Advancements in the Management of Sickle Cell Disease

A Presentation for HealthTrust Members
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Bhavini Shah, PharmD
PGY-1 Pharmacy Resident
Atlantic Health System
Christine Robinson, PharmD, Preceptor

Disclosures

The presenter and her preceptor have no financial relationships with any commercial interests pertinent to this presentation.

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Learning Objectives for Pharmacists & Nurses

Describe the pathophysiology of sickle cell disease (SCD).

List current therapies for SCD based on guidelines and standards of care.

Identify new therapies for SCD and discuss their role in management.

Learning Objectives for Pharmacy Technicians

List common signs and symptoms of vaso-occlusive crisis (VOC).

Describe special handling requirements for agents utilized in the management of SCD.

Outline storage requirements for agents used in the management of SCD.

Sickle Cell Disease

Introduction to Sickle Cell Disease

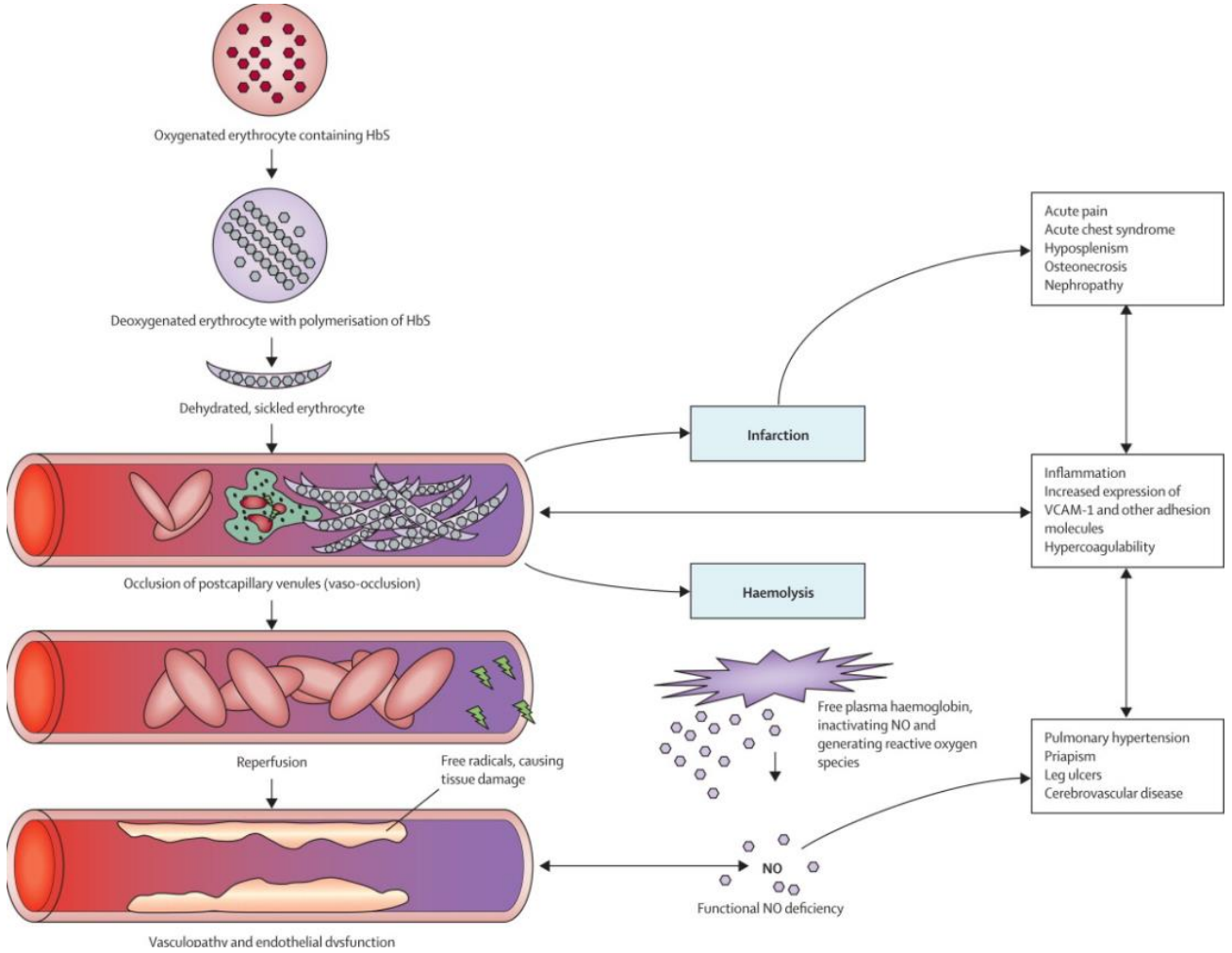
Inherited blood disorder with lifelong complications

Mutation in the beta-hemoglobin gene results in sickle cell hemoglobin (HbS)

Affects multiple organ systems

Source: Rees DC, et al. *Lancet*. 2010 Dec 11;376(9757):2018-31.

Pathophysiology



Source: Rees DC, et al. *Lancet*. 2010 Dec 11;376(9757):2018-31.

