Sickle Cell Disease
New Treatment Options for Patients
(FINALLY!)

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Speaker Disclosure Statement

Robin Pitts, C-FNP, MN, BSN, CPHON has no industry relationships to disclose

Objectives

- Encourage session attendees to view caring for sickle cell patients as
  - COMPELLING
  - CHALLENGING
  - REWARDING
- Review historical significance of sickle cell disease
- Discuss pathophysiology of pain in sickle cell disease
- Discuss established and new treatment options
- Where do we go from here?

History

- 1910 - Dr. Herrick and Dr. Irons, Chicago IL
  - First to note “odd shaped red blood cells that looked like a sickle” in a patient with pneumonia
- 1922 – John Hopkins Hospital
  - First noted use of the term “sickle cell anaemia”
- 1933 – Memphis TN
  - Terms “latent” and “active” were used to describe the disease
  - Clarified as heterozygous and homozygous inheritance that same year by a geneticist in Ann Arbor MI

History

- 1954
  - Hemoglobin electrophoresis widely available

- 1960's
  - The Black Panther Party championed and pushed for implementation of a national sickle cell screening program along with establishing grass roots health clinics to serve primarily Black and impoverished communities

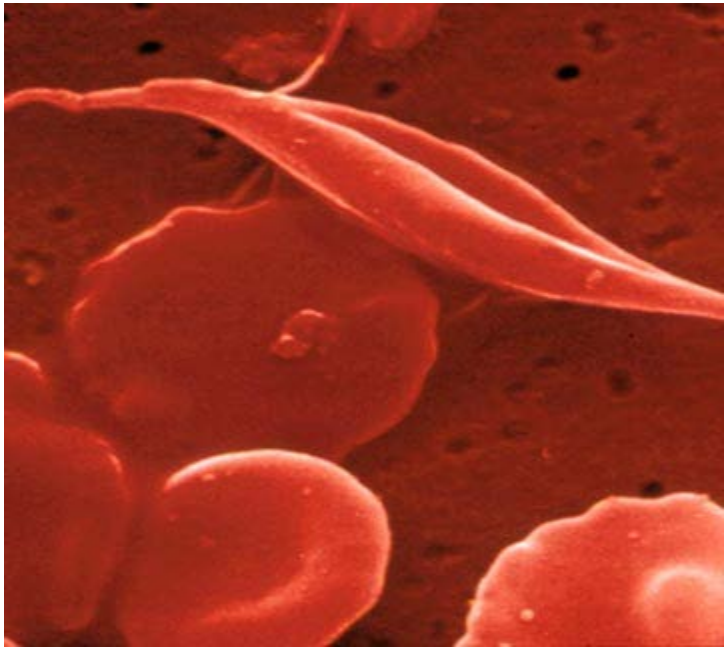
- 1972
  - Sickle Cell Anemia Control Act passed by Congress
    - "Sickle cell anemia is a debilitating inheritable disease that afflicts approximately 2 million American citizens and has been largely neglected".

History

- 1986 - PROPS study
  - Studied efficacy of Penicillin prophylaxis in infancy for those with sickle cell disease in decreasing incidence of life threatening pneumococcal infection
- 1987 - NIH Consensus Conference
  - Recommendation for universal newborn screening for sickle cell disease
- 2006 – ALMOST 20 YEARS LATER
  - All states require and provide universal newborn screening for sickle cell disease
  - Mortality has decreased by 50% in ages 1-4yo

Sickle Cell Overview

- Autosomal recessive disease
- Valine is found in place of glutamic acid on the beta chain of the hemoglobin (Hgb) molecule
- This defect causes the cell to polymerize or “sickle” when oxygen is released
- Sickled cells have increased adhesive properties and bind with platelets and leukocytes
- Life span of erythrocyte is decreased significantly
- Cell death leads to chronic hemolytic anemia



Statistics

- Over 100,000 people in the United States are affected by sickle cell disease
- Average life expectancy is 40-45 years old
- Average cost over a lifetime $1 million/patient
- Approximately 75% of hospital admissions start with an ED visit (*where they may or may not have seen a hematologist or been treated with a standard of care for sickle cell pain)
- Sickle cell patients (on average) wait 25% longer than general patients to be seen in a hospital emergency room

