Bleeding disorders

Objectives:
1. Discuss briefly the physiology of hemostasis.
2. Define the mechanisms of thrombocytopenia and the relative bleeding risk at any given platelet count.
3. Be able to describe the common ways that bleeding disorders present in childhood as congenital (e.g. congenital ITP, hemophilia) or acquired conditions (e.g. ITP or Disseminated Intra-Vascular Coagulation).
4. Describe the usual presentation and laboratory tests in the child who has acute idiopathic thrombocytopenic purpura, review the treatments, and know the usual prognosis.
5. Be able to outline the principles of acute and chronic management of bleeding disorders of childhood dependent upon their cause.

Normal hemostasis
It is the active process that clots blood in areas of blood vessel injury, yet simultaneously limits the clot size only to the areas of injury. As a result of injury to the blood vessel endothelium, three events take place simultaneously:
- Vasoconstriction (vascular phase)
- Platelet plug formation (primary haemostatic mechanism — platelet phase)
- Fibrin thrombus formation (secondary haemostatic mechanism — plasma phase)

Hemostatic failure:
Inappropriate and excessive bleeding either spontaneous or in response to injury.

Bleeding manifestations
In disorders of hemostasis the bleeding manifestations are commonly at more than one site.
1. Spontaneous bruising or purpura (In general, bruises that are not limited to the distal extremities and are associated with hematomas and bruising out of proportion to the mechanism of injury are more indicative of an underlying hemostatic disorder.)
2. Bleeding from mucous membranes, e.g. nose/mouth, gastrointestinal tract, urogenital tract. (Epistaxis is a common childhood complaint and most likely is due to local factors such as drying of the nasal mucosa, trauma, or allergic rhinitis. However, among patients referred to a pediatric hematology clinic for recurrent epistaxis, 25% to 33% are diagnosed as having a bleeding disorder).
3. Bleeding from venepuncture, intravenous cannulation and operation sites and from tooth sockets post dental extraction (Surgical bleeding in children is associated most often with circumcision, tonsillectomy, and dental extractions. In addition to uncontrolled bleeding in the surgical field, bleeding in an affected individual may extend beyond the surgical site (ie, drains, vascular access), with associated poor wound healing and infection.)
4. Bleeding into muscles, joints or deep tissues. Intramuscular hematomas may be more difficult to see, but they cause swelling of the muscle group and pain with use of the muscle. Hemarthrosis (bleeding into a joint) causes joint effusion, warmth, and pain with passive movement of the joint and is a common feature of hemophilia. For young children, refusal to walk or use the affected limb may be the only apparent sign.

5. Menorrhagia

6. Cerebral haemorrhage

**What is the clinical phenotype of the bleeding?**

I. Mucosal bleeding characterized by easy bruisability, epistaxis, menorrhagia, petechiae, and oozing from surgical wounds is most consistent with a defect in primary hemostasis. The pediatrician should consider defects in platelets, vWF, or the vessel wall.

II. Deep-tissue bleeding (hematomas, joint and muscle hemorrhages) and “delayed” surgical bleeding are more suggestive of a coagulation factor abnormality. The most common disorder in this group is hemophilia, but other rare clotting factor deficiencies can occur.

**Clinical manifestations of disorders hemostasis:**

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Platelets defect</th>
<th>Clotting factor deficiency</th>
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<tbody>
<tr>
<td>Site of bleeding</td>
<td>Skin, mucous membranes(gingival, nares, GI and genitourinary tracts)</td>
<td>Deep in soft tissues (joints, muscles)</td>
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<tr>
<td>Bleeding after minor cuts</td>
<td>Yes</td>
<td>Not usually</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Ecchymoses</td>
<td>Small, superficial</td>
<td>Large, palpable</td>
</tr>
<tr>
<td>Hemarthroses, muscle hematomas</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Bleeding after surgery</td>
<td>Immediate, mild</td>
<td>Delayed, severe</td>
</tr>
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Clinical Evaluation of Hemostasis

