Pediatric Hematology/Oncology Board Review Prep
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ABP General Pediatric Content Outline after September 2017

ABP General Pediatric Content Outline beginning January 2016
Hematology

Erythrocyte Disorders

Approach to Anemia

Low MCV
- Iron Deficiency
- Thalassemia
- Lead Poisoning
- Chronic Disease
- Sideroblastic Anemia

Normal MCV
- Chronic Disease
- RBC membrane disorder
- RBC enzyme defect
- Sickle cell disease

High MCV
- Folate deficiency
- Vitamin B12 deficiency
- Aplastic Anemia
- Immune hemolytic anemia
Approach to Anemia cont’d.

Reticulocyte
- High
- Low

Bilirubin
- Normal
- High
- Low

WBC and Platelet count
- Normal
- High
- Low

Hemorrhagic anemia
- Bone marrow failure
- Aplastic anemia
- Malignancy
- Sideroblastic anemia
- TEC

Hemolytic anemia
- Bone marrow failure
- Aplastic anemia
- Malignancy
- Spinocytosis
- TEC

Bone marrow aplasia
- Aplastic anemia
- Marrow infiltrative disease
- Anemia of chronic disease
- Endocrinopathies
- Diamond Blackfan anemia

Infection-dependent anemia
- Autoimmune hemolysis
- Malaria
- DIC

Production Defect

Decreased retic count and normal morphology

1. Decreased Erythropoietin: chronic renal disease
2. Bone marrow failure - aplastic anemia, marrow infiltrative disease, anemia of chronic disease, endocrinopathies

Survival Defects

- Intrinsic (inherited): increased retic
  - Membrane Defects: HS, HE
  - Metabolic enzymes: G-6PD def.
  - Hemoglobinopathies: HbSS, HbSC, HbC
- Extrinsic (acquired): increased retic
  - Autoimmune hemolysis, malaria, DIC
Maturation Defect

- Cytoplasmic: decreased retic, hypochromic, microcytic
  - Impaired Hb synthesis: iron deficiency
  - Hemosiderin deficiency: sideroblastic anemia
  - Globin synthesis deficiency: thalassemia
- Nuclear: decreased retic, megaloblastic
  - DNA synthesis defects: Vitamin B12 or folate deficiency

Physiologic Anemia of Early Infancy

- Hemoglobin at birth ~15-20 g/dL
- Progressive decline during first 2-3 mos of life

<table>
<thead>
<tr>
<th>Age (wks)</th>
<th>Hemoglobin Nadir</th>
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<tr>
<td>Term infant</td>
<td>12</td>
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<tr>
<td>Premature infant</td>
<td>6 - 8</td>
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(The smaller the premie, the earlier and deeper the physiologic hemoglobin nadir)

Factors Determining Hemoglobin Values in Normal Children

- Gender
- Race
- Degree of sexual maturation
- Increasing Hemoglobin and MCV with age
- Altitude
- Heredity
Nutritional Anemias

Iron Deficiency Anemia
- Etiology of iron deficiency
  - Rapid growth, low levels of dietary iron, inadequate absorption, blood loss (epistaxis, menstruation, GI, intrapulmonary, renal)
- Clinical findings
  - Non-specific findings of anemia, pica
- Diagnostic evaluation
  - Microcytic anemia, low serum iron, high TIBC, low ferritin, increased RDW, low retic
- Non-hematological effects of iron deficiency
  - Neurocognitive: impaired function, impaired mental and motor function
- Management
  - Identify and eliminate cause
  - Administer elemental iron: 4-6 mg/kg/day

Megaloblastic Anemia
- Folate and Vitamin B12 deficiency
- Folate deficiency
  - Decreased intake, intestinal malabsorption, increased requirement, hemolytic
- Vitamin B12 deficiency
  - Reduced B12 intake, decreased intestinal B12 absorption, malabsorption despite a normal intrinsic factor, increased intestinal utilization
Hemolytic Anemias

Clinical Features
- Fatigue
- Respiratory distress
- Tachypnea
- Cardiac failure
- Pallor
- Jaundice/icterus
- Dark urine (intravascular hemolysis)
- Hepatomegaly
- Splenomegaly

Hereditary Spherocytosis
- RBC membrane defect
- Most common cause of non-immune hemolytic anemia
- Clinical findings
  - Prolonged neonatal jaundice, intermittent symptoms of hemolysis (especially with viral infections like parvovirus B19), spherocytosis, high MCHC (>36), spherocytes on smear
- Management
  - Close monitoring of Hb and retic counts
  - pRBC transfusion if symptomatic and worsening anemia
  - Splenectomy to prolong RBC survival
    - Prior to splenectomy, routine vaccines (pneumococcal, H. influenzae, and meningococcal) to minimize post-splenectomy sepsis
    - Penicillin prophylaxis
G6PD deficiency

- X-linked recessive
- Clinical findings
  - Prolonged hyperbilirubinemia in the newborn period, sudden onset of anemia and pallor
  - Smear will show bite cells and blister cells
- Management
  - Avoid oxidant exposure
  - Avoid moth balls, fava beans, sulfas, pyridium, nitrofurantoin, dapsone, rasburicase

Sickle Cell Disease

- Early identification with universal newborn screening
- Clinical findings
  - Chronic hemolytic anemia: Jaundice, pallor, fatigue; Parvovirus aplastic crisis; Cholestatis
  - Acute complications: Pain crisis, dactylitis, Priapism; Acute chest syndrome; Spleenic sequestration; Aplastic crisis; Overt stroke
  - Chronic organ damage: Spleen, Heart, Kidneys, Lung, Bones, Eyes
  - Susceptibility to infection (at risk for infection with encapsulated organisms)

Sickle Cell Disease cont’d.

