



## **Introduction to Bleeding Disorders**

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Bleeding disorders are relatively rare genetic disorders characterized by increased or prolonged bleeding due to abnormal coagulation (the ability of the blood to clot). The cause is a decrease in amount or function of one of the 11 proteins in the blood, called clotting factors, that work together to make the blood clot.

### **NORMAL COAGULATION**

There are three stages in normal hemostasis or coagulation. First, the injured blood vessels constrict to reduce potential loss of blood. Second, the blood platelets adhere to endothelial cells in the wall of the damaged blood vessel at the site of vessel injury, and platelets then begin to stick to each other (aggregate), promoting formation of a platelet plug (primary clot). Finally, plasma clotting proteins are activated in sequence in order to convert fibrinogen to fibrin to establish a mature clot that contains a stabilizing fibrin network. Formation of this network is accomplished through the intrinsic and extrinsic pathways of coagulation, both of which trigger the final, common steps (common pathway) involved in the conversion of fibrinogen into fibrin.

The 11 plasma clotting factors circulate in inactive form until they are converted in sequential order to fully activated enzymes that can activate the next factor in the sequence. There are two pathways that lead to the formation of fibrin from fibrinogen. The intrinsic pathway is activated by contact of blood with the damaged vessel wall and the conversion of factor XII into its active form (FXIIa). Subsequently, factor XI, factor IX, and factor VIII with von Willebrand factor are activated and in turn activate factor X, which, in the presence of factor V through the common pathway, activates prothrombin (factor II) into thrombin (FIIa). Thrombin then converts fibrinogen (factor I) into fibrin (FIIa). In the shorter, extrinsic pathway, subendothelial tissue factor that is released during tissue injury activates Factor VII, which in turn activates Factor X, which then through the common pathway activates FV and FII and finally converts fibrinogen to fibrin.

### **DEFECT IN A BLEEDING DISORDER**

In a person with a bleeding disorder, the first two stages of hemostasis function normally – the blood vessels constrict, an immature platelet plug is formed, and bleeding may stop or slow down. However, since one of the clotting factors is decreased or absent, a mature fibrin clot is not formed; instead, a soft, ineffective clot is formed. The soft platelet plug breaks down, the bleeding resumes, and the process begins again, leading to repeated cycles of bleeding and partial clotting. If the missing clotting factor is FVIII or FIX, then the disorder is called hemophilia A or B. If the absent or malfunctioning clotting factor is von Willebrand factor (VWF), then the resulting bleeding disorder is called von Willebrand Disease (VWD). VWD is discussed in Chapter 2. If one of the other 8 clotting factors is decreased or absent from the

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plasma, the resulting bleeding disorder is characterized as a rare bleeding disorder; these are discussed in Chapter 5.

## **HEMOPHILIA A AND B**

The most common bleeding disorder, hemophilia, is an X-linked genetic disorder characterized by a deficiency or absence of factor VIII (FVIII) (hemophilia A or classic hemophilia) or factor IX (FIX) (hemophilia B or Christmas disease). FVIII and FIX deficiencies are clinically indistinguishable. Although there is currently no cure for hemophilia, the goals of treatment are prevention, early recognition of bleeding episodes, and appropriate intervention to prevent complications.

### **INCIDENCE**

In the United States, the incidence of hemophilia has been found to be one in 5032 live male births. (1) Based on this number, it is estimated that about 400 babies with hemophilia are born in the United States every year. There are currently about 17,000 people living with hemophilia in the United States. FVIII deficiency is approximately four times more common than FIX deficiency. Hemophilia occurs in all racial and ethnic groups.

