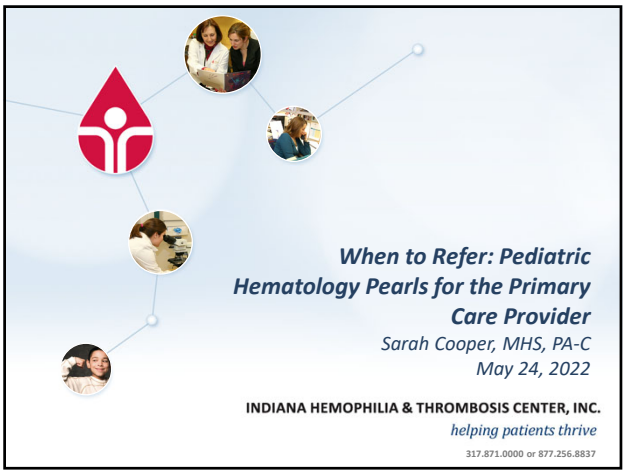

When to Refer: Pediatric Hematology Pearls for the Primary Care Provider

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May 24, 2022

INDIANA HEMOPHILIA & THROMBOSIS CENTER, INC.
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1

Disclosures

- **I have no relevant relationships with ineligible companies to disclose within the past 24 months.**

2

Educational Objectives

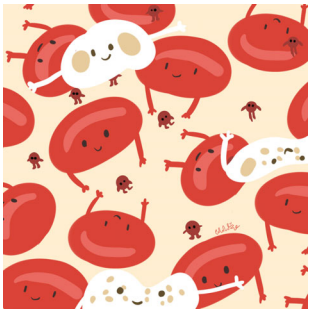
At the conclusion of this session, participants should be able to:

- **Recognize typical clinical presentations of common hematologic disorders**
- **Determine necessity and urgency of referrals to pediatric hematology**
- **Develop an understanding of primary care and general pediatric management of hematologic disorders.**

3

Outline

- **What can pediatric hematology do for me?**
- **RBC Disorders**
- **WBC Disorders**
- **Platelet Disorders**
- **Coagulation Disorders**
- **Specific challenges in the management of patients with chronic hematologic conditions**



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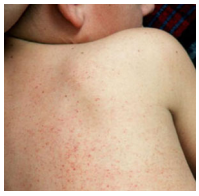
What can Pediatric Hematology do for me?

- **Provide guidance for laboratory workup in your setting**
- **Conduct a diagnostic workup in the hematology clinic**
- **Provide treatment for acute and chronic hematologic conditions**
- **Co-manage patients with hematologic conditions**

5

Most Common Referrals to Pediatric Hematology

- **Referrals come from every specialty and practice setting!**
  - Emergency department
  - Inpatient
  - Primary care
  - Pediatric subspecialties
- **Children present with a variety of signs/symptoms**
  - Anemia
  - Easy bruising/atypical bleeding
  - Neutropenia
  - Thrombocytopenia/thrombocytosis
  - Thromboses



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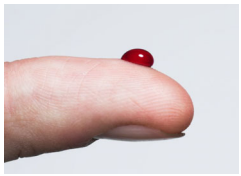
Acute vs. Chronic Disorders Managed by Pediatric Hematology

Acute

- **Acquired anemias**
- **Immune thrombocytopenia**
- **Neonatal alloimmune thrombocytopenia**
- **Neutropenia**
- ***Etc.***

Chronic

- **Hemoglobinopathies**
- **Enzymopathies**
- **Membranopathies**
- **Bleeding/Clotting disorders**
- ***Etc.***



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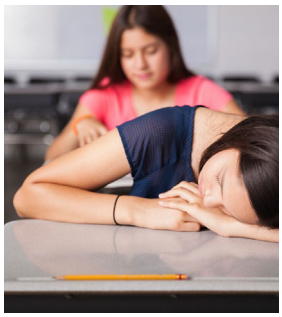
Erythrocyte Disorders – Case Study 1



- **A 16 year old girl presents to your clinic with complaints of restless legs, fatigue, pica, heavy periods.**

  Ferritin 1 ng/mL (RR 21-275 ng/mL)

  Hemoglobin 9 g/dL

- **Started on an OCP to control menses**
- **Trial of oral iron only raised ferritin to 5 ng/mL, hemoglobin unchanged**

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Etiologies of Anemia

Anemia: reduction in red cell mass or hemoglobin concentration

- Hemoglobin/hematocrit < 2.5th percentile for age, race, and sex
- 2 million RBC produced every second in the bone marrow
- Erythrocytes have a 120 day lifespan
  - 500,000 trips through the circulation