- Prevention and screening
  - Prophylactic penicillin
    - Starting at birth and until 5 years old
  - Immunizations
    - Pneumococcal, meningococcal vaccines
  - Screening TCD
Splenic Sequestration

- Spleen becomes massively enlarged and engorged with blood
- Hypovolemia and severe anemia
- Rapid, severe worsening anemia
- Hb at least 2 g/dl lower than baseline, reticulocytosis with increased MNC's, marked severe thrombocytopenia, splenomegaly
- Treatment
  - Emergency repletion of intravascular volume with RBC transfusion (not fluid bolus!!!)
  - Transfusions must be given in small aliquots of 5 ml/kg
  - May need more than one transfusion
  - Splenectomy may be considered to prevent further episodes

Aplastic Crisis

- Usually due to parvovirus, Strep pneumoniae, salmonella, EBV
- Retic count (0), low Hb level, normal platelets, MNCs
- Usually short and self-limited
- Transfusions as needed
  - Transfuse slowly to prevent fluid overload and CHF

Thalassemia

- Microcytic anemia
- Decreased or absent production of β or α chains
- Imbalance between β or α chains
- Globins in excess precipitate and damage the RBC membrane
- Ineffective erythropoiesis
  - Anemia
  - Bone marrow expansion
  - Extra medullary hematopoeisis
  - Increased intestinal iron absorption
**β Thalassemia Major (Cooley Anemia)**

- No β-globin chain production
- HbEIP - shows almost all HbF and HbA2
- Intramedullary hemolysis
- Erythroid hyperplasia in the bone marrow
- By 6-12 m/o: pallor, irritability, growth retardation, HSM and jaundice
- Expansion of bone marrow space in facial bones

**Autoimmune Hemolytic Anemias**

- Immune destruction of RBC’s mediated by autoantibodies directed against antigens on the patient’s RBC’s
- Idiopathic, drug induced or in association with other disorders (hematologic, autoimmune, infectious, or neoplastic)
- Presentation is highly variable
- Pts insidiously develop anemic symptoms: weakness, dizziness, fatigue, and dyspnea on exertion
- Most commonly, warm AIHA is associated with IgG antibodies
- Cold AIHA is complement mediated
- Typically associated with Mycoplasma infection
- Other Findings
  - Reticulocytosis, Hyperbilirubinemia (indirect), Increased LDH, Low Haptoglobin, Positive DAT, Spherocytes on the smear

**Aplastic and Hypoplastic Erythrocyte Disorders**
Diamond-Blackfan Syndrome

- Autosomal dominant
- Mutations/deletions in ribosomal proteins
- Diagnostic Criteria:
  - Age < 1 yr, Macrocytic anemia, Reticulocytopenia, Pancytopenia
- Congenital anomalies:
  - Craniofacial, upper extremity, GU, cardiac, short stature
- Malignancy risk:
  - AML, ALL, osteosarcomas
- Treatment:
  - Prednisone for steroid-refractory patients; chronic RBC transfusions; HCT for transfusion-dependent pts or bone marrow abnormalities

Transient Erythoblastopenia of Childhood

- An acquired, self-limiting red cell aplasia unique to childhood
- Incidence of 5 per million per year
- Most common age of presentation is 2 years with range of 6 mo to 5 years old
- Hemoglobin is usually 3-8 g/dL
- Retic 0%
- WBC and platelets are normal
- Normochromic, normocytic anemia with reticulocytopenia
- Presumed to be a post-viral process (though NOT associated with Parvovirus)
- Complete recovery usually within 4-8 weeks of presentation. Rarely recurs.
- Treatment with pRBC if there's cardiovascular compromise

Blood Product Transfusion

- Complications associated with transfusions
  - Transfusion transmitted disease
    - HIV: 1.4 – 4 million
    - Hepatitis C: 1.5 million
    - Hepatitis B: 1.5 million
    - HTLV I & II: 1.5 – 10 million
  - Transfusion reactions
    - Acute hemolytic transfusion reaction
    - Delayed hemolytic transfusion reaction
    - Febrile (non-hemolytic) transfusion reaction
    - Hypersensitivity reactions
    - Thrombosis
Leukocyte Disorders

Neutropenia

- Absolute neutrophil count (ANC): WBC x (% neutrophils and band forms)
  - Severe neutropenia: ANC of < 500
  - Moderate neutropenia: ANC between 500-1000
  - Mild neutropenia: ANC between 1000 and 1500
- Patients with severe neutropenia are at risk for developing serious bacterial infections
- Those with less severe neutropenia frequently develop skin infections, otitis media or stomatitis
- Recurrent bacterial infection is a manifestation of all white blood cell disorders

Evaluation of Neutropenia

- History
  - Presence and frequency of infections, in the form of sore throats, oropharyngeal ulcers, fever, otitis, respiratory symptoms, and skin infections (cellulitis, abscesses)
  - Medication history
  - Family history of serious infections, neutropenia, hematologic diseases
Evaluation of Neutropenia

- Physical exam
  - Pay close attention to mouth, skin, LAD and organomegaly
  - Significant gingivitis if issues with neutrophil function or number
- Labs
  - CBC with diff and smear to assess neutrophil morphology
  - Bone marrow: aspirate, biopsy, cytogenetics
  - Blood chemistries: LDH, uric acid, alkaline phosphatase
  - Anti-neutrophil antibodies

Kostmann Syndrome

- Familial Severe Neutropenia
- Autosomal recessive disorder
- ANC is chronically low, usually < 200
- Maturation arrest at the promyelocyte stage
- First year of life: omphalitis, otitis media, pneumonitis, URIs and skin abscesses
- Treatment
  - G-CSF will improve neutrophil counts
  - Goal: achieve an ANC of 1,000 to 1,500, and maintain the patient free of infections
  - Those who don't respond can receive an allogeneic stem cell transplant

