# UNDERSTANDING SICKLE CELL DISEASE AND CRISIS MANAGEMENT

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Northwell℠
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# UNDERSTANDING SICKLE CELL DISEASE

## SCD is a blood disorder

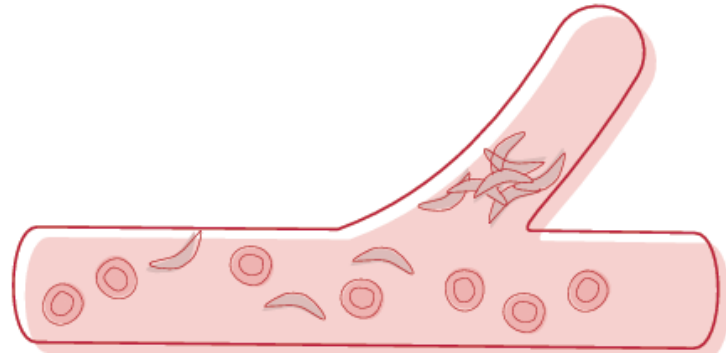
Sickle cell disease (SCD) is an inherited blood disorder that affects red blood cells. Normal red blood cells are round and flexible, which lets them travel through small blood vessels to deliver oxygen to all parts of the body.

## It causes misshapen blood cells

SCD causes red blood cells to form into a crescent shape, like a sickle.

## And creates painful complications

The sickle-shaped red blood cells break apart easily, clump together, and stick to the walls of blood vessels, blocking the flow of blood, which can cause a range of serious health issues.



# WHAT CAUSES SCD?

SCD is a genetic condition that is present at birth. It is inherited when a child receives two sickle cell genes—one from each parent. If only one sickle cell gene is inherited, the result is sickle cell trait (SCT). People with SCT can pass on the disease when they have a child.

**When both parents have sickle cell disease**

**100%** chance a child is born with SCD

**When one parent has sickle cell disease, one parent has sickle cell trait**

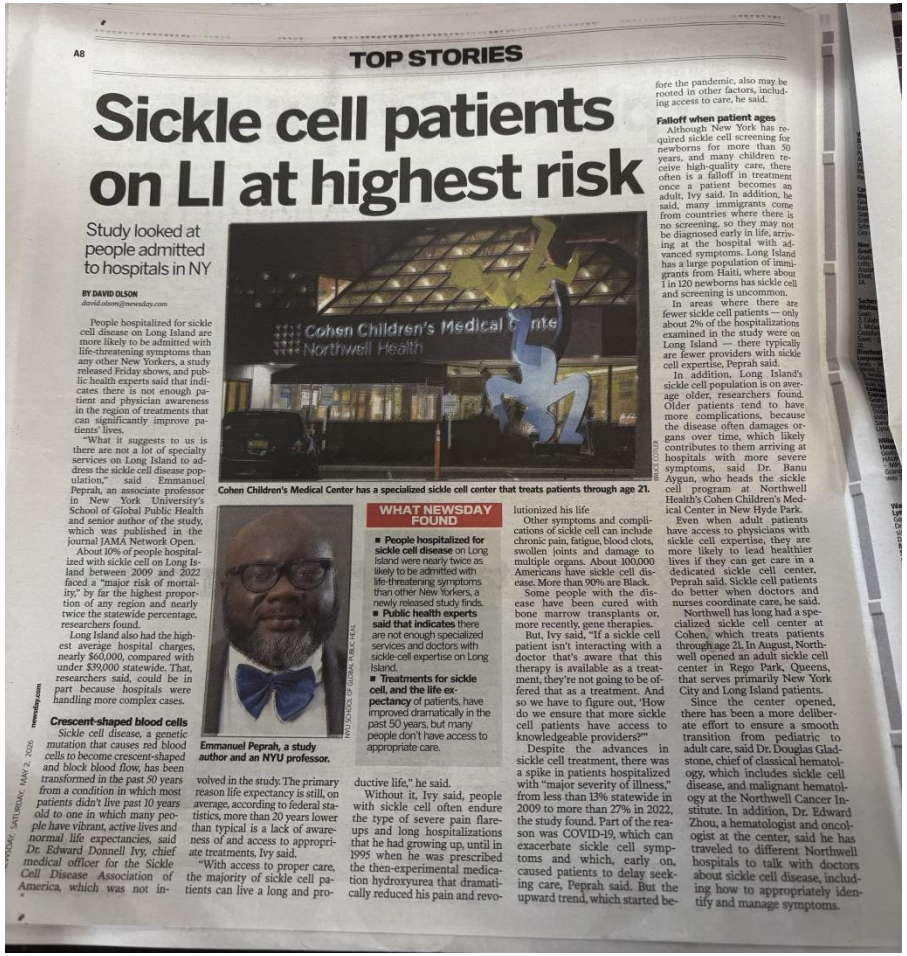
**50%** chance a child is born with SCD

**When both parents have sickle cell trait**

**25%** chance a child is born with SCD

# EPIDEMIOLOGY

- WHO estimates that 5% of the world population carries a hemoglobinopathy gene
- Incidence is about 1 to 2% in sub-Saharan Africa
- Estimations for incidence/prevalence of SCD in the US
  - 1 in 500 live births among Americans of African descent
  - About 100,000 Americans live with sickle cell disease
  - 1 in 12 American of African descent have sickle trait



A8 TOP STORIES

## Sickle cell patients on LI at highest risk

Study looked at people admitted to hospitals in NY

BY DAVID OLSON
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People hospitalized for sickle cell disease on Long Island are more likely to be admitted with life-threatening symptoms than any other New Yorkers, a study released Friday shows, and public health experts said that indicates there is not enough patient and physician awareness in the region of treatments that can significantly improve patients' lives.

