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# Sickle Cell Anemia: Gene Editing

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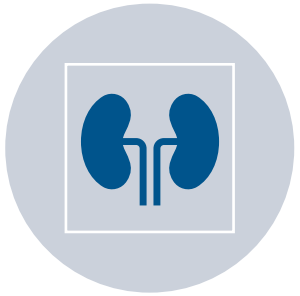
# Outline

- Background
- Epidemiology
- Pathophysiology
- Complications
- Non-pharmacological therapies
- Current pharmacological therapies
- New gene editing therapies

# Background

Sickle cell disease (SCD) is an inherited disorder that affects hemoglobin: autosomal recessive



Serious health problems result from SCD: pain crisis, stroke, lung problems, infections, and kidney disease

Treatment reduces or helps manage symptoms

December 2023, the FDA approved 2 new gene therapies

# Epidemiology – CDC

## SICKLE CELL DISEASE WORLDWIDE

- Sickle cell disease affects millions of people throughout the world and is particularly common among those whose ancestors come from parts of the world where malaria is common:
  - Sub-Saharan Africa
  - Spanish-speaking regions in the Western Hemisphere (South America, the Caribbean, and Central America)
  - Saudi Arabia
  - India
  - Mediterranean countries such as Turkey, Greece, and Italy

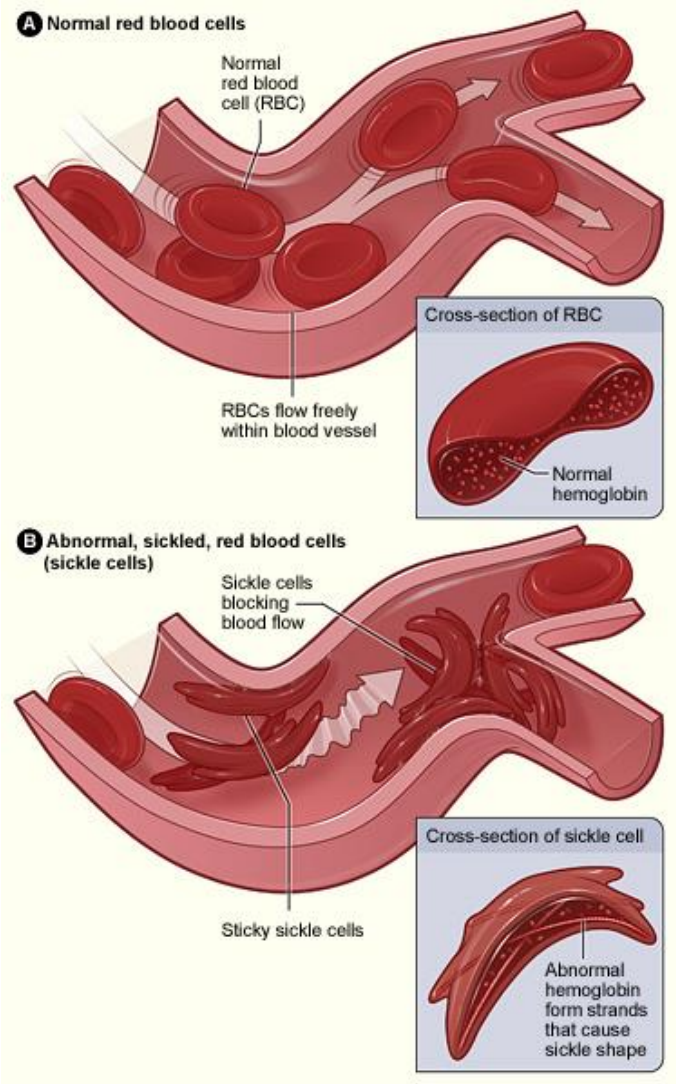
# Epidemiology – CDC

## SICKLE CELL DISEASE IN THE UNITED STATES

- Exact number of people living in the US with SCD is unknown, studies published in 2010 approximate 100,000
- More than 90% of people in the US with SCD are non-Hispanic Black or African American (Black), and an estimated 3 to 9% are Hispanic or Latino
- SCD occurs in about 1 out of every 365 Black or African American births and about 1 out of every 16,300 Hispanic American births
- About 1 in 13 Black or African American babies is born with sickle cell trait (SCT)