Pain
Sickle Cell Disease

- Pain is known as the hallmark of sickle cell disease

- Genotypes most likely to experience pain
  - Hgb SS
  - Hgb SC
  - Hgb Sbeta (0/+) thal

Pain Triggers

- Extreme temperature changes
- Dehydration
- Change in barometric pressure
- Stress
- Fatigue
- Overexertion
- Unknown etiologies

“10 Redefined” artist Hertz Nazaire

Pain
Patient Description

- Feels like I am drowning in the pain.
- Feels like a toothache all over, magnified 100 times
- Feels like a migraine headache, except that it affects my whole body
- Sickle cell pain is enveloping, you can do nothing about it. It controls you, you have no control over it

Pain
Medical Definition

- An unpleasant sensation that can range from mild, localized discomfort to agony.
- Has both physical and emotional components.
- The physical part of pain results from nerve stimulation.
- Is mediated by specific nerve fibers that carry the pain impulses to the brain where “their conscious appreciation can be modified by many factors”

Pain
Influencing factors

- Developmental stage
  - Ability to self regulate and cope with discomfort
- Previous pain experiences
- Precipitating events
- Gender
- Family and sociocultural factors
- Inflammation
- Chronic opioid use

Pain Considerations

- Subjective
- Highly personal
- Unique
- Almost impossible to measure or quantify clinically


Someday we will understand
how the same virus
can cause a runny
nose in women and
a life threatening man
flu in men...
someecards

Pain
Sickle Cell Disease

- The medical definition of CHRONIC pain is very inadequate

- Clearly patients with sickle cell disease can have several different types of pain including concurrent acute and chronic pain

- Multiple factors in sickle cell disease contribute to chronic pain over time
  - Vessel wall damage
  - Chronic inflammation with increased inflammatory markers
  - Central nervous system sensitization

"Wow. That Tylenol really took away my pain." said no one ever.

Sickle Cell Pain Components

- Micro-vascular obstruction (vaso-occlusion)
- Decreased oxygen supply to tissues
- Cellular adhesion
- Cell death
- Inflammation
- All these lead to a “noxious micro-environment” which can trigger peripheral and central pain pathways

Noxious micro-environment

- Chemical mediators released following tissue damage and inflammation
  - Cytokines
  - Growth factors
  - Tryptase
  - Substance P
  - Amines

- These inflammatory mediators directly activate nerve endings which evoke the initial pain response

- When in constant production the nerve endings are constantly being impacted

Noxious micro-environment

- Endothelin-1 levels elevated
  - Potent, long acting amino acid peptide
  - Mediator of vaso-constriction and inflammation
  - Increased production with hypoxemia

- PGE2 levels elevated
  - Potent inflammatory mediator
  - Sensitizes nociceptors
  - Induces hyperalgesia

- Tryptase, Substance P and P-selectin
  - Activation of mast cells
  - Mediators of chronic inflammation
  - Urticaria
  - Neuropathic pain

Noxious micro-environment

- Blood vessel obstruction leading to tissue ischemia
  - Vaso-occlusion
- Cellular adhesion
  - Platelets, lymphocytes
- Release of cytokines with cell death
  - Substance P, P-selectin
  - Endothelin-1
  - Mast cell activation
- Chronic inflammation
  - Vessel wall irritation and narrowing

What Doesn’t Kill You Makes You Stronger (?)