Shwachman-Diamond Syndrome

- Autosomal recessive disorder
- SBDS gene mutations are the cause
- Patients p/w neutropenia, pancreatic insufficiency (FTT, diarrhea, steatorrhea), short stature and metaphyseal dysostoses
- Recurrent infections and FTT are common
- Treatment:
  - Nutritional deficiencies can be corrected with pancreatic enzymes
  - G-CSF can be used to increase neutrophils
  - Aggressive antibiotic therapy and supportive care for infection
  - Bone marrow transplant can be curative for the neutropenia or myelodysplasia that may develop
Cyclical Neutropenia

- Autosomal dominant disorder
- Occurs at a regular interval of every 21 +/- 3 days, lasts about 3 to 6 days
- Defective maturation of uncommitted stem cells
- Mutations in the ELA gene
- Patients present with fever, aphthous stomatitis, cervical lymphadenitis, and rectal/vaginal ulcers
- Infections can be severe, even fatal in about 10% of patients
- Management
  - G-CSF will prevent the episodic neutropenia
  - Oral hygiene
  - Antibiotics at the nadir pre

Drug-induced Neutropenia

- It may occur within several hours to days of exposure to a medication, resulting in severe neutropenia or agranulocytosis
- Drugs implicated include anticonvulsants, antithyroid, NSAIDs, antihistamines, sulfa, and synthetic penicillins
- If a drug is the suspected cause, it should be discontinued

Viral induced Neutropenia

- Viral induced neutropenias are very common and don’t require specific treatment
- Usually acute, resolves days to months
- Causes:
  - Viral: EBV, CMV, influenza, RSV, HCV, parvovirus
  - Bacterial: gram negative sepsis, tuberculosis, tularemia, typhoid
  - Fungal: Histoplasmosis
  - Protozoal: malaria, leishmaniosis
  - Rickettsia
Disorders of Neutrophil Function

- Recurrent infections and a normal neutrophil count in association with aphthous ulcers, stomatitis, otitis media, cervical lymphadenopathy and skin abscesses in the first few months of life
- Initial workup: neutrophil count, neutrophil morphology and either a test for respiratory burst or flow cytometry
- Leukocyte Adherence Deficiency I (LAD1)
  - Absent or impaired adhesion molecules involved in trafficking
  - Mutation in the gene that encodes CD18
  - Delayed separation of the umbilical cord and omphalitis are frequently the first signs
  - Recurrent bacterial infections (skin and mouth)

Disorders of Neutrophil Function

- Hyperimmunoglobulin E syndrome
  - Eczema, boils and increased IgE
  - Sinopulmonary infections, fungal infections of nails and mucosa
- Chediak-Higashi Syndrome
  - Partial oculocutaneous albinism with “silver” hair, recurrent skin infections
  - Giant granules in neutrophils

Chronic Granulomatous Disease

- Disorder of neutrophil function in which there's a defect in the respiratory burst
  - Defects in phagocyte NADPH oxidase complex
  - No toxic oxygen metabolites are produced
  - Absent or decreased ability to kill catalase-positive bacteria/fungi
- Recurrent pyrululent infections with catalase-positive bacteria and fungi involving skin and mucous membranes
  - Pneumonia or sinuses, and necrotizing fungal infections of deep tissue or bone
- Serious infection occurs in those organisms that produce catalase
  - Staph aureus, Staph epidermidis, E. coli, Serratia marcescens, Salmonella and Candida
Chronic Granulomatous Disease cont’d.

- Testing
  - NBT dye test will quantitate reduction of NBT to NBTH
  - Confirm: look for failure to induce an oxidative metabolic burst during phagocytosis
  - Dihydrohodamine 123 (DHR) - flow based
  - Early use of Bactrim and interferon gamma decreases the number of serious infections and has been shown to improve survival

Platelet Disorders

- Bleeding is immediately following injury (primary hemostasis)
  - Usually skin and mucous membranes
  - Petechiae is a specific finding for plt disorders
  - Hemarthroses and intramuscular hematomas are uncommon
  - Careful personal and family history of abnormal bleeding very important

Evaluation for Thrombocytopenia
Assessment of Function

- Bleeding time
  - Normal range: 2-10 min
  - Poorly reproducible and operator dependent
  - Usually prolonged if platelets markedly reduced in number or defective in function
- Automated plt function tests (PFA-100)
  - Exposure of blood to a membrane coated with Col/ADP or Col/Epi
  - Formation of plt plug closes the aperture
  - Not technician dependent
- PFI aggregation studies
  - Assesses primary and secondary plt aggregation
  - Not reliable with plt count < 100

Thrombocytopenia in the Newborn Period

Differential Diagnosis

- Immune Destruction
- Impaired Production
- Consumption/Sequestration
- Infectious
- Genetic/Congenital thrombocytopenias
Neonatal Alloimmune

- Most common cause of thrombocytopenia in the fetuses and newborns
- Leading cause of ICH
- Incompatibility between parents' HPA's
- Evaluation with daily plt count and a head ultrasound for ICH
- Treatment
  - Recommended for plt < 30; higher thresholds for bleeding and ICH
  - Gold standard is transfusion with maternal plt's
  - Can give donor plt’s +/- IG and corticosteroids

Neonatal Alloimmune cont’d.

