The Pulmonary Complications of Sickle Cell Disease

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Learning Objectives

- Understand the Pathophysiology of Sickle Cell Disease
- Review the effects of sickle cell disease on the lung.
- Discuss screening and treatment of pulmonary complications

What is it?

Sickle Cell Disease (SCD) describes a group of inherited blood disorders that affect the structure of hemoglobin, leading to sickling of red blood cells. Consequences include hypoxemia, damage to vasculature/organisms, episodic pain crises, and ultimately premature death.

Demographics

- Affects approximately 4.4 million people worldwide
  - Approx. 100,000 individuals in the United States
    - Most common inherited blood disorder
  - Research funding is limited, and no national data registry exists

Mortality

- Sub-Saharan Africa
  - 50-80% in patients <5 yrs
  - Infection Sepsis
- United States
  - Data from CA and GA 2004-2008
    - 43 years for females
    - 41 years for males
  - Cardiopulmonary complications
  - Renal disease
  - Stroke

Disclosures

The speaker has no financial interests or relationships regarding the subject matter of this presentation to disclose.
Background

- Group of blood disorders
- SCD has an autosomal recessive inheritance pattern
- Understood as a spectrum disorder with varying severity of clinical phenotypes

Disparities

Sickle Cell Disease
- 1/400 African Americans
- 100,000 US
- Life Expectancy 42+
- Drugs in Pipeline: 2
- Comprehensive Centers: 4
- Foundation budget 2014: $980,500

Cystic Fibrosis
- 1/800 Caucasians
- 30,000 US
- Life Expectancy 40+
- Drugs in Pipeline: 34
- Comprehensive Centers: 115
- Foundation budget 2016: $3,931,907,061

Background

- Group of blood disorders
- SCD has an autosomal recessive inheritance pattern
- Understood as a spectrum disorder with varying severity of clinical phenotypes

Sickle Cell Genotypes

Genetic mutation on Chromosome 11
1. Homozygous HbS mutation (HbSS)
   - 60-70% of all cases
   - Point mutation substitution of valine for glutamic acid at position 6
     of β-globin chain
2. Heterozygous for HbS and βthalassemia mutations that also
   have sickle cell anemia (SCA)
3. Other compound heterozygous β-globin chain mutations (i.e
   HbSC or HbSβ+)

Altered Hemoglobin

- Abnormal β-globin chain alters structure of Hb and its characteristics
  - Less soluble
  - As HbS increases, erythrocytes sickle
  - Repetitive sickling becomes permanent
  - Increases with decreased O2 and pH, dehydration, fever, and
    increased intracellular HbS

Pathological Effects of Sickling

- Sequestration
  - Trapping of RBC’s
  - Occurs in highly vascular organs
  - Contributes to acute liver damage, acute chest syndrome, and priapism
- Hemolytic Anemia
  - Shortened RBC survival
  - Normal mean RBC survival is 120 days, can be reduced to 10 days in HbSS
  - Extravascular and Intravascular hemolysis
- Microvascular Occlusion
  - Mechanism in acute pain crisis and acute chest syndrome
- Large Vessel (Arterial) Lesions
  - Result from long term endothelial damage
  - Cause changes in vessel wall, loss of elasticity, fibrosis

RBC Polymerization
Consequences of Sickling

- Erythrocytic Damage
  - Damage to membrane and cytoskeleton
  - Changes in red cell membrane, promoting adherence to endothelium and clotting
  - Red cell dehydration
  - Impaired anti-oxidant mechanisms
- Vaso-Occlusion
- Nitric Oxide Depletion
- Inflammation and Tissue Damage

Pathophysiology of Sickle Cell Disease

Gas Exchange

Chronic Sickle Lung Disease

- Progressive decline in lung function
  - Starts early in life, decline similar to CF
  - Airway obstruction and progressive restriction
- Abnormal lung function (70% of patients)
  - 16-35% obstructed
  - 26% restrictive
  - 39-70% normal

Acute Chest Syndrome (ACS)

