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Sickle Cell Disease

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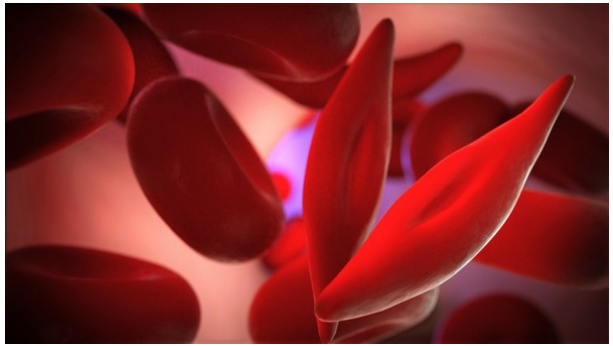

Objectives

1. Define Sickle Cell disease
2. Discuss diagnosis, risk factors and pathogenesis
3. Review different forms of the disease
4. Review management/treatment
5. Discuss future gene therapy

Definition

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According to the National Heart, Lung and Blood Institute, sickle cell disease (SCD) is defined as a group of inherited red blood cell disorders in which there are abnormal protein in red blood cells.

Normal Red Blood Cell

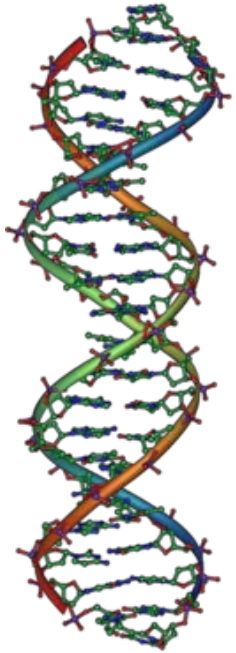
Sickle Cell

Diagnosis

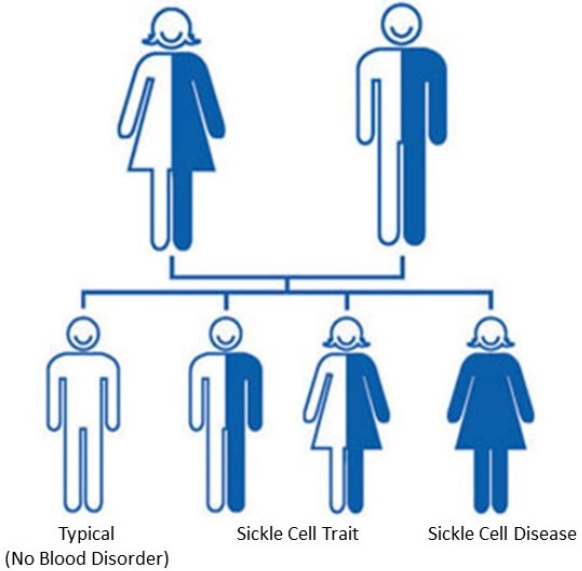
- Typically diagnosed at birth via “universal newborn screening” which is done by isoelectric focusing (IEF), hemoglobin electrophoresis (HbEp), etc…

Risk Factors

- Living in high prevalence area for SCD (Africa/Malaria)
- Family History of SCD (genetics)



Pathogenesis



www.cdc.gov

Different Forms of Sickle Cell Disease

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- Sickle Cell Trait
- HbSS (most common & severe)
- HbSC (less severe)
- HbSβ^0 -Thalassemia (severe)

Exhibit 1a. Typical Laboratory Findings in Sickle Cell Disease

Genotype	Hb* (g/dL)†	HbS (%)	HbA (%)	HbA2 (%)	HbF (%)	HbC (%)
SS	6–9	>90	0	<3.5	<10	0
Sβ^0-thalassemia	7–9	>80	0	>3.5	<20	0
Sβ^+-thalassemia	9–12	>60	10–30	>3.5	<20	0
SC	9–14	50	0	<3.5	≤1.0	45

* Definitions for abbreviations are as follows: Hb = hemoglobin; HbS = sickle hemoglobin; HbA = normal adult hemoglobin; HbA_2 = minor variant of adult hemoglobin; HbF = fetal hemoglobin; HbC = hemoglobin variant that causes manifestations of SCD when paired with HbS

† The hemoglobin values in this exhibit apply in the absence of a blood transfusion in the last 4 months, are not absolute, and are applicable to adults and children only (not newborns).