Anemia due to ↓ RBC production

- Nutritional
- Anemia of chronic disease

Anemia due to ↑ RBC destruction

- Enzymopathies
- Membranopathies
- Hemoglobinopathies
- Autoimmune

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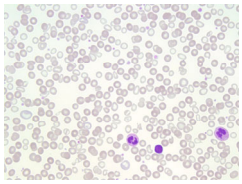
Anemia – History

- **Family history of anemias or blood transfusions**
- **Family history of early cholecystectomy or splenectomy**
- **Recent or chronic illness**
- **History of blood loss**
  - Epistaxis, heavy menses, GI blood loss
- **Dietary history**
  - Milk intake, tea intake, nutrient poor diet, vegan/vegetarian diet
  - Pica, pagophagia
- **Medication history**
- **Travel history**
- **Also consider**
  - Age
  - Ethnicity
  - Home environment



Increased incidence of certain anemias by ethnic background

Mediterranean: beta thalassemia, sickle cell disease
Asian: alpha thalassemia, Hemoglobin E disease
African: sickle cell disease, Hemoglobin C disease, thalassemia
Northern European: hereditary spherocytosis

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Anemia – Physical Exam

You may see

- Tachycardia, tachypnea, hypotension, hypoxia
- Pallor
- Jaundice
- Bruising
- Lymphadenopathy
- Hepatosplenomegaly

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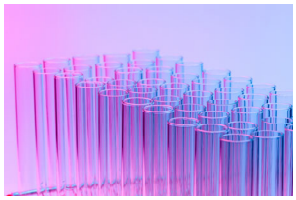
Anemia – Laboratory Evaluation

- **CBC**
  - Hb/Hct
  - MCV
  - MCH, MCHC
  - RDW
- **Reticulocyte Count**
- ***Consider***
  - CMP/LDH
  - Fractionated bilirubin
    - Hemolysis → elevated indirect bilirubin
  - Iron studies + ferritin
  - Hemoglobin electrophoresis
  - Direct Antiglobulin Test (DAT/Coombs Test)
  - Peripheral blood smear
  - Workup for specific diagnosis suspected (e.g. viral/bacterial/parasitic infection, autoimmune disorder, pregnancy)



Mentzer index:
< 13 = likely beta thalassemia trait
> 13 = likely iron deficiency

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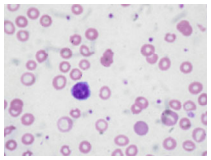
Iron Deficiency

- **Most common cause of anemia in young children**
  - Also common in teenage girls
- **Average age at diagnosis: 10-18 months**
- **Risk increases with exclusive breastfeeding or excessive cow's milk intake**
- **Lab findings:**
  - **CBC:** decreased Hb, decreased MCV, increased RDW, increased platelet count
  - **Iron studies:** decreased ferritin, decreased serum iron, increased TIBC.
  - Consider hemoccult testing.
- **Clinical history: iron-poor diet, excessive milk/tea consumption, heavy menstrual bleeding, epistaxis**



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Iron Deficiency

- **PO treatment: 3 mg/kg/day elemental iron, divided BID. Take with Vitamin C.**
- **Increase dietary consumption of iron-rich foods**

Iron Formulation	Pros	Cons
Ferrous Sulfate	Inexpensive, readily available	Associated with poor GI tolerance
Ferrous Gluconate	Better GI tolerance	Lower concentration of elemental iron → higher daily dose required
Ferrous Fumarate	Higher concentration of elemental iron → lower daily dose required	Expensive

Remember!

The most common reason for failed response to iron supplementation is not taking it!

Anticipate:
- Nausea
  - Take with food
- Constipation
  - Laxative
- Poor taste of liquid formulation
  - Pudding
  - Orange juice chaser

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Erythrocyte Disoders Case Study 1 – Iron Deficiency Anemia

16 yo girl with IDA poorly responsive to PO iron replacement
- **Referred to Hematology**
- **Deemed suitable candidate for IV iron therapy**
  - Admitted inconsistent adherence to PO iron due to side effects
  - Menses continue to deplete iron stores
  - Symptoms limit activities of daily living
- **Received 4 doses of IV iron sucrose with correction of iron deficit.**

Risks of IV iron administration
- **Anaphylaxis**
- **Urticaria**
- **Palpitations**
- **Dizziness**
- **Muscle spasms**

IV Iron Formulations
Iron sucrose • Good safety data, most common parenteral iron used in children • Usually requires multiple doses
LMW iron dextran • Requires test dose due to increased risk of reaction • Single infusion
Ferric gluconate • Approved for CKD
Ferric carboxymaltose • Single dose • Risk of hypophosphatemia • Less data available on use in children