- Subsequent pregnancies
  - Future pregnancies are at risk and might be more severely affected
  - Most important risk factor is ICH in the previous infant
- Treatment
  - Maternal IG weekly +/- daily steroids

Neonatal Autoimmune

- Can occur even if the mother is in remission
- No correlation between maternal and neonatal plt counts
- Plts nadir around 3-4 days of age
- For clinical bleeding treat with IVIG
- Most infants show recovery by 7 days
- Can persist for several weeks
Drug-Induced Thrombocytopenia

- Caused by antibodies that bind to plt GPIIb/IIA or GPIb/IX in the presence of the drug
- Can be severe and lead to significant bleeding
- Most common offending agents
  - Aspirin: Irreversibly inhibits cyclooxygenase; 7 days
  - NSAIDS: Reversible inhibition of cyclooxygenase; half-life of drug
  - Heparin, Quinine, Penicillins, Vaproic acid
- Withdrawal of drug results in prompt rise in plt count

Immune Thrombocytopenia (ITP)

- Acute onset of thrombocytopenia in an otherwise healthy child
- Most kids p/w skin findings only
- Bleeding is mucosal in nature
- Development of severe hemorrhage is rare
- Can be associated with viral illnesses

ITP Lab Features

- Markedly reduced plt count (isolated thrombocytopenia)
- Large plt on blood smear
- Bone marrow biopsy usually not needed unless
  - Atypical features
  - Constitutional symptoms
ITP Natural History

- Reduction or cessation of new hemorrhage within 3 to 10 days
- Rise in plt count within 1 to 3 weeks
- Normalization of plt count
  - 50% of cases within 3 months
  - 60% of cases within 6 months
  - 80% of cases within 12 months

ITP Treatment

- Treatment depends on bleeding symptoms, family comfort and assurance regarding follow-up
- First Line Treatment
  - Observation and Education
  - Steroids
    - Reticuloendothelial blockade and decreases synthesis of anti-plt antibodies
  - IVIG
  - Reticuloendothelial blockade
  - Anti-D immunoglobulin
    - Forces the body to induce an immune response to RBCs
- Second Line Treatment
  - Rituximab
  - Splenectomy

Kasabach-Merritt Syndrome

- Thrombocytopenia associated with localized intravascular consumption in giant hemangiomas
- Presentation
  - Usually presents within the first week of life
  - Cutaneous lesions
  - Imaging is necessary to determine the depth of the lesion
  - Labs: thrombocytopenia, decreased fibrinogen, increased D-dimer, microangiopathic hemolytic anemia
- Management: steroids, vincristine, anti-fibrinolytic agents, supportive care
Wiskott-Aldrich Syndrome

- Triad of thrombocytopenia, eczema, and frequent infections
- X-linked recessive
- Mutation of WASP gene
- Small platelets
- Associated with defects in T and B cells and inability to form antibodies

Treatment
- Supportive care of eczema and infections
- Stem cell transplant

Thrombocytopenia Absent Radii (TAR) Syndrome

- Radial abnormalities but normal thumbs
- Diminished or absent megakaryocytes with elevated TPO levels
- Management: platelet transfusions
- Increase in platelet count by 12 to 24 months

Qualitative Disorders

- Membrane Receptors
  - Bernard-Soulier syndrome, Glanzmann's Thrombasthenia
- Storage Granules
  - Alpha granules, dense granules
- Signal Transduction
Bernard-Soulier Syndrome

- Abnormal or absent surface receptor for von Willebrand factor: GP Ib/IX complex
- AR
- Mucocutaneous bleeding starting in infancy
- Mild to moderate macrothrombocytopenia
- Diagnosis: normal plt aggregation in response to ADP, epi and col but abnormal or absent aggregation in response to ristocetin

Glanzmann’s Thrombasthenia

- Deficiency or absence of plt membrane fibrinogen receptor GPIIb/IIIa
- AR
- Severe mucocutaneous bleeding starting in infancy
- Diagnosis: absent plt aggregation in response to ADP, Epi, Col; normal ristocetin-induced plt aggregation

Storage Pool Disorders

- Alpha Granules
  - Light microscopy
  - Contents
    - Fibrinogen, VWF, vWF, Factor V, Factor VIII, Thrombospondin, Beta-thromboglobulin
  - Absent in gray plt syndrome
- Dense Granules
  - Electron microscopy
  - Contents
    - Serotonin, calcium, ATP, ADP
  - Absent in dense granule storage disease, Hermansky-Pudlak syndrome, Chediak-Higashi
Coagulation Disorders

Factor Deficiencies and Coagulation Assays

- aPTT
  - Contact factors
    - F1, HAM, FX, FIXI
  - Factor IX
  - Factor VIII
  - Common Pathway
    - Factor V
    - Factor VIII
    - Factor IX (antithrombin)
    - Fibrinogen

- PT
  - Factor VII
  - Common Pathway
    - Factor X
    - Factor V
    - Factor II
    - Fibrinogen

Diagnosis of Bleeding Disorders

Factor deficiency vs. Platelet/Vessel Interactions

- Factor Deficiency
  - Deep
  - Muscul/oart

- Platelet/Vessel
  - Immediate
  - Superficial
  - Mucosal
Hemophilia

- PTT is increased and PT is normal
- Factor assays - measure specific factor activity levels
- Severity based on factor level:
- Heterozygous females (carriers) can be symptomatic
- Factor VIII deficiency (Hemophilia A)
  - X-linked recessive
- Factor IX deficiency (Hemophilia B)
  - X-linked recessive
- Factor XI deficiency (Hemophilia C)
  - AR, bleeding is less common, risk of bleeding doesn’t correlate with the level of FXI, and tend to have more mucosal bleeding

Hemophilia cont’d.

Severe (<1%)
- Present at: Birth - 3 years
- PT, neonatal bleeding, bruising, vaccine related bleed, mucosal bleed, joint bleed

Moderate (1-5%)
- Present at: 2-10 years
- PT, neonatal bleeding, bruising, vaccine related bleed, mucosal bleed, joint bleed

Mild (5-40%)
- Present at: 5-21 years
- Post-traumatic or post-surgical bleed

Severe (<1%)
- Present at: Birth - 3 years

Moderate (1-5%)
- Present at: 2-10 years

Mild (5-40%)
- Present at: 5-21 years

Post-traumatic or post-surgical bleed
### Patterns of Bleeding By Age

- **Neonatal**
  - Circumcision, umbilical cord, cephalohematoma

- **Infant**
  - Tongue/teeth/frenulum, soft tissue, post-vaccination bleeding/bruising

- **Children**
  - Hemarthrosis, muscle, soft tissue

- **Bleeding in Hemophilia**
  - Spontaneous is the hallmark
  - Triggers: trauma and hemarthrosis/surgery

### Treatment

- On demand (episodic) vs. prophylaxis
  - Prophylaxis is the regular administration of factor replacement therapy in order to prevent bleeding and its complications.
  - Types of prophylaxis:
    - Primary prophylaxis: Initiation of factor prior to any joint bleeding (or after 1-2 joint bleeds before any obvious joint disease) and maintenance prophylaxis: Dosage of factor replacement after the onset of joint disease in order to prevent further bleeding.

