



IN THE NAME OF GOD

# *Hemophilia*

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# *Introduction*

- Inheritance: X-linked, recessive
- Bleeding disorder caused by a deficiency in the activity of coagulation factor VIII, IX.
- Hemophilia is typically expressed in males and carried by females
- Hemophilia occurs in approximately 1 in 5000 males.
- 80-85% Hemophilia A and 10-15% Hemophilia B.
- No racial and ethnic predilection

# Historical Background

- Hemophilia is one of the oldest described genetic diseases.
- An inherited bleeding disorder in males was recognized in Talmudic records of the second century AD.
- The first modern description of hemophilia in 1803 by John Conrad Otto, a Philadelphia physician.
- Hemophilia B was described in 1952.
- Hemophilia is sometimes referred to as the royal disease, because it affected the royal families of England, Germany, Russia and Spain in the 19<sup>th</sup> and 20<sup>th</sup> centuries.



# Epidemiology

- F VIII: 1 in 5000 live male births
- Half to two-thirds have severe disease
- F IX: 1 in 30,000 live male births
- One-thirds to half have severe disease
- Affect males almost exclusively

# *Hemophilia*

- Hemophilia A (factor VIII deficiency)
- Hemophilia B (factor IX deficiency)
- Hemophilia C (factor XI deficiency)

## *Hemophilia B*

- It is called “Christmas” disease because it was first discovered and found in a boy named Stephan Christmas in 1950s.

# *Severity of Hemophilia*

- **Severe :** <1% factor VIII clotting activity
- **Moderate:** 1-5 % factor VIII clotting activity
- **Mild :** 6-40 % factor VIII clotting activity
- **Normal factor** VIII or IX level = 50-150%
- **Hemostatic level F VIII:** 30-40%
- **Hemostatic level F IX:** 25-30%