### **INHERITANCE**

Hemophilia is an X-linked recessive disorder. The abnormal gene responsible for hemophilia is carried on the X chromosome (see Figure 1). (1) Females have two X chromosomes. A female with the hemophilia gene on one of her 2 X chromosomes is called a hemophilia carrier. But the presence of the hemophilia gene on one X may not cause her to have hemophilia if the normal gene on the other X chromosome compensates. Males have only one X chromosome, so the presence of the hemophilia gene on a male's X chromosome results in the deficiency or absence of FVIII or FIX. Affected men do not transmit the disorder to their sons, but all of their daughters are obligate carriers. In approximately one third of hemophilia cases, no family history of the disease exists. Such cases are thought to be the result of a recent genetic mutation. (2)

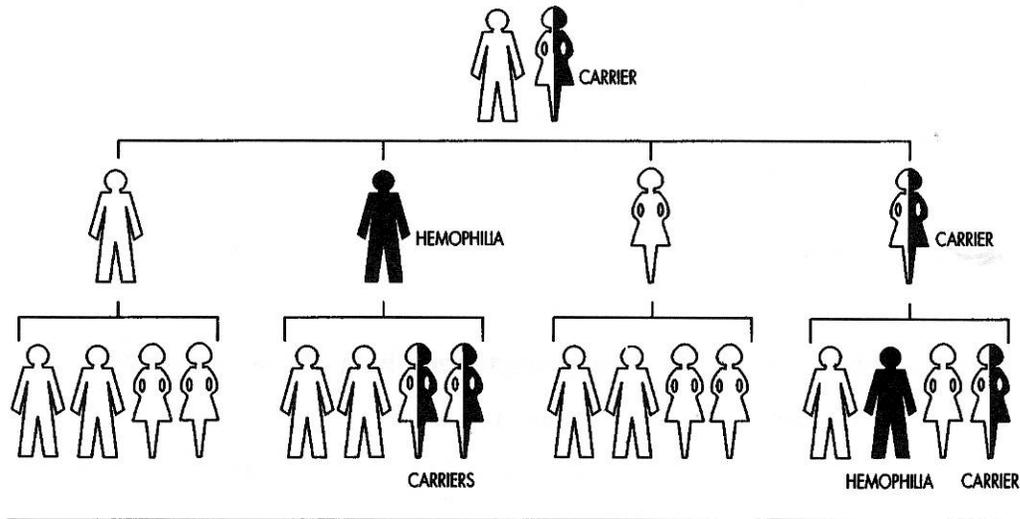
## **DIAGNOSIS**

Making a diagnosis of hemophilia involves consideration of the individual's history, the family history, and the laboratory findings.

### **CLINICAL PRESENTATION**

If no family history is present, hemophilia may be suspected if prolonged bleeding from circumcision or a cephalohematoma occurs in the newborn period, or if easy bruising raised hematomas, or prolonged mouth bleeding are noted in the first year of life. In older children and adults, bleeding episodes may occur in the joints, muscles, mouth with tooth loss or extraction, or at the time of trauma or surgery.

**Figure 1: Inheritance of Hemophilia**



In some texts you will see the X and Y chromosomes used to denote a family tree. An X with a small “o” or “h” ( $X^o$  or  $X^h$ ) signifies a female chromosome with the gene for hemophilia.

$XX$  = normal female chromosome  
 $X^oX$  = carrier female  
 $XY$  = normal male  
 $X^oY$  = hemophilic male

### **PATIENT HISTORY**

A detailed history is important to identify challenges to hemostasis, including any history of bleeding from circumcision or heel or finger sticks, raised bruises or other incidents of prolonged oozing or swelling, joint or muscle pain and swelling, bleeding from the mouth after loss of teeth, or bleeding with trauma or surgery.

### **FAMILY HISTORY**

History of any abnormal bleeding is important, especially in male members of the maternal family. Because approximately 30% of children with hemophilia have no family history, absence of bleeding in relatives does not rule out hemophilia.

### **LABORATORY STUDIES**

In a male baby of a known or suspected carrier of FVIII or FIX deficiency, plasma can be obtained from umbilical cord blood for a FVIII or FIX assay to diagnose or rule out hemophilia. In a bleeding newborn with no family history of hemophilia, FVIII and FIX testing can be done on blood from a peripheral venipuncture. FVIII levels in the newborn are the same as in older children and adults. However, newborn testing is less reliable in FIX deficiency because FIX levels are normally low in all newborns. Full production of FIX does not occur until 6-9 months of age, when the liver becomes fully mature. Thus an absence of FIX in the newborn implies hemophilia B, but the severity cannot be determined until age 6-9 months. In older children and adults with a positive family history of hemophilia, specific factor assays can be performed on peripheral blood samples.