- Medications
  - **Factor replacement**
    - Desmopressin (DDAVP)
  - **Anti-fibrinolytics**

- Special situations
  - Surgery
  - Dental procedures
  - Hematuria

### Von Willebrand Disease

- Most common bleeding disorder

- Variable clinical manifestations

- **vWF Function**
  - Platelet binding
  - Carries molecule for FVIII
  - vWF is circulating, and binds to unfurling subendothelium
  - vWF binding "capturing" platelets via platelet glycoprotein-IB receptor
  - Platelet adhesion via vWF and platelet activation
Von Willebrand Disease (cont’d)

- wVF is increased by physiologic stress, DDAVP, estrogen, pregnancy and is an acute phase reactant
- 3 types of vWD (characterized by physiologic defect):  
  - Type 1: most common form, AD, reduced production of normal vWF  
  - Type 2: - AD, qualitative defect  
  - Type 3: - AD, absence of vWF production  
- Symptoms:  
  - Mostly mucocutaneous bleeding except type 3  
  - Epistaxis, easy bruising, oral bleeding, post-surgical (oropharyngeal) bleeding  
  - Menorrhagia and post-partum bleeding in females of child-bearing age

Lab Testing

- Screening  
  - No screening tests rule out vWD; PT is normal, PTT is only abnormal if FVIII is low, bleeding time and PFA-100 are not sufficiently sensitive
- Diagnostic Tests  
  - vWF antigen: how much vWF is present  
  - Ristocetin cofactor activity: plt binding function; measure how well vWF binds to plt  
  - FVIII activity: assesses FVIII activity in blood and vWF:VIII binding function  
  - VWF multimer analysis: assesses molecular structure of VWF on an agarose gel

Treatment

- Increase circulating vWF  
  - DDAVP (releases stored vWF from Weibel-Palade bodies in endothelium)  
  - Replacement with plasma-derived vWF concentrate  
- Hematologic therapy  
  - Antifibrinolics  
- Hormonal therapy  
  - Effective for menorrhagia treatment; estrogen increases vWF and FVIII, and reduces blood flow to endothelium
- Topical therapy  
  - Antifibrinolics for oral bleeding  
  - Topical thrombin for oral or nose bleeding  
  - Celulose or collagen embedded gauze
Among the contact factors, only Factor XI deficiency is associated with bleeding. Deficiency of Factor XII, High molecular weight kininogen (HMWK) and prekallikrein (PK) does not cause bleeding.

Factor XIII
- It has the longest half-life of all the clotting factors (10 days)
- Autosomal Recessive
- Common presentation is bleeding from the umbilical stump and intracranial hemorrhage
- Screening coagulation tests (PT and PTT) are normal
  - aPTT and PT reactions are complete once fibrin monomers are formed
  - Don't take into account the cross-linking effect of FXIII
- Diagnosis: Factor XIII level and clot solubility test
- Treatment: FFP or cryoprecipitate every 3-5 weeks

Pancytopenia
Aplastic Anemia

- Presentation is often insidious with inciting event at least 6-8 weeks previously.
- Rarely present with infections, weight loss, fever, pain, LAD and HSM that are commonly seen in malignancy.
- Often present with thrombocytopenia, uncommonly with clinical bleeding.
- MCV is increased with a normal RDW.
- HbF is increased due to bone marrow stress.
- High MCV macrocytosis suggest bone marrow failure.

Suspicion for an Inherited Bone Marrow Failure Syndrome

- Presence of characteristic physical anomalies with hematological abnormalities.
- Unexplained macrocytosis in a pt with or without characteristic birth defects.
- Children with aplastic anemia or myelodysplasia.
- Patients with malignancy who are highly sensitive to chemotherapy or radiation.
- Cancer in a pt at an atypically early age.
  - Head/neck/esophageal cancer < 40 yrs.
  - Voluminous cancer > 30 yrs.
- Family members with any of the above.

Bone Marrow Failure

- Inherited
  - Fanconi Anemia
  - Dyskeratosis Congenita
  - Diamond-Blackfan Anemia
  - Shwachman-Diamond Syndrome
  - Congenital amegakaryocytic thrombocytopenia
  - Severe Congenital Neutropenia
- Acquired
  - Medications
  - Chemicals
  - Toxins
  - Viral Infection
  - PNH
  - Idiopathic (immune)
Evaluation

- Bone marrow aspirate and biopsy
  - To see in situ representation of cells and how they relate to each other
- Cytogenetics on marrow; FISH for MDS
- R/o inherited bone marrow failure syndromes
  - Chromosome breakage assessment with DES or HMC to r/o Fanconi Anemia
  - Telomere length to r/o Dyskeratosis Congenital

Evaluation cont’d.

- Assess PNH clone size by flow cytometry
- R/o viral infection assessment by serology or PCR
  - EBV, CMV, Hepatitis A/B/C, HIV, parvovirus
- Evaluation of renal, hepatic and thyroid function

Treatment

- Immunosuppressive therapy
  - ATG
  - Cyclosporin (CsA)
- Acquired Aplastic Anemia
  - Moderate Aplastic Anemia
    - Observation vs. ATG/CsA
  - Severe or very severe Aplastic Anemia
    - Matched related donor
      - Yes → HLA matched SCT
    - No → ATG/CsA
Fanconi Anemia

- Congenital anomalies
  - Not always present, may be subtle
  - Not required for diagnosis

- Cancer predisposition
  - AML, squamous cell carcinomas, brain tumors, Wilms tumors, other solid tumors

- Family history
  - All are autosomal recessive except FANC-B which is X-linked recessive

Fanconi Anemia cont'd.