What doesn’t kill you makes you stronger

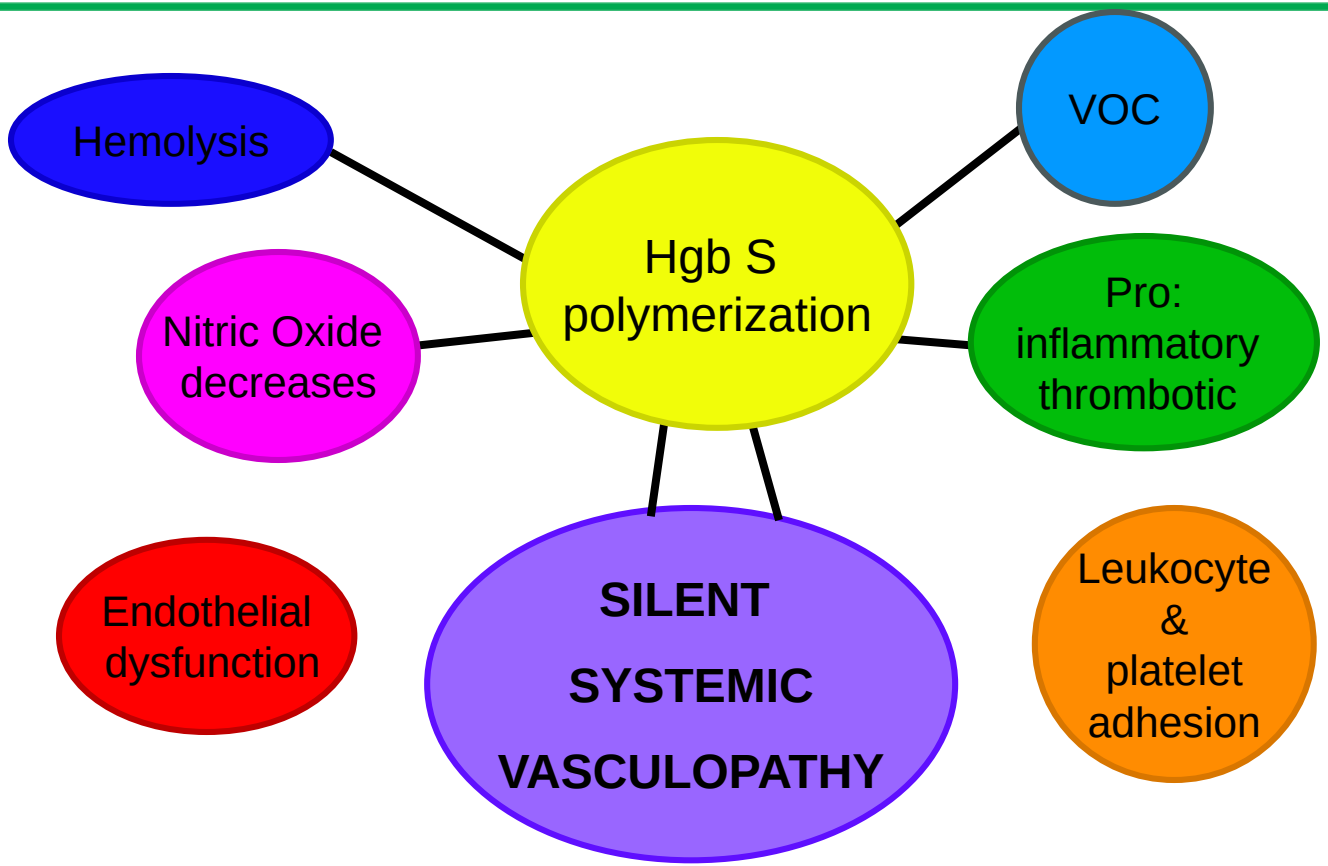
Stand a little taller

Doesn’t mean I’m lonely when I’m alone

What doesn’t kill you makes a fighter

Footsteps even lighter

Conceptualization



Hydroxyurea

- **Chemotherapeutic agent - antimetabolite**

- **Mechanism of action**
  - Increases fetal hemoglobin production
  - Increases size, oxygen carrying capacity and life span of erythrocyte
  - Decreases expression of erythrocyte adhesion receptors