- Potentially fatal acute respiratory illness, often preceded by acute pain crisis 24-72 hours prior
- Most common reason for admission and leading cause of premature death
- Diagnosis
  - New infiltrate on CXR plus
  - FEVER
  - Cough, dyspnea, chest pain, wheezing
  - \(O_2\) need
Asthma/Airway Reactivity

- Difficult to diagnose
  - Many features of asthma common in SCD
- Significant co-morbidity
  - Increased morbidity/mortality
- Risk factor for
  - Acute Chest Syndrome
  - Pain Episodes
  - Stroke
- Complex Relationship between Asthma and Sickle Cell

Bronchial Hyperresponsiveness in SCD

Incidence of ACS co-morbid with asthma

Hypoxemia

"An abnormally low concentration of oxygen in the blood"

Risks
- Low daytime oximetry (<94% SpO2) is associated with nocturnal desaturation and OSA
  - Up to 40% of patients may experience nocturnal desaturations
- Daytime desaturation is a risk factor for stroke

Consequences
- Risk of developmental delay by 9 months of age
- Lower IQ scores
- Increase TCD velocity
  - Transcranial Doppler

Sleep Problems

Obstructive Sleep Apnea
- Snoring > 3 times/week
- Witnessed apnea
- Enuresis
- Headaches
- Daytime sleepiness
- School problems
  - ADHD/Learning problems
  - Tonsillar Hypertrophy

Most U.S. middle and high schools start the school day too early

5 out of 6 U.S. middle and high schools start the school day before 8:30 AM

Teens need at least 8 hours of sleep per night.
Younger students need at least 9 hours.

2 out of 3 U.S. high school students sleep less than 8 hours on school nights

Pulse oximetry should be a standard measurement taken with vital signs

Pulmonary complications of sickle cell disease in children.
Caboot, Jason; Allen, Julian
DOI: 10.1097/MOP.0b013e3282ff62c4
Pulmonary Hypertension

- Pulmonary arterial pressure (mPAP) ≥25 mmHg
  - 30% of Adults
  - 10-20% of Children (Ambrusko, 2006; Lee 2009)
  - >10 years old 31%
  - <10 years old 38%
  - Our center: 28% (Nelson, 2007)

Cardiac ECHO

- Screening tool
  - Beginning at age 10, unless risk factors indicate earlier screening
  - Pulmonary arterial pressure is estimated from TR jet velocity
  - Hypoxemia/pulse oximetry monitoring is poor prognostic indicator

Smoke Exposure

- Associated with
  - Abnormal lung function
  - Increased frequency and duration of VOCs
  - Acute Chest Syndrome

Sickle Cell Comprehensive Clinic

- Integrate Pulmonary Care to Sickle Cell Comprehensive Clinic
- Multidisciplinary TEAM
  - Hem, Neuropsych, LSW, Patient Coordinator, RT, RN, Genetics
- Emphasis on personalized, preventative, proactive care

Pulmonary History

- Asthma
  - lingering chest colds, chronic cough
  - Exertional dyspnea
  - recurrent wheezing, bronchitis, pneumonia
  - eczema, allergies, family history
- Restrictive Lung Disease
  - Acute Chest Syndrome, VOC’s
- Sleep
  - daytime fatigue, school performance, snoring, enuresis
- Smoke exposure
Physical Exam

- Pertinent Positives
  - Scleral icterus
  - Turbinate edema
  - Tonsillar hypertrophy
  - Wheezing
  - Cardiac: murmur
  - Splenomegaly
  - Eczema
  - Obesity/FTT

Treatment

- Asthma
  - ICS/LABA
  - Hydroxyurea
- Snoring
  - Nasal steroid before sleep study
  - Adenotonsillectomy
  - Hydroxyurea
- Hypoxemia
  - Sleep study
  - Home oxygen therapy
  - Transfusion
  - Hydroxyurea
- Pulmonary Hypertension
  - Transfusion Program
  - Home oxygen therapy
  - Hydroxyurea

Hydroxyurea

- OLD, CHEAP, CHEMO AGENT
- 30 years experience in SCD
- Myelo-suppressive agent
- Increases HbF
- Decreases neutrophils
- Decreases platelets
- NO donor
- Safe in infants young children

Future therapies

- Hematopoietic stem cell transplant
  - Only curative treatment
  - Complex, expensive, allogeneic
  - Reversed disease in 26 of 30 patients
  - HLA matching
- Gene editing
  - CRISPR/Cas9
  - Remove sickle cell mutation
  - Edited stem cells formed normal RBCs with very little HbS
- Editing autologous stem cells
  - Produce abundance of HbF
References


References, cont.


