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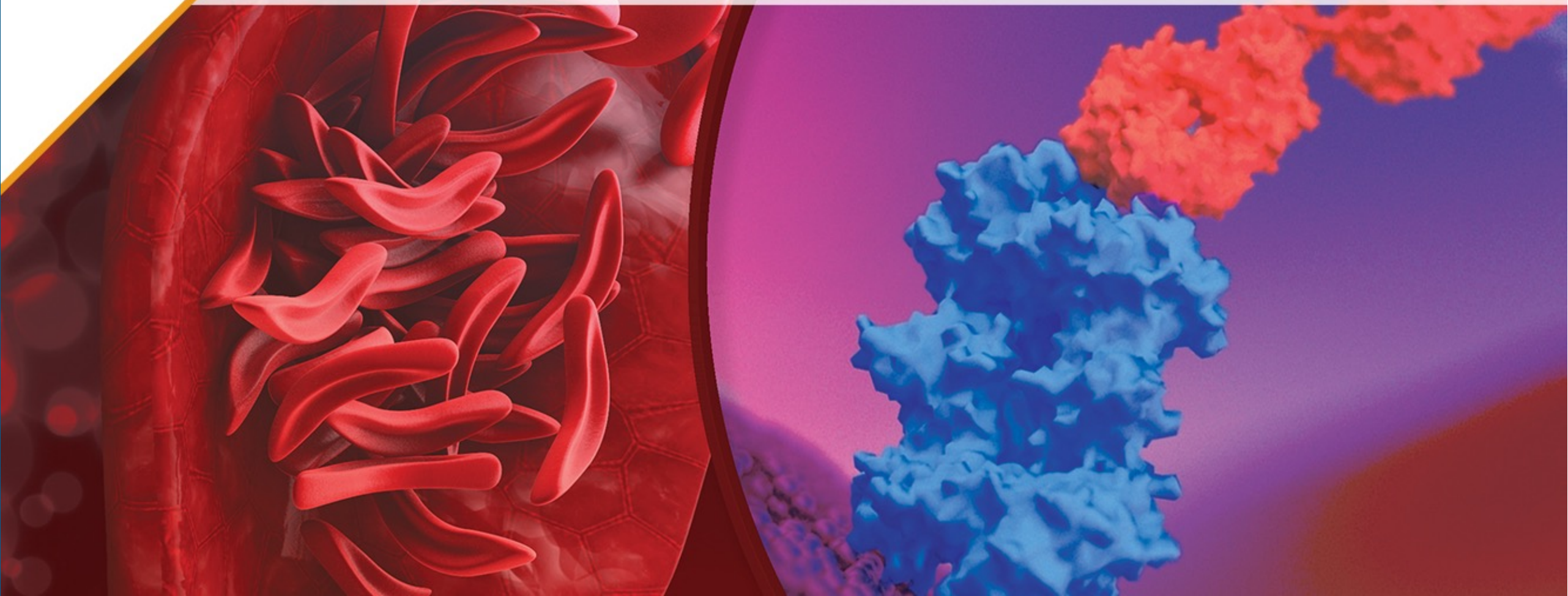
Improving Interprofessional Management of Sickle Cell Disease with Disease-Directed Therapies



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Disclosure of Conflicts of Interest

- Fuad El Rassi, MD, reported a financial interest/relationship or affiliation in the form of *Consultant*: Novartis Pharmaceuticals Corp; bluebird bio, Inc; and GBT. *Contracted research*: Cyclerion Therapeutics; Novartis Pharmaceuticals Corp; and Pfizer, Inc.

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Activity Agenda

- Understanding patient and societal burdens of sickle cell disease (SCD)
- Evaluating contributing factors, causes and pathophysiology of SCD and the various syndrome subtypes
- Overview of acute and chronic SCD complications by organ system
- Understanding vaso-occlusive crisis (VOC) in the sickle cell patient
- Understanding acute chest syndrome (ACS) in the sickle cell patient
- Targeting SCD-related complications with disease-directed therapies
- Novel Agents for Prevention of Vaso-Occlusive Crisis and Pain Management
- Practical application case series

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Assess the mechanisms and burden of SCD, specifically VOCs and vaso-occlusion-mediated end organ damage in adult and pediatric populations
- Integrate the latest safety and efficacy data of current and emerging therapeutic options for SCD into clinical practice in order to reduce and prevent VOCs, minimize tissue and organ damage, and improve patient outcomes
- Implement multidisciplinary collaborations to create personalized SCD treatment plans based on the latest evidence to improve care and QoL for SCD patients

SCD, sickle cell disease; VOCs, vaso-occlusive crises.

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Setting the Stage: Understanding Patient and Societal Burdens of Sickle Cell Disease

Peculiar Elongated and Sickle-Shaped Red Blood Cells in a Case of Severe Anemia

Herrick. *Arch Intern Med*. 1910;6:517-521.

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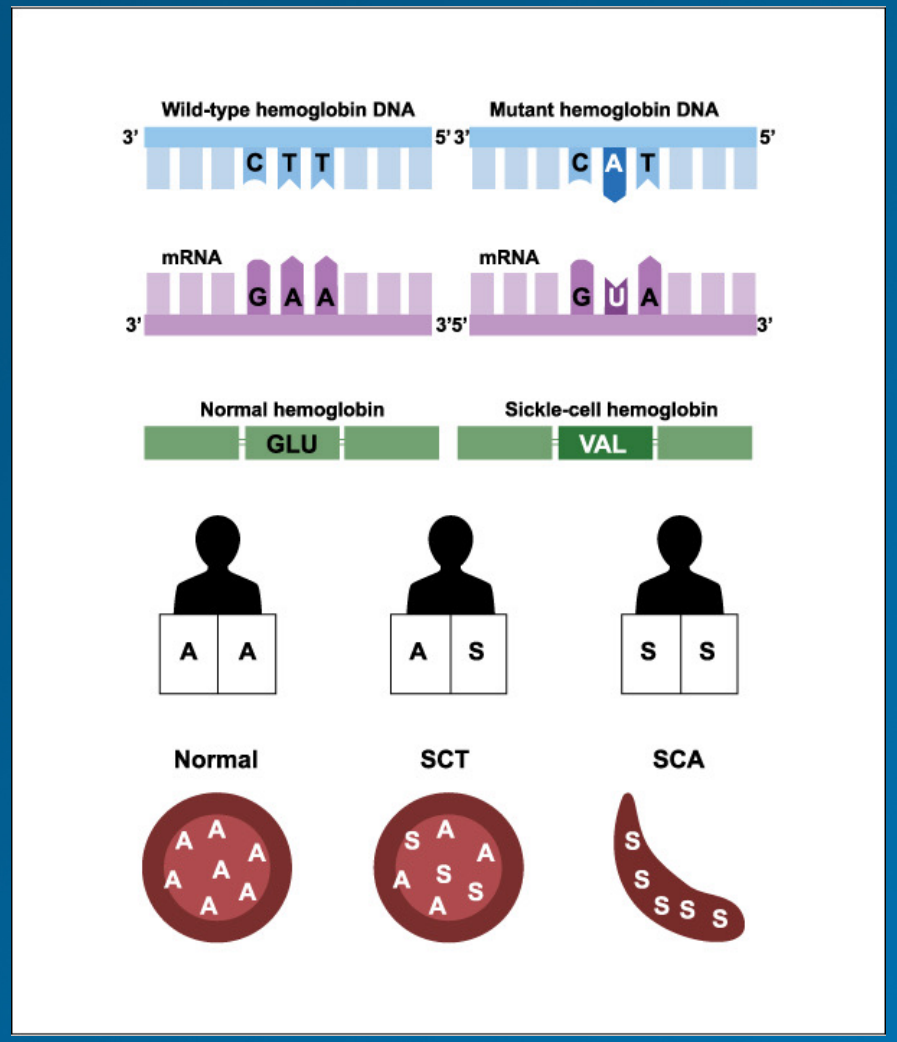
Sickle Cell Syndromes



	Percent Expression in Population of SCD	Severity	Life Expectancy (y)
SS	65	●●●●	40s
Sb^0	5	●●●◐	40s
SC	25	●●	60s
Sb^+	5	◐	60+

SCD, sickle cell disease.
Adapted from Hoffbrand et al. 2019. https://www.wiley.com/en-us/Hoffbrand%27s+Essential+Haematology,+8th+Edition-p-9781119495901.

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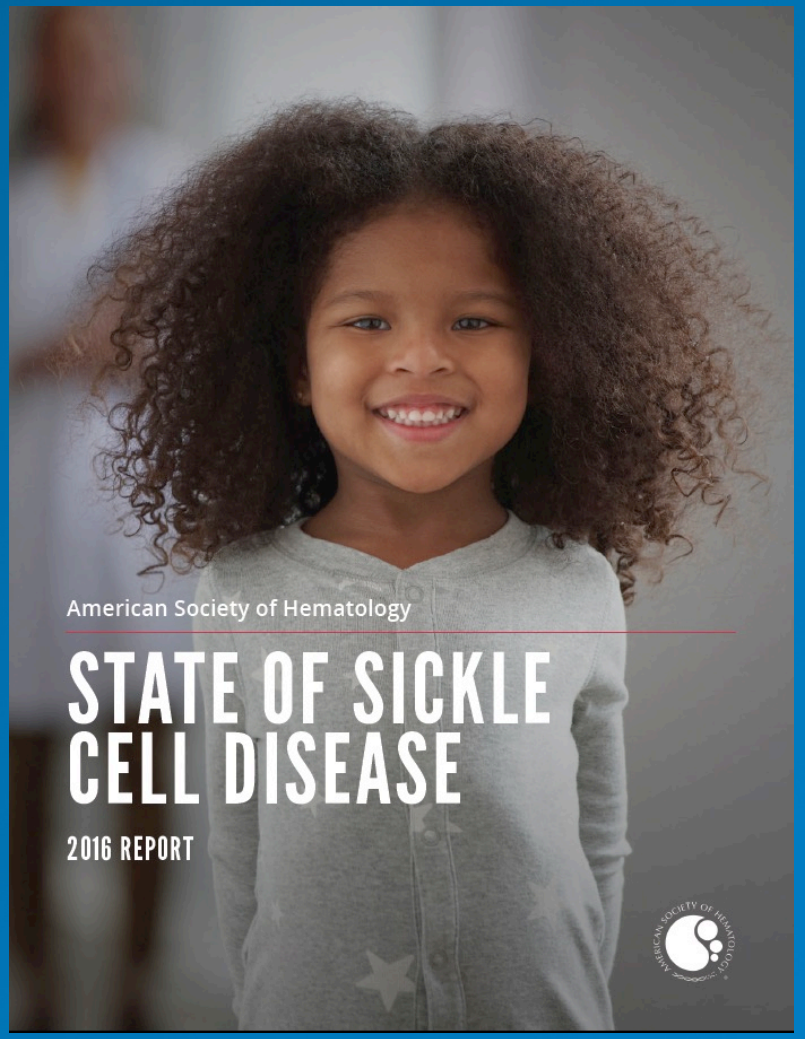
Sickle Cell Disease

- SCD is a chronic disease that has **been neglected for far too long**
- Those affected by this disease are among the most vulnerable and underserved, and the disease has a profound impact on their lives
- The status quo is **unacceptable**
- It is imperative that we vastly improve the circumstances under which care is provided



SCD, sickle cell disease.
http://www.scdcoalition.org/pdfs/ASH%20State%20of%20Sickle%20Cell%20Disease%202016%20Report.pdf

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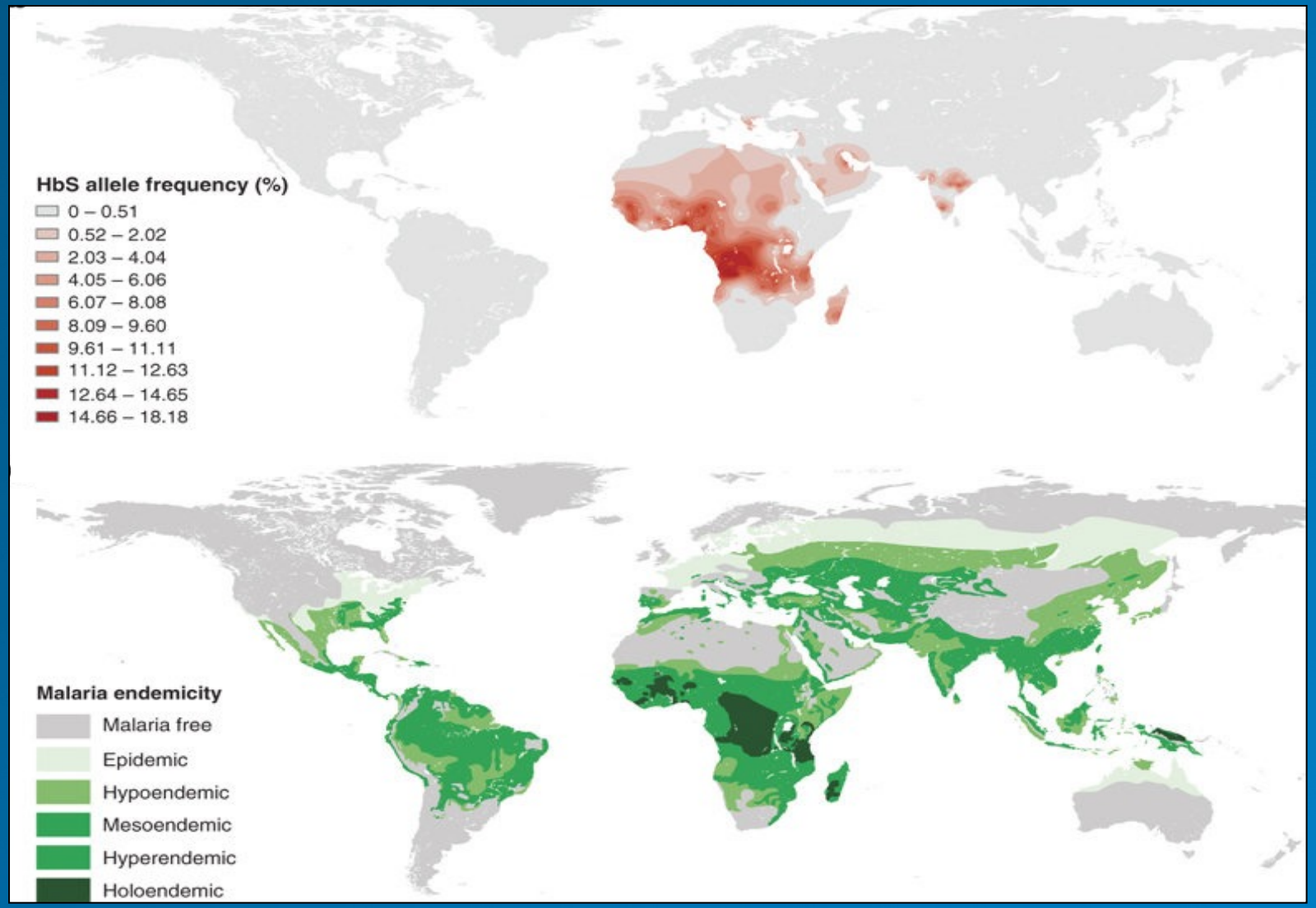
Global Distribution of the Sickle Cell Gene



Piel et al. *Nat Commun*. 2010;1:104.