- Congenital anomalies
  - Skin (café au lait, hypopigmented)
  - Short stature
  - Upper limb (thumb)
  - Skeletal
  - Eyes
  - Renal
  - Cardiac
  - Genital tract
  - GI
  - CNS

- Congenital anomalies
  - Primarily radial ray deformities
  - Total absence of radius in majority of patients
  - Hypoplastic thumb
  - Scapula, thenar eminence often reduced in size

Fanconi Anemia cont'd.

- Diagnostic Tests
  - DNA repair defect: increased chromosomal breakage
  - Screening test: peripheral blood karyotype w/o exposure of patient cells
    - Breakage inducing agent: diepoxybutane (DEB) or mitomycin C (MMC)
  - Flow Cytometry
  - Specific mutation analysis
  - Diagnose disease based on physical exam and chromosomal breakage
Oncology

Hematologic Malignancies

Acute Lymphoblastic Leukemia (ALL)

- Most common malignancy in childhood
- Incidence peaks between 2 and 5 years of age
- Certain disorders are associated with an increased risk of ALL:
  - NF Type I, Li Fraumeni syndrome, Bloom syndrome, ataxia telangiectasia,
    Kniest distortible congenital immunodeficiencies (Cancer predisposition syndromes)
  - Down Syndrome
- Diagnosis requires a bone marrow aspirate
Clinical and Lab Features

- Bone pain, hepatosplenomegaly, generalized lymphadenopathy, purpura, fever, pallor, bleeding, infection
- WBC count may be low, normal or high
- Tumor lysis
  - Increased potassium, phosphorous, uric acid, and hypercalcemia
- Decreased RBCs
  - Pallor and fatigue
- Decreased platelets
  - Bleeding, bruising and petechiae
- Decreased neutrophils
  - FEVER, oral ulcers and infections

Prognostic Indicators

- Good Prognostic Indicators
  - Age (>1 or < 10 y/o), hyperdiploidy, trisomy 4 and 10, t(12; 21)
- Poor Prognostic Indicators
  - Age (<1 or > 10 y/o), hypodiploidy, t(9;22), MLL rearrangements, WBC > 50K at diagnosis, CNS disease, testicular disease, + MRD

Treatment

- Importance of risk-adjusted therapy for ALL prognostic subgroups
- Outcomes of HR subgroups can be improved with more intensive therapy
- Most valuable drugs for remission induction of ALL
  - Corticosteroids (dexamethasone, prednisone), vincristine, asparaginase +/- anthracycline
Outcomes

- Overall Survival
  - Standard risk: 5 yr OS is 95%
  - Infants: 5 yr OS is 43%
  - >10 y/o: 5 yr OS is 73-85%

- Sites of relapse
  - Bone marrow, Testes, CNS

Acute Myeloid Leukemia (AML)

- AML accounts for 15-20% of childhood acute leukemias
- Fever, fatigue, pallor, skin/mucosal bleeding, bone pain, infection
- Anemia, thrombocytopenia, neutropenia
- Major leukemia predispositions
  - Down syndrome, Marrow failure syndromes, AML-related conditions, Ataxia-telangiectasia, Bloom syndrome, Li-Fraumeni
- Diagnosis requires a bone marrow aspirate
- Classification
  - Old: FAB classifies based on morphologic/phenotype; 30% blasts
  - New: WHO classifies based on clinical/molecular; 20% blasts

Acute Promyelocytic Leukemia (M3)

- Granules/Auer rods
- DIC and bleeding
- t(15;17), PML-RARα fusion
- Good prognosis with ATRA/arsenic therapy
Therapy

- Drug combinations most effective in the treatment of AML are cytarabine and anthracycline.
- Standard of care in pediatric AML is for all children to receive prophylactic therapy for CNS involvement.
- There is no role for extended maintenance (a survival benefit has never been demonstrated).

Hodgkin Lymphoma

- Hodgkin Lymphoma is the #1 cancer in 15-19 year olds.
- 3 distinct forms:
  - Childhood, young adult and older adult form
  - Childhood form tends to increase with increasing family size and lower socioeconomic status.
  - Young adult form is associated with a higher socioeconomic status in industrialized nations.
  - Hodgkin disease may occur in families.

Subtypes of Hodgkin Lymphoma

- Nodular lymphocyte predominant (NLPHL)
- Classical HL:
  - Nodular sclerosing
  - Mixed cellularity
  - Lymphocyte predominant
  - Lymphocyte depleted
Reed-Sternberg cell

- "Owl's eye"
- Binuclear

Clinical Presentation

- Fatigue, anorexia, weight loss
- B symptoms: fevers (3 days), weight loss (10% in 6 mo) and night sweats
- Pruritus, alcohol induced pain
- Painless, supraventricular/cervical adenopathy
- Lymph nodes rubbery/firm

Clinical Presentation cont’d.

