Basics of pediatric hematology

- Anemia
  - RBC size
  - Reticulocyte count
  - Lack of production vs. hemolysis/loss
  - Fe++ deficiency, hemolytic, RBC aplasia

- Hemoglobinopathies
  - Sickle cell & thalassemias

- Thrombocytopenia
  - ITP
  - Platelet alloimmunization
  - Other (DIC, infection, malignancy, drug-induced, etc.)

- Coagulation
  - Tests of coagulation
  - Hypercoagulable states
  - Bleeding disorders


Review: Anemia

- RBC size/color
  - micro-, normo-, or macrocytic
  - hypo-, normochromic

- Reticulocyte count
  - lack of production, or hemolysis/loss

- Specific causes
  - Fe++ deficiency
  - hemolytic
  - RBC aplasia

Reticulocyte vs RBC

- Maturation of reticulocytes to erythrocytes takes 24-48 hours. During this change the reticulocyte loses its mitochondria and ribosomes, ability to produce Hb, and ability to engage in oxidative metabolism.
- Reticulocyte Production Index (RPI) corrects the reticulocyte count for the degree of anemia
  - indicates whether the bone marrow is responding appropriately to the anemia.
  - an RPI > 3 suggests increased production and implies either hemolysis or blood loss.
  - an RPI < 2 suggests decreased production or ineffective production for the degree of anemia.

RPI = retic ct X Hgb observed/ Hgb normal X 0.5

Review: Hematopoiesis

- Production of blood cells varies with age
  - By birth, virtually all bone marrow cavities are actively hematopoietic
  - In childhood, hematopoiesis moves to central bones (vertebrae, sternum, ribs, pelvis)

- Pluripotent stem cells
  - develop into precursor cells that give rise to mature erythrocytes, monocytes, megakaryocytes, or lymphocytes
Review: Hematopoiesis

- Regulation of hematopoiesis by cytokines
  - stimulate proliferation, differentiation, and functional activation of various blood cell precursors in bone marrow.

RBC maturation

Physiologic Anemia of the Newborn

- At one week postnatal all RBC indices begin declining to a minimum value reached at about 2 months of age.
  - decreased RBC production
  - plasma dilution associated with increasing blood volume
  - shorter life span on neonatal RBCs (50-70 days)
  - more fragile RBCs
  - switch from HbF to HbA
    - HbF decreases about 3% per week
    - at 6 mo. HbF represents only 2% of total Hb
    - switch to HbA provides for greater unloading of oxygen to tissues due to lower oxygen affinity of HbA relative to HbF.
  - seldom produces symptoms
  - not altered by nutritional supplements

Erythopoietic lineages

Anemia of Prematurity

- Occurs in low birth weight infants w/ poor erythropoietin response
  - Protein content of breast milk may not be sufficient for hematopoiesis in the premature infant.
  - Hb level rapidly declines after birth to a low of 7-10 g/dl at 6 weeks of age.
  - Signs and Symptoms
    - apnea
    - poor weight gain
    - pallor
    - decreased activity
    - tachycardia

Anemia at Birth

- Etiology: usually caused by congenital hemolytic disease of the newborn.
- Other causes include:
  - bleeding from umbilical cord
  - internal hemorrhage
Erythroblastosis fetalis

- Rh+ infants with Rh- mothers who have been previously sensitized
- Rh- mother usually becomes sensitized during the first few days after delivery when fetal Rh+ RBCs from the placental site are released into the maternal circulation.
- Rh antibodies of the mother are transferred to subsequent babies through placental circulation causing agglutination and hemolysis of the fetal RBCs.

Signs and Symptoms

- Severe anemia
- Compensatory hyperplasia & enlargement of blood forming organs (spleen and liver)

Treatment

- Prevention of sensitization (sensitization has dropped 80% with the use of Rh immune globulin). Rh immune globulin must be used within 72 hrs. after delivery.
- Intrauterine transfusion of affected fetuses (peritoneal or intravascular)

Fe++ deficiency

- Most common anemia of childhood
  - LBW, dietary, occult GI bleeding (e.g. hookworm), cow’s milk intolerance
- Presentation—
  - Pallor, irritability, anorexia when Hgb<5, tachycardia, cardiac dilatation, murmur, poss. splenomegaly
- Lab—
  - CBC: microcytic, hypochromic, low-normal retic. count
  - Decr. ferritin and serum iron
  - Incr. TIBC
- DDX— be suspicious!
  - Chronic disease, thalassemia, plumbism
- Tx—
  - Fe++ replacement (watch for constipation) gives dramatic response reticulocytosis in 72 hr, Hgb responds at ~1g/L per wk, iron stores us. replenished by 3 mo

Hemolysis

- Increased RBC turnover, shortened RBC lifespan
- Due to variety of factors, usually RBCs are fragile
- Spleen filters out and breaks down senescent RBCs, and must work overtime, and can result in effective asplenia (e.g. in Sickle Cell)
- RBC degradation products must be handled

Iron overload

- Long-term hemolysis and/or transfusions lead to iron overload, which affects all organs
- Ferritin levels to follow
- Chelation when necessary
Sickle Cell & Thalassemias

