MANAGEMENT AND ADVANCEMENTS IN SICKLE CELL DISEASE

A presentation for HealthTrust Members
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Disclosures

The presenter has no financial relationships with any commercial interests pertinent to this presentation.

The presenter's preceptor serves as a consultant for Wolters Kluwer and Bristol-Myers Squibb.

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Pharmacist and Nursing Objectives

- Recall sickle cell disease pathophysiology and clinical manifestations
- Identify current therapeutic options for sickle cell disease
- Recognize the role of new therapeutic agents compared to current therapy in sickle cell disease management

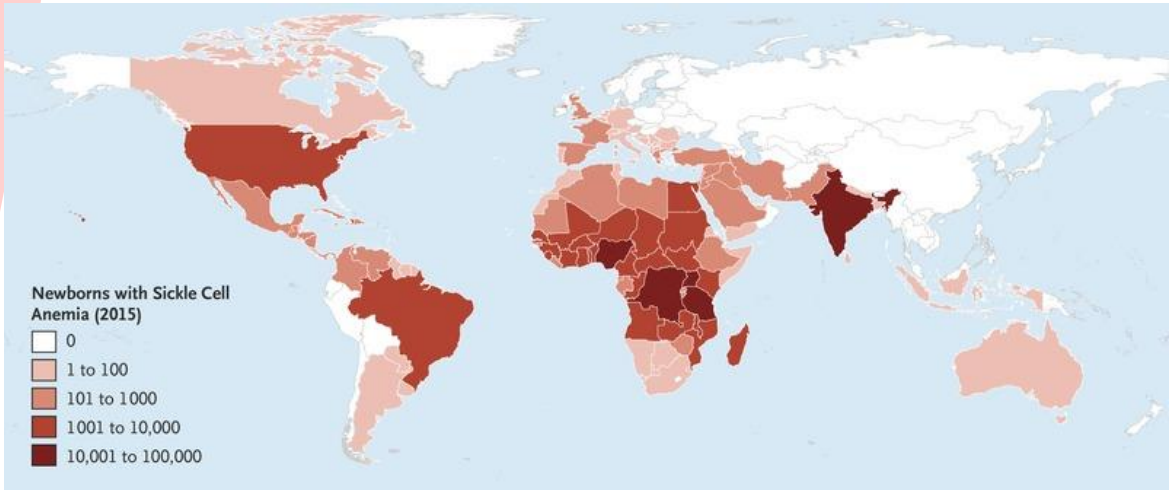
Pharmacy Technician Objectives

- Recall the most common complications of sickle cell disease
- Identify pertinent medications in the treatment of sickle cell disease
- Recognize relevant dispensing information for the newer therapeutic agents for sickle cell disease management

Sickle Cell Disease (SCD)

- **Monogenic blood disorder** with various disease modifying factors and multiorgan complications
- While screening and treatment has improved the average life expectancy to 60 years, **quality of life is often poor**
- Access to treatment in lower income countries is a **global public health issue**

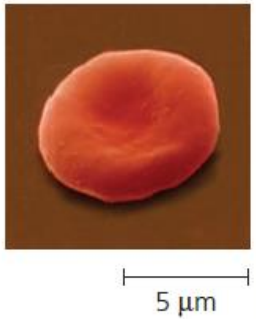
Epidemiology



- Estimated 300,000 newborns are born every year with sickle cell disease worldwide
- Prevalent in areas where malaria was historically endemic: Africa, India, the Middle East, and the Mediterranean
- 100,000 Americans are affected by SCD; 1 in 13 Black or African-American newborns are born with sickle cell trait

Piel FB, et al. NEJM 2017; 376:1561-1573

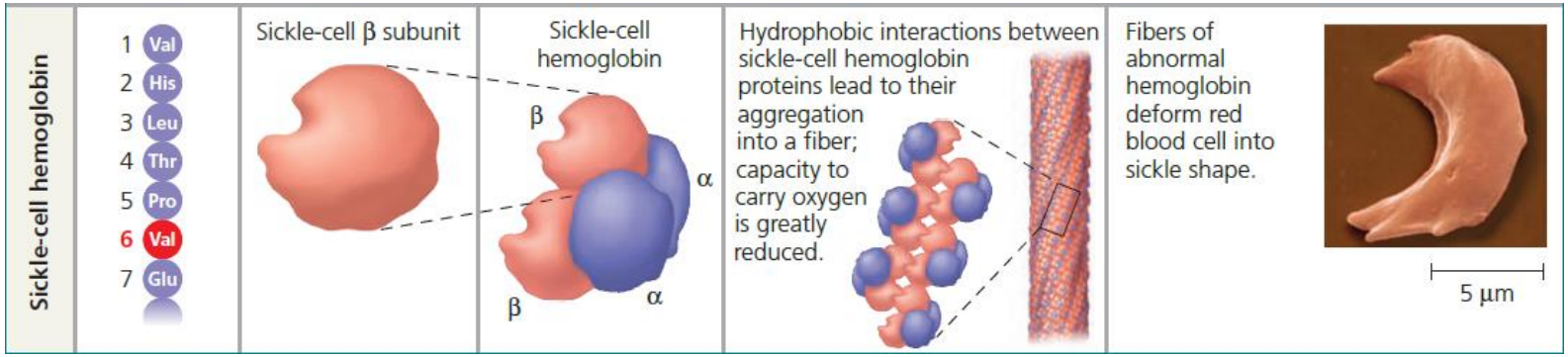
Sickle Cell Etiology

	Primary Structure	Secondary and Tertiary Structures	Quaternary Structure	Function	Red Blood Cell Shape
Normal hemoglobin	1 Val 2 His 3 Leu 4 Thr 5 Pro 6 Glu 7 Glu	Normal β subunit	Normal hemoglobin β α β α	Normal hemoglobin proteins do not associate with one another; each carries oxygen.	Normal red blood cells are full of individual hemoglobin proteins. 

- Caused by a change to the 6th codon for the beta chain of hemoglobin
- Results in amino acid change from glutamic acid to valine
- Alters structure of hemoglobin to sickle shape

Reece, JB et al. Campbell Biology. Boston: Benjamin Cummings / Pearson, 2011.

Sickle Cell Etiology



Genotype:

Phenotype: Normal Hemoglobin | Sickle Cell Trait | Sickle Cell Anemia

Reece, JB et al. *Campbell Biology*. Boston: Benjamin Cummings / Pearson, 2011.