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Erythrocyte Disorders – Case Study 2

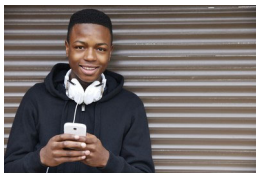
- **A 12 year old boy who recently entered the foster care system presents to your primary care clinic for a new patient visit. You have no access to past medical records, and his foster mother only knows that he has sickle cell disease. He tells you that he has pain very infrequently.**

CBC

Hb 10.6 g/dL
MCV 68 fL
Retic 4.7%

Hemoglobin Electrophoresis

HbS 66.7%
HbF 17.5%
HbA 10%
HbA2 5.8%



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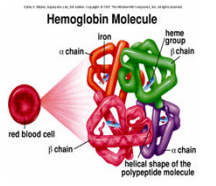
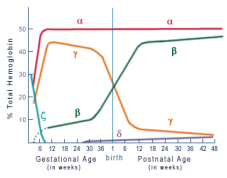
Hemoglobin Structure

- Each erythrocyte has 200-300 million hemoglobin molecules
- Each hemoglobin A molecule has 4 globin chains
  - 2 α chains
  - 2 β chains
- Each globin chain contains 1 heme moiety to bind oxygen
- Hemoglobin S results from a mutation in the β globin gene

Hemoglobin A: $\alpha_2\beta_2$
Hemoglobin F: $\alpha_2\gamma_2$
Hemoglobin A_2: $\alpha_2\delta_2$





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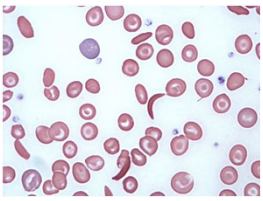
Sickle Cell Disease

- **Autosomal recessive inheritance**
  - Any ethnicity may be affected
  - 1/500 African American births
- **Most commonly identified disease on newborn screen in the US**
- **Any hemoglobinopathy with HbS (e.g. HbSS, HbSC, HbSβ⁰ thal, HbSβ⁺ thal, HbSD, HbSE)**
- **The term "sickle cell anemia" is reserved for SS and S beta zero thalassemia subtypes, which have the most severe phenotypes.**
  - Average lifespan of HbSS patient: 40-50 years



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Sickle Cell History and ROS for the Pediatric Patient

- Sickle genotype
- Baseline hemoglobin
- Acute chest syndrome
- History of pneumococcal bacteremia, meningitis
- Stroke – recent TCD and/or MRI results
- Spleen complications – sequestration, splenectomy
- Priapism
- Transfusions – transfusion problems (e.g. alloantibodies)
- Penicillin, hydroxyurea
- Immunizations

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Erythrocyte Disorders Case Study 2 - Sickle Cell Disease

- **Labs are consistent with a diagnosis of Hemoglobin Sβ+ thalassemia**
- **Refer to Hematology**
  - Anticipatory guidance for fever precautions, hydration, avoidance of temperature extremes
  - Immunizations: seasonal influenza, COVID-19, Hepatitis A/B, pneumococcal, meningococcal
  - Recommended screenings

CBC

Hb 10.6 g/dL
MCV 68 fL
Retic 4.7%

Hemoglobin Electrophoresis

HbS 66.7%
HbF 17.5%
HbA 10%
HbA2 5.8%

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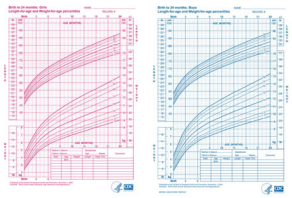
Health Maintenance for the Child with SCD

- Penicillin prophylaxis
- Hydroxyurea for HbSS and HbSβ^0 thalassemia
- Other disease-modifying therapies as indicated
- Annual TCD screenings between ages 2-16 for HbSS and HbSβ^0 thalassemia
- MRI/MRA at school entry
- Immunizations against encapsulated organisms
- Annual ophthalmology exams beginning at age 10
- Baseline pulmonary function testing
- Educational support (IEP/504 plans as indicated)
- Support for the transition process and transfer to adult care



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Outpatient Management of Vaso-Occlusive Pain

- **Increased hydration**
- **Application of heat**
- **Anti-inflammatory (ibuprofen) alternating with oral opioid**
- **Adequate rest**
- **Non-pharmacologic techniques**
  - Distraction
  - Deep Breathing
  - Guided Imagery
  - Acupuncture
  - Massage
  - Cognitive Behavioral Therapy
  - Yoga
  - Prayer