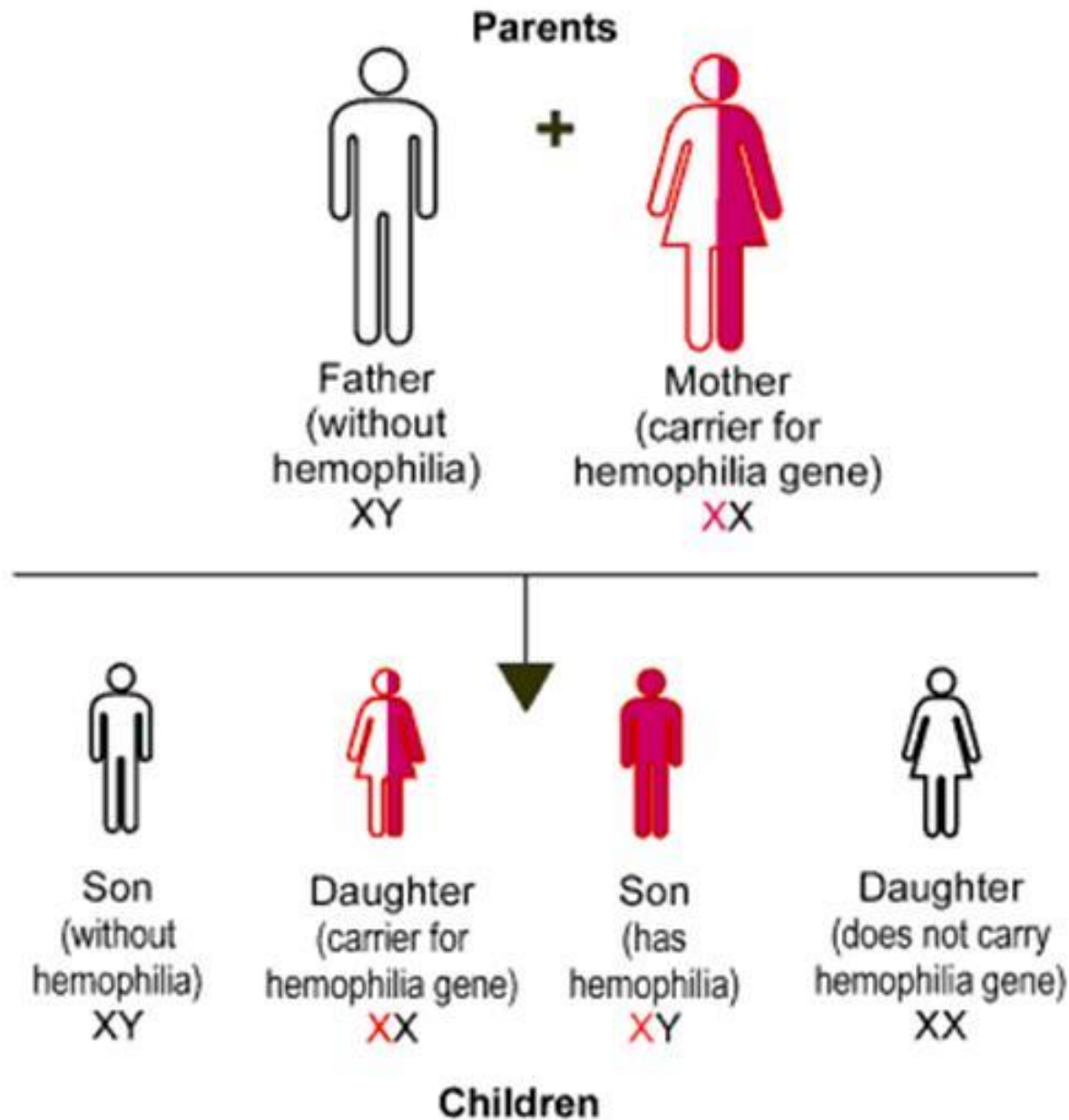


# *Genetics*

- Carrier females have a 50% chance of transmitting the F8 mutation in each pregnancy.
- Sons who inherit the mutation will be affected.
- Daughters who inherit the mutation are carriers.
- Affected males transmit the mutation to all of their daughters and none of their sons.
- ~30 % of cases of hemophilia are new mutations
- Inversion intron 22 in 45% of severe hemophilia A

# Inheritance of Hemophilia

## "Carrier" Mother and Father Without Hemophilia



**Father**  
(with hemophilia)

**XY**



+



**Mother**  
(without hemophilia)

**XX**



### **Affected children**

**Daughter**  
(carrier of  
hemophilia gene)

**XX**

**Daughter**  
(carrier of  
hemophilia gene)

**XX**

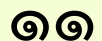
### **Unaffected children**

**Son**  
(without  
hemophilia)

**XY**

**Son**  
(without  
hemophilia)

**XY**



# Clinical Manifestations

## *Common site of hemorrhage*

Hemarthrosis

Intramuscular hematoma

Hematuria

Mucous membrane hemorrhage

- Mouth

- Dental

- Epistaxis

- Gastrointestinal

High-risk hemorrhage

- Central nervous system

  - Intracranial

  - Intraspinal

- Retropharyngeal

- Retropitoneal

Hemorrhage causing compartment syndrome/nerve compression

- Femoral (iliopsoas muscle)

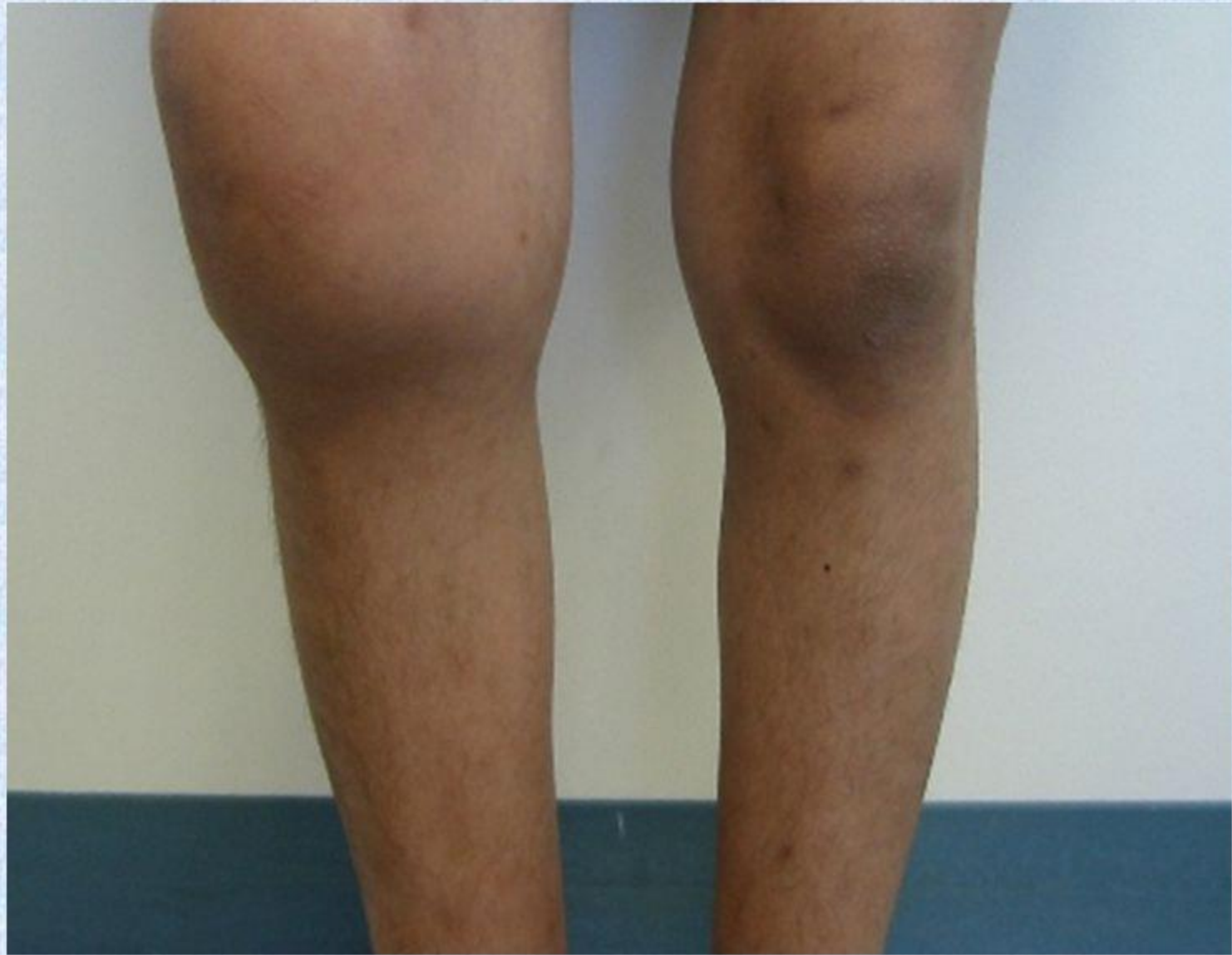
- Sciatic (buttock)

