Hemophilia B: Causes, Inheritance, Diagnosis and Treatment

Hemophilia B, also known as *Christmas disease* or the *royal disease*, is a congenital bleeding disorder caused by a deficiency or dysfunction of coagulation factor IX. It is inherited in an **X-linked recessive** pattern and leads to **impaired blood clotting**, resulting in a tendency for spontaneous or excessive bleeding after trauma or surgical procedures.

Hemophilia B is **clinically indistinguishable** from Hemophilia A (factor VIII deficiency), but is approximately **four times less common**, affecting about **1 in 75,000 male births** worldwide. It affects all ethnic groups equally.

Why Is It Called “Christmas Disease”?

The disorder is eponymously named after **Stephen Christmas**, the first patient described with the condition in 1952. Notably, Hemophilia B was prevalent among **European royal families**, especially descendants of **Queen Victoria**, leading to its alternate name: the *royal disease*.

Etiology and Genetics

Hemophilia B results from **mutations in the F9 gene**, located on the **X chromosome (Xq27.1-q27.2)**. The F9 gene encodes **coagulation factor IX**, a vitamin K–dependent serine protease essential for blood clotting.

Inheritance Pattern

- **X-linked recessive**.
- Affected males inherit the **mutated X chromosome from carrier mothers**.
- Females with one mutated X are typically **asymptomatic carriers**, but may present with mild symptoms depending on **X-chromosome inactivation (lyonization)**.
- **"True" hemophiliac females** are rare and occur only if:
    - The female inherits two mutated X chromosomes.
    - There is extreme skewing of X-inactivation.
    - One X is mutated, and the other is lost (Turner syndrome, XO).

De Novo Mutations

- **~30–33%** of Hemophilia B cases result from **spontaneous mutations**, with **no prior family history**.

Pathophysiology

Factor IX is a crucial component of the **intrinsic coagulation cascade**. Upon activation by factor XIa, it forms a complex with **factor VIIIa**, calcium ions, and phospholipids on platelet surfaces, leading to the activation of **factor X**. Activated factor X (Xa) then converts **prothrombin to**

thrombin , which facilitates **fibrin clot formation** .

Deficiency Consequences

- Impaired generation of thrombin.
- Inadequate fibrin clot formation.
- Increased risk of **spontaneous bleeding** or **prolonged bleeding** after injury/surgery.

Clinical Features

Severity Classification

Severity	Factor IX Activity	Clinical Presentation
Mild	6–49%	Bleeding with trauma/surgery
Moderate	1–5%	Rare spontaneous bleeding, bleeding with minor trauma
Severe	<1%	Frequent spontaneous bleeding, especially into joints and muscles

Common Bleeding Sites

- **Hemarthrosis** (joints – knees, elbows, ankles)
- **Muscle hematomas**
- **Epistaxis** (nosebleeds)
- **Hematuria**
- **Gastrointestinal bleeding** (melena, hematochezia)
- **Intracranial hemorrhage** (life-threatening)
- **Prolonged bleeding post-circumcision or tooth extraction**

Hemophilia B Leyden

- A rare variant characterized by **severe bleeding in childhood** with **spontaneous improvement after puberty** due to **androgen-responsive elements in the F9 promoter region** .

Diagnosis

Clinical Evaluation

- Detailed **personal and family history** of bleeding.
- History of **excessive bleeding after minor trauma or surgery** .
- **Joint pain/swelling** from recurrent hemarthroses.

Laboratory Investigations

Test	Expected Result
Prothrombin Time (PT)	Normal
Thrombin Time (TT)	Normal
Bleeding Time	Normal
Activated Partial Thromboplastin Time (aPTT)	**Prolonged**
Factor IX assay	**Decreased**
Factor VIII, vWF assays	Normal
Genetic testing (F9 mutation analysis)	Confirms diagnosis and risk of inhibitor development

Complications

- **Chronic arthropathy** due to repeated hemarthroses.
- **Inhibitor development** : Some patients develop **neutralizing antibodies** (inhibitors) against factor IX.
- **Psychosocial burden** due to chronic disease and disability.
- **Complications from treatment** : Viral infections (historically), allergic reactions, thrombosis.

Management and Treatment

General Principles

- **Patient education** : Genetic counseling, early bleeding recognition, avoid trauma.
- **Avoid NSAIDs** , especially **aspirin** , due to platelet inhibition.
- **Multidisciplinary care** : Hematologists, orthopedic surgeons, physiotherapists.

Factor Replacement Therapy

1. **Recombinant Factor IX**

   - First-line therapy.
   - **On-demand** or **prophylactic** infusion.
   - Long-acting formulations available.

2. **Plasma-derived Factor IX Concentrates**

   - Alternative when recombinant products are unavailable.

3. **Fresh Frozen Plasma (FFP)**

   - Only used in emergencies or when factor IX is unavailable.

Other Therapies

- **Tranexamic acid** : Antifibrinolytic agent used adjunctively, especially for mucosal bleeding.
- **Gene therapy** (emerging): Promising treatment with **AAV vector–based F9 gene transfer** , currently under trial or limited clinical use.

Inheritance Counseling

- All **daughters of affected males** are **obligate carriers** .
- Female carriers have a **50% chance** of transmitting the mutation to male offspring.
- **Prenatal genetic testing** or **preimplantation genetic diagnosis (PGD)** may be considered in high-risk families.

High-Yield Points

- **Hemophilia B** is caused by **factor IX deficiency** due to **F9 gene mutations** .
- It is **X-linked recessive** , affects **males predominantly** , and presents with **prolonged bleeding** .
- **Prolonged aPTT** with **normal PT, TT, and bleeding time** is typical.
- Treatment involves **recombinant factor IX** replacement.
- **Prophylactic therapy** improves quality of life and prevents complications.
- Genetic counseling is essential for affected families.