- **Side effects**
  - cytopenias, decreased sperm count, teratogen

Hydroxyurea

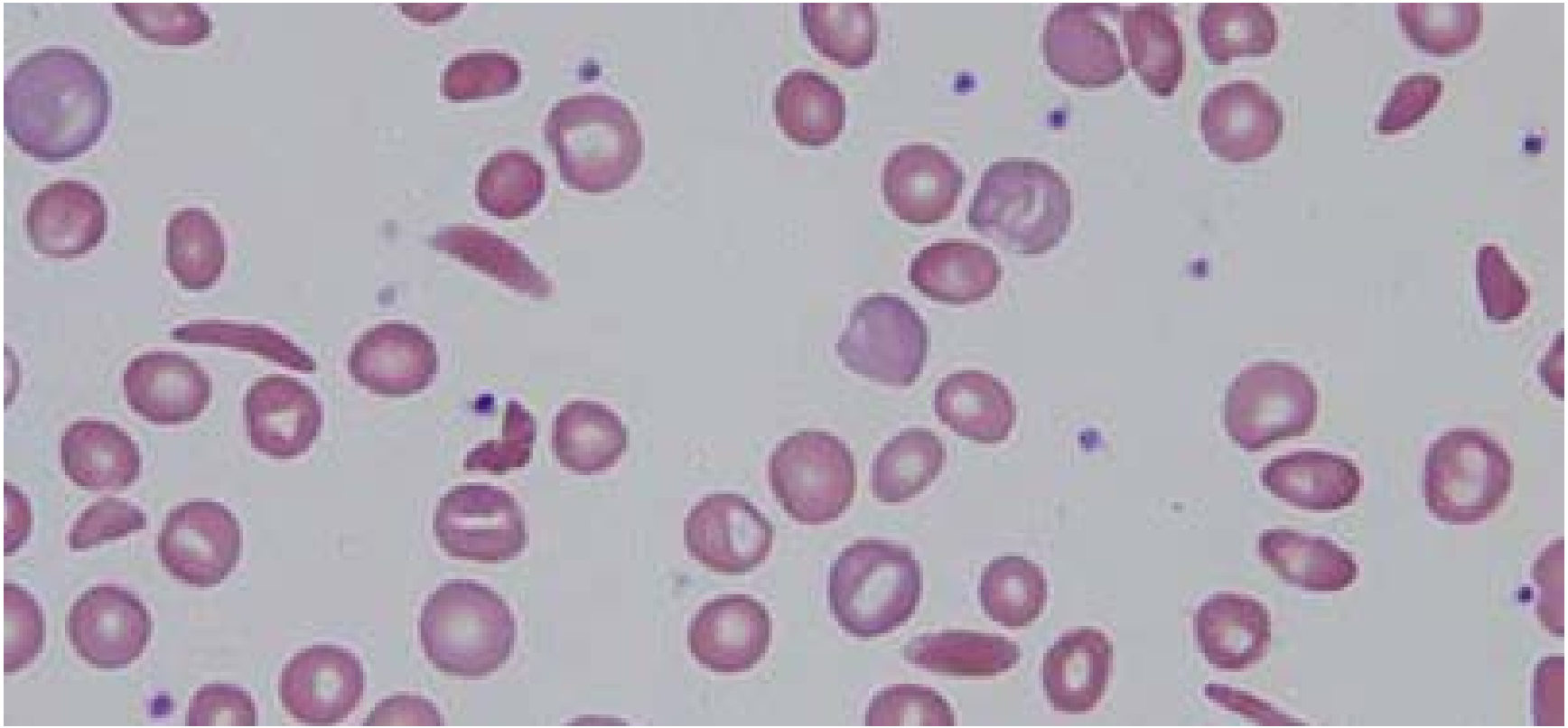
- FDA approved in 1998 for the treatment of adults with sickle cell disease.

- Available products
  - Droxia 200mg, 300mg, 400mg, Hydrea 500mg
  - Siklos 100mg (non- scored tabs), 1000mg (scored)
  - Liquid suspension