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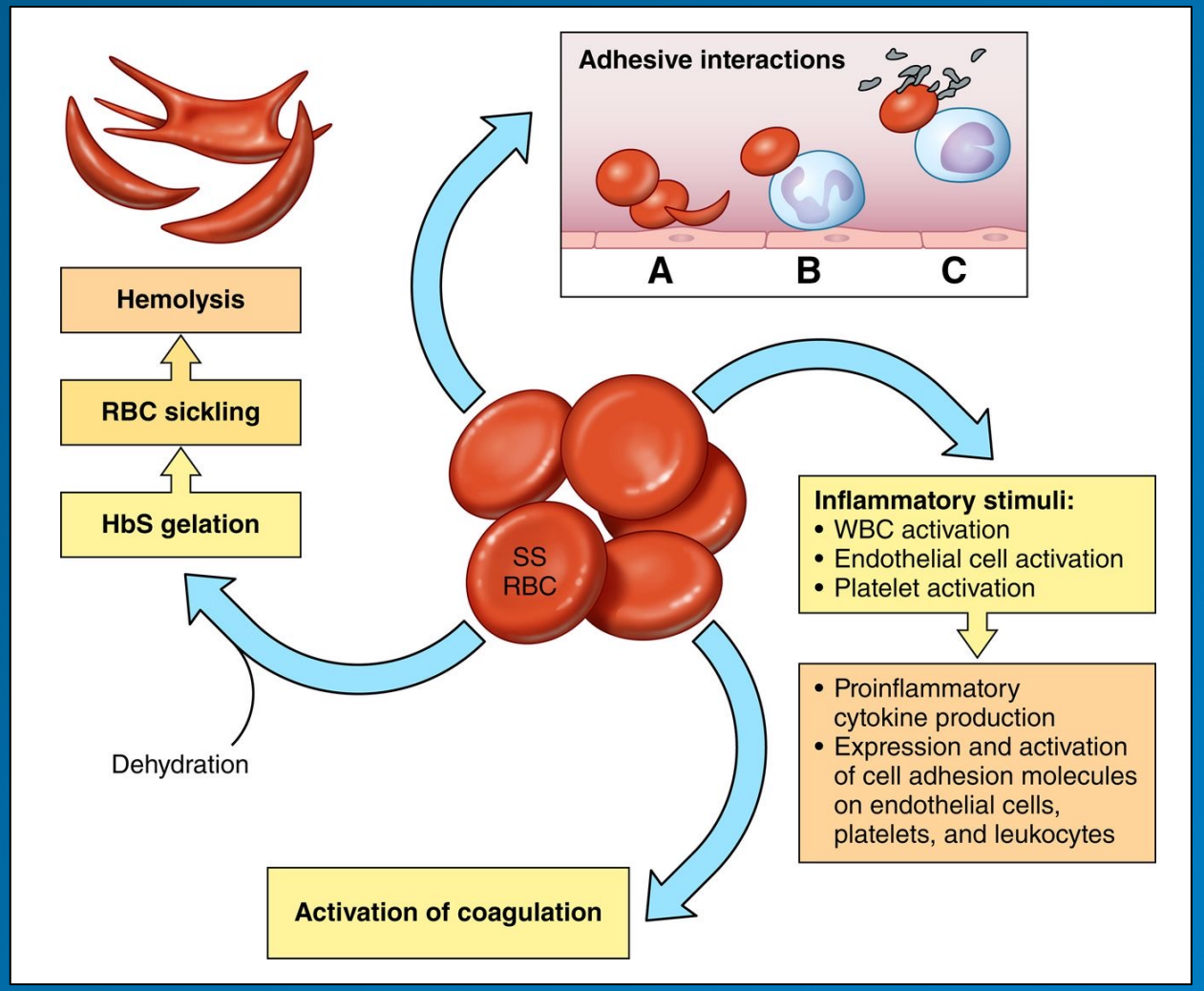
Evaluating Contributing Factors, Causes, and Pathophysiology of Sickle Cell Disease and Various Subtypes

The Sickled Red Blood Cell as a Source of Multiple Pathophysiologic Pathways



Telen. *Blood* 2016;127(7):810-819.

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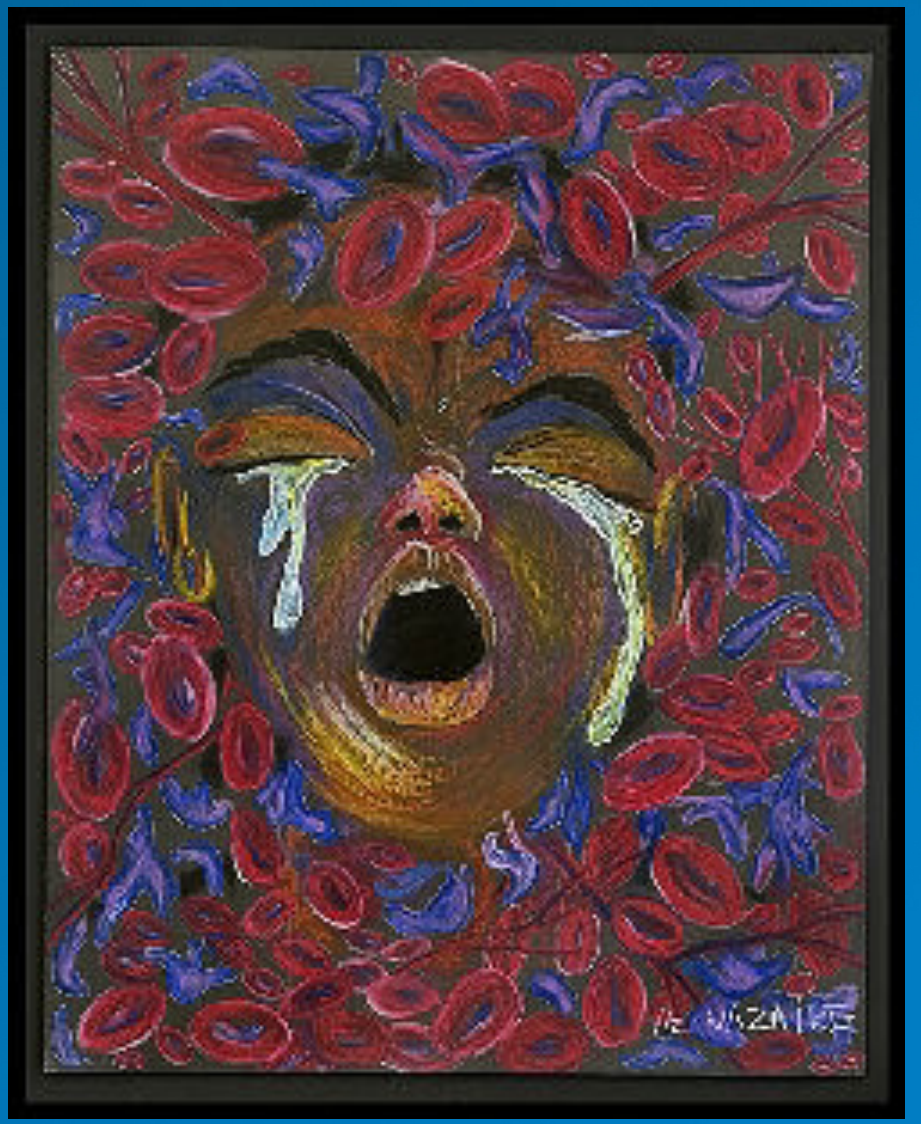
Acute Vaso-Occlusive Pain

“Unimaginable”

“Unpredictable”

“Indescribable”

“Inescapable”



Hertz Nazaire, 2007

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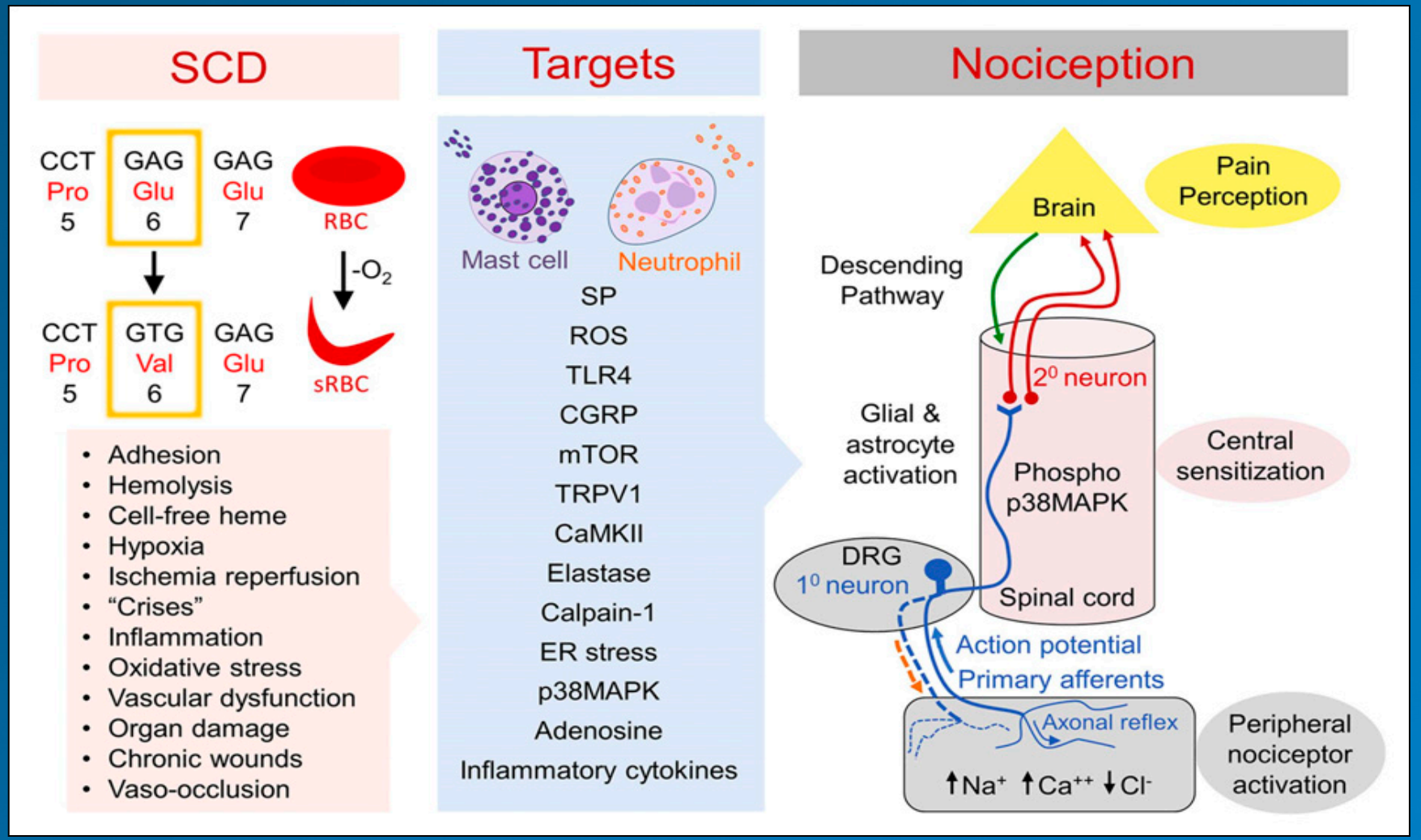
The Detailed Picture



ER stress, endoplasmic reticulum stress; Glu, glutamic acid; Pro, proline; sRBC, sickle red blood cell; TLR4, Toll-like receptor 4; Val, valine.
Tran et al. *Blood* 2017;130(22):2377-2385.

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United States Sickle Cell Disease Population

Calculation based on birth prevalence and census data, correcting for early mortality:

- Total: ~100,000 individuals
  - 60% adults (at least)
  - 90% Black
  - 10% Hispanic
- Genotype distribution in the United States
  - At birth: HbSS 60%; HbSC 30%; HbSβ-thalassemia 10%
  - In adulthood:
    - At age 30: HbSS 50%
    - At age 60: HbSS 25%

HbSS, sickle cell anemia; HbSC, sickle cell with hemoglobin C disease; HbSβ, hemoglobin S-beta.
Hassell et al. *Am J Prev Med.* 2010;38:S512; Brousseau et al. *Am J Hematol.* 2010;85:77.

