The McMaster *at night* Pediatric Curriculum

Consolini, DM. “Thrombocytopenia in Infants & Children”. *Pediatrics in Review 32 (4)*. 2011.

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. $10 \times 10^9/L$
B. $50 \times 10^9/L$
C. $100 \times 10^9/L$
D. $150 \times 10^9/L$

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-menarchal 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, dysmorphyisms and malformations: (cataracts, hearing loss, limb defects, hemangiomas)
- Palpate all accessible lymph nodes, liver, spleen
- Check neurological status and focal deficits

Workup

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	
Immune-mediated	Platelet Consumption
Immune Thrombocytopenia Purpura	Hemolytic-Uremic Syndrome
Neonatal *Alloimmune* Thrombocytopenia	Thrombotic Thrombocytopenic Purpura
Neonatal *Autoimmune* Thrombocytopenia	Disseminated Intravascular Coagulation
Systemic Lupus Erythematosus	Kasabach-Merritt Syndrome
Drug-induced thrombocytopenia	Splenic sequestration
Evans Syndrome	Malaria
Mechanical Destruction	Sickle-cell disease
Dialysis	Portal hypertension
ECMO	Von-Willebrand Subtypes

Differential Diagnosis

Decreased Production	
Infection	Bone Marrow Failure/Infiltration
EBV	Leukemia
HIV	Myelodysplastic syndromes
HCV	Other malignancies
Parvovirus	Acquired aplastic anemia
Varicella	Genetic Causes
CMV (congenital or acquired)	Fanconi anemia
Rubella (congenital)	Wiscott-Aldrich Syndrome
Nutritional Deficiencies	Dyskeratosis congenita
Folate	Thrombocytopenia Absent Radii
Vitamin B12	Congenital amegakaryotic thrombocytopenia

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 10^9/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 tranfusion, topical steroids, antibiotics), to hematopoietic stem cell transplant

Test Your Knowledge

- You have been following a 14-year old girl with ITP for 10 months, and her platelets have never recovered past 40 x 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

The Answer

- 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


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