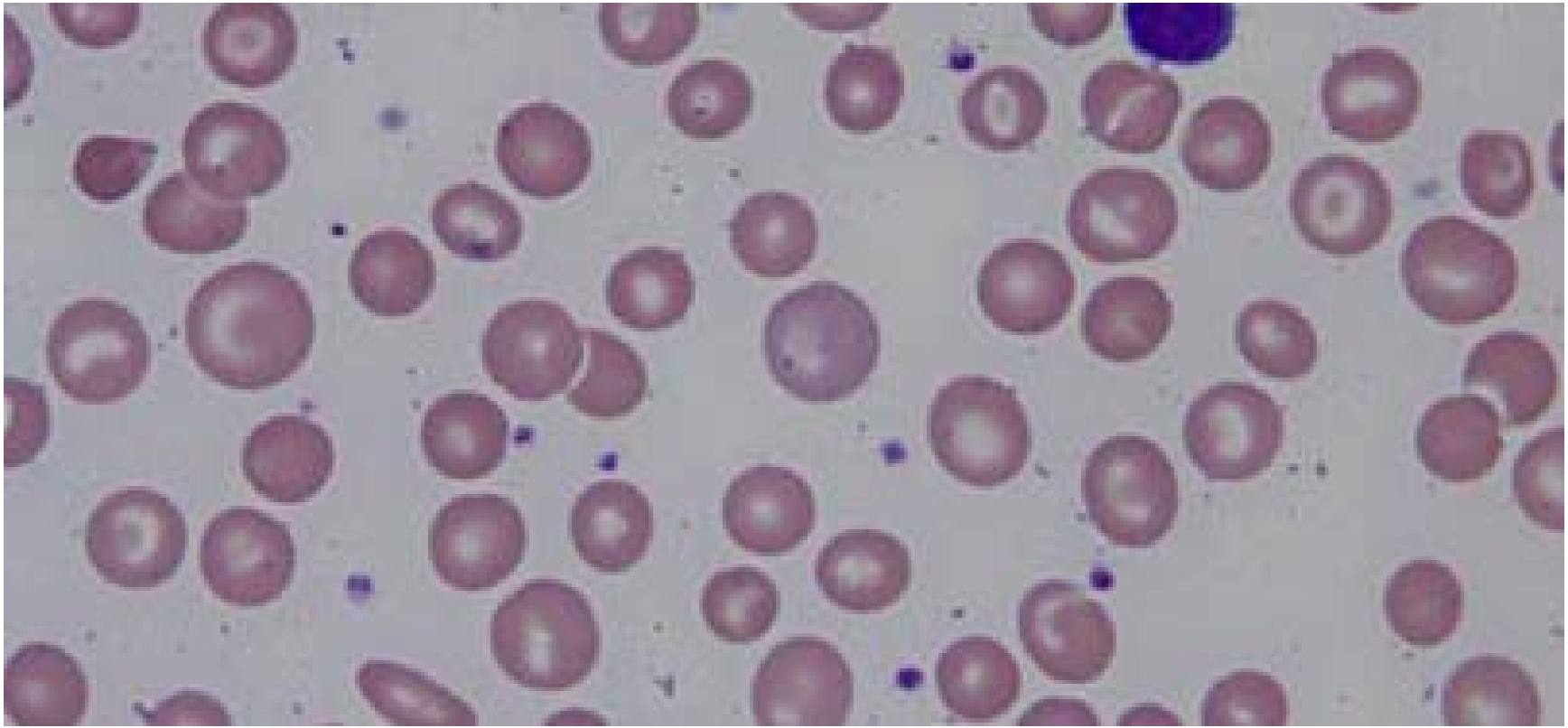
- Cost
  - Approx $1000/year

- Outcomes
  - Decreased incidence of VOC, increased hemoglobin levels

Pre Hydroxyurea



Post Hydroxyurea



New(er) Treatment Considerations

- Vitamin D
- Glutamine
- Voxelotor
- Crizanlizumab

Vitamin D

- **Fat soluble vitamin, critical for bone growth**

- **Mechanism of action**
  - Significant anti-inflammatory action

- **Sources**
  - Fortified dairy products (milk, yogurt, cheese) and breakfast cereals
  - Fatty fish, beef liver, egg yolks
  - Sunlight

- **Vitamin D3 supplement – cholecalciferol**
  - Chemically similar to what is found naturally in the body

Glutamine

- **L-glutamine is an essential amino acid**

- Sickled cells are in a constant state of oxidative stress/imbalance

- **Mechanism of action**
  - Increased availability of L-glutamine for use by stressed erythrocytes
  - Decreased erythrocyte adhesion
  - Reduces oxidative damage in red blood cells (RBC), increasing their flexibility and ability to transport oxygen