Sickle Cell Variants

HbSC

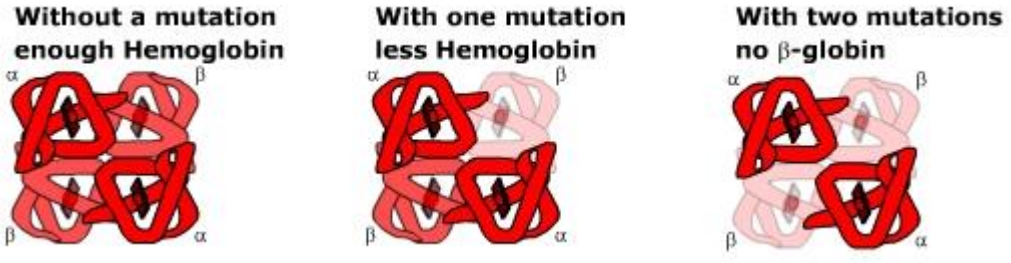
Heterozygous variant; Similar symptoms to HbS, but less anemia

HbSβ⁺

Beta-thalassemia carrier with one mutation of beta globin gene

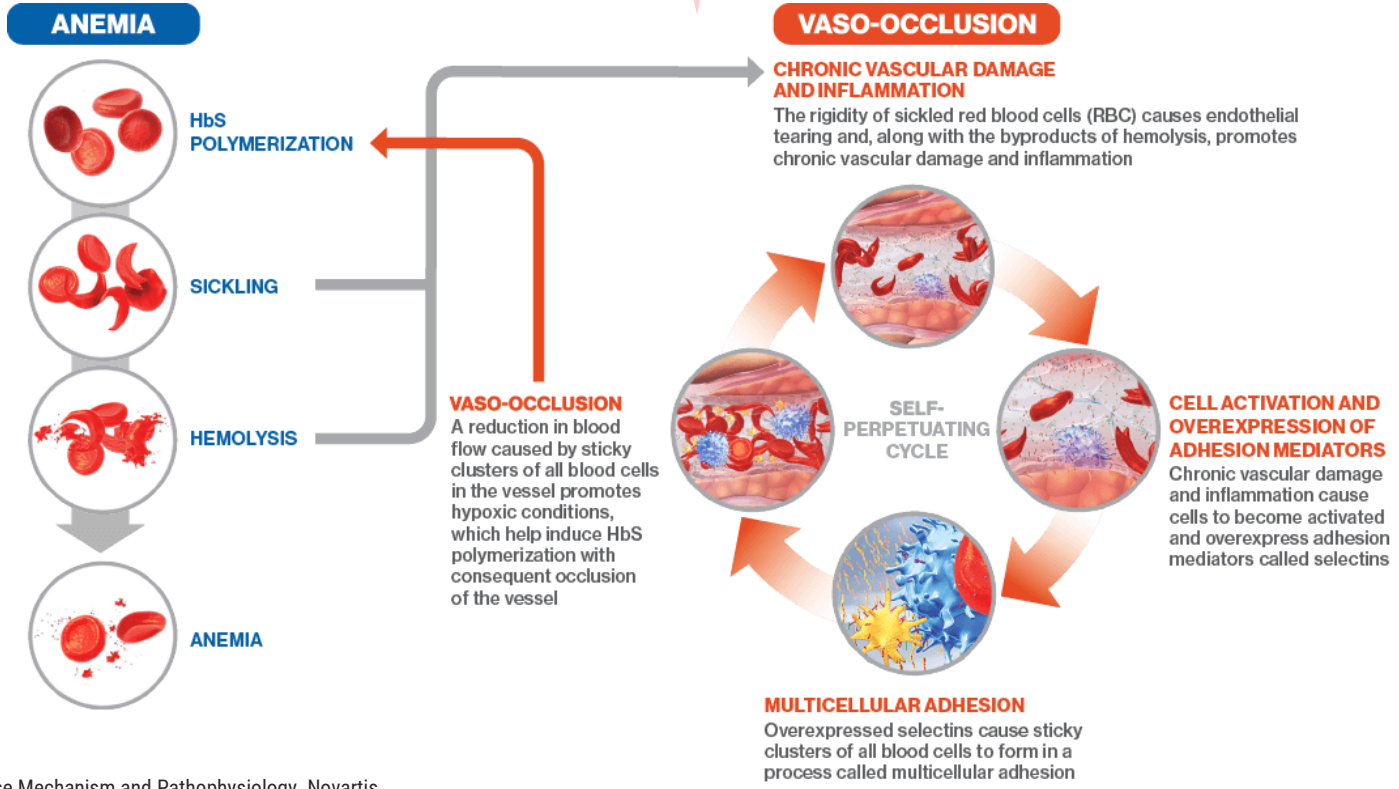
HbSβ°

Major beta thalassemia with two mutations of beta globin gene; Results in severe anemia



Piel FB, et al. NEJM 2017; 376:1561-1573
Thalassemia [Internet]. Thalassemia & Sickle Cell Society of NSW; 2020

Pathophysiology



Source: Sickle Cell Disease Mechanism and Pathophysiology. Novartis Pharmaceuticals Corporation; 2021 [cited 2022Mar20].

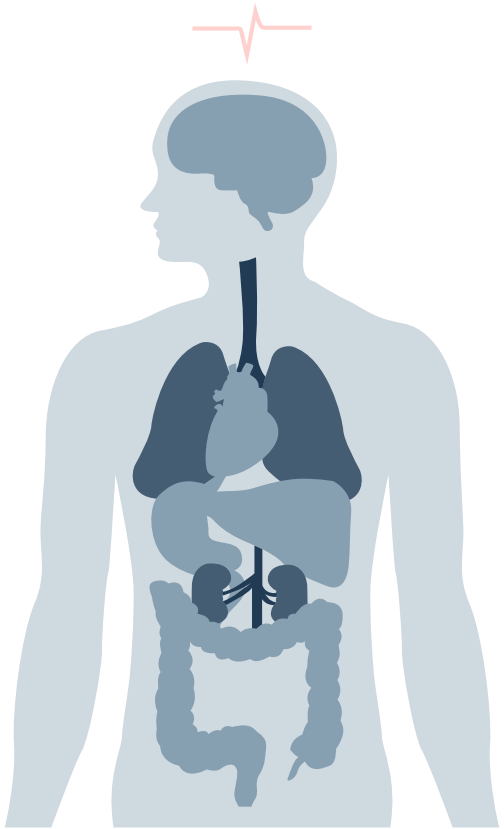
Clinical Manifestations

Cardiothoracic System

- **Acute Chest Syndrome**
- Sudden death
- Dysrhythmias

Nervous System

- **Acute Vaso-occlusive Pain Crises (VOC)**
- **Chronic Pain**
- **Acute Ischemic Stroke**
- Cognitive Impairment
- Hemorrhagic Stroke
- Proliferative Retinopathy



Reticuloendothelial System

- **Anemia**
- **Hemolysis**
- **Venous Thromboembolism**
- Splenic Sequestration
- Functional Hyposplenism

Other

- **Acute and Chronic Infections**
- Avascular necrosis
- Priapism
- Hepatopathy
- Renal Failure/Acute Kidney Injury
- Leg ulceration

Houwing ME, et al. Blood Reviews 2019;37:100580

Bolded = Most common clinical manifestations

Infection Risk Pathophysiology

Patients with SCD are more likely to experience functional asplenia due to persistent sequestration of RBCs in the spleen. With reduced function of the spleen, patients are at risk for:

Pathogens of concern include Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Salmonellae

Yawn BP, et al. NHLBI. 2014 Sep.