References


References, cont.


Cardiotoxicity and Childhood Cancer: Clinical Challenges and Complexities Across the Continuum of Care

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Disclosures
• The speaker has no off-label use to be discussed and no relationship to disclose.

Learning Objectives
• Discuss Anthracycline Induced Cardiotoxicity (AIC).
• Identify various tests to diagnose the condition.
• Describe how to manage the condition from acute to chronic state.

Case
• A 6 year old child diagnosed with AML. She was treated with Daunorubicin, Cytarabine and Etoposide. Baseline Echo was WNL.
• She was given Consolidation chemotherapy composed of ARA-C and Daunorubicin.
• She started having dyspnea, fatigue and poor appetite after starting consolidation therapy. Her total Daunorubicin dose was 280 mg/m2. Repeat Echo was normal.

Chemotherapy and Cardiotoxicity

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline</td>
<td>Daunorubicin, Doxorubicin</td>
<td>Acute HF, Arrhythmias, QT changes, Ventricular depolarization</td>
</tr>
<tr>
<td>Alkylating Agents</td>
<td>Cyclophosphamide</td>
<td>Acute HF, Pericardial effusion, Arrhythmias</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Cisplatin, 5FU</td>
<td>MI, Arrhythmias</td>
</tr>
<tr>
<td>Vinca Alkaloids</td>
<td>Vincristine, Vinblastine</td>
<td>MI</td>
</tr>
<tr>
<td>Tyrosine Kinase</td>
<td>Bevacizumab, Trastuzumab</td>
<td>LV dysfunction, Hypertension, Venothrombosis</td>
</tr>
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Anthracycline
• Therapeutic: interfere with replication of cancer cells
• Cardiotoxicity: loss of myofibrils
Anthracycline Cell Injury

• Process of cell injury (Heart, 2017)

Cardiotoxic Dose

• Cumulative dose of > 400 mg/m² (Adult study)
• Cumulative dose of > 300 mg/m² or sometimes less (Children study)
• No true safe dose especially in children - collaboration with Oncologist and Cardiologist
• Use of Dexrazoxane (DRZ)

Risk Factors

• Age: younger age (< 4 years old)
• Concomitant radiation treatment
• Concomitant chemotherapy: other Anthracyclines
• Features of metabolic syndrome (hyperlipidemia, hypertension, obesity)
• Certain genetic mutation - Down’s syndrome, Hemochromatosis

Anthracycline Induced Cardiotoxicity (AIC)

• Cardiomyopathy
• Signs of Congestive Heart Failure (CHF)
• LVEF with and without signs of CHF

Cardiotoxicity Severity

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Life threatening)</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF decline</td>
<td>No symptoms with positive diagnostic tests</td>
<td>Symptoms with mild to moderate activity or exertion</td>
<td>Severe with symptoms at rest</td>
<td>Urgent intervention</td>
</tr>
<tr>
<td>Resting EF ≥ 40% or 10-19% decline from baseline</td>
<td>Resting EF ≥ 20% or 20% decline from baseline</td>
<td>Resting EF &lt; 20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardiac Review and Evaluation of treatment

• Any of the following: 1) Cardiomyopathy 2) Symptoms of HF 3) Signs associated with HF 4) Decrease LVEF > 5% from baseline or < 55%

Case Progression

• She was admitted in the middle of Consolidation therapy due to dyspnea and hypotension. Transferred to the PICU due to worsening of symptoms.
• While in the PICU, she was intubated, Milrinone and Epinephrine drips were started. Echo showed decrease in LVEF to 20-30%.
Types of AIC

- Acute onset - during infusion up to 1 week post infusion
- Early onset - within 1 year of Anthracycline dose
- Late or Chronic - 1 year or more after treatment, mimics dilated cardiomyopathy