- Tibial (calf muscle)

- Perineal (anterior compartment of leg)

- Median and ulnar nerve (flexor muscles of forearm)

# Hemarthrosis (acute)







# *Diagnosis*

- Family history: negative in one-third
- Symptoms
- Laboratory testing
  - Prolonged aPTT
  - Factor VIII, IX assay
  - Platelets , PT , BT, TT is normal
- Genetic testing



- aPTT may be normal in milder factor deficiency( factor activity  $> 15\%$ ) especially in hemophilia B.
- FVIII level may increase with stress, leading to a normalization of the aPTT.
- The aPTT corrects in mixing studies, unless an inhibitor is present.
- VWF:Ag is normal in hemophilia.

# DDX of Hemophilia

- VWD: type 2N and type 3 have bleeding patterns similar to hemophilia
- F XI deficiency
- Combined F V and VIII deficiency
- Inherited platelet disorders
- F XIII deficiency
- Other factor deficiencies with prolonged aPTT: F XII, Prekallikrein, HMWK deficiency
- Acquired factor inhibitors



# *Treatment of Hemophilia*

- Replacement of missing clotting protein
  - On demand
  - Prophylaxis
- DDAVP / Stimate
- Antifibrinolytic Agents
  - Amicar
- Supportive measures
  - Icing
  - Immobilization
  - Rest
- Gene Therapy

## *Factor VIII Concentrate*

- Intravenous infusion
  - IV push
  - Continuous infusion
- Dose varies depending on type of bleeding
  - Ranges from 20-50 units/kg.
- Half-life 8-12 hours
- Each unit infused raises serum factor VIII level by 2 %

## *Calculation of Dose*

- Dose factor VIII (units) = U/dL desired rise in plasma factor VIII  
x BW(kg) x 0.5
- Example:
- for treatment of hemarthrosis in a 20-kg child with severe hemophilia A, to achieve a plasma level of 60 UI/dL, the dose would be  $60 \text{ U/dL} \times 20 \text{ kg} \times 0.5 = 600 \text{ units of factor VIII}$ .

## *Factor IX Concentrate*

- Intravenous infusion
  - IV push
  - Continuous infusion
- Dose varies depending on type of bleeding
  - Ranges from 20-100 units/kg.
- Half-life 18-24 hours
- Each unit infused raises serum factor IX level by 1%

## *Calculation of Dose*

- Dose of factor IX (units) = U/dL (percent) desired rise x BW(kg)
- Example:
  - for the treatment of hemarthrosis in a 20 kg child in whom a level of 80 U/dL is desired, the dose would be  $80 \text{ U/dL} \times 20 \text{ kg} = 1600$  units of factor IX



Haemonine® 500

Powder and solvent for solution for injection  
Active ingredient: human coagulation factor IX