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Primary Care Workup and Management of Anemia

Diagnosis	Iron Deficiency Anemia	Hemolytic Anemia	Red Cell Aplasia
Labs	• CBC • Reticulocyte Count • Iron Studies • Ferritin	• CBC • Reticulocyte Count • Peripheral Smear • DAT/Coombs Test • CMP	• CBC/differential • Reticulocyte Count • Peripheral Smear • Viral Studies
Treatment	3 mg/kg elemental iron PO daily	Diagnosis-dependent	• Acquired: Observation/supportive care • Congenital: Counsel select patients re: Hematopoetic Stem Cell Transplant
Response	Improved Hb in 1-2 months Normalized iron stores in 3-4 months	Diagnosis-dependent	Goal of resolution

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Erythrocyte Disorders – When to Refer

- **Symptomatic anemia**
- **Congenital anemia**
- **Anemia failing to respond to therapy**
- **Anemia with other cytopenias**

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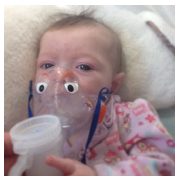
Leukocyte Disorders – Case Study

- **A previously healthy 18 month old girl presents to the ED with fever and symptoms of bronchiolitis. She is stabilized and otherwise ready for discharge, except that her CBC/differential unexpectedly returned with an ANC of 800.**
  - Other cell lines WNL



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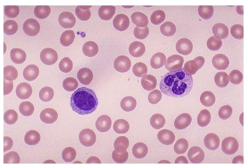
Leukocyte Disorders – Non-Malignant

- **Leukocytosis**
  - Umbrella term that may include neutrophilia, monocytosis, basophilia, lymphocytosis, eosinophilia
    - Infection
    - Inflammation
    - Medication-induced
    - Atopic disease
    - Asthma
- **Leukopenia**
  - Neutropenia: many significant etiologies
  - Lymphopenia: infection, medication, autoimmune disorders, malnutrition
  - Eosinopenia: infection, systemic steroids, thymoma
  - Basopenia: infection, thyrotoxicosis, acute hypersensitivity reactions
  - Monocytopenia: infection, steroids, GI resection, malignancy, GATA2 deficiency



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Leukocyte Disorders - History

- **Inquire about**
  - Fevers (recent or recurrent)
  - Skin infections, otitis, pneumonia
  - Autoimmune disorders
  - Medication history
  - Atopic disease
  - Asplenia
  - Renal disease
  - Malnutrition

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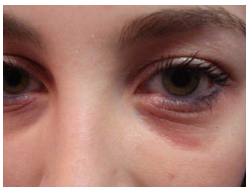
Leukocyte Disorders – Physical Exam

You may see

- **Abscesses**
- **Cellulitis**
- **Allergic shiners**
- **Hypertrophied nasal turbinates**
- **Eczema**



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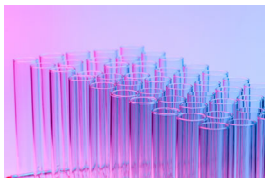
Leukocyte Disorders – Laboratory Evaluation

- **CBC/Differential**
- **Peripheral smear**
- ***Consider***
  - Additional workup for underlying cause, e.g., infection, autoimmune disorder



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Neutropenia

- **Mild neutropenia: ANC 1000-1500**
  - No increased risk of infection
- **Moderate neutropenia: ANC 500-1000**
  - Slightly increased risk of infection
- **Severe neutropenia: ANC <500**
  - Significant risk of infection
  - Fevers require inpatient management and parenteral antibiotics

Intrinsic causes	Extrinsic causes
Bone marrow failure syndromes	Autoimmune Disorders
Cyclic neutropenia	Infections
Familial benign neutropenia	Medications
Malignancy	Nutritional deficiencies (Vitamin B12, folate, copper)
Metabolic disorders	
Severe congenital neutropenia	

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Acquired Neutropenia

Infection-related neutropenia

- Common with childhood viral exanthems
  - Often resolves 3-8 days after onset of viral illness
- Also seen with HIV, CMV, EBV, and Hepatitis A
- Bacterial causes include typhoid fever, *Shigella*, and tuberculosis

Drug-induced neutropenia

- Offending agents include anti-inflammatory medications, antibiotics (macrolides, cephalosporins, etc.), antifungals, antivirals, anticonvulsants, psychotropic medications

Autoimmune neutropenia

- Granulocyte-specific antibodies
- Often an incidental finding without evidence of significant underlying disorders
- Primary autoimmune neutropenia
  - Typically occurs between 5-15 months old
- Secondary autoimmune neutropenia
  - Typically occurs between 40-60 years old
- Remission is typically spontaneous after 1-2 years

