

Hemophilia

- It is the most common severe inherited bleeding disorders.
- **Incidence** → 1/5000 males.
- **Types** → 1. *Hemophilia A* (classic hemophilia, factor 8 deficiency, 85% of the total).
2. *Hemophilia B* (Christmas disease, factor 9 deficiency, 10-15% of the total).
3. *Hemophilia C* (usually mild, factor 11 deficiency, 2% of the total).
- Reduced levels of contact factors (factor 12, high molecular weight kininogen & prekallikrein) are associated with significant prolongation of APTT(PTT) but are not associated with hemorrhage
- **Pathophysiology**→ Factor 8 & 9 participate in a complex required for the activation of factor 10. Together with phospholipids & calcium, they form the "tenase" or factor 10 activating complex. Prothrombin time (PT) measures the activation of factor 10 by factor 7 & is therefore normal in factor 8 or factor 9 deficiency.
- **Inheritance** → • Hemophilia A & B → X-linked recessive.
 - Hemophilia C → autosomal recessive.
 - about 30% of cases are due to new mutations.

Clinical presentations

- Hemophilia A & B result in clinically indistinguishable bleeding disorders of variable severity according to the levels of factor 8 (F8) or factor 9 (F9) in the plasma.
- The severity of hemophilia is classified into 3 grades :
 1. *Mild* → The concentration of the factor in the plasma > 5 unit (U)/dl (> 5%) → it requires significant trauma for bleeding to occurs.
 2. *Moderate* → The concentration of the factor in the plasma is 1-5 U/dl (1-5%) → it requires mild trauma for bleeding to occurs.
 3. *Severe* → The concentration of the factor in the plasma < 1U/dl (<1%) → spontaneous bleeding.
- The hemostatic level for F8 is > 30-40 IU/dl (%) & that for F9 is > 25-30 IU/dl (%).
- The normal level is 100 IU/dl (%). The lower normal limit is 50 IU/dl (%).
- Neither F8 nor F9 crosses the placenta → bleeding may present at birth or may occur in the fetus. Only 2% of neonates with hemophilia sustain intracranial hemorrhage & 30% of male infants with hemophilia bleed with circumcision. Obvious symptoms as easy bruising, intramuscular hematoma, & hemarthrosis begin when the child begins to cruise.

Bleeding from minor traumatic laceration of the mouth (a torn frenulum) may persist for hours or days & may cause the parents to seek medical evaluation.

- Although bleeding may occur at any area of the body, ***the hallmark of hemophilia is "hemarthrosis"*** i.e. bleeding into the joints. The earliest joint hemorrhages appear most commonly in the ankle. In the older child & adolescent, hemarthroses of the knees & elbows are also common. Whereas the child's early joint hemorrhages are recognized only after major swelling & fluid accumulation in the joint space, older children are frequently able to recognize bleeding before the physician does. They complain of warm, tingling sensation in the joint as a first sign of an early joint hemorrhage. Repeated bleeding episodes into the same joint in a patient with severe hemophilia may lead to a "**target**" joint with recurrent spontaneous bleeding due to the underlying pathologic changes in the joint.
- Other types of bleeding can be easy bruising, subcutaneous hematoma, mouth bleeds, & intramuscular hematoma.
- Occasionally, there may be a **life-threatening hemorrhage** as in bleeding into vital structures (intracranial hemorrhage & upper airways hemorrhage) or by exsanguinations (external trauma, GIT or iliopsoas hemorrhages).
- Some female carriers may have mild bleeding (lyonization of X-chromosome).

Differential Diagnosis → In young infants with severe bleeding manifestations, the differential diagnosis includes: severe thrombocytopenia, severe platelet function disorders (as Bernard-Soulier syndrome & Glanzmann thromasthenia), type 3 (severe) von Willebrand disease & vitamin K deficiency.

Diagnosis

- Prolonged PTT (partial thromboplastin time). In severe hemophilia, the PTT value is usually 2-3 times the upper limit of the normal.
- ↓ F8 or F9 levels in the plasma.
- Normal platelet count, bleeding time, prothrombin time (PT) & thrombin time (TT)
- Unless the patient has inhibitors to F8, the mixing of normal plasma with patient's plasma → correction of prolonged PTT.

