Sickle Cell Review and Health Disparities

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UVA HEALTH, LYMPHOMA AND MYELOMA PHARMACIST

Disclosures

I have nothing to disclose. I will not be discussing off-label indications.

Objectives

To review the pathophysiology and long-term complications of sickle cell disease (SCD)

To discuss pharmacotherapy and literature used to mitigate complications of SCD

To identify the impact of healthcare disparities on SCD care and to propose actionable solutions to minimize these experiences

Today's Discussion

Disease Review | Current Management | Disparities in SCD | Potential Solutions

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SCD Overview

Group of inherited red blood cell disorders leading to these red blood cells to become a sickle shape and break down

Highest prevalence in sub-Saharan Africa, Middle East, and India

Estimated to impact approximately 100,000 Americans

Estimated 2500-4999 SCD patients live in Virginia

Median lifespan of 54 years

Estimated total lifetime healthcare cost of a person with SCD: $9,000,000

Hassell KL. Am J Prev Med. 2010 Apr;38(4 Suppl):S512-21.

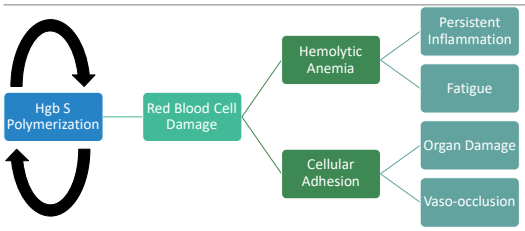
SCD: Sickle Cell Disease

Pathophysiology

- Inherited in an autosomal recessive fashion
- An alternation in one DNA base-pair on codon 6 resulting in a modified hemoglobin conformation (Hgb S)
- Cell sickling is driven by the recurrent polymerization of Hgb S
- Recurrence leads to to persistent vaso-occlusion, inflammation, and hemolysis

Kavanagh PL, et al. JAMA. 2022 Jul 5;328(1):57-68.

SCD Pathophysiology Cascade



Ware RE, et al. Lancet. 2017 Jul 15;390(10091):311-323.; Kavanagh PL, et al. JAMA. 2022 Jul 5;328(1):57-68.

SCD Genotypes

Disease	HgbA (%)	HgbS (%)	HgbF (%)	Clinical Course	Prevalence (%)
Sickle Cell Anemia	0	80-95%	5-15%	Severe	50-60%
Sickle-C disease	0	50-55%	<3%	Moderate	25-30%
S/β^0 thalassemia	0	80-90%	5-15%	Severe	1-3%
S/β^+ thalassemia	10-25%	70-80%	<3%	Mild	5-10%
S/Other	0	50-60%	Variable	Variable	1-2%

Ware RE, et al. Lancet. 2017 Jul 15;390(10091):311-323.

Hgb A: adult hemoglobin; Hgb F: fetal hemoglobin

SCD-Related Complications

	Childhood	Adolescence	Adulthood
During Life Stages	Delayed growth	Delayed puberty	Hemorrhagic Stroke | Leg Ulcers | Reproductive Complications | Pulmonary HTN
Spanning Stages	Aplastic Crisis | Splenic Complications| Infection		Avascular Necrosis | Chronic Pain | Priapism | Retinopathy | Gallstones | Nephropathy | VTE
During All of Life	Acute Pain | Acute Chest Syndrome | Ischemic Stroke		

Kavanagh PL, et al. JAMA. 2022 Jul 5;328(1):57-68.

HTN: hypertension; VTE: venous thromboembolism

Audience Response Question 1

Which of the following is not a complication commonly seen with SCD?