- Most common clinical presentation of Hodgkin disease in children
- Painless LAD, mediastinal mass, constitutional symptoms
- Lab abnormalities
- Leukocytosis, lymphopenia, eosinophilia, monocytosis
- Increased ESR/CRP/ferritin/serum copper
- Anemia of chronic inflammation
Non-Hodgkin Lymphoma

- Third most common malignancy in children
- Pediatric NHL are more common in younger kids, males and Caucasians
- Subtypes: Can be T cell or B cell derived, and immature or mature
- Burkitt Lymphoma
- Lymphoblastic Lymphoma
- Treatment: chemotherapy +/- surgery

Burkitt Lymphoma

- Most common form of NHL in the U.S.
- In children, non-Hodgkin’s lymphoma has been found to be the lead point in intussusception involving the terminal ileum

Lymphoblastic Lymphoma

- Can be T cell or B cell in origin
- Can present as an anterior mediastinal mass

Solid Tumors
Neuroblastoma

- 8-10% of all childhood cancer
- Most common extracranial solid tumor
- Median age diagnosis: 19 months of age
- Most common cancer in infancy

Clinical Presentation

- Heterogeneous disease process
- Symptoms based on primary or metastatic sites of disease
  - Neck mass, abdominal distension, HSM, spinal cord compression, Horner syndrome, GU symptoms, hypertension, neurologic abnormalities
  - Bone pain, proptosis (raccoon eyes), resp distress, skin nodules
- Lab findings:
  - Elevated serum or urine catecholamines (HVA and VMA)

Diagnostic Evaluation

- Tumor biopsy
- Histopathology and molecular testing
- Anatomic imaging (CT, MRI)
- Primary and metastatic sites
- MIBG scintigraphy
- Bilateral bone marrow aspirates and biopsies
- Urinary VMA and HVA
Paraneoplastic Syndromes

- Opsoclonus Myoclonus Ataxia Syndrome
  - Occurs in approximately 4% NB diagnoses
  - Myoclonic jerking and random eye movement, with or without cerebellar ataxia
  - Long term neurologic and cognitive deficits, including psychomotor retardation

- Kerner-Morrison Syndrome
  - Tumor secretes Vasoactive Intestinal Peptide (VIP) causing secretory diarrhea
  - Tumor resection reduces secretion

- Wilms Tumor
  - Most common primary malignant tumor of the kidney in childhood
  - Median age: 4.5 years girls; 3.7 years boys
  - P/w asymptomatic abdominal or flank mass
  - Can have abd pain, fever, anemia, hematuria, HTN or hypercalcemia
  - Association of Wilms tumor with other congenital anomalies
    - WAGR syndrome
    - Beckwith-Wiedemann syndrome
    - Denys-Drash Syndrome

Prognosis

- Stage of disease at diagnosis
- Tumor size
- Histopathologic features of the tumor
- Molecular features of the tumor
- Patient age

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
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<td>Large</td>
<td>10</td>
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</table>
Brain Tumors
Clinical Findings

- General and non-localizing symptoms
  - Headache, vomiting, behavioral changes, developmental delay, weight changes, endocrine dysfunction
- Increased intracranial pressure
  - Headache, emesis, vomiting, bulging fontanelle, papilledema, visual changes

- Localizing signs
  - Brain stem: weakness, cranial neuropathies, autonomic function
  - Cerebellum: ataxia, muscle movement
  - Frontal lobe: personality changes, seizures, decreased speech
  - Hypothalamus: autonomic function, endocrinopathies
  - Occipital lobe: poor/loss of vision
  - Parietal lobe: decreased sense of touch/pain, poor spatial and visual perception
  - Temporal lobe: seizures, poor memory, language comprehension
  - Thalamus: weakness/motor control, consciousness, sleep/wake cycle

Craniopharyngioma

- Benign tumors
- Invasive
- Can affect the optic chiasm, carotid arteries, 3rd cranial nerve and pituitary stalk
- P/W headaches, vomiting, visual changes, endocrinopathies

Bone Mass

- No lab test
- Non-specific signs of tumor or inflammation
  - Increased ESR, anemia, leukocytosis, elevated LDH
- Plain films of primary site
- MRI/CT of primary site
- CT chest/CXR
- Bone scan
- PET scan
- Bone marrow aspirate and biopsy
- Tissue biopsy
Osteosarcoma

- Clinical Presentation
  - Pain, +/- mass at primary site, typically involves the metaphyses of long bones
  - Most common primary sites: distal femur > proximal tibia > proximal humerus

Osteoid Osteoma

- Benign tumors
- Unremitting and worsening pain, worse at night, relieved with aspirin
- Commonly involves the proximal femur and tibia
- X-ray will show a round or oval metaphyseal or diaphyseal lucency surrounded by sclerotic bone

Histiocytosis Syndromes of Childhood

- Clinical Features
  - Presenting symptoms are highly variable
    - Bone marrow: cytopenias
    - Spleen: splenomegaly, abdominal pain, thrombocytopenia
    - Liver: hepatomegaly, abdominal pain, jaundice, ascites
    - Skin: pruritic, scaly, erythematous
    - Bones: painful swelling, mastoiditis
    - Jaw: early tooth eruption
    - Lymph nodes: lymphadenopathy
    - Pulmonary: interstitial pattern with cysts and nodules, spontaneous pneumothorax
    - Gastrointestinal: diarrhea, fever, edema
    - Endocrine: diabetes insipidus, growth hormone deficiency, hypothyroidism, hypoadrenalism, hypogonadism
Other Tumors

- Germ Cell Tumor
  - Presentation:
    - Ovarian: abdominal pain, palpable mass
    - Testicular: irregular, non-tender mass
    - Extragonadal tumors:
      - Sacrococcygeal: constipation, urinary retention
      - Mediastinal: chest pain, resp distress
  - Lab Findings: Alpha-fetoprotein and human chorionic gonadotropin are elevated

- Hepatoblastoma
  - Lab Findings: Elevated alpha-fetoprotein

- Embryonal Tumors
  - Clinical Findings:

Retinoblastoma

- Two clinical forms
  - Non-hereditary, unilateral
    - 75% of patients
    - Mutation of both alleles is a somatic event
    - Median time to diagnosis: 29-30 months
  - Hereditary, bilateral
    - 25% of patients
    - Germline mutation of RB1
    - Median time to diagnosis: 14-16 months

Retinoblastoma cont’d.