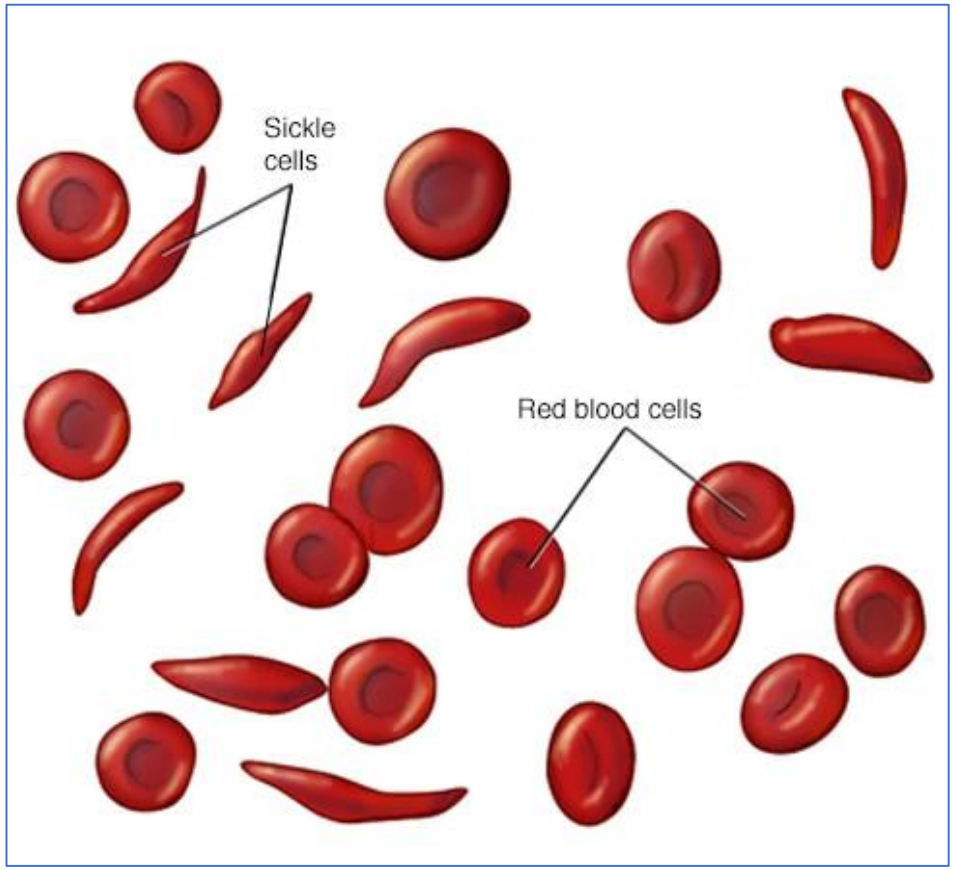
# Pathophysiology

- Genetic mutations in the beta subunit of hemoglobin cause SCT and SCD
  - SCD is the result of "sickling" of red blood cells
  - SCD affects the rheologic properties of blood flow to all organs and throughout the body
  - Leads to:
    - Sickle cell anemia
    - Increase in blood viscosity and cell adhesion
    - Increase in acute and painful vaso-occlusion crisis (VOC)



# Complications of Sickle Cell Disease

- Stroke
- Pain
- Acute Chest Syndrome
- Pulmonary hypertension
- Kidney disease
- Liver problems
- Splenic sequestration
- Blindness
- Sleep apnea
- Priapism
- Pregnancy complications



# Non-Pharmacological Treatment

# Non- Pharmacological Treatment

Transcutaneous electrical nerve stimulation

Yoga

Massage

Guided Audiovisual Relaxation

Cognitive Behavioral Therapy

# Pharmacological Treatment

# Classification of Pain

## ACUTE PAIN

Vaso-occlusion of sickled red blood cells with ischemia reperfusion injury and tissue infarction

Presentation:

- One or multiple anatomic locations

## CHRONIC PAIN

Sensitization of the central and/or peripheral nervous system

Presentation:

- Neuropathic pain
- Pain occurring over 6 months
- One or multiple anatomic locations

# 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
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

## 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
- Conditional recommendation adults: moderate certainty in the evidence about effects ⊕⊕⊕◯
- Conditional recommendation children: low certainty in the evidence about effects ⊕⊕◯◯

## Adjuvant Therapy

- Refractory: subanesthetic analgesic ketamine infusion 0.1- 0.3 mg/kg/hour every 4-6 hours as needed
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

