Pediatric Hematology Primer

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Disclosures

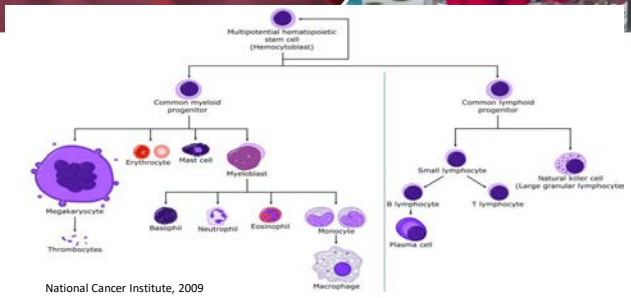
- Paige Johnson DNP, RN, MPH, CPNP has no financial relationships with commercial interests to disclose
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

Learning Objectives

- Discuss lab value interpretation and how to differentiate between different types of anemia and treatments
- Discuss assessment and plan of care for childhood neutropenia, ITP, and the difference between inherited and acquired bleeding disorders
- Discuss Hemophilia and Von Willebrand disease, common problems seen in primary care and when to refer to a specialist

HEMATOLOGY LABORATORY VALUES

Blood Cell Lines



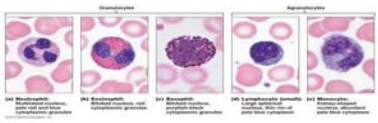
National Cancer Institute, 2009

WBCs

- Protects the body from invasion by organisms and other immune system responses
- Normal count 5,000-10,000
- Elevated means infection or bone marrow dysfunction (leukemia)
- Low could be infection, autoimmune process, but also could be an oncologic disease

Cells in Differential

- Granulocytes
  - Cells have large granules in it
  - Horse-shoe shaped nuclei connected by thin strands
  - Cytoplasm stains blue
  - Neutrophils, basophils, eosinophils
- Agranulocytes
  - Lymphocytes, monocytes



Quora, 2019

Granulocytes

- Neutrophils (also PMNs or Polys)
  - 40-70% of differential
- Basophils
  - Less than 1% of circulating cells
- Eosinophils
  - 1-2% of WBCs

Agranulocytes

- Lymphocytes
  - 25-35% of WBCs
- Monocytes
  - 4-6% of WBCs

Hemoglobin

- Normals
  - 2wks: 13-20
  - 3mo: 9.5-14.5
  - 6mo-6yrs: 10.5-14
  - 7-12yrs: 11-16
  - Menstruating females: 12-16
  - Teen/adult males: 14-18
  - Decreased with RBC destruction, chemotherapy, anemia, bleeding
  - Increased with polycythemia, high altitudes, chronic lung disease

Reticulocytes

- Young RBCs
- After release from bone marrow
  - stay in circulation for 1 day before maturing to RBCs
- Reticulocyte count
  - % of circulating RBCs
  - Reflect bone marrow production of new RBCs
- Will be low in anemia

Other Values with Hemoglobin

- Hematocrit: % of RBCs in a given volume of blood (decaliter)
- RBC count: how many circulating RBCs
  - High with volume loss, diarrhea, burns, dehydration, polycythemia
  - Low with anemia
- Mean corpuscular volume (MCV): volume of the average RBC
  - High (macro) with B12 (folate) deficiency or hypothyroid
  - Low (micro) with Fe deficiency, thalassemia, Pb poisoning, anemia of chronic disease
- Mean corpuscular Hgb (MCH): amount of Hgb in the RBC-mirrors MCV

Other Values with RBCs

- Ferritin
  - Increased with iron overload (repeated transfusions), ESRD, spherocytosis, megaloblastic anemia, porphyria
  - Decreased with iron def
- Total Iron Binding Capacity (TIBC)
  - Increased with iron def, acute/chronic blood loss, acute liver damage
  - Decreased in hemochromatosis, cirrhosis, thalassemia, nephrosis, hyperthyroidism, chronic infection
- Serum Iron
  - Increased in excessive iron intake (iron therapy, transfusions), decreased RBC formation, acute liver damage, pregnancy, hemochromatosis
  - Decreased in iron def, neoplasms, nephrosis, menstruation

Platelets

- Normal is 150,000 to 300,000
- Smallest cellular component
- Fragments of megakaryocytes (precursor in BM)
- When bleeding occurs
  - Platelets go to site, form hemostatic plug
  - As degrade, cause release of clotting factors
  - Bring about clotting cascade
- Increased with sudden exercise, trauma, fracture, after surgery, leukemia, after childbirth, Fe def
- Decreased with DIC, ITP, HUS, burns, marrow suppression, viral infections, ASA use, pre/eclampsia