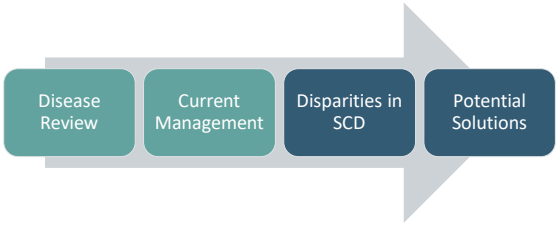
A. Stroke

B. Priapism

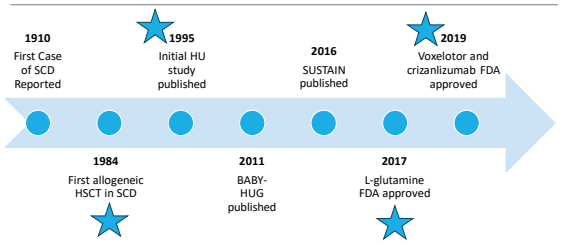
C. Asplenia

D. Pancreatitis

Today's Discussion



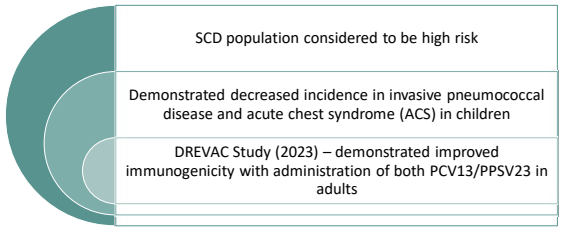
Innovations in SCD



Salinas Cisneros G, et al. Front Physiol. 2020 May 20;11:435.

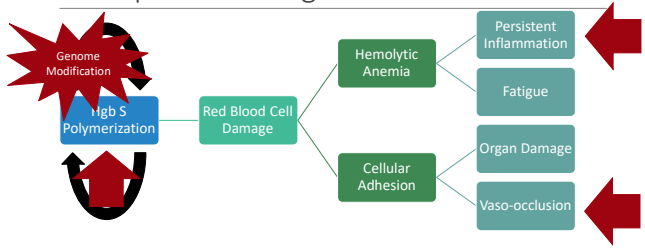
HSCT: hematopoietic stem cell transplantation; HU: hydroxyurea

Pneumococcal Vaccination



Chang TP, et al. Pediatr Emerg Care. 2013 Jul;29(7):781-6.; Melica G, et al. Clin Infect Dis. 2023 Jun 8;76(11):1949-1958.

Therapeutic Strategies



Ware RE, et al. Lancet. 2017 Jul 15;390(10091):311-323.; Kavanagh PL, et al. JAMA. 2022 Jul 5;328(1):57-68.; Salinas Cisneros G, et al. Front Physiol. 2020 May 20;11:435.

Therapeutic Strategies

Targeting Polymerization	Targeting Vaso-occlusion	Targeting Inflammation	Modifying the Genome
• Hydroxyurea • Voxelotor	• L-Glutamine • Crizanlizumab		• Allogenic HSCT

Salinas Cisneros G, et al. Front Physiol. 2020 May 20;11:435. HSCT: hematopoietic stem cell transplantation

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Established Strategies – Polymerization

Agent	FDA Approval Date and Indication	Mechanism of Action	Dosing	Common ADEs
Hydroxyurea	1998: Adults, to reduce incidence of pain crises 2017: Children ≥ 2 years to reduce pain crises	-Increase in fetal hemoglobin and NO -Decrease adhesion and inflammation	Start dose at 15-20 mg/kg/day	Neutropenia (13%), Thrombocytopenia (7%), Nausea (3%)
Voxelotor	2019: Ages ≥ 12 to increase hemoglobin concentration	-Allosteric modification of hemoglobin with aim to stabilize the oxygenated state	1500mg daily	Diarrhea (20%), Abdominal Pain (19%), Nausea (17%), Headache (16%), Rash (14%), Fatigue (14%), Fever (12%)

Brandow AM. *J Hematol Oncol.* 2022;15(1):20. NO: nitric oxide

Established Strategies – Polymerization

Agent	Trials	Result
Hydroxyurea	Charache, et al. (1995)	-Rate of annual crises: 2.5 vs 4.5 (P<0.001) -Median time to crisis: 3.0 vs 1.5 months (P=0.01)
	BABY HUG (2011)	-No differences in splenic or renal function -Pain Events: 177 vs 375 (p=0.002) -Potential decreases in ACS, hospitalizations, and transfusion needs
	TWiTCH (2016)	Non-Inferiority was demonstrated between HU and standard transfusions for primary stroke prevention
	SWiTCH (2013)	Administration of HU with phlebotomy resulted in an increased risk of serious AEs than transfusion/chelator arm.
Voxelotor	HOPE (2021)	-Change in mean Hgb from baseline: 1.0 vs 0.0 (p<0.0001) -Improvements in hemolysis markers