Epidemiology

- Disproportionately affects certain communities world-wide
  - Highest prevalence in sub-Saharan Africa
  - Affects ~100,000 Americans
  - Affects 1 in every 365 Black or African American babies born in the United States
- Mortality rate has decreased substantially with pharmacologic advancements

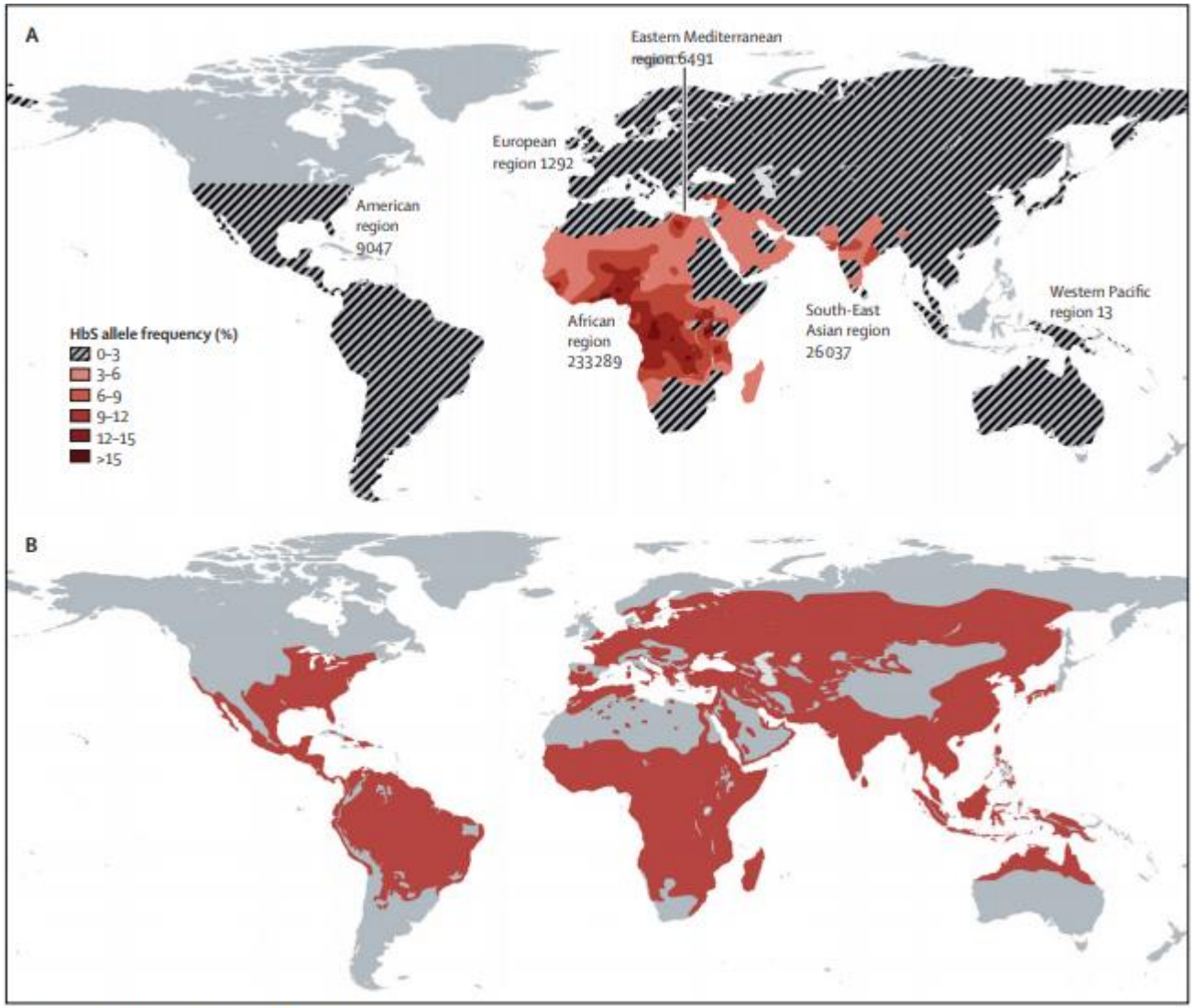
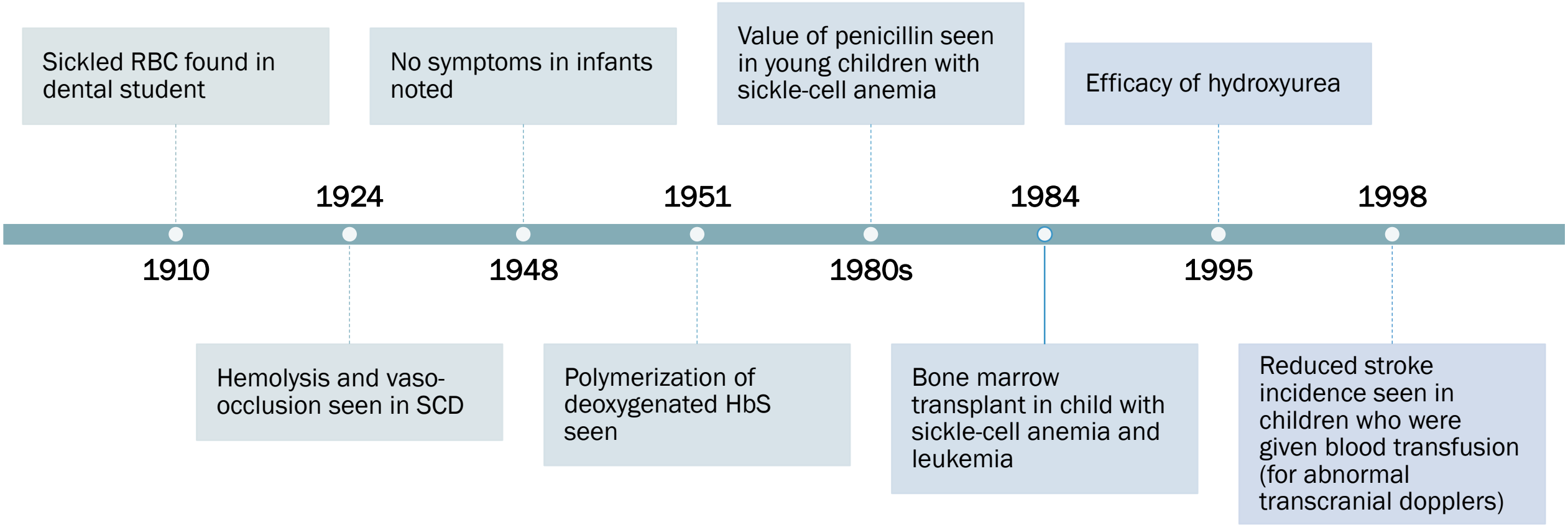


