Background

• Hemoglobin
  o Metalloprotein found within erythrocytes that binds oxygen and carries it from the lungs to cells of the body
  o Heterotetramer composed of four globular protein subunits
    o Each subunit is wound around a non-protein heme group, a heterocyclic ring that forms the functional portion of the hemoglobin molecule
    o The iron molecule at the center of the heme group is normally maintained in the ferrous, Fe^{2+}, state. At times it is oxidized to the ferric, Fe^{3+}, state. When hemoglobin has ferric iron it is called methemoglobin.
    o Methemoglobin is unable to bind oxygen and through the process of cooperativity shifts the oxygen-saturation curve to the left
  o Forms of Hemoglobin
    ▪ The embryonic and fetal forms of hemoglobin have a higher affinity for oxygen which helps to extract it from maternal circulation
    ▪ The variant form of adult hemoglobin is normally 3% of total circulating hemoglobin
  o Inherited Hemoglobin Disorders
    ▪ Thalassemias- disorders of abnormal hemoglobin synthesis
    ▪ Disorders of abnormal hemoglobin structure

Thalassemias

• Defects in the synthesis of globin chain subunit
• Nomenclature of disorders is based on the specific subunit affected
  o α Thalassemia- disorder in synthesis of α subunits
  o β Thalassemia- disorder in synthesis of β subunits
• Normally, ratio of production of α to β subunits is tightly controlled at 1.00 ± 0.05
• α-Thalassemia
  o 2 genes from each parent for a total of 4 genes located on Chromosome 16
  o If there is a defect in a gene then there is the potential to disrupt the tight ratio of α to β subunits. This leads to excess β subunits
  o Autosomal recessive

<table>
<thead>
<tr>
<th>α-Globin Gene</th>
<th>Genotype</th>
<th>Phenotype</th>
<th>No. of Functional α-Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>α²α²</td>
<td>Normal</td>
<td>Normal</td>
<td>4</td>
</tr>
<tr>
<td>α²α¹</td>
<td>α²α¹</td>
<td>Silent carrier α-thal trait</td>
<td>3</td>
</tr>
<tr>
<td>α²α¹</td>
<td>α²α¹</td>
<td>Microcytosis α-thal trait</td>
<td>2</td>
</tr>
<tr>
<td>α²α¹</td>
<td>α²α¹</td>
<td>Microcytosis α-thal trait</td>
<td>2</td>
</tr>
<tr>
<td>α²α¹</td>
<td>α²α¹</td>
<td>Hb H disease</td>
<td>1</td>
</tr>
<tr>
<td>α²α¹</td>
<td>α²α¹</td>
<td>Hydrops fetalis with Hb Bart's</td>
<td>0</td>
</tr>
</tbody>
</table>
Excess β subunits are able to form tetramers Hemoglobin H
Excess β subunits are able to form tetramers known as Hemoglobin Barts
These tetramers are unstable and have the potential to precipitate out forming Heinz bodies (Heinz-Ehrlitch bodies)
- Heinz bodies cause damage to erythroblast cell walls
- Circulating erythrocytes containing Heinz bodies are rapidly removed by the spleen and destroyed
Silent Carrier State
- Deletion of single α gene
- Slight decrease in production of α subunit
- Asymptomatic
- May have microcytosis
α-Thalassemia Trait
- Deletion of two genes in total
  - - / α α, a double deletion on a single chromosome is more common in Asian population
  - - α / α α, a single deletion on each of the two chromosomes is more common in African population
- The clinical characteristics of [- - / α α] and [-α / - α] are the same
  - The major implication in the offspring of these patients
  - Passing on a double deletion increases the risk of a triple deletion or inheritance of no α genes
- Clinically may have microcytosis, minimal or no anemia. Typically will have no physical signs
Hemoglobin H Disease
- Only one functional α gene is inherited [- - / - α]
- Clinically, have moderate-to-severe hypochromic microcytic anemia, splenomegaly
Hydrops Fetalis
- No functional α genes inherited
- In fetal circulation the γ subunits precipitate to form Hemoglobin Barts
- Clinical: generalized edema, pleural and pericardial effusions, cardiac and urogenital defects
- Most die in utero or shortly after birth
- Transfusion dependent for survival
- Intrauterine hematopoietic stem cell transplantation is being investigated