"What it suggests to us is there are not a lot of specialty services on Long Island to address the sickle cell disease population," said Emmanuel Peprah, an associate professor in New York University's School of Global Public Health and senior author of the study, which was published in the journal JAMA Network Open.

About 10% of people hospitalized with sickle cell on Long Island between 2009 and 2022 faced a "major risk of mortality," by far the highest proportion of any region and nearly twice the statewide percentage, researchers found.

Long Island also had the highest average hospital charges, nearly $60,000, compared with under $39,000 statewide. That, researchers said, could be in part because hospitals were handling more complex cases.

**Crescent-shaped blood cells**

Sickle cell disease, a genetic mutation that causes red blood cells to become crescent-shaped and block blood flow, has been transformed in the past 50 years from a condition in which most patients didn't live past 10 years old to one in which many people have vibrant, active lives and normal life expectancies, said Dr. Edward Donnell Ivy, chief medical officer for the Sickle Cell Disease Association of America, which was not involved in the study. The primary reason life expectancy is still, on average, according to federal statistics, more than 20 years lower than typical is a lack of awareness of and access to appropriate treatments, Ivy said.

"With access to proper care, the majority of sickle cell patients can live a long and productive life," he said.

Without it, Ivy said, people with sickle cell often endure the type of severe pain flare-ups and long hospitalizations that he had growing up, until in 1995 when he was prescribed the then-experimental medication hydroxyurea that dramatically reduced his pain and revolutionized his life.

Other symptoms and complications of sickle cell can include chronic pain, fatigue, blood clots, swollen joints and damage to multiple organs. About 100,000 Americans have sickle cell disease. More than 90% are Black.

Some people with the disease have been cured with bone marrow transplants or, more recently, gene therapies.

But, Ivy said, "If a sickle cell patient isn't interacting with a doctor that's aware that this therapy is available as a treatment, they're not going to be offered that as a treatment. And so we have to figure out, 'How do we ensure that more sickle cell patients have access to knowledgeable providers?'"

Despite the advances in sickle cell treatment, there was a spike in patients hospitalized with "major severity of illness," from less than 13% statewide in 2009 to more than 27% in 2022, the study found. Part of the reason was COVID-19, which can exacerbate sickle cell symptoms and which, early on, caused patients to delay seeking care, Peprah said. But the upward trend, which started before the pandemic, also may be rooted in other factors, including access to care, he said.

**Falloff when patient ages**

Although New York has required sickle cell screening for newborns for more than 50 years, and many children receive high-quality care, there often is a falloff in treatment once a patient becomes an adult, Ivy said. In addition, he said, many immigrants come from countries where there is no screening, so they may not be diagnosed early in life, arriving at the hospital with advanced symptoms. Long Island has a large population of immigrants from Haiti, where about 1 in 120 newborns has sickle cell and screening is uncommon.

In areas where there are fewer sickle cell patients — only about 2% of the hospitalizations examined in the study were on Long Island — there typically are fewer providers with sickle cell expertise, Peprah said.

In addition, Long Island's sickle cell population is on average older, researchers found. Older patients tend to have more complications, because the disease often damages organs over time, which likely contributes to them arriving at hospitals with more severe symptoms, said Dr. Banu Aygun, who heads the sickle cell program at Northwell Health's Cohen Children's Medical Center in New Hyde Park.

Even when adult patients have access to physicians with sickle cell expertise, they are more likely to lead healthier lives if they can get care in a dedicated sickle cell center, Peprah said. Sickle cell patients do better when doctors and nurses coordinate care, he said.

Northwell has long had a specialized sickle cell center at Cohen, which treats patients through age 21. In August, Northwell opened an adult sickle cell center in Rego Park, Queens, that serves primarily New York City and Long Island patients.

Since the center opened, there has been a more deliberate effort to ensure a smooth transition from pediatric to adult care, said Dr. Douglas Glaistone, chief of classical hematology, which includes sickle cell disease, and malignant hematology at the Northwell Cancer Institute. In addition, Dr. Edward Zhou, a hematologist and oncologist at the center, said he has traveled to different Northwell hospitals to talk with doctors about sickle cell disease, including how to appropriately identify and manage symptoms.



Cohen Children's Medical Center has a specialized sickle cell center that treats patients through age 21.


Emmanuel Peprah, a study author and an NYU professor.

