Inhibitors to factor VIII, XIII, and other factors have been reported; these can develop during pregnancy or in patients with an underlying systemic disorder such as rheumatoid arthritis, systemic lupus erythematosus, malignancy, or a drug reaction. Acquired inhibitors during pregnancy can cross the placenta and impair hemostasis in the fetus or neonate. Like hemophilia, acquired inhibitors may present with bleeding and a prolonged aPTT. Unlike hemophilia, acquired inhibitors most commonly present in adulthood, and mixing studies fail to show correction of the aPTT when patient plasma is mixed with control plasma because the inhibitory antibody is present in excess. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)" and "Clinical use of coagulation tests", section on 'Use of mixing studies'.)

  The antiphospholipid antibody syndrome (APS) is due to an acquired autoantibody that prolongs the aPTT in vitro, but clinically manifests as a prothrombotic state rather than impaired hemostasis. Patients with APS may have thromboembolism and/or recurrent pregnancy loss. Rarely, APS may be associated with prolongation of the PT and acquired prothrombin deficiency. Unlike hemophilia, the prolonged aPTT in APS does not show correction when patient plasma is mixed with control plasma; additional laboratory findings of APS are presented separately. (See "Clinical manifestations of antiphospholipid syndrome" and "Diagnosis of antiphospholipid 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".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hemophilia (The Basics)")

## SUMMARY AND RECOMMENDATIONS

- **Definitions** – Hemophilia A (factor VIII [8] deficiency) and hemophilia B (factor IX [9] deficiency) are heritable X-linked recessive bleeding disorders. Severity depends largely on the factor activity level, with severe disease defined as <1 percent of normal; moderate disease as 1 to 5 percent, and mild disease as >5 percent. (See 'Definitions' above and "Genetics of hemophilia A and B".)

- **Presentation** – Severe hemophilia causes spontaneous bleeding and bleeding after minor trauma out of proportion to the degree of injury, which can begin as early as birth. Delayed bleeding after trauma is common. In contrast, mild hemophilia may only become apparent when there is significant trauma or surgery. (See 'Initial presentation' above.)

  - Most infants with severe hemophilia present within the first year to one and a half years with bruising, hemarthrosis, or bleeding after oral injury or a procedure. Life-threatening bleeding can occur at delivery, with trauma, or spontaneously. Approximately 3 to 5 percent of infants with severe hemophilia develop subgaleal or intracerebral hemorrhage perinatally. (See 'Age at first bleeding' above.)

  - Once children are mobile (crawling, walking), joint and other musculoskeletal bleeding, frenulum and oral injuries, and forehead hematomas become more common. (See 'Initial site of bleeding' above.)

- **Bleeding sites** – Common sites of bleeding include joints and soft tissues, muscles, oral mucosa, and intracranial hemorrhage (ICH). ICH is rare compared with other sites, but it is one of the most dangerous and life-threatening events. Hemarthrosis is the most common site for bleeding in ambulatory patients. (See 'Sites of bleeding' above.)

- **Complications** – Late complications include neurologic sequelae of ICH and joint destruction from repetitive hemarthroses (hemophilic arthropathy). Complications of treatment include the potential for infection, which has declined dramatically since the mid-1980s and is extremely low, and development of antibodies to the infused factor. (See 'Late complications' above.)

- **Female heterozygotes** – Female carriers are heterozygotes and are expected to have approximately 50 percent of normal factor, which is generally sufficient to prevent bleeding. Some females have symptoms similar to males with mild hemophilia. Potential carriers should be tested using genetic testing. If carrier status is confirmed, measurement of factor levels is appropriate to guide management during hemostatic challenges. (See 'Bleeding in females/carriers' above and 'Carrier detection' above.)

- **Evaluation** – The evaluation begins with the personal and family bleeding history; approximately one-third of patients with hemophilia have a de novo mutation and negative family history. Laboratory testing includes coagulation tests, factor activity levels, and/or genetic testing. In individuals with reduced factor VIII activity, von Willebrand factor antigen (VWF:Ag) should be tested to exclude von Willebrand disease. (See 'Diagnostic evaluation' above.)

- **Diagnosis** – Confirm the factor activity level is <40 percent (<0.40 international units [IU]/mL) or document a pathogenic variant in a hemophilia gene (*F8* or *F9*). Individuals with factor levels ≥40 percent who carry a familial hemophilia variant can also be diagnosed with hemophilia. (See 'Diagnosis' above.)

- **Prenatal diagnosis** – Carriers who become pregnant should undergo fetal sex determination by ultrasound. Confirmatory testing is generally performed in male children at birth, on cord blood. Circumcision should be deferred until the diagnosis is confirmed or excluded. Maternal factor levels should be determined prior to invasive procedures including neuraxial anesthesia. Maternal and fetal risks of vaginal versus Cesarean delivery should be discussed. (See 'Carrier detection' above and 'Obstetric considerations' above.)