β Thalassemia
- Dysfunction in the production of the β subunits leading to excess α subunits
- α subunits can form tetramers that are more unstable than their β tetramer counterparts
- Each person inherits a single HBB gene, encoding for the β subunit, from each parent.
  - The HBB gene is located on Chromosome 11
  - Most often due to a point mutation leading to defects in transcription, splicing or translation
- Nomenclature
  - β⁺: Normal allele
  - β⁺: mutation that prevents any production
  - β⁺: mutation that allows decreased production
β Thalassemia Minor
- Heterozygous
  - β⁺/β⁺ or β /β⁺
- Mostly asymptomatic, may have a mild anemia and RBC abnormalities seen on smear
β Thalassemia Major
- Homozygous
  - β⁺/β⁺, β⁺/β⁺ or β⁺/β⁺
- Also known as Cooley’s Anemia
- Mostly in Mediterranean population
- Highly variable phenotypic presentation
Hemoglobinopathies

- Rarely symptomatic at birth due to presence of Hb F
- Developmental effects
- Complications
  - Poor growth
  - Skeletal abnormalities
  - Jaundice
  - Iron Overload secondary to repeated transfusions
    - Deposited in heart, liver and endocrine glands
    - Hypogonadism
    - Diabetes
    - Cardiac failure- most die by age 30 of cardiac complications
- Treatment
  - Transfusion schedule to maintain Hb > 9.5
  - Chelation therapy usually started between ages 5-8 years old
  - Bone marrow transplantation is the only known cure
- \( \beta \) Thalassemia Intermedia
  - Homozygous
    - Genotype: \( \beta^0/\beta^0, \beta^+/\beta^0 \text{ or } \beta^+/\beta^+ \)
    - “…too hematologically severe to be called minor, but too mild to be called major” - Rietti, Greppi and Micheli, 1955
  - Mild clinical characteristics may be due to:
    - Inheritance of a mild or silent \( \beta \) chain mutation
    - Co-inheritance of determinants associated with increased gamma-chain production
    - Co-inheritance of \( \alpha \)-Thalassemia

Sickle Cell
- Terminology
  - \textbf{Sickle Cell Disease}- refers to all the different genotypes that cause the characteristic clinical syndrome
  - \textbf{Sickle Cell Anemia}- refers specifically to homozygosity for the \( \beta S \) allele
- Sickle Cell Anemia
  - Molecular pathology
    - Genetic mutation responsible is a substitution of tyrosine for adenine in the 6th codon of the \( \beta \)-globin gene.
    - Changes the amino acid from glutamine to valine forming the \( \beta \)-“s” globin chain.
    - Absence of a polar amino acid at position 6 of the \( \beta \)-globin chain promotes the non-covalent polymerization of hemoglobin, which distorts rbc’s into a sickle shape and decreases their elasticity
  - Genetics
    - Autosomal Recessive
    - 8% of African Americans carry trait
    - Gene frequency approaches 30% in some areas where malaria is endemic
    - 1 in 600 African Americans have SCA
Hemoglobinopathies

Pathology
- The rate and extent of HbS polymerization is proportional to the extent and duration of hemoglobin deoxygenation, pH, intracellular HbS concentration and the presence of fetal hemoglobin in the erythrocyte.
- Most of the pathology is thought to be caused by entrapment of erythrocytes and leukocytes in the microcirculation
  - This causes vascular obstruction and tissue ischemia leading directly to infarction and hemolysis.
  - Also causes inflammation and release of hemoglobin into the plasma.
  - Free hemoglobin inactivates nitric oxide and generates reactive oxygen species. This results in vasculopathy and endothelial dysfunction.