Figure 3: **Global distributions of HbS and malaria**
(A) This map shows the distribution of the HbS allele. It was constructed with digitised data derived from Cavalli-Sforza and colleagues.[51] The figures indicate estimates for the combined yearly total number of individuals affected by HbSS, HbSC, and HbS/β-thalassaemia by WHO region (adapted from Modell and Darlison[52]). (B) This map shows the global distribution of malaria (red) before intervention to control malaria (adapted from Lysenko and Semashko,[53] and Hay and colleagues.[54] HbS=sickle haemoglobin.

Sources: Rees DC, et al. *Lancet*. 2010 Dec 11;376(9757):2018-31.
Centers for Disease Control and Prevention. Data & statistics on sickle cell disease. Available at https://www.cdc.gov/ncbddd/sicklecell/data.html. Accessed May 15, 2021.



Timeline (Discovery)

Source: Rees DC, et al. *Lancet*. 2010 Dec 11;376(9757):2018-31.

Barriers & Improvements to Care

- Slow development in treatment modalities
- 2017: first new treatment in ~20 years (L-glutamine)
- Poor health outcomes
  - Lack of access to quality comprehensive care
  - Under-prescribing/negative prescriber attitudes towards patient reports of pain

2018: Centers for Disease Control and Prevention established the Sickle Cell Data Collection program

Goal: long-term collection of health information of SCD patients to better understand diagnosis, treatment, and healthcare access needs

Sources: Farooq F, et al. *JAMA Netw Open*. 2020;3(3):e201737.
Centers for Disease Control and Prevention. Sickle cell disease monitoring. Available at https://www.cdc.gov/ncbddd/sicklecell/features/sickle-cellawareness.html. Accessed May 15, 2021.

Pharmacist and Nurse Assessment Question #1

Which of the following best describes the pathophysiology of sickle cell disease?

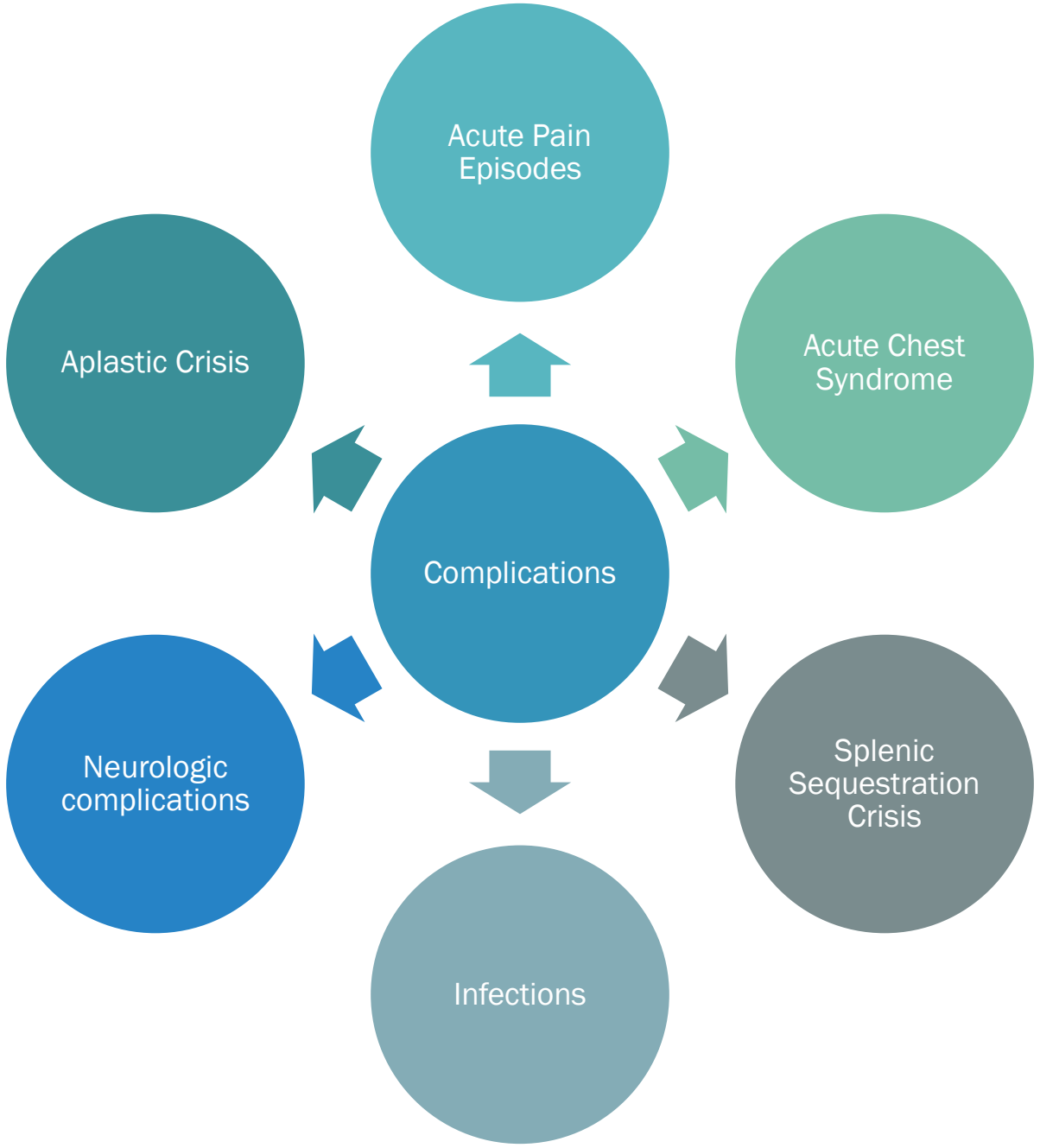
a. Mutation of the beta-hemoglobin gene resulting in sickle cell hemoglobin (HbS)
b. Mutation of the alpha-hemoglobin gene resulting in HbS
c. Mutation of the beta-hemoglobin gene resulting in normal hemoglobin (Hb) formation
d. Mutation of the alpha-hemoglobin gene resulting in normal Hb formation