- Bilialtic inactivation of RB1
  - First hit is germline in heritable form and sporadic in sporadic non-heritable form
  - Additional events required for transformation
    - Germline mutation + ~90% penetrance for RB, autosomal dominant pattern
    - Genetic counseling and proposal for genetic testing is indicated in all patients with RB and their families

- Clinical Presentation
  - Intraocular: leukocoria, strabismus, nystagmus
  - Advanced intraocular: glaucoma, periorbital cellulitis
  - Extraocular: proptosis, lymph nodes, metastasis
Oncologic Emergencies

Spinal Cord Compression

- Masses compromising the integrity of the spinal cord require immediate attention to preserve neurologic dysfunction
- Most commonly seen in: Ewing’s sarcoma, neuroblastoma, other sarcomas, primary spinal cord/CNS tumors
- Diagnosis confirmed by MRI
- General emergent treatment options include radiation, chemotherapy, and surgery
- Steroids - dexamethasone 1-2 mg/kg

Mediastinal Mass

- A true medical emergency
- Most common diagnoses:
- Initial concern is for respiratory failure
- The masses often grow very rapidly
- With even slight change in positioning, the mass can compress the airways
Mediastinal Mass cont’d.

- **SVC syndrome:**
  - Dyspnea, cough, orthopnea, hoarseness
  - Edema, plethora, venous distention
- **Management**
  - CXR, CT scan
  - Have the patient lie prone, and not flat
  - ICU care with multidisciplinary team
  - Diagnosis should be obtained in least invasive manner possible
  - Consider emergent steroid therapy

Mediastinal Mass cont’d.

Questions
A previously healthy, 4-year-old girl with known seasonal allergic rhinitis is seen at her pediatrician’s office with a 3-day history of worsening rhinorrhea, cough, fever, and a 1-day history of a mouth sore. She has been taking oral montelukast and intranasal fluticasone for the past 2 months. For the past 3 days, her mother has been giving her oral amoxicillin clavulanate, acetaminophen, and an albuterol inhaler at night, which were prescribed by a walk-in clinic physician. On examination, she is afebrile, has one erythematous-based, buccal vesicle and nasal discharge, and has lungs clear to auscultation. Her pediatrician calls you to review her complete blood cell count results: hemoglobin, 11.9 g/dL (119 g/L); platelets, 200 × 10^3/μL (200 × 10^9/L); white blood cells, 2300/μL (2.3 × 10^9/L); neutrophils, 10%; lymphocytes, 74%; monocytes, 10%; and eosinophils, 6%.

Of the following medications, which is the MOST likely cause of the patient’s acute-onset neutropenia?

A. Montelukast
B. Fluticasone
C. Amoxicillin clavulanate
D. Acetaminophen
E. Albuterol

A healthy 5 y/o boy has a 2 day h/o fever, physical exam is normal, no HSM, no LAD, no focus of infection. On the CBC, WBC=3, neutrophils 25%, Hb=12, Plt=200 and ANC=750. Most appropriate step

A. Amoxicillin for 10 days
B. G-CSF for 10 days
C. Send aspirate
D. Refer to a hematologist
E. Repeat CBC in 1 to 2 weeks

You are caring for an 18 year old girl who was diagnosed 6 months ago with Crohn disease affecting the terminal ileum and colon. Her medications include prednisone 10 mg/day, sulfasalazine 1 g three times per day, and 6-MP 75 mg/day. She has experienced an excellent symptomatic response to treatment and presents today complaining only of occasional streaks of blood in an otherwise normal daily bowel movement. Since diagnosis she has gained 2.5 kg on a regular diet with only iron supplements. Of the following, the girl is MOST at risk of developing a deficiency of

A. Copper
B. Folic acid
C. Selenium
D. Vitamin D
E. Zinc
You are performing a follow up evaluation on a 4 y/o boy in whom anemia was diagnosed during a Head Start screening. He has been receiving 3 mg/kg/day of elemental iron for the past 6 weeks. His mother reports no changes in activity or appetite. He drinks 2 to 3 glasses of milk each day and eats a relatively diverse diet. His growth parameters are in the 75% and his exam findings are normal. Results of lab tests include: Hb 9.4, Hct 29, MCV 66, RDW 12.2, RBC 5.8, retic 1%, ferritin 54. Of the following, the MOST appropriate next step is to

- Obtain a direct and indirect Coombs tests
- Obtain Hemoglobin electrophoresis
- Perform a bone marrow aspirate
- Repeat the course of iron
- Transfuse with pRBCs

A 6 y/o child has become pale and tired over the past 48 hours. He has had no fever, respiratory or gastrointestinal symptoms. He has a past history of anemia, as does his father. On exam, he has a HR 128, RR 20, BP 92/64, T 36.8. He is pale and has scleral icterus. His spleen is palpable 3 cm BCM. Other findings on his exam are normal. An initial CBC shows a Hb of 7.6, MCHC 37 (mean for age 34), and smear shows anisocytosis and numerous spherocytes. Of the following, the MOST important study(ies) to guide management of this patient’s condition is (are)

- Acute hepatitis panel
- ALT, AST, conjugated bilirubin
- Gallbladder US
- Serial CBC and retic counts
- Viral cultures

The parents of a 22 m/o boy are concerned because he appears pale. About 3 weeks ago he had a viral illness with fever and respiratory symptoms. It resolved within 6 days. Since then, he has had no fever, rashes or complaints of discomfort. His appetite is fair, and activity level has decreased. On exam, he is pale. HR 132, RR 20. No LAD and no organomegaly. Labs: WBC 7.2; Hb 6.8; Plt 402; MCV 78; RDW 11.5%; Retic 0.5%; LDH is normal and DAT is negative. Of the following, the MOST appropriate treatment for this patient at this time is

- Close observation
- Erythropoietin
- Iron
- Prednisone
- pRBC transfusion