# Chronic Pain Management Treatment

## 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)
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

## Nonsteroidal Anti-inflammatory

- Ibuprofen: 400-600 mg every 6 hours as needed
- Acetaminophen: 650- 1000 mg every 4-6 hours as needed
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

## Tricyclic Antidepressants

- Amitriptyline: 10-25 mg po once daily at bedtime (max 150 mg/day)
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

# Chronic Pain Management Treatment Continued

## Gabapentinoids

- Pregabalin: 75 mg by mouth twice daily
- Gabapentin: 300 mg once daily to three times a day
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

## 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
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

# Hydroxyurea (Xromi, Droxia, Siklos)

FDA Approved: Adults 1998 , Children 2017

Mainstay sickle cell management

- Mechanism of action
  - Target the ribonucleotide reductase enzymes, iron-containing enzymes that convert ribonucleoside diphosphates to deoxyribonucleotide triphosphates
- Dose
  - Children: 20 mg/kg/day by mouth once daily
  - Adults: 15 to 20 mg/kg/day by mouth once daily
  - CrCl <60 mL/min: 7.5 mg/kg/day by mouth once daily
  - Dose adjustments after 12 weeks by 2.5 mg/mL (max 35 mg/kg/day)
- Black Box Warnings
  - Bone marrow suppression, secondary malignancy
- Monitoring Parameters
  - Bone marrow suppression and CBC with Differential every 2 weeks
  - Avoid in Pregnancy
- Side Effects
  - Neutropenia, thrombocytopenia, nausea

# Clinical Implication

- Reduction benefits
  - Frequency of Vaso-occlusive crisis in adults
    - p= < 0.001
  - Acute chest syndrome
    - Adults: p= < 0.01
    - Children: p= < 0.02
  - Hospitalizations
    - Children p= < 0.001
  - Stroke
    - p= 0.03
  - Transfusion
    - Adults: p= 0.001
    - Children: p= < 0.001

- Mortality:
  - Associated with a decreased mortality in symptomatic patients compared to patients without
    - 10- year survival improvement (86% compared to 65%, p= 0.001
  - Significantly reduced the median in both first and second pain crisis

# L-Glutamine (Endari)

FDA Approved: 2017

- Mechanism of action
  - An amino acid that reduce SCD complication by decreasing oxidative stress
- Dose
  - <30 kg: Oral: 5 g twice daily (total dose 10 g/day)
  - 30 to 65 kg: Oral: 10 g twice daily (total dose 20 g/day)
  - >65 kg: Oral: 15 g twice daily (total dose 30 g/day)
- Side effect
  - Constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain
- Patient counseling
  - Mix with 8 oz of apple juice, water, or milk
  - Mix with 4-6 oz of yogurt or apple sauce

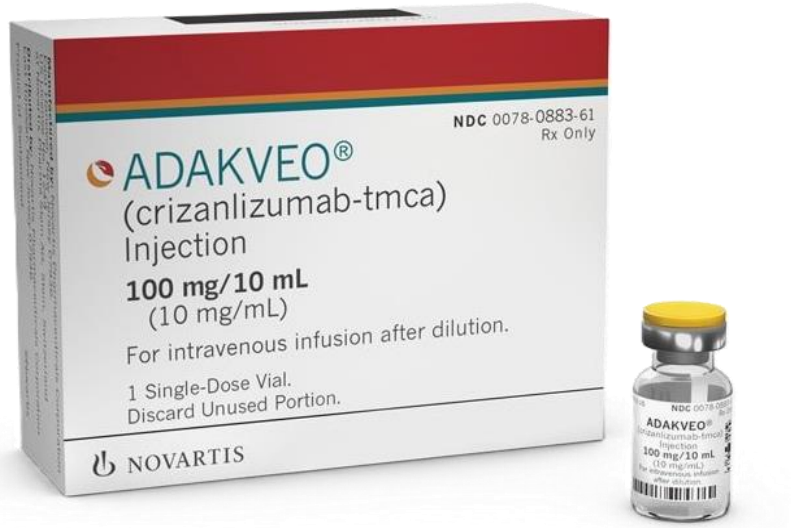
# Clinical Implication

- Primary outcome
  - Significantly reduced annual rate of pain crises
    - 3.0 vs placebo 4.0,  p=0.005
- Secondary Outcome
  - Longer median time to first crisis
    - 84 days vs placebo 54 days,  p=0.02
  - Longer median time to second crisis
    - 212 days vs placebo 133 days, p=0.02
  - Reduced episodes of acute chest syndrome
    - 8.6% vs placebo 23.1%, p=0.003
  - Reduced rate of hospitalization
    - 2.0 vs placebo 3.0, p=0.005
- Efficacy
  - Reductions in the frequency of VOCs with hydroxyurea use
    - 36% of patients who received treatment compared to 17% of patients in placebo group did not experience a VOC
- Safety
  - L-glutamine showed lower adverse events compared to placebo