Salinas Cisneros G, et al. Front Physiol. 2020 May 20;11:435.; Charache S, et al. N Engl J Med. 1995 May 18;332(20):1317-22.; Wang WC, et al. Lancet. 2011 May 14;377(9778):1663-72. ; Ware RE, et al. Lancet. 2016 Feb 13;387(10019):661-670.; Alvarez O, et al. Am J Hematol. 2013 Nov;88(11):932-8.; Howard J, et al. Lancet Haematol. 2021 May;8(5):e323-e333.

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HSCT: hematopoietic stem cell transplantation

Established Strategies – Vaso-occlusion

Agent	FDA Approval Date and Indication	Mechanism of Action	Dosing	Common ADEs
L-Glutamine	2017: Ages ≥ 5 to reduce pain crises and ACS	Increase nicotinamide adenine dinuclotide (NAD) redox potential	<30 kg: 5g BID 30-65 kg: 10g BID >65 kg: 15g BID	Constipation (21%), Nausea (19%), Headache (18%), Abdominal pain (17%), Cough (16%)
Crizanlizumab	2019: Ages ≥ 16 to reduce frequency of VOC	Binds to P-selectin	5mg/kg/dose IV weeks 0, 2, and then 4-week intervals	Nausea (18%), Arthralgia (18%), Back pain (15%), Fever (11%)

Brandow AM. *J Hematol Oncol.* 2022;15(1):20.

BID: twice daily

Established Strategies – Vaso-occlusion

Agent	Trials	Result
L-Glutamine	Niihara, et al. (2018)	-Annual pain crisis rate: 3 vs 4 (p=0.005) -Hospitalization rate: 2.0 vs 3.0 (p=0.005) -High rate of therapy discontinuation
Crizanlizumab	SUSTAIN (2017)	-Vaso-occlusive crises per year: 1.63 vs 2.98 (p=0.01) -Median time to first crisis: 4.07 vs 1.38 months (p=0.001)

Salinas Cisneros G, et al. Front Physiol. 2020 May 20;11:435.; Niihara Y, et al. N Engl J Med. 2018 Jul 19;379(3):226-235.; Ataga KI, et al. N Engl J Med. 2017 Feb 2;376(5):429-439.

Therapeutic Strategies

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Established Strategies – Transplantation

- Considered to be the only curative option for patients with severe SCD
- Available to <20% of patients with SCD
- Has demonstrated ability to not only establish donor-derived erythropoiesis but also stabilize/restore function to previously damaged organs
- Studies have demonstrated worse OS and increased incidence of GVHD in patients over 16 years

Salinas Cisneros G, et al. Front Physiol. 2020 May 20;11:435.

OS: overall survival; GVHD: graft-versus-host disease

Demonstrated Benefits

Benefit	Hydroxyurea	L-Glutamine	Voxelotor	Crizanlizumab
Pain Crisis	X	X		X
Time to First Pain Crisis	X	X		X
Time to Second Pain Crisis	X	X		X
Acute Chest Syndrome	X	X		
Need for Transfusions	X			
Hospitalizations	X	X		X
Hemoglobin	X		X	
Hemolysis Labs			X	
Mortality	?			
Quality of Life				

Cost of Therapy

Medication	Supplied As	Cash Price
Hydroxyurea	500 mg capsule	$1.64/capsule $3.28/dose for a 70kg patient $98.40/month for 70kg patient
L-glutamine	5 g packet	$23/packet $46-138/day $1380-4140/month
Voxelotor	500 mg tablet	$138.89/tablet $416.67/dose $12,500/month
Crizanlizumab	100 mg/10 mL vial	$282.86/mL $2,828.60/10 mL $9,900/month for 70kg patient

Therapeutic Strategies – Summary

- **Hydroxyurea**
  - Standard of Care
- ↓
- **Voxelotor**
  - Clinical benefit lacking
- ↓
- **L-Glutamine**
  - Can consider as an add-on agent
  - Cost and GI tolerance can be prohibitive
- ↓
- **Crizanlizumab**
  - Can consider as a final add-on agent
  - Cost and monthly infusion must be considered

The Future is Bright!