Biotest

octanine® F

octanine® F 500

AQUA AD

**TABLE 30-1 Treatment of Specific Hemorrhages in Hemophilia**

Type of Hemorrhage	Hemophilia A	Hemophilia B*
Hemarthrosis <sup>†</sup>	50 U/kg factor VIII concentrate initially, <sup>‡</sup> 20 U/kg the following day; consider additional treatment every other day, depending on response	80 U/kg factor IX concentrate initially, 40 U/kg the following day; consider additional treatment every other day, depending on response
Muscle or significant subcutaneous hematoma	50 U/kg factor VIII concentrate; may need 20 U/kg every other day until well resolved	80 U/kg factor IX concentrate; may need 40 U/kg every other day until well resolved
Mouth, deciduous tooth, or tooth extraction	20 U/kg factor VIII concentrate (40 U/kg if molar extraction), antifibrinolytic therapy; remove loose deciduous tooth	40 U/kg factor IX concentrate (80 U/kg if molar extraction), antifibrinolytic therapy; remove loose deciduous tooth
Epistaxis	Apply pressure for 15-20 min, Nosebleed QR, pack with petrolatum gauze, antifibrinolytic therapy; 20 U/kg factor VIII concentrate if above fails	Apply pressure for 15-20 min, Nosebleed QR, pack with petrolatum gauze, antifibrinolytic therapy <sup>§</sup> ; 30 U/kg factor IX concentrate if above fails
Major surgery, life-threatening hemorrhage (e.g., central nervous system, gastrointestinal, airway)	50-75 U/kg factor VIII concentrate, then initiate continuous infusion of 3 U/kg/hr to maintain factor VIII > 100 U/dL for 24 hr, and then give 2-3 U/kg/hr for 5-7 days to maintain the level greater than 50 U/dL and an additional 5-7 days at a level >30 U/dL (bolus dosing to maintain these levels is acceptable); monitor factor VIII levels	80-100 U/kg factor IX concentrate, then 20-40 U/kg every 12-24 hr to maintain factor IX > 40 U/dL for 5-7 days, and then >30 U/dL for 5-7 days <sup>  </sup> ; monitor factor IX levels
Iliopsoas hemorrhage	50 U/kg factor VIII concentrate, then 25 U/kg every 12 hr until asymptomatic, and then 20 U/kg every other day for a total of 10-14 days <sup>¶</sup>	80 U/kg factor IX concentrate, then 20-40 U/kg every 12-24 hr to maintain factor IX > 40 IU/dL until asymptomatic, and then 30 U/kg every other day for a total of 10-14 days <sup>¶</sup>
Hematuria	Bed rest, 1.5 × maintenance fluids; if not controlled in 1-2 days, 20 U/kg factor VIII concentrate; if not controlled, prednisone if human immunodeficiency virus negative	Bed rest, 1.5 × maintenance fluids; if not controlled in 1-2 days, 30 U/kg factor IX concentrate; if not controlled, prednisone if human immunodeficiency virus negative

## *Prophylaxis*

- Scheduled infusions of factor concentrates to prevent most bleeding
- Frequency: 2 to 3 times weekly to keep trough factor VIII or IX levels at 2-3%
- Types
  - primary prophylaxis
  - secondary prophylaxis

# ***DDAVP***

*(Desmopressin acetate)*

- Synthetic vasopressin
- Method of action
  - release of stores from endothelial cells raising factor VIII and vWD serum levels
- Administration
  - Intravenous
  - Subcutaneously
  - Nasally (Stimate)
- Side effects

## *Stimate*

- How supplied
  - 1.5 mg./ ml (NOT to be confused with DDAVP nasal spray for nocturnal enuresis)
  - 2.5 ml bottle - delivers 25 doses of 150 mcg.
- Dosing
  - Every 24-48 hours prn
  - <50 kg. body weight - 1 spray (150 mcg.)
  - >50 kg. body weight - 2 sprays (300 mcg.)

## *Complications of Treatment*

- Inhibitors/Antibody development
- Hepatitis B
- Hepatitis C
- HIV

# *Inhibitors*

- *Definition*

- IgG antibody to infused factor VIII or IX concentrates, which occurs after exposure to the extraneous VIII or IX protein.

- *Prevalence*

- 20-30% of patients with severe hemophilia A
- 1-4% of patients with severe hemophilia B

## *Hemophilia Treatment Center Team Members*

- Patient / Family
- Hematologist
- Nurse
- Social Worker
- Physical Therapist
- Orthopedist
- Primary Care
- Infectious Disease
- Genetics
- Pharmacy
- Dentist
- Hepatology



# Sistan - Spring ۱۳۹۳

