BLEEDING (PLATELET) DISORDER
APPREACH

The initial set of questions should establish the following:

(1) the most common site and type of bleeding (e.g., mucocutaneous versus articular or deep muscle),

(2) bleeding on hemostatic challenge such as surgeries or trauma, and

(3) family history of bleeding.
<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Primary Hemostatic Defect</th>
<th>Clotting Factor Deficiency</th>
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</thead>
<tbody>
<tr>
<td>Site of bleeding</td>
<td>Skin, mucous membranes</td>
<td>Soft tissues, muscles, joints</td>
</tr>
<tr>
<td>Bleeding after minor cuts</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Petechiae</td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>Small, superficial</td>
<td>Large, deep, palpable</td>
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<tr>
<td>Hemarthrosis</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Bleeding after trauma/surgery</td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
</tbody>
</table>
PLATELET IN VASCULAR INJURY
HISTORY

- Large bruises without previous significant trauma, disseminated petechiae, intramuscular hematomas, hemarthrosis (joint effusion, warmth, and pain with passive movement) usually indicate a bleeding disorder.

- In young children, refusal to walk is often a sign for an extremity-related bleed and could represent the first sign of hemarthrosis in a boy with hemophilia.
HISTORY

- Symptoms of bleeding disorders, could be easy bruising and mucosal bleeding (e.g. Epistaxis, menorrhagia, oropharyngeal)

- Inflicted trauma is most likely to manifest over the head, chest, back, and long bones (and may retain the outlines of the instrument used to inflict harm), whereas bruises associated with primary hemostasis defects are usually located over areas of typical childhood trauma, such as bony protuberances of extremities or spinous processes
Epistaxis is a frequent presenting sign in children with hemostatic disorders.

Epistaxis is also a common complaint among healthy children, usually the result of local aggravating factors (dry nasal mucosa, trauma, allergic rhinitis).
Menorrhagia is also a frequent presenting sign for mild or moderate bleeding disorders (including VWD, platelet function disorders, and other coagulopathies) and can quickly lead to severe anaemia and decreased quality of life.
HISTORY

- Profuse bleeding into soft tissues or joints suggests deficiency of a coagulation factor (such as factors VIII or IX).

- Umbilical stump bleeding is typically seen with factor XIII deficiency, but it may also occur with deficiencies of prothrombin, factor X, and fibrinogen.
The main categories to be considered should include anatomic abnormalities, quantitative and qualitative platelet defects affecting platelet plug formation (primary hemostasis), and quantitative and qualitative defects of clot propagation (secondary hemostasis).

Differentiation also must be made between inherited and acquired disorders.
HISTORY

• Information about the patient’s previous response to hemostatic challenges (e.g., surgical procedures, invasive dental work, traumatic injuries) is an essential part of the initial evaluation.

• Family history is also a key component in establishing both the likelihood of an inherited bleeding disorder and its specific nature.
The three phases of coagulation occur on different cell surfaces: initiation on the tissue-factor bearing-cell; amplification on the platelet as it becomes activated; and propagation on the activated platelet surface.
HISTORY

- A sick child with fever, shock, and mucocutaneous purpura may have disseminated intravascular coagulation (DIC) associated with bacteremia.
- Hemophilia should be considered in a male toddler who has just started crawling and exhibits subcutaneous or joint bleeding, or who bleeds after circumcision.
- A girl who has had severe menorrhagia since menarche may have VWD.
HISTORY

- A well-appearing child covered with petechiae likely has immune thrombocytopenia, but if the lesions are localized to the buttocks, ankles, and feet, and they present as palpable bruises, Henoch-Schönlein purpura should be considered.

- The prevalence of bleeding disorders in women with menorrhagia is as high as 20%, and menorrhagia is a common initial symptom in women with VWD (approximately 90% of female patients).
HISTORY

- Medical disorder that may affect hemostasis, hepatic or renal disease, Malabsorption syndrome, or Ehlers-Danlos syndrome (EDS) or another connective tissue disorder.