Screening and Diagnosis

Methods for diagnosis of SCD can vary with the age of the patient

- Prenatal hemaglobinopathy testing
- Newborn Screening Programs (selective or universal)
- High performance liquid chromatography (HPLC)
- Point of Care diagnostics (Sickle SCAN, HemoTypeSC)
- DNA based testing (to confirm diagnosis)

Goals of Therapy

- Improve quality of life
- Management of chronic pain
- Management of vaso-occlusive crises
- Management and prevention of complications
- Prevention of Infection
- Prevention of stroke
- Prevent mortality

Knowledge Check – Pharmacy Technician

Which of the following acute complications is the least common?

a. Vaso-occlusive crises
b. Bacterial infections
c. Stroke
d. Acute Kidney Injury

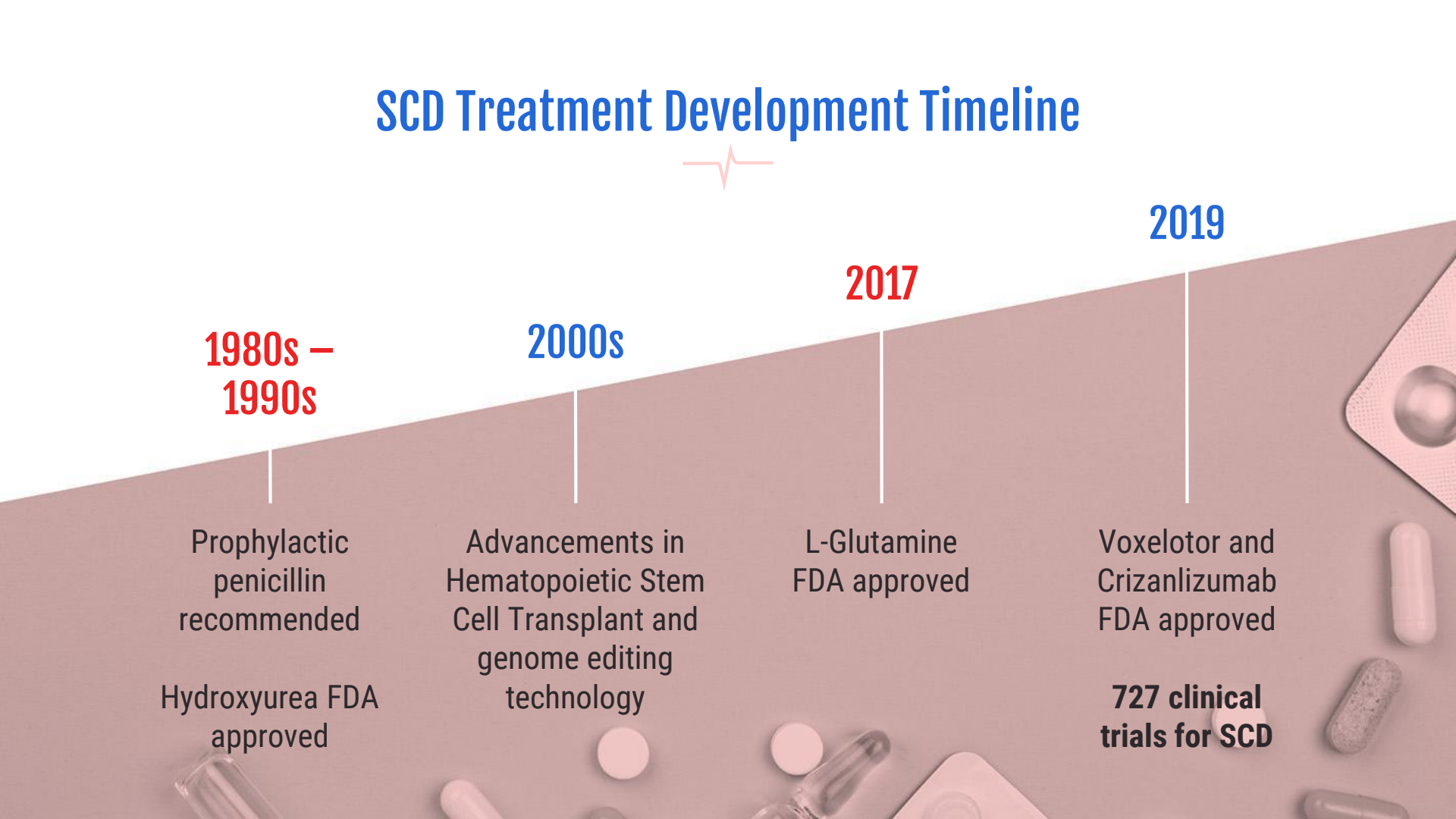
Knowledge Check – Pharmacy Technician

Which of the following acute complications is the least common?

a. Vaso-occlusive crises
b. Bacterial infections
c. Stroke
d. Acute Kidney Injury

Review of Treatments – Chronic Management

SCD Treatment Development Timeline



1980s – 1990s

Prophylactic penicillin recommended

Hydroxyurea FDA approved

2000s

Advancements in Hematopoietic Stem Cell Transplant and genome editing technology

2017

L-Glutamine FDA approved

2019

Voxelotor and Crizanlizumab FDA approved

727 clinical trials for SCD

Chronic Management of Sickle Cell Disease

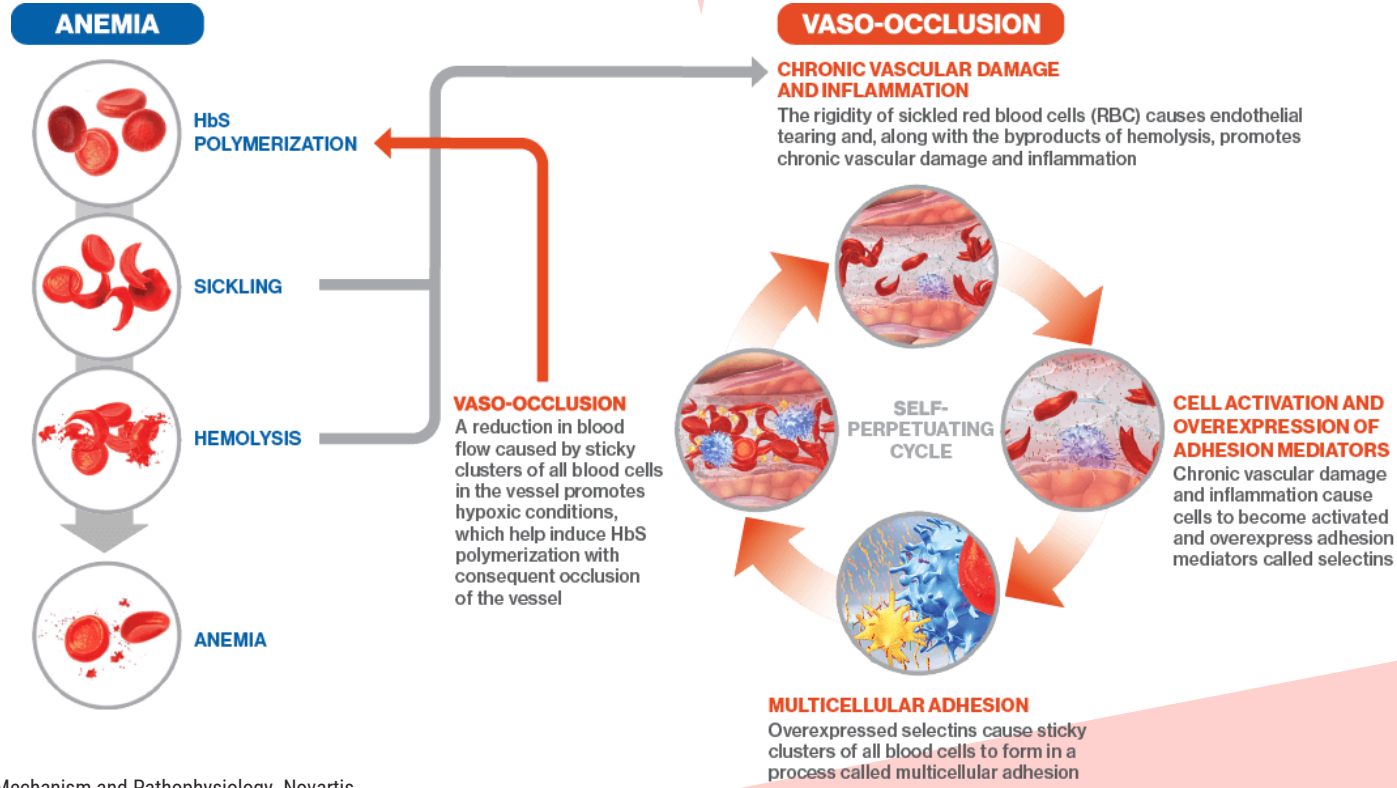
Targeting HbS Polymerization:
Hydroxyurea
Voxelotor

Targeting Inflammation:
Pending FDA Approval

Targeting Vaso-occlusion:
L-Glutamine
Crizanlizumab

Targeting Genotype and Other:
Hematopoietic Stem Cell Transplant (HSCT)
Folic Acid

Pathophysiology



Source: Sickle Cell Disease Mechanism and Pathophysiology. Novartis Pharmaceuticals Corporation; 2021 [cited 2022Mar20].