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Congenital Neutropenia

Benign Ethnic Neutropenia

- Mild-moderate neutropenia at baseline
- Increased prevalence in individuals of African ancestry
- Must rule out other causes of neutropenia
- Typically no history of infection and no clinical manifestations
- Not associated with an increased risk of infection but may affect ability to mount a leukocytosis in response to infection
- No indication for treatment or serial CBCs once diagnosis is established

Cyclic Neutropenia

- Rare (1:1,000,000)
- Males:females 1:1
- Typically first seen in the first year of life
- Associated with mutations in the *ELANE* gene
- Recurrent neutropenia
  - Cycle typically lasts 3 weeks and is consistent for the individual
  - Symptoms are also cyclical
    - Fever
    - Malaise
    - Mucosal ulcerations

Severe Congenital Neutropenia (Kostmann syndrome)

- Rare (2-3:1,000,000)
- Males:Females 1:1
- More frequent in people of Caucasian descent
- Average ANC < 200
- Treatment: G-CSF injections, hematopoietic stem cell transplant

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Leukocyte Disorders Case Study - Neutropenia

- **18 month old girl with moderate neutropenia (ANC 800) in the setting of bronchiolitis**
  - Call to Hematology
  - Records review revealed a normal ANC of 2200 one year earlier
  - Questioning of parents revealed no recent use of medications associated with neutropenia
  - History and physical exam are suggestive of an infectious cause of this child's neutropenia
  - Plan to repeat CBC/differential 7-10 days later with instructions to parents to call in the event of fever.
  - Repeat ANC 2500. No additional laboratory monitoring or Hematology follow-up required.

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Primary Care Workup and Management of Leukocyte Disorders

Diagnosis	Neutropenia	Deficiencies of other WBCs	Leukocytosis
Labs	• CBC/differential • Peripheral smear	• CBC/differential • Peripheral smear	• CBC/differential • Peripheral smear
Treatment	• Diagnosis-dependent • May include treatment of infection, medication discontinuation, or G-CSF	• Diagnosis-dependent • Treatment of underlying disease state	• Medication discontinuation • Treatment of underlying disease state
Response	• Varies	• Varies	• Varies

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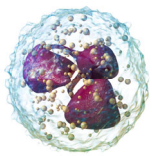
Leukocyte Disorders – When to Refer

- **Call Hematology to discuss referral for any borderline abnormal leukocyte counts.**
  - Neutrophil count <1000 typically warrants a referral
- **Moderate-severe neutropenia**
- **Suspicion of a congenital neutropenia**
- **Significant leukocytosis**



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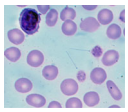
Platelet Disorders – Case Study

- **A 3 year old boy presents to your clinic with new onset bruising and petechiae following a non-traumatic bath. His parents endorse a recent history of viral URI symptoms.**
- **No fever/night sweats/bone pain/weight loss to suggest malignancy**
- **Platelet count 7K**
  - Hb 12 g/dL, WBC 9
- **Rare large platelets on peripheral smear review**
  - Manual count consistent with automated count



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Platelet Disorders

- **Thrombocytopenia**
  - Congenital
  - Acquired
    - Autoimmune thrombocytopenia
    - Alloimmune thrombocytopenia
    - Drug-induced
- **Thrombocytosis**
  - Essential thrombocythemia
  - Reactive thrombocytosis
- **Platelet Function Disorders**
  - Drug-induced
  - Giant platelet disorders
  - Storage pool disorders
  - Hepatic disease
  - Wiskott-Aldrich syndrome

- **Signs/symptoms of platelet disorders**
  - Petechiae
  - Wet purpura
  - Atypical bruising
  - Mucosal bleeding

Child abuse should be ruled out in any child with unexplained bruising

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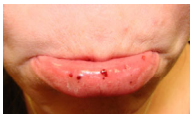
Platelet Disorders - History

- **Family history of early hearing loss, cataracts, or nephropathy**
  - Can be associated with certain congenital platelet disorders
- **Recent illness**
- **History of bleeding**
  - Epistaxis, gingival bleeding, heavy menses, GI blood loss
  - Skin findings
    - Petechiae
    - Wet purpura
- **History of atypical bruising**
  - Disproportionate to injury
  - Hematomas
  - Unusual locations
- **Medication history**



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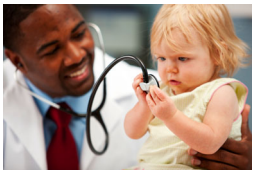
Platelet Disorders – Physical Exam