**WHAT NEWSDAY FOUND**

- **People hospitalized for sickle cell disease** on Long Island were nearly twice as likely to be admitted with life-threatening symptoms than other New Yorkers, a newly released study finds.
- **Public health experts said that indicates** there are not enough specialized services and doctors with sickle-cell expertise on Long Island.
- **Treatments for sickle cell, and the life expectancy** of patients, have improved dramatically in the past 50 years, but many people don't have access to appropriate care.

# TYPES OF SICKLE CELL DISEASE

The 4 main types of sickle cell disease include:

- Hb SS disease
- Hb SC disease
- Hb SB+(beta) thalassemia
- Hb SBO (beta zero) thalassemia

**Hb SS Disease**

Hemoglobin SS disease is the most common and most severe type of sickle cell disease. It occurs when you inherit the hemoglobin S gene mutation from both parents. It is called sickle cell anemia

**Hb SC Disease**

Hemoglobin SC disease is the second most common type of sickle cell disease. It occurs when you inherit the hemoglobin beta S gene from one parent and hemoglobin C gene from the other parent. Individual with hemoglobin SC have the same symptoms with individuals with hemoglobin SS but may be less severe.

# TYPES OF SICKLE CELL CRISIS

- Vaso occlusive crisis
- Aplastic crisis
- Splenic sequestration
- Hyper hemolytic crisis

**VASO OCCLUSIVE CRISIS (VOC)**

Vaso-occlusive crisis is the most common type of crisis which occur when the sickled red blood cells block the blood flow to the point that the tissue becomes deprived of oxygen. It is evidenced by fever, acute abdominal pain, chest, and leg pain.

**APLASTIC CRISIS (MEGALOBLASTIC)**

This occurs when the bone marrow of someone with sickle cell disease suddenly stops producing red blood cells. This can cause sudden and severe anemia.

# Contd.

**SPLENIC SEQUENSTRATION CRISIS**

This occurs when the red blood cells get trapped in the spleen, causing severe anemia. It's the repeated sickling in the spleen causing scarring and making the spleen not to work very well. This is a medical emergency.

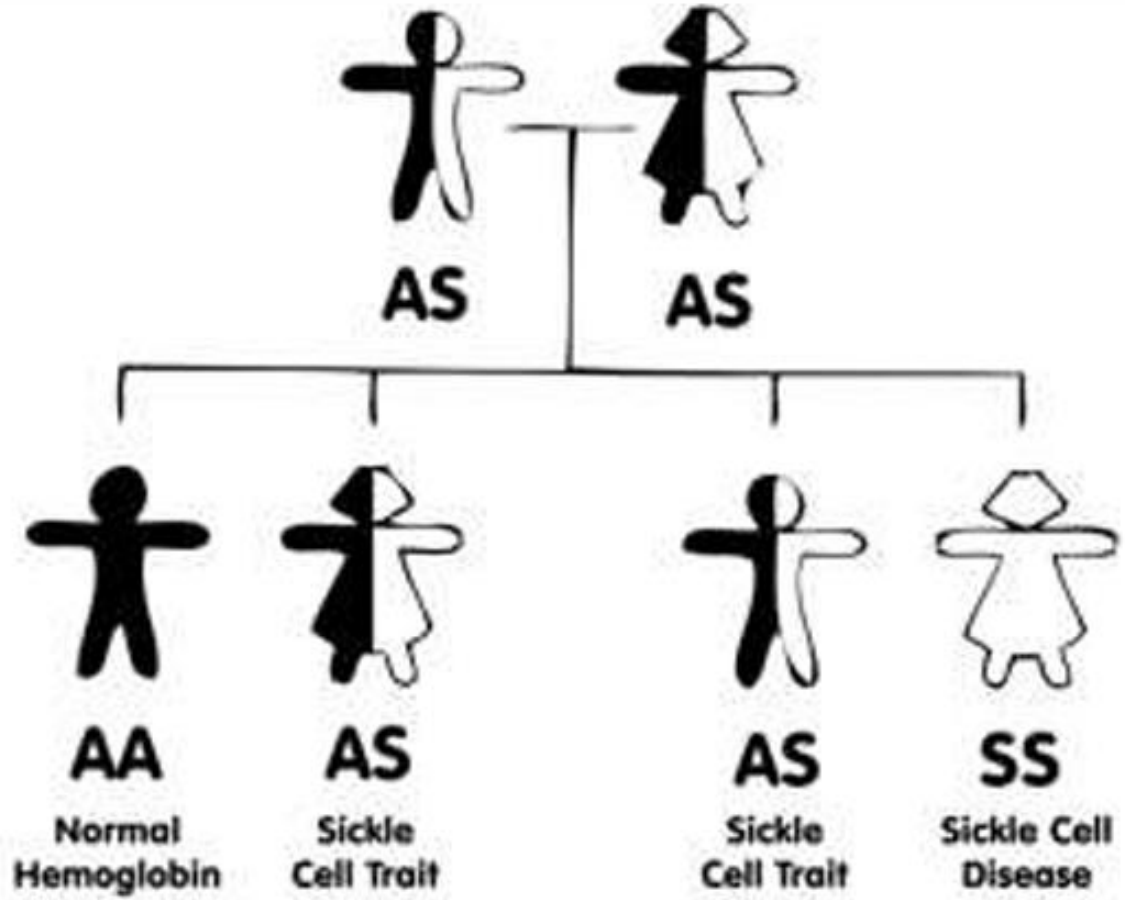
**HYPERHEMOLYTIC CRISIS**

This is a rare and dangerous complication of the sickle cell disease where the hemoglobin level drops rapidly, this can lead to organ failure and death.

