



Brave New World: Guidelines and Treatment Strategies for Sickle Cell Disease

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Disclosure

- Dr. Krichbaum has nothing to disclose
- Dr. Miransky has nothing to disclose

Learning Objectives

- Summarize the healthcare disparities in accessing care for patients with sickle cell disease (SCD)
- Describe strategies to effectively manage acute and chronic pain in patients with SCD
- Review the recently published guidelines for SCD treatment and management
- Discuss the newly FDA-approved and emerging treatments for adult and pediatric patients with SCD
- Recognize effective communication techniques when diagnosing, treating, and managing patients with SCD

Hugs and Drugs

- When you see the “Hugs & Drugs” logo:



Indicates speakers' practice recommendations in the absence of a Guideline recommendation

Pretest Question #1

- Which of the following medications is associated with decreased mortality in sickle cell disease?
 - A. Hydroxyurea
 - B. L-glutamine
 - C. Voxelotor
 - D. Crizanlizumab

Pretest Question #2

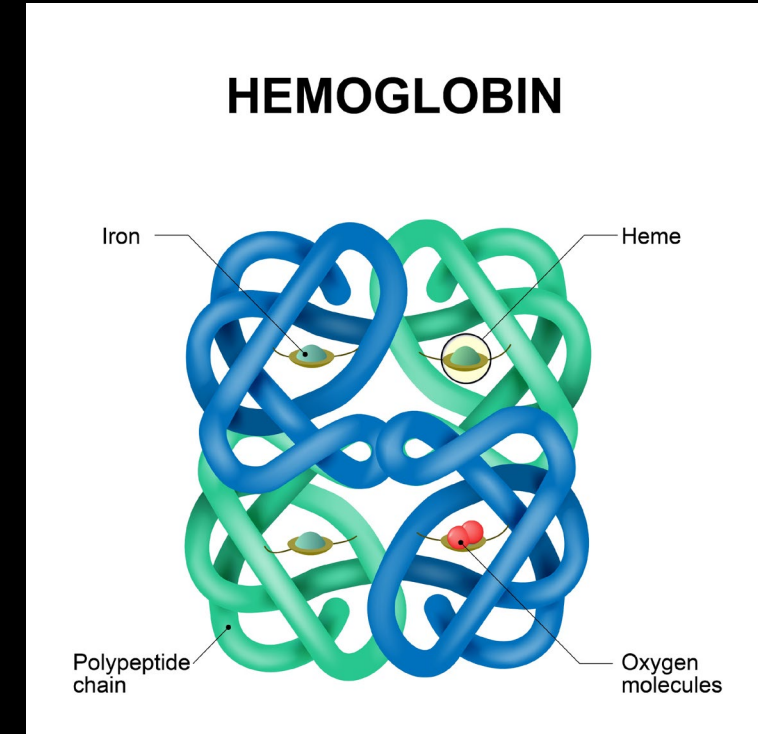
- DS is a 15 y/o AAF with HbSS disease with avascular necrosis of the right hip, well-known to your service. She is readmitted for vaso-occlusive crisis. Her home medications include morphine sulfate extended release 60mg PO q 12h and morphine sulfate immediate release 15mg PO q 4H PRN breakthrough pain. She averages 3 doses/day when she has a pain flare. Which of the following analgesic recommendations is the best choice for this patient?
 - A. Morphine sulfate extended release 60mg PO q12h and ketorolac 30mg IV q6H x 5 days
 - B. Morphine sulfate extended release 60mg PO q12h and morphine 2mg IV q 3h prn breakthrough pain
 - C. Morphine sulfate extended release 60mg PO q12h and morphine 4mg IV q 3h prn breakthrough pain
 - D. Morphine sulfate extended release 60mg PO q12h and Morphine 6mg IV q 3h prn breakthrough pain

Pretest Question #3

- Which of the following is not an appropriate consideration when interacting with a patient with sickle cell disease?
 - A. The patient has a lifelong progressive medical condition with a shorter than average life expectancy
 - B. Patients have been experiencing the symptoms associated with vaso-occlusive crisis their entire life span and have insight regarding their bodies response to specific treatment modalities
 - C. The treating team should try to reserve high potency opioid interventions in an effort to keep an effective treatment option available for later in life
 - D. Patients with sickle cell disease have a similar rate of Substance Use Disorder as the general U.S. population