You may see

- **Petechiae**
  - Do not blanch
- **Wet purpura**
- **Atypical bruising**
  - Hematomas
  - Unusual locations (face, trunk)
  - Increased number
- **Lymphadenopathy**
  - May indicate malignancy
- **Hepatosplenomegaly**
  - May indicate malignancy



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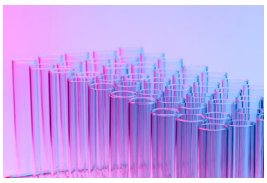
Platelet Disorders – Laboratory Evaluation

- **CBC**
  - Platelet count
  - MPV
- **Peripheral smear**
- ***Consider***
  - PT/PTT
  - von Willebrand studies



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Immune Thrombocytopenia (ITP)

- **Autoantibodies targeting antigens on the platelet membrane**
  - Shortened platelet half life
  - Cleared by macrophages (spleen-predominant)
  - Isolated thrombocytopenia on CBC
- **Typical presentation is a young child with a recent history of viral illness**
  - Peak age 3-5 years
  - 80% post-infectious
  - Mortality low: <1%
  - Most episodes are acute and do not recur

- **A diagnosis of exclusion**
  - Rule out other potential causes of thrombocytopenia
    - Malignancy
    - Bone marrow failure
    - Congenital thrombocytopenia
    - Medication-induced thrombocytopenia
    - A bone marrow biopsy may show an increased number of platelet precursors
- **First line of management is observation**
  - Treatment is recommended in pediatrics only in the event of mucosal or other significant bleeding (American Society of Hematology Clinical Practice Guidelines 2019)
  - ITP in childhood typically resolves spontaneously ≤ 3 months post-diagnosis
  - No reliable prediction for development of chronic/refractory ITP

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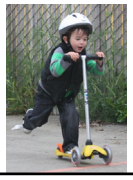
Platelet Disorders Case Study - ITP

3 year old boy with recent viral URI and new onset cutaneous bleeding with platelet count of 7K.

- **Referred to Hematology**
- **Observation with weekly platelet counts recommended given absence of "wet" bleeding symptoms**
  - CBC via venipuncture rather than fingerstick due to risk of platelet clumping
- **3 weeks later, he presents to your clinic with epistaxis. Platelet count is 10K.**
  - Sent to Hematology and deemed suitable candidate for IVIG infusion
  - Excellent platelet response with a 24 hour post-IVIG platelet count of 90K
  - Counseled regarding injury precautions and advised to continue to follow with regular CBCs and IVIG PRN future significant bleeding episodes



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Primary Care Workup and Management of Platelet Disorders

Diagnosis	Thrombocytopenia	Thrombocytosis	Platelet Function Disorders
Labs	• CBC/differential • Peripheral smear	• CBC/differential • Peripheral smear	• CBC/differential • Peripheral smear
Treatment	• Observation • Medication management • Lab monitoring	• Observation • Treatment of underlying disease state • Lab monitoring	• Observation
Response	• Diagnosis-dependent	• Diagnosis-dependent	• Typically a lifelong condition

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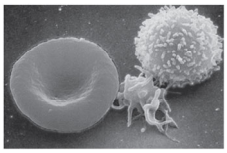
Platelet Disorders – When to Refer

- **Call Hematology to discuss referral for any atypical platelet counts.**
  - Platelet counts >100K and <500K typically warrant repeating a CBC in the primary care setting before placing a formal referral
- **Moderate-severe thrombocytopenia**
- **Significant thrombocytosis**
- **Suspicion of a congenital thrombocytopenia or a platelet function disorder**



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Bleeding Disorders – Case Study

- **A 16 year old girl presents to your clinic with complaint of worsening fatigue over the past 6 months. She struggles to make it through the school day and takes a 2 hour nap when she gets home. She craves nonnutritive items such as ice, paper, and dirt. She denies recent illness.**
- **History of heavy menstrual bleeding: requires doubling of hygiene products and often bleeds through to clothing or bedsheets. Changes products every 2 hours on days of heaviest flow. Reports passing clots and a sensation of flooding.**

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Bleeding Disorders

- **Von Willebrand Disease**
  - Most common inherited bleeding disorder
  - Quantitative or qualitative defect of von Willebrand factor
- **Hemophilia**
  - Bleeding disorders with a procoagulant deficiency
  - Used specifically to refer to Factor VIII deficiency (Hemophilia A), Factor IX deficiency (Hemophilia B), or Factor XI deficiency (Hemophilia C)
  - 30% are de novo mutations
- **Other clotting factor deficiencies**
  - Vitamin K deficiency
    - Required for action of coagulation factors II, VII, IX, and X
    - Must be administered at birth to prevent CNS bleeds
- **Platelet function defects**