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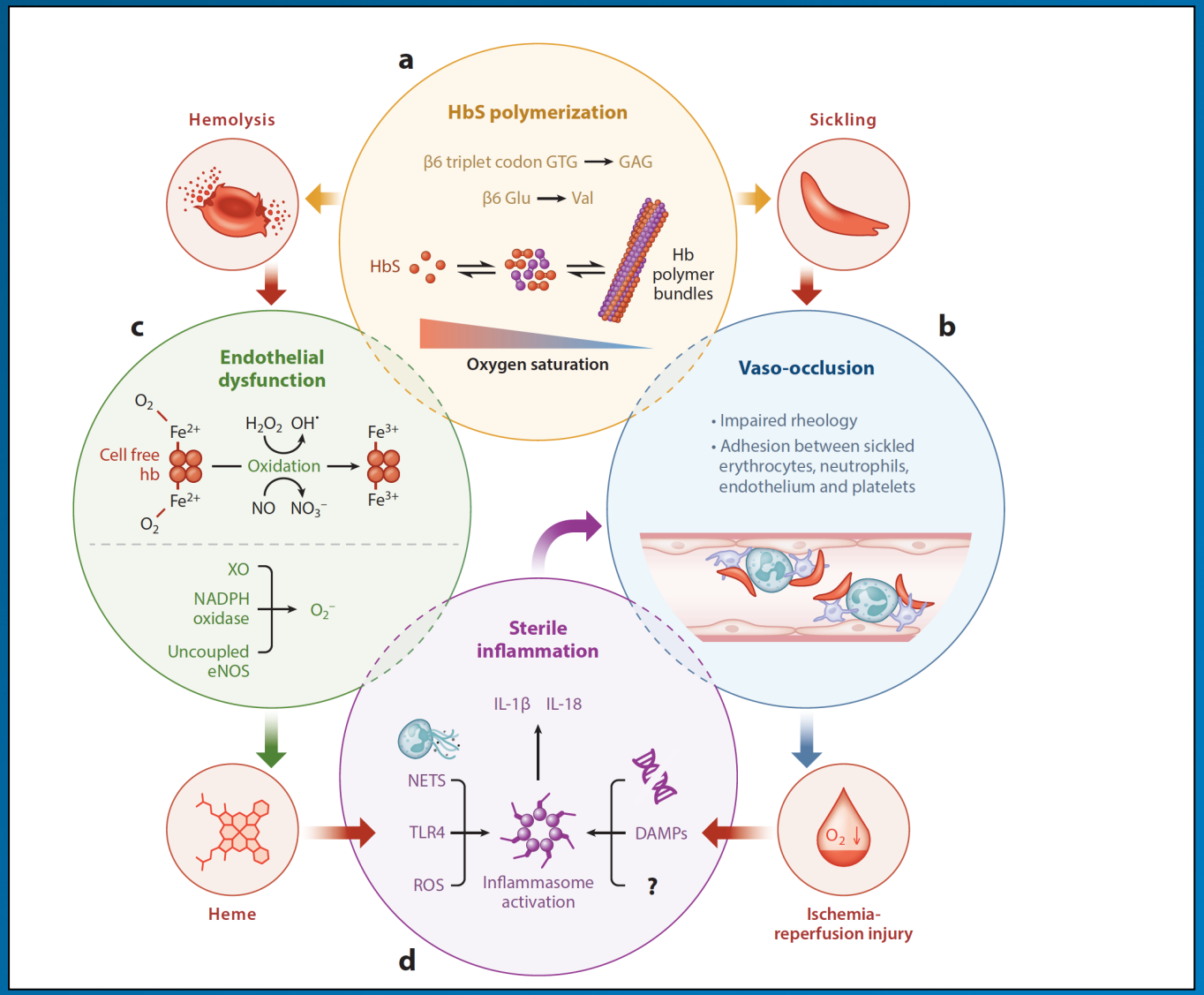
Molecular Pathophysiology of Sickle Cell Disease



Sundd et al. *Annu Rev Pathol*. 2019;14:263-292.

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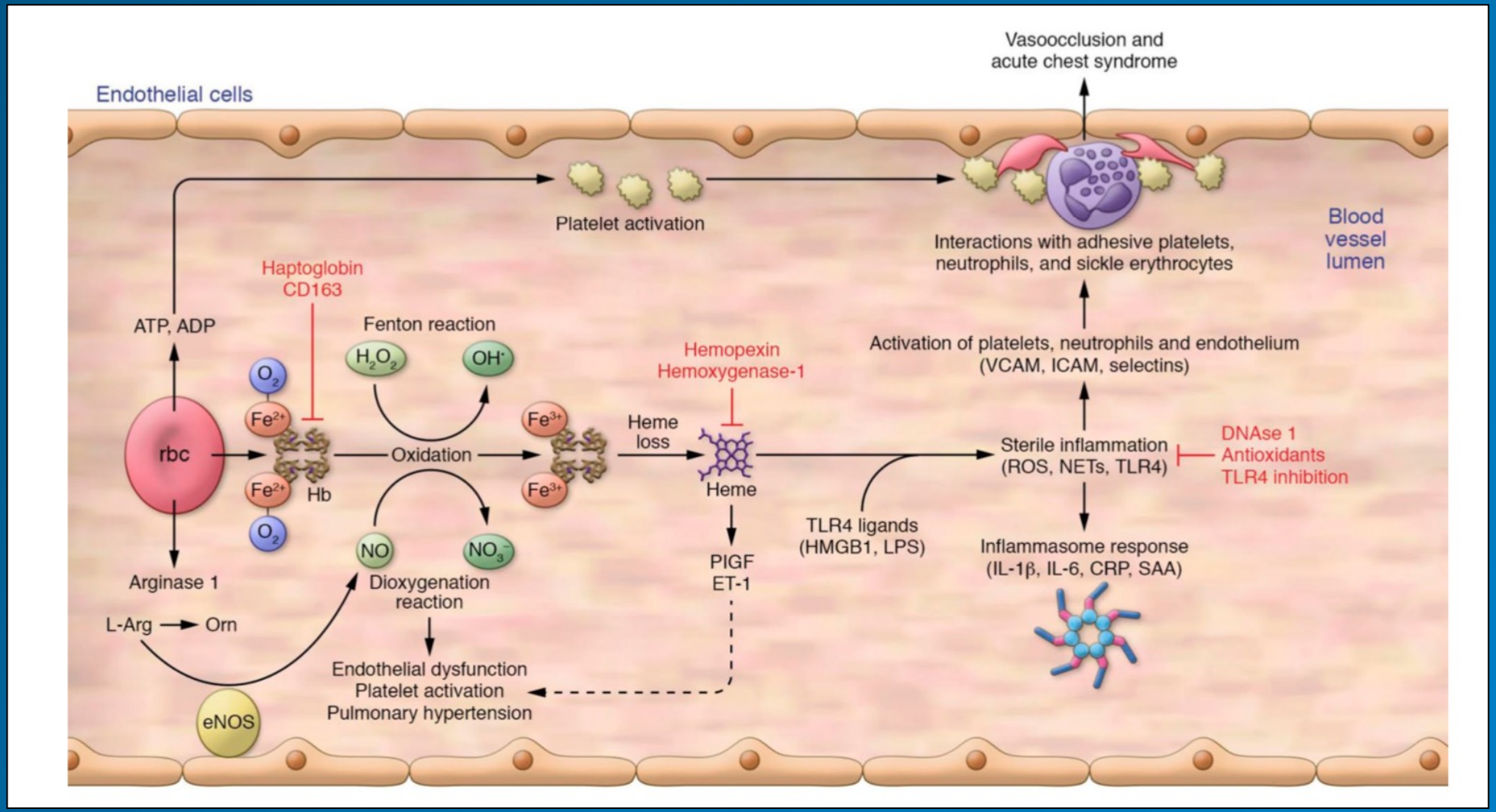
Overview of Acute and Chronic Sickle Cell Disease Complications by Organ System—Understanding Current and Downstream Implications

Contribution of Intravascular Hemolysis to Vasculopathy and Vaso-Occlusion



Kato et al. *J Clin Invest* 2017;127:750-760.

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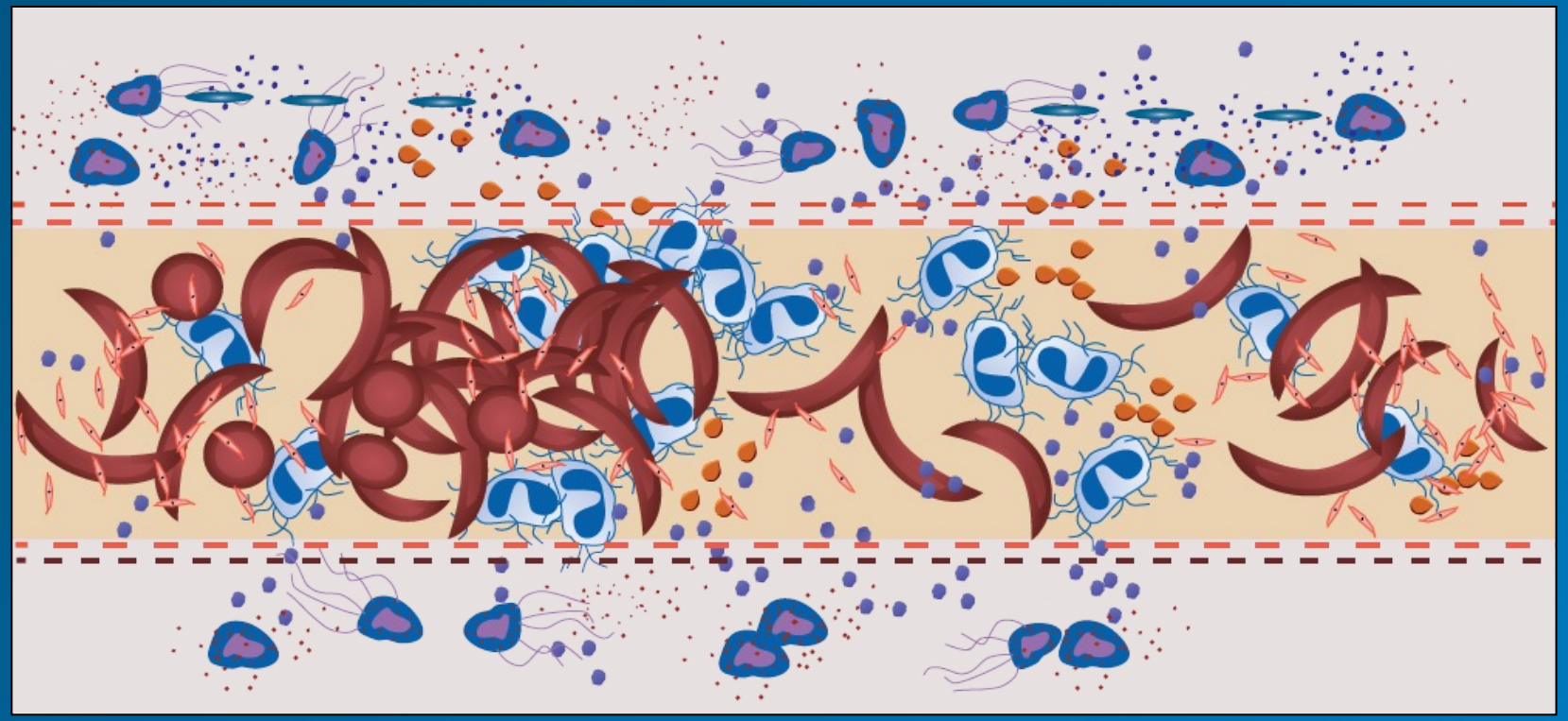
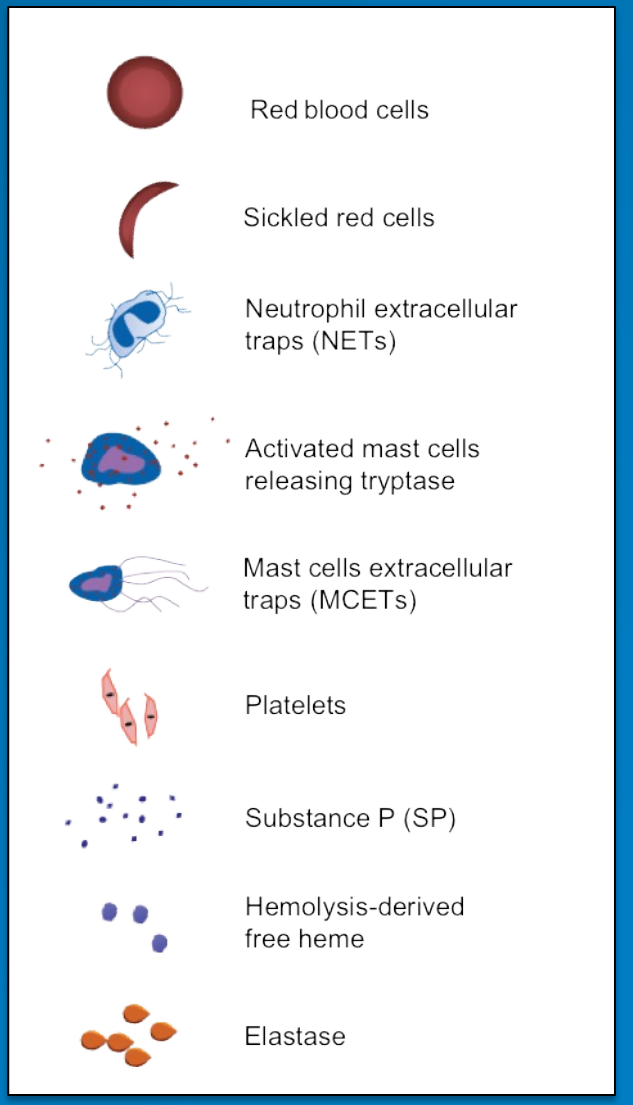
Vaso-Occlusion in Sickle Cell Disease





Adapted from Aich et al. *Curr Opin Hematol*. 2019;26(3):131-138.