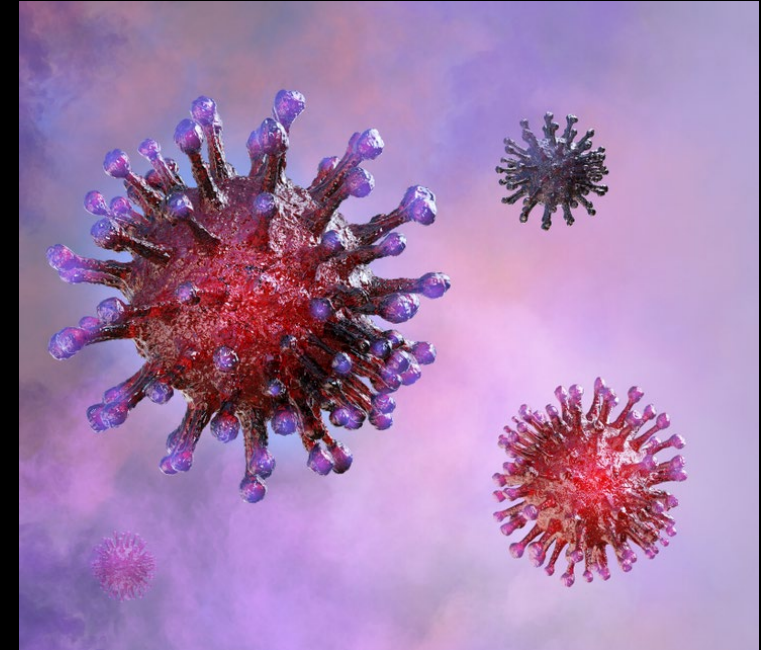
Background

- Inherited red blood cell disorder
- Amino acid substitution in the beta globin chain forms hemoglobin S rather than hemoglobin A
- Genotypes
 - HbSS
 - HbS β^0 -thalassemia
 - HbS β^+ -thalassemia
 - HbSC



Complications

- Begin as early as 5 months old
- Vaso-Occlusive Crisis (VOC) or Pain Crisis
- Anemia
- Infection
- Acute Chest Syndrome (ACS)
- Splenic Sequestration
- Leg Ulcers
- Avascular necrosis
- Deep vein thrombosis (DVT)/ Pulmonary Embolism (PE)
- Stroke



Epidemiology

- Over 100,000 Americans suffer from SCD
- 1 in 365 Black or African American births
- 1 in 16,300 Hispanic births (including Central and South America)
- Also affects people of Middle Eastern, Asian, Indian, and Mediterranean descent
- Mortality:
 - Mean Age at Death:
 - Females: 41.9
 - Males: 39.3
 - Leading causes of death:
 - Circulatory disorders
 - Infections



Healthcare Disparities

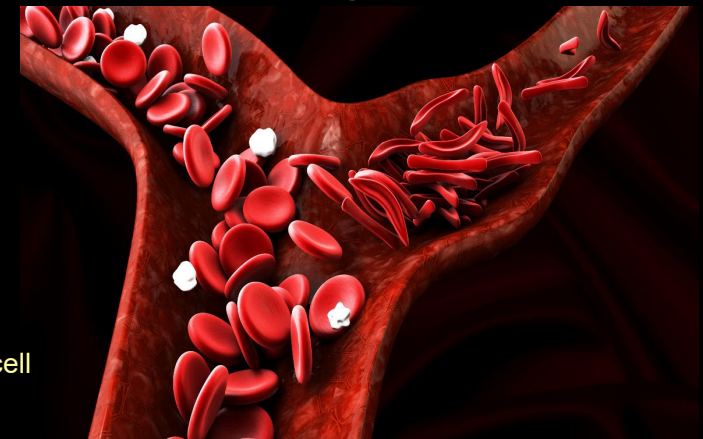
- Despite the significant pain, management needs, and challenges in patients with sickle cell disease, this patient population often faces more restrictive access than patients with cancer-related pain
 - As of 2020, 33 states have enacted legislation that limits opioid prescribing
 - 19 states include cancer as an exception to those limitations
 - 0 states include sickle cell disease as an exception
- Over 30,000 people in the U.S. have cystic fibrosis (CF), of which ~94% are Caucasian
 - Federal funding per person for CF was 3.4 times greater than SCD
 - Foundational expenditures for CF were 75 times greater than for SCD
 - Funding disparity may be associated with decreased research productivity and novel drug development

Farooq, F., Mogayzel, P. J., Lanzkron, S., Haywood, C., & Strouse, J. J. (2020). Comparison of US federal and foundation funding of research for sickle cell disease and cystic fibrosis and factors associated with research productivity. *JAMA network open*, 3(3), e201737-e201737.