Hydroxyurea

Mechanism of Action (MOA): Ribonucleotide diphosphate reductase inhibitor that increases fetal hemoglobin levels; Partially successful as homogenous HbF distribution is dependent on genotypic variants

2014 NIH Expert Panel Report recommends to initiate hydroxyurea for the following (Strong Recommendation, High–Moderate Quality Evidence)**:**

- Adults with sickle cell anemia (SCA) who have ≥ 3 moderate to severe pain crises associated with SCD during a 12-month period
- Adults with sickle cell associated pain that interferes with daily activities and quality of life
- Adults with SCA with a history of severe or recurrent acute chest syndrome (ACS)
- Infants 9 months of age and older, in children, and adolescents with SCA regardless of clinical severity to reduce complications such as pain, dactylitis, ACS, and anemia

Yawn BP, et al. NHLBI. 2014 Sep.
Hydroxyurea [monograph]. Lexicomp Online [online database]. Hudson, OH: Lexi-Comp 2022.

Hydroxyurea

Hydroxyurea	
Indication	To reduce the frequency of painful crises associated with sickle cell anemia • DROXIA- Adults • SIKLOS – Age ≥ 2
Dosage Forms	Tablets/Capsules
Dosing	15 mg/kg once daily, rounding up to nearest 500 mg Max Daily Dose – 35 mg/kg/day
Administration	Administer at the same time each day Impervious gloves should be worn when handling medication
CI/Warning	Bone marrow suppression, hypersensitivity, embryo-fetal toxicity, vasculitic toxicities
SE	Macrocytosis, neutropenia, eczema, bacterial infection, headache
Monitoring	Neutrophils, Hemoglobin, Reticulocytes, Mean Corpuscular Volume (MCV), Platelets, Renal and Liver Function Tests
Cost (WAC)	DROXIA 200 mg (60 each) - $45 SIKLOS 100 mg (60 each) - $300 Generic 500 mg (100 each) - $97

Yawn BP, et al. NHLBI. 2014 Sep.
Hydroxyurea [monograph]. Lexicomp Online [online database]. Hudson, OH: Lexi-Comp 2022.

WAC = Wholesale Acquisition Cost

Voxelotor

MOA: Binds to N-terminus on alpha subunit of HbS to increase oxygen affinity, inhibit HbS polymerization, and reduce likelihood of sickling

FDA approved in 2019

OXYBRYTA (voxelotor)	
Indication	Treatment of sickle cell disease in adults and pediatric patients ≥ 4 years of age
Dosage Forms	Tablets/Tablets for oral solution; No generic available
Dosing	1.5 grams once daily Dose adjustments for severe hepatic impairment
Administration	Swallow whole; Do not cut, crush, or chew tablets Can be administered with or without hydroxyurea therapy
CI/Warning	Hepatic impairment, hypersensitivity, laboratory test interference (chromatography)
SE	Rash, abdominal pain, nausea, diarrhea, headache, fever
Monitoring	Liver function tests
Cost (WAC)	500 mg (90 tablets) - $10,417 Estimated Yearly Cost - $84,000

ASH Clinical News; 2020
OXBRYTA (voxelotor) [package insert]. San Francisco, CA: Global Blood Therapeutics, Inc; 2019

WAC = Wholesale Acquisition Cost

Voxelotor Efficacy – Phase 3 HOPE Trial

HOPE: Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (2019)	
Objective	To evaluate the efficacy and safety of voxelotor in adolescents and adults with sickle cell disease
Design	• Multicenter, phase 3, double-blind, randomized, placebo-controlled trial • Studied two doses of voxelotor – 1500 mg once daily and 900 mg once daily • Duration – 24 weeks
Inclusion Criteria	• Age 12-65 • Confirmed sickle cell disease • Experienced 1-10 vaso-occlusive crises in past 12 months • Hemoglobin level between 5.5 and 10.5 g/dL during screening
Endpoints	Primary • Percentage of patients who had a hemoglobin response (increase of more than 1 g/dL from baseline at week 24) Secondary • Change in hemoglobin level from baseline to week 24 • Laboratory markers associated with hemolysis (indirect bilirubin level, absolute reticulocyte level, and percentage of reticulocytes, and lactate dehydrogenase level)

Vichinsky E, et al. NEJM 2019; 381:509-519

Voxelotor Efficacy – Phase 3 HOPE Trial

HOPE: Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (2019)	
Results	**N= 274;** 1:1:1 randomization to voxelotor 1,500 mg, 900 mg, or placebo; Intent-to-Treat analysis Majority of patients at baseline had sickle cell anemia (Homozygous hemoglobin S) 2/3 patients were receiving hydroxyurea therapy at baseline **Primary Endpoint: % Patients with a hemoglobin response at 24 weeks compared to baseline** • 1,500 mg group: 51%; 95% CI 41-61; p<0.001 • 900 mg group: 33%; 95% CI 23-42 • Placebo: 7%; 95% CI 1-12 **Secondary Endpoints: 1,500 mg group vs. placebo** • Change in indirect bilirubin level: -29.1% vs. -3.2%, p<0.001 • Change in percentage of reticulocytes: -19.9% vs. 4.5%, p<0.001
Conclusion	Voxelotor significantly increased hemoglobin level and reduced markers of hemolysis. The findings are consistent with inhibition of HbS polymerization and indicated disease modifying potential

Vichinsky E, et al. NEJM 2019; 381:509-519

New Therapies Targeting HbS Polymerization

Study	MOA	Objective	Intervention	Outcomes
Sanguinate **NCT02411708** Single-blinded randomized, placebo-controlled study	Bovine PEGlyated hemoglobin product targeting carbon monoxide delivery	Determine the safety and efficacy of sanguinate on sickle cell disease patients experiencing a vaso-occlusive crisis	Single infusion of sanguinate 320 mg/kg or Placebo 2 hour in-clinic infusion	Primary – Time to readiness for discharge from ambulatory site
Decitabine **NCT01685515** Single-blinded, randomized, placebo-controlled study	5-azacytidine analog that inhibits DNA Methylransferase 1 to reactivate HbF	Determine if oral tetrahydrouridine and decitabine can increase HbF and be less cytotoxic than current standard of care	Oral Decitabine & Oral Tetrahydrouridine (THU) or Placebo Given for 2 consecutive days over 8 weeks	Primary – Non-hematologic toxicities

Salinas G, et al. Frontiers in Physiology, May 2020; 11:435

Knowledge Check – Pharmacist/Nurses

1. **Which of the following is a pertinent laboratory value to monitor for hydroxyurea therapy?**
   a. Mean Corpuscular Value (MCV)
   b. White Blood Cell Count (WBC)
   c. Platelet Count
   d. All of the above