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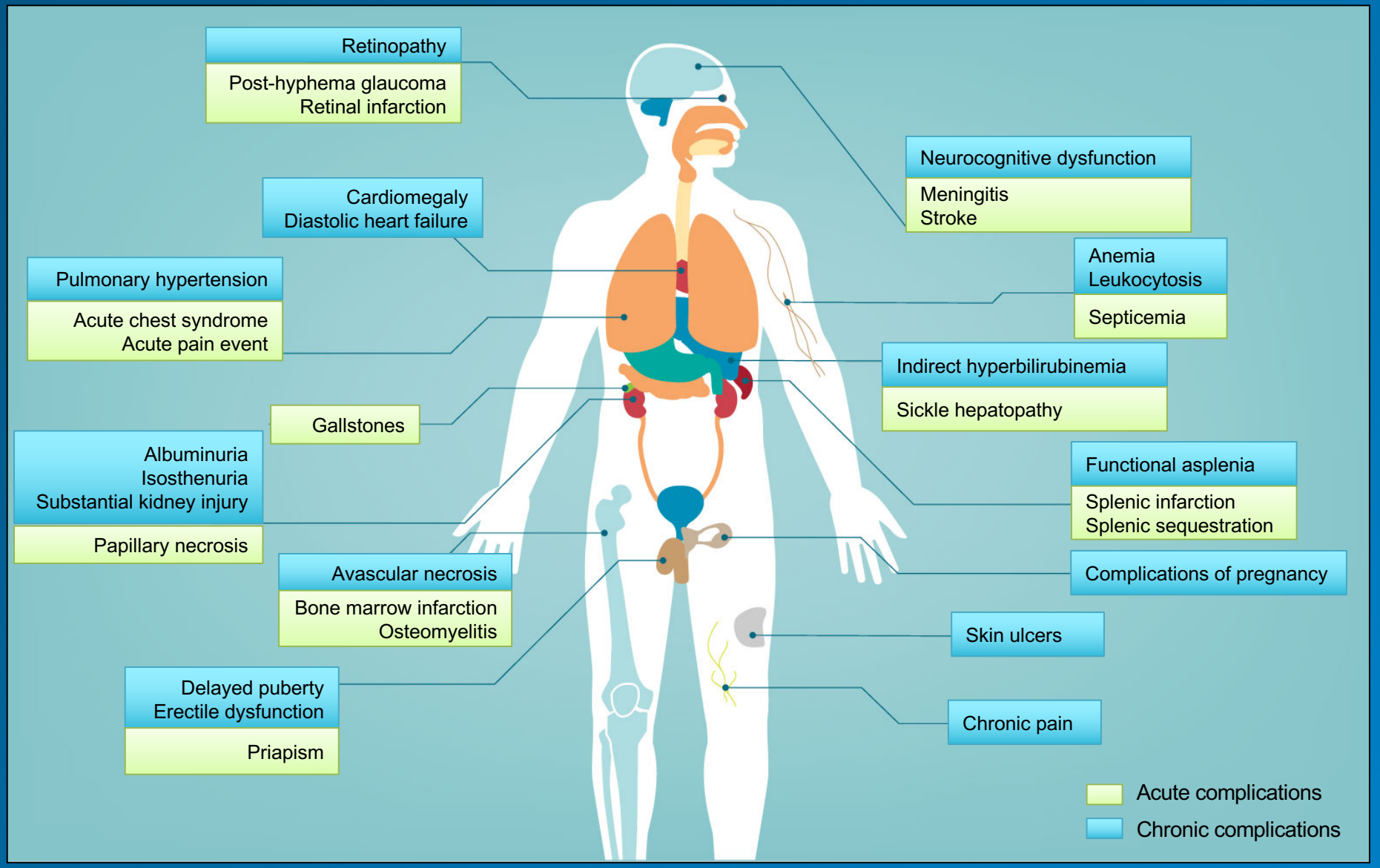
Complications in Sickle Cell Disease



Adapted from Kato et al. *Nat Rev Dis Primers* 2018;4:18010.
https://media.nature.com/m685/nature-assets/nrdp/2018/nrdp201810/images_hires/nrdp201810-f5.jpg.

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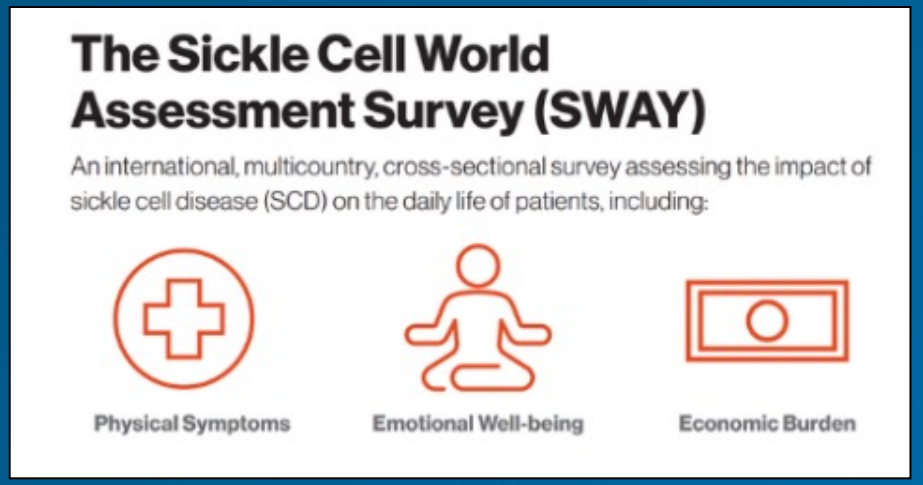
Sickle Cell World Assessment Survey Results (SWAY): Impact of Sickle Cell Disease on Patients' Daily Lives



2,100 patients and 300 clinicians

- VOCs are considered the clinical hallmark of SCD
- Patients experienced >5 VOCs each year on average
- >90% experienced at least 1 VOC in previous 12 months
- 11,000 VOCs reported:
  - ~25% managed at home
  - 33% resulted in hospitalization
- ~1/4 of patients avoid seeking medical assistance

HCPs, healthcare providers; SCD, sickle cell disease; VOCs, vaso-occlusive crises.

Osunkwo et al. *Blood* 2019;134(suppl 1):1017; *Am J Hematol*. 2021;96:404-417.

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Understanding the Implications of Vaso-Occlusion and Vaso-Occlusive Crisis in Sickle Cell Disease

Pain: The Hallmark of SCD

- Primary reason people seek care
- Secondary to vaso-occlusion
- Present throughout life

NOT ALL PAIN IS VOC PAIN

NOT ALL PAIN IS SCD PAIN

SCD, sickle cell disease; VOC, vaso-occlusive crisis.
Artwork used with permission Hertz Nazire.

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VOCs – What Are They, and Why Do They Occur?

- Normal RBCs are doughnut-shaped and flexible, rolling through the vasculature supplying oxygen and nutrients to the body[1]
- RBCs with sickle cell hemoglobin have different properties and are more likely to stick to the cells (endothelium) on the inside of the blood vessel
- WBCs and activated endothelial cells can also trigger adhesive interactions with sickled RBCs, other WBCs, and platelets due to chronic vascular damage[3]
- Blockage of small blood vessels results in vaso-occlusion
- VOCs: Recurrent episodes of vaso-occlusion can lead to severe unpredictable acute pain that may require hospitalization[2-5]

RBCs, red blood cellsVOCs, vaso-occlusive crises; ; WBC, white blood cells.

1. CDC. https://www.cdc.gov/dotw/sickle-cell-disease/. 2. Rees et al. *Lancet* 2010;376(9757):2018-2031. 3. Piel et al. *N Engl J Med.* 2017;376:1561-1573.
4. Zhang et al. *Blood* 2016;127(7):801-809. 5. Habara and Steinberg. *Exp Biol Med.* 2016;241(7):689-696.

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Long-Term Impact of Vaso-Occlusion on Organs

- Associated with increased risk for organ damage, organ failure, and death[1-4]
- Damage occurs due to vaso-occlusion (lack of oxygen), blood vessel damage, and secondary complications
- Ongoing inflammatory response, cell activation, and multicellular adhesion contribute to tissue damage
- Vaso-occlusion and VOCs associated with **decreased organ function and can result in life-threatening complications:**[7,8]
  - Acute chest syndrome
  - Pulmonary hypertension
  - Renal failure
  - Stroke

VOCs, vaso-occlusive crises.

1. Belcher et al. *Am J Physiol Heart Circ Physiol.* 2005;288:H2715-H2725. 2. Powars et al. *Medicine* (*Baltimore*).2005;84(6):363-376.
3. Elmariah et al. *Am J Hematol.* 2014;89(5):530-535. 4. Platt et al. *N Engl J Med*. 1994;330(23):1639-1644.
5. Nath Grande et al. *Am J Pathol*. 2005;166(4):963-972. 6. Tran et al. *Blood* 2017;130(22):2377-2385.
7. Ballas et al. *Blood* 2012;120(18):3647-3656. 8. Piel et al. *N Engl J Med.* 2017;376(16):1561-1573.

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SCD Can Affect Quality of Life for Children and Adults

- Emotional complications of SCD include depression, anxiety, catastrophizing
- Affected individuals often have to miss school/work due to SCD-related complications
- Concerns for VOC may prevent individuals from engaging with others or pursuing certain activities

SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Rizio et al. *Value Health* 2017;20:A679-A680. Kato et al. *Nat Rev Dis Primers* 2018;4:18010.

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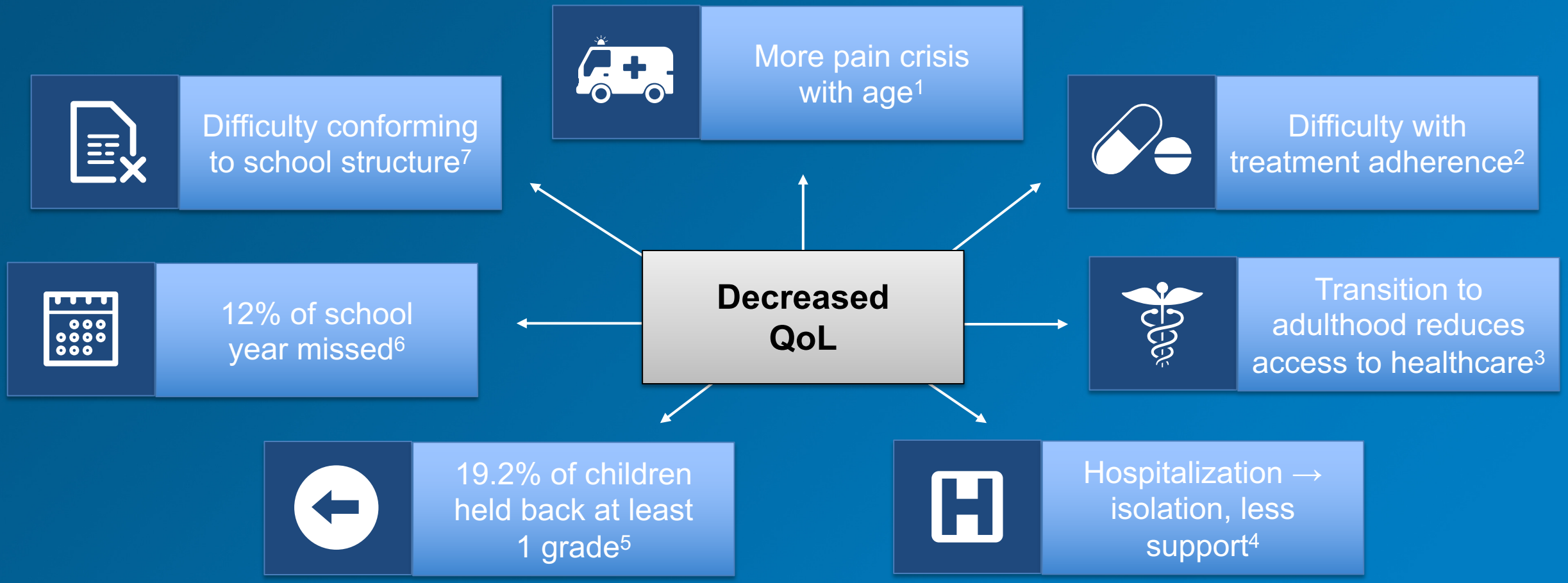
The Effect of SCD on Patients' Quality of Life and Performance



QoL, quality of life; SCD, sickle cell disease.

1. Kanter and Kruse-Jarres. *Blood Rev*. 2013;27(6):279-287. 2.Fisak et al. *Child:Care Health Dev*. 2011;38(2):204-210.
3. Blinder et al. *Paediatr Blood Cancer* 2013;60(5):828-835. 4. Weisberg et al. *J Hosp Med*. 2013;8(1):42-46.
5. Ladd et al. *Paediatr Blood Cancer* 2014;61(7):1252-1256. 6. Schwartz et al. *Paediatr Blood Cancer*. 2009;52(1):92-96.
7. Dyson et al. *Sociol Health Illn*. 2011;33(3):465-483.