Diagnostic Exam

- Echo: LVEF vs. Regional WMA
- Cardiac MRI
- EKG - arrhythmias
- Troponin I
- BNP - detection of subclinical dysfunction is inconsistent

Clinical Manifestations of HF

- Poor feeding/intake with diaphoresis
- Growth failure
- Coughing
- Tachypnea/Grunting
- Edema
- Hepatomegally/JVD
- Abdominal pains/nausea - older children
- Exercise intolerance - older children

Classification of Heart Failure (Modified Ross)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>2</td>
<td>Mild tachypnea or diaphoresis with feeding (infants). Dyspnea with exertion in older children</td>
</tr>
<tr>
<td>3</td>
<td>Marked tachypnea or diaphoresis with feeding (infant). Prolonged feeding times with growth failure. In older child - marked dyspnea on exertion</td>
</tr>
<tr>
<td>4</td>
<td>Life threatening symptoms</td>
</tr>
</tbody>
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Acute Management

- Intensive monitoring and treatment
- Likely PICU admission - invasive or non-invasive ventilation, Milrinone, +/- Epinephrine drip and other management of critically ill child
- Transition to oral medication when stable and weaning vasoactive drips

Pediatric AIC Management

- Medical Intervention for A1 symptomatic and asymptomatic cardiotoxicity during and after treatment of childhood cancer
- Objective: To compare the effect of medical intervention on AIC
- Result: Decrease in LVESWS with Enalapril (post-hoc analysis)
Chronic Care

- Long term medication - ACEi, Diuretics, B Adrenergic Antagonist (Carvedilol)
- Follow-up monitoring and care
- Supportive - Pain and symptom control, Nutrition, Exercise, Child Development strategies

Clinical Pearls

- Cardiotoxic dose of Anthracycline vary in children.
- AIC can be subclinical.
- Understand the mechanism of HF in AIC and recognize signs and symptoms.
- Use of ACE inhibitor has promising outcome in ventricular remodeling.
- Collaborative management with Oncologist and Cardiologist to optimize care.

Questions

- Email: riza.v.mauricio@uth.tmc.edu

References

Anemia in the Emergency Department and urgent care setting

Tricia K. Huey DNP, CPNP

Disclosures

• I do not have any disclosures

Learning Objectives

• Develop a differential diagnosis for anemia based on history physical exam, and diagnostic criteria
• Discuss appropriate diagnostic criteria for different types of anemia
• Discuss how to manage pediatric anemia in the urgent care setting

Anemia

• Types of Anemia
  • Age
    - Birth-3mo
    - 3-6 mo
    - Toddlers/preschool
    - 6-12 mo
  • Race/Ethnicity
    - Hemoglobin C & S
    - G6PD
    - Thalaseemia
• Reduction at or below 2.5 percentile
  – Hemoglobin
  – Hematocrit
• Age specific
  – Birth-3mo
  – 3-6 mo
  – Toddlers/preschool
  – 6-12 mo

Anemia

• Types of Anemia
  – Race/Ethnicity
    • Hemoglobin C & S
    • G6PD
    • Thalaseemia
Anemia

- History
  - Family
  - Birth
  - Developmental
  - Travel
  - Diet
  - Past medical
  - Drug/Toxin exposure

- Physical Exam
  - Pallor
  - Lethargy
  - Jaundice
  - Hepatosplenomegaly
  - Tachycardia

- What to look for
  - Hemolytic disorder
    - Urine color change
    - Icteric sclera
    - Jaundice
  - Infection
    - Fever
    - Cough
  - Iron deficiency/blood loss
    - Epistaxis
    - Bloody stool
    - Hemeatemesis
  - Severe menstural bleeding

- Labs
  - CBC
  - RBC
  - HGB
  - HCT
  - MCV
  - MCHC
  - Retic count
  - WBC
  - Platelets

- Microcytic
- Macrocytic
- Normocytic
- Hemolytic
- Combination with other cell lines

- Blood conservation
- PRBC’s
- Iron
  - Blood transfusion first if unstable
  - Nutrition
    - 6mg/kg elemental iron Q day bid, or tid
    - Give between meals
    - Never with milk
    - With citrus helps with absorption
- Referral
REFERENCES