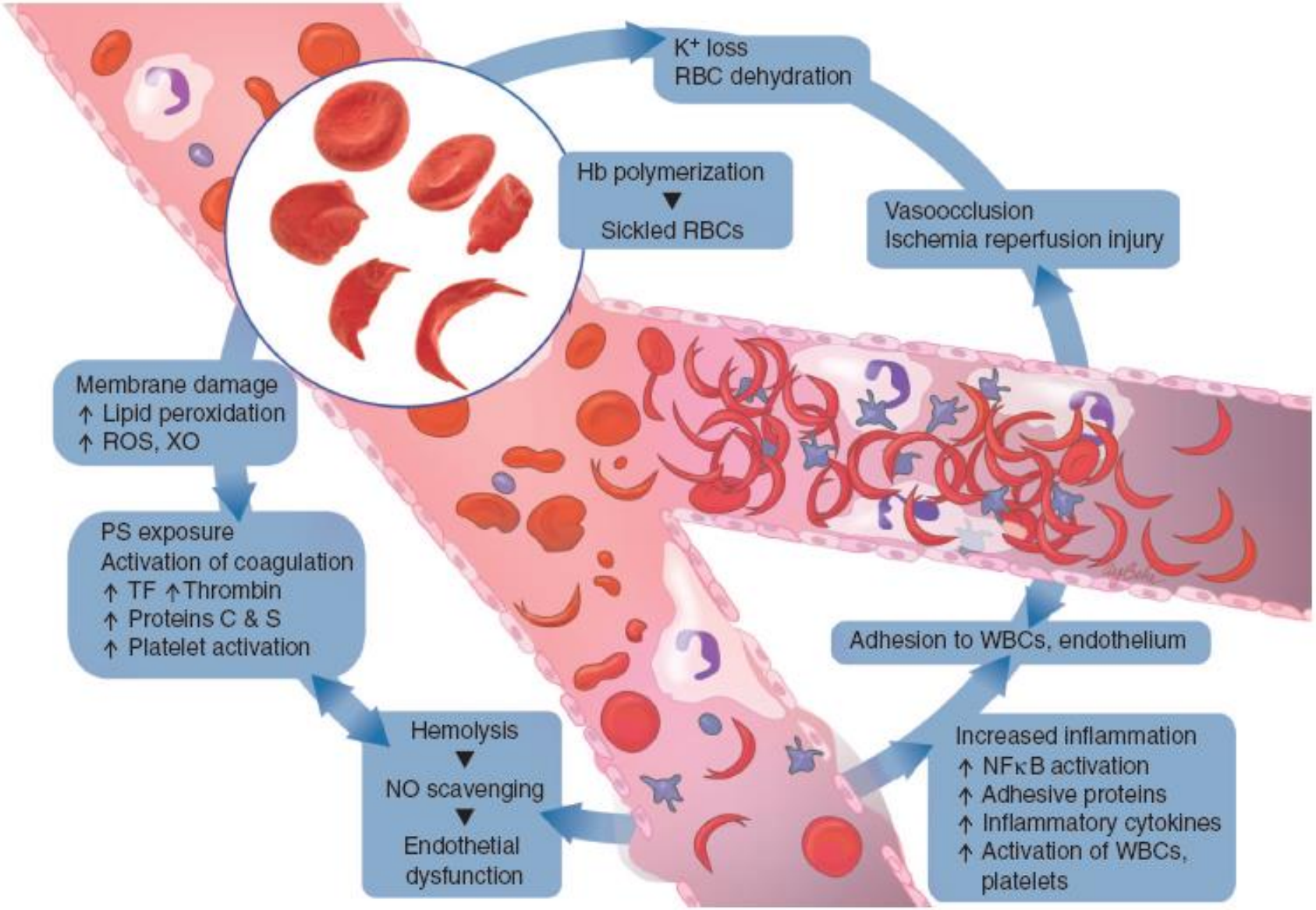
# COMMON COMPLICATIONS OF SCD

# CAUSES OF SICKLE CELL DISEASE AND CRISIS

- Genetic factor
- Sudden change in the temperature which can make the blood vessels to narrow
- Very strenuous or excessive exercise due to shortage of oxygen
- Dehydration due to low blood volume
- High altitude due to low oxygen concentration