Coagulation Factors

- PT (Prothrombin Time)
  - Prolonged by low Vit K, prematurity, poor fat absorption, drugs (coumadin, ASA), heparin, factor disorders, DIC
- PTT (Partial Thomboplastin time)
  - Prolonged by factor disorders, heparin, DIC
- INR (International Normalizing ratio)
  - Used to monitor how well warfarin is working (only for this drug)
  - Usually use 2-3 for normal. If high, at risk for bleeding.
- D Dimer
  - associated with fibrinolytic breakdown of fibrin
  - Helps evaluate DVT/PE
  - Increased with DVT, PE, MI, CVA, SS crisis, cancers, renal failure, CHF, sepsis
- Fibrinogen
  - Decreased with DIC
  - See increase in fibrin split products with DIC

COMMON PRIMARY CARE ISSUES

IRON DEFICIENCY ANEMIA

What is it?

- Iron deficiency is a world-wide problem
- Significantly can increase the risk of developmental delays and behavioral issues
- Most common causes are LBW, prematurity, exposure to lead, exclusive breast feeding beyond 4mo, weaning of whole milk to non-iron fortified formula
- Other factors: feeding problems, poor growth, low SES, children with special health care needs

Iron Requirements (AAP/WHO)

- Iron requirements differ with age:
  - Pre-term: 2mg/kg/day by 1mo of age through 12mo of age
  - Term Breastfed: add 1mg/kg/day starting at 4mo if exclusively breastfed
    - Or use iron fortified foods to achieve needs
  - Term, Formula-Fed: iron fortified formula is 12mg/L is standard
  - Toddlers (1-3 yrs): 7mg/day through foods or supplementation if a picky eater

Symptoms of IDA

- Usually asymptomatic
- Lethargy/decreased energy
- Pale
- Poor Feeding
- Tachypnea
- PICA-craving of nonfood items (ice, paper, dirt, rocks, chalk, soap)

Diagnosis

- Low hemoglobin for age and elevated MCV

Age	Average Normal Hgb	Diagnostic of Hgb	MCV
3-6months	11.5	9.5	91
6-12months	12	10.5	78
2-6 years	12.5	11.5	81
6-12 years	13.5	11.5	86

- Once anemia is diagnosed, check serum ferritin

Short, Domaglaski. (2013). American Family Physician

Treatment

- Oral Iron Therapy
  - Elemental iron (Ferrous Sulfate only one in liquid form)
  - Poly-Vi-Sol + Iron is not enough for treatment
  - 4-6mg/kg/day daily or BID if not tolerated well
  - Recommended CBC/d, retic, ferritin at 1 mos, 3 mos and 6 mos
- Parenteral Iron (needs referral to Hematologist)
  - Won't take po or failed po challenge in clinic
  - Cannot absorb iron (gastrectomies, SB surgeries)
  - Recheck CBC, ferritin in 1mo

Dietary Considerations

- Infants younger than 12mo:
  - Breast fed or receive iron-fortified formula.
  - If exclusively breastfed at 4mo, add iron supplement
  - Cow's milk can cause cow's milk protein induced colitis leading to intestinal blood loss
- Children over 12mo:
  - Cow's milk should be limited to 20oz per day
  - Introduction of other foods (~3 servings a day is ideal)

Healthy Little Foodies, 2019

OTHER PEDIATRIC ANEMIAS

Alpha Thalassemia

- Loss of alpha globin production
  - Severity depends on location of loss or how much of a loss
- α Thalassemia syndromes can present with either complete absence of α globin (hydrops fetalis) or slightly reduced (silent carrier).
  - α Thal carrier (1 missing α globin genes)-asymptomatic
  - α Thal minor (2 missing α globin genes);may have microcytic anemia
  - Patients with HbH (3 missing α globin genes); may cause microcytosis, anemia, mild splenomegaly and icteric sclera/cholelithiasis.
    - Chronic transfusions are usually not needed
  - Hb Barts Hydrops Fetalis (4 missing α globin genes); very severe disease
    - Need to treat in utero with transfusions; still could be born with congenital and developmental delays
    - life long transfusion dependent and HSCT is the only cure
    - If not treated, infants can die
- Seen by Hematology