NHLBI

Epidemiology

- Most common for individuals from Africa/African descent, Middle East, India, Mediterranean countries, Caribbean, and parts of South/Central America.
- 15 million Africans affected by SCD; 100,000 in the United States; 12,500 in the UK
- 1 out of every 365 African Americans born have sickle cell disease.

Mortality

- Children and adults with homozygous sickle cell anemia (HbSS) had a median age of death of 42 years for males and 48 years for females
- HbSC median age of death was 60 years for males and 68 years for females
- 18% of deaths were due to organ failure (primarily renal failure)

Cost

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- Study from University of Florida looked at 11,821 patients (0-96 years) and assessed cost burden
- Using national prevalence data, SCD has a cost burden of $2.98 billion per year in the US
- Of that, 57% are inpatient costs, 38% are outpatient, and 5% are patient out of pocket costs

Social and Behavioral Implications

- Children ages 1.5 to 5 years of age with SCD were studied
- Compared to placebo, higher levels of:
  - Depression
  - Anxiety
  - Aggressive behavior
  - Internalizing symptoms

Studies have also shown adults have coping issues as well

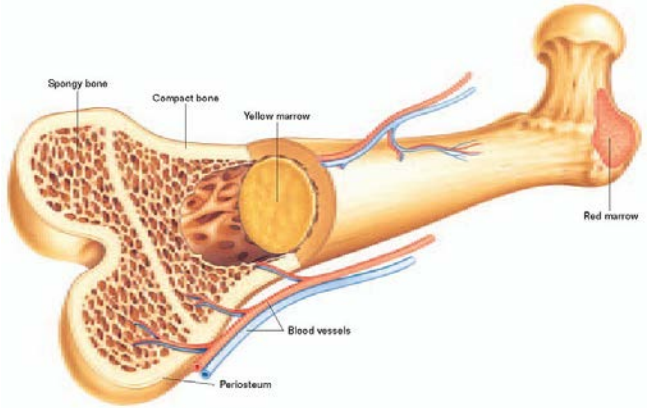
Medical complications of abnormal RBC

- Vasco-occlusive crisis
- Anemia
- Splenic Sequestration
- Acute Chest Syndrome
- Infection
- Stroke

Management/Treatment

Cure

- Bone marrow transplantation
- Difficult due to cost, donor match, and surgery risk



Sickle Cell Guidelines

- 2014 American Society of Hematology (adapted from National Heart Lung Blood Institute)
- 2009 American Society of Pediatric Hematology/Oncology
- 2016 British Society for Hematology
- 2008 Canadian College of Medical Geneticists Prenatal Diagnosis

Hydroxyurea in Adults with SCD

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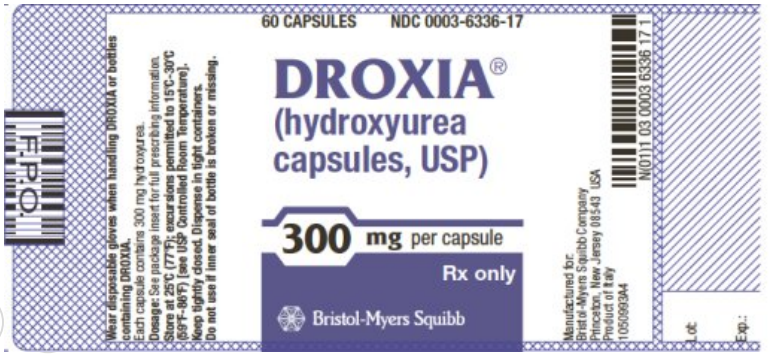
- Indicated for adults with 3 or more moderate-severe pain crises in 1 year
- Severe or recurrent acute chest syndrome
- Chronic anemia