- **Differential diagnosis** – The differential diagnosis of hemophilia includes other inherited bleeding disorders (eg, VWD, platelet disorders, other factor deficiencies) and acquired

coagulation factor inhibitors. (See 'Differential diagnosis' above.)

- **Management** – Management is discussed separately. (See "Hemophilia A and B: Routine management including prophylaxis" and "Acute treatment of bleeding and surgery in hemophilia A and B" and "Chronic complications and age-related comorbidities in people with hemophilia" and "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication".)

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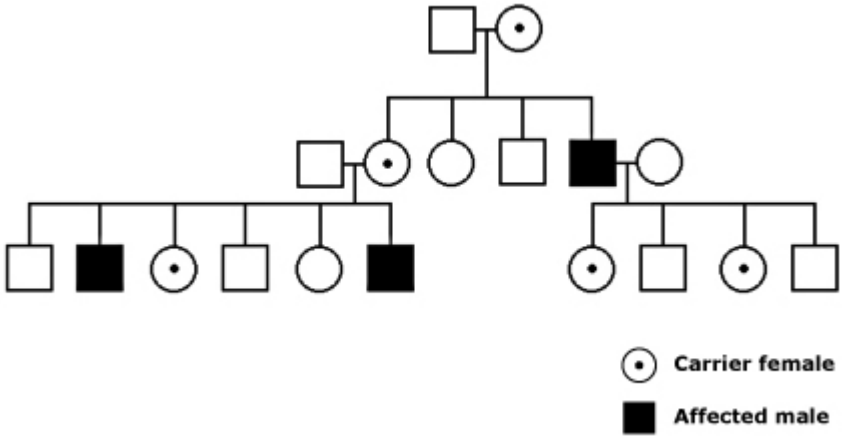
Topic 1310 Version 41.0

## GRAPHICS

### Example of a pedigree showing X-linked recessive inheritance




X-linked recessive. Features of X-linked recessive inheritance seen here include: male-affected status bias, lack of father-son transmission; 50% affected status rate among sons of female carriers.

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Graphic 55180 Version 6.0

## 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.

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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.

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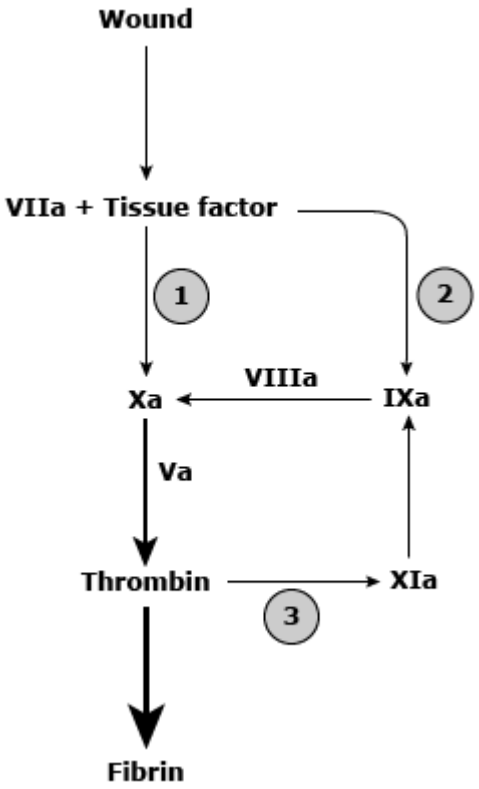
Graphic 79969 Version 11.0

## Coagulation cascade overview




This schematic shows a revised version of the coagulation cascade that emphasizes the importance of pathways for hemostasis in vivo. Coagulation factors are shown as Roman numerals. Only the activated forms (with the suffix "a") are shown in this diagram for simplicity. Thrombin is activated factor II (factor IIa); unactivated factor II is prothrombin.

Tissue factor exposed at a wound interacts with factor VIIa and initiates clotting by two pathways:

- (1) – Activation of factor X to factor Xa (the extrinsic ten-ase complex).
- (2) – Conversion of factor IX to factor IXa, which activates factor X to factor Xa (the intrinsic ten-ase complex).

Pathways 1 and 2 are equally important.

In a third pathway (3), thrombin also activates factor XI to factor XIa, which can lead to further generation of factor IXa; it serves as an amplification pathway required during severe hemostatic challenges.

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Graphic 90873 Version 11.0

## 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

## 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:<br>▪ Fanconi anemia<br>▪ Dyskeratosis congenita<br>▪ Shwachman-Diamond syndrome<br>▪ 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:<br>▪ Thrombocytopenia 2 (*ANKRD26* mutation)<br>▪ 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.

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