Knowledge Check Answer – Pharmacist/Nurses

1. **Which of the following is a pertinent laboratory value to monitor for hydroxyurea therapy?**
   a. Mean Corpuscular Value (MCV)
   b. White Blood Cell Count (WBC)
   c. Platelet Count
   d. All of the above

Knowledge Check – Pharmacy Technician

True or False: Voxelotor must be infused over 30 minutes with a 0.2 micron in-line filter.

a. True
b. False

Knowledge Check Answer – Pharmacy Technician

True or False: Voxelotor must be infused over 30 minutes with a 0.2 micron in-line filter.

a. True

b. False

Targeting Vaso-occlusion – L-Glutamine

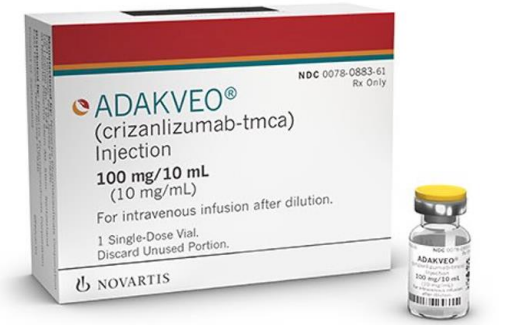
MOA: Repletion of glutamine to reduce red blood cell damage and adhesion

ENDARI (L-Glutamine)	
Indication	To reduce the acute complications of sickle cell disease in adults and pediatric patients 5 years and older
Dosage Forms	Oral powder
Dosing	<30 kg: 5 g (1 packet) twice daily 30-65 kg: 10 g (2 packets) twice daily >65 kg: 15 g (3 packets) twice daily
Administration	Mix in 8 oz. of cold or room temperature beverage (water, milk, apple juice) or 4 to 6 oz. of food (applesauce, yogurt) prior to administration
CI/Warning	None
SE	Constipation, nausea, headache, abdominal pain, cough, pain in extremities, back pain, chest pain
Monitoring	Renal function tests, Liver function tests
Cost (WAC)	5 grams per packet (60 each) - $1,230 Estimated Yearly Cost - $24,000

ASH Clinical News; 2020
ENDARI (L-Glutamine Oral Powder) [package insert]. Torrence, CA: Emmaus Medical, Inc; 2017

WAC = Wholesale Acquisition Cost

Crizanlizumab



100 mg/10 mL vial

MOA: Humanized IgG2 kappa monoclonal antibody that binds to P-selectin on endothelial cell surface to block interactions with platelets, red blood cells, and leukocytes

FDA approved in 2019

ADAKVEO (Crizanlizumab)	
Indication	To reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease
Dosage Forms	Single dose vial for injection
Dosing	5 mg/kg via IV infusion on Week 0, Week 2, and every 4 weeks thereafter Use actual body weight for dose calculation
Administration	May be given with or without hydroxyurea Dilute with 0.9% sodium chloride USP or 5% dextrose injection USP Administer over 30 minutes via IV line which must contain a sterile, nonpyrogenic 0.2-micron inline filter
CI/Warning	Infusion related reactions, interference with automated platelet counts (platelet clumping)
SE	Nausea, arthralgia, back pain, and pyrexia
Monitoring	Infusion related reactions (fever, chills, dyspnea, tachycardia)
Cost (WAC)	10 mg/1mL (10 mL vial) - $2,411 Estimated Yearly Cost - $88,000 - $113,000

ASH Clinical News; 2020
ADAKVEO (crizanlizumab-tmca) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2019

WAC = Wholesale Acquisition Cost

Crizanlizumab Efficacy – Phase 2 SUSTAIN Trial

Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises (2017)	
Objective	To determine the efficacy and safety of crizanlizumab with or without hydroxyurea therapy on rate of sickle – cell related crises
Design	• Multicenter, randomized, placebo-controlled, double-blind study • Studied two doses of crizanlizumab – 2.5 mg/kg (low dose); 5 mg/kg (high dose); placebo • Subject receives 2 doses2 weeks apart then each dose every 4 weeks thereafter • Duration – 52 weeks with 6 week follow up phase
Inclusion Criteria	• Age 16-65 • Confirmed sickle cell disease • Experienced 2-10 sickle-cell related pain crises in past 12 months • EXCLUDED – Patients undergoing long term red cell transfusion therapy
Endpoints	**Primary** • Annual rate of sickle cell related pain crises **Secondary** • Annual rate of days hospitalized • Times to first and second crises • Annual rate of acute chest syndrome

Ataga K et al. NEJM 2017; 376:429-439

Crizanlizumab Efficacy – Phase 2 SUSTAIN Trial

Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises (2017)	
Results	**N= 198;** 1:1:1 randomization to crizanlizumab 2.5 mg/kg, 5 mg/kg, or placebo; Intent-to-Treat analysis Majority of patients at baseline had sickle cell anemia (Homozygous hemoglobin S) 2/3 patients were receiving hydroxyurea therapy at baseline **Primary Endpoint: Median rate of crises per year** • High dose 5 mg/kg: 1.63 (IQR 0.00-3.97) p<0.01 • Low dose 2.5 mg/kg: 2.01 (IQR 1.00-1.98) p<0.18 • Placebo: 2.98 (1.25-5.87) **Secondary Endpoints: High dose 5 mg/kg vs. Placebo** • Annual rate of days hospitalized: 4.00 vs 6.87 days, p=0.45 • Times to first and second crises: 4.07 vs. 1.38 months, p=0.001
Conclusion	Crizanlizumab therapy resulted in significantly lower rates of sickle cell-related pain crises than placebo

Ataga K et al. NEJM 2017; 376:429-439

New Therapies Targeting Vaso-occlusion

Study	MOA	Objective	Intervention	Outcomes
Sevuparin **NCT02515838** Multicenter, double blinded, randomized, placebo-controlled study (Phase 2)	Heparin derivate polysaccharide that binds to P and L selectins to inhibit sickle RBC adhesion and TNF induced vaso-occlusion	Determine if sepuvarin could shorten vaso-occlusive crisis duration in hospitalized patients with sickle cell disease	Sevuparin 18 mg/kg IV or Placebo Treated for 2-7 days until VOC crisis resolution	Primary – Time to VOC resolution defined as freedom from parenteral opioid use

Results:

N = 144

Primary endpoint:

- 100.4 hours vs. 86.4 hours (HR 0.89; p=0.55)

Conclusions:

Sevuparin, as a selectin adhesion inhibitor, was not efficacious in treating acute VOC in sickle cell disease. Further studies are needed to clarify the how selectin-mediated adhesion affects vaso-occlusive pathophysiology.

Salinas G, et al. Frontiers in Physiology, May 2020; 11:435
Biemond BJ, et al. Lancet Haematol. 2021 May;8(5):e334-e343.