Management- Disease Modifying Agents

- **Hydroxyurea**
- MOA: Increases fetal hemoglobin (HbF) and reduces vaso-occlusion
- Side effects: increased LFTS, uric acid, BUN, SCR, teratogenic (contraception), BBW: myelosuppression.
- Monitor ANC levels every 2-4 weeks initially, then 2-3 months (Hold if ANC< 2,000/mm^3 or platelets <80,0000/mm^3)
- Folic supplementation



Different Formulations of Hydroxyurea

	Generic Hydroxyurea	Droxia®	Siklos®
Indication	SCD (standard of care)	SCD	SCD
Age	9 months*	Adults only	2 years and older
Dose	10-15 mg/kg/day a single dose. Increase by 5 mg/kg every 4-6 weeks	Initial 15 mg/kg/day. Increase dose by 5 mg/kg/day every 12 weeks	Initial 20 mg/kg/day. Increase dose by 5 mg/kg/day every 8 weeks
Max Dose	35 mg/kg/day (SCD)	35 mg/kg/day	35 mg/kg/day
Dose Adjust	CrCl< 60 ml/min	CrCl< 60 ml/min	CrCl< 60 ml/min

**Recommended for ages 9 months to adolescent regardless of disease severity (*NHLBI)*

Management- Disease Modifying Agents

- **Endari® (L-glutamine Powder)** Approved 2017 by FDA
- MOA: improves the redox potential in sickle RBC by increasing the availability of reduced glutathione.
- Side effects: constipation, abdominal pain, nausea and headache
- Dosage:10 to 30 grams given BID per body weight
- Reduces acute complications of SCD in adults/pediatrics (5 years+) such as pain crises, acute chest syndrome, and hospitalization
- Hepatic/renal monitoring

Management- Disease Modifying Agents

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- **Oxbryta® (voxelotor)**
- MOA: inhibits hemoglobin S polymerization, the central abnormality in SCD, which increases affinity/stabilizes the oxygenated hemoglobin state and improves RBC deformity, sickling, and whole blood viscosity
- Side effects: headache, diarrhea, and fatigue
- Dosage: 1500 mg orally once daily (Hepatic dose adjusted)
- Indicated for SCD patients 12 years of age or older
- May increase hemoglobin levels and reduce hemolysis. Use chromatography for precise measurement
- Can be given with or without hydroxyurea

Management- Disease Modifying Agents

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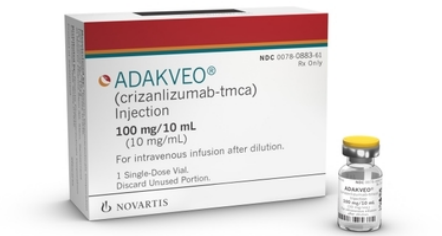
- **Adakveo® (crizanlizumab-tmca)** FDA approved on November 15, 2019
- MOA: inhibits P-selectin glycoprotein ligand 1 (adhesion substance) and prevents sickled red blood cells, platelets, endothelial cells, and leukocytes from sticking to each other
- Side effects: infusion related reactions, nausea, back pain, joint pain, and fever
- Dosage: 5mg/kg @ 100 mg/10 ml injection (dosage form)
- Administer via 30 minutes infusion at Week 0, Week 2, and every 4 weeks thereafter.
- For SCD patients 16 years of age or older



Adakveo® (crizanlizumab-tmca) cont.

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- Lowers rates of vaso-occlusive crisis resulting in better management of symptoms including pain, organ damage, and hospitalization
- Studies showed that patients receiving Adakveo had a median annual hospitalization rate of 1.63 visits compared to the placebo of 2.98 median annual visits (p-value= 0.01)
- Can be used with or without hydroxyurea
- Can interfere with platelet count in blood samples (falsely decreased platelet count)

Supportive Care for Medical Complications

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- Vasco-occlusive crisis (occlusion causing pain)
- Anemia
- Splenic Sequestration
- Acute Chest Syndrome
- Infection
- Stroke

Pain (Vaso-occlusive Crisis)