Prescribing Policies: States Confront Opioid Overdose Epidemic. National Conference of State Legislatures. June 30, 2019 Update.
<http://www.ncsl.org/research/health/prescribing-policies-states-confront-opioid-overdose-epidemic.aspx>. Last Accessed July 7, 2021

Pathophysiology of Vaso-Occlusive Crisis (VOC)

- 3 major mechanisms of VOC:
 - Polymerization: Deoxygenated hemoglobin in red blood cells (RBC) form long rods altering the traditional concave, doughnut shape of the RBC to a more rigid, sickle cell shape
 - Adhesion: Sickled RBCs adhere to the vascular endothelium, platelets, leukocytes, and activated neutrophils
 - Leads to vaso-occlusion in smaller vessels
 - Inflammation: inflammatory response in body due to neutrophil activation, inflammatory chemokines, and occlusions causing reperfusion injury further promoting chronic inflammation



Focus on VOC and its treatment

- VOCs are the most common cause of emergency room visits and hospitalizations for the SCD patient population
- Previous data has shown that frequent VOCs were associated with higher mortality
 - Modern studies demonstrate VOCs are an independent risk factor for mortality
- Recurrent VOC episodes have a significant negative impact on health-related quality of life
 - Incidence of pain was shown to have a greater impact than cumulative organ damage

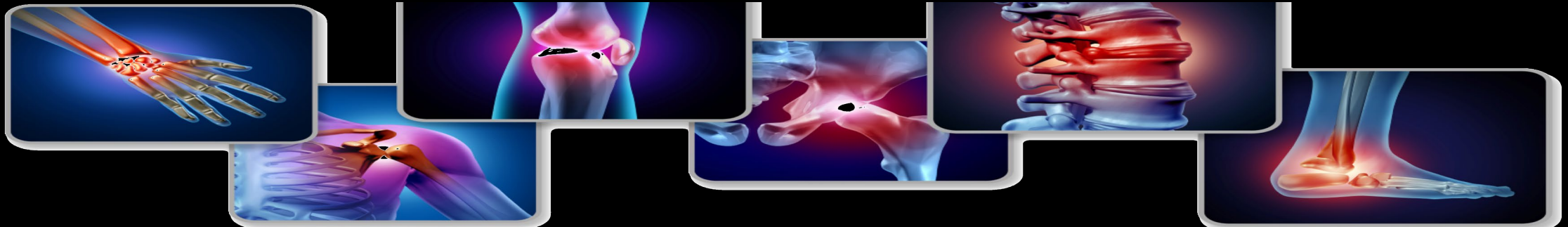
Brandow AM, Zappia KJ, Stucky CL. (2017). Sickle Cell Disease: A Natural Model of Acute and Chronic Pain. *Pain*. 158(Suppl 1): S79.

Darbari DS, et al. (2018). Severe Painful Vaso-Occlusive Crises and Mortality in a Contemporary Adult Sickle Cell Anemia Cohort Study. *PloS one*, 8(11), e79923.

van Tuijn, C. F., Van Beers, E. J., Schnog, J. J. B., & Biemond, B. J. (2010). Pain rate and social circumstances rather than cumulative organ damage determine the quality of life in adults with sickle cell disease. *Amer J. Hematol*, 85(7), 532.

The PQRST of VOC

Provocative:	<ul style="list-style-type: none">• Stress, physical exhaustion, temperature extremes, dehydration, oxidative stress
Palliative:	<ul style="list-style-type: none">• Opioid analgesics, NSAIDs, fluids
Quality:	<ul style="list-style-type: none">• Sharp, throbbing
Region:	<ul style="list-style-type: none">• Low back, joints, extremities
Severity:	<ul style="list-style-type: none">• Severe, often requiring hospitalization
Timing:	<ul style="list-style-type: none">• Sudden onset• May have prodromal phase for 1-2 days, pain peak on day 3, then last for additional 4-5 days