Gene therapy	Gene editing	Panobinostat	Decitabine ± tetrahydrouridine ± nicotinamide	Sanguinate	IMR-687
Sevuparin	IVIG	Arginine	Imatinib	Fish Oil	Rifaximin
AG-348	Crovalimab	ALXN1820	AG-948	Fostamatinib	Inclacumab

Audience Response Question 2

Which of the following agents has been demonstrated to cure SCD?

A. Allogeneic HSCT

B. Hydroxyurea

C. Voxelotor

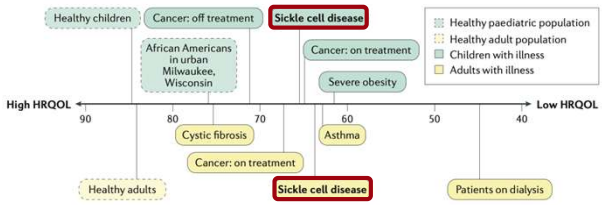
D. Crizanlizumab

Today's Discussion

Demonstrated Benefits

Benefit	Hydroxyurea	L-Glutamine	Voxelotor	Crizanlizumab
Pain Crisis	X	X		X
Time to First Pain Crisis	X	X		X
Time to Second Pain Crisis	X	X		X
Acute Chest Syndrome	X	X		
Need for Transfusions	X			
Hospitalizations	X	X		X
Hemoglobin	X		X	
Hemolysis Labs			X	
Mortality	?			
Quality of Life				

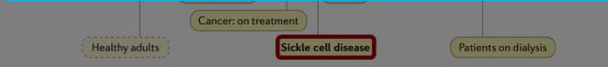
Health-Related Quality of Life (HRQOL)



Kato GJ, et al. Nat Rev Dis Primers. 2018 Mar 15;4:18010.

Health-Related Quality of Life

Despite recent treatment innovations, why do patients with SCD have a diminished health-related quality of life and only live to a median age of 54?



Terms and Definitions

Health Disparities

Preventable differences in the burden of disease or outcomes experienced by populations

Can be classified as structural, institutional, and interpersonal

Pharmacoequity

Fair access to medications regardless of race or socioeconomic background

https://www.cdc.gov/aging/disparities/index.htm; Lee L, et al. *Public Health Rep.* 2019;134(6):599-607.; Kavanagh PL. *JAMA.* 2022;328(1):57-68.; Brandow AM. *J Hematol Oncol.* 2022;15(1):20.

Opportunities for SCD Disparities

Structural

- Social Determinants of Health (SDOH)
- National research funding and medication development

Institutional and Interpersonal

- Transitions of care
- Implicit biases
- Lack of provider familiarity
- Lack of specialized SCD centers
- Lack of patient education or understanding
- Poor adherence
- Treatment limitations

Power-Hays A, et al. *N Engl J Med.* 2020;383(20):1902-1903.; Lee L, et al. *Public Health Rep.* 2019;134(6):599-607.

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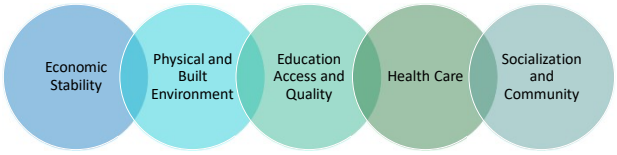
Structural Disparities – SDOH



Power-Hays A, et al. *N Engl J Med*. 2020;383(20):1902-1903.; Lee L, et al. *Public Health Rep*. 2019;134(6):599-607.