- **Side effects**
  - nausea, fatigue, non-cardiac chest pain, back pain

Glutamine

- FDA approved for ages 5 and older in 2017
- Once daily, tablet
- Cost
  - $24-50K/year
- Outcomes
  - Median number of pain crises was 25% lower with L-glutamine vs placebo
  - Decreased hospitalizations by 33%
  - Significantly lower numbers of acute chest syndrome with L-glutamine vs placebo

Voxelotor

- **Polymerization inhibitor**

- **Mechanism of action**
  - Binds to hemoglobin to increase oxygen affinity of erythrocytes
  - Normal erythrocyte function and oxygen delivery is restored

- **Side effects**
  - headache, diarrhea, abdominal pain, fatigue

Voxelotor

- Fast tracked FDA approval for ages 12 and older in 2019
- Once a day, tablets (500mg each)
- Cost
  - $80-120K/year
- Outcomes
  - 65% of patient receiving 1500mg dosing achieved >1g/dl increase in hemoglobin
  - Within 2 weeks, hemoglobin level increased by approx 40% from baseline

Crizanlizumab

- **Anti P-selectin monoclonal antibody**

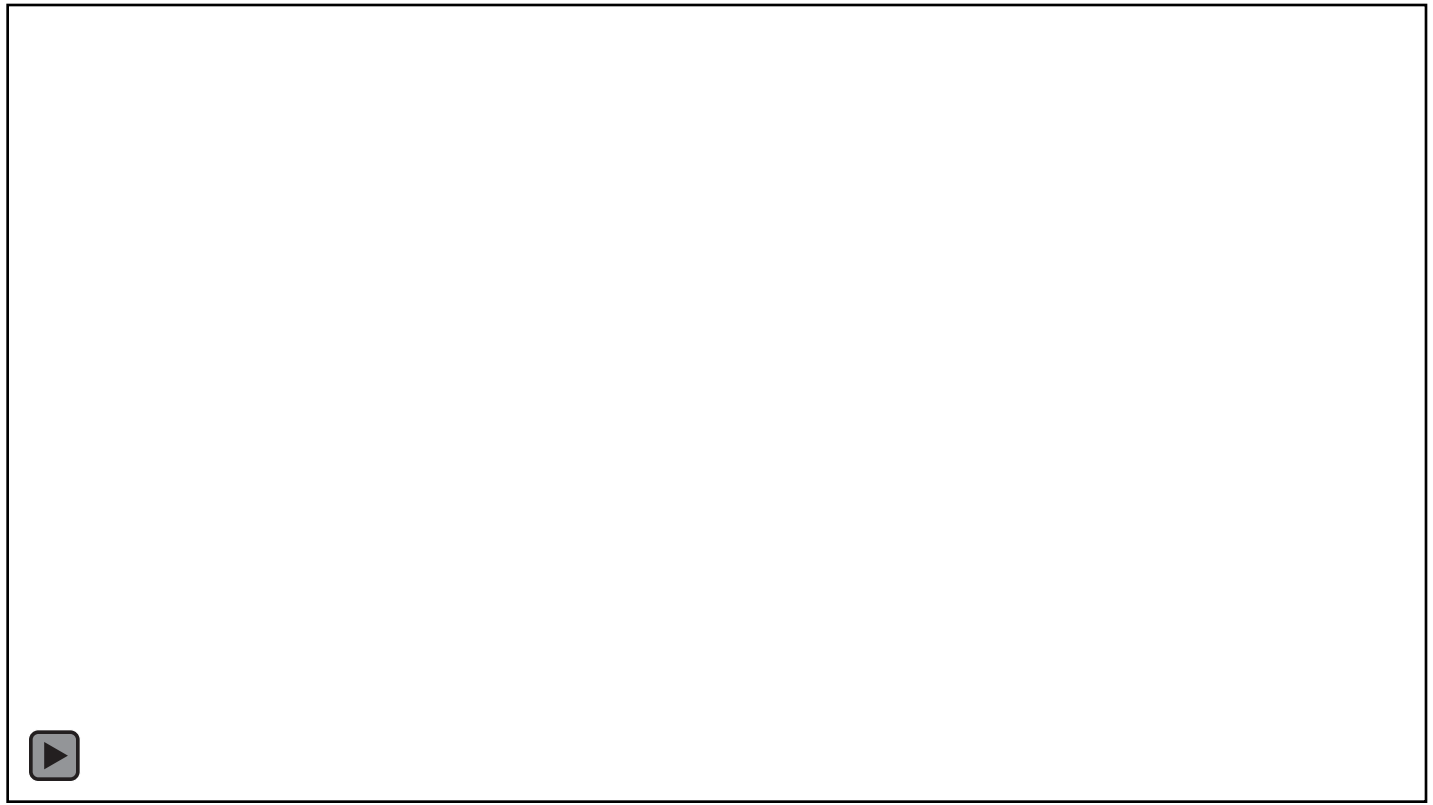
- **Mechanism of action**
  - Binds to and blocks P-selectin
  - Reduces the ability of erythrocytes to stick to other cells (mainly platelets and leukocytes)
  - Reduces inflammation and stickiness of the endothelial wall
  - Decreases vessel wall irritation

