Bleeding Disorders

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Normal hemostasis

The normal hemostatic response involves interactions among:

- The blood vessel wall (endothelium) and vascular smooth muscles, as part of vasoconstriction
- The platelets (thrombocytes)
- The plasma protein clotting (coagulation) cascade
Responses to vessel injury

1. Vasoconstriction to reduce blood flow

2. Platelet plug formation (von Willebrand factor binds platelets to subendothelial collagen)

3. Activation of clotting cascade with generation of fibrin clot formation

4. Fibrinolysis (clot breakdown)
What Causes Bleeding Disorders?

- VESSEL DEFECTS
- PLATELET DISORDERS
- CLOTTING FACTOR DEFICIENCIES
VESSEL DEFECTS

- SIMPLE PURPURA (easy bruising)
- SENILE PURPURA
- VITAMIN C DEFICIENCY
- BACTERIAL & VIRAL INFECTIONS
- AMYLIDOSIS
- HEREDITARY
What Causes Bleeding Disorders?

- VESSEL DEFECTS
- PLATELET DISORDERS
- FACTOR DEFICIENCIES
NORMAL COAGULATION

There are 3 stages in normal coagulation:

- **Primary hemostasis** is provided by platelets (adhesion & aggregation).

- **Secondary hemostasis** is provided by the plasma protein clotting factors.

- **Tertiary hemostasis** is the formation of fibrin polymers (Fibrin cross linking) and their subsequent resolution through fibrinolysis.
What tests used to evaluate bleeding disorders

- **Bleeding time**
  2-9 minutes. Prolonged in thrombocytopenia

- **Platelet counts**
  150-450 $10^3$/mm$^3$

- **Prothrombin time (PT)**
  Measures the adequacy of the extrinsic (V, VII, X) and common (prothrombin, fibrinogen) coagulation pathways
  10-15 secs

- **activated Partial thromboplastin time (aPTT)**
  Measures the adequacy of the intrinsic (V, VIII, IX, XI, VII) and common (prothrombin, fibrinogen) coagulation pathways
  The normal range is ~30 – 50 secs

- **Thrombin time**
  Time for thrombin to convert fibrinogen to fibrin
  9-13 secs

- **Other specific tests**
Coagulation

- **Primary hemostasis (platelet plug)**
  - **Adhesion**…vWF released from injured endothelium increases the “stickiness” of platelets.
  - Attached platelets release various chemicals including **arachidonic acid** which is converted by **cyclooxygenase** to **thromboxane A_2** which accelerates the **aggregation** of platelets and is a potent vasoconstrictor.
  - **Fibrinogen** with **factor XIII** forms a bridge between the proteins on the surface of platelets, producing the **platelet plug**.
PLATELET DISORDERS

THROMBOCYTOPENIA

Reduced platelets count

<100,000/μl  BT prolonged
≈20,000  Bleeding in trauma
<10,000  Spontaneous, CNS bleeding
Causes of thrombocytopenia

1. **Bone marrow disorders** (decreased platelet production due to failure of megakaryocyte maturation)
   - Hypoplasia
     - Idiopathic
     - Drug-induced (cytotoxic, alcohol, thiazides)
   - Infiltration
     - Tumors (leukemia, myeloma, carcinoma)
   - B12/folate deficiency

2. **Increased consumption of platelets**
   - Disseminated intravascular coagulation (DIC)
   - Hypersplenism due Lymphomas, Liver disease, & Malaria

3. **Increase destruction of platelets**
   - Idiopathic thrombocytopenic purpura
Clinical presentation of thrombocytopenia

Superficial Bleeding in the skin & mucus membrane, like
1. Petechiae (reddish purple spots)
2. Purpura
3. Gum bleeding
4. Epistaxis
5. Gastrointestinal bleeding (Fresh blood or melena)
6. Hematuria
Petechiae → Purpura → Ecchmosis

Petechiae
(typical of platelet disorders)

- Do not blanch with pressure
  (DD. angiomas)
- Not palpable (DD. vasculitis)
Petechiae

Purpura

Ecchymosis
Diagnosis

- The first step in the laboratory evaluation of a thrombocytopenic should include a complete blood count with examination of a peripheral blood smear and a coagulation screen. These tests can help to diagnose potentially life threatening conditions such as infections, DIC, or NEC.