Treatment

■ Treatment of the bleeding episodes

1. **Replacement therapy** → When bleeding occurs, the levels of F8 or F9 must be raised to the "hemostatic level" or to the level of 100 U/dl in the state of life-threatening or major hemorrhage :

- **F8 concentrate** (250 or 500 U/20 ml)
 - **Hemarthrosis** → F8 50 IU/kg on day 1, then 20 IU/kg on days 2,3,5 until the joint function is normal or back to baseline. Consider additional therapy every other day for 7-10 days. Consider prophylaxis.
 - **Intramuscular & significant subcutaneous hematoma** → F8 concentrate 50 IU/kg. 20 IU/kg every other day may be needed until resolved.
 - **Mouth, deciduous tooth, or tooth extraction** → F8 20 IU/kg, antifibrinolytic therapy, remove loose deciduous tooth.

- Epistaxis → apply pressure for 15-20 min, pack with petrolatum gauze, give antifibrinolytic therapy, F8 20 IU/kg if this treatment fails.

- Major surgery & life threatening hemorrhage → F8 concentrate 50-75 IU/kg, then initiate continuous infusion of 2-4 IU/kg/hr to maintain F8 >100 IU/dl for 24 hr then give 2-3 IU/kg/hr continuously for 5-7 days to maintain the level at >50 IU/dl & an additional 5-7 days to maintain the level at >30 IU/dl.

- Iliopsoas hemorrhage → F8 50 IU/kg, then 25 IU/kg every 12 hr until asymptomatic, then 20 IU/kg every other day for a total of 10-14 days with radiologic assessment.

- Hematuria → Bed rest, 1.5 maintenance fluids, if not controlled in 1-2 days → F8 20 IU/kg, if not controlled → prednisolone (unless patient HIV infected).

- Prophylaxis → F8 20-40 IU every other day to achieve a trough level $\geq 1\%$.

- Others → as "cryoprecipitate" which contains 125 U of F8/25 ml / bag, blood, or plasma (less effective).

2. *Drug therapy* → as desmopressin as intranasal spray or oral form (useful in mild hemophilia A, not effective for hemophilia B) & aminocaproic acid..

3. *Local hemostatic measures* :

- Application of a cold sponge & a pressure on the bleeding site.

- Hemarthrosis → immobilization of the affected joint for 2 days followed by gradual passive exercises. In severely painful joint with very tense overlying skin, aspiration of the blood after adequate F8 therapy will provide some relief.

■ Protective measures

1. Prophylactic treatment with F8 concentrate has been recommended for many young children with severe hemophilia to prevent spontaneous bleeding & early joint deformities.

2. Prevention of trauma.

3. Avoidance of aspirin & other NSAID.

4. Hepatitis B immunization.

5. Periodic investigations (for patients using plasma derivatives) like viral hepatitis B & C, AIDS & liver function tests.

6. Early psychological intervention helps the family achieve a balance between overprotection & permissiveness.

7. Today, patients with hemophilia are best managed through comprehensive hemophilia care centers with different specialities.

■ Genetic counseling → The patient & his family should realize that the disease is an X-linked disease, carried by asymptomatic mother to affect 50% of her sons, while 50% of her daughters will be a carriers as their mother

■ Note → The treatment of hemophilia B is F9 concentrate & of hemophilia C is fresh frozen plasma.

Complications

1. Chronic joint destructions.

2. Infections as hepatitis B & C, & AIDS. These infections may be ↓ by the use of the recombinant F8 or F9.

3. Inhibitors to F8 or F9 (25-35% in hemophilia A & somewhat lower in hemophilia B). treatment by desensitization programs (infusion of high doses of F8 or F9 to induce immune tolerance). If this fails → Rituximab (not approved by FDA) & bleeding episodes are treated with either recombinant activated factor 7 or activated prothrombin complex concentrate (may bypass the inhibitors but may increase the risk of thrombosis).

von Willebrand Disease (VWD)

- It is the most common hereditary bleeding disorder.
- **Incidence** → it may be as high as 1-2% of the population (males = females).
- **Functions of VW factor (VWF) :**
 1. Carrier protein for F8.
 2. Causes platelets adhesion to the damaged epithelium.
- Severe deficiency of VWF may → 2ry deficiency of F8.
- **Clinical presentations** → The bleeding is mild in most cases & restricted to the mucocutaneous bleeding, easy bruising, epistaxis, menorrhagia, post-surgical, & post-traumatic bleeding. Homozygous VWD (type 3) may → severe bleeding which may be clinically similar to, but milder than hemophilia.
- **Types** → There are several variants of VWD. The most common variants are :
 1. *Type 1* → The *most common* type (about 85% of cases). It is caused by the "*quantitative*" ↓ of *VWF*. It is inherited as autosomal dominant inheritance.
 2. *Type 2* (4 variants: A,B,M,N) → It is rare , more severe, & less responsive to treatment than type 1. It is caused by the "*qualitatively*" *abnormal VWF*. It is inherited as autosomal recessive inheritance.
 3. *Type 3* → it is also rare, more severe, & less responsive to treatment than type 1. It is caused by the *absence of VWF*. It is inherited as autosomal recessive inheritance.
 4. Platelet-type (pseudo-) VWD : associated with thrombocytopenia.
- **Diagnosis**
 1. Prolonged bleeding time (BT).
 2. prolonged PTT.
 - Note → Both PTT & BT may be normal in type 1 VWD.
 3. VWF assay → ↓ VWF antigen (quantity) or ↓ VWF activity.
 4. There may be ↓ F8 or thrombocytopenia.
- **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, caused by iron deficiency.