Table 1. Expected Laboratory Values

FACTOR VIII DEFICIENCY		FACTOR IX DEFICIENCY	
Test	Result	Test	Result
PT	Normal	PT	Normal
PTT	Prolonged	PTT	Prolonged
BT	Normal	BT	Normal
Factor VIII	Low	Factor IX	Low

When a bleeding disorder is suspected in an older child or adult with a negative family history, screening tests such as the prothrombin time (PT) and partial thromboplastin time (PTT) are indicated to screen for possible clotting factor deficiencies. Normal values for PT and PTT vary by laboratory and also by gestational age of the newborn. Results are compared to a normal control. A prolonged PTT indicates the need to perform specific coagulation factor assays. Normal FVIII and FIX levels range from 50% to 150%. Diagnosis of hemophilia A or B is confirmed by a low or absent FVIII or FIX.

The bleeding time (BT) test is usually normal in patients with hemophilia, although occasionally a patient with hemophilia may have a prolonged BT. Bleeding times are not recommended to evaluate a patient for hemophilia or other bleeding disorders because of their unreliability.

## LEVELS OF SEVERITY

The amount of bleeding that can be expected in an individual with hemophilia depends upon the severity of the deficiency. Normal plasma levels of FVIII and FIX range from 50% to 150%. People with no measurable FVIII or IX (FVIII or FIX < 1%) are considered to have the severe form of hemophilia. Severe hemophilia can result in frequent bleeding episodes. In many cases, bleeding, particularly into joints, can occur spontaneously, without any trauma or injury that can be remembered by the patient or family.

Factor levels of 1% to 5% of normal are indicative of moderate hemophilia. These patients may have abnormal bleeding after minor trauma but should not experience spontaneous bleeding. However, after repeated bleeding into the same joint, spontaneous bleeding may occur in that joint, even if the individual has moderate hemophilia.

Persons with 6% to 49% of factor activity are considered to have mild hemophilia and are expected to have relatively few problems with bleeding, except during surgery or after severe trauma. Carrier women can have lower than normal plasma levels of FVIII or IX and thus can experience symptoms of mild hemophilia.

## SITES OF BLEEDING

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The clinical manifestations of hemophilia involve joint and muscle bleeding; prolonged, potentially fatal bleeding after surgery; and numerous raised hematomas. Excessive bleeding after minor cuts or scrapes is uncommon. (3) Joints and muscles are the most common sites of bleeding, with knees, ankles, elbows and hips being the most frequently affected joints. However, bleeding can occur in any part of the body, with complications dependent on the site of bleeding. Bleeding into the head, neck, abdomen or gastro-intestinal tract is considered life-threatening and must be treated as an emergency. Other bleeding episodes requiring prompt treatment include nerve compression from muscle bleeding, hematuria, deep lacerations, epistaxis, and bleeding from the mouth or tongue. These various kinds of bleeding episodes will be discussed in detail in chapter 5.

## **TREATMENT OF BLEEDING**

The treatment for bleeding in hemophilia A and B involves replacing the deficient factor VIII or IX. This usually requires intravenous infusion of clotting factor. For patients with mild FVIII deficiency, desmopressin (DDAVP) may be used to release FVIII from endothelial cells and increase the circulating FVIII level sufficiently to stop bleeding. Specific factor replacement products, doses, additional drugs, and nursing interventions depend on the site and severity of bleeding and will be discussed in Chapter 6.

