Objectives

• Understand the evaluation of an infant or child presenting with thrombocytopenia

• Recognize signs and symptoms that suggest life-threatening diagnoses

• Triage patients for appropriate treatment based on underlying etiology and risk of bleeding
Background

- **Platelets** are irregular cell fragments derived from bone marrow megakaryocytes.
- Platelets are responsible for **primary hemostasis** through the formation of platelet plugs.
- The coagulation cascade participates in **secondary hemostasis** by creating a firm, stable fibrin clot.
- **Thrombocytopenia** is defined as a platelet count less than $150 \times 10^9/L$. 
Test Your Knowledge

• At what level of platelets are children at risk for spontaneous hemorrhage?

A. 10 x 10^9/L
B. 50 x 10^9/L
C. 100 x 10^9/L
D. 150 x 10^9/L
The Answer

- The normal platelet count is 150-450 x 10^9/L
- Patients with moderate thrombocytopenia (30-50 x 10^9/L) are rarely symptomatic even with trauma
  - **Spontaneous** bleeding does not occur until platelets are < 10 x 10^9/L, and may consist of petichiae and bruising
- Critical bleeding (ICH) occurs < 5 x 10^9/L
- Platelets should be > 50 x 10^9/L for invasive procedures
The Case

• A 3-year old boy presents to the emergency department with a 24h history of bruising, primarily over the lower extremities, and a nosebleed for the past 15 minutes

• His parents deny any trauma

• The child has no significant medical history and no family history of bleeding or bruising
The Case
History

What would you ask?
History

• Past and current bleeding symptoms, including bruising with little or no trauma, nosebleeds, hematuria, hematochezia, melena, bleeding from the gums

• Remember to ask about bleeding with dental and surgical procedures

• Remember to ask post-menarcheal females about excessive menstrual bleeding

• Family history of all of the above
History

• Have symptoms been present since birth?

• Recent drug exposure, recent respiratory or GI infection

• Constitutional symptoms (fever, night sweats, weight loss, fatigue) and bone pain

• Always include non-accidental injury on the differential of a child presenting with bruising without a history of trauma
Physical Exam

What would you look for?
Physical Exam

• Ensure hemodynamic stability

• Examine skin, gingivae, oral cavity for evidence of bleeding, pallor; look for eczema in male patients

• For infants, dysmorphysisms and malformations: (cataracts, hearing loss, limb defects, hemangiomas)

• Palpate all accessible lymph nodes, liver, spleen

• Check neurological status and focal deficits
What would you order?
Workup

• CBC
  • Absolute platelet count
    • Assess severity of thrombocytopenia
  • Mean platelet volume
    • High suggests destructive process or congenital macrothrombocytopenia
    • Low suggests Wiskott-Aldrich syndrome
  • Hemoglobin
    • Concurrent anemia suggests autoimmune hemolytic anemia, leukemia, or infiltration
  • Leukocyte counts and differential
    • Leukopenia suggests leukemia, infiltration
Workup

• Peripheral Blood Smear
  • Confirm platelet count
    • Improper collection results in clumping and spurious thrombocytopenia
  • Red cell morphology
    • Spherocytes suggest autoimmune hemolytic anemia (coupled with immune thrombocytopenia defines Evans syndrome)
    • Schistocytes suggest microangiopathic destruction (as in HUS, DIC, and TTP)
Workup

• The remainder of the workup is guided by clinical presentation

• A positive direct Coombs test suggests an immune-mediated process

• Consider ANA and auto-antibodies in patients with persistent thrombocytopenia

• Fibrin degradation products are present in DIC; uremia is present in HUS
Workup

• A **bone marrow** exam is not usually necessary, but is indicated if there is pancytopenia, peripheral blasts, constitutional symptoms, or bone pain.

• For infants with multiple **congenital anomalies**, consider head U/S, MRI, abdominal U/S, and echo.

• Consider **genetic testing** for patients with poor growth or dysmorphic features.

• **HIV** and **Hepatitis C** can be associated with chronic thrombocytopenia.
## Differential Diagnosis

### Increased Destruction

<table>
<thead>
<tr>
<th>Immune-mediated</th>
<th>Platelet Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Thrombocytopenia Purpura</td>
<td>Hemolytic-Uremic Syndrome</td>
</tr>
<tr>
<td>Neonatal <em>Alloimmune</em> Thrombocytopenia</td>
<td>Thrombotic Thrombocytopenic Purpura</td>
</tr>
<tr>
<td>Neonatal <em>Autoimmune</em> Thrombocytopenia</td>
<td>Disseminated Intravascular Coagulation</td>
</tr>
<tr>
<td>Systemic Lupus Erythematous</td>
<td>Kasabach-Merritt Syndrome</td>
</tr>
<tr>
<td>Drug-induced thrombocytopenia</td>
<td>Splenic sequestration</td>
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<tr>
<td>Evans Syndrome</td>
<td>Malaria</td>
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</tbody>
</table>

### Mechanical Destruction

<table>
<thead>
<tr>
<th>Dialysis</th>
<th>Sickle-cell disease</th>
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<tbody>
<tr>
<td>ECMO</td>
<td>Von-Willebrand Subtypes</td>
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</table>
# Differential Diagnosis