- **History:**
  1. The site or sites of bleeding
  2. The severity and duration of hemorrhage, and the age at onset.
  3. Was the bleeding spontaneous, or did it occur after trauma, did the symptoms correlate with the degree of injury or trauma?
  4. Was there a previous personal or family history of similar problems?
  5. If a child or adolescent has had surgery affecting the mucosal surfaces, such as a tonsillectomy or major dental extractions, the absence of bleeding usually rules out a hereditary bleeding disorder
  6. It is important to take a careful menstrual history
  7. Drugs: especially anticoagulants, aspirin, non-steroidal anti-inflammatory agents and Cytotoxics

- **Laboratory Evaluation**

An appropriate and reliable laboratory approach, including first-line (screening) and second-line (specific) testing, is essential to screen, diagnose, and monitor patients who have bleeding diatheses. The available clinical assays also can be grouped according to whether they evaluate components of primary hemostasis or coagulation factors.

**First-line (screening) tests:**

1. A complete blood count and evaluation of the peripheral blood smear
2. Bleeding time: bleeding usually stops within 4–8 min
3. Platelet function analyzer (PFA-100): to evaluate the platelet function and Von Willebrand Factor (VWF) interaction
4. PT is a measure of the extrinsic (FVII) and common pathway (FV, FX, prothrombin, fibrinogen) clotting factors.
5. PTT measures the contact system (prekallikrein, FXII) as well as the intrinsic (FVIII, FIX, FXI) and common pathway clotting factors.

**Second-line (specific) tests:**

- Clotting factor assays
Coagulation factor deficiency

Congenital
Usually single factor deficiencies. Sometimes clinically apparent at birth, but mild deficiencies may not become apparent until adolescence or adult life, e.g. Haemophilia A (Factor VIII) and B (Factor IX, Christmas disease), Von Willebrand's disease, Factor XI deficiency.

Acquired
Commoner; Usually associated with multiple factor deficiencies, secondary to underlying disease or drug treatment.
1. Decreased production: e.g. liver disease, Vitamin K deficiency –neonates, malabsorption
2. Increased consumption: DIC
3. Circulating inhibitors: e.g. antibodies –especially to F. VIII and associated with SLE.
4. Drugs: heparin and warfarin.
5. Dilution: massive, rapid blood transfusion.

Factor VIII or Factor IX Deficiency (Hemophilia A or B)
Deficiencies of factors VIII and IX are the most common severe inherited bleeding disorders.
Pathophysiology
Factors VIII and IX participate in a complex required for the activation of factor X. Together with phospholipid and calcium, they form the “tenase,” or factor X-activating, complex.
After injury, the initial hemostatic event is formation of the platelet plug, together with the generation of the fibrin clot that prevents further hemorrhage.
In hemophilia A or B, clot formation is slow & soft, it may be friable, and re-bleeding occurs during the physiologic lysis of clots or with minimal new trauma.
Clinical Manifestations
Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus.
Only approximately 2% of neonates with hemophilia sustain intracranial hemorrhages and 30% of male infants with hemophilia bleed with circumcision.
Obvious symptoms of easy bruising, intramuscular hematomas, and hemarthroses begin when the child “begins to cruise.”
The hallmark of hemophilia is hemarthrosis. Bleeding into the joints may be induced by minor trauma; many hemarthroses are spontaneous. The earliest joint hemorrhages appear most commonly in the ankle. In the older child and adolescent, hemarthroses of the knees and elbows are also common.
Life-threatening bleeding in the patient with hemophilia is caused by bleeding into vital structures (central nervous system, upper airway, gastrointestinal, or iliopsoas hemorrhage)

Laboratory Findings & Diagnosis
- The laboratory screening test that is affected by a reduced level of factor VIII or factor IX is PTT
- Platelet count, bleeding time, prothrombin time, and thrombin time are normal
- The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia

Genetics & Classification
Hemophilia occurs in approximately 1:5,000 males, with 85% having factor VIII deficiency and 10–15% having factor IX deficiency. Hemophilia shows no apparent racial predilection, appearing in all ethnic groups.
The genes for factors VIII and IX are carried near the terminus of the long arm of the X chromosome and are therefore X-linked traits.

