Sickle Cell Disease - An update on the management and prevention of complications

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Objectives for Pharmacists:

- Discuss the history and presentation of sickle cell disease.
- Describe the complications of sickle cell disease.
- List treatment and prevention strategies for complications of sickle cell disease.
- Discuss the advancements of medication therapies in this patient population.

Objectives for Pharmacy Technicians

- Discuss the history and presentation of sickle cell disease.
- Describe the complications of sickle cell disease.
- Recognize the support measures used for complications associated with sickle cell disease.
- Review the new medications used in the treatment of sickle cell disease.

Disclosure

- I have nothing to disclose at this time

Pre-test:

True or False:

Sickle cell disease is diagnosed only when a child begins to have symptoms.

Pre-test

Which of these is a complication associated with Sickle Cell Disease:

- a. Vaso-occlusive Crisis
- b. Cerebrovascular Accident
- c. Splenic Sequestration Crisis
- d. Infection
- e. All of the above
True or False

Penicillin prophylaxis must be given for life in all Sickle Cell patients

True or False

For Sickle Cell patients receiving chronic transfusions iron chelation therapy may be administered only IV.

What is the use of hydroxyurea in Sickle Cell Disease?

a. Induce erythropoiesis
b. Fetal hemoglobin induction
c. Chelating agent for iron
d. Replace folic acid supplementation

First described in 1910
Most common in people with African heritage
Inherited hemoglobinopathy with predominance of HbS
Recessive genetic disorder
Newborn screen to diagnose

Sickle Cell Trait

Incidence:
- 2000 cases confirmed each year in US infants
- >200,000 new cases per year in Africa

Incidence in South Carolina
- 1/375 AA born with SCD
- 85 babies born in SC in 2009 with sickle cell disease*
  (1/300 AA babies in SC)
- 8% AA carry HbS trait
- 3% AA carry HbC trait

Types of Sickle Cell Disease

- Sickle Cell Disease
  - Hemoglobin SS disease
    - HbSS (~65%)
  - Hemoglobin SC disease
    - HbSC (~25%)
  - Sickle β-thalassemia
    - HbSβ+,-thal (~8%)
    - HbSβ0-,thal (~2%)
  - Sickle Cell Trait
Substituted valine for glutamic acid at 6th position of β-globin chain
- HbS polymerizes when deoxygenated
  - Changes shape of RBC-sickled appearance
    - ↓ deformability
    - Affects membrane
    - Sticks to endothelium
    - Vaso-occlusion and hemolytic anemia

White Blood Cells
- Also stick to endothelium
- ↑ number
- ↑ inflammation
- Acute & Chronic organ damage
  - Vaso-occlusion
  - Hemolysis

Normal Hemoglobin (HbA)
- Moves through vasculature easily
- Iron-rich protein
- Adequate oxygenation
C-shaped Hemoglobin (HbS)
- Stiff and Sticky
- Tend to clump in the vessels

Life span
- Normal RBC
  - 120 days
- Sickle Cell
  - 10-20 days

EDUCATION
- Regular check-ups
  - PE & Lab monitoring
  - Brain & Lungs
  - Maintenance medications- folic acid
  - Vaccinations
  - Antibiotic prophylaxis
  - Psychosocial Intervention

Complications of Sickle Cell
- Vaso-occlusive Pain Crisis
- Acute Chest Syndrome
- Infection
- Cerebrovascular Accident (CVA)
- Splenic Sequestration Crisis
- Gall bladder
- Bone & Joint
- Eyes
Complications of Sickle Cell

- Aplastic crisis
- Cardiovascular manifestations
- Hepatic Disease
- Renal manifestations
- Priapism
- Pulmonary
- Growth & Development
- Psychosocial

Vaso-occlusive Pain Crisis

- Most common complication of SCD
- Acute painful infarction
- Tissue ischemia from obstructed blood flow
- Dactylitis seen in infants & toddlers
- Pain can be anywhere in older patients

Vaso-occlusive Pain Crisis

- Precipitating factors:
  - Infection
  - Extreme weather conditions
  - Dehydration
  - Stress
  - Severity of crisis determines inpatient or outpatient management
  - Fever often present during crisis