- **Side effects**
  - arthralgias, back pain, nausea, pyrexia

Crizanlizumab

- Approved by FDA for ages 16 and older in 2019
- Monthly, IV infusion over 30 minutes
- Cost
  - $80-125K/year
- Outcomes
  - 50% of participants on highest dose had no crisis vs placebo group
  - Annual rate of days hospitalized 4 vs 6.87
  - Delayed onset of first and second VOC

Now What?



Chronic Pain

- 30% of adults with sickle cell disease report daily pain
- 50% have enough symptoms to meet the diagnosis of chronic pain

Chronic Pain

"Chronic sickle pain
may be a distinct pathophysiologic entity
because the initial origin of injury
may not be relevant
once sensory pathways shift
to a state of hyperexcitability"

Tran, 2017

Chronic Pain

- Mechanism of pain in sickle cell disease remains poorly understood

- Traditionally defined as pain lasting longer than 3 months
  - Damaged neurons continually send impulses in absence of stimulus
  - Intense pain can be perceived with low intensity stimuli
  - Hypersensitive reaction to pain
  - Real physical pain – not primarily a psychological or psychiatric situation

- An acquired nervous system disorder

- Involves pathological alterations at all levels of the nervous system

Chronic Pain

- The most common cause of emergency room visits and hospital admissions for patients with sickle cell disease is VOC pain

- Total medical costs exceed $1.1 billion annually

- Minority patients are at greater risk for perceived discrimination and under-treatment of their pain which contributes to:
  - Greater clinical pain severity
  - Decreased coping strategy
  - Greater psychological impact of pain
  - Decreased trust in medical providers

Non-pharmacologic Treatment

- Music
- Art
- Child life
- Exercise
- Acupuncture
- Heat and Massage
- Physical therapy
- Hypnosis/Biofeedback
- Psychology/Counseling support
- Activities of Daily Living – school, work, sleep hygiene, diet

Pharmacologic Treatment

- Hydration
- Non-steroidal medications (NSAIDS) – ketorolac, ibuprofen
- Topical patches – lidocaine 5%
- NSAID lotions/creams – diclofenac
- Anticonvulsants – pregabalin, gabapentin
  - turn down sensitivity of damaged nerve fibers
  - decrease pain signals sent out by damaged nerve fibers
- Tricyclic Antidepressants - amitriptyline, nortriptyline
  - increase neurotransmitters in spinal cord that reduce pain signals
- Opioids - second line therapy
  - approximately 25% of patients prescribed opioids for chronic pain misuse them
  - approximately 10% will develop an opioid use disorder

Thoughts

- Once the damage is done it is very difficult to undo – both physically and psychologically

- Providers and caregivers must learn how to be PROACTIVE vs REACTIVE

- Use all the tools in the pain toolbox
  - Non-pharmacologic interventions
  - Pharmacologic interventions

Final Thoughts

"The lack of research funding, attention, and treatment of sickle cell are considered a matter of racial inequity.
It is a **Black Lives Matter** issue
because it is primarily a genetic disease that affects Black people who often also have fewer financial resources."

W. Bloom, 2019