2020 American Society of Hematology Guidelines for SCD: Management of Acute and Chronic Pain

Acute Pain Management

Initial Management of VOC

2020 ASH Guidelines	2014 NHLBI's Evidence-Based Management of Sickle Cell Disease
Rapid assessment and administration of analgesia	Treat pain aggressively and promptly
Administer 1 st dose of analgesics within 1 hour of arrival to emergency department	Administer 1 st dose of analgesics within 30 minutes of arrival
Non-IV routes of administration (e.g. SubQ or intranasal) can facilitate rapid analgesic treatment	Administer IV or SubQ opioids (morphine or hydromorphone) per patient-specific protocol
Reassess pain frequently (q 30-60 minutes) to optimize pain control	Reassess for pain (q 15-30 minutes) and re-administer opioids until pain is controlled; maintain or consider escalation of the dose by 25% until pain is controlled
Tailor opioid dosing based on patient's baseline opioid therapy and prior effective therapy	Use an individualized prescribing and monitoring protocol (written by patient's SCD provider) or an SCD specific protocol whenever possible

Non-opioids for VOC

- Suggests a short course (5 to 7 days) of nonsteroidal anti-inflammatory drugs (NSAIDs) in addition to opioids for acute pain management
- Suggests *against* corticosteroids for acute pain management
- Suggests a subanesthetic (analgesic) ketamine infusion as adjunctive treatment of pain that is refractory or not effectively treated with opioids alone
 - Initial: 0.1 to 0.3 mg/kg/hour
 - Max: 1 mg/kg per hour
- Suggests regional anesthesia treatment approaches for localized pain that is refractory or not effectively treated with opioids alone

IV Fluids

■ASH:

- No recommendation for or against IV fluids in addition to standard pharmacological management for the treatment of acute pain
- No randomized controlled trials exist evaluating the use of rehydration in VOC

■NHLBI:

- In euvolemic adults and children who are unable to drink fluids, provide IV hydration at no more than maintenance rate to avoid over-hydration



Fluid administration Considerations

Goal

- Increase plasma volume
 - Decrease blood viscosity
 - Indirectly decrease RBC dehydration and intracellular hemoglobin S
 - Ultimately slow or stop the sickling process
-
- A recent retrospective analysis showed a significant association between receiving > 3 L of IV fluid in the 1st 24 hours of VOC admission and the development of any of the following adverse events ($p = 0.029$)
 - Oxygen requirement, ACS, Aspiration event, Hospital acquired infection, AKI, ICU transfer
 - No association between > 3 L of IV fluid and specific adverse events

Risks

- Excessive fluid administration can lead to:
 - Pulmonary edema
 - Acute Chest Syndrome (ACS)

Hugs & Drugs Recommendation



- $\frac{1}{2}$ NS in euvolemic patients with SCD
 - Warmed if available



Basal Opioid Dosing

- ASH:
 - No recommendation for or against basal (continuous IV opioid infusion) opioid dosing in conjunction with on-demand dosing or scheduled intermittent dosing
- NHLBI:
 - Initiate around-the-clock opioid administration by patient-controlled analgesia (PCA) or frequently scheduled doses versus “as requested” (PRN) administration

Hugs & Drugs Recommendation

- If on long-acting opioids or continuous opioid therapy at home:
 - Prefer initiating PCA with basal plus on demand pushes
 - Smoother, consistent plasma level using PCA with pushes as needed
- OR
- Restart home oral therapy with 10-25% breakthrough PRN doses ordered at frequent intervals (parenteral: 2-3 hours, oral: 3-4 hours)



www.bd.com/en-us/offerings/capabilities/infusion-therapy/infusion-system-devices/alaris-pca-module

Anti-Histamines

- ASH:
 - Not mentioned
- NHLBI:
 - In adults and children with a VOC who require antihistamines for itching secondary to opioid administration, prescribe agents orally, and do not re-administer with each dose of opioid in the acute VOC management phase
 - Re-administer q 4-6 hours PRN

Anti-Histamines

- Histamine promotes adhesion of sickle erythrocytes
 - Stimulates endothelial histamine H₂ and H₄ receptors
 - Induces P-selectin expression and release of von Willebrand factor
- 3-year prospective observational study of 247 patients
 - Plasma histamine level elevation:
 - 18% of patients in steady state
 - 61% during VOC
 - Steady state levels of histamine
 - Negatively correlated with fetal hemoglobin (HbF) percentage ($P=0.02$)
 - Positively correlated with absolute neutrophil count and absolute platelet count ($P=0.03$, $P=0.007$)
 - VOC levels of histamine
 - Positively correlated with C-reactive protein (CRP) levels ($P=0.02$)