Diagnosis
- Screening tests (ie, Sickledex)
  - Performed automatically in all 50 States
- Definitive testing by Gel Electrophoresis

Complications
- Skin
  - Stasis Ulcer
- CNS
  - Stroke
- Eye
  - Retinal hemorrhage
  - Retinopathy
- Genital
  - Priapism
  - Impotence
- Vascular
  - Occlusive Disease
- Cardiac
  - CHF
- Pulmonary
  - Shunting
  - Acute Chest Syndrome
- Liver
  - Hepatic infarct
- Spleen
  - Sequestration
  - Splenic infarct
- Skeletal
  - Bone infarcts
  - Osteomyelitis
  - Aseptic Necrosis

Severe Pain Episodes
- No laboratory test to definitively rule-in or rule-out
  - ESR, CRP, VCAM-1, Pentraxin-3 have been studied
- Patients typically develop a well-defined pattern of their “typical” pain crises

Treatment
- Mainstay of treatment is opioid analgesia
- No proven benefit with addition of NSAIDs
- Corticosteroids have been shown to reduce pain in short-term
  - Led to increased rebound pain and hospital readmission
- Oxygen therapy not proven benefit in patients not hypoxic
  - Oxygen may lead to vasoconstriction which could potentially worsen vaso-occlusion
- Inhaled Nitric Oxide not shown to be of benefit

Acute Chest Syndrome
- Term coined in 1979 by Cardiche reflecting the difficulty in determining cause of problem as infectious versus infarction
- Constellation of findings
  - New infiltrate on chest radiograph- involving at least one complete lung segment
  - Fever
  - Respiratory distress (shortness of breath, cough, wheezing)
  - Pain that often occurs in the chest but may be in the back or abdomen
- Causes
  - Pulmonary infection
Fat emboli
- Pulmonary infarction

- In landmark paper (Vichinski, 2000) only 52% of patients were admitted with diagnosis of ACS. The rest developed signs and symptoms a mean of 2.5 days after admission
- Chest radiograph underestimates the extent of pulmonary involvement

- Supportive Care
  - IV, O2, Monitor, Pain Control
  - IV hydration with D51/2NS at 1.5-2 times maintenance
  - Broad spectrum antibiotics
    - 3rd Generation Cephalosporin & Macrolide
  - Transfusion
  - Steroids (???)
  - New Algorithm in Pediatrics, 2011 (Crabtree, et al)
    - Calculate the Clinical Respiratory Score

**TABLE 2 Clinical Respiratory Score**

<table>
<thead>
<tr>
<th>Assess</th>
<th>CRS 0</th>
<th>CRS 1</th>
<th>CRS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (&gt;12 mo)</td>
<td>&lt;30</td>
<td>30-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Auscultation</td>
<td>Good air movement, scattered wheezing (only expiratory), loose crackles</td>
<td>Depressed air movement, inspiratory and expiratory wheezes</td>
<td>Diminished or absent breath sounds, severe wheezing, or marked prolonged expiration</td>
</tr>
<tr>
<td>Use of accessory muscles</td>
<td>Mild to no use of accessory muscles; mild to no retractions or nasal flaring on inspiration</td>
<td>Moderate intercostals retractions, mild-to-moderate use of accessory muscles, nasal flaring</td>
<td>Severe intercostals and substernal retractions, nasal flaring</td>
</tr>
<tr>
<td>Mental status</td>
<td>Normal to mildly irritable</td>
<td>Irritable, agitated, restless</td>
<td>Lethargic</td>
</tr>
<tr>
<td>Room-air oxygen saturation, %</td>
<td>&gt;95</td>
<td>90-95</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Color</td>
<td>Normal</td>
<td>Pale to normal</td>
<td>Cyanotic, dusky</td>
</tr>
</tbody>
</table>

- Apply to Algorithm

### FOLLOW flowchart for patients with SC with pain and fever with the following modifications:
- Encourage ambulation (may come off pulse oximeter to ambulate)
- ACC asthmatics: 10 mg/kg PO in day 1 (MAX: 500 mg/dose), then 5 mg/kg PO once daily (MAX: 250 mg/dose) for 4 days (asthmatics may be told to use, but not to exceed MAX doses)
- Consider intubation only for clinical deterioration
- Continue ISH therapy in patients <5 y as follows: 10 breaths ISH and 10 breaths PEP alternating every 2 h between 6 and 10 h
- In patients <5 y old, PEP and/or ISH can be introduced, but lack of cooperation should lead to earlier consideration of use of vest therapy
- CONSIDER using inhaled sympathomimetics
- CONSIDER furanosamide 0.5 mg/kg IV X 1 dose IF signs of fluid overload (MAX: 40 mg/dose)