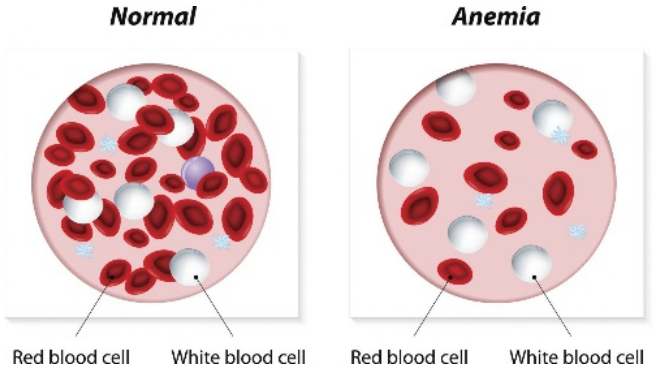
- Typically in a hospital setting
- Initiate analgesic therapy within 30-60 minutes
- For mild to moderate pain: NSAIDs
- Severe Pain: parenteral opioids
- Meperidine is commonly used due to long prescribing history but is not recommended due to CNS toxicity (dysphoria, irritable mood, and seizures)
- Parental morphine, hydromorphone, and fentanyl are recommended

Pain cont.

- Chronic Pain: long and short acting opioids
- Use of oral long acting or sustained release opioids is recommended for management of chronic pain
- Short acting opioids may be used for breakthrough pain

Acute Anemia

- Decline of 2 g/dL or more from baseline or less than 6 g/dL when baseline in unknown
- For symptomatic acute cases of anemia:
  - Blood transfusion

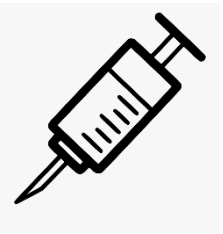


Acute Chest Syndrome

- Frequent cause of death for SCD patients aged 1 to 3 years
- Acute illness: fever and respiratory symptoms
- Pulmonary infiltrate
- Treatment:
  - Oxygen (if oxygen saturation is less than 90%)
  - Blood Transfusion (if a decrease in hemoglobin > 1 g/ml)
  - Broad Spectrum IV Antibiotics (cephalosporin + macrolide)
  - Pain control and spirometry

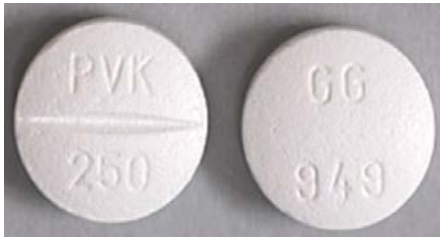
Infection

- *Streptococcus pneumonia* main culprit for death in children with SCD
- Susceptibly is due splenic malfunction with failure to make specific IgG antibodies
- New Vaccination Record: PCV13 before the age of 2 (2 doses 8 weeks apart)
- After completion of PCV13, give 2 doses of PPSV23 (1st dose 8 weeks after last dose of PCV13, and second dose at least 5 years after first dose of PPSV23)
- Meningococcal Vaccine age > 2 years (2 doses 8 weeks apart)
- One dose of Hib vaccine for ages > 5 years



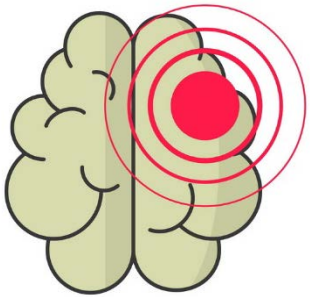
Infection cont.

- Prophylactic Antibiotics
- Shown to prevent life threatening infections in children with SCD
- New born to 3 years: Penicillin VK 125 mg PO BID
- 3 to 5 years: Penicillin VK 250 mg PO BID
- After 5 years age, continuation of prophylactic penicillin based on clinical judgement.
- Consider withholding penicillin prophylaxis for patients with SCD HbSC and HbSβ$^+$unless they have had splenectomy



Acute Stroke

- Typically presented with severe headache, altered level of consciousness, seizures, speech issues, and/or paralysis
- Treat with exchange transfusion
- If unable to transfuse, initiate hyrdoxyurea treatment