New Studies for Therapies Targeting Inflammation

Therapy	Objective	Outcomes	Status
Simvastatin NCT03599609 Open Label, Single Group Study	To study the effects of simvastatin administration on CNS structural and functional vascular changes in adults with SCD	**Primary** – Stroke prevention **Secondary** – Improvement in hemodynamic parameters in MRI	Results Pending
N-acetylcysteine (NAC) NCT01800526 Open Label, Non-Randomized Pilot Study	To study the effects of NAC on von Willebrand factor (VWF) activity in patients with SCD	**Primary** – Laboratory measures of VWF activity **Secondary** – Laboratory measures of RBC hemolysis and oxidation; Adverse events; Pain during VOC; Use of pain medications; Hospital length of stay	Results Pending

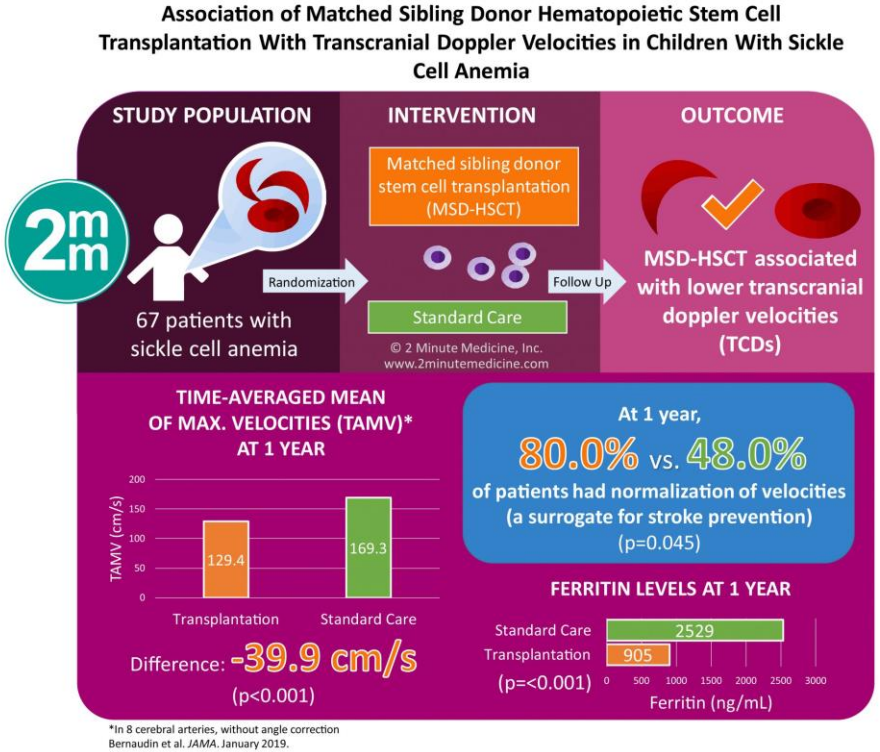
Salinas G, et al. Frontiers in Physiology, May 2020; 11:435

Targeting Genotype – Hematopoietic Stem Cell Transplant

- Potential curative therapy for SCD
- Limited by lack of suitable human leukocyte antigen (HLA) matched sibling donors
- Limited to high-resourced settings/middle income nations
- Complications such as graft versus host disease (GVHD), treatment toxicities, and graft rejection risk morbidity and mortality

American Society of Hematology 2021 Guidelines for Sickle Cell Disease – Stem Cell Transplantation

- Recommendations involve donor considerations, stem cell source, conditioning, patient age, and SCD complications (such as stroke risk)



Kanter J, et al. Blood Adv 2021; 5 (18): 3668–3689.

Other Chronic Management – Folic Acid

MOA: Synthetic water soluble B vitamin used for nucleoprotein synthesis to maintain RBC production

- Requires supplementation from nutrition
- Used for SCD patients who may be at risk for folate deficiency due to high RBC turnover
- Unclear benefit in influencing sickle cell severity

Folic Acid	
Dosage Forms	Tablet, Capsule
Dosing	Folate deficiency – 1 to 5 mg by mouth daily
Administration	Can take with or without food, however administration with food improves bioavailability
CI/Warning	Hypersensitivity, Can mask B12 deficiencies which can lead to neurological manifestations
SE	Flushing, malaise
Drug Interactions	Methotrexate – folate antagonist Phenytoin, carbamazepine, valproate – Can reduce serum folate levels
Monitoring	Can utilize serum folate levels or erythrocyte folate concentrations
Cost (WAC)	1 mg tablets (each) - $0.01 to $0.08

WAC = Wholesale Acquisition Cost

NIH Office of Dietary Supplements. U.S. Department of Health and Human Services; 2021

Knowledge Check– Pharmacist/Nurses

Which of the following best described the mechanism of action of crizanlizumab?

a. P-selectin blocker
b. Ribonucleotide reductase inhibitor
c. Hemoglobin S polymerization inhibitor
d. Reticulocyte production inhibitor

Knowledge Check Answer– Pharmacist/Nurses

Which of the following best described the mechanism of action of crizanlizumab?

a. **P-selectin blocker**
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c. Hemoglobin S polymerization inhibitor
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Knowledge Check – Pharmacist/Nurses

Which of the following new sickle cell disease therapies are <u>correctly matched</u> to their studied clinical outcome?

a. Sanguinate – Laboratory measures of VWF activity
b. Decitabine – Stroke prevention
c. Sevuparin – Time to vaso-occlusive crisis resolution
d. Simvastatin – Non-hematologic toxicities

Knowledge Check Answer – Pharmacist/Nurses

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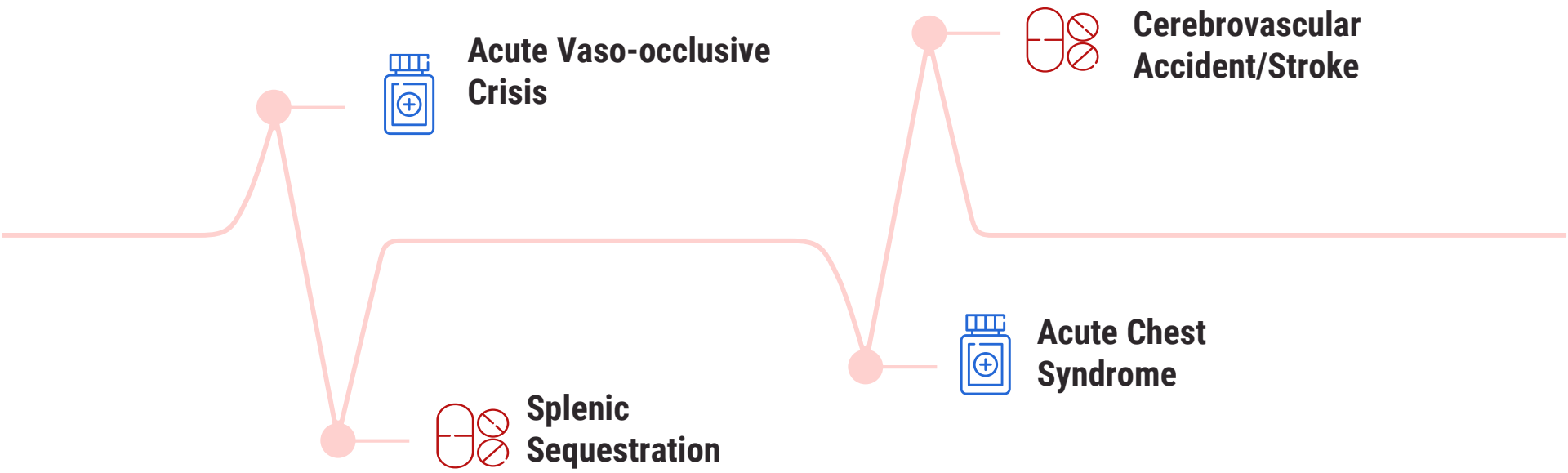
b. Decitabine – Stroke prevention
c. **Sepuvarin – Time to vaso-occlusive crisis resolution**
d. Simvastatin – Non-hematologic toxicities

Review of Treatments – Acute Management

Considerations for Acute SCD Management



Acute Vaso-occlusive Crisis

Cerebrovascular Accident/Stroke

Acute Chest Syndrome

Splenic Sequestration

Acute Vaso-occlusive Crises

Most common complication of SCD, often involving severe pain

Effective triaging, evaluation, and administration of analgesics are necessary to decrease risk of ACS and mitigate symptoms