Alpha Thalassemia

- Complications
  - Minor/Moderate
    - anemia, fatigue, shortness of breath (r/t hypoxia/anemia)
    - Skeletal changes (r/t increase size of intramedullary spaces with anemia)
    - Hepatosplenomegaly
  - Severe
    - Iron overload-chelation needed

Alpha Thalassemia

- Clinical Presentation
  - Low hemoglobin
  - Low MCV and MCH
  - Smear-microcytic/hypochromic cells, target cells
  - Hgb Electrophoresis-diagnostic
  - Genetic testing-diagnostic-looks for gene mutations; done in utero

Beta Thalassemia

- Inadequate β-globin gene production
  - reduced to absent production leading to ineffective erythropoiesis
  - Tested on newborn screen
- β-thal Minor-only one mutated gene; no symptoms
- β-thal Intermedia-2 muted genes for reduced production; not transfusion dependent
- β-thal Major/Cooley Anemia (homozygous β-thal)-ineffective erythropoiesis
  - Don't develop symptoms until 3-6mo of age due to Hgb F
  - transfusion dependent-monitor for Fe overload

Beta Thalassemia

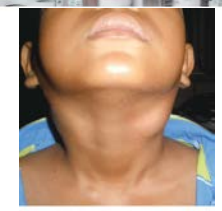
- Clinical Presentation
  - Low hemoglobin
  - Low MCV
  - Low RDW
  - Smear show microcytic/hypochromic RBCs
  - Target cells
  - Elevated serum Iron
  - Hgb Electrophoresis-diagnostic tool

Beta Thalassemia

- Long term complications (Major)
  - Fatigue, pallor, shortness of breath (r/t anemia)
  - Jaundice/hepatosplenomegaly/enlarged abdomen (r/t hemolysis of RBCs)
    - May need splenectomy
  - Growth delays
  - Cardiac arrhythmias, cirrhosis, hypothyroidism, pericarditis, DM (r/t hemochromatosis)
  - Facies (r/t enlarging of the bone marrow space due to anemia); "hair on end" appearance of skull on x-rays; chimp monk face if untreated
  - Iron overload requiring chelation

Abdou, nd

LYMPHADENOPATHY



Izani, Irfan, Suhaimi, 2011

What is it?

- Term that indicates any abnormality of a lymph node
  - Lymphadenitis indicates inflammation of a lymph node
- Can be regional or systemic
  - If regional, nodes that are proximal to the infection will be enlarged
- Can be acute or chronic
  - Acute are usually tender to the touch
  - Chronic may be non-tender

What to think about

- Common Infection causes:
  - Bacterial
  - Viral (EBV, CMV, HIV)
  - Parasitic (toxoplasmosis)
  - STDs (Syphilis)
- Rare Causes:
  - Leukemia, Lymphoproliferative diseases, LCH, Lymphoma
  - TB
  - Measles
  - SLE/JRA
  - Sarcoidosis
  - Fungal infections, plague
  - Drug reactions

What is Normal?

- Most lymph nodes are not palpable in newborns
- Cervical, axillary, inguinal nodes can sometimes be palpable in children
  - Posterior cervical nodes with URIs, allergies
- It is not considered abnormal until the diameter exceeds 1cm for cervical and axillary; 1.5 cm in inguinal
- Generalized adenopathy is not normal and systemic illness should be suspected
- Firm, fixed nodes should be suspicious for cancer
  - Usually nontender, rubbery in consistency

Work up

- Should be considered infectious until otherwise proven
- Detailed history and physical
- Diagnostics-labs, micro studies (EBV, CMV, HIV, Bartonella), TB; CT or US if needed, biopsy is last resort
- If infection, should respond to treatment. Failure to respond after 14 days, requires more work up

When to Refer to Hematology

- Lymph nodes that don't respond to therapy
- Abnormal CBC
- Other symptoms-weight loss, night sweats, fevers
- Supraclavicular lymph nodes

NEUTROPENIA

What is it?

- A decrease in the absolute number of circulating neutrophils (segs and bands) in the peripheral blood
  - Absolute Neutrophil Count (ANC)=Bands + Segs X Total WBC count/100 (in %)
  - Low normal is 1500 in children under 12mo
- Can be acute or chronic

What is it?

