Sickle Cell Anemia: Pain Management

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Background

Sickle Cell Disease (SCD) is an inherited disorder that is commonly caused by homozygous hemoglobin S (HbSS)

The hallmark symptom is pain, primarily due to vaso-occlusive crises (VOCs), which result from Sickled Red Blood Cells (RBC) obstructing microvasculature

Treatment reduces or helps manage symptoms such as pain

Pain may be acute, chronic, or acute-on-chronic, and begins as early as infancy

Epidemiology

Sickle Cell Disease (SCD) affects millions of people throughout the world

Global prevalence: ~7.74 million people, with 515,000 new births annually, mostly in sub-Saharan Africa.

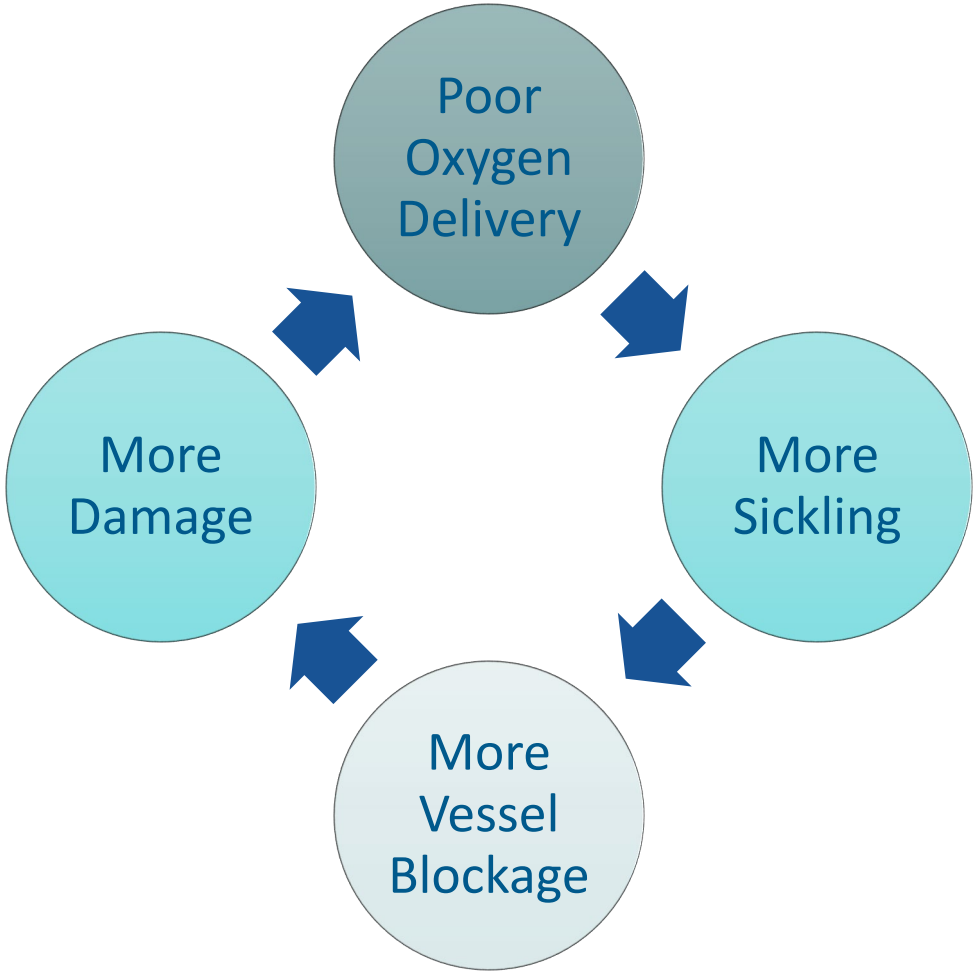
U.S. prevalence: ~100,000 individuals in the U.S., with >90% being non-Hispanic Black or African American.