### **GOALS OF THERAPY**

The traditional goal of hemophilia management has been to recognize the earliest signs of bleeding and to treat promptly with the appropriate product and dose to stop bleeding and avoid resulting complications. This is called on-demand therapy. (4)

### **PROPHYLAXIS**

The current standard of care for children with severe hemophilia in the United States is prevention of bleeding episodes, particularly into joints, by treating in advance of any bleeding symptoms, a regimen known as prophylaxis. Primary prophylaxis is the regular infusion of factor replacement products from an early age to prevent bleeding. The goal of prophylaxis is to maintain FVIII or FIX levels above 1% at all times to prevent spontaneous bleeding. The Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) has recommended that primary prophylaxis be considered for young children with severe hemophilia. (5) While all HTCs recommend prophylaxis for such children, specific protocols vary from center to center.

Many adults in the U.S. are also maintained on prophylactic regimens to prevent bleeding. Secondary prophylaxis is prophylaxis that is initiated after repeated bleeding episodes in a particular site.

## **CARRIER DETECTION**

Carrier detection testing of at-risk women to determine carrier status is currently performed using DNA analysis of a peripheral blood sample to study the FVIII or FIX gene. (6) DNA analysis first requires determination of the mutation causing the hemophilia in an affected male

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relative in the family. Once the mutation has been identified, female relatives can be tested. Several family members may need to be tested to establish results in a distant relative such as a female cousin of the individual with hemophilia. Genetic counselors can assist in determining which family members need to be tested.

Most DNA analysis takes a number of months to complete. However, if the individual's severe hemophilia A is due to an inversion mutation in the FVIII gene, inversion testing takes only a few days to complete. DNA analysis can identify an inversion on the FVIII gene in 50% of patients with severe FVIII deficiency. The possible female carriers in the family can then also be tested quickly. If an affected male is not available for testing, the inversion test can be performed in potential carriers. A positive result in the female indicates that she is a carrier, but a negative result does not rule out the carrier state, since the exact mutation in the family is unknown.

In some families, carrier status cannot be determined by DNA analysis, especially if there is no affected male relative to test first. Then the only way to decide if a female is a carrier is to do a FVIII or FIX level. A level below 50% indicates a likelihood that the female is a carrier; the lower the level, the greater the likelihood of a positive carrier state.

If the woman is determined to be a carrier of hemophilia, then with each male pregnancy there is a 50% chance that the infant will have hemophilia. The type and severity will be the same as that of other affected members of the family.

## **PRENATAL DIAGNOSIS**

Prenatal diagnosis for hemophilia A or B can be performed. If DNA analysis has already been done and has revealed the causative mutation, then either chorionic villus sampling (CVS) or amniocentesis can be used to determine whether the fetus will have hemophilia. If the DNA analysis has not been done or has not been informative, then direct percutaneous umbilical blood sampling (PUBS) of the fetus can be done to determine the presence or absence of the FVIII or FIX clotting protein in the fetal blood.

### **DETERMINATION OF FETAL SEX**

The first step in doing prenatal diagnosis of hemophilia is to determine the sex of the fetus, since only male fetuses are at risk of having hemophilia. Thus, subsequent testing may not need to be done if the fetus is found to be a female.

If CVS is to be performed, then the fetal sex will be determined by rapid DNA analysis looking for the presence or absence of a Y chromosome. If amniocentesis or PUBS is to be performed, then an ultrasound will be done first to look for the presence or absence of a penis. If no penis is seen, then further testing is not necessary. Note, however, that this method is not 100% reliable; it depends on the position of the fetus at the time of testing and so may need to be repeated to be certain that no penis is present.