- Acquired Disorder
  - Aplastic Anemia
  - Vit B12, copper, folate deficiencies
  - Leukemia (ALL, AML)
  - Myelodysplasia
  - Prematurity with birthweight <2kg
  - Paroxysmal nocturnal hemoglobinuria (stem cell defect)
- Extrinsic Insult
  - Infection (such as Flu A/B, HHV6, RSV, Enterovirus, Parvo B19, EBV, CMV, HIV, severe bacterial inf, rickettsial or fungal inf)
  - Drug induced (sulfa, PCN, antipsychotics, antithyroid, anti-rheumatologics, antipyretics)
  - Immune neutropenia (autoimmune)
  - Reticuloendothelial sequestration (hypersplenism)
  - Bone marrow replacement (myelofibrosis, malignancy)
  - Chemotherapy/radiation

Neutropenias of Infancy

- Alloimmune neonatal neutropenia
- Neonatal passive autoimmune neutropenia

Neutropenia of Infancy

- Autoimmune neutropenia (AIN) of infancy:
- AIN in older children can be related to other conditions (autoimmune disorders, complications of infection, drugs, malignancy)
  - Treat underlying disorder

Presentation

- Those with ANC less than 500, are at high risk for infections
- Fever, stomatitis and gingivitis are most common presentation
- Also can present with whole host of infections
- Most common pathogen is *Staphylococcus aureus* and gr- bacteria
- Typical presentation of infections (exudate, fluctuance, LAD) may be diminished due to neutropenia

Other Neutropenias

- Cyclic Neutropenia:
  - Autosomal dominant congenital granulopoietic disorder
  - Rare-0.5-1 case per 1 million
  - Oscillatory period of about 21 days; ANC can be normal to <200
  - Need to get serial labs 3 times a week for 6-8 weeks to diagnose

Treatment

- Treat underlying process, if exists
- Remove offending drug
- G-CSF can be helpful in those with serious neutropenias to reduce risk of severe infection
- Refer to hematology for guidance

BLEEDING DISORDERS IN PEDIATRICS

Hemostasis

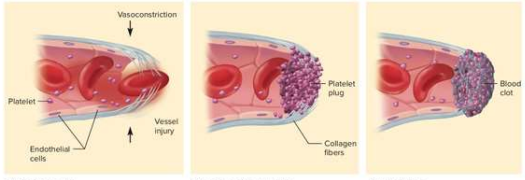
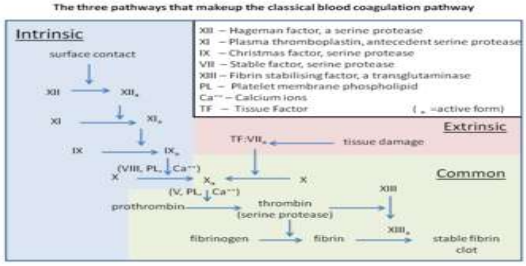


FIGURE 18.21 Hemostasis. (a) Vasoconstriction of a broken vessel reduces bleeding. (b) A platelet plug forms as platelets adhere to exposed collagen fibers of the vessel wall. The platelet plug temporarily seals the break. (c) A blood clot forms as platelets become enmeshed in fibrin threads. This forms a longer-lasting seal and gives the vessel a chance to repair itself.

How does a blood clot differ from a platelet plug?

Quora, 2018

Clotting Cascade



Acquired vs Inherited Disorders

- Acquired:
  - ITP
  - Vit K deficiencies
  - DIC
- Inherited:
  - Hemophilia
  - Von Willebrand Disease
  - Platelet disorders
  - Factor deficiencies

IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

What is it?

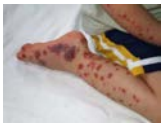
- Most common cause of thrombocytopenia in well children
- Usually occurs 1-4 weeks after a viral infection
  - Autoantibody develops against platelet surface antigen
  - Sudden onset of thrombocytopenia
  - No difference between males and females
  - Seems to have a seasonal prevalence-late Winter and early Spring are times of higher respiratory viral illnesses
  - Most common viruses have been associated with it including EBV and HIV
- Approximately 20% of children develop chronic ITP (longer than 90 days)

Diagnosis

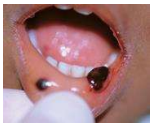
- Thrombocytopenia, platelet count less than 20,000
- WBC, Hgb, differential should be normal
- Bone marrow evaluation not necessary unless have abnormal CBC results

Clinical Presentation

- Sudden onset of generalized petechiae and purpura
- May be bleeding from gums and mucous membranes
- PE is usually normal apart from petechiae and purpura
- Splenomegaly, lymphadenopathy, bone pain and pallor are



Bellenza, 2018



Bailey, 2019

Treatment (2019 ASH Guidelines)

