Hemorrhagic and Thrombotic Diseases

Hemostasis is the active process that clots blood in areas of blood vessel injury yet simultaneously limits the clot size only to the areas of injury. Over time, the clot is lysed by the fibrinolytic system, and normal blood flow is restored. If clotting is impaired, hemorrhage occurs. If clotting is excessive, thrombotic complications ensue. The hemostatic response needs to be rapid and regulated such that trauma does not trigger a systemic reaction but must initiate a rapid, localized response.
The main components of the hemostatic process are the vessel wall, platelets, coagulation proteins, anticoagulant proteins, and fibrinolytic system.
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<th>CLOTTING FACTOR</th>
<th>SYNONYM</th>
<th>DISORDER</th>
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<tr>
<td>I</td>
<td>Fibrinogen</td>
<td>Congenital deficiency (afibrinogenemia) or dysfunction (dysfibrinogenemia)</td>
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<tr>
<td>II</td>
<td>Prothrombin</td>
<td>Congenital deficiency or dysfunction</td>
</tr>
<tr>
<td>V</td>
<td>Labile factor, proaccelerin</td>
<td>Congenital deficiency (parahemophilia)</td>
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<tr>
<td>VII</td>
<td>Stable factor or proconvertin</td>
<td>Congenital deficiency</td>
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<tr>
<td>VIII</td>
<td>Antihemophilic factor</td>
<td>Congenital deficiency is hemophilia A (classic hemophilia)</td>
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<td>IX</td>
<td>Christmas factor</td>
<td>Congenital deficiency is hemophilia B</td>
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<td>X</td>
<td>Stuart-Prower factor</td>
<td>Congenital deficiency</td>
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<tr>
<td>XI</td>
<td>Plasma thromboplastin antecedent</td>
<td>Congenital deficiency, sometimes referred to as hemophilia C</td>
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<tr>
<td>XII</td>
<td>Hageman factor</td>
<td>Congenital deficiency is not associated with clinical symptoms</td>
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<tr>
<td>XIII</td>
<td>Fibrin-stabilizing factor</td>
<td>Congenital deficiency</td>
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Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are the most common and serious congenital coagulation factor deficiencies. The clinical findings in hemophilia A and hemophilia B are virtually identical. Hemophilia C is the bleeding disorder associated with reduced levels of factor XI.
Deficiencies of factors VIII and IX are the most common severe inherited bleeding disorders. Recombinant factor VIII and factor IX concentrates are available to treat patients with hemophilia and thereby avoid the infectious risk of plasma-derived transfusion-transmitted diseases.
Pathophysiology

Factors VIII and IX participate in a complex required for the activation of factor X. Together with phospholipid and calcium, they form the “tenase,” or factor X–activating, complex.

In vivo, the complex of factor VIIa and tissue factor activates factor IX to initiate clotting. In the laboratory, prothrombin time (PT) measures the activation of factor X by factor VII and is therefore normal in patients with factor VIII or factor IX deficiency.
After injury, the initial hemostatic event is formation of the platelet plug, together with the generation of the fibrin clot that prevents further hemorrhage. In hemophilia A or B, clot formation is delayed and is not robust. Inadequate thrombin generation leads to failure to form a tightly cross-linked fibrin clot to support the platelet plug. Patients with hemophilia slowly form a soft, friable clot. When untreated bleeding occurs in a closed space, such as a joint, cessation of bleeding may be the result of tamponade.
Clinical Manifestations

Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus.

Only 2% of neonates with hemophilia sustain intracranial hemorrhages, and 30% of male infants with hemophilia bleed with circumcision.

Thus, in the absence of a positive family history (hemophilia has a high rate of spontaneous mutation), hemophilia may go undiagnosed in the newborn. Hallow mark of hemophilic bleeding is hemarthrosis.
Obvious symptoms such as easy bruising, intramuscular hematomas, and hemarthroses begin when the child begins to cruise. Bleeding from minor traumatic lacerations of the mouth (a torn frenulum) may persist for hours or days and may cause the parents to seek medical evaluation. Even in patients with severe hemophilia, only 90% have evidence of increased bleeding by 1 yr of age. Although bleeding may occur in any area of the body
Bleeding into the joints may be induced by minor trauma; many hemarthroses are spontaneous. The earliest joint hemorrhages appear most commonly in the ankle. In the older child and adolescent, hemarthroses of the knees and elbows are also common. Whereas the child's early joint hemorrhages are recognized only after major swelling and fluid accumulation in the joint space, older children are frequently able to recognize bleeding before the physician does. They complain of a warm, tingling sensation in the joint as the first sign of an early joint hemorrhage.
Repeated bleeding episodes into the same joint in a patient with severe hemophilia may become a “target” joint. Recurrent bleeding may then become spontaneous because of the underlying pathologic changes in the joint. Although most muscular hemorrhages are clinically evident owing to localized pain or swelling, bleeding into the iliopsoas muscle requires specific mention. A patient may lose large volumes of blood into the iliopsoas muscle, verging on hypovolemic shock, with only a vague area of referred pain in the groin.
Laboratory Findings and Diagnosis