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VOCs Associated With Increased Emergency Department Visits and Hospitalizations

7x-30x
more likely to be hospitalized
than black patients without SCD[1]

2x-6x
more likely to visit an ED
than black patients without SCD[1]

Emergency department and inpatient treatment costs for SCD patients

ED, emergency department; SCD, sickle cell disease; VOCs, vaso-occlusive crises.

Shankar et al. *Am J Hematol*. 2005;80(4):262-270. 2. Lanzkron et al. *Am J Hematol*. 2010;85(10):797-799. 3. Blinder et al. *Pediatr Blood Cancer*. 2013;60(5):828-835.

Adapted from Lanzkron et al. *Am J Hematol*. 2010;85(10):797-799

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Developing an Individualized Pain Plan in Collaboration With Patients

Individualized Care Plans

- Discuss a pain action plan for individuals at home that includes information about when to seek acute care (ED or hospital care)
- Ensure patients understand their pain plan and have the support of other caregivers
- Develop an acute pain plan for ED and hospital use that can be viewed in the EMR system
- Plans should reflect the perspectives, values, past experiences of the patient and/or caregivers, thus integrating shared decision making in pain management
- Having a pain plan can minimize stigma in SCD and improve aggressive, appropriate opioid therapy in acute VOC

ED, emergency department; EMR, electronic medical record; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

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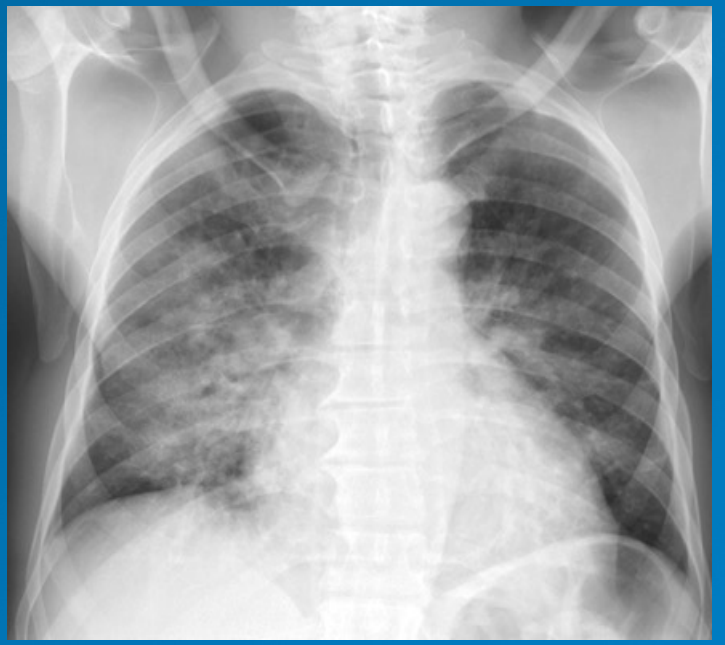
Understanding Acute Chest Syndrome in Sickle Cell Disease

Acute Chest Syndrome: Clinical Findings

- Etiology - multifactorial
  - Rib infarct causing splinting/atelectasis
  - Pulmonary fat embolism
  - Infection (mycoplasma, chlamydia, viral)
- Indistinguishable from pneumonia
  - Pleuritic chest pain, fever, cough, tachypnea, hypoxia
- Laboratory diagnosis
  - Worsening anemia
  - Infiltrate on chest radiograph



Acute chest syndrome with bilateral opacities more confluent in the right midlung zone

Restrepo et al. *Radiographics* 2007;27:941-956.

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Acute Chest Syndrome: Incidence by Hemoglobinopathy

Hemoglobinopathy	Episodes/100 patient-years
SS	12.8
Sb^o thalassemia	9.4
SC	5.2
Sb^+ thalassemia	3.9

Castro et al. *Blood* 1994; 84:643.

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Acute Chest Syndrome: Treatment

- Treat possible underlying infection
  - Cover community acquired and atypical infections
- Bronchodilators and supplemental oxygen to correct hypoxia
- Adequate pain management: Minimize splinting while avoiding over-sedation
- Immediate RBC transfusion therapy
  - Simple transfusion:
    - Milder illness/single lobe
    - Severe anemia
  - Exchange transfusion for:
    - Multiple lobes involved
    - Rapidly progressing
    - Worsening hypoxia
    - Hgb already near 10 g/dL

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Targeting SCD-related Complications With Disease-directed Therapies

Hydroxyurea: Mainstay of SCD Therapy

- First FDA-approved medication for SCD
- Can improve clinical course of SCD by increasing the production of HgF, thereby reducing frequency and intensity of vaso-occlusive pain crises
- Maximal tolerated doses may not be necessary to achieve a therapeutic effect
  - Standard initial dosing:
    - Adults: 15 mg/kg once daily
    - Children: 20 mg/kg once daily
- Pediatric studies in hydroxyurea have shown similar safety

FDA, US Food & Drug Administration; MTD, maximum tolerated dose; SCD, sickle cell disease.

Charache et al. *N Engl J Med*. 1995;332:1317-1322. Heeney et al. *Hematol Oncol Clin North Am*. 2010;24:199-214.

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Multicenter Hydroxyurea Trial

Group	Hydroxyurea	Placebo	*P*
Pain Episodes	2.5/y	4.5/year	<.001
Pain Admits	1.0/y	2.4/year	<.001
Acute Chest	25 episodes	51 episodes	<.001
Transfused	48	73	<.001
Total Units	336	586	.004

Charache et al. *N Engl J Med*. 1995;322:1317.

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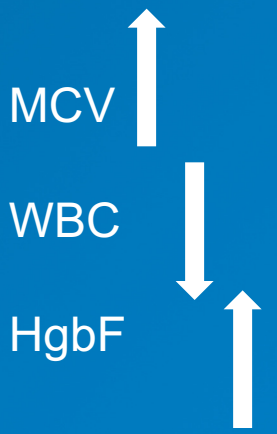
Hydroxyurea

Laboratory Effects of Hydroxyurea Treatment

Variable	Change from Month 0 to Month 12 (95% CI)
Hemoglobin (g/dL)	+1.0 (0.8-1.0)
Mean corpuscular volume (fl)	+13 (12-13)
Fetal hemoglobin (g/dL)	+12.5 (11.8-13.1)
White cells per mm^3	-6,300 (-6,900 to -5,600)
Absolute neutrophil count per mm^3	-2,500 (-2,700 to -2,200)
Platelets per mm^3	-67,600 (-82,000 to -52,000)



HgbF, fetal hemoglobin; MCV, mean corpuscular volume; WBC, white blood cell.
Tshilolo et al. *Blood* 2019;380:121-131.

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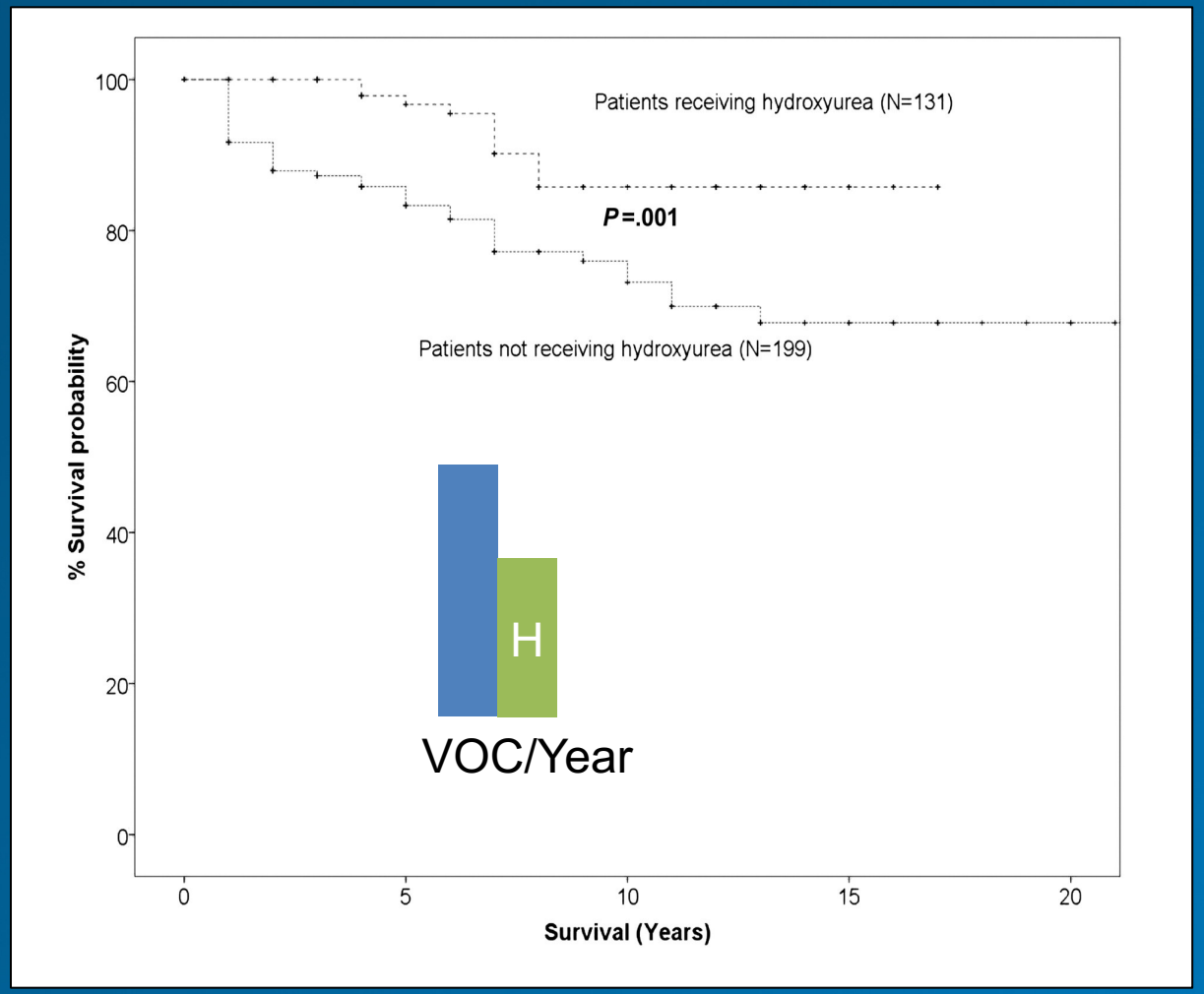
Hydroxyurea



- Probability of 10-year overall survival in patients with SCD with and without hydroxyurea:
  - Hydroxyurea: 86%
  - Conventionally treated: 65%
  - *P* = .001

Voskaridou et al. *Blood* 2010;115:2354-2363.

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What Is the Issue With Hydroxyurea?

- Although very effective, hydroxyurea is not universally accepted among patients and providers
- Minimal side effects
- Disproportionate perceptions of carcinogenicity, teratogenicity, and reduced fertility
- Widely underutilized in the Western world
  - Pharmacy data: filling 1 or more hydroxyurea prescriptions during the 3, 6, or 12 months after a third pain crisis = 22.7%
- Access to hydroxyurea in areas of high disease burden needs to improve

Stettler et al. *JAMA* 2015;313:1671-1672; Voskaridou et al. *Blood* 2010;115:2354-2363.

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Transfusion Therapies: Three Therapeutic Modalities

- Blood transfusion is a disease-modifying therapy for the treatment and prevention of acute and chronic complications of SCD[1]
- Blood may be administered by:
  - Simple transfusion[1]
  - Manual exchange
  - Automated red blood cell exchange
- Main complications of transfusion[1,2]:
  - Alloimmunization
  - Iron overload
  - Hyper-hemolytic transfusion reactions
  - Transfusion-associated circulatory overload

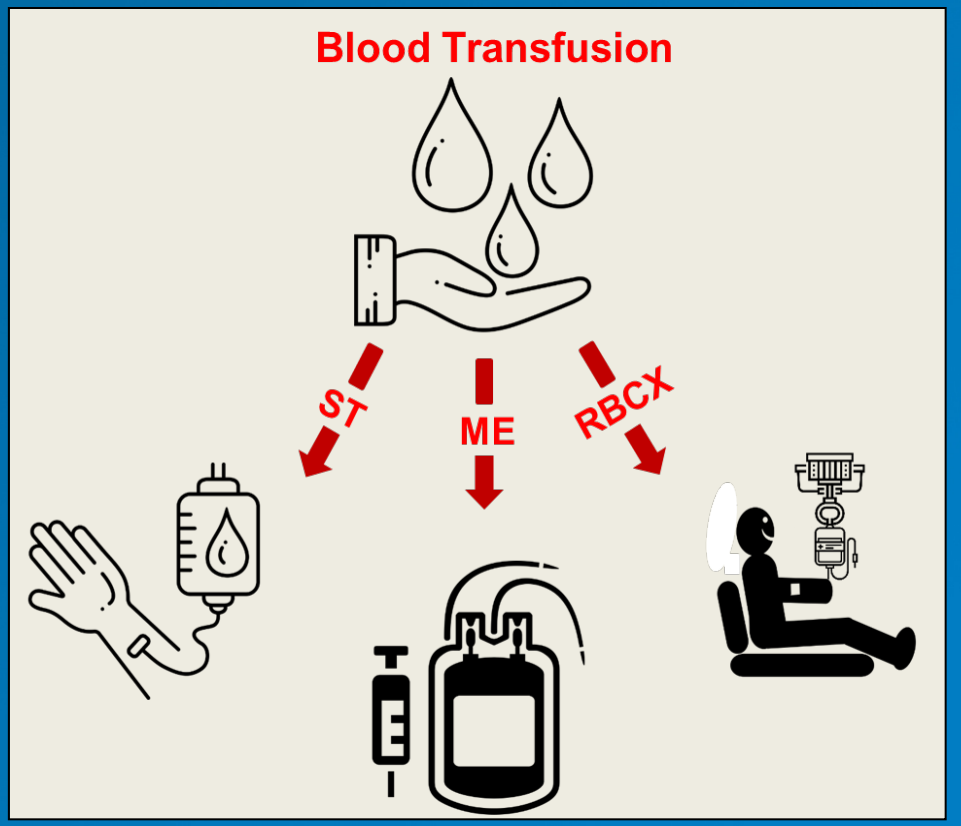

Image courtesy of Fuad El Rassi, MD.