## Decreased Production

<table>
<thead>
<tr>
<th>Infection</th>
<th>Bone Marrow Failure/Infiltration</th>
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<tbody>
<tr>
<td>EBV</td>
<td>Leukemia</td>
</tr>
<tr>
<td>HIV</td>
<td>Myelodysplastic syndromes</td>
</tr>
<tr>
<td>HCV</td>
<td>Other malignancies</td>
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<tr>
<td>Parvovirus</td>
<td>Acquired aplastic anemia</td>
</tr>
<tr>
<td>Varicella</td>
<td>Genetic Causes</td>
</tr>
<tr>
<td>CMV (congenital or acquired)</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Rubella (congenital)</td>
<td>Wiscott-Aldrich Syndrome</td>
</tr>
<tr>
<td><em>Nutritional Deficiencies</em></td>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td>Folate</td>
<td>Thrombocytopenia Absent Radii</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Congenital amegakaryotic</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia</td>
</tr>
</tbody>
</table>
ITP

- Acquired immune-mediated disorder characterized by isolated thrombocytopenia

- Annual incidence of 3-8/100,000 children with peak incidence at 2-5 years

- Sudden appearance of bruising or mucocutaneous bleeding in an otherwise healthy child (no constitutional symptoms and no HSM); often preceded by viral infection

- Over 2/3 will recover spontaneously within 6mo
ITP

• Treatment is considered if platelets < 20 x 10⁹/L and is controversial unless there is active bleeding or significant risk of bleeding

• IVIG induces rise in 95% of patients within 48h; other options include corticosteroids and anti-D for Rh+ patients (platelet transfusion is contraindicated unless there is significant active hemorrhage)

• < 1% will develop intracranial hemorrhage

• 20% of children will develop chronic ITP and alternative etiologies should be considered
Evans Syndrome

- Immune thrombocytopenia with autoimmune hemolytic anemia
- Bruising and bleeding accompanied by pallor, fatigue, tachycardia +/- jaundice with positive Coombs test
- Treatments include steroids, IVIG, immunosuppressant medications
- More likely to have a chronic relapsing course, often associated with other autoimmune disorders
Neonatal Alloimmune Thrombocytopenia (NAIT)

- Isolated destruction of platelets by maternal antibodies directed against paternal antigens
- Begins in utero and presents with petichiae, bruising and bleeding in an otherwise well neonate
- Platelets recover over weeks, but ICH occurs in 10-20% of infants (50% in utero)
- Treatment includes IVIG, steroids, maternal-matched platelet infusion
Neonatal Autoimmune Thrombocytopenia (NAT)

- Isolated destruction of platelets by maternal antibodies directed against maternal antigens, as in the case of antepartum maternal ITP or SLE
- Clinical presentation similar to NAIT, but higher platelet levels and lower risk of serious hemorrhage
- Treated with steroids or IVIG; maternal-matched platelet infusion is ineffective
Kasabach-Merritt

• Infant thrombocytopenia caused by a large or rapidly-growing hemangioma that traps platelets

• Aside from significant bleeding, complications include DIC from consumption of coagulation factors and high-out cardiac failure

• If surgery is not an option, treatment includes steroids, vincristine, and embolization
Test Your Knowledge

• An 8-month old boy presents to your office 1 week after discharge from the ICU for streptococcal sepsis. You note scattered petichiae and eczema which his parents say have been present off-and-on since birth. What is the most likely diagnosis?

A. Congenital HIV infection
B. Leukemia
C. Wiskott-Aldrich syndrome
D. Congenital rubella syndrome
The Answer

• Wiskott-Aldrich syndrome is a rare X-linked recessive immunodeficiency disorder characterized by the triad of recurrent bacterial infections, eczema, and thrombocytopenia with variable severity
  • WAS is caused by a mutation in the WAS protein which regulates platelet production and antibody function
  • Treatment ranges from conservative, to symptomatic (platelet transfusion, topical steroids, antibiotics), to hematopoietic stem cell transplant
You have been following a 14-year old girl with ITP for 10 months, and her platelets have never recovered past $40 \times 10^9$/L. On review of her most recent labs you notice a Hb of 97. You request a urine dip that shows 3+ protein and 2+ blood. What is the most likely diagnosis?

A. Evans syndrome
B. Chronic ITP
C. Hemolytic uremic syndrome
D. Lupus
Persistent ITP can be the initial presentation of autoimmune disorders such as SLE, characterized by hematological manifestations, athralgias, skin manifestations, serositis, nephritis, and other features.

- The older the ITP patient, the higher the likelihood of chronicity and SLE.

Chronic ITP is defined as >12 months duration.

- Evans syndrome alone does not feature nephritis, and HUS is not chronic.
Summary

• Thrombocytopenia is caused by increased destruction (immune, microangiopathic) or decreased production (congenital, infectious, marrow dysfunction) or sequestration of platelets

• In a preschool child, ITP is the most common diagnosis but thrombocytopenia must be isolated and a thorough history and physical must rule out serious disorders such as malignancy and NAI

• Further investigation is required for chronicity, clinical features that suggest alternative diagnoses or treatment failure
Summary

• There is no absolute threshold for treatment, which should be administered based on underlying cause and an estimate of risk of significant hemorrhage

• Platelet transfusions have limited utility in immune-mediated disorders