Vaso-occlusive Pain Crisis

- Educating caregivers for home management
  - Algorithm for pain management
  - Side effects of medications
  - Have proper medications in the home
  - Recognize when home management has failed - ? Hospital

Vaso-occlusive Pain Crisis

- Infection
- Acute Chest Syndrome
- Cerebrovascular Accident (CVA)
### Vaso-occlusive Pain Crisis

**Pain Management**
- **Mild**: ibuprofen + acetaminophen/mild opioid
- **Moderate**
  - Ketorolac + acetaminophen/opioid
  - Ketorolac + IV opioid bolus
- **Severe**
  - Ketorolac + Opioid IV bolus
  - Ketorolac + Continuous Opioid/PCA

**2014 NHLBI Guidelines-Sickle Cell**
- Strongly recommended rapid initiation of parenteral opioids in severe pain
- Strongly recommended individualized SCD protocols to promote rapid, effective, and safe analgesic management
- Strongly recommended use of IS to reduce risk of ACS

### Supportive care
- IV hydration
- Nausea
- Pruritis
- Constipation
- Respiratory
  - Oxygen saturation monitoring
  - Acute chest syndrome prevention
- Fever

### Infection
- Major cause of morbidity & mortality in patients with SCD
- Splenic dysfunction
  - Sickling of the red cells within the spleen
  - Splenic infarction
    - Usually occurs by 2 to 4 years of age
- Lower threshold for empiric therapy than general population
**Infection**

- Encapsulated organisms
  - *S. pneumoniae*
  - *H. influenzae*
- Atypical bacteria
- *Salmonella*
- *Staph aureus*
- Viruses - parvovirus, H1N1

**Prophylactic Penicillin Study I (PROPS I)**

- Effectiveness of prophylactic oral penicillin in prevention of severe pneumococcal infection
  - Children < 3 years of age
    - Children received oral penicillin BID vs. placebo
    - Oral PCN 84% reduction in incidence of infection
  - Impact on Management of Sickle Cell:
    - Neonates should be screened for sickle hemoglobinopathies
    - Those with SC anemia should be started on oral prophylactic penicillin by 4 months of age

**Penicillin Prophylaxis in Sickle Cell Disease II (PROPS II)**

- No significant benefit found in penicillin group as compared to placebo group
- Impact on Management of SC anemia:
  - Penicillin prophylaxis can be stopped safely after age 5

**2014 NHLBI Guidelines**

1. In people with SCD and a temperature >101.7°F (38.7°C), immediately evaluate with history and physical examination; complete blood count (CBC) with differential, intracranial, spinal fluid, and urine culture when urinary tract infection is suspected.
   \[(\text{Consensus-Penfex Expert})\]
2. In children with SCD and a temperature >103.7°F (39.3°C), promptly administer empiric parenteral antibiotics that provide coverage against bacterial pneumococci, and pneumatic and gram-negative enteric organisms. Subsequent outpatient management using an oral antibiotic is feasible in people who do not appear ill.
   \[(\text{Consensus-Penfex Expert})\]
3. Hospitalize people with SCD and a temperature >101.7°F (38.7°C) and who appear ill for close observation and intravenous antibiotic therapy.
   \[(\text{Consensus-Penfex Expert})\]
4. In people with SCD whose history reveals is accompanied by shortness of breath, cough, or night sweats, manage according to the preceding recommendations and obtain an immediate chest x-ray to investigate for ACS.
   \[(\text{Consensus-Penfex Expert})\]
5. In people with SCD who have localized or multiorgan tenderness, especially if accompanied by symptoms and findings, include bacterial osteomyelitis in the differential diagnosis and manage accordingly.
   \[(\text{Consensus-Penfex Expert})\]

**To Admit or Not?**

**ADMISION CRITERIA**

- Temp ≥ 103.1
- Ill- appearance
- WBC > 30K or < 5K μL
- Hgb < 5g/dL
- History of sepsis
- Infiltrate on CXR or abnormal O2 saturation
- Other acute complications
- Cephalosporin allergy