- Generally, early age of onset correlates with more severe bleeding and may indicate a congenital cause. Bleeding that develops later in childhood may indicate either an acquired problem or a milder congenital bleeding disorder.
HISTORY

- An X-linked recessive inheritance pattern (maternal cousins, uncles, and grandfather) suggests a diagnosis of hemophilia A or B,
- Autosomal dominant pattern would be more consistent with VWD or hereditary haemorrhagic telangiectasia.
- Most other clinically relevant clotting factor deficiencies are inherited in an autosomal recessive manner.
HISTORY

- A number of drugs can cause thrombocytopenia (e.g., quinine or quinidine, rifampin, trimethoprim-sulfamethoxazole, carbamazepine, cimetidine, ranitidine, valproic acid)

- platelet dysfunction (nonsteroidal anti inflammatory drugs [NSAIDs] such as ibuprofen [reversible effect] and aspirin [irreversible]).
PHYSICAL EXAMINATION

- Signs of severe bleeding-related anaemia or intravascular volume loss, such as tachycardia (early finding) or hypotension (late finding).

- observe the pattern of bleeding stigmata

- the presence of petechiae indicates a defect in primary hemostasis (platelet number or function or vascular integrity).
Ecchymoses are palpable purplish lesions induced by subcutaneous bleeding and usually indicate a defect in secondary hemostasis (clot propagation), such as deficiency of a coagulation factor.

Hemarthrosis, associated with severe coagulation factor deficiency.
PHYSICAL EXAMINATION

- Hepatomegaly and splenic enlargement may point toward coagulopathy associated with systemic disorders such as leukaemia or hepatocellular disease.
LAB

- Complete blood count with evaluation of platelet number, size, morphology, PT, APTT, and thrombin time (TT) to help in the process of differential diagnosis
LAB

PTT

PT

Prolonged

Normal

Prolonged

Normal

TT

F VII deficiency

F XII, XI, IX, VIII, deficiency

Fletcher trait

Fitzgerald trait

Circulating anticoagulant

Heparin effect

Liver disease

Vitamin K deficiency

Circulating anticoagulant

Coumadin effect

Afibrinogenemia

Dysfibrinogenemia

Disseminated intravascular coagulation

Heparin effect
PLATELETS

- **Size:** 1–4 μm (younger platelets are larger).
- **Distribution:** one-third in the spleen, two-thirds in circulation
- **Average lifespan:** 9–10 days
- **Platelets critical component for the first phase of hemostasis (formation of the platelet plug), which can halt the loss of blood from vessels whose endothelial integrity has been interrupted**
PLATELETS

- Typically involve the skin or mucous membranes and include petechiae, ecchymosis, epistaxis, menorrhagia, and gastrointestinal hemorrhage. Intracranial bleeding can occur, but it is infrequent.

- Inherited platelet disorders can involve a qualitative and/or quantitative defect and are often broadly classified according to one of these two categories.
Bernard-Soulier syndrome, a severe congenital platelet function disorder, is caused by absence or severe deficiency of the VWF receptor (GPIb complex) on the platelet membrane.

Thrombocytopenia, with giant platelets and markedly prolonged bleeding time (>20 min) or PFA-100 closure time.

Platelet aggregation tests show absent ristocetin-induced platelet aggregation, but normal aggregation to all other agonists.
GLANZMANN THROMBASTHENIA

- Glanzmann thrombasthenia is a congenital disorder associated with severe platelet dysfunction that yields prolonged bleeding time and a normal platelet count.
- Platelets have normal size and morphologic features on the peripheral blood smear, and closure times for PFA-100 or bleeding time are markedly abnormal.
GLANZMANN THROMBASTHENIA

- This disorder is caused by deficiency of the platelet fibrinogen receptor αIIb-β3, the major integrin complex on the platelet surface that undergoes conformational changes by inside out signalling when platelets are activated.
• Dense body deficiency is characterized by absence of the granules that contain ADP, ATP, Ca2+, and serotonin. This disorder is diagnosed by the finding that ATP is not released on platelet aggregation studies and ideally is characterized by electron microscopic studies.

• Gray platelet syndrome is caused by the absence of platelet α granules, resulting in platelets that appear gray on Wright stain of peripheral blood. In this rare syndrome, aggregation and release are absent with most agonists other than thrombin and ristocetin.
For both Bernard-Soulier syndrome and Glanzmann thrombasthenia, the diagnosis is confirmed by flow cytometric analysis of the patient's platelet glycoproteins.

For individuals with Bernard-Soulier syndrome or Glanzmann thrombasthenia, platelet transfusions of 1 U/5-10 kg corrects the defect in hemostasis and may be lifesaving.