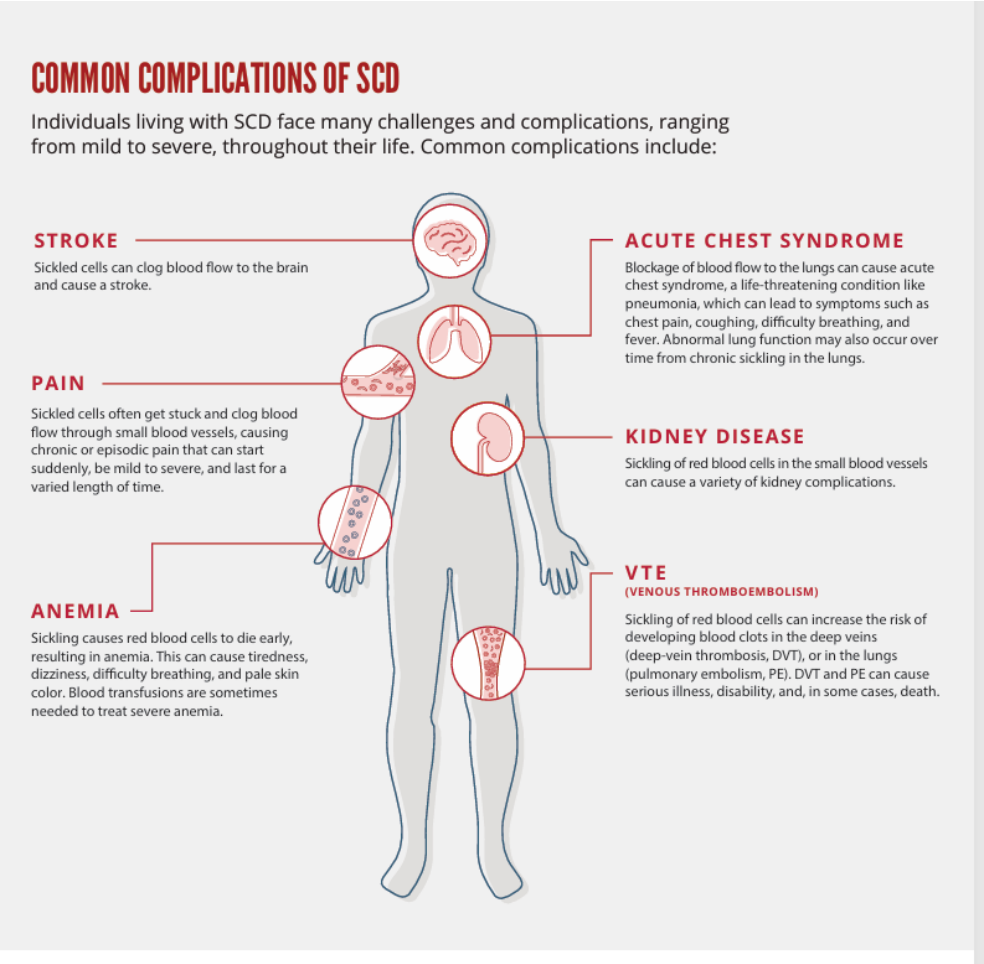
# PATHOPHYSIOLOGY



# COMMON COMPLICATIONS OF SCD

## SIGNS AND SYMPTOMS OF SCD/CRISIS

- Chronic fatigue
- Unexplained dyspnea
- Joint swelling
- Chest pain
- Severe anemia
- Fever
- Acute abdominal pain
- Pallor
- Delayed growth and puberty
- Difficulty walking or talking



# COMPLICATIONS ASSOCIATED WITH SCD /CRISIS

Sickle cell diseases/crisis leads to a host of complications including:

| | | | |
|---|---|---|---|
| Stroke | Acute chest syndrome | Pulmonary hypertension | Organ damage |
| Blindness | Leg ulcer | Priapism | Deep vein thrombosis |
| Delayed growth and puberty | Sleep disorder | Liver problem | |

# ACUTE CHEST SYNDROME

- Diagnostic Criteria
  - New pulmonary density on chest imaging involving at least one complete lung segment AND at least one of the following:
    - T ≥38.5°C
    - >3 percent decrease in SpO2 (oxygen saturation) from a documented steady-state value on room air
    - Tachypnea (per age-adjusted normal)
    - Intercostal retractions, nasal flaring, or use of accessory muscles of respiration
    - Chest pain
    - Cough
    - Wheezing
    - Rales
- Causes
  - Infection (~30%)
  - Fat embolization from marrow (~10%)
  - Pulmonary infarction
- Treatment
  - Broad spectrum antibiotics
    - 7 to 10 days of 3rd gen cephalosporin
    - 5 days of azithro
  - Red cell exchange (RCE)
  - Simple transfusion if too anemic for RCE

# SCD MANAGEMENT

# OUTPATIENT MANAGEMENT

- Labs
  - H/H, reticulocyte count, WBC
- Prevention of Sickle Cell Crisis
  - Hydration
  - Avoid high altitudes
  - Manage stress
  - Avoid Extreme temperatures
  - Prevent infections

Outpatient Management

- Psychosocial support
- BTP Pain Medications for Crisis
  - Short acting Opiods
- Chronic Pain Medications
  - LA Opioids
  - Neuropathic agents
- Maximize non-opioid mediations and non-pharmacological measures
- Hydroxyurea
- Other Medications on the market
- Gene Therapy
- Stem Cell Transplant