Structural Disparities – Monetary Support

	SCD	CF	P-Value
Disease Characteristics			
National Patient Population	90,000	30,000	NA
Life Span, mean (yr)	58	46	NA
Estimated lifetime costs per individual, $	460,151	306,332	NA
Annual NIH Funding			
NIH funding, per person affected, mean (SD), $	812 (147)	2807 (175)	<0.001
Research Output (2008-2018)			
Annual PubMed publications, mean (SD)	926 (157)	1594 (225)	<0.001
Annual clinical trials, mean (SD)	24 (6.3)	27 (6.9)	0.23
New FDA drug approvals	1	4	NA
New FDA drug indications	2	11	NA

Farooq F, et al. *JAMA Netw Open*. 2020;3(3):e201737. Published 2020 Mar 2.

Opportunities for SCD Disparities

Structural

- Social Determinants of Health (SDOH)
- National research funding and medication development

Institutional and Interpersonal

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- Implicit biases
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- Lack of specialized SCD centers
- Lack of patient education or understanding
- Poor adherence
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Where we can have the most impact!!

Power-Hays A, et al. *N Engl J Med*. 2020;383(20):1902-1903.; Lee L, et al. *Public Health Rep*. 2019;134(6):599-607.

Impacting Patient Care Perceptions

Study	Assessment	Outcomes
Kanter, et al. (2020) N=440	-Survey conducted to evaluate pain interference, quality of care, and self-ability to manage pain -Evaluated at 8 SCD Implementation Consorium sites	-82.6% of patients reported access to non-acute care -92.1% reported satisfaction with their usual care -Perceptions were primarily driven by pain and pain management in outpatient setting -66% reported an emergency department visit in the past year for acute pain
Haywood, et al. (2014) N=354	-Observational cohort study of patient experiences at two academic medical centers	-Disease based discrimination was associated with a greater range of self-reported pain -Patients who experienced discrimination were associated with poorer medication adherence

Haywood C, et al. *J Pain Symptom Manage.* 2014;48(5):934-943.; Haywood C, et al. *J Gen Intern Med.* 2014;29(12):1657-1662.; Kanter J, et al. *JAMA Netw Open.* 2020;3(5):e206016. Published 2020 May 1.

Today's Discussion

Disease Review → Current Management → Disparities in SCD → Potential Solutions

Proposed Actions to Reduce Impact

Structural
- Universal Screening for SDOH
- Federal funding for SCD centers and research
- Development of updated treatment guidelines

Institutional
- Develop formal report systems to document responses to biased behaviors
- Include patients with SCD or advocates on task forces
- Institute SCD-specific pain-management protocols
- Empower patients with SCD to safely report concerns about inequities
- Develop community health centers and/or day hospitals
- Provide psychosocial support

Interpersonal
- Speak explicitly about disparities with a focus on experiences
- Recognize opportunities to educate providers on patient's healthcare experiences
- Implement mandatory implicit bias training
- Practice mindfulness and reflection in the care of SCD patients

Power-Hays A, et al. *N Engl J Med.* 2020;383(20):1902-1903.; Lee L, et al. *Public Health Rep.* 2019;134(6):599-607.

The Role of a Pharmacist

- SDOH Assessments
- Identification of knowledge gaps
- Vaccination status
- Treatment Adherence
- Medication Reconciliation
- Assessment for Additional Therapies

Audience Response Question 3

Which of the following actions can you take to help in minimizing health inequities for patients with SCD?

A. Ensuring the patient is up-to-date on their vaccinations

B. Assessing the patient barriers to adherence

C. Performing an in-depth medication reconciliation

D. All of the above

Conclusion

SCD is the most prevalent hemoglobinopathy in the United States and is a large public health concern

Multiple therapeutic strategies exist for SCD; however, even more are in the pipeline including gene therapy

Despite recent scientific development, there are many opportunities for health disparities to be exacerbated throughout the care of patients with SCD and pharmacists can take action to minimize these