Life expectancy is reduced by 20–30 years compared to the general population

Pathophysiology

Genetic cause:	• Mutation in the β-globin gene replaces glutamic acid with valine, producing Hemoglobin S (HbS).
Sickling of RBCs:	• When oxygen levels drop, HbS sticks together (polymerizes), making red blood cells stiff and crescent-shaped.
Membrane damage:	• Repeated sickling damages RBC membranes, causing hemolysis (breakdown of RBCs) and shortened cell lifespan.
Vascular blockage:	• Rigid, sticky sickled cells clump and block small blood vessels (microvascular occlusion).
Endothelial injury:	• Blocked vessels cause inflammation, reduced nitric oxide, and vasoconstriction, worsening blood flow.

The Cycle of Destruction Continues…



How does it lead to pain?

Vaso-occlusive crisis (VOC): Blocked blood vessels cut off oxygen to tissues, leading to ischemia (lack of oxygen).

Ischemic pain: Deprived tissues release pain-causing chemicals (prostaglandins, bradykinin, cytokines), activating pain nerves.

Inflammation: Inflammatory mediators further sensitize pain receptors, increasing pain intensity.

Bone and muscle pain: Bone marrow infarction and muscle ischemia are common pain sources.

Chronic changes: Repeated VOCs cause nerve sensitization and tissue damage, leading to chronic pain even between crises.

Complications

Acute pain crises (VOCs)

Acute chest syndrome

Stroke Infections (due to splenic dysfunction)

Kidney and liver damage

Chronic pain syndromes

Delayed growth and vision problem

Non-Pharmacological Treatment

Non-Pharmacologic Therapies

Underutilized despite ASH recommendations (barriers include access and provider awareness)

- Cognitive Behavioral Therapy
- Guided Audiovisual Relaxation
- Psychological Counseling
- Physical and occupational therapy
- Yoga
- Massage
- Art and Music therapy

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Pharmacological Treatment

Treatment Overview

Acute Pain:

- Rapid assessment and analgesia within 30–60 minutes.
- Hydration, oxygen if hypoxic, and infection screening.

Chronic Pain:

- Multimodal approach: pharmacologic + behavioral + physical therapies.
- Regular reassessment and adjustment of regimen

Acute Pain

- Caused by blockage of small blood vessels by sickled red blood cells. This blockage leads to a lack of oxygen to tissues and sometimes reperfusion injury which is damage that happens when blood flow returns. The result is tissue infarction like local cell death due to loss of oxygen.

- Patient Presentation:
  - Sudden onset of severe pain in one or more parts of the body.
  - Pain can last for hours to days and varies from mild to excruciating.
  - Often triggered by dehydration, infection, stress, or temperature changes

Acute Pharmacological Treatment

- NSAIDs for inflammation and mild pain.
- Opioids for moderate to severe pain
- Ketamine may be used for opioid-resistant pain.
- Patient-controlled analgesia (PCA): allows patients to self-administer small doses of opioids safely for better control.

Acute Pain Management Treatment

Mild to Moderate

- Ibuprofen: 400-600 mg every 6 hours as needed
- Acetaminophen: 650-1000 mg every 4-6 hours as needed

Severe Pain

- Morphine: 0.1-0.15mg/kg IV q 2-4 hours as needed
- Hydromorphone: 0.015-0.02 mg/kg IV q 3-4 hours as needed
- Opioid dosing based on consideration of baseline opioid therapy and prior effective therapy

Adjuvant Therapy

- Refractory: subanesthetic analgesic ketamine infusion 0.1- 0.3 mg/kg/hour every 4-6 hours as needed