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Bleeding Disorders - History

- **Personal or family history of excessive or prolonged bleeding with injury or surgical procedure**
  - Ask about circumcision, umbilical stump oozing, hematomas with immunizations
- **History of mucocutaneous bleeding symptoms**
  - Epistaxis, gingival bleeding, heavy menses
- **History of joint or muscle bleeds**
  - Pain, swelling, warmth of affected area
- **History of GU or GI bleeding**
  - Hematemesis, hematuria, hematochezia, melena

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Bleeding Disorders – Physical Exam

- **Abnormal platelet number/function**
  - Mucocutaneous bleeding
  - Petechiae
  - Abnormal bruising
- **Abnormal procoagulants**
  - Bleeding in deep tissues, muscles, joints
  - Abnormal bruising
  - Bleeding with injury or surgery
- **Abnormal fibrinolysis**
  - Delayed bleeding

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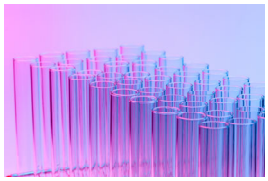
Bleeding Disorders – Laboratory Evaluation

- **PT/aPTT**
  - Prolonged PT or aPTT suggests a factor deficiency or an inhibitor of normal coagulation
  - Normal ranges vary by laboratory
- **Prolonged PT** + Normal aPTT
  - Factor VII deficiency, liver disease
- Normal PT + **Prolonged aPTT**
  - Factor VIII, IX, or XI deficiency (clinically significant bleeding)
  - Factor XII deficiency (not clinically significant)
- **Prolonged PT + Prolonged aPTT**
  - Prothrombin, fibrinogen, Factor V, or Factor X deficiencies
  - Combined factor deficiencies
  - Severe Vitamin K deficiency
- **Von Willebrand Disease requires a VWD panel** (PT/aPTT does not tell the full story)



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von Willebrand Disease

- **Mucosal bleeding**
  - Epistaxis
  - Heavy menses
  - Easy bruising
  - Gingival bleeding
- **Excessive bleeding with trauma**
  - Bleeding after dental extraction
  - Postoperative bleeding
  - Bleeding from minor cuts or abrasions
- **If mucocutaneous bleeding history is strong, initial VWD assays may be performed at first visit**
  - Von Willebrand antigen
  - Factor VIII
    - Activity often parallels VWF levels
  - Von Willebrand factor activity assays are used to measure ability of VWF to interact with platelets
    - Ristocetin cofactor
    - GP1bM activity
    - VWF multimer analysis

- **Conditions associated with higher VWF levels**
  - Age
  - Acute and chronic inflammation
  - Diabetes
  - Malignancy
  - Pregnancy or oral contraceptive use
  - Stress, exercise
  - Hyperthyroidism
- **Conditions associated with reduced VWF levels**
  - Hypothyroidism
  - Blood type O
- **VWD has no predilection for specific gender or racial/ethnic groups**

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Bleeding Disorders Case Study – von Willebrand Disease

- **A 16 year old girl with fatigue, pica, and heavy menses.**
  - CBC/differential and iron studies consistent with iron deficiency anemia
  - Initiated ferrous sulfate supplementation at 3 mg/kg/day
  - Referred to Hematology for a bleeding disorder workup
    - Decreased von Willebrand antigen
    - Decreased ristocetin cofactor
    - Slightly decreased Factor VIII
  - Diagnosed with Type I von Willebrand Disease
  - Prescribed tranexamic acid to stabilize clots and decrease menstrual bleeding.

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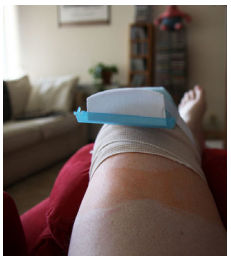
Thrombotic Disorders – Case Study

- **A 17 year old female on combined oral contraceptives presents to your clinic for clearance prior to an upcoming knee surgery.**
  - Newly revealed family history of deep vein thromboses at age < 50 years.
  - Genetic testing for inherited thrombophilias reveals her to be heterozygous for a Factor V Leiden mutation.