**OUTPATIENT CRITERIA**

- Clinically stable 3 hrs post- ceftriaxone
- Compliance with PCN
- Immunizations UTD
- Reliable social situation
- Send home on a course of cefdinir
- Follow-up in 24 hrs
Acute Chest Syndrome (ACS)

- Leading cause of death in SC patients
- Characteristics:
  - Acute new pulmonary infiltrates
  - Respiratory symptoms:
    - Cough
    - Dyspnea
    - Chest Pain
    - Wheezing
    - Fever

- Infarction
- Infection
- Pulmonary edema
- Fat embolism
- Hypoventilation → atelectasis

- Early use of broad spectrum antibiotics:
  - Ceftriaxone 75mg/kg/day every 24 hours
  - Macrolide (i.e., azithromycin)
  - Vancomycin if critically ill
- Pain management
- Avoid fluid overload
- Respiratory intervention

- Respiratory management
  - Incentive spirometry or bubble therapy
  - Albuterol +/- PEP
  - +/- Red cell simple or exchange transfusion
    - Goal HCT 30 and 30% S if exchange
  - +/- oxygen
    - CPAP
    - Mechanical Ventilation
  - +/- Steroids

- Prevention
  - Incentive spirometry
    - 10 puffs every 2 hours while awake
  - Proper pain control
  - Avoid over-sedation
  - Avoid splinting
  - Avoid fluid overload
  - Albuterol +/- PEP
Cerebrovascular Accident (CVA)

- Serious complication - 2nd Leading cause of death in SCD
- Incidence ~ 7-11% in SCD children worldwide
- More common in pediatrics, 8% HbSS affected
- TCD to detect pre-stroke condition
- "Silent" stroke in 20% with HbSS

- Signs & Symptoms of stroke
  - Drowsiness
  - Paralysis
  - Transitory or permanent blindness
  - Convulsions
  - Spinal cord infarction

- Treatment of CVA
  - Exchange transfusion → Chronic Transfusions
  - Rehabilitation

Cerebrovascular Accident (CVA)

- Inclusion
  - Children 2-16 years of age
  - Those that were at risk for a first time stroke
    - Transcranial Doppler velocity > 200cm/sec

- Randomized:
  1. Periodic transfusions: HbS level < 30%
    - Low occurrence of side effects
  2. Standard supportive care

- Chronic exchange blood transfusions
  - Reduces incidence of stroke

Cerebrovascular Accident (CVA)

- Role in acute illness
- Primary indication:
  - Prevent future Strokes
- Goal:
  - Maintain HbS concentration < 30% of total Hb
- Main side effects:
  - Iron Accumulation
  - Alloimmunization
  - Hyperviscosity
  - Volume Overload

Stroke Prevention Trials - STOP I

Stroke Prevention Trials - STOP II

- Inclusion
  - 2 normal TCDs after 30 months transfusions
- Randomization
  - Continued vs no transfusions
  - Trial was stopped early
  - Transfusions are highly effective in preventing strokes

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**Chronic Transfusions**
- Iron Accumulation/overload
- Deferoxamine (Desferal®)
  - Subcutaneous administration
  - Compliance
- Deferasirox (Exjade®/Jadenu®)
  - Enrollment process
  - Prior authorization
  - Compliance

**Deferasirox**
- Oral iron chelator
- Exjade® – soluble tablet
  - 125mg, 250mg, 500mg
- Jadenu®- tablet
  - 90mg, 180mg, 360mg
- Conversion from Exjade® to Jadenu®
- Monitoring-ADR, labs, eye and hearing exam

**Hydroxyurea**
- Broad antitumor activity:
  - Leukemia
  - Solid Tumors
- Radiation sensitizer
- HbF inducer in SCD

**Hydroxyurea**
- Leads to HbF inductions
  - Inhibits intracellular HbS polymerization
  - Improves erythrocyte rheology
  - ↑: Total hemoglobin, Fetal hemoglobin
  - ↓: WBC, Cell-adhesion molecules (ie. L-selectin in neutrophils)
  - Adhesion of RBC to vascular endothelium
  - Which contribute to vaso-occlusion