Hugs & Drugs Recommendation



- Initiate frequent, as-needed oral or parenteral antihistamines in patients presenting in VOC, unless risk outweighs benefit
 - Monitor for excess sedation
 - Use caution due to anticholinergic effects
- Raises question on opportunities for new research

Case – Acute VOC with Pain

- 15 YO Male with HbSS disease presents to the ED with acute pain in his mid back and right arm. He also notes that he has cough and low-grade fever without hypoxemia for last 24 hours. Patient relays and review of Prescription Drug Monitoring Program reports no current opioid prescriptions.
- Chest x-ray reveals left lower lobe pneumonia
- How should we treat this patient?

Case – Acute VOC with Pain

- Initiate warmed ½ NS 100mL/hr
- Ketorolac 30mg IV q 6H
- Morphine 2mg, 4mg, and 6mg IV q 2H prn mild, moderate, and severe pain
 - Or equivalent hydromorphone (0.2mg, 0.5mg, 1mg)
 - Re-assess pain and vitals every 30 minutes
 - Naloxone 0.4mg q 2 minutes prn respiratory depression
- Diphenhydramine 25mg PO q 4H prn itching
- Offer warm blankets/heating pads

- Patient was then admitted for treatment of viral pneumonia

Case – Acute VOC with Pain

- After 12 hours, patient has received 42mg IV morphine, and has analgesic benefit but end of dose failure at 2 hours
- 3 treatment strategies
 - 1) Long-acting oral agent with PRN IV breakthrough coverage
 - 2) PCA with basal rate and patient-controlled bolus
 - 3) Scheduled intermittent IV administration \pm IV PRN breakthrough coverage

Long-acting Oral Agent With PRN IV Breakthrough Coverage

- Long-acting oral opioid with PRN IV morphine
 - Half as oral long acting, half as PRN
 - Morphine 84mg IV/day x 3 = 252 mg PO morphine/day
 - Morphine sulfate ER 60mg po q 12h and morphine IV 2mg, 4mg, 6mg (prn mild, moderate, severe pain)
- As PRN usage decreases, reduce long-acting opioid
- Rationale: if a patient's pain is expected to continue or increase over the next 24 hours, then long-acting oral analgesic with reasonable onset will help the patient safely titrate their dose with PRN medication, while maintaining adequate analgesic control. Do not use this method for a patient whose pain is not constant, and reliably present for at least the next 24 hours

PCA with Basal and Bolus

- Half as basal, half as PRN bolus
- Morphine 84mg IV/day
 - Basal: morphine 42mg IV
- Basal:
 - Morphine 42mg IV/day ÷ 24 hours = 1.75mg/hour, rounded to 2mg/hour
- PRN patient-controlled bolus
 - Morphine 3mg IV q 1H with 1 hour lockout
- Rationale: Patient does not have reliable oral route and do not believe patient's pain will decrease in next 24 hours.

Scheduled Intermittent IV Administration

- Morphine 84mg IV/day
 - Half as scheduled intermittent IV, half as IV PRN
- Schedule Intermittent:
 - Morphine 42mg IV \div 8 (q 3 Hour dosing) = 5.3mg IV, round to 6mg IV q 3H
- PRN:
 - Morphine 4mg IV q3H prn moderate pain, or 6mg IV q3H prn severe pain
- Rationale: Pain may decrease in next 24 hours. Patient may not have oral route. Allows for rapid dose adjustment and facilitates frequent nursing re-assessment for effectiveness and side effects

2020 American Society of Hematology Guidelines for SCD: Management of Acute and Chronic Pain

Chronic Pain Management

Avascular Bone Necrosis

- Bone death due to compromised blood supply
 - Prevalence: 50% by age 33 in HbSS
- ASH (Adults):
 - Suggests use of duloxetine as an option for management
 - includes other serotonin and norepinephrine reuptake inhibitor (SNRI) medications, due to evidence of class effect
 - Suggests the use of NSAIDs as an option
- ASH (Children): No recommendation for SNRIs or NSAIDs
- NHLBI:
 - Treat with analgesics and consult physical therapy and orthopedics for assessment and follow-up
 - Most orthopedists consider core decompression to be most beneficial in early stages