The laboratory screening test that is affected by a reduced level of factor VIII or factor IX is PTT. In severe hemophilia, the PTT value is usually 2-3 times the upper limit of normal. Results of the other screening tests of the hemostatic mechanism (platelet count, bleeding time, prothrombin time, and thrombin time) are normal.

The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia. If correction does not occur on mixing, an inhibitor may be present.

In 25-35% of patients with hemophilia who receive infusions of factor VIII or factor IX, a factor-specific antibody may develop. These antibodies are directed against the active clotting site and are termed inhibitors.
Differential Diagnosis

In young infants with severe bleeding manifestations, the differential diagnosis includes
- severe thrombocytopenia.
- severe platelet function disorders
- type 3 (severe) von Willebrand disease
- vitamin K deficiency
Genetics and Classification
Hemophilia occurs in approximately 1 : 5,000 males, with 85% having factor VIII deficiency and 10-15% having factor IX deficiency. Hemophilia shows no apparent racial predilection, appearing in all ethnic groups.

Severe hemophilia is characterized as having <1% activity of the specific clotting factor, and bleeding is often spontaneous. Moderate hemophilia have factor levels of 1-5% and usually require mild trauma to induce bleeding. Mild hemophilia have levels >5%, may go many years before the condition is diagnosed, and frequently require significant trauma to cause bleeding.

The hemostatic level for factor VIII is >30-40%, and for factor IX, it is >25-30%. The lower limit of levels for factors VIII and IX in normal individuals is approximately 50%.
Early, appropriate therapy is the hallmark of excellent hemophilia care. When mild to moderate bleeding occurs, values of factor VIII or factor IX must be raised to hemostatic levels, in the 35-50% range. For life-threatening or major hemorrhages, the dose should aim to achieve levels of 100% activity.

Calculation of the dose of recombinant factor VIII (FVIII) or recombinant factor IX (FIX) is as follows:

Dose of FVII (IU) = % desired (rise in FVII) ×
Body weight (kg) × 0.5

Dose of FIX (IU) = % desired (rise in plasma FIX) ×
Body weight (kg) × 1.4

For factor VIII, the correction factor is based on the volume of distribution of factor VIII. For factor IX, the correction factor is based on the volume of distribution and the observed rise in plasma level after infusion of recombinant factor IX.
With mild factor VIII hemophilia, the patient's endogenously produced factor VIII can be released by the administration of desmopressin acetate (DDAVP). In patients with moderate or severe factor VIII deficiency, the stored levels of factor VIII in the body are inadequate, and desmopressin treatment is ineffective. The risk of exposing the patient with mild hemophilia to transfusion-transmitted diseases and the cost of recombinant products warrant the use of desmopressin, if it is effective.
A concentrated intranasal form of desmopressin acetate, not the enuresis or pituitary replacement dose, can also be used to treat patients with mild hemophilia A. The dose is 150 ?g (1 puff) for children weighing <50 kg and 300 ?g (2 puffs) for children and young adults weighing >50 kg. Most centers administer a trial of desmopressin to determine the level of factor VIII achieved after its infusion. Desmopressin is not effective in the treatment of factor IX–deficient hemophilia.
<table>
<thead>
<tr>
<th>TYPE OF HEMORRHAGE</th>
<th>HEMOPHILIA A</th>
<th>HEMOPHILIA B</th>
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<tbody>
<tr>
<td>Hemarthrosis*</td>
<td>50 IU/kg factor VIII concentrate[^1] on day 1; then 20 IU/kg on days 2, 3, 5 until joint function is normal or back to baseline. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.</td>
<td>80-100 IU/kg on day 1; then 40 IU/kg on days 2, 4. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.</td>
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<td>Muscle or significant subcutaneous hematoma</td>
<td>50 IU/kg factor VIII concentrate; 20 IU/kg every-other-day treatment may be needed until resolved.</td>
<td>80 IU/kg factor IX concentrate[^4]; treatment every 2-3 days may be needed until resolved.</td>
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<tr>
<td>Mouth, deciduous tooth, or tooth extraction</td>
<td>20 IU/kg factor VIII concentrate; antifibrinolytic therapy; remove loose deciduous tooth.</td>
<td>40 IU/kg factor IX concentrate[^4]; antifibrinolytic therapy[^7]; remove loose deciduous tooth.</td>
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<tr>
<td>Epistaxis</td>
<td>Apply pressure for 15-20 min; pack with petrolatum gauze; give antifibrinolytic therapy; 20 IU/kg factor VIII concentrate if this treatment fails.[^1]</td>
<td>Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy; 30 IU/kg factor IX concentrate[^4] if this treatment fails.</td>
</tr>
<tr>
<td>Major surgery, life-threatening hemorrhage</td>
<td>50-75 IU/kg factor VIII concentrate, then initiate continuous infusion of 2-4 IU/kg/hr to maintain factor VIII &gt;100 IU/dL for 24 hr, then give 2-3 IU/kg/hr continuously for 5-7 days to maintain the level at &gt;50 IU/dL and an additional 5-7 days to maintain the level at &gt;30 IU/dL. [^7]</td>
<td>120 IU/kg factor IX concentrate[^4], then 50-60 IU/kg every 12-24 hr to maintain factor IX at &gt;40 IU/dL for 5-7 days, and then at &gt;30 IU/dL for 7 days.</td>
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<tr>
<td>Iliopsoas hemorrhage</td>
<td>50 IU/kg factor VIII concentrate, then 25 IU/kg every 12 hr until asymptomatic, then 20 IU/kg every other day for a total of 10-14 days.**</td>
<td>120 IU/kg factor IX concentrate[^4]; then 50-60 IU/kg every 12-24 hr to maintain factor IX at &gt;40 IU/dL until patient is asymptomatic; then 40-50 IU every other day for a total of 10-14 days.**[^11]</td>
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<tr>
<td>Hematuria</td>
<td>Bed rest; 1/2 ? maintenance fluids; if not controlled in 1-2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected).</td>
<td>Bed rest; 1/2 ? maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate[^4]; if not controlled, give prednisone (unless patient is HIV-infected).</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>20-40 IU/kg factor VIII concentrate every other day to achieve a trough level ≥1%.</td>
<td>30-50 IU/kg factor IX concentrate[^4] every 2-3 days to achieve a trough level ≥1%.</td>
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</table>
Prophylaxis

Many patients are now given lifelong prophylaxis to prevent spontaneous joint bleeding. The National Hemophilia Foundation recommends that prophylaxis be considered optimal therapy for children with severe hemophilia.

Usually, such programs are initiated with the first joint hemorrhage. Young children often require the insertion of a central catheter to ensure venous access. Such programs are expensive but are highly effective in preventing or greatly limiting the degree of joint pathology.
Treatment is usually provided every 2-3 days to maintain a measurable plasma level of clotting factor (1-2%) when assayed just before the next infusion.

Whether prophylaxis should be continued into adulthood has not yet been adequately studied. If moderate arthropathy develops, prevention of future bleeding will require higher plasma levels of clotting factors.

In the older child who is not given primary prophylaxis, secondary prophylaxis is frequently initiated if a target joint develops.
Chronic Complications

Long-term complications of hemophilia A and B include chronic arthropathy, the development of an inhibitor to either factor VIII or factor IX, and the risk of transfusion-transmitted infectious diseases. Although an aggressive, or prophylactic, approach to treatment has reduced the problems of chronic arthropathy, these problems have not been eliminated.
The natural history of untreated hemophilia is one of cyclic recurrent hemorrhages into specific joints, including hemorrhages into the same (target) joint.

In young children, the joint distends easily and a large volume of blood may fill the joint until tamponade ensues or therapy intervenes.

After joint hemorrhage, proteolytic enzymes are released by white blood cells into the joint space, and heme iron induces macrophage proliferation, leading to inflammation of the synovium.
Inhibitor Formation

Infusion of the deficient clotting factor may initiate an immune response in patients with either factor VIII or factor IX deficiency. Inhibitors are antibodies directed against factor VIII or factor IX that block the clotting activity.

Failure of a bleeding episode to respond to appropriate replacement therapy is usually the first sign of an inhibitor. Less often, inhibitors are identified during routine follow-up testing.