ME, manual exchange; RBCX, red blood cell exchange; SCD, sickle cell disease; ST, simple transfusion

1. Howard. *ISBT Science Series* 2013;8:225-228; 2. Agnihotri and Agnihotri. *Indian J Crit Care Med*. 2014;18(6):396-398.

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Primary Use of Transfusion Therapy in SCD

Chronic RBC Transfusion Therapy

- Primary stroke prevention (abnormal blood vessels)
- Secondary stroke prevention (previous stroke)
- Recurrent acute chest syndrome

Acute RBC Transfusion Therapy

- Severe symptomatic anemia
- Acute chest syndrome
- Acute stroke or neurologic compromise
- Inability to make RBCs (aplastic anemia)

Transfusions are not indicated for typical sickle cell vaso-occlusive pain management

RBC, red blood cell; SCD, sickle cell disease.

Howard. *ISBT Science Series* 2013;8:225-228. Agnihotri and Agnihotri. *Indian J Crit Care Med*. 2014;18(6):396-398.

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Pain Management in Sickle Cell Disease

- Aggressive opioid therapy remains the mainstay for all individuals presenting with acute VOC in SCD
- Pain plans should be individualized for patients
- Opioid medication should be individually dosed and given in regular intervals with frequent reassessment for efficacy of pain control
- Chronic pain management is poorly studied, and therapy is less guideline-based

SCD, sickle cell disease; VOC, vaso-occlusive crisis.

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Curative Therapies in SCD

- Stem cell transplant is the only known cure for SCD at this time
- Optimal outcomes are achieved with matched, sibling donor transplant
- Alternative donor transplants (unrelated donor and haplo-identical donor) are still under development
- Autologous gene therapy/gene editing is currently being studied and the potential for cure is unclear

SCD, sickle cell disease.

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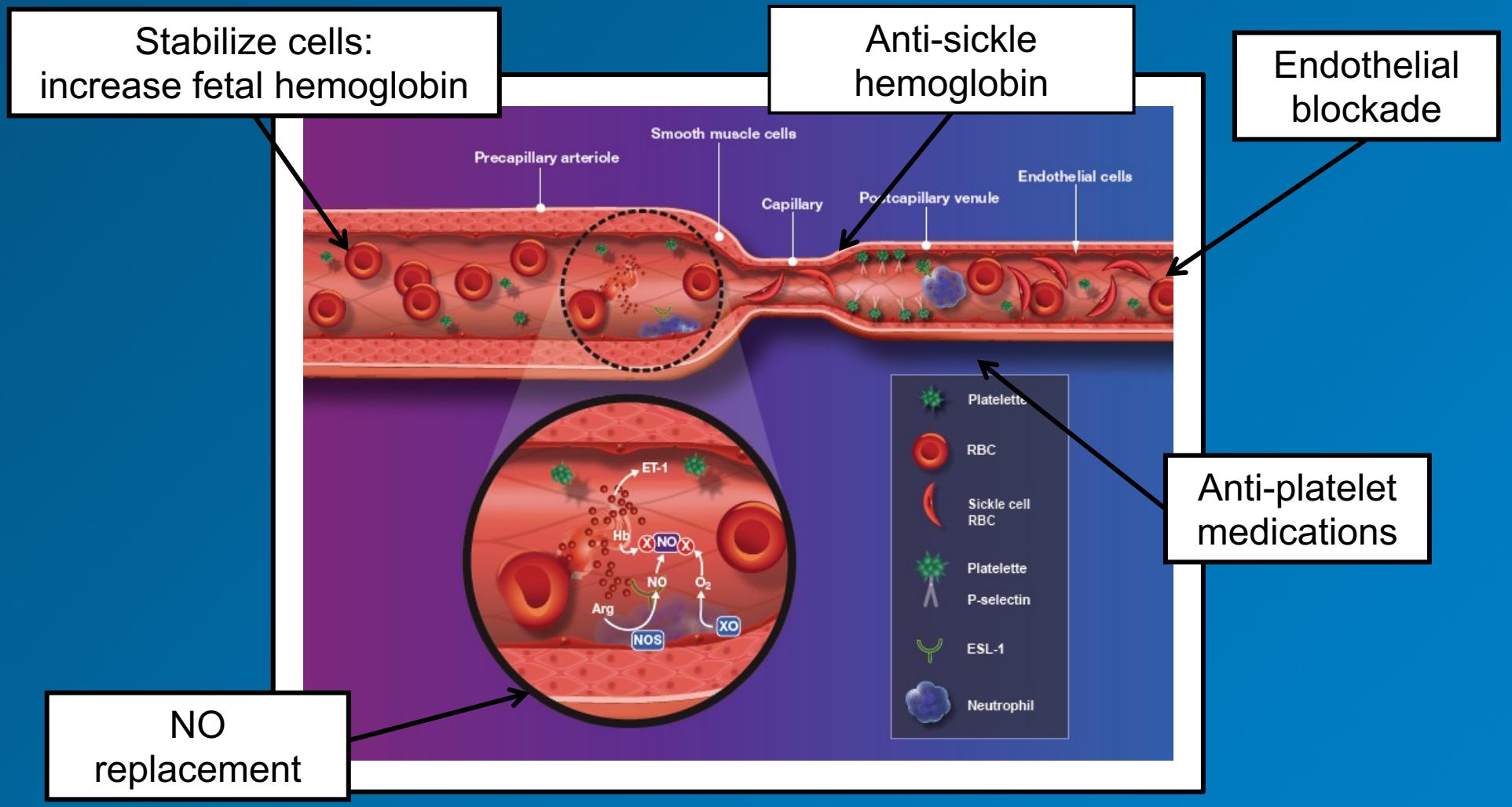
Novel Agents for Prevention of Vaso-Occlusive Crisis and Pain Management

Targets to Improvement



Arg, arginine; ESL-1, E-selectin ligand-1; RBC, red blood cell; SCD, sickle cell disease.
Kanter and Kruse-Jarres. *Blood Rev*. 2013;27:279-287.

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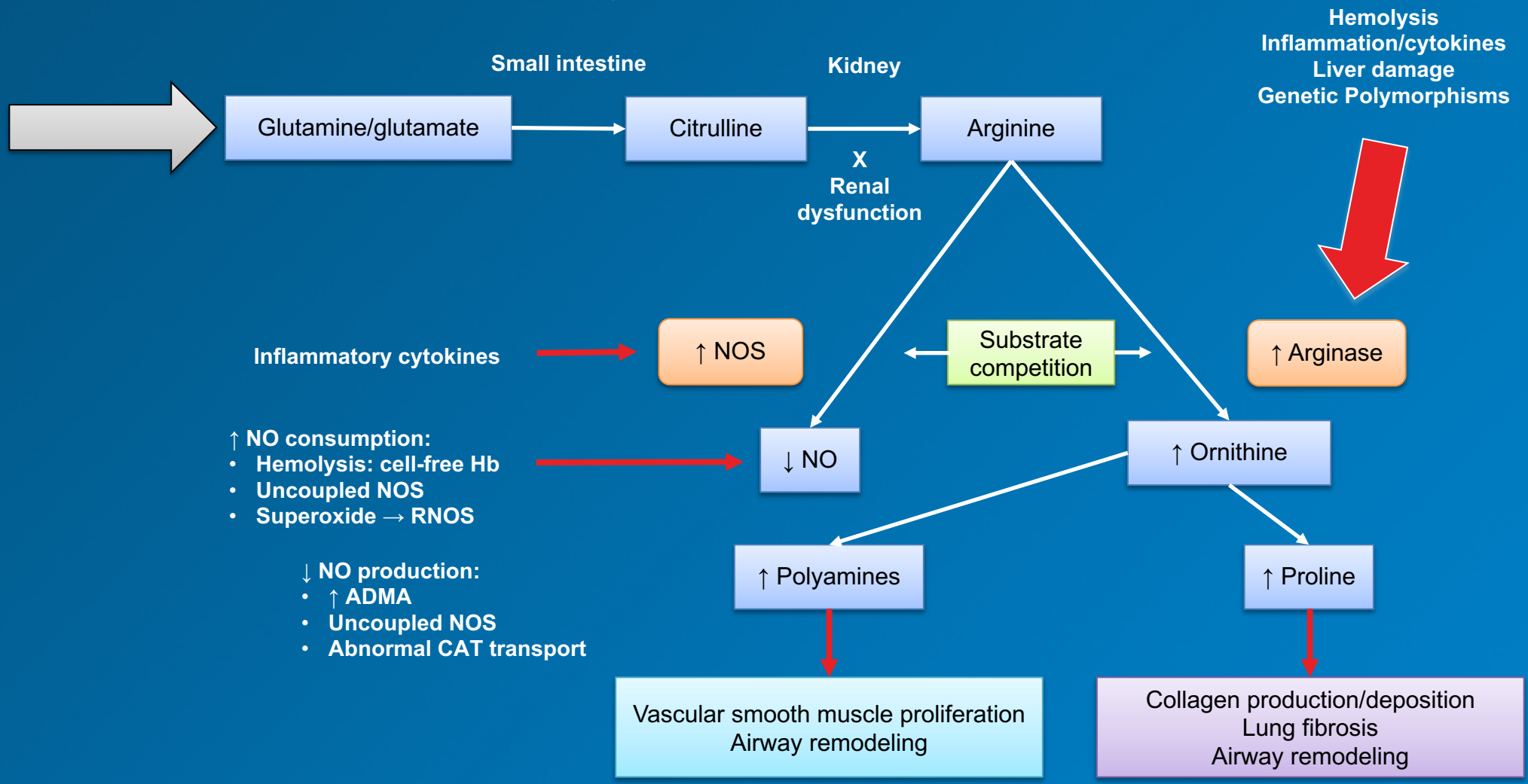
Anti-Inflammatory Modulators in SCD

1. Nitric Oxide Donors
2. Arginine and Glutamine



NO, nitric oxide; NOS, nitric oxide synthases; SCD, sickle cell disease.

Adapted from Morris. *Hematol Am Soc Hematol Educ Program*. 2008;2008:177-185. © 2008 American Society of Hematology.

AXIS Medical Education

L-glutamine: FDA Approval

Date	July 7, 2017
Indication	to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older
Recommended Dose	• 5 grams to 15 grams orally, twice daily based on body weight • Each dose should be mixed in 8 oz. (240 mL) of cold or room temperature beverage or 4 oz. to 6 oz. of food before ingestion
Administration	Oral powder
Trial	Phase 3, NCT01179217

Reduction in the number of sickle cell crises through Week 48 and prior to the start of tapering	• Median number of sickle cell crises
	  • L-glutamine: 3
	  • Placebo: 4
	• Median number of hospitalizations for sickle cell pain:
	  • L-glutamine: 2
	  • Placebo: 3

Most common adverse reactions (>10%)	Constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain

US Food & Drug Administration. July 7, 2017.

AXIS Medical Education

L-Glutamine

- L-Glutamine: NO pathway
- 5-15 grams twice daily based on body weight, approved by FDA in 2017
- Oral powder dissolved in fluids, increase NO level
- Safe side effect profile
- Effect
  - ↓ Vaso-occlusive events by 25% compared to placebo

NO, nitric oxide.
Niihara et al. *N Engl J Med*. 2018;379:226-235.