- Refer to Hematology
- For Children with platelet count <20,000 who have no or mild bleeding (skin manifestations only-bruising or petechiae)
  - Observation is recommended
  - Children with mucotaneous bleeding/Non-life threatening mucosal bleeding (Refer to Hematology)
  - Corticosteroids: Prednisone-1-4mg/kg/24hours for 7 days until platelet count rises above 20,000
  - Immunoglobulin (IVIG)-0.8-1gm/kg/day for 1-2 days
    - World wide shortage of IVIG
- Nplate vs Rituximab for ITP that doesn't respond to first line therapy

VON WILLEBRAND'S DISORDER

VWD

- Is a common bleeding disorder
  - Up to 1% of population have it
  - Some may not know they have it or have not had a significant bleeding challenge to be tested
- 3 types
  - Type 1: reduction in VWF protein (concentration and activity)
  - Type 2: dysfunctional VWF
  - Type 3: absent or severely reduced VWF

Type I

- Accounts for 75% of all cases
- Variable degrees of bleeding
  - Majority are mild, mucotaneous bleeding only

Type 2

- Several subtypes dependent on protein interactions
- Bleeding is moderate to severe
  - Mucocutaneous to soft tissues/gastrointestinal/surgical

Type 3

- Severe bleeding
  - Mucotaneous AND joint/soft tissues, gastrointestinal or surgical
  - Often presents in infancy (circumcision)

Diagnosing

- Increased history of bleeding
  - Abnormal bruising, nose bleeds, abnormal uterine bleeding
- Family hx of VWD
- Mild thrombocytopenia or prolonged aPTT not explained by another condition
- Apparent hemophilia A in female
- Need personal bleeding history of individual
- Refer to Hematology for specialized tests

Women with Menorrhagia

- vWD is a common bleeding disorder in women with DUB
- Diagnosed:
  - Family hx of bleeding disorder
  - Epistaxis, mouth bleeding
  - Heavy menstrual bleeding since menarche
  - Surgery related/dental related bleeding
- ACOG and ASH provides guidance to work up

Treatment

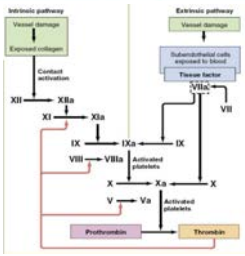
- DDAVP (desmopressin)-helps to stimulate vWF from cells and factor VIII to help make a stable clot
  - Is an anti-diuretic-need fluid restrictions and sodium monitoring
  - Helpful in Type 1; less in Type 2 and not at all in 3
- Recombinant vWF-replaces the lost factor (Vonvendi)
  - vWF with Factor VIII also used (Humate P, Alphanate, Wilate)
- Hormonal contraception for women
- Need planning with any surgery/dental procedure

HEMOPHILIA

Hemophilia

- X-liked Recessive bleeding disorders
  - Predominantly affect males; females are usually carriers
  - Factor deficiency that affects clotting
  - Severity of the disease is determined by factor levels in plasma (higher the factor level is, less severe disease)
  - Testing of at risk family members with hemophilia and preconception counseling of those with family history of hemophilia is important
  - Hemophilia A-Factor VIII deficiency
  - Hemophilia B-Factor IX deficiency

Clotting Cascade Review



Quizlet, nd

- Hemophilia types affects either factor VIII or IX
- Without these factors, clotting cannot occur
- The clotting cascade is interrupted

Signs/Symptoms

- Nearly identical with Types A and B
  - Easy bruising
  - Hematomas
  - Severe nose bleeds
  - Prolonged bleeding
  - Oozing after dental procedures
  - Gastrointestinal bleeding
  - Hematuria
  - Hemarthrosis (bleeding into joints)
  - Bleeding into brain

Diagnosis

- Labs
  - Platelets-usually normal
  - PT (tests extrinsic and common pathways-factors I, II, V, VII, X)
    - Will be normal
  - PTT (tests intrinsic and common pathways-factors I, II, V, VIII, IX, X, XI, XII)
    - Will be delayed with Hemophilia
  - Specific Factor tests are done to look for deficiencies/mutations

Treatment

- Injections of the missing factor
  - Advate/Feiba/NovoSeven/Alphanate (Factor VIII)
  - BeneFIX/AlphaNine/Bebulin (Factor XI)
- With severe disease, can develop antibodies to factors (inhibitors)
  - Reduces the effectiveness of the treatment
- For Mild Hemophilia A-can use DDAVP
  - Stimulates vWF to stabilize residual Factor VIII
- Need planning with any surgical/dental procedures
- Children should be managed through Hemophilia Centers for precise care and access to life time resources

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