# Crizanlizumab (Adakveo)

FDA Approved: 2019

- Mechanism of action
  - A humanized IgG2 kappa monoclonal antibody which binds to P-selectin and blocks interaction with ligands
- Dose
  - Adults : Injection  5 mg/kg IV once every 2 weeks for 2 doses (at week 0 and week 2), followed by 5 mg/kg IV once every 4 weeks
  - Can be used in combination with or without hydroxyurea
- Side effects
  - Infusion-related reaction, nausea, arthralgia, back pain, fever



# Clinical Implication

- Primary outcome
  - Reduced annual rate of pain crises
    - 1.63 High-dose vs 2.98 placebo , 45.3% reduction , p= 0.01
- Secondary Outcome
  - Longer median time to first crisis
    - 4.07 vs. 1.38 months, p= 0.001
  - Longer median time to second crisis
    - 10.32 vs. 5.09 months, p= 0.02
  - Reduced rate of uncomplicated crises
    - 1.08 High-dose vs 2.91 placebo,  62.9% reduction , p= 0.02
- Efficacy
  - Reductions in the pain crises were observed with high-dose Crizanlizumab  with or without hydroxyurea use
- Safety
  - Treatment showed similar incidence of adverse events compared to the placebo group

# Disease Specific Treatment

## Cardiopulmonary Disease

- Hydroxyurea
- Chronic red blood cell transfusion
- Asthma: Beta-adrenergic bronchodilators and oxygen prn

## Stroke prevention in children with abnormal TCD

- Primary Stroke: chronic red blood cell transfusion
  - After 1 year transition to hydroxyurea
- Secondary and Acute Stroke: chronic red blood cell transfusion

## Chronic Kidney Disease

- IV fluids
- Hydroxyurea
- ACE or ARB therapy

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# Hematopoietic Stem Cells Transplantation (HSCT)

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# Background Information

- Initially performed in 1984
- Mechanism
  - Healthy donor stem cells replace defective bone marrow cells. The transplanted cells will produce red blood cells with hemoglobin.
- Indications:
  - Severe SCD with complications of stroke, acute chest syndrome, recurrent pain crisis, nephropathy, retinopathy, osteonecrosis of multiple joints, and priapism
- Complications
  - Graft rejection, infection, chronic GVHD, and organ damage
- Cost: $87,000 -$300,000
- HLA Matching
  - HLA Class 1 (A, B, C) and Class II (DRB1, DQ)
  - 10/10 Match, 8/8 Match
  - Haploidentical Transplant
  - Cord Blood

# Gene Therapy

# Background Information

- Two available options:
  - Casgevy (exagamglogene autotemcel)
  - Lyfgenia (lovotibeglogene autotemcel)
- FDA Approval: December 8, 2023
  - For patients 12 years old and up
  - Indicated for patients with history of VOCs
- Cost: ~$2-3 million
- Duration of treatment: ~1 year

# Comparison to Available Treatment

## HEMATOPOIETIC STEM CELL TRANSPLANT

- Allogeneic
  - Requires a donor
    - Matched= limited availability
    - Haploidentical= only half matched
  - Risk of complications, including GVHD, rejection, and infections

## GENE THERAPY

- Autologous
  - Utilizes patient's own stem cells
    - Avoids wait and search for potential donors
  - Avoids complications such as GVHD or rejection

# Obstacles and Risks With Gene Therapy

- Availability of authorized treatment center (ATC)
  - Patient required to visit and be admitted at an ATC for various steps of treatment journey
    - Travel and cost must be considered
- Use of chemotherapy and associated side effects
  - Myeloablative conditioning utilized may cause reproductive harm
    - Reproductive health of patient must be discussed

# Treatment Course Overview:

## 1- Determine if therapy is appropriate

- Weigh risks and benefits
- Discuss accessibility of treatment

## 2- Preparation for stem cell collection

- RBC transfusions
- Discontinue specific concomitant medications

## 3- Stem cell collection

- Mobilization: Medication given to help move blood stem cells from bone marrow into blood
- Apheresis: Separation and collection of stem cells from blood