# HYDROXYUREA

- Mechanism of Action
  - Not entirely clear despite being used for over 30 years
  - Literature strongly suggests that increased NO and NO-dependent activation of guanylyl cyclase leads to increased HbF production
  - Also inhibits ribonucleotide reductase (RNR), preventing conversion of ribonucleotides to deoxyribonucleotides.
- Administration
  - Start at 15 mg/kg and titrate by 500 mg qd until max dose of 35 mg/kg
- Adverse Effects
  - Myelosuppression
  - Skin ulcers (controversial but favor continuing despite the ulcers)
  - Pregnancy Category D – known fetal toxicities but in certain situations benefits may outweigh risks

# L-GLUTAMINE (ENDARI)

- Mechanism of Action
  - Not entirely clear
  - L-glutamine is required for NAD synthesis. With oxidative stress, L-glutamine is consumed at a higher rate.
- Administration
  - Oral powder

| Weight | Dose |
|---|---|
| < 30 kg (66 lb) | 5 grams BID |
| 30 kg (66 lb) < weight < 65 kg (143 lb) | 10 grams BID |
| > 65 kg (143 lb | 15 grams BID |

- Adverse Effects
  - Low grade nausea, non-cardiac chest pain, fatigue, and musculoskeletal pain

# NON-PHARMACOLOGICAL THERAPIES FOR ACUTE PAIN

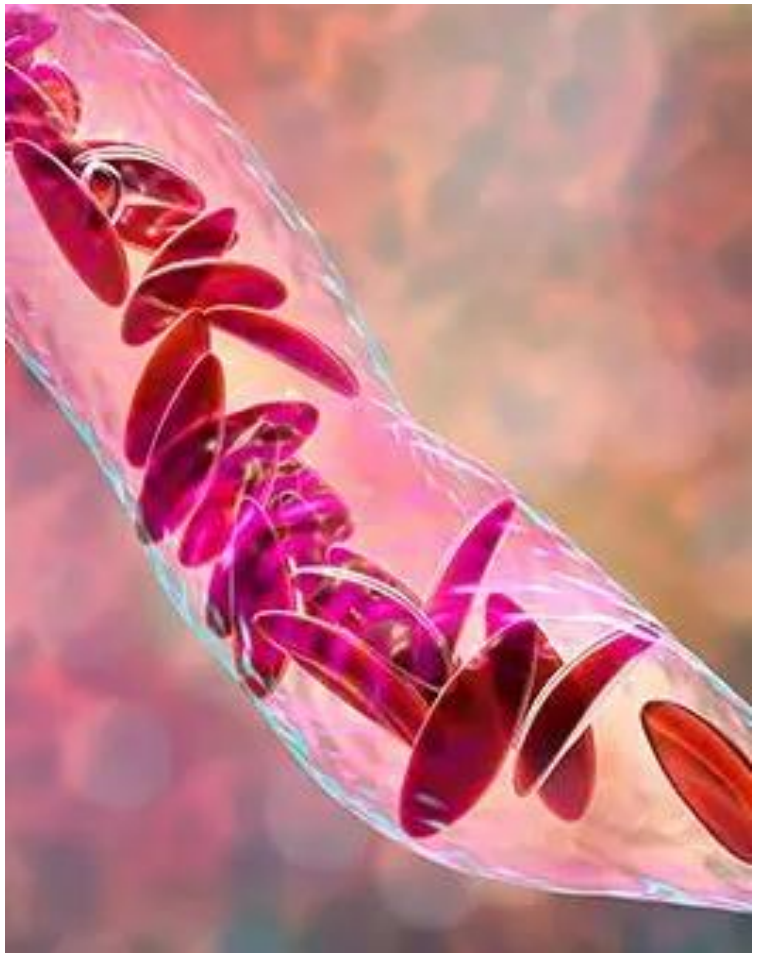
- The first line of treatment of SCD pain is pharmacological therapies, such as NSAIDs and opioids, but may not always be enough
- Nonpharmacological interventions have the potential to ease pain and reduce the need for opioids or other pharmacological treatments
  - Massage, yoga, transcutaneous electrical nerve stimulation (TENS), Virtual Reality (VR), guided audiovisual (AV) relaxation, acupuncture, biofeedback, mindfulness, spirituality, cognitive behavioral therapy (CBT), meditation
- Panel examined impact of nonpharmacological therapies on patient-centered outcomes
  - Improved pain intensity, pain coping strategies, and health related quality of life, reduction in total opioid consumption, length of stay, and return to baseline pain

# GENERAL NOTES ABOUT MANAGING ACUTE SICKLE CELL CRISIS

- Identifying Pain
  - The national goal for time from door to first dose of analgesic administration is within 60 minutes.
  - Most patients are adjusted to their severe chronic pain. Though they may not look like they are in pain, they may very well be in excruciating pain.
  - The mechanism of chronic pain in sickle cell disease is not understood
  - Check ISTOP but just because they do not have any entries in iSTOP does not mean they are not prescribed controlled substances in other states.
- Pain Crisis Triggers
  - Please do NOT give cold packs to any patients with sickle cell disease