Pharmacist Assessment Question #1 Answer

Which of the following best describes the pathophysiology of sickle cell disease?

a. **Mutation of the beta-hemoglobin gene resulting in sickle cell hemoglobin (HbS)**
b. Mutation of the alpha-hemoglobin gene resulting in HbS
c. Mutation of the beta-hemoglobin gene resulting in normal hemoglobin (Hb) formation
d. Mutation of the alpha-hemoglobin gene resulting in normal Hb formation

SCD Complications


Acute Pain Episodes
Aplastic Crisis
Acute Chest Syndrome
Complications
Neurologic complications
Splenic Sequestration Crisis
Infections

Acute Pain Episodes/VOC

- Cell aggregation occludes blood flow in small vessels
  - Downstream effects: tissue deprivation of nutrients and oxygen, resulting in tissue ischemia and death
  - Excruciating pain that can last hours to days
- Prodromal phase lasts 1 to 2 days, followed by peak pain on Day 3 until Day 6 or 7
- Pain location varies by age
  - Younger children: extremities
  - Older patients: head, chest, abdomen, back
- Leading cause of SCD-related hospitalizations
- Treatment: opioids

Sources: Darbari DS, et al. *Eur J Haematol.* 2020;105(3):237-246.
U.S. Department of Health and Human Services. Report on pain management best practices: Updates, gaps, inconsistencies, and recommendations. Available at https://www.hhs.gov/ash/advisorycommittees/pain/reports/index.html. Accessed May 15, 2021.
National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: Expert panel report, 2014.
Brandow AM, et al. *Blood Adv.* 2020;4(12):2656-2701.

Acute Pain Episodes/VOC

- Triggers
  - Patient-related: acidosis, alcohol consumption, anxiety/depression, dehydration, fever, hypoxia, infection, menstruation, obstructive sleep apnea, pain, physical exhaustion, and pregnancy
  - Environmental: exposure to high temperatures, humidity, wind speed

Signs and Symptoms

- Severe pain
  - May be described as originating in the arms, legs, chest, or spine/back
- Painful swelling of the small bones of the hands and feet (dactylitis) may occur
- May be accompanied by headache or dizziness

Source: Darbari DS, et al. *Eur J Haematol.* 2020;105(3):237-246.

Technician Assessment Question #1

Which of the following are common signs and symptoms of a vaso-occlusive crisis in SCD?

a. Severe pain or dactylitis

b. Congestion

c. Retinopathy

d. Frequent urination

Technician Assessment Question #1 Answer

Which of the following are common signs and symptoms of a vaso-occlusive crisis in SCD?

a. Severe pain or dactylitis

b. Congestion

c. Retinopathy

d. Frequent urination

Acute Chest Syndrome

- New pulmonary infiltrate
- Etiologies: emboli, pneumonia, pulmonary infarction
- Accompanied by fever, chest pain, tachypnea, wheezing, or cough
- Occurs in 10 to 20% of hospitalized patients
- Can manifest 1 to 3 days after admission for VOC
- High incidence of morbidity and mortality
- Rapid progression to acute respiratory distress syndrome, respiratory failure, pulmonary infarction, or death
- Treatment: antibiotics, supplemental oxygen, intravenous fluids, blood transfusions

Source: Rees DC, et al. *Lancet*. 2010 Dec 11;376(9757):2018-31.

Splenic Sequestration Crisis

- Sickled RBCs are unable to pass through small endothelial openings of venous sinuses
- Over time, this can cause splenic auto-infarction due to oxygen shortage
- RBC trapping in the spleen leads to mechanical obstruction
  - Downstream effects: acute drop in Hb (2 g/dL) and splenomegaly
- Typically follows a febrile illness
- Increases risk of infections and sepsis
- Occurs in 10 to 30% of young children (ages 6 months to 3 years) with SCD
- Treatment of acute splenic sequestration: RBC transfusion

Sources: National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: Expert panel report, 2014.
Rees DC, et al. *Lancet*. 2010 Dec 11;376(9757):2018-31.