Leg Ulcers

- SCD-related leg ulcers (Adults and Children)
 - No recommendation
- Hugs & Drugs
 - Consider topical opioid preparations due to peripheral opioid receptor modulation
 - Consider topical lidocaine



Chronic Pain in SCD: No Identifiable Cause

- SCD-related chronic pain with no identifiable cause (Adults)
 - Suggests use of duloxetine (and other SNRIs) as an option for management
 - Suggests tricyclic antidepressants
 - Suggests gabapentinoids
- SCD-related chronic pain with no identifiable cause (Adults & Children)
 - No recommendation either for or against chronic monthly transfusion therapy



- Hugs & Drugs: Any of the aforementioned medications are reasonable options as long as they improve quality of life and level of function, as assessed by objective, statistically validated tools

Chronic Pain in SCD Adults and Children: Chronic Opioid Therapy (COT)

- Suggests against the initiation of COT unless pain is refractory to multiple other treatment modalities



- Hugs & Drugs: We are in support of the judicious use of opioids *including* chronic opioid therapy for patients with SCD
 - Approximately half of SCD patients are on daily opioid therapy

FDA Approved Treatments for SCD

Stem Cell Transplant

- Only cure for SCD
- 5-year overall survival 95% for patients <16 YO
 - 81% for patients \geq 16 YO
 - 9% risk of graft rejection and a 15% risk of chronic graft-versus-host disease
- For patients with severe sickle cell disease who have complications including stroke, acute chest syndrome, recurrent pain crisis and exchange transfusions, nephropathy, retinopathy, osteonecrosis of multiple joints, and priapism
- Only 18% of persons with SCD in the US will have a human leukocyte antigen (HLA) -identical sibling donor and only 19% will have an HLA-identical unrelated donor

Ashorobi D, Bhatt R. Bone Marrow Transplantation In Sickle Cell Disease. [Updated 2021 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Available from: <https://www.ncbi.nlm.nih.gov/books/NBK538515/>

Kassim, A. A., & Sharma, D. (2017). Hematopoietic stem cell transplantation for sickle cell disease: The changing landscape. *Hemat Oncol Stem Cell Ther*, 10(4), 259-266.

Krishnamurti, L., et al. (2019). Bone marrow transplantation for adolescents and young adults with sickle cell disease: Results of a prospective multicenter pilot study. *AM. J. Hematol.* 94(4), 446-454.

Hydroxyurea

- MOA: Increases non-sickling fetal hemoglobin (HbF)
- Age: \geq 6 months
- Evidence:
 - Decreases frequency of VOCs and ACS
 - Decreases RBC transfusions
 - Decreases hospitalizations
 - Reduces mortality
- Adverse Effects:
 - Infection, eczema, macrocytosis, neutropenia ($>10\%$)
 - Boxed warnings: severe myelosuppression, carcinogenic

Charache, S., et al. (1995). Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med*, 332(20), 1317-1322.

Hydroxyurea Lexi-Drugs. Lexicomp. <http://online.lexi.com> Last Accessed July 7, 2021.

Rodgers, G. P., Dover, G. J., Noguchi, C. T., Schechter, A. N., & Nienhuis, A. W. (1990). Hematologic responses of patients with sickle cell disease to treatment with hydroxyurea. *N Engl J Med*, 322(15), 1037-1045.

L-glutamine

- MOA:
 - Glutamine is a “conditionally essential” amino acid during metabolic stress and injury
 - Increases glutamine to improve NAD redox potential to prevent RBC oxidative damage
- Age: ≥ 5 years of age
- Evidence:
 - Decreases frequency of VOCs
 - Decreases hospitalizations
- Used as adjunct or in lieu of hydroxyurea
- Adverse Effects:
 - Headache, flatulence, constipation, nausea, abdominal pain, cough (>10%)

Voxelotor

- MOA: Inhibits deoxygenated sickle hemoglobin polymerization which results in less RBC sickling and binding
- Age: ≥ 12 years of age
- Evidence:
 - Increases Hg
 - Lowered levels of reticulocytes and bilirubin (biomarkers of hemolysis)
 - Reticulocytes: -19.9% vs +4.5% placebo (P<0.001)
 - Bilirubin: -29.1% vs -3.2% placebo (P<0.001)
 - Decreases frequency of VOCs
 - Annualized adjusted incident rate of VOC: 2.77 in 1500mg group, 2.76 in 900mg group, 3.19 in placebo group
- Adverse Effects:
 - Headache, diarrhea, abdominal pain, fatigue, nausea, skin rash, fever (>10%)