Desmopressin 0.3 µg/kg IV may be used for mild to moderate bleeding episodes.
WISKOTT ALDRICH SYNDROME

- This syndrome has X-linked inheritance and has the classic features of thrombocytopenia, eczema, recurrent bacterial and viral infections
- WAS has abnormal T cell function and a propensity to develop autoimmune disorders
WISKOTT ALDRICH SYNDROME

- Recurrent pyogenic infections, including otitis media, pneumonia and skin infections. There is also lowered resistance to nonbacterial infections, including herpes simplex and Pneumocystis jiroveci (formerly carinii) pneumonia.
- Thrombocytopenia (platelet count 10,000–100,000/mm³); microthrombocytes; low mean platelet volume (MPV).
CAMT

- Congenital Amegakaryocytic Thrombocytopenia (CAMT) is a bone marrow failure syndrome that presents with isolated thrombocytopenia in the neonatal period. Inheritance is autosomal recessive.

- The most common age at diagnosis of the thrombocytopenia is within the first month, because of petechiae and other bleeding symptoms.

- The diagnosis of CAMT, however, is not usually made until the infant is several weeks or months old when the bone marrow is examined.
TYPE 2 b VWD

- Type 2B von Willebrand Disease. Type 2B VWD is due to a mutant VWF molecule that binds spontaneously to platelets under physiologic shear.
- This results in clearance of the highest-molecular-weight multimers and usually mild thrombocytopenia
immune thrombocytopenia is a disorder caused by antiplatelet antibodies which lead to an accelerated destruction of platelets and an inhibition of the production of platelets.

- ITP is the most common cause of thrombocytopenia in children.
- Peak occurrence is between 2 and 5 years of age.
- In most children the disease is self-limited, with resolution in 80% of patients within 6–12 months from diagnosis.
Antibody-mediated destruction:
Most of the identified autoantibodies are directed against GPIIb-GPIIIa, GPIb-GPIX and GPIa-IIa

Impaired megakaryopoiesis
Antibody and cellular cytotoxicity and immune-cell-derived cytokines have been implicated in impairment of megakaryocytes
CLINICAL FEATURES

- Typically patients are otherwise well and present with petechiae, purpura and no palpable ecchymosis 1–3 weeks after a viral infection.
- It may also occur after rubella, rubeola, chickenpox or live virus vaccination.
- Occasionally patients may present with mucosal bleeding (hematuria, hematochezia, Menometrorrhagia, or epistaxis).
- Most often, bleeding symptoms are mild, but rarely patients may develop severe bleeding including intracranial hemorrhage.
American Society of Hematology (ASH)
DEFINITIONS

- Primary ITP was defined by the IWG as a platelet count less than $100 \times 10^9/L$.
- The IWG also defines ITP as newly diagnosed (diagnosis to 3 months), persistent (3 to 12 months from diagnosis), or chronic (lasting for more than 12 months).
- Complete response (CR): A platelet count $100 \times 10^9/L$ measured on 2 occasions 7 days apart and the absence of bleeding.
ASH DEFINITIONS

- **Response (R)** : A platelet count $30 \times 10^9/L$ and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions 7 days apart and the absence of bleeding.

- **No response (NR)** : A platelet count $30 \times 10^9/L$ or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart.
Blood smear and bone marrow aspirate from a child who had ITP showing large platelets (blood smear [left]) and increased numbers of megakaryocytes, many of which appear immature (bone marrow aspirate)
TREATMENT

- No therapy other than education and counselling of the family and patient for patients

- “A single dose of IVIG [intravenous immunoglobulin] (0.8-1.0 g/kg) 1-2 days

- Prednisone. 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
TREATMENT

- Intravenous anti-D therapy. For Rh-positive patients, IV anti-D at a dose of 50-75 μg/kg causes a rise in platelet count to >20 × 10⁹/L in 80-90% of patients within 48-72 hr.

- The role of splenectomy in ITP should be reserved for 1 of 2 circumstances.

- The older child (≥4 yr) with severe ITP that has lasted >1 yr (chronic ITP) and whose symptoms are not easily controlled with therapy is a candidate for splenectomy.
ASH GUIDELINES

- Bone marrow examination is unnecessary in children and adolescents with the typical features of ITP (grade 1B).

- Bone marrow examination is not necessary in children who fail IV Ig therapy (grade 1B).
Thank You