Infections

- Functional asplenia from sickling increases risk of recurrent infections
  - Increased incidence in children
  - Encapsulated bacteria
    - *Streptococcus pneumoniae, Neisseria meningitides, and Haemophilus influenzae* type b
  - Other infections
    - Osteomyelitis secondary to *Staphylococcus aureus* and *Salmonella species*
- Prevention: vaccinations (pneumococcal conjugate vaccine) and penicillin prophylaxis have decreased pneumococcal disease incidence

Age	Prophylaxis
3 months to 3 years	Penicillin VK 125 mg orally twice daily
3 to 5 years	Penicillin VK 250 mg orally twice daily
> 5 years	Patients may continue or discontinue treatment based on physician recommendation

Source: Abboud MR. *Hematol Oncol Stem Cell Ther.* 2020;13(2):85-90.

Neurologic Complications

- Cerebral blood flow abnormalities, cerebral hemorrhage, microvascular disease, silent cerebral infarcts (SCIs), stroke
  - Stroke is a leading cause of disability in SCD
- Variation in incidence based on age:
  - Ischemic stroke is more common in children
  - Hemorrhagic stroke is more common in adults
- Recurrent strokes occur in 50 to 70% of SCD patients within three years

Source: Farooq S, et al. *Curr Neurol Neurosci Rep*. 2019;19(4):17.

Aplastic Crisis

Primary pathogen

- Parvovirus

Causes acute life-threatening anemia that interrupts erythropoiesis for 8 to 10 days

- Can result in hemoglobin (Hb) drop of 1 g/dL per day
- Ultimately may require RBC transfusion
- Normal RBC life span: 100 to 120 days
- Sickled RBC life span: 7 to 12 days

Source: Novelli EM, et al. Crises in Sickle Cell Disease. *Chest*. 2016;149(4):1082-93.
Pinto VM, et al. *Intern Emerg Med.* 2019;14(7):1051-1064.

Pharmacologic Therapy

Hydroxyurea

- FDA-approved in 1998 for SCD treatment
  - 2017: approval for patients aged ≥ 2 years with SCD and recurrent moderate to severe pain crises
- National Heart, Lung, and Blood Institute (NHLBI) guideline statement:
  - Offer hydroxyurea in all infants with SCD beginning at 9 months of age regardless of clinical severity
- Proposed mechanisms
  - Inhibition of ribonucleotide reductase results in S-phase arrest and fetal hemoglobin (HbF) induction
  - Increased HbF:HbS per erythrocyte results in less polymerization
  - Reduction in hemolysis, adhesion, and VOC events
  - Nitric oxide release results in vasodilatation and increased vascular responsiveness

Sources: Siklos [package insert]. Addmedica; 2017.
Droxia [package insert]. Bristol-Myers Squibb Company; 2019.
McGann PT, Ware RE. *Expert Opin Drug Saf.* 2015;14(11):1749-1758.
National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: Expert panel report, 2014.

Hydroxyurea in Adults

Multicenter Study of Hydroxyurea in Sickle Cell Anemia	
Design	• Phase 3, double-blind, randomized, controlled
Population	• Patients with severe SCD
Arms	• Hydroxyurea initial dose 15 mg/kg per day (titrated up by 5 mg/kg per day as tolerated) • Placebo
Primary Outcome	• Median incidence of pain crises per year: 2.5 vs. 4.5, $p<0.001$
Secondary Outcomes	• Median time to first crisis: 3.0 vs. 1.5 months, $p=0.01$ • Median time to second crisis: 8.8 vs. 4.6 months, $p<0.001$ • Acute chest syndrome: 25 vs. 51, $p<0.001$ • Transfusions: 48 vs. 73, $p=0.001$

17.5-year follow up study showed that hydroxyurea improved survival without major serious adverse effects

Sources: Charache S, et al. *N Engl J Med.* 1995; 332:1317-1322.
Steinberg MH, et al. *Am J Hematol.* 2010;85(6):403-408.

Hydroxyurea in Children

BABY HUG	
Design	• Randomized, controlled, multicenter
Population	• Patients aged 9 to 18 months with SCD (HbSS or HbSβ^0 thalassemia), (n=193)
Arms	• Hydroxyurea 20 mg/kg per day (n=96) • Placebo (n=97)
Primary Outcomes	• Decreased splenic function: 27% vs. 38% (difference -11, 95% confidence interval [CI] -26 to 5) • Mean increase in glomerular filtration rate: 18% vs. 17% (difference 2, 95% CI -16 to 20)
Secondary Outcomes	• Dactylitis (hazard ratio [HR] 0.27, 95% CI 0.15 to 0.50), p<0.001 • Pain (HR 0.59, 95% CI 0.42 to 0.83), p=0.002 • Hospitalizations (HR 0.73, 95% CI 0.53 to 1.00), p=0.05 • Transfusions (HR 0.55, 95% CI 0.32 to 0.96), p=0.03

Source: Wang WC, et al. *Lancet.* 2011;377(9778):1663-1672.