**Hydroxyurea**
- Use:
  - Reduce frequency of sickle cell complications:
    - Painful crisis
    - ACS
    - Secondary stroke
  - Individuals with iron overload with exchange transfusions
  - Only FDA approved agent for treatment in SCD
  - Adults: Approved in 1998
  - Children: off label use
Hydroxyurea

- **Dosing**
  - Starting dose 15-20mg/kg
  - Goal 30-35mg/kg
- **Adverse Effects:**
  - Myelosuppression
    - Thrombocytopenia
    - Leukopenia
    - Reticulocytopenia

Hydroxyurea

- **Compliance**
- **Availability**
  - Capsules
  - Compounding required for suspension
  - Pharmacy availability
- **Insurance issues - prior authorization for suspension**

Hydroxyurea

- **MultiCenter Study of Hydroxyurea in Sickle Cell Anemia (MSH Trial)**
  - Randomized Double-blind, placebo controlled trial
  - **Purpose:**
    - Test the efficacy of HU in rate of painful events
  - **Results:**
    - ↓ painful sickle cell episodes or crises
    - ↓ hospitalizations for painful episodes
    - ↓ ACS
    - ↓ total number of units of blood transfused by ~50%
    - Hydroxyurea approved by FDA in 1998
      - First agent for prevention of painful episodes in adults with SC anemia

Hydroxyurea

- **Study of Hydroxyurea in Children (PED HUG)**
  - **Phase I/II Trial**
    - Children 5-15 years of age
    - **Results:**
      - ↑ hemoglobin concentration
      - ↑ HbF level
      - ↑ WBC, neutrophil, platelet and reticulocyte count
      - Laboratory toxicities observed
        - Similar in adults
        - Reversed upon cessation of HU therapy
      - Led to a phase III trial for children with SC anemia to determine whether HU can prevent chronic end-organ damage

Hydroxyurea

- **Study of Hydroxyurea in younger children (Baby Hug)**
  - **Phase III trial**
    - Children 9 to 18 months of age
    - **Results:**
      - ↑ hemoglobin concentration
      - ↑ HbF level
      - ↑ WBC, neutrophil, platelet and reticulocyte count
      - Toxicity: mild to moderate neutropenia
      - Based on safety and efficacy – should be considered in all very young children with SCA
      - Future follow up in 2016
**2014 Hydroxyurea Guidelines**

- Educate all patients with SCA and their family members about hydroxyurea therapy.
- In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications.
  - Ages 9-42 Months: Strong recommendation, high-quality evidence.
  - Children > 42 Months and Adolescents: Moderate recommendation, moderate-quality evidence.
- Ensure proper use of hydroxyurea and maximize benefits and safety by using an established prescribing and monitoring protocol.

- In those with HbSβ+ thalassemia or HbSC who have recurrent sickle cell-associated pain that interferes with daily activities or quality of life, consult an expert for consideration of therapy.
- In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy.

**TWiTCH Trial**

- Hydroxyurea versus chronic transfusion:
  - Age 4-16
  - Patients with abnormal TCD’s
  - Received at least 1 year of transfusions
  - Randomized-continue transfusions or begin hydroxyurea
- Results- Hydroxyurea can be substituted for chronic transfusions to maintain TCD velocities and help prevent primary stroke.

**The Future......**

- Increase usage of hydroxyurea.
- New medications:
  - “Epic” Trial- vepoloxamer- adult study completed enrollment.
  - Gene therapy- vaccines.

**Summary**

- Sickle Cell Anemia affects many organ systems.
- Requires Comprehensive patient management.
- Goals of management include:
  - To reduce number of sickle cell crises.
  - Improve quality of life for the patient.
  - Regular health maintenance and check-ups.
- Prevent pneumococcal sepsis in children.
- Transfusions or hydroxyurea to prevent stroke in children with high CNS blood flow.
- Used of hydroxyurea to decrease Crisis in children with severe SCD.

**Post-test**

True or False:

Sickle cell disease is diagnosed only when a child begins to have symptoms.
Which of these is a complication associated with Sickle Cell Disease:

a. Vaso-occlusive Crisis  
b. Cerebrovascular Accident  
c. Splenic Sequestration Crisis  
d. Infection  
e. All of the above

True or False

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