Chronic Pain

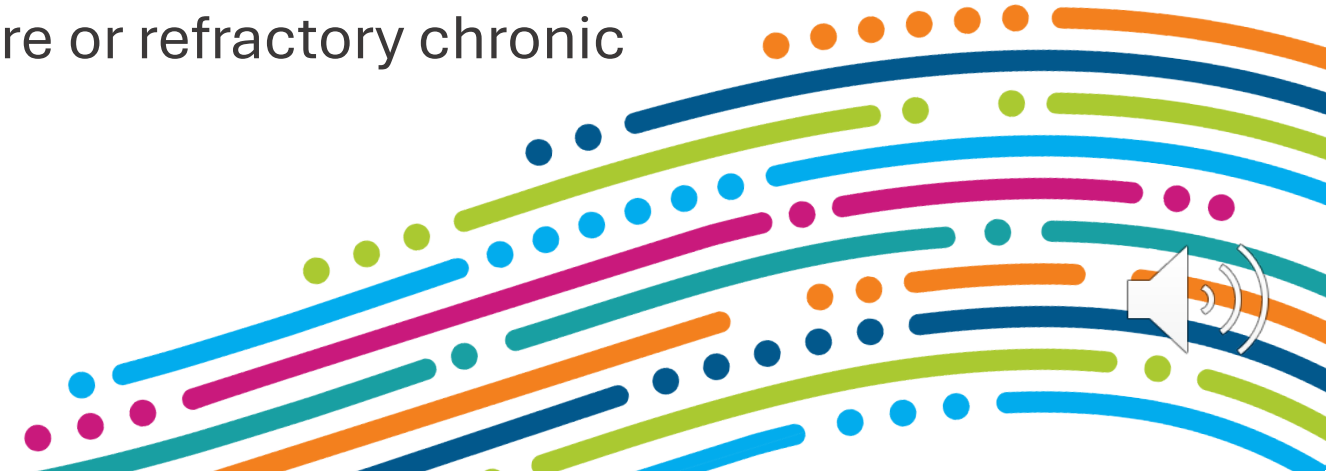
- Develops over time due to repeated vaso-occlusive episodes and nerve sensitization. The central and peripheral nervous systems become more sensitive that even minor signals are perceived as pain.

- Patient Presentation:
  - Persistent pain lasting more than 6 months.
  - May be neuropathic (burning, tingling, shooting) or musculoskeletal (aching, deep pain).
  - Often affects one or more body areas and may coexist with acute crises. Can significantly impact daily functioning, mood, and sleep.

Chronic Pharmacological Treatment

Chronic Treatment

- Hydroxyurea: reduces frequency of vaso-occlusive episodes by increasing fetal hemoglobin (HbF).
- Gabapentinoids (gabapentin, pregabalin): for neuropathic pain.
- SNRIs (e.g., duloxetine) and TCAs (e.g., amitriptyline): help with neuropathic and chronic pain.
- APAP (acetaminophen) and NSAIDs for mild to moderate baseline pain.
- Opioids may be used carefully for severe or refractory chronic pain.



Chronic Pain Management

Tricyclic Antidepressants

- Amitriptyline: 10-25 mg po once daily at bedtime (max 150 mg/day)

Serotonin and Norepinephrine Reuptake Inhibitors:

- Duloxetine: 30 mg by mouth once daily (max 120 mg/day)
- Milnacipran: 12.5 mg by mouth once daily (max 200mg/day)

Gabapentinoids

- Pregabalin: 75 mg by mouth twice daily
- Gabapentin: 300 mg once daily to three times a day

Chronic Pain Management

Nonsteroidal Anti-inflammatory

- Ibuprofen: 400-600 mg every 6 hours as needed
- Acetaminophen: 650- 1000 mg every 4-6 hours as needed

Severe Pain

- Morphine Extended Release: 15 mg to 30 mg by mouth every 8 to 12 hours
- Methadone: 2.5 mg by mouth every 8 to 12 hours
- Used ONLY if refractory to multiple other interventions, chronic opioid therapy should be considered after risk stratification

Clinical Implications

Clinical Pearls

- Pain may begin in infancy and evolve into chronic pain by adolescence.
- Avoid under-treatment due to stigma or opioid hesitancy.
- Use validated pain scales and assess psychosocial impact.
- Early initiation of hydroxyurea improves outcomes.
- Integrative therapies are underutilized but beneficial.
- Consider ketamine or PCA for refractory VOCs

Guidelines

ASH 2020 Guidelines:	Emphasize individualized, interdisciplinary care.
	Recommend both pharmacologic and non-pharmacologic approaches.
	Most recommendations are conditional due to low-certainty evidence.
	Encourage shared decision-making and patient-centered care

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