Hydroxyurea

	Siklos®	Droxia®
Initial Dose	• 20 mg/kg orally once daily	• 15 mg/kg orally once daily
Dose Titration	• 5 mg/kg/day every 8 weeks until maximum tolerated dose (MTD) or 35 mg/kg/day	• 5 mg/kg/day every 12 weeks to MTD or 25 mg/kg/day
Renal impairment	• Reduce dose by 50% for CrCl < 60 mL/min	
Monitoring	• Blood counts: every two weeks • Toxic hematologic ranges (warrant discontinuation of treatment): ▪ Neutrophils < 2,000/mm^3 ▪ Platelets < 80,000/mm^3 ▪ Hb < 4.5 g/dL ▪ Reticulocytes < 80,000/mm^3 if Hb is <9 g/dL	
Restarting Treatment	• 5 mg/kg/day less than the dose associated with hematologic toxicity	• Resume treatment after a dose reduction of 2.5 mg/kg/day from the dose associated with toxicity

Sources: Sources: Siklos [package insert]. Addmedica; 2017.
Droxia [package insert]. Bristol-Myers Squibb Company; 2019.

Hydroxyurea

Adverse Effects >10%	
Diarrhea	Nail/skin hyperpigmentation
Leukopenia	Nausea/vomiting
Mouth sores	Neutropenia/reticulocytopenia

- Avoid live vaccines while on hydroxyurea
- Avoid concomitant use with antiretroviral drugs (risk for hepatotoxicity, pancreatitis, and peripheral neuropathy)

Sources: Sources: Siklos [package insert]. Addmedica; 2017.
Droxia [package insert]. Bristol-Myers Squibb Company; 2019.

Hydroxyurea

Storage

- Store at 20°C to 25°C
- Keep bottle tightly closed
- Siklos®: use split tablets within three months

Special Considerations

- Hazardous agent
- Available as tablets and capsules
- Capsules should not be opened, broken, or chewed
- Impervious gloves should be worn when handling bottles containing hydroxyurea or when handling/administering intact capsules/tablets
- Wash hands with soap and water before and after contact with hydroxyurea
- Avoid exposure to crushed capsules/tablets or open capsules

Sources: Sources: Siklos [package insert]. Addmedica; 2017.
Droxia [package insert]. Bristol-Myers Squibb Company; 2019.

Pharmacist and Nurse Assessment Question #2

Until recently, what was the only disease-modifying therapy FDA-approved for sickle cell disease?

a. Hydroxyurea

b. Hydroxyzine

c. Penicillin VK

d. Crizanlizumab

Pharmacist Assessment Question #2 Answer

Until recently, what was the only disease-modifying therapy FDA-approved for sickle cell disease?

a. Hydroxyurea

b. Hydroxyzine

c. Penicillin VK

d. Crizanlizumab

Technician Assessment Question #2

True/False. Gloves should always be worn when handling hydroxyurea.

a. True

b. False

Technician Assessment Question #2 Answer

True/False. Gloves should always be worn when handling hydroxyurea.

a. True

b. False

Voxelotor (Oxbryta®)

- FDA-approved in 2019 for SCD treatment in adults and pediatric patients aged ≥ 12 years
- Mechanism of action
  - Stabilizes the oxygenated Hb state and results in the inhibition of HbS polymerization
  - Inhibits sickling, reduces viscosity, and improved red blood cell (RBC) deformity

Source: Oxbryta [package insert]. Global Blood Therapeutics, Inc; 2019.

Voxelotor (Oxbryta®)

HOPE	
Design	• Randomized, double-blind, placebo-controlled, multicenter
Population	• Sickle cell anemia (HbSS or HbSβ^0 thalassemia), (n=272) • Two-thirds of patients received hydroxyurea at baseline
Arms	• Voxelotor 1500 mg (n = 90), voxelotor 900 mg (n = 90), or placebo (n = 92)
Primary Outcome	• Hb response (increase of >1 g/dL from baseline at week 24) ▪ 1500 mg (51%, 95% CI 41 to 61) vs. placebo (7%, 95% CI 1 to 12)
Secondary Outcomes	• Decrease in indirect bilirubin from baseline to week 24: 1500 mg vs. placebo (mean change, −29.1% vs. −3.2%), p<0.001 • Reticulocytes (relative change in percentage): 1500 mg vs. placebo (mean decrease −19.9% vs. 4.5%), p<0.001 • Transfusion: 1500 mg (33%), 900mg (32%), placebo, (25%)

Source: Vichinsky E, et al. *N Engl J Med.* 2019;381(6):509-519.

Voxelotor (Oxbryta®)

Dosing	• 1500 mg orally once daily with or without food • Missed dose: continue dosing as usual the day following the missed dose
Monitoring	• Hepatic impairment (Child Pugh C) • Decrease to 1000 mg once daily

Drug-drug Interactions	• Strong CYP3A4 inhibitors or inducers induce oxidation of voxelotor
	  ▪ Avoiding concurrent administration
	  ▪ If unavoidable:
	  • ↓ dose to 1000 mg once daily with strong/moderate CYP3A4 inhibitors
	  • ↑ dose to 2500 mg once daily with strong/moderate CYP3A4 inducers

Adverse Effects	• Headache, hypersensitivity reactions, diarrhea, vomiting
Clinical Pearls	• Can be taken with hydroxyurea

Sources: Oxbryta [package insert]. Global Blood Therapeutics, Inc; 2019.
Vichinsky E, et al. *N Engl J Med.* 2019;381(6):509-519.

Voxelotor (Oxbryta®)

Storage

- Store at ≤ 30°C (86°F)

Special Considerations

- Available only as tablets
- Look-alike/sound-alike
  - May be confused with venetoclax or vorinostat

Source: Oxbryta [package insert]. Global Blood Therapeutics, Inc; 2019.