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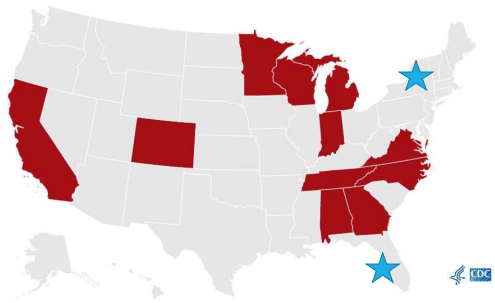
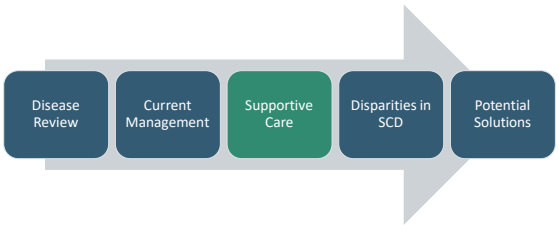
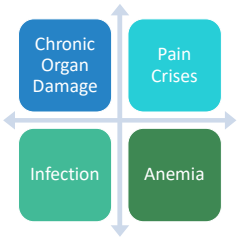


https://www.cdc.gov/ncbddd/hemoglobinopathies/scdc-data.html

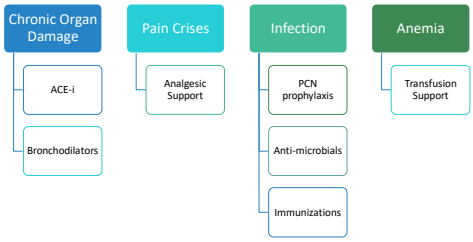
Today's Discussion



Most Common Areas of Support



Supportive Care Strategies



SCD Public Health Impact

Exact number of patients in the United States is unknown	Estimated 2500-4999 SCD patients live in Virginia	1 in 13 Black or African American patients are born with the sickle cell trait
1 in 365 Black or African American patients are born with SCD	Median lifespan for someone with SCD is 54 years	Estimated total lifetime healthcare cost of a person with SCD is estimated to be $9 million dollars

Hassell KL. Am J Prev Med. 2010 Apr;38(4 Suppl):S512-21.

Genome Modification with OTQ923

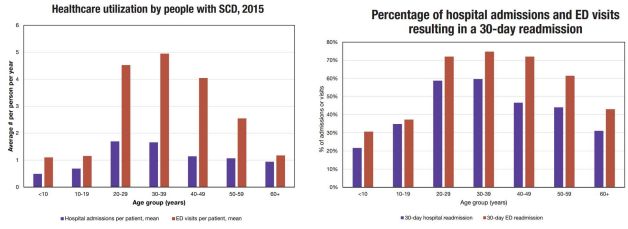
- Autologous, ex vivo CRISPR-Cas9-edited CD34+ stem cell product
- Phase 1-2 clinic study assessed use in the initial three patients
- Prior to collection, patients received monthly red-cell exchange transfusions for at least 2 months
- Mobilization occurred with plerixafor and then the apheresis product was enriched for CD34+ cells and then electroporated with the CRISPR-Cas9-gRNA-68 complex
- Conditioning with myeloablative busulfan
- Reported an improvement in hemoglobin and fetal hemoglobin percentage
- Demonstrated a potential role for gene modification in SCD

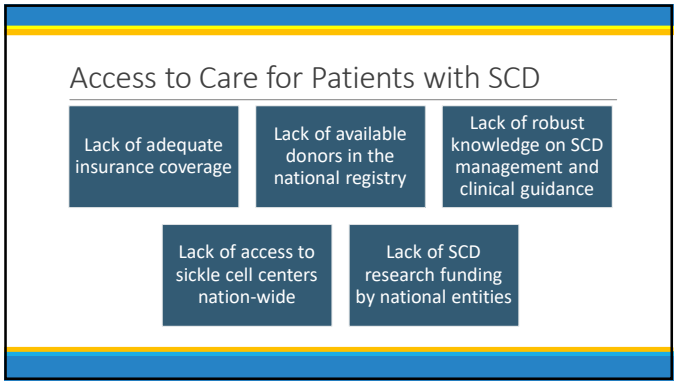
Sharma A, et al. N Engl J Med. 2023 Aug 31;389(9):820-832.

Other Resources

CDC Public Health Webinar Series on Blood Disorders

Healthcare Utilization of those with SCD




Access to Care for Patients with SCD
Lack of adequate insurance coverage
Lack of available donors in the national registry
Lack of robust knowledge on SCD management and clinical guidance
Lack of access to sickle cell centers nation-wide
Lack of SCD research funding by national entities