Crizanlizumab

- MOA: Inhibits selectin which reduces cellular adhesion
- Age: ≥ 16 years of age
- Evidence:
 - Decreases frequency of VOCs
 - Median rate of VOC per year was 1.63 with high-dose crizanlizumab vs 2.98 with placebo (P=0.01)
 - Increases time to 1st VOC and 2nd VOC
 - Median time to 1st VOC was 4.07 months with high-dose crizanlizumab vs 1.38 months with placebo (P=0.001)
 - Median time to 2nd VOC was 10.32 months with high-dose crizanlizumab vs 5.09 months with placebo (P=0.02)
- Adverse Effects:
 - Nausea, arthralgia, back pain, fever, (>10%)
 - Diarrhea, pruritus, vomiting, chest pain (1-10%)

Effective Communication

Communication Issues

- Patients with SCD report that they do not feel listened to or respected by providers, and they do not have enough time spent with their provider
- Patients with SCD report stigma and discrimination from health care providers due to their disease status, race, and acute and chronic pain management with opioids
- Clinicians should prioritize fertility and family planning discussions early
 - Studies show that females with SCD have high rates of unplanned pregnancies and pregnancy-related complications
 - Fertility and reproductive health knowledge in adolescents (age 12-20) with SCD was low

Bulgin D, Tanabe P, Jenerette C. Stigma of Sickle Cell Disease: A Systematic Review. *Issues in Mental Health Nursing*. 2018;39(8):675-686.

Haywood Jr C, et al. An Unequal Burden: Poor Patient-Provider Communication and Sickle Cell Disease. *Patient Education and Counseling*. 2014;96(2):159-164.

James AH. Reproductive Issues in Sickle Cell Disease. *Contemporary OB/GYN*. 2019;64(7):20-24.

Nahata L, Caltabellotta NM, Ball K, O'Brien SH, Creary SE. Desire for Parenthood and Reproductive Health Knowledge in Adolescents and Young Adults with Sickle Cell Disease and Their Caregivers. *Pediatric Blood and Cancer*. 2018;65(2):e26829.

Verbal Communication

- Listen carefully to the patient
 - Pain and fatigue are extremely common for patients
 - Validate the patient's experience by naming their emotions
- Listen to yourself
 - Recognize your own emotions and their impact on the interaction (unconscious bias)
- Let the patient, including minors, talk and ask questions
 - Let caretakers ask questions, but prioritize patient (support patient's autonomy)
- Respect for what patients have to say
 - People with SCD have experienced the symptoms associated with VOC their entire life and have insight regarding their bodies response to specific treatment modalities
- Pain affects patients physically, emotionally, psychologically, and spiritually
- Share decision making with patients and caregivers

Written Communication

- Ensure patient education materials are at appropriate reading levels including literacy and numeracy, as well as culturally appropriate
 - Have a variety of resources to match patient's literacy level
 - CDC Clear Communication Index is an online tool to develop and assess communication tools
 - www.cdc.gov/ccindex/index
 - Documents with appropriate health literacy will score \geq 90th percentile
 - A review of 13 US based educational materials for SCD showed none in the 90th percentile with 2 scoring <50th percentile



Post Test Question #1

- Which of the following medications is associated with decreased mortality in sickle cell disease?
 - A. Hydroxyurea
 - B. L-glutamine
 - C. Voxelotor
 - D. Crizanlizumab

Post Test Question #2

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 - D. Morphine sulfate extended release 60mg PO q12h and Morphine 6mg IV q 3h prn breakthrough pain

Post Test Question #3

- Which of the following is not an appropriate consideration when interacting with a patient with sickle cell disease?
 - A. The patient has a lifelong progressive medical condition with a shorter than average life expectancy
 - B. Patients have been experiencing the symptoms associated with vaso-occlusive crisis their entire life span and have insight regarding their bodies response to specific treatment modalities
 - C. The treating team should try to reserve high potency opioid interventions in an effort to keep an effective treatment option available for later in life
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