AXIS Medical Education

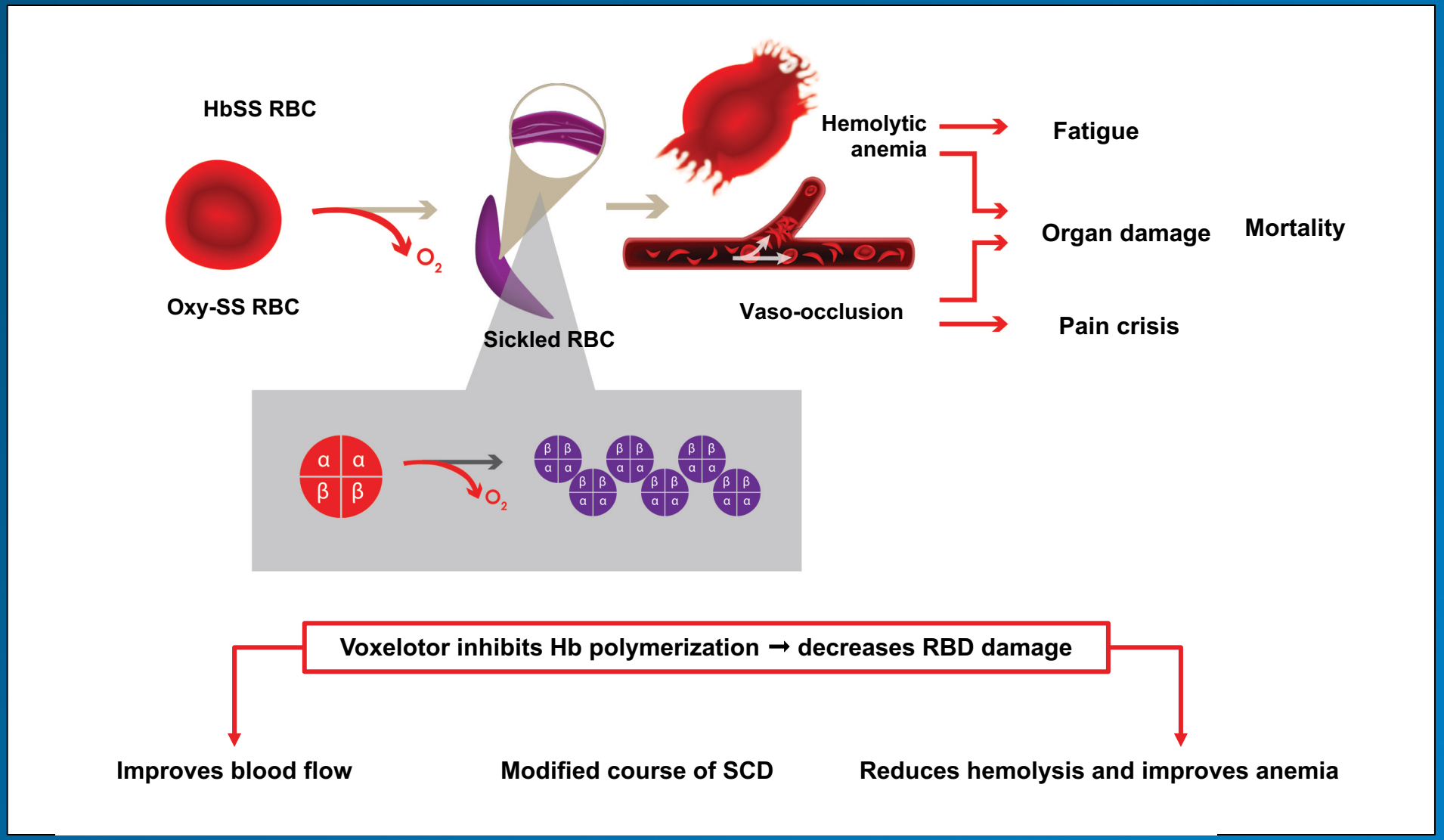
Voxelotor

- Oral, once-daily, direct-acting hemoglobin modifier
- HbS polymerization inhibitor
- Prevents sickling of RBCs: increases hemoglobin's affinity for oxygen, delays polymerization of HbS, restores normal RBC function in preclinical SCD models
- Phase 2/3 trial of GBT440 in SCD started in December 2016

HbS, hemoglobin S; RBCs, red blood cells; SCD, sickle cell disease.
Dufu et al. *Blood* 2014;124:217.
NCT02285088.

AXIS Medical Education

Voxelotor Trials



Deoxy, deoxygenated; Hb, hemoglobin, HbS, sickle hemoglobin; O_2, oxygen; oxy, oxygenated; RBC, red blood cell; SCD, sickle cell disease; SS, sickle cell anemia.
Adapted from Lehrer-Graiwer et al. *Haematologica* 2016;101:125.
https://clinicaltrials.gov/ct2/show/NCT03036813. https://clinicaltrials.gov/ct2/show/NCT02850406.

AXIS Medical Education

HOPE Trial: Voxelotor

- **Study Population:** SCD patients randomly assigned in a 1:1:1 ratio to receive a once-daily oral dose of 1,500 mg of voxelotor, 900 mg of voxelotor, or placebo

- **Results**: Voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis
  - Participants who had a Hb response (>1 g/dL increase in Hb from baseline to Week 24):
    - 51% in the 1,500 mg voxelotor group
    - 7% in the placebo group

- **Adverse Reactions:**
  - Grade 3/4 adverse events:
    - 26% in the 1,500 mg voxelotor group
    - 23% in the 900 mg voxelotor group
    - 26% in the placebo group
  - Most common adverse reactions: headache, diarrhea, abdominal pain, nausea, rash, and pyrexia

HbS, sickle hemoglobin; Hb, hemoglobin; SCD, sickle cell disease.

Vichinsky et al. *N Engl J Med*. 2019; 381:509-519; Oxbryta prescribing information, 2021.

AXIS Medical Education

HOPE Kids Trial: Voxelotor

- **Study Population:** Pediatric patients with SCD aged 4 to 11 years received once-daily voxelotor 1500 mg or 1500 mg weight-based-equivalent dosing for up to 48 weeks

- **Results**: Voxelotor increased Hb and decreased markers of hemolysis
  - Participants who had a Hb response (>1 g/dL increase in Hb from baseline to Week 24): 36%

- **Adverse Reactions:**
  - Most common treatment-related AEs: diarrhea (11%), vomiting (11%), and rash (11%)
  - Most common adverse reactions: pyrexia, vomiting, rash, abdominal pain, diarrhea, and headache

HbS, sickle hemoglobin; Hb, hemoglobin; SCD, sickle cell disease.
Estepp et al. EHA2021. Abstract: S260; Oxbryta prescribing information, 2021.

AXIS Medical Education

Voxelotor: FDA Approvals

	Age ≥12	Ages 4-11
Date	November 2019	December 2021
Indication	accelerated approval for the treatment of SCD in adults and pediatric patients 12 years of age or older	accelerated approval to treat SCD in pediatric patients 4-11 years of age
Recommended Dose	1,500 mg once daily	Based on body weight: • 40 kg or greater: 1,500 mg once daily • 20 kg to <40 kg: 900 mg once daily • 10 kg to <20 kg: 600 mg once daily
Administration	Oral	Oral (tablets or tablets for oral suspension)
Trial	Phase 3 HOPE	Phase 2 HOPE-KIDS 1 (Phase 3 HOPE-KIDS 2 ongoing, NCT04218084)
Hb response rate (Hb increase of >1 g/dL from baseline to week 24)	51.1% vs 6.5% (placebo)	36%
Most common adverse reactions (>10%)	Headache, diarrhea, abdominal pain, nausea, rash, fatigue, and pyrexia	Pyrexia, vomiting, rash, abdominal pain, diarrhea, and headache
Warnings	Hypersensitivity reactions Potential laboratory test interference	

SCD, sickle cell disease .

US Food & Drug Administration. 2019. 2021. Oxbryta prescribing information, 2021.

AXIS Medical Education

Voxelotor

- Voxelotor: hemoglobin affinity inducer- reduction of hemolysis, approved by FDA in late 2019 (≥12 years) and 2021 (ages 4-11)
- 1,500 mg orally; if GI side effects, can titrate down to 1,000 mg then uptitrate
- Weigh-based dosing for ages 4-11
- Increases binding of oxygen to red blood cells, with left shift of oxygen dissociation curve
- Effects
  - ↑ Hgb by 1 g/dL
  - ↓ Reticulocytes, bilirubin

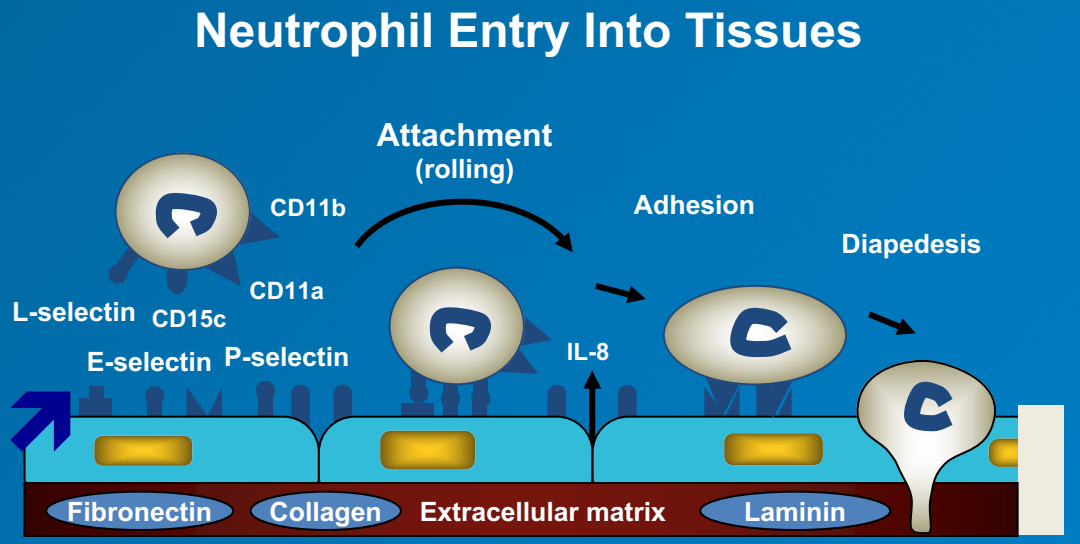
FDA, US Food & Drug Administration; GI, gastrointestinal; Hgb, hemoglobin.

Vichinsky et al. *N Engl J Med*. 2019; 381:509-519.

AXIS Medical Education

Selectins Mediate WBC Adhesion, Rolling

- Selectins are expressed on endothelial cells, platelets, and leukocytes, as well as other cell types[1]
- P-selectin and E-selectin mediate rolling and tethering of blood cells to the endothelium[2]
  - May initiate vaso-occlusion in the post-capillary venules[2]
- SCD cellular and animal models: interruption of selectin-mediated cellular adhesion decreases erythrocyte and leukocyte adhesion and improves blood flow[3-7]



SCD, sickle cell disease; WBC, white blood cell.

1. Tedder et al. *FASEB J*. 1995;9:866-873. 2. Ley et al. *Nat Rev Immunol*. 2007;7:678-689. 3. Chang et al. *Blood* 2010;116:1779-1786. 4. Matsui et al. *Blood* 2001;98:1955-1962. 5. Matsui et al. *Blood* 2002;100:3790-3796. 6. Embury et al. *Blood* 2004;104:3378-3385. 7. Kutlar et al. *Am J Hematol*. 2012;87:536-539.

Figure adapted from *Nat Rev Immunol*. 2007;7:678-689.

AXIS Medical Education

SUSTAIN Trial: Crizanlizumab

- Crizanlizumab is a humanized monoclonal antibody to P-selectin
- **Study Population:** SCD patients (16-65 years of age) who have experienced between 2 and 10 sickle cell–related pain crises within the preceding 12 months
- **Results**: Median annual rate of VOC was **REDUCED by 45.3%** compared to placebo
  - Drug effect was dose-dependent
  - Post-hoc analysis: Absence of VOC episodes greater in patients treated with crizanlizumab vs placebo: 35.8% vs 16.9%
- **Adverse Reactions:** Most frequently reported adverse reactions in patients (N = 111) treated with 5 mg/kg crizanlizumab were back pain, nausea, pyrexia, and arthralgia
  - Severe (grade 3) arthralgia and pyrexia rate of 0.9% (1 case each)

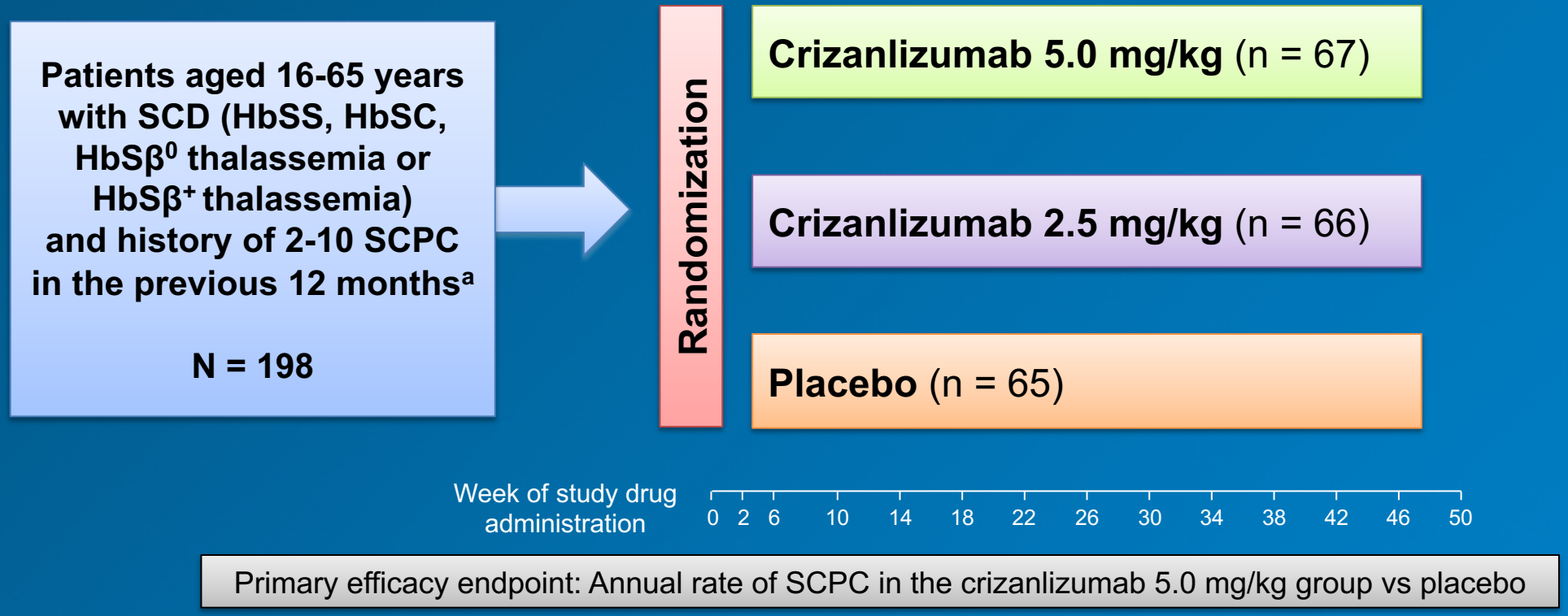
SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Ataga et al. *N Engl J Med*. 2017;376:429-439; Kutlar et al. *Am J Hematol*. 2019;94(1):55-61.