Patient Assessment involves:

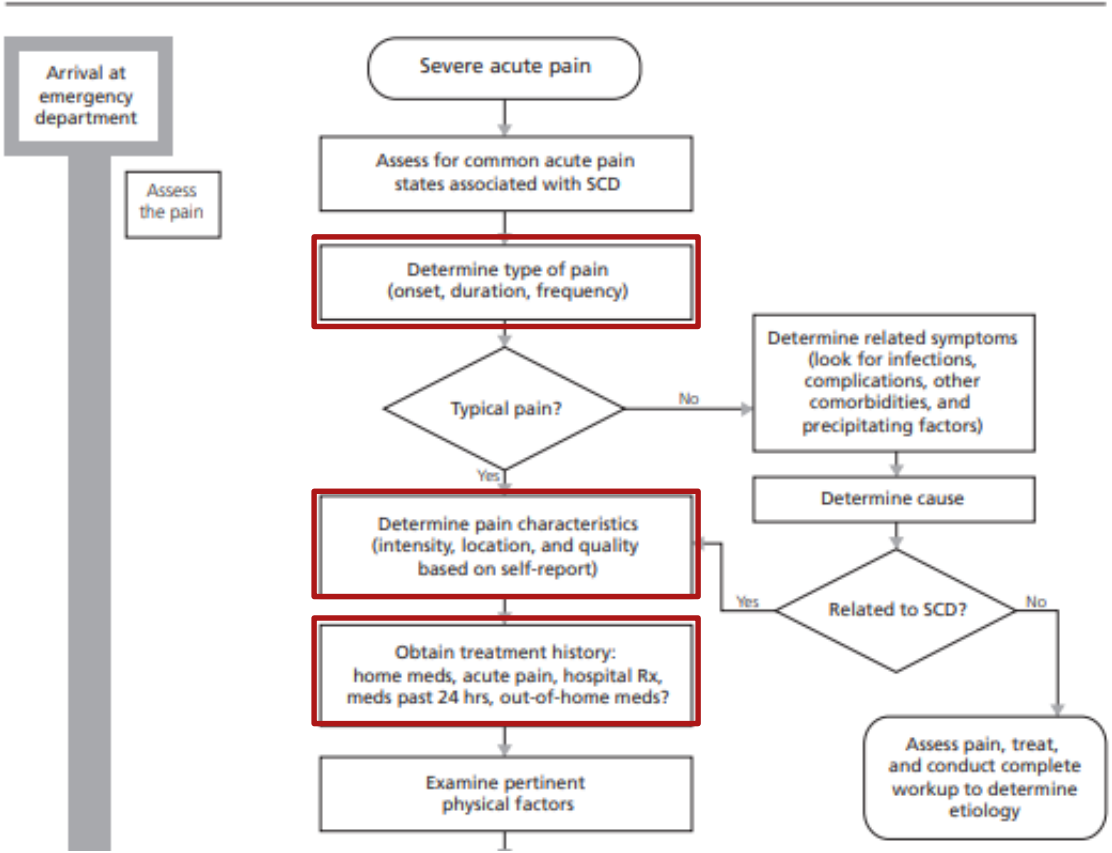
- Thorough pain assessment utilizing validated pain scales
- Comprehensive medication reconciliation of patient's pain medication history
- Frequent reassessment to gauge response to therapy

2014 NIH Expert Panel Report Recommends the Following for Managing VOCs:

- Continue treatment with NSAIDs in adults and children with mild to moderate pain in those who report relief with NSAIDs (Mod, Low Quality Evidence)
- Rapidly initiate treatment with parenteral opioids in adults and children reporting severe pain (Strong, High-Quality Evidence)
- Initiate around the clock opioid administration by patient-controlled analgesia (PCA) compared to as requested administration in adults and children with severe pain (Mod, Low Quality Evidence)
- In euvolemic adults and children with SCD and a VOC who are unable to drink fluids, provide intravenous hydration at no more than maintenance rate to avoid over-hydration. (Consensus Statement)

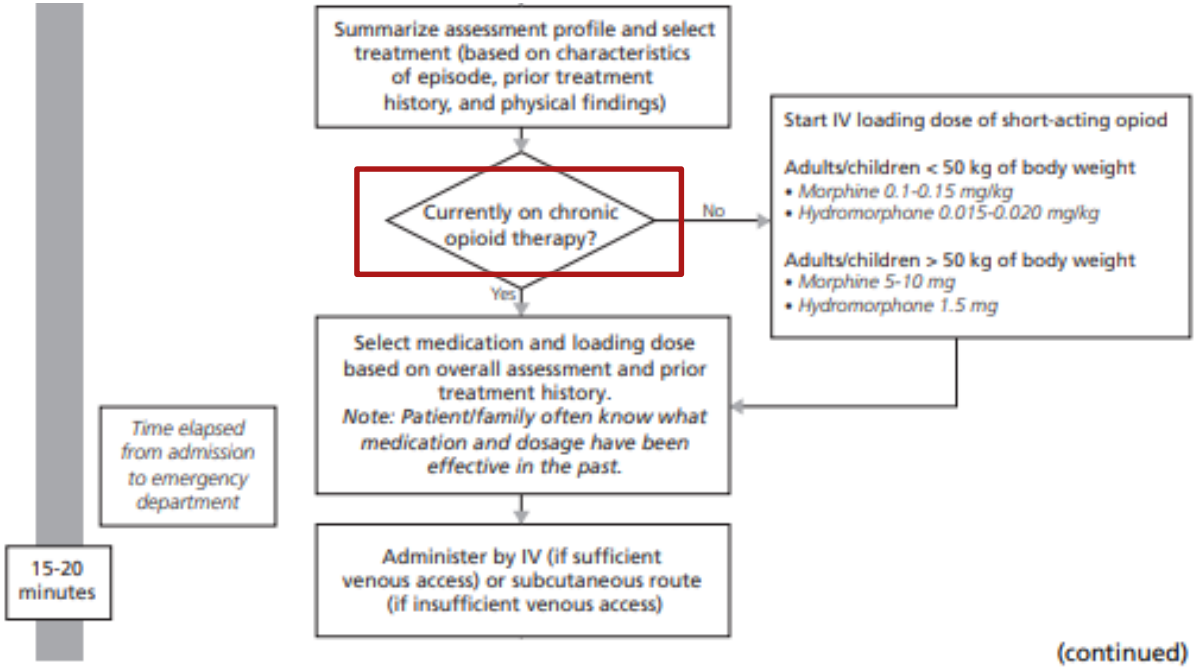
Yawn BP, et al. NHLBI. 2014 Sep.