Treatment
Early, appropriate therapy is the hallmark of excellent hemophilia care.
- When mild to moderate bleeding occurs, levels of factor VIII or factor IX must be raised to hemostatic levels in the 35–50% range.
- For life-threatening or major hemorrhages, the dose should aim to achieve levels of 100% activity.
- A concentrated intranasal form of desmopressin acetate can also be used to treat patients with mild hemophilia A, it is not effective in hemophilia B

With the availability of recombinant replacement products, prophylaxis has become the standard of care for most children with severe hemophilia to prevent spontaneous bleeding and early joint deformities
Supportive Care

- Advise parents that their child should avoid trauma
- Avoid violent contact sports
- Early psychosocial intervention helps the family to achieve a balance between overprotection and permissiveness.
- Avoid aspirin and non-steroidal anti-inflammatory drugs that affect platelet function.
- Receive the vaccinations against hepatitis B, even with the use of recombinant products
- Patients exposed to plasma-derived products should be screened periodically for hepatitis B and C, HIV, and abnormalities in liver function.

Chronic Complications

Long-term complications of hemophilia A and B include:
1. Chronic arthropathy.
2. The development of an inhibitor to either factor VIII or factor IX.
3. The risk of transfusion-transmitted infectious diseases.

Von Willebrand Disease (VWD)

It is the most common hereditary bleeding disorder, it is present in 1–2% of the general population. VWD is inherited autosomally, but most centers report more affected women than men. Because menorrhagia is a major symptom, women may be more likely to seek treatment and thus to be diagnosed. VWD is classified on the basis of whether the protein is quantitatively reduced, but not absent (type 1); qualitatively abnormal (type 2); or absent (type 3)

Clinical Manifestations

Patients with VWD usually have symptoms of mucocutaneous hemorrhage, including excessive bruising, epistaxis, menorrhagia, and postoperative hemorrhage, particularly after mucosal surgery, such as tonsillectomy or wisdom tooth extraction

Because VWF is an acute-phase protein, stress will increase its level. Thus, patients may not bleed with procedures that incur major stress, such as appendectomy and childbirth, but may bleed excessively at the time of cosmetic or mucosal surgery

Laboratory Findings

Although patients with VWD have a long BT and a long PTT, these findings are frequently normal in patients with type 1 VWD. So Normal results on screening tests do not exclude the diagnosis of VWD. If the history is suggestive of a mucocutaneous bleeding disorder, VWD testing should be undertaken
Treatment
It is directed toward increasing the plasma level of VWF and factor VIII.
In type 1 VWD, the synthetic drug DDAVP induces the release of VWF from endothelial cells
Current replacement therapy uses plasma-derived VWF containing concentrates that also contain factor VIII.
Purified or recombinant VWF concentrates (containing no factor VIII) may become available in the near future
Dental extractions and sometimes nosebleeds can be managed with both DDAVP and an antifibrinolytic agent

Platelet abnormalities

Quantitative

I. Decreased bone marrow production:
   1. Malignant marrow infiltration—leukemia, lymphoma
   2. Drugs—Co-trimoxazole, Cytotoxics
   3. Severe megaloblastic anemia
   4. Hypoplastic anemia

II. Decreased platelet survival (peripheral consumption):
   1. Immune mechanisms:
      A. Primary—immune thrombocytopenia (ITP)
      B. Secondary—SLE, lymphoma
      C. Drugs—Thiazides, Sulfonamides
   2. Excessive consumption:
      A. Disseminated intravascular coagulation (DIC)
      B. Sequestration with splenomegaly

Qualitative

Inherited: e.g. Bernard Soulier syndrome, thrombasthenia

Acquired: e.g. myeloproliferative diseases, uraemia, Drugs, e.g. aspirin and non-steroidal anti-inflammatory drugs.
Idiopathic Thrombocytopenic Purpura (ITP)

Bleeding disorder characterized by isolated low platelet count (Plts < 130 - 150 x 10⁹/L)

The most common cause of acute onset of thrombocytopenia in an otherwise well child. 1–4 wk after exposure to a common viral infection, an autoantibody directed against the platelet surface develops.