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Thrombotic Disorders

Inherited Thrombophilias		Acquired Thrombophilias
Autosomal dominant		Antiphospholipid antibody syndrome (APS)
Most commonly associated with VTE		Heparin-induced thrombocytopenia (HIT)
Diagnosed with PCR testing or functional assays		Malignancy
Pro-coagulant factor mutations	Factor V Leiden (activated protein C resistance)	Myeloproliferative disorders
	Prothrombin gene mutation	Nephrotic syndrome
Deficiencies of natural anticoagulants	Protein C deficiency	Paroxysmal nocturnal hemoglobinuria (PNH)
	Protein S deficiency	
	Antithrombin deficiency	

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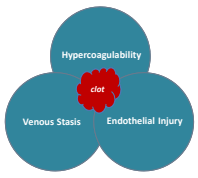
Thrombotic Disorders - History

- **Personal or family history of**
  - DVTs/PEs
  - Late miscarriage/fetal loss
  - Multiple miscarriages
  - MI or stroke < 50 years of age
  - Known thrombophilia
- **Risk factors**
  - Current or recent history of trauma, surgery, infection, dehydration
  - Sudden chest pain, dyspnea, anxiety
  - Exogenous estrogen use
  - Malignancy
  - Central venous line
- **80% of venous thromboses in children have an identifiable cause**



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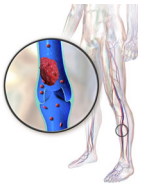
Thrombotic Disorders – Physical Exam

- **Upper/lower extremity thrombus**
  - Cold, pale, blue extremity with poor/absent pulse (if arterial thrombus)
  - Pain, swelling, discoloration, warmth (if venous thrombus)
- **Pulmonary embolus (PE)**
  - Dyspnea; unexplained cough; sharp, inspiratory chest pain; anxiety
- **Cerebral Sinus Venous Thrombosis (CSVT)**
  - Seizure (neonates)
  - Headache, papilledema/optic disc swelling, emesis, seizure (older children)
- **Renal vein thrombosis**
  - Hematuria, abdominal mass



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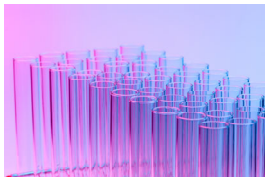
Thrombotic Disorders –Evaluation

- **Labs**
  - D-dimer
    - Normal (< 500 ng/mL) – unlikely to be DVT/PE if risk factors are minimal
  - PCR testing or functional assays
    - Used to diagnose inherited thrombophilias
- **Imaging**
  - Duplex ultrasound for DVT
  - CT pulmonary angiography for PE



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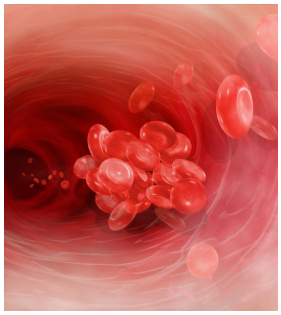
Factor V Leiden Mutation (a.k.a. activated Protein C resistance)

- **Most common inherited thrombophilia**
  - Responsible for 30% of VTEs
- **Heterozygous – mildly increased risk of thrombosis**
- **Homozygous – strongly increased risk of thrombosis**
- **Risk of VTE sharply increased with**
  - Estrogen-based OCP
  - Surgery
  - Prolonged immobility



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Thrombotic Disorders Case Study – Factor V Leiden Mutation

- **A 17 year old female with personal and familial risk factors for thrombosis to your clinic for clearance prior to orthopedic surgery. She is found to be heterozygous for Factor V Leiden mutation.**
  - You refer this patient to Hematology for surgical clearance.
    - Due to family history of VTE at young ages, personal use of combination OCPs, surgical procedure, and immobility, prophylactic anticoagulation (enoxaparin Q12H) is administered postoperatively for the duration of immobility in addition to mechanical prophylaxis during admission.
  - You change the patient's OCP to progesterone-only.

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Primary Care Workup and Management of Bleeding and Thrombotic Disorders

Diagnosis	Bleeding Disorders	Thrombotic Disorders
Labs	• CBC • PT/aPTT • VWD studies	• D-dimer • PCR testing • Functional assays
Imaging	• Only as indicated for injury	*Consider* • Duplex ultrasound • CTA
Treatment	• Observation • Medication management	• Observation • Medication management

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Bleeding and Clotting Disorders – When to Refer

- **Call Hematology for guidance for initial bleeding or thrombotic disorder workup**
- **Refer to Hematology for any suspected or newly diagnosed bleeding or thrombotic disorder**
- **Consult Hematology if surgical clearance is required for a high-risk patient**

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Conclusion

- **Managing hematologic disorders is often possible in the primary care setting**

  but….

- **Hematology is here to help!**
  - Phone consults
  - Co-management
  - Primary management

Questions?
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