## 4- Treatment production

- Stem cells edited accordingly
- Stem cells undergo testing

## 5- Conditioning and Infusion

- Chemotherapy followed by gene therapy

## 6- Follow up

- Short and long term monitoring

# Casgevy Mechanism of Action

## Gene editing

- Utilizes CRISPR/Cas9

## Edits BCL11A gene

- Allows for higher production of fetal hemoglobin (HbF)
- Increases overall hemoglobin levels and decreases HbS concentration

# Casgevy Safety Data

- Adverse reactions and incidence:
  - Febrile neutropenia= 48%
  - Mucositis= 86%
  - Decreased appetite= 41%
  - Musculoskeletal pain= 14%
  - Abdominal pain= 11%
  - Cholelithiasis= 11%
  - Pruritis= 11%
- Laboratory abnormalities and incidence:
  - Neutropenia= 100%
  - Thrombocytopenia= 100%
  - Leukopenia= 98%
  - Anemia= 84%
  - Lymphopenia= 50%
  - Hyperbilirubinemia= 14%

No reported case of GVHD, graft failure, or graft rejection

# Casgevy Efficacy Data

Measured until at least 12 months after infusion

- Primary Endpoint:
  - Proportion of patients without severe VOC
    - 93.5% (n= 29/31)
- Secondary Endpoints:
  - Proportion of patients not hospitalized due to severe VOC
    - 100% (n= 30/30)
  - Median duration of severe VOC-free period
    - 22.2 months

# Lyfgenia Mechanism of Action

## Gene addition

- Modifies autologous CD34+ cells

## Uses BB305 lentiviral vector to add βA-T87Q globin gene

- Now able to pair with α-globin to produce functional HbA
- Inhibits polymerization of HbS and reduces HbS levels

# Lyfgenia Safety Data

- Adverse reactions and incidence:
  - Stomatitis= 71%
  - Febrile neutropenia= 44%
  - Decreased appetite= 11%
  - Pharyngeal inflammation= 11%
  - Nausea= 9%
  - Pyrexia= 7%
  - Bacteremia= 7%
- Laboratory abnormalities and incidence:
  - Thrombocytopenia= 69%
  - Neutropenia= 60%
  - Anemia= 33%
  - Leukopenia= 33%

# Lyfgenia Safety Data

- Incidence of increased hepatic laboratory values:
  - Aspartate aminotransferase= 18%
  - Alanine aminotransferase= 13%
  - Gamma-glutamyl transferase= 13%
  - Blood bilirubin= 7%
- Black Box Warning: Hematologic malignancy
  - 1 patient developed acute myeloid leukemia and another developed myelodysplastic syndrome
    - Clinical trial resumed since both cases found to be unlikely related to vector

# Lyfgenia Efficacy Data

Measured from 6 to 18 months post infusion

- Primary Endpoint:
  - VOE-CR (complete resolution of VOC)
    - 88% of patients (n= 28/32)
- Secondary Endpoint:
  - sVOE-CR (complete resolution of severe VOC)
    - 94% of patients (n= 30/32)

# ICER Ratings

| LYFGENIA | CASGEVY |
| --- | --- |
| *B+: Incremental or Better* | *C++: Comparable or Better* |
| **Advantages:** | **Advantages:** |
| • Improvement in severe SCD<br>• Short-term improvements in clinical symptoms | • Similar benefits as Lyfgenia |
| **Disadvantages:** | **Disadvantages:** |
| • Uncertainties about duration of benefit<br>• Potential harm from myeloablative conditioning and insertional oncogenesis | • Similar concerns to Lyfgenia about duration of benefit and harm<br>• Uncertainty due to being first CRISPR therapy available<br>• Uncertainty about generalizability of data due to small sample size |

# Clinical Pearls:

- Drugs to be discontinued:

| Hydroxyurea | Disease-modifying agents | Iron chelators | Anti-retroviral |
|---|---|---|---|
| • 8 weeks prior to mobilization | • 8 weeks prior to mobilization | • 7 days prior to conditioning until 6 months post infusion | • 4 weeks prior to mobilization (for Lyfgenia specifically) |

# Clinical Pearls:

- Unspecified contraindications:
  - Lacking data for patients who have already undergone a hematopoietic cell transplant
- Monitoring Parameters:
  - Neutrophils, platelets, and CBC frequently until engraftment and recovery
  - Lyfgenia only: malignancy screening at least every 6 months post infusion

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