### **CHORIONIC VILLUS SAMPLING (CVS), AMNIOCENTESIS**

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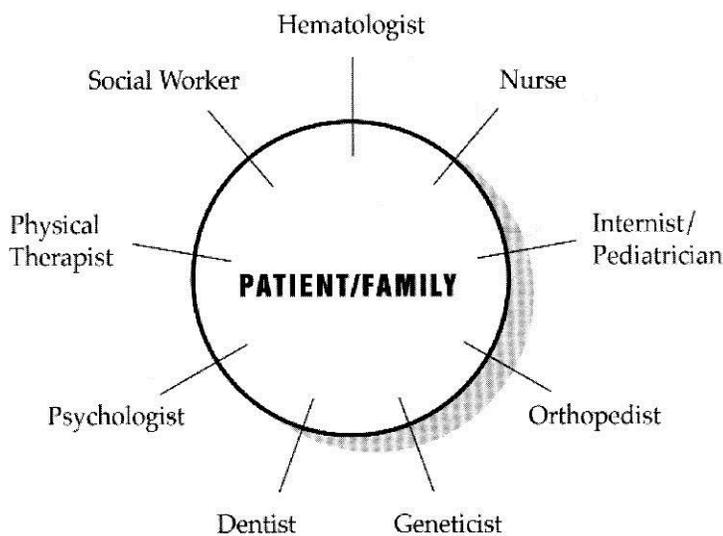
Prenatal testing for FVIII and FIX deficiencies can be done in many families through DNA analysis. This method is very successful for mothers who have already been tested and found to have informative markers. Fetal cells for analysis are obtained by chorionic villus sampling, usually done between the 10th and 12th weeks of pregnancy, or amniocentesis, usually performed between the 15th and 16th weeks of pregnancy. The cells are cultured and then analyzed for the causative mutation. If the mutation is an inversion, this process can be completed in about a week. However, if a more detailed DNA analysis is required, this can take up to 4-6 weeks.

### **PERCUTANEOUS UMBILICAL BLOOD SAMPLING (PUBS)**

FVIII deficiency can be detected prenatally by obtaining a fetal blood sample at 18-20 weeks of gestation from the umbilical cord. An assay is performed to detect the FVIII coagulant antigen (FVIII:C:Ag) rather than the activity, which is low at this gestational age. Fetal blood testing can also be done to determine FIX deficiency prenatally but is less successful than FVIII detection because many individuals with severe hemophilia B do make a FIX protein that is inactive. PUBS is done infrequently now because many families are candidates for DNA analysis. (6)

### **COMPREHENSIVE CARE**

Comprehensive care is a system of care that utilizes a team approach to provide optimal care for the individual with hemophilia and his family. The Hemophilia Treatment Center (HTC) is the model for delivering comprehensive care. The HTC team consists of multi-disciplinary healthcare providers and includes the patient and family as team members (see Figure 2). (7)



**Figure 2: Comprehensive Care Team**

The goal of comprehensive care is to promote optimal physical and emotional health through family-centered care, to minimize complications from bleeding and treatment, to reduce school and work absences, and to minimize lifestyle disruptions.

The functions of the HTC staff include diagnosis and evaluation of individuals with bleeding disorders; treatment of bleeding episodes and complications; education of the patient and family, the community and other medical providers; communication and advocacy; supervision of home care; and research and data collection.

### **NURSING CARE**

Nurses are an integral part of the HTC comprehensive care team. Caring for persons with hemophilia presents many challenges and rewards for the nurse. Nursing care begins with

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education for the parents and the child or the adult with hemophilia to enable them to participate in their care. This education is an ongoing process and includes formal and informal teaching that is reinforced at each nursing encounter. (7)

Nurses also play key roles in assessing the severity of bleeding episodes, helping families to choose treatment products, calculating appropriate doses, developing treatment protocols, selecting candidates for prophylaxis or home therapy, and carefully observing clinical progress. In addition, nurses participate in providing adjunct measures to promote comfort and healing for patients with hemophilia.

## **HEMOPHILIA TREATMENT CENTERS (HTCs)**

In the United States, there is a network of HTCs that serve as resource and reference centers for persons with hemophilia. These HTCs are supported in part by grants from the Maternal and Child Health Bureau of the Department of Health and Human Services and by the Centers for Disease Control and Prevention. Some HTCs are also funded by state agencies and research grants. Staffs at these treatment centers are experts in the care and treatment of persons with hemophilia and other bleeding disorders. A list of these centers can be found on the NHF Web site ([www.hemophilia.org](http://www.hemophilia.org)) or by calling NHF's information clearinghouse, HANDI, at 800-42-HANDI.

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