- Other: mean platelet volume determination, reticulated platelet counts, platelet survival study, platelet-associated immunoglobulin G (IgG) assay, and measurement of thrombopoietin levels.
Treatment

- Currently, platelet transfusions remain the only treatment option for most sick thrombocytopenic infants.
- However, there is general agreement that in sick preterm infants, the platelet count should be maintained well above 50*10^9/L, especially during the first week of life to reduce the risk of intraventricular hemorrhage (IVH).
Idiopathic (immune) Thrombocytopenic Purpura

- the most common cause of isolated thrombocytopenia
- autoimmune disease with shortened platelets life span
- forms of ITP
  - acute ITP
    - children (90% of pediatric cases of immune thrombocytopenia)
    - preceded by viral infection
    - Self Limited and > 90% remission rate
    - spontaneous recovery within 4-6 weeks in 60% of patients
  - chronic ITP
    - 20-40 years
    - women predominance F:M = 3:1
Idiopathic (immune) Thrombocytopenic Purpura

- **Clinical features**
  - petechiae
  - ecchymoses
  - Mucous membranes bleeding
  - rare internal, intracranial bleeding

- **Diagnosis**
  - Low platelet count
  - bleeding time - prolonged
  - peripheral blood smear - large platelets
  - bone marrow examination - increased number of megakaryocytes
  - antibodies against glycoprotein IIb/IIIa (*not widely available*)
Treatment

The choice of treatment depends on the severity of the thrombocytopenia.

1. Prednisone 2 to 4mg/kg/24hrs 2 weeks
2. IV Immunoglobine 1g/kg/24hrs for 1 to 2 days
3. IV Anti D 50 to 75 ug/kg for Rh+
4. Splenectomy
5. immunosuppressive
What Causes Bleeding Disorders?

- VESSEL DEFECTS
- PLATELET DISORDERS
- FACTOR DEFICIENCIES
Coagulation

- **Secondary hemostasis**
  - It's due to clotting factors deficiency
Coagulation Tests

- **PT prolonged, but aPTT normal**
  - Factor **VII** decrease or defect
  - Defect in common pathway

- **aPTT prolonged, but PT normal**
  - Decrease or defect of factors **VIII, IX, XI, XII**
  - Defect in common pathway

- **PT and aPTT both prolonged**
  - Common pathway
  - Multiple factors involved (**both arms**)
FACTOR DEFICIENCIES
(CONGENITAL)

- HEMOPHILIAS
  Caused by lack of coagulation factors

- VON WILLEBRAND’S DISEASE
  Caused by lack of von willebrand’s factor
Types of Hemophilia

- **Hemophilia A**
  Absence or deficiency of Factor VIII

- **Hemophilia B** (Christmas Disease)
  Absence or deficiency of Factor IX

- **Hemophilia C**
  Absence or deficiency of Factor XI
  Very rare and mild
Haemophilia Inheritance

- Hemophilia is an X-linked gene disease.
- A father with the X-linked gene will pass it to all his daughters resulting in heterozygous carriers.
- A mother who is a carrier of the mutant gene will pass the gene on to half her sons and half her daughters. All her sons will have hemophilia and all her daughters will be heterozygous carriers.

- Females are carriers
- Males have the disease
Hemophilia A & B

- Hemophilia A is 90-80% of all Hemophiliacs
- Hemophilia B is 10-15% of all Hemophiliacs
- Factor VIII ... 1:10,000 males
- Both X-linked recessive
- Rare females..., inherited from both parents.
- One-third of new cases represent spontaneous genetic mutation.
Hemophilia A & B

Clinical manifestations are indistinguishable

- Hemarthrosis (most common)
  Fixed joints
- Soft tissue hematomas (e.g., muscle)
  Muscle atrophy
  Shortened tendons
- Other sites of bleeding
  Urinary tract
  CNS, neck (may be life-threatening)
- Prolonged bleeding after surgery or dental extractions
Severity of hemophilia depends upon the level at which factor VIII is deficient.

<table>
<thead>
<tr>
<th>Factor VIII levels</th>
<th>Type</th>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td>6% - 30%</td>
<td>Severe hemophilia</td>
<td>Severe hemorrhage, deep tissue bleeding.</td>
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<td></td>
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<td>Present within first year of life.</td>
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<tr>
<td>1% - 5%</td>
<td>Moderate hemophilia</td>
<td>Bleeding after mild trauma.</td>
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<td>Present during childhood.</td>
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<tr>
<td>&lt; 1%</td>
<td>Mild hemophilia</td>
<td>Bleeding after severe trauma and surgery.</td>
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<tr>
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<td></td>
<td>Present during adulthood.</td>
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Joint Hemorrhages (Hemarthrosis)

- Most common problem in haemophilia
- Symptoms include prolonged bleeding, pain and disabled joints
- Repeated joint bleeding leads to synovial inflammation and increased vascularity and thickening of the synovium.
Thigh muscle bleedings
Ecchymoses (severe)

(typical of coagulation factor disorders)
TREATMENT

- administration of FVIII and FIX concentrates (highly purified or recombinant) is the treatment of choice for hemophilia.