Acute Vaso-occlusive Crises



Source: NIH Pub. No. 04-2117

Acute Vaso-occlusive Crises



(continued)

Source: NIH Pub. No. 04-2117

Acute Splenic Sequestration

Acute Splenic Sequestration – Acute splenic enlargement with a >20% fall in hemoglobin level from baseline

Causes:
- Idiopathic

Symptoms:
- Enlarged mass in left upper quadrant
- Abdominal pain
- Distension
- Hypovolemia
- Hemodynamic changes

2014 NIH Expert Panel Report Recommends the Following for Managing Splenic Sequestration:

- Immediate IV fluid resuscitation in patients with hypovolemic presentation
- Consider transfusions in these patients with severe anemia to increase hemoglobin to a stable level
- Consult an SCD expert to address the performance and timing of splenectomy in patients with recurrent sequestration or symptomatic hypersplenism

Yawn BP, et al. NHLBI. 2014 Sep.
Houwing ME, et al. Blood Reviews 2019;37:100580

Cerebrovascular Accident/Stroke

- Signs and symptoms of stroke similar to patients without SCD
- Assessed inpatient via transcranial Doppler ultrasound screening, MRI, and MRA
- Cumulative risk for an over stroke is 11% by age 20
- Silent cerebral infarctions occur in approximately ¼ of children before the age of 6
- Silent cerebral infarctions can present with nonfocal signs such as developmental delays or declining school/work performance

2014 NIH Expert Panel Report Recommends the Following for CVA Management:

- For acute strokes confirmed by neuroimaging, perform exchange transfusion (Consensus Statement)
- Initiate monthly regular transfusion therapy program to prevent recurrence (Moderate, Low-Quality Evidence)
- Initiate hydroxyurea therapy in patients where it is not possible to initiate a transfusion program (Moderate, Low-Quality Evidence)

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Houwing ME, et al. Blood Reviews 2019;37:100580

Acute Chest Syndrome

Symptoms and Presentation Include:

- Cough
- Shortness of Breath
- Retractions
- Rales
- Pulmonary infiltrate on chest x-ray
- Decline in hemoglobin concentrations

Etiology:

- Infection (viral, bacterial, chlamydia, Mycoplasma)
- Bone marrow embolism
- Intrapulmonary sickled cell aggregates
- Atelectasis
- Pulmonary edema

2014 NIH Expert Panel Report Recommends the Following for ACS Management:

- Initiate antibiotics that cover pathogens of concern with an IV cephalosporin and oral macrolide, adjusting based on bacterial cultures
- Maintain O2 saturation >95%
- Give simple blood transfusion (10 mL/kg of RBC) to improve oxygen carrying capacity in patients with symptomatic ACS and whose hemoglobin concertation is >1.0 g/dL below baseline
- Perform urgent exchange transfusion when ACS rapidly progresses with O2 <90% despite supplementation, increasing respiratory distress, progressive pulmonary infiltrates, or decline in hemoglobin concentration despite simple transfusion

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Houwing ME, et al. Blood Reviews 2019;37:100580

Knowledge Check – Pharmacy Technician

Which class of medications are recommended for treating mild to moderate pain during vaso-occlusive crises?

a. Opioids
b. NSAIDs
c. Benzodiazepines
d. Muscle Relaxants

Knowledge Check Answer– Pharmacy Technician

Which class of medications are recommended for treating mild to moderate pain during vaso-occlusive crises?

a. Opioids

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c. Benzodiazepines

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Review of Treatments – Preventative Care

Immunizations, Infection Prophylaxis, and Stroke Screening

Immunizations

Goals of Care: Prevent infections due to invasive pneumococcal disease and prevent contraction of hepatitis C due to frequent transfusions

Population	2022 CDC/ACIP Recommendations
Children 2-18 years with SCD/functional or anatomic asplenia with no history of either PCV13 or PPSV23	1 dose PCV13, 2 doses PPSV23 (PPSV23 Dose 1 administered 8 weeks after any prior PCV13 and Dose 2 at least 5 years after dose 1 of PPSV23)
Adults ≥ 19 who are pneumococcal vaccine naive but have functional/anatomic asplenia	1 dose PCV15 or 1 dose PCV20 If PCV15 used → Follow with PPSV23 at least 1 year after dose with minimum of 8 weeks between
Adults ≥ 19 with previous PPSV23 vaccination and functional/anatomic asplenia who have received ≥ 1 doses of PPSV23	Adults may either receive a PCV15 or PCV20 ≥ 1 year after their last PPSV23 dose. If PCV15 is used, it does not need to be followed by another dose of PPSV23

2014 NIH Expert Panel Report Recommends the Following for HCV Screening:

- Screen for HCV infection in persons at high risk for infections and offer 1 time screening for adults born between 1945 and 1965

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Houwing ME, et al. Blood Reviews 2019;37:100580
Kobayashi M, et al. MMWR Morb Mortal Wkly Rep 2022;71:109–117

Immunizations

Goals of Care: Prevent infections due to other pathogens of concern in sickle cell disease

Vaccine	2022 CDC Recommendation for Ages 19 and Older	2022 CDC Recommendation for Ages 18 and Younger
Meningococcal Serotype A, C, W, Y	Menactra, Menveo, or MenQuadfi 2-dose series at least 8 weeks apart and revaccinate every 5 years if risk remains	Menveo • Dose 1 at age less than 24 months: Dose series varies; Refer to CDC immunization schedule • Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart Menactra • Age 9–23 months: Not recommended • Age 24 months or older: 2-dose series at least 8 weeks apart MenQuadfi • Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
Meningococcal Serotype B	• Bexsero: 2-dose series at least 1 month apart • Trumenba: 3-dose series at 0, 1–2, 6 months	Minimum age: 10 years • Bexsero: 2-dose series at least 1 month apart • Trumenba: 3-dose series at 0, 1–2, 6 months
Haemophilus Influenzae	• No previous Hib vaccine: 1 dose • Elective splenectomy: 1 dose, preferably at least 14 days before splenectomy	Vaccinate according to the routine recommendation with 2- or 3-dose primary series at 2 and 4 months, or at 2, 4, and 6 months, Age 12–59 months • Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart • 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose Unvaccinated* persons age 5 years or older - 1 dose Elective splenectomy and unvaccinated* persons age 15 months or older - 1 dose (preferably at least 14 days before procedure)

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Houwing ME, et al. Blood Reviews 2019;37:100580
Kobayashi M, et al. MMWR Morb Mortal Wkly Rep 2022;71:109–117

Infection Prophylaxis

Goals of Care: Prevent infections due to invasive pneumococcal disease

2014 NIH Expert Panel Report Recommends the Following for Penicillin Prophylaxis:

- Administer oral penicillin prophylaxis twice daily until age of 5 in all children with HbSS (125 mg for children < 3 years; 250 mg for those age ≥ 3)
- Discontinue prophylactic PCN in children with HbSS at age 5 years unless they have had a splenectomy or invasive pneumococcal infection → Ensure completion of pneumococcal vaccination series before discontinuation
- Ensure persons of all ages with SCD have been vaccinated against Streptococcus Pneumoniae

Yawn BP, et al. NHLBI. 2014 Sep.
Houwing ME, et al. Blood Reviews 2019;37:100580

Stroke Screening

Goals of Care: Regular neuroimaging monitoring for early intervention of cerebral infarction

2014 NIH Expert Panel Report Recommends the Following for Stroke Screening:

- In patients with SCA, screen annually starting at age 2 until at least age 16 with Transcranial Doppler (TCD), assessing high maximal mean velocity cerebral artery flow and other parameters
- In children with conditional (170-199 cm/s) or elevated (>200 cm/s) TCD results, refer to a specialist with expertise in long term transfusions therapy aimed at preventing stroke
- In children with other genotypes other than SCA (thalessemias) → Do not perform screening with TCD
- In asymptomatic children, do not perform screening with MRI or CT
- In asymptomatic adults, do not perform screening with MRI, CT, or TCD

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Houwing ME, et al. Blood Reviews 2019;37:100580

Conclusion

- Sickle cell disease is a complex genetic condition with disease modifying factors that complicate management
- Pharmacotherapy for SCD continues to advance as new treatments are more targeted towards SCD pathophysiology

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THANK YOU

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