ITP is caused by an antiplatelet antibody that binds to the platelet surface and enhances its destruction by Fc receptor-mediated phagocytosis in the spleen and liver.

Demography

Estimate incidence: about 2.5-5 / 100,000 children per year

Sex distribution: M = F

Age distribution: More frequent in children aged between 2 and 8 years

Seasonal predilection: springtime

Duration: Usually 2-6 weeks

Clinical Manifestations

- No symptoms
- Mild symptoms: bruising and petechiae, occasional minor epistaxis, very little interference with daily living
- Moderate: more severe skin and mucosal lesions, more troublesome epistaxis and menorrhagia
- Severe: bleeding episodes—menorrhagia, epistaxis, melena—requiring transfusion or hospitalization, symptoms interfering seriously with the quality of life

The classic presentation is that of a previously healthy 1–4 yr old child who has sudden onset of generalized petechiae and purpura.

Often there is bleeding from the gums and mucous membranes, particularly with profound thrombocytopenia (platelet count <10 x 10⁹/L).

Findings on physical examination are normal, other than the finding of petechiae and purpura.

The presence of hepatosplenomegaly or remarkable lymphadenopathy, suggests other diagnoses (leukemia).
Laboratory Findings
Platelets < 130 - 150 x 10^9/L, often have severe thrombocytopenia (platelet count < 20 x 10^9/L) is common
The hemoglobin value, white blood cell (WBC) count, and differential count should be normal
Bone marrow examination is normal with normal or increased megakaryocytes.
Indications for bone marrow aspiration include an abnormal WBC count or differential or unexplained anemia, findings suggestive of bone marrow disease on history and physical examination.

ITP is a Diagnosis of exclusion
- History: careful drug history
- Examination: healthy appearing child, no hepatosplenomegaly, no lymphadenopathy, has petechiae, purpura and occasionally mucous membrane bleeding.
- Blood counts: CBC should be normal except thrombocytopenia
- Peripheral smear evaluation: essential to
  - Rule out platelets clumping
  - Evaluate WBC and RBC morphology
  - Evaluate size of platelets

General Considerations for Initial Management:
The majority of patients with no bleeding or mild/moderate bleeding (defined here as skin manifestations only, such as petechiae and bruising) can be treated with observation alone regardless of platelet count.
The goal of all treatment strategies for ITP is to achieve a platelet count that is associated with adequate hemostasis (> 20 x 10^9/L) and prevent the rare development of intracranial hemorrhage, rather than a normal platelet count.
First-line treatment includes observation, corticosteroids, IV Ig, or anti-D immunoglobulin (anti-D).
There are no data showing that treatment affects either short- or long-term clinical outcome of ITP
- Prednisone; 2 mg/kg/d or for 14 days, followed by a tapering down dose and discontinuation on day 21.
- Intravenous immunoglobulin (IVIG) at a dose of 0.8–1.0 g/kg/day for 1–2 days induces a rapid rise in platelet count (usually>20× 10⁹/L) in 95% of patients within 48 hr.
- Intravenous anti-D for Rh positive patients causes a rise in platelet count to>20× 10⁹/L in 80–90% of patients within 48–72 hr.
- In the special case of intracranial hemorrhage, multiple modalities should be used, including platelet transfusion, IVIG, high-dose corticosteroids, and prompt surgical consultation, with plans for emergency splenectomy.

**Prognosis**

In 70–80% of children who present with acute ITP, spontaneous resolution occurs within 6 mo. Less than 1% of patients have intracranial hemorrhage. Approximately 20% of children who present with acute ITP go on to have chronic ITP.

**Laboratory evaluation of bleeding disorders:**
Henoch-Schönlein Purpura

(HSP) is characterized by the sudden development of a purpuric rash, arthritis, abdominal pain, and renal involvement.

The characteristic rash, consisting of petechiae and often palpable purpura, usually involves the lower extremities and buttocks.

Coagulation studies are normal.

The pathologic lesions in the skin, intestines, and synovium, inflammatory damage to the endothelium of the capillary mediated by WBC & macrophages.

The trigger for HSP is unknown. In the kidney, there is focal glomerulonephritis with deposition of immunoglobulin A.