

Pediatric Hemophilia — Pathophysiology and Types

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Hemophilia is a X-linked disorder, inherited in a recessive pattern. Hemophilia A and B are the two main types. The male sex is affected commonly as the disease is transmitted through the X chromosome. Deficiency of the clotting factor VIII and IX is the cause of Hemophilia A and B, respectively. Haemarthrosis is a common symptom, besides a list of other hemorrhagic symptoms. Early investigations and diagnosis is a pre-requisite for an effective treatment.



Discussion of Pediatric Hemophilia

Hemophilia is a **rare blood clotting disorder in which the body lacks blood-clotting factors**. If a child is suffering from Hemophilia, he will continue to bleed for a longer duration after an injury. **Bleeding can occur spontaneously or after a minor trauma**. The biggest problem with the disease is internal bleeding, which can even be **life-threatening**.

The joints like elbows, knees, and ankles manifest the signs and symptoms of

bleeding. The bleeding from the GI tract, brain, and internal organs can go unnoticed, which can pull the person into a state of hypovolemic shock.

Hemophilia has the two basic types – Hemophilia A and Hemophilia B. Rarely, another form, Hemophilia C, can also occur, but the bleeding is far less than with A and B types. Hemophilia A and B mostly occur in male babies as the disease is **X-linked recessive**.

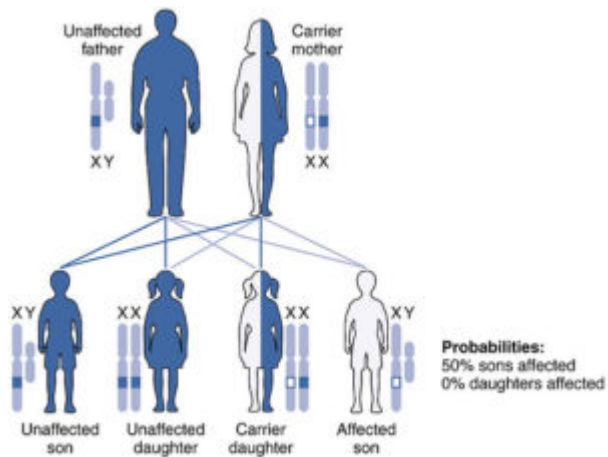


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There are three ways to get this disorder:

- Inherited (X-linked recessive)
- Spontaneous mutations
- Acquired immunological defects

Hemophilia A

It is an X-linked disorder caused by the **deficiency of clotting factor VIII**. It is the **most common type of Hemophilia**, occurring with a frequency of 1/4000.

Hemophilia B

It is also known as **Christmas disease**. Hemophilia B occurs due to the **deficiency of clotting factor IX**. It constitutes 20% of the total Hemophilia cases. It is less common than Hemophilia A, occurring in 1 out of 20,000 babies.

Hemophilia C

It is rarer than the above two types. It also occurs due to the **deficiency of factor IX**. The **symptoms are few and mild in intensity**. It is not transmitted in an X-link recessive pattern, so both the sexes are equally susceptible to the disease.

Etiology of Pediatric Hemophilia

The mutations occur in the genes that code for the proteins, which make the clotting factors. Blood clotting is a complex process that involves thirteen clotting factors. The factors are written in Roman numerals like I, II and so on up to XIII.

When an injury occurs to the blood vessels, platelets get recruited to form a plug. Activated platelets release a number of chemicals to initiate the clotting cascade. Finally,

a mesh is formed which is made up of fibrin. A final clot is formed that stops the bleeding and covers the injured areas. **In Hemophilia, the clotting factors are missing so the process is defective and bleeding does not stop.**

Epidemiology

Congenital hemophilia A occurs in approximately 1 out of every 5000 men/boys. The frequency of congenital hemophilia B is approximately 1 for every 30,000 men/boys. About 400 children are born with hemophilia each year in the US.

Grading of Pediatric Hemophilia

Before moving to the symptoms, it is important to grade the disease:

- **Mild:** The concentration of the clotting factor (VIII or IX) is 5-40 %
- **Moderate:** 1-5 % of the clotting factors are available for the clotting mechanism
- **Severe:** < 1 % of the clotting factors are present for the cascade

Symptoms and Signs of Pediatric Hemophilia

They **depend on the severity of the disease** as discussed above. In severe form, the symptoms begin to appear early and without any apparent history of trauma or injury. The episodes of bleeding start in the first or second year of life. The disease mostly gets diagnosed at the time of circumcision when the bleeding cannot be controlled with the traditional measures. In moderate and mild forms, the bleeding is more occasional with traumas or minor injuries. The general signs and symptoms of the disease are:



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Haemarthrosis: 'Haem' is blood and 'arthrosis' stands for joints, 'bleeding in the joint spaces'. It is a specific sign of the disease. Ankles and knees are more commonly affected than the smaller joints. Repeated bleeds can lead to joint destruction.

Bleeding into muscles: Hematoma formations can even lead to the compartment

syndrome. It has its own worse consequences.