Pharmacist and Nurse Assessment Question #3

Which of the following is a new therapy for the management sickle cell disease?

a. Hydroxyurea

b. Voxelotor

c. Folic acid

d. Diphenhydramine

Pharmacist Assessment Question #3 Answer

Which of the following is a new therapy for the management sickle cell disease?

a. Hydroxyurea

b. Voxelotor

c. Folic acid

d. Diphenhydramine

L-Glutamine (Endari®)

- FDA-approved in 2017 for SCD treatment in adults and pediatric patients aged ≥ 5 years
- Proposed mechanism
  - Essential amino acid that serves as precursor to nicotinamide adenine dinucleotide (NAD) and improves NAD redox potential
  - Improving redox potential may prevent oxidative damage to RBCs

Source: Endari [package insert]. Torrance, CA: Emmaus Medical, Inc; 2017.

L-Glutamine (Endari®)

Phase 3 Trial of L-Glutamine in SCD	
Design	• Multicenter, randomized, placebo-controlled, double-blind
Population	• Patients (ages 5 to 58 years) with sickle cell anemia (HbSS or HbSβ^0 thalassemia) and a history of two or more pain crises during the previous year • ~67% patients received concurrent hydroxyurea treatment
Arms	• L-glutamine 0.3 g/kg per dose twice daily (n=152) vs. placebo (n=78)
Primary Outcome	• Median number of pain crises (48-week study duration): 3 vs. 4, p=0.005
Secondary Outcomes	• Hospitalizations for SCD-related pain: 2 vs. 3, p=0.005 • Number of emergency room visits were not signficiantly different • No significant differences in hematologic markers (Hb, hematocrit, reticulocyte count)

Source: Niihara Y, et al. *N Engl J Med*. 2018;379(3):226-235.

L-Glutamine (Endari®)

Dosing	• 5 to 15 g orally twice daily based on body weight
	  ▪ Weight < 30 kg: 5 g twice daily
	  ▪ Weight 30 to 65 kg: 10 g twice daily
	  ▪ Weight > 65 kg: 15 g twice daily
	• Available as oral powder in 5 g packets

Monitoring	• No hepatic or renal dose adjustments per labeling but drug undergoes hepatic metabolism to glutamate and ammonia
Adverse Effects (> 10%)	• Nausea, flatulence, non-cardiac chest pain, fatigue, musculoskeletal pain
Clinical Pearls	• Only Endari® is approved for SCD; avoid the use of other glutamine brands/formulations

Sources: Endari [package insert]. Torrance, CA: Emmaus Medical, Inc; 2017.
Niihara Y, et al. *N Engl J Med*. 2018;379(3):226-235.

L-Glutamine (Endari®)

Storage

- Store at 20°C to 25°C
- Protect from direct sunlight

Special Considerations

- Mix each dose in 8 ounces of a cold or room temperature beverage or 4 to 6 ounces of food
  - Complete dissolution is not required prior to administration

Source: Endari [package insert]. Torrance, CA: Emmaus Medical, Inc; 2017.

Crizanlizumab (Adakveo®)

- FDA-approved in 2019 to reduce VOC frequency in patients with SCD aged ≥ 16 years
- Mechanism of action
  - Monoclonal antibody that binds to P-selectin and blocks its ligand interactions
  - Results in decreased interaction between platelets, endothelial cells, RBCs, and leukocytes

Sources: Adakveo [package insert]. Novartis Pharmaceuticals Corporation; 2019.
Liem RI, et al. *Blood Adv* 2019; 3 (23): 3867–3897.

Crizanlizumab (Adakveo®)

SUSTAIN	
Design	• Double-blind, randomized, placebo-controlled
Population	• SCD patients (HbSS, HbSC, HbS, HbSβ^0 thalassemia, HbSβ-positive thalassemia), (n=198) • ~62% used hydroxyurea concurrently
Arms	• Crizanlizumab 5 mg/kg (n = 67), 2.5 mg/kg (n = 66), or placebo (n = 65) ▪ Crizanlizumab administered on weeks 0 and 2, and every four weeks thereafter
Primary Outcome	• Annual rate of SCD-related pain crises: crizanlizumab 5 mg/kg vs. placebo (median 1.63 vs. 2.98), p=0.01
Secondary Outcomes	• Median time to first crisis: 5 mg/kg vs. placebo (4.07 vs. 1.38 months), p=0.001 • Median time to second crisis: 5 mg/kg vs. placebo (10.32 vs. 5.09 months), p=0.02

- Post-hoc analysis: more patients in the 5 mg/kg arm were event-free; treatment significantly increased time to first VOC
- In-progress: Phase 3 clinical trial to assess the efficacy and safety of 5 mg/kg and 7.5 mg/kg of crizanlizumab +/- hydroxyurea vs. placebo

Sources: Ataga KI, et al. *N Engl J Med.* 2017;376(5):429-439.
Kutlar A, et al. *Am J Hematol.* 2019;94(1):55-61.
Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients (STAND). ClinicalTrials.gov. identifier: NCT03814746. Updated May 21, 2021. Available at https://clinicaltrials.gov/ct2/show/NCT03814746?term=crizanlizumab&phase=2&draw=2&rank=1. Accessed on May 21, 2021.