- Individuals with type 3 VWD can manifest joint or muscle bleeding similar to individuals with hemophilia
- **Treatment**
 1. *Desmopressin* (DDAVP) (for type 1 & some of type 2) : A dose 0.3 µg/kg IV will increase the level of VWF and factor VIII by 3- to 5-fold. Intranasal DDAVP (Stimate) is particularly helpful for the outpatient treatment of bleeding episodes. The dose is 150 µg (1 puff) for children weighing <50 kg and 300 µg (2 puffs) for those weighing >50 kg.
 2. *Replacement therapy* → VWF concentrate (for all types).

Idiopathic Thrombocytopenia Purpura (ITP)

- The most common cause of acute onset of thrombocytopenia in an otherwise well child.
- The normal platelet count is $150\text{--}450 \times 10^9/\text{L}$. *Thrombocytopenia* refers to a reduction in platelet count to $<150 \times 10^9/\text{L}$.

Etiology & Pathogenesis

- In about 1/20000 of children, 1-4 weeks after exposure to a common viral infection, an autoantibody directed against the platelet surface develops (for unknown reasons) with resultant sudden onset of thrombocytopenia.
- The peak age is 1-4 yr, although the age ranges from early in infancy to the elderly. In childhood, males and females are equally affected. ITP seems to occur more often in late winter and spring after the peak season of viral respiratory illness.
- A recent history of viral illness is described in 50-65% of cases of childhood ITP. Most common viruses have been described in association with ITP, including Epstein-Barr virus (ITP is usually of short duration & follows infectious mononucleosis) & HIV virus (ITP is usually chronic). In some patients, ITP appears to arise in children infected with *Helicobacter pylori* or rarely following the measles, mumps, rubella vaccine.
- After binding of the antibody to the platelet surface, circulating antibody-coated platelets are recognized by the FC-receptors on the splenic macrophage → ingestion & destruction of platelets.

Clinical manifestations

- The classic presentation of ITP is that of *a previously healthy 1-4 yrs old child who has sudden onset of generalized petechiae & purpura*.
- Often, there is bleeding from the gums & mucus membranes, particularly with profound thrombocytopenia (platelets count $< 10 \times 10^9 /\text{L}$).

- Findings on physical examination are normal, other than the finding of petechiae and purpura. Splenomegaly, lymphadenopathy, bone pain, and pallor are rare.
- An easy to use **classification system** has been proposed from the U.K. to characterize the severity of bleeding in ITP on the basis of symptoms and signs, but not platelet count: **1**→ **No symptoms**. **2**→ **Mild symptoms**: bruising and petechiae, occasional minor epistaxis, very little interference with daily living. **3**→ **Moderate**: more severe skin and mucosal lesions, more troublesome epistaxis and menorrhagia. **4**→ **Severe**: bleeding episodes—menorrhagia, epistaxis, melena—requiring transfusion or hospitalization, symptoms interfering seriously with the quality of life.
- The presence of abnormal findings as hepato-splenomegaly, bone or joint pain, or remarkable lymphadenopathy suggests other diagnosis (leukemia).
- When the onset is insidious especially in adolescents, chronic ITP, or a possibility of systemic illnesses as systemic lupus erythematosus (SLE), is more likely.
- Severe bleeding is rare (<3% of cases in 1 large international study).
- About 70-80% of cases of acute ITP will have *spontaneous resolution* within 6 months from the onset.
- Treatment does not appear to affect the natural course of ITP.
- *Less than 1%* of patients will develop *intracranial hemorrhage (ICH)*. Those who favor interventional therapy argue that the objective of early therapy is to raise the platelet count to $>20 \times 10^9/L$ and prevent the rare development of intracranial hemorrhage. There is no evidence that therapy prevents serious bleeding.
- Approximately 20% of children who present with acute ITP go on to have chronic ITP. The outcome/prognosis may be related more to age, as ITP in younger children is more likely to resolve whereas the development of chronic ITP in adolescents approaches 50%.