**Assess patient according to CRS**

- Vital signs every 4 h
- Continuous pulse oximeter, goal SpO2 ≥ 94%
- Transfer to Thoracic or Intensive Care Unit
- IV or IV therapy every 4 h
- Inhaled bronchodilator/Respiratory Assessment and Management Protocol (RAMP)
- Consider SPPAP
- IF wheezing or crackles present:
  - Assess every 4 h
  - Continuous pulse oximeter, goal SpO2 ≥ 94%
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o **Venous Thromboembolism**
  - Long thought that Sickle Cell Anemia was a risk factor for VTE complications
  - 2 recent studies have shown an almost 4-fold increase in risk of PE
    - Even in those with only trait!
    - No increase in DVT was found
  - VQ scans are often abnormal at baseline
    - “Others have suggested that sickle cell trait or disease increases the risk to patients; however, in neither case is there evidence of any clinically significant risk, particularly after the injection of low-osmolality contrast media (LOCM)”

o **Stroke**
  - Incidence of 1% per year between ages 2-5
  - 11% have had stokes by age 20
  - 50% recurrence rate after first stroke
  - Screen using Transcranial doppler between ages 2-16 years
    - Flow velocities > 2 m/s associated with critical stenosis and those patients are started on a transfusion regimen
  - Formation of **Moyamoya aneurysm** increases risk of intracerebral hemorrhage

o **Skin Ulcers**
  - 25% of patients with HbSS
  - Increased rate in males
  - 75% recurrence rate

o **Priapism**
  - Commonly occurs in children or adolescents
  - Treatment often difficult
    - Opioid pain medications
    - Intravenous fluids
    - Aspiration and irrigation of the corpus cavernosum
    - Blood transfusion
  - Impotence occurs with repeated episodes

o **Spleenic Sequestration**
  - Sudden trapping of blood within the spleen
  - Usually occurs in infants under the age of 2 y
  - Clinical
    - Splenomegaly
    - May be associated with fever, pain, respiratory distress
    - Circulatory collapse and death can occur rapidly
  - Hemoglobin SS
    - Incidence is increased in ages 6 m to 36 m
    - Overall incidence ~15%
  - Hemoglobin SC
    - Incidence is increased in ages 2-17 y
    - Overall incidence ~5%
  - Treatment
    - IV Fluids
    - Cautious blood transfusions
    - Splenectomy in some cases

o **Long Term Therapy**
  - Pneumococcal vaccine (Prevnar) according to normal childhood schedule
    - Add 23-valent vaccine at age 2 and a booster 3-5 years later
  - Influenza vaccine yearly for those > 6 m old
  - Penicillin prophylaxis at least until age 5
  - Consider folate supplements
  - Yearly eye exams
  - Yearly transcranial dopplers age 2 – 16 y
- **Hydroxyurea** (Hydroxycarbamide)
  - Ribonucleotide inhibitor that impedes DNA synthesis by preventing the formation of deoxyribonucleotides
  - Increases the formation of Hb F
  - Improves RBC hydration and pliability
  - May generate nitric oxide, a potent vasodilator
  - **Indications (per NIH, 2003)**
    - Frequent pain episodes
    - History of ACS
    - History of other severe vaso-occlusive events

- **Sickle Cell Disease (Variants)**
  - **Hb C Disease**
    - Substitution of lysine for glutamine at 6\textsuperscript{th} position of \( \beta \) chain
    - Hb C precipitates in deoxy-form
    - Patients with trait (Hb AC) are asymptomatic
    - Homozygous (Hb CC) patients
      - Mild hemolytic anemia, abundant target cells
      - Sporadic musculoskeletal pain
      - Dental infarctions
    - Patients with one S allele and one C allele (Hb SC)
      - Complications are the same as for Hb SS but tend to be less severe and less frequent
      - Life expectancy is 65 y (life exp for Hb SS is 45 y)
  - **Hb D Disease**
    - Includes multiple forms of various hemoglobin species
      - Ex: Hb D-Los Angeles, Hb D-Punjab
    - Patients with trait are normal
    - Hb DD show some lab findings but are clinically normal
    - Hb SD is similar to Hb SS

- **Hemoglobin M**
  - A special kind of hemoglobinopathy
  - Due to various mutations that result in the inability to reduce ferric iron back to ferrous iron
  - AKA Blue Baby Syndrome
  - MetHb level tend to be in the 15-30% range and are well tolerated by patient

**Selected References**

Hemoglobinopathies