Crizanlizumab (Adakveo®)

Dosing	• 5 mg/kg intravenous infusion over 30 minutes at weeks 0 and 2, and every four weeks thereafter
	• Missed dose: administer as soon as possible
	  ▪ If administered within 2 weeks of missed dose, can continue original dosing schedule
	  ▪ If administered > 2 weeks of missed dose, continue dosing every 4 weeks thereafter

Monitoring	• Infusion site reactions • Discontinue infusion for severe reactions and initiate medical care as warranted
Adverse Effects (> 10%)	• Arthralgia, diarrhea, pruritus, vomiting, chest pain
Clinical Pearls	• Can be taken with or without hydroxyurea • Biological proteins pose risk for immunogenicity • Administer using a sterile, nonpyrogenic 0.2-micron inline filter and flush line with ≥ 25 mL of normal saline or dextrose 5% in water

Source: Adakveo [package insert]. Novartis Pharmaceuticals Corporation; 2019.

Crizanlizumab (Adakveo®)

Storage

- Store and transport of intact vials: 2°C to 8°C
- Do not freeze
- Do not shake
- Store in original carton
- If not used immediately, solution diluted for infusion may be stored at up to 25°C (77°F) for ≤ 4.5 hours (from piercing the first vial) to infusion completion
- Diluted solution may also be stored at 2°C to 8°C (36°F to 46°F) for ≤ 24 hours (from piercing the first vial) to infusion completion

Source: Adakveo [package insert]. Novartis Pharmaceuticals Corporation; 2019.

Technician Assessment Question #3

Which of the following agents used in the management of sickle cell disease must be refrigerated?

a. Hydroxyurea
b. Voxelotor
c. Crizanlizumab
d. L-glutamine

Technician Assessment Question #3 Answer

Which of the following agents used in the management of sickle cell disease must be refrigerated?

a. Hydroxyurea

b. Voxelotor

c. **Crizanlizumab**

d. L-glutamine

Costs and Considerations

	Hydroxyurea	Voxelotor	L-glutamine	Crizanlizumab
Cost	$1,200 per year	$10,400 for a 30-day supply	$3,500 for a 30-day supply	$2,500 per vial
Additional Considerations	• Has historically had low utilization even in eligible patients • Utilization in recent years has increased by 4.7%	• Specialty medication	• Specialty medication	• Specialty medication • May have additional administration and facility fees • Patients typically require ~3 vials per treatment session

Sources: McGann PT, Ware RE. *Expert Opin Drug Saf.* 2015;14(11):1749-1758.
Black V, *Blood*. 2019;134(Supplement_1):2293-2293.
Pharmacist's Letter. Management of Sickle Cell Disease. March 2020. Available at https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2015/Feb/Management-of-Sickle-Cell-Disease-8101. Accessed May 15, 2021.

Investigational Therapies

Rivipansel

- Mechanism of action
  - Selectin antagonist with greatest activity against E-selectin
  - Antagonism of selectin-mediated cell adhesion may result in inhibition of RBC interactions, normalization of blood flow, and reduction in inflammation and VOC
- Phase 2 study: significant reduction in the mean cumulative intravenous opioid dose with rivipansel vs. placebo during VOC episodes
- Phase 3 study terminated early by investigators for not meeting its primary endpoint (time to readiness to discharge) and secondary endpoints (time to discharge, cumulative intravenous opioid use, and time to intravenous opioids discontinuation)
  - Post-hoc analysis: patients treated with rivipansel within 26 hours of pain onset experienced statistically significant improvements in the primary endpoint

Source: Theodore Wun. Presentation at American Society of Hematology Annual Meeting and Exposition, December 5-8, 2020.

Niprisan

- Mechanism of action
  - Herbal agent that may increase hydrated cell volume and thus reduce HbS concentration and delay time to polymerization
- Dry extract preparation of Piper guineense (West African black pepper) seeds, Eugenia caryophyllum (a variety of cloves) fruits, Pterocarpus osun (a tropical tree) stem, and Sorghum bicolor (a millet grain) leaves
- May be safe and effective in reducing painful crisis (studied over a 6-month follow-up period)
- FDA orphan drug status in 2003, but unavailable due to manufacturing issues

Sources: Adzu B, et al. *Eur J Drug Metab Pharmacokinet*. 2015;40(1):115-118.
Oniyangi O, et al. *Cochrane Database Syst Rev.* 2018;2(2):CD004448.
Perampaladas K, et al. *BMC Int Health Hum Rights.* 2010;10 Suppl 1(Suppl 1):S11.

SC411

- Mechanism of action
  - May replace insufficient levels of docosahexaenoic acid (DHA) ethyl ester in blood membranes of patients with SCD
  - Formulation enhances bioavailability
- SCOT trial:
  - Children with SCD (ages 5 to 17) were given three doses of SC411 (n=67)
  - ~67% were taking concomitant hydroxyurea
  - Treatment group: reduced pain, analgesic use, and absence from school at higher doses of 36 mg/kg and 60 mg/kg vs. placebo
  - Adverse effects: nausea and abdominal pain

Source: Daak AA, et al. *Blood Adv.* 2018;2(15):1969-1979.

Conclusion

- SCD can result in life-threatening complications
- Patients with SCD face barriers to treatment
- Since the approval of hydroxyurea, a number of new therapies are available
- Pharmacists should play a role in patient education, counseling, and drug acquisition for SCD management

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Thank You!

Bhavini Shah, PharmD

PGY-1 Pharmacy Resident

Bhavini.Shah@atlantichealth.org