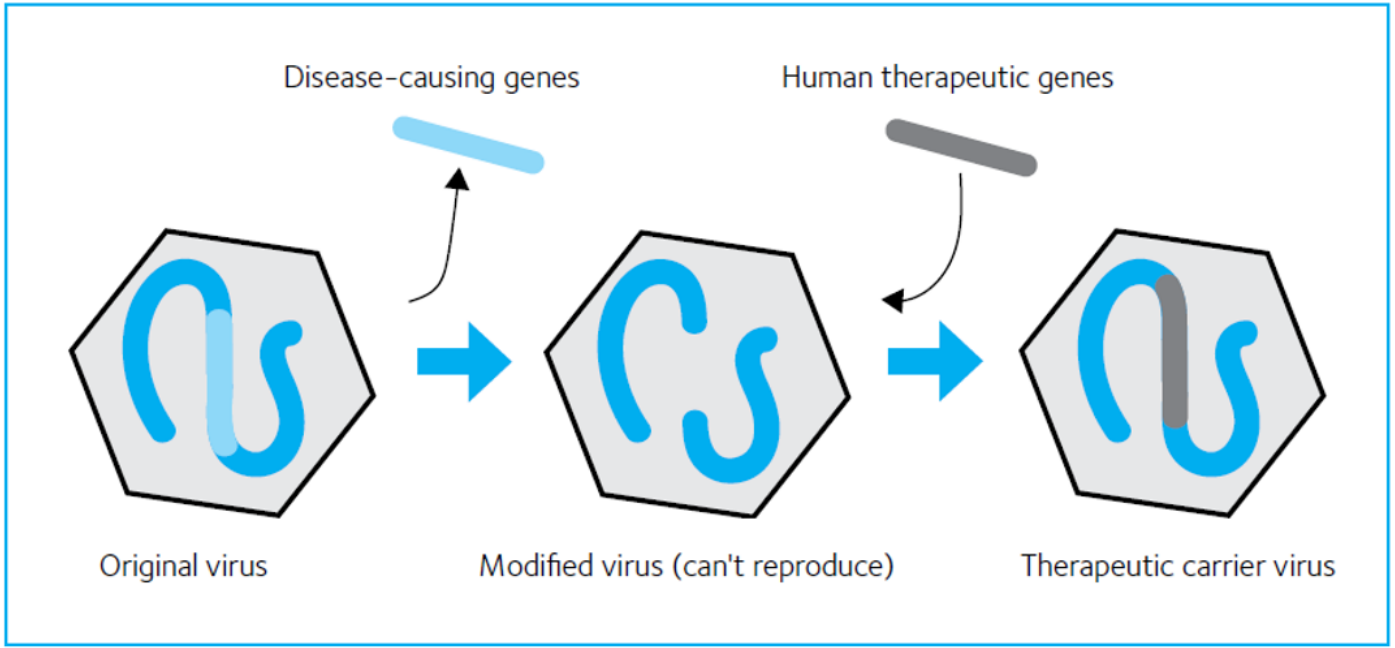
Acute Splenic Sequestration Complication (ASSC)

- Intrasplenic trapping of red blood cells causing rapid drop (2 g/dL) in hemoglobin with increased chance of hypoxic shock
- Leading cause of death in children with SCD (more common in SCD-SS)
- Evidence of increased erythropoiesis (elevated reticulocyte)
- Acutely enlarged spleen

Treatment of ASSC

- Treat with immediate red blood cell transfusion and IV fluid resuscitation
- Partial splenectomy has been recommended for children with recurrent ASSC (no RCT data)
- Splenectomy does not increase the risk of death or bacterial illness in patients with SCD-SS

The Future (Gene Therapy)



Gene Therapy (ongoing clinical trials)

- 2 general mechanisms of action:
  - Remove patients hematopoietic stem cells and replace the mutated gene with a healthy gene in hopes that when replaced will continue to produce healthy RBCs.
  - To genetically modify the stem cell to produce more fetal hemoglobin.
- 4 trials in Phase II (two are concluding in 2022)

Conclusion

- Sickle cell disease is rare, however it has both clinical complications and a cost burden. Therefore standard of care can help improve patient outcomes and decrease hospitalization.
- To improve quality of care and improve outcomes, a clinical pharmacy program is being developed to promote hydroxyurea use and improve medication adherence

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Questions