# LABORATORY STUDIES

- Basic admission labs:
  - CBC with differential
  - Reticulocyte count
  - Hemoglobin electrophoresis
  - CMP
  - Fractionated bilirubin
  - LDH
- Labs to monitor routinely for ongoing hemolysis*
  - CBC
  - Reticulocyte count
  - CMP (bilirubin)
  - LDH



# GENERAL NOTES ABOUT MANAGING SICKLE CELL CRISIS

- IV Fluids
  - Please use hypotonic fluids (0.45% NaCl, D5W). No NS or LR
- Concerns About 1st Generation Anti-histamines
  - In the past, IV diphenhydramine was used for opioid-induced pruritus. When pushed, it can give a euphoric effect, especially when administered with IV opiates.
  - IV promethazine can give a similar euphoric effect when pushed
  - Make a habit of checking iSTOP to identify any unusual prescription patterns. If you have questions, please feel free to reach out to the ordering provider.
  - Outpatient infusion of controlled substances also appear on iSTOP

**Lactated Ringer vs Normal Saline Solution During Sickle Cell Vaso-Occlusive Episodes**

Augusta K Alwang [1], Anica C Law [2], Elizabeth S Klings [2,3], Robyn T Cohen [3,4], Nicholas A Bosch [2,5,✉]

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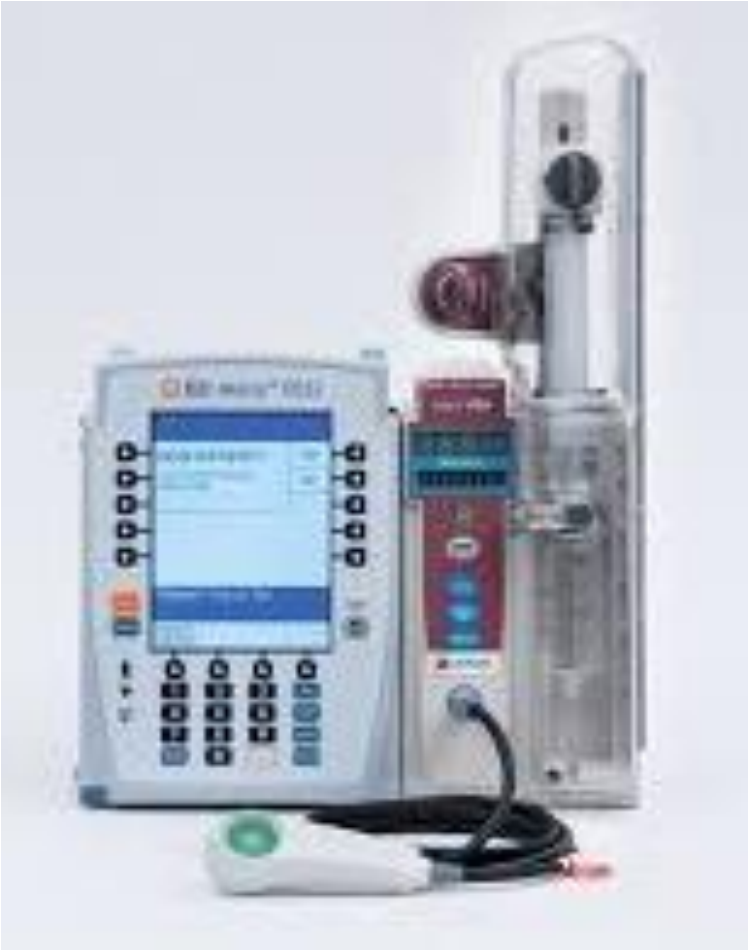
PMCID: PMC11385329 PMID: 39250114

# OPIOIDS

- Short acting
  - Oxycodone
  - Morphine
  - Hydromorphone
- Long acting
  - Oxycontin
  - MS Contin
  - Methadone

- Acute Management
  - Morphine 0.1-0.15mg/kg/dose (max 8mg)
  - HYDROmorphone 0.02-0.05mg/kg/dose (max 2 mg)
  - *Ketorolac 0.5mg/kg/dose (max 30mg)
  - PCA modality– tailored to patient



# CLINICAL TIPS

- IV Fluid Therapy
- Maximize non-opioids (ATC- dosing)
  - NSAIDs*
  - Muscle Relaxants
  - Neuropathic agents
- Utilize non-pharmacological modalities
  - Guided imagery
  - Heat packs
- Opioids (Check I-stop)
  - IV – Acute Crisis
    - If pain not controlled with IV pushes, strongly consider PCA
- Continue long-acting opioids
  - MS Contin, Oxycontin, Methadone
- Hydroxyurea
- Bowel Regimen
- Transition to oral opioids as early as possible
- Clear expectations of plan of care and opioid tapering
- Follow up post discharge plan and social support
- ED Management of pain
  - IV analgesia in ED setting
  - Follow up with hematology/PCP
  - short term prescription of opioids

# OTHER IMPORTANT CONSIDERATIONS

- Surgical Populations
  - If possible – develop a pain plan prior to procedure
  - Involve Anesthesia and Pain Team (if available)
- Provider and Nursing Education
  - Ordering and Administering high dose opioids
- Drug Concentration
  - 5mg/ml
- Transfusion Management
- A common misconception is that patients with sickle cell disease have a higher risk of opioid misuse or addiction
- VTE Prophylaxis
- Review previous records for guidance
- Communication and collaboration is Key!