Inhibitors develop in approximately 25-35% of patients with hemophilia A; the percentage is somewhat lower in patients with hemophilia B.
Factor XI Deficiency (Hemophilia C)

Factor XI deficiency is an autosomal deficiency associated with mild to moderate bleeding symptoms. It is frequently encountered in Ashkenazi Jews but has been found in many other ethnic groups. In Israel, 1-3/1,000 individuals are homozygous for this deficiency.
von Willebrand Disease

The most common hereditary bleeding disorder is von Willebrand disease (VWD), and some reports suggest that it is present in 1-2% of the general population. VWD is inherited autosomally, but most centers report more affected women than men. Because menorrhagia is a major symptom, women may be more likely to seek treatment and thus to be diagnosed.

VWD is classified on the basis of whether the protein is quantitatively reduced, but not absent (type 1); qualitatively abnormal (type 2); or absent (type 3). Mutations in different loci that code for different functional domains of the von Willebrand factor (VWF) protein cause the different variants of VWD.
Pathophysiology

A large multimeric glycoprotein that is synthesized in megakaryocytes and endothelial cells, VWF is stored in platelet α-granules and endothelial. The highest molecular weight multimers of VWF are responsible for the normal interaction of VWF with the subendothelial matrix and platelets. During normal hemostasis, VWF adheres to the subendothelial matrix after vascular damage. When VWF binds to the subendothelial matrix, the conformation of VWF is altered by shear so that it causes platelets to adhere to VWF through their glycoprotein IB (GPIb) receptor.
Clinical Manifestations

Patients with VWD usually have symptoms of mucocutaneous hemorrhage, including excessive bruising, epistaxis, menorrhagia, and postoperative hemorrhage, particularly after mucosal surgery, such as tonsillectomy or wisdom tooth extraction.

Because a teenager's menstrual history is usually put in the context of other family members, excessive menstrual bleeding is not always recognized as being abnormal, because others in the family may be affected with the same disorder.

If a menstruating female has iron deficiency, a detailed history of bruising and other bleeding symptoms should be elicited and further hemostatic evaluation undertaken.
Laboratory Findings

Long bleeding time and a long partial thromboplastin time, these findings are frequently normal in patients with type 1 VWD.

Normal results on screening tests do not preclude the diagnosis of VWD. Because there is no single assay that has demonstrated the ability to rule out VWD, if the history is suggestive of a mucocutaneous bleeding disorder, VWD testing should be undertaken, including a quantitative assay for VWF antigen, testing for VWF activity (ristocetin cofactor activity), testing for plasma factor VIII activity, determination of VWF structure (VWF multimers), and a platelet count. Platelet count is usually normal in most patients, those with type 2B disease or platelet-type disease (pseudo-VWD) may have lifelong thrombocytopenia.
Von Willebrand Disease Variants

- Type 1 VWD
- Type 2A VWD
- Type 2B VWD
- Type 2N VWD
- Platelet-type (pseudo-) VWD
- Type 2M VWD
- Type 3 VWD
Differential Diagnosis

The differential diagnosis of mucocutaneous bleeding includes abnormalities of platelet number, platelet function, or the vessel wall non accidental trauma—child abuse.
Complications

Complications of bleeding due to VWD are rare. In adolescent females, blood loss due to menorrhagia can lead to severe anemia, either acutely, with signs and symptoms of hypovolemia, or chronically from iron deficiency.

Individuals with type 3 VWD can manifest joint or muscle bleeding similar to individuals with hemophilia.
**Treatment**

Treatment of VWD is directed toward increasing the plasma level of VWF and factor VIII. Because the gene for factor VIII is normal in patients with VWD, elevating the plasma concentration of VWF permits normal recovery and survival of endogenously produced factor VIII.

The most common form of VWD is type 1. In these patients, the synthetic drug desmopressin induces the release of VWF from the patient's endothelial cells.

In some patients with type 2 or 1C variants, desmopressin may be similarly effective, but in other circumstances, the released VWF is dysfunctional.
Patients with VWD may not respond adequately to desmopressin because they release an abnormal VWF molecule (most type 2 variants); because they have type 3 disease, in which there is no VWF to be released; or because they have accelerated clearance of released VWF (type 1C VWD). A small subset of children and adults, especially infants, do not release VWF in response to desmopressin. In these cases, replacement therapy must be used. Current replacement therapy uses plasma-derived VWF containing concentrates that also contain factor VIII. VWF distributes only to the intravascular space, because it is so large. During plasma fractionation, VWF multimers are altered to a variable extent. Therefore, 1 U/kg will increase the plasma level by 1.5%. The plasma half-life of both factor VIII and VWF is 12 hr, but the alteration of VWF during fractionation results in half-lives of 8-10 hr when concentrates are infused. Purified or recombinant VWF concentrates (containing no factor VIII) may become available in the near future.