- In cases of severe bleeding with pending factor assay results, FFP may be used.

- Dosage of replacement factor strongly depends on the site and severity of the bleed.

- Target levels of FVIII/IX range from 40% to 50% in muscular bleeds to 100% in ICH.
<table>
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<tr>
<th>Clinical Features of Bleeding Disorders</th>
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<tbody>
<tr>
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<tr>
<td><strong>Site of bleeding</strong></td>
</tr>
<tr>
<td>Petechiae</td>
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<tr>
<td>Ecchymoses (&quot;bruises&quot;)</td>
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<tr>
<td>Hemarthrosis / muscle bleeding</td>
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<tr>
<td>Bleeding after cuts &amp; scratches</td>
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<tr>
<td>Bleeding after surgery or trauma</td>
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<td></td>
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<tr>
<td><strong>Platelet disorders</strong></td>
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<tr>
<td><strong>Coagulation factor disorders</strong></td>
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<tr>
<td><strong>Superficial in Skin</strong></td>
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<tr>
<td>Mucous membranes (epistaxis, gum, GIT)</td>
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<tr>
<td>Deep in soft tissues</td>
</tr>
<tr>
<td>(joints, muscles)</td>
</tr>
<tr>
<td>Yes</td>
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<tr>
<td>Small, superficial</td>
</tr>
<tr>
<td>Extremely rare</td>
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<tr>
<td>Yes</td>
</tr>
<tr>
<td>Immediate, usually mild</td>
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<tr>
<td>No</td>
</tr>
<tr>
<td>Large (hematomas), deep</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>No</td>
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<tr>
<td>Delayed (1-2 days), often severe</td>
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</tbody>
</table>
- Remember the basic differences between bleeding associated with coagulation factor deficiencies and bleeding associated with platelet problems.

- **Superficial bleeding** such as petechiae, bruises, epistaxis, and hematuria generally reflect a quantitative or qualitative deficiency of platelets.

- **Deep bleeding** such as in joints and hematomas generally arise as the result of a coagulation deficiency.
FACTOR DEFICIENCIES
VON WILLEBRAND’S DISEASE
von Willebrand’s Disease

- von Willebrand factor (vWF) is a glycoprotein synthesized in endothelial cells and megakaryocytes.

- vWF has two functions:
  - Directs platelets to adhere to sites of endothelial injury (1st homeostasis).
  - Complexes with factor VIII in the plasma protecting it from inactivation and destruction “Protein carrier”. (2nd homeostasis).

- Therefore in vW disease:
  - Bleeding time is prolonged due to poor platelet adhesion.
  - As a carrier of factor VIII, aPTT may be prolonged due to the decrease in the available amount of activated factor VIII in the plasma.
von Willebrand Disease

- Autosomal inheritance disease
  - Males and females are equally affected
- Most frequent inherited bleeding disorder
  - Incidence - 1/10,000
  - Very wide range of clinical manifestations
- Clinical features - mucocutaneous bleeding
Clinical Manifestations

- Epistaxis
- Easy bruising / hematomas
- Gingival bleeding
- GI bleeding
- Dental extraction bleeding
- Trauma/wound bleeding
- Post-operative bleeding
Von Willebrand Disease

- **Types:**

  - **Type 1 (60-80%)**
    - 5-30% quantitative reduction in vWF and factor VIII levels
  
  - **Type 2 (10-30%)**
    - Qualitative reduction in vWF
    - Sub-types 2a, 2b, 2m, 2n

  - **Type 3 (1-5%)**
    - Very low levels vWF and factor VIII
    - This type may also present with a clinical picture of hemophilia A
Treatment

- Treatment of hereditary hemorrhagic disorders is aimed at increasing plasma concentrations of the deficient coagulation protein to a minimal hemostatic level when a newborn is bleeding or a hemostatic challenge is planned.
- The minimal hemostatic plasma concentration of a particular coagulation protein varies and is dependent on the protein and the nature of the hemostatic challenge.
- Specific replacement therapy is available for deficiencies of FVII, FXI, FXIII, and fibrinogen and for vWD.
- Nonspecific treatment modalities comprise FFP, cryoprecipitate, and antifibrinolytics.
THANK YOU