# NON-OPIOID PHARMACOLOGIC INTERVENTIONS FOR ACUTE PAIN REFRACTORY TO OPIOIDS

**Recommendation 2c.** For *adults and children* presenting with acute pain related to SCD who are hospitalized, the ASH guideline panel *suggests* a sub-anesthetic (analgesic) ketamine infusion as adjunctive treatment for pain that is refractory or not effectively treated with opioids alone (**conditional** recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

**Remarks:**

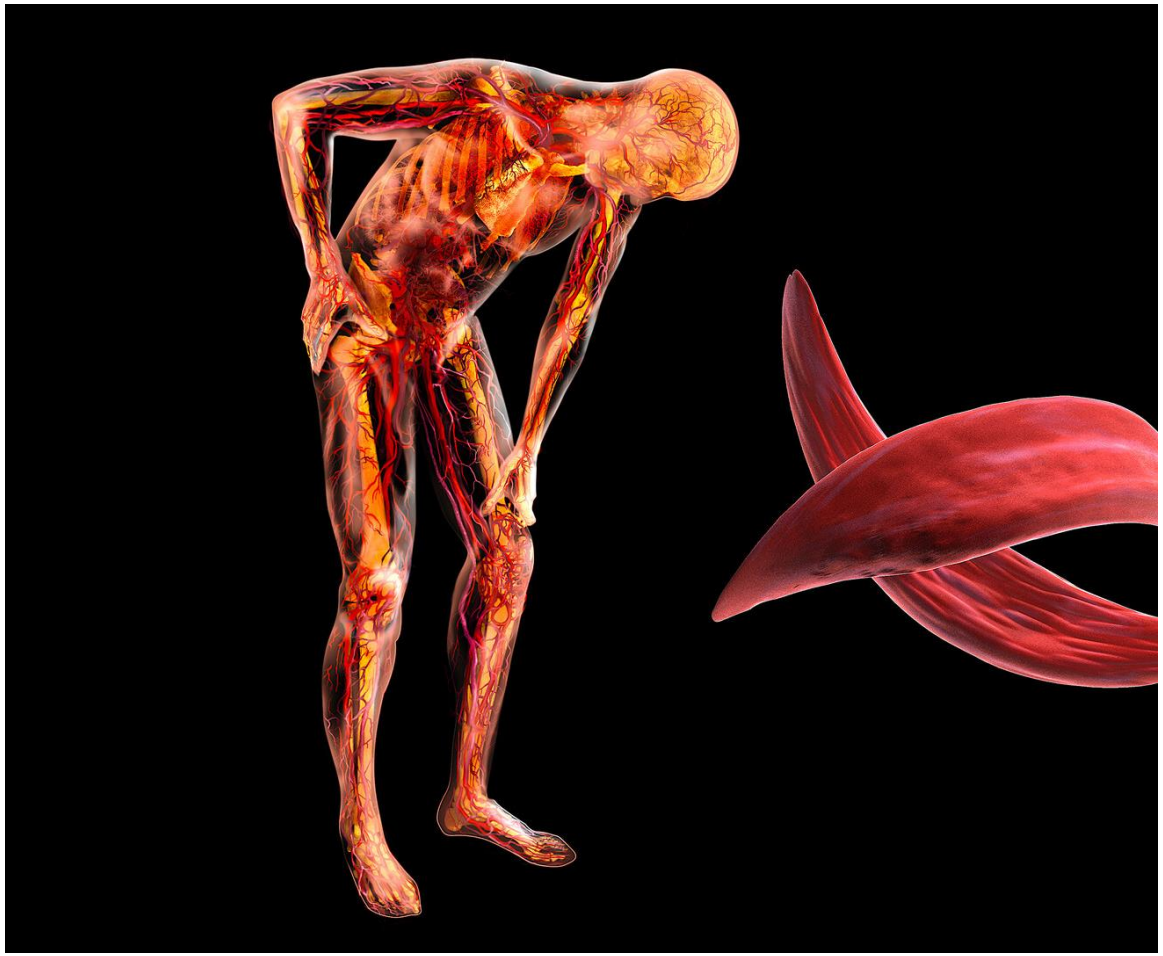
This recommendation assumes safe administration of sub-anesthetic ketamine infusions in the hospital inpatient unit in centers that have appropriate expertise to administer the drug.

Recommended dose for sub-anesthetic (analgesic) infusion for acute exacerbation of SCD pain starts at 0.1 to 0.3 mg/kg/h with a maximum of 1 mg/kg/h.

Currently, there is no standardized, widely accepted definition for the word “refractory”; thus, whether pain is considered refractory is determined at the clinician’s discretion.

# CASE REVIEW

- 34-year-old male with sickle cell disease presents to ED with “joint pain” and fears that he may be having a crisis.
- What information do you need?
- Labs
- Medications
- Imaging?
- Plan of care?



# THANK YOU.