AXIS Medical Education

SUSTAIN Trial: Study Design

- A phase 2, multicenter, randomized, placebo-controlled, double-blind, 12-month study to assess safety and efficacy of crizanlizumab with or without hydroxyurea therapy in SCD patients with sickle cell–related pain crises



[a]Patients receiving hydroxyurea or erythropoietin were included if prescribed for the preceding 6 months and dose was stable for ≥3 months.
SCD, sickle cell idsease; SCPC, sickle cell–related pain crisis.
Ataga et al. *N Engl J Med*. 2017;376(5):429-439.

AXIS Medical Education

SUSTAIN Trial Summary

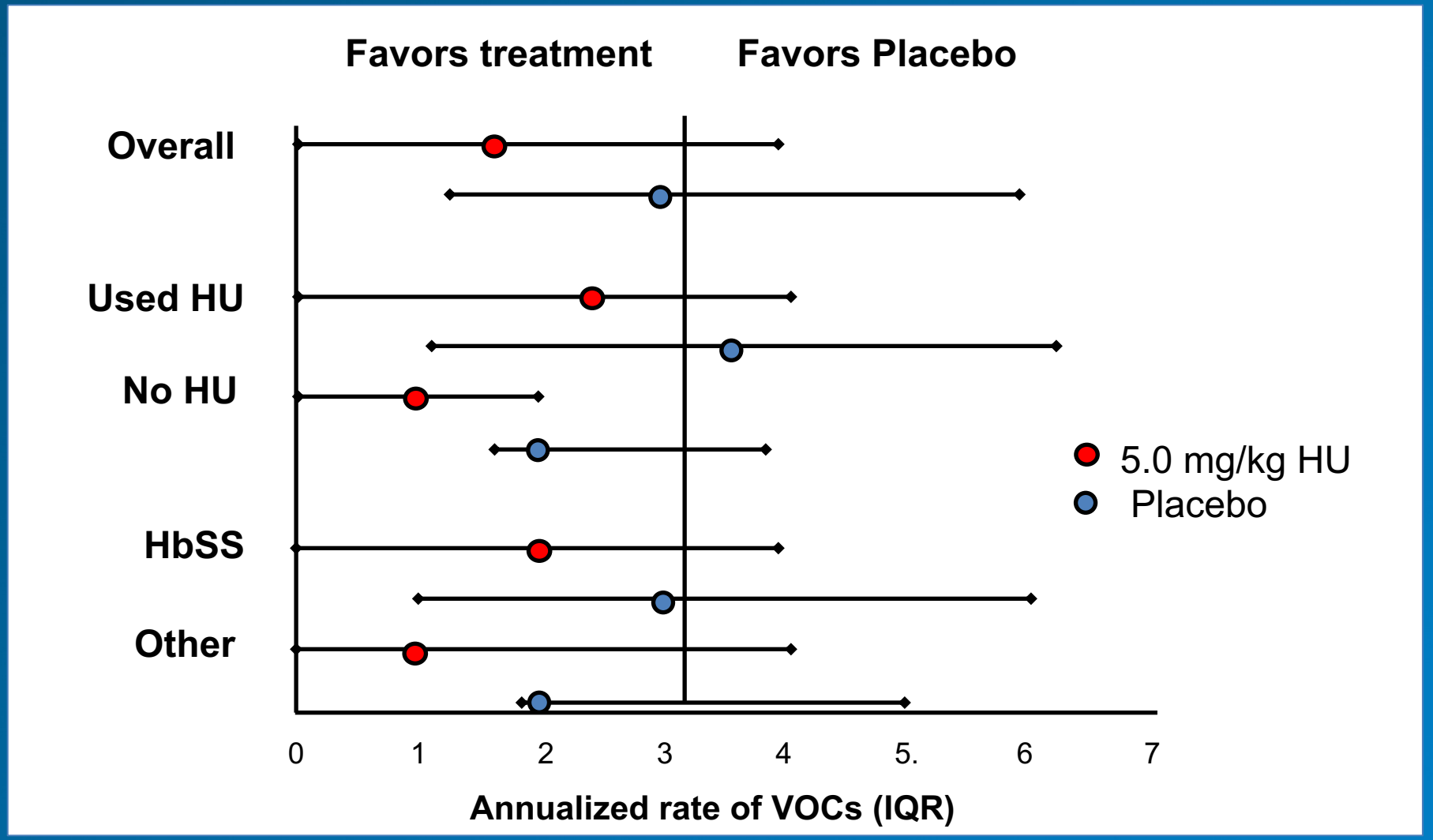
Endpoint	High-Dose Crizanlizumab, 5 mg/kg (N = 67)	Low-Dose Crizanlizumab, 2.5 mg/kg (N = 66)	Placebo (N = 65)
Annual rate of crises, ITT			
Median rate of crises/year	1.63	2.01	2.98
Difference from placebo (%)	**-45.3**	-32.6	-
P	.01	.18	-
No (%) of pts with crisis rate of 0 at end of trial	24 (36) >2-fold increase vs placebo	12 (18)	11 (17)
Median annual rate of days hospitalized/year	4.00	6.87	6.87
Difference from placebo (%)	**-41.8**	0.0	-
P	.45	.84	-
Median time to 1st sickle cell–related pain crisis (months)	4.07 3-fold longer vs placebo	2.20	1.38
P	.001	.14	-
Median time to 2nd sickle cell–related pain crisis (months)	10.32	9.20	5.09
P	.02	.10	-

ITT, intention to treat.

Ataga et al. *N Engl J Med*. 2017;376:429-439.

AXIS Medical Education

SUSTAIN Trial: Primary Endpoint Results Consistent Regardless of HU Use or HbSS Status



HU, hydroxyurea; IQR, interquartile range; VOCs, vaso-occlusive crises.
Adapted from Ataga et al. *N Engl J Med*. 2017;376:429-439.

AXIS Medical Education

Crizanlizumab-tmca: FDA Approval

Date	November 2019
Indication	to reduce the frequency of VOCs in adults and pediatric patients aged 16 years and older with sickle cell disease
Recommended Dose	5 mg/kg
Administration	Intravenously over a period of 30 minutes on weeks 0, 2, and every 4 weeks thereafter
Trial	Phase 2 SUSTAIN
Annual rate of VOCs leading to a healthcare visit, defined as an acute episode of pain with no cause other than a VOC event requiring a medical facility visit and oral or parenteral opioids, or parenteral NSAIDs	Significant 45% reduction in the median annual rate of VOCs vs. placebo: • Voxelotor: 1.63 median annual rate of VOC • Placebo: 2.98 median annual rate of VOC • *P* = .010
Most common adverse reactions (>10%)	Nausea, arthralgia, back pain, abdominal pain, and pyrexia
Warnings	Infusion-related reactions, interference with automated platelet counts (platelet clumping)

NSAIDs, nonsteroidal anti-inflammatory drugs; VOCs, vaso-occlusive crises.
US Food & Drug Administration. November 15, 2019.

AXIS Medical Education

Crizanlizumab

- Crizanlizumab: monoclonal inhibitor of P-selectin adhesion pathway
- Dosing 5 mg/kg, approved by FDA in late 2019
- IV infusion monthly- first infusion prophylactic agent in sickle cell
- Well tolerated with minimal side effect profile
- Effect
  - ↓ VOC events by 45% compared to placebo, and prolongs time to next event

FDA, Us Food & Drug Administration.
Ataga et al. *N Engl J Med*. 2017;376:429-439.

AXIS Medical Education

Ongoing Clinical Trials Summary

Drug	Trial	Phase	Treatment Setting	Status
Crizanlizumab	STAND NCT03814746	3	2 different doses of crizanlizumab (5.0 mg/kg and 7.5 mg/kg) vs. placebo, with or without hydroxyurea/hydroxycarbamide, in adolescent and adult SCD patients with VOC, age ≥12 years	Recruiting
	SPARTAN NCT03938454	2	SCD patients with priapism	Recruiting
	STEADFAST NCT04053764	2	SCD patients ≥ 16 years with chronic kidney disease due to sickle cell nephropathy	Active, not recruiting
	SOLACE-kids NCT03474965	2	Dose and safety of crizanlizumab with or without hydroxyurea/hydroxycarbamide in pediatric SCD patients with VOC, ages 6 months to 17 years	Temporarily halted recruitment until dose in Group 2 is confirmed
	SOLACE-adults NCT03264989	2	PK/PD of crizanlizumab with or without hydroxyurea/hydroxycarbamide in SCD patients with VOC, ages 16 to 70 years	Active, not recruiting
Voxelotor	HOPE Kids NCT02850406	2	Pediatric SCD patients, ages 6 months to 17 years (in 4 parts)	Recruiting
	HOPE Kids 2 NCT04218084	3	Pediatric SCD patients, aged ≥ 2 to < 15 years old, vs. placebo	Recruiting

PK, pharmacokinetics; PD, pharmacodynamics.

AXIS Medical Education

Practical Application Case Series

Case Study 1: Pediatric Patient

Patient and Disease Characteristics

- A 6 year-old girl with sickle cell-beta thalassemia
- Has VOCs requiring hospitalization every 3 to 4 months
- Takes 20 mg/kg of hydroxyurea and 1 mg of folic acid daily
- Requires blood transfusions approximately every 6 weeks to maintain Hgb at > 6 g/dL and is symptomatic when Hgb < 6 g/dL
- WBC count ~ 2.6/uL and platelets ~130 x 10^9/L
- Takes desferasirox daily for iron overload
- A donor search is currently being conducted for possible stem cell transplant

Treatment Selection

- What would you recommend to decrease this patient's need for RBC transfusions?
  a) Decrease her dose of hydroxyurea to 10 mg/kg daily
  b) Start her on 900 mg of voxelotor PO daily (based on weight)
  c) Start her on 5 mg PO BID of L-glutamine (based on weight)
  d) Prescribe 4,000 units/mL of erythropoietin once weekly
  e) Make no changes in her current treatment regimen

BID, twice daily; Hgb, hemoglobin; PO, orally; RBC, red blood cell; WBC, white blood cell.

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Case Study 2: Young Adult Patient

Patient and Disease Characteristics

- A 17 year-old black man with HbSS disease
- Admitted to hospital at least twice monthly for the last year for recurrent VOCs
- His teachers have recommending that he repeat his Junior year in high school because of so many missed school days
- Rx: 1,000 mg of hydroxyurea daily and 1 mg of folic acid daily but is poorly compliant
- Baseline Hgb ~ 8.5 g/dL
- WBC count ~ 7.5/uL
- Platelet count ~ 260 x 10^9/L
- Fetal hemoglobin is 22%

Treatment Selection

- What would you recommend to reduce his hospitalizations for VOC?
  a) Double his dose of hydroxyurea
  b) Increase his daily folic acid to 2 mg
  c) Prescribe crizanlizumab 5 mg/kg IV q 2 weeks, then once monthly
  d) Prescribe a baby aspirin (81 mg) daily
  e) None of the above

Hgb, hemoglobin; Rx, prescription; VOC, vaso-occlusive crisis.

AXIS Medical Education

Case Study 3: Adult Patient

Patient and Disease Characteristics

- A 34 year-old black man with HbSS
- Moved to your city and is seeing you for the first time
- Takes 1,000 mg of hydroxyurea daily
- Takes 1 mg of folic acid daily
- Takes 20 grams daily of L-glutamine
- Current Hgb is 9.7 g/dL
- WBC count is 11.4/uL and platelets 360 x 10^9/L
- Total bilirubin is 2.6 g/dL
- Peripheral blood smear with rare sickle cells and occasional target cells
- Has had exchange transfusions for acute chest syndrome and priapism previously
- Has recently been admitted to hospital 3 times in the past 6 weeks for recurrent episodes of pain in the arms and legs
- Currently taking hydrocodone/acetaminophen for pain every 6 hours and 2 mg of hydromorphone PO q 3 hr prn for breakthrough pain
- He rates his current pain at 8/10

Treatment Selection

- What would you recommend to address this patient's pain events?
  a) Imaging of the hips for AVN
  b) Starting on a long-acting narcotic
  c) Add crizanlizumab to reduce the incidence of VOCs
  d) Set up a pain contract because you suspect that he is over utilizing narcotics
  e) Add voxelotor at 1,500 mg daily

AVN, avascular necrosis; Hgb, hemoglobin; PO, orally; prn, as needed; VOCs, vaso-occlusive crises; WBC, white blood cell.

AXIS Medical Education

Key Takeaways

- Sickle cell disease is a very common “rare” disease with multiple disease-specific acute and chronic complications and implications
- To formulate optimal treatment plans for the management of SCD, you need to assess the patients’ needs and specific concerns as well as current guideline recommendations
- Vaso-occlusion can cause both organ damage and pain, and individualized care plans improve pain control
- **Crizanlizumab** is now FDA approved to reduce the frequency of VOCs in adults and pediatric patients aged 16 years and older with SCD
- **Voxelotor** is now FDA approved for the treatment of SCD in adults and pediatric patients 4 years of age and older
- **L-glutamine** is FDA approved to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older

FDA, US Food & Drug Administration; SCD, sickle cell disease; VOC, vaso-occlusive crises.

AXIS Medical Education

Axis Advocacy

Axis Advocacy is a 5013c in California that is uniquely positioned to address the Sickle Cell Disease community and Stakeholders with the purpose of addressing their broad needs and concerns. From advocating for federal laws to assisting individual patients at multiple points of care, Axis is committed to improving the lives of patients and community members nationwide. This is more important now as we are in the intersection of racial bias and inequities, financial burdens, political division, opioid hysteria, and new medical advancements.

www.axisadvocacy.org

Axis Advocacy
Sickle Cell Disease Community and Support

AXIS Medical Education

Improving Interprofessional Management of Sickle Cell Disease with Disease-Directed Therapies