Diagnosis

- Severe *thrombocytopenia* (platelets count $<20 \times 10^9/L$) is common. Platelet size is normal or \uparrow .
- Hb is usually normal but may be \downarrow with severe bleeding (as nose bleeds & menorrhagia).
- *Bone marrow examination* reveals normal granulocytic & erythrocytic series & characteristic normal or \uparrow megakaryocytes. Some of the megakaryocytes may appear to be immature and are reflective of increased platelet turnover.

■ Indications of bone marrow examination :

1. Abnormal WBC count or differential count.
2. Unexplained anemia.
3. findings on history and physical examination suggestive of a bone marrow failure syndrome or malignancy.

- Other investigations according to the history & physical examination :
 - Antinuclear antibody (ANA) for adolescent females to evaluate SLE.
 - HIV studies should be done in at-risk populations, especially sexually active teens.
 - Coomb's test for unexplained anemia & Evan's syndrome (acute hemolytic anemia + thrombocytopenia) or before instituting therapy with IV anti-D.

Differential diagnosis → • Exposure to medications • Splenic sequestration due to previous Portal hypertension • Early aplastic process as fanconi anemia
• Amegakaryocytic thrombocytopenia • HUS • DIC • SLE
• Thrombocytopenia & absent radius (TAR) • HIV • Lymphoma
• Wiskot-Aldrich syndrome

Treatment

- There are no data showing that treatment affects either short- or long-term clinical outcome of ITP.
- Initial approaches to the management of ITP include the following:
 1. **No therapy other than education and counseling** of the family and patient for patients with minimal, mild, and moderate symptoms, as defined earlier. This approach emphasizes the usually benign nature of ITP. This approach is far less costly, and side effects are minimal.
 2. **Intravenous immunoglobulins (IVIG)** at a dose of 0.8-1 g/kg/day for 1`-2 days induces a rapid rise in platelet count (usually $>20 \times 10^9/L$) in 95% of patients within 48 hr. It is expensive & time consuming to administer. Additionally, after infusion, there is a high frequency of headaches and vomiting, suggestive of IVIG-induced aseptic meningitis. IVIG appears to induce a response by downregulating Fc-mediated phagocytosis of antibody-coated platelets.
 3. **Intravenous anti-D therapy.** For Rh positive patients, IV anti-D at a dose of 50-75 mg/kg causes a rise in platelet count to $>20 \times 10^9/L$ in 80-90% of patients within 48-72 hr. When given to Rh positive individuals, IV anti-D induces mild hemolytic anemia. RBC-antibody complexes bind to macrophage Fc receptors and interfere with platelet destruction, thereby causing a rise in platelet count. IV anti-D is ineffective in Rh negative patients. Rare life-threatening episodes of intravascular hemolysis have occurred in children and adults following infusion of IV anti-D.
 4. **Prednisone.** Corticosteroid therapy has been used for many years to treat acute and chronic ITP in adults and children. Doses of prednisone of 1-4 mg/kg/24 hr appear to induce a more rapid rise in platelet count than in untreated patients with ITP. Whether bone marrow examination should be performed to rule out other causes of thrombocytopenia, especially acute lymphoblastic leukemia, before institution of prednisone therapy in acute ITP is controversial. Corticosteroid therapy is usually continued for 2-3 wk or until a rise in platelet count to $>20 \times 10^9/L$ has been achieved, with a rapid taper to avoid the long-term side effects of corticosteroid therapy, especially growth failure, diabetes mellitus, and osteoporosis.

5. *Splenectomy* → Indications :

- Older child ≥ 4 yrs old with severe ITP that has lasted >1 yr (chronic ITP) and whose symptoms are not easily controlled with therapy.
- With life-threatening hemorrhage (as ICH) & not corrected by platelets transfusion, IVIG or steroids.
- Splenectomy is associated with a lifelong risk of overwhelming postsplenectomy infection caused by encapsulated organisms and the potential development of pulmonary hypertension in adulthood.

6. *Platelets transfusion* → rarely needed in life-threatening hemorrhage.

■ In the special case of intracranial hemorrhage, multiple modalities should be used, including platelet transfusion, IVIG, high-dose corticosteroids, and prompt consultation by neurosurgery and surgery.