- Both have abnormal hemoglobin
- Variant Hb is recessive, although variable changes in RBC in heterozygotes
- Hemoglobin electrophoresis is diagnostic
  - HbSS = Sickle Cell disease
  - HbSA = Sickle Cell carrier
  - HbSβββ = Severe Sickle β-thalassemia
  - HbSββ = Not as severe
  - HbF (fetal Hb) allows O₂ carrying at lower O₂ tension
    - will remain elevated in SCD

Blood smears

- Normal (HbAA)
- SCD (HbSS)
- HbSC (thal)

SC disease problems

- Anemia
  - cardiomegaly (high output)
  - low Pulse Ox
  - high WBC
- Infarction
  - low O₂ -> sickling due to Hb structure changes
  - pain crises
  - strokes
- Infection/sepsis
  - asplenia from filtering abnormal RBCs
  - fever a serious sign

Sickle Cell Disease

- Family history is key, neonatal screening by Hgb electrophoresis
- All SCD patients should be followed by specialist
- Pneumococcal, influenza, meningococcal vaccines
  - functional asplenia, high risk for sepsis
- Prophylactic penicillin 125 mg BID until after age 3, then 250 mg BID until age 5, then D/C
  - greatly decreased mortality rates due to sepsis

Sickle Cell Disease

- Labs—
  - Hgb values 5.5-9.5 g/dL (~7.5 avg)
  - Retic count ~12% (5-30%)
  - will have chronic anemia, elevated WBC, which increases with vaso-occlusive event to 18-22K (in the absence of fever)

Sickle Cell Disease

- Fever—
  - Serious in SCD, patient should see provider for any fever
  - Seek source, blood cultures, CXR
  - I.V. fluids, antipyretics
  - Hospitalize for any pneumonia
  - Outpatient if not toxic, reliable family, get 24 hr follow up of cultures
Sickle Cell Disease

- Pain—
  - Frequent occurrence, treat mild with ibuprofen, patient and family know pain patterns
  - Trust the patient and family, and treat the pain
  - Fluid, pain control (Toradol if no renal disease, morphine, hydromorphone), avoid Demerol
  - O₂ only if needed (can suppress RBC production)
  - Priapism an emergency

- Acute Chest Syndrome
  - Infection or infarction
  - 25% of premature deaths in SCD
  - 25% after surgery
  - Signs: pain crisis, hypoxia, fever, neurological manifestations
  - Admit, avg ~10 day stay, 2-3 days in ICU
  - Aggressive physiotherapy/spirometry
  - Transfusion, not too much fluid, O₂, prophylactic antibiotics

- Stroke
  - long term transfusion therapy
  - will need chelation for iron overload if transfused more than 1 yr

- Aplastic crisis
  - remember Parvovirus B19!
  - can be post-op, need good hydration, O₂

- Splenic sequestration
  - blood can pool in spleen, causing hypovolemia
  - fluids, transfuse only to 8 or 9 g/dL

- Hydroxyurea
  - increases Hgb F, which carries O₂ at lower O₂ tension, good efficacy, but teratogenic effects in pregnancy

- Stem cell transplants
  - patients with multiple strokes, frequent crises, if long term transfusion therapy needed, possible GVHD

- Need team approach for sickle cell

Idiopathic Thrombocytopenic Purpura (ITP)

- Most common form of immunologic thrombocytopenia
- Acute & chronic, acute often following viral illness, usually resolving in 1-3 mo
- Petechiae on dependent extremities is main expression in childhood acute ITP
- Chronic, in adults, may have associated bleeding (e.g. GI, nose, gingivae, etc.)
- Immune attack can be demonstrated in some cases by anti platelet antibodies

Coagulopathies

- Various errors in clotting cascade
- Hypercoagulable states
  - antithrombin, protein C, protein S.
  - genetic abnormalities of Factor V, causing less protein C inactivation, leading to increased circulating prothrombin, are common
- Bleeding disorders
  - hemophilia
  - von Willebrand disease
**von Willebrand disease**

- Family of bleeding disorders caused by an abnormality of the von Willebrand factor (vWF), carrier protein for Factor VIII
  - can range from almost undetectable to severe bleeding propensity
- vWF binds on platelets to its specific receptor *glycoprotein Ib* and acts as an adhesive bridge between the platelets and damaged subendothelium at the site of vascular injury
  - i.e. causes platelets to stick
- vWF also protects FVIII from degradation

**von Willebrand disease**

- Type 1 (70-80% of vWFD) is quantitatively less of qualitatively normal vWF
  - autosomal dominant, variable penetrance
  - generally mild, can be asymptomatic and vary with time
- Type 2A and 2B (~15%) have qualitatively abnormal vWF
  - autosomal dominant
  - moderate severity
- Type 3 most severe, low vWF and Factor VIIIc in plasma, vWF absent on platelets
  - autosomal recessive, consanguinity an issue
  - possible mild disease in heterozygotes

**von Willebrand disease**

- History–
  - often mild bleeding (e.g. bruising, epistaxis, primary menorrhagia)
- Lab–
  - CBC us. normal, prolonged bleeding time, PT normal, aPTT variably increased
  - vWF and Factor VIII variably decreased
- Treatment–
  - often, none needed
  - DDAVP increases vWF and Factor VIII
  - Factor VIII plasma concentrates for severe