Gastrointestinal tract bleeding: A small peptic ulcer cannot get healed and lead to continuous bleeding.

Urinary tract bleeding: It can present as haematuria.

Intracranial bleeds: Symptoms such as a headache, lethargy, nausea and vomiting start to appear. It needs immediate treatment.

Bleeding after trauma and surgery: It is a common scenario in hemophilic children.

Newborn period	Later presentation
<ul style="list-style-type: none">• Bleeding after circumcision (50% of undiagnosed infants)• Intracranial hemorrhage at birth• Large cephalohematoma at birth• Bleeding after umbilical stump falls off	<ul style="list-style-type: none">• Hemarthrosis (average 10 months)• Hematomas, but not usually bruising or petechiae<ul style="list-style-type: none">• GI bleed• Intracranial bleed

Diagnosis of Pediatric Hemophilia

There are **three main steps of diagnosis**. It is important to go step-wise as the warning signs can be missed.

Examination

After taking a detailed history of the patient, go towards the general **physical and systemic examination**. All the systems should be examined in detail.

- **Neurological:** Look for any abnormal findings, altered mental status, and signs of meningism
- **Musculoskeletal:** Joint tenderness, warmth, swelling, and limited range of motions
- **Gastrointestinal:** Examine for hepatic tenderness, splenic, and signs of peritonitis
- **Genitourinary:** Bladder distensions, irritation, and tenderness of costovertebral angles
- **Other signs of airway obstruction and compartment syndrome** should also be checked

Laboratory Investigations

- Complete blood cells count and hemoglobin levels
- Bleeding Time (BT) and clotting time (CT)
- Coagulation studies: PT (Prothrombin time) and APTT (Activated Partial Thromboplastin Time)
- Factor VIII, IX, and vWF (Von Willebrand factor) Assays
- Testing for infections like hepatitis or AIDS
- Genetic Testing

Differentiation between Hemophilia A and B on lab tests

Hemophilia A = Factor VIII is reduced. APTT and CT are prolonged. Platelet count, PT, and BT are normal.

Hemophilia B = Factor IX deficiency, APTT is prolonged; platelet count and PT is normal.

Radiological Investigations

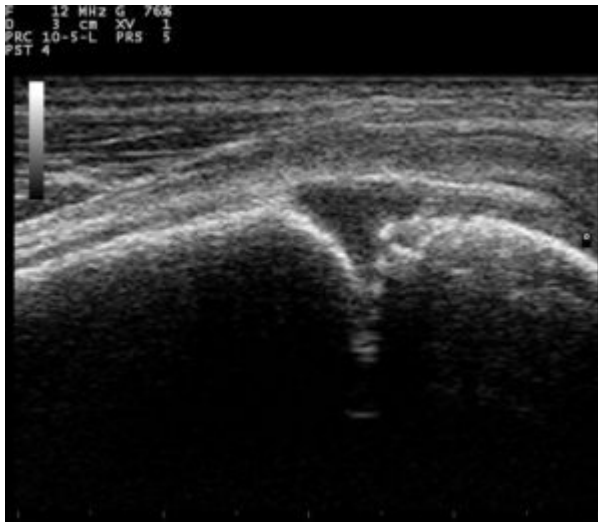


Image: "Knee ultrasound" by Nevit Dilmen. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

- Head CT to look for a hemorrhage
- MRI brain
- Ultrasound for signs of effusions in the joint spaces

Management of Pediatric Hemophilia

General Approach

- Advise avoiding the trauma
- Do not use aspirin
- Immunization against infectious diseases like hepatitis
- Genetic counseling

Specific treatment

- Factor IX concentrates (Hemophilia B)
- Factor VIII concentrates (Hemophilia A)
- If the concentrates are not available, then consider these options:
 - Whole blood
 - Fresh frozen plasma
 - Cryoprecipitate
- Synthetic vasopressin analog, Desmopressin Acetate
- Antifibrinolytics: Aminocaproic Acid and Tranexamic acid
- Monoclonal antibodies (Rituximab)
- Analgesics (acetaminophen)

Overview:

Acute bleeding	Primary prophylaxis (severe cases)	Transfusion of pRBC
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<ul style="list-style-type: none"> • Recombinant factor • Dose depends on desired % factor to be achieved and weight of child 	<ul style="list-style-type: none"> • Typically given 2-3 times per week (long-acting is now available) • Goal is to raise severe patient up to 1% factor level, which is equivalent of moderate disease <ul style="list-style-type: none"> • Very expensive 	<p>Indicated for severe bleeds of hemodynamic consequence</p>
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Prognosis

With replacement therapy, people with Hemophilia A now have a considerably higher life expectancy. There is a 2 to 8 % lifetime risk of intracranial bleeding with the condition. Out of all the patients with severe hemophilia, around 10 % have intracranial bleeding. Compared to the healthy male population, the mortality rate is about two times higher for people with the condition and about four to six times higher for people with severe cases of the condition.

References

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