Where are we now with

Sickle Cell Disease

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FLASCO

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JOHNS HOPKINS
MEDICINE
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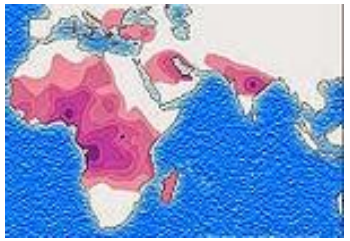
Objectives

- Overview of Sickle Cell Disease (SCD)
- Review Common Presentations of SCD
- Review Medical Management
- Review Treatment Management

The origin



- Equatorial Africa in a region where malaria is rampant, that the incidence of sickle cell anemia is highest
- The origin of the mutation that led to the sickle-cell gene derives from at least four independent mutational events, three in Africa and a fourth in either Saudi Arabia or central India.
- Dr. Charles F. Whitten was a trailblazer in medical education and sickle cell disease awareness and pioneering efforts to advocate for the needs of people with sickle cell disease, the Sickle Cell Disease Association of America (SCDAA) was born.

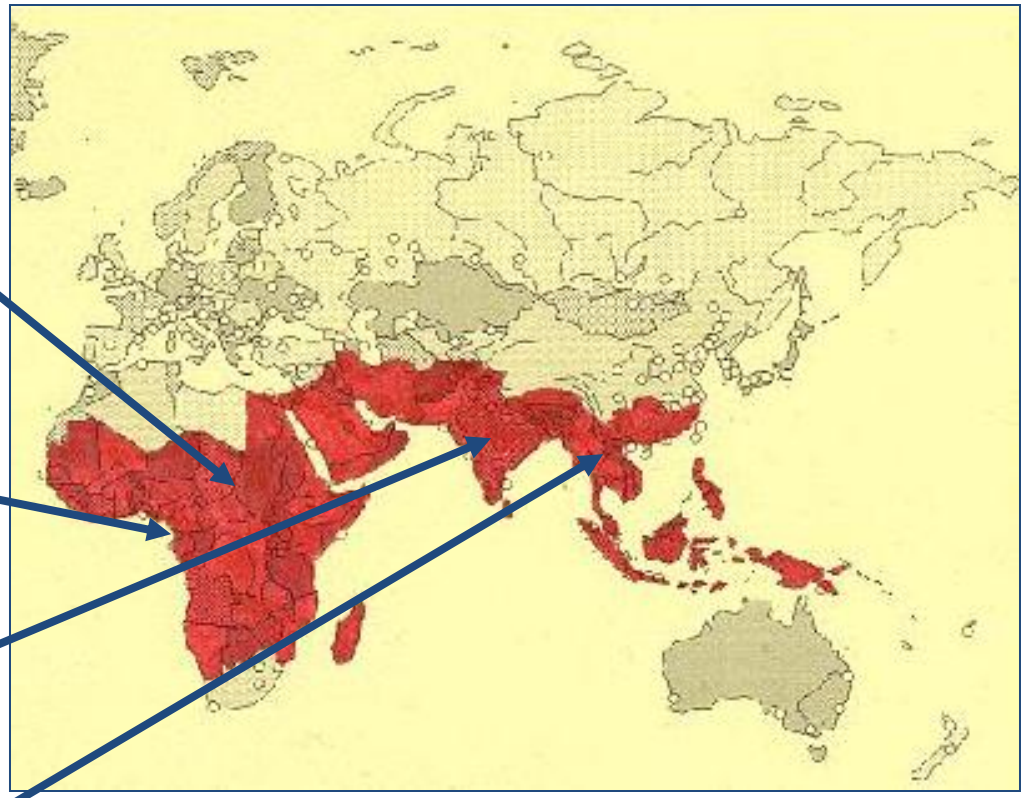
Historical Distribution of Hemoglobin Variants

Hemoglobin S

Hemoglobin C

Hemoglobin D

Hemoglobin E



Malarial Regions of Africa and Asia
Alpha thalassemia occurs in all these regions as well

When did it all begin in the US?

- 1910

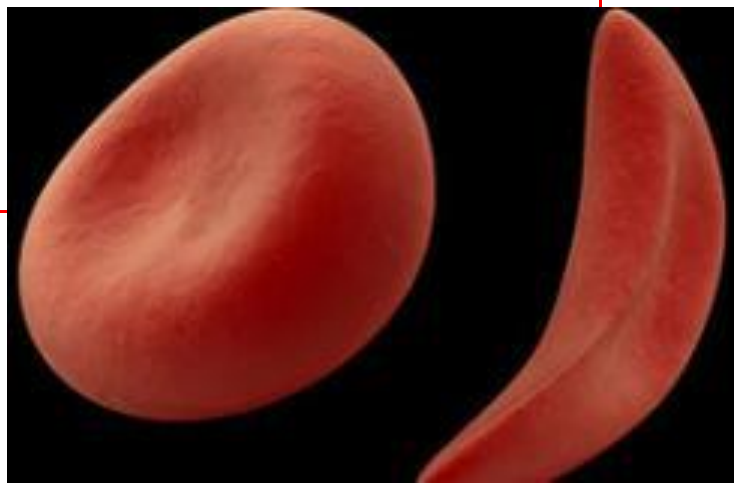
YALE JOURNAL OF BIOLOGY AND MEDICINE 74 (2001), pp. 179-184.

CLASSICS OF BIOLOGY AND MEDICINE

Peculiar Elongated and Sickle-shaped Red Blood Corpuscles in a Case of Severe Anemia[a]

James B. Herrick, M.D.

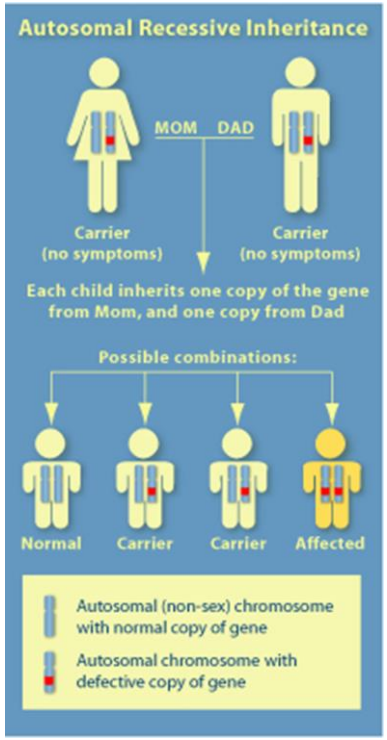
1013 State Street, Chicago, Illinois



Peculiar elongated and sickle-shaped" is how sickle cells were first described in 1904 by intern Ernest Edward Irons when examining the blood of Walter Clement Noel, a 20-year-old first-year dental student from a wealthy Black family in Grenada.

Sickle Cell Disease

- Most common inherited blood disorder
- Autosomal recessive inheritance
- U.S. Statistics:
  - Black American
    - 1 in 365 births have Hb SS
    - 1 in 13 births Hb S Carrier (Sickle Cell Trait)
    - 1 in 50 births Hb C Carrier
    - 1 in 100 births β-thalassemia Carrier
  - Hispanic American
    - 1 in 16,300 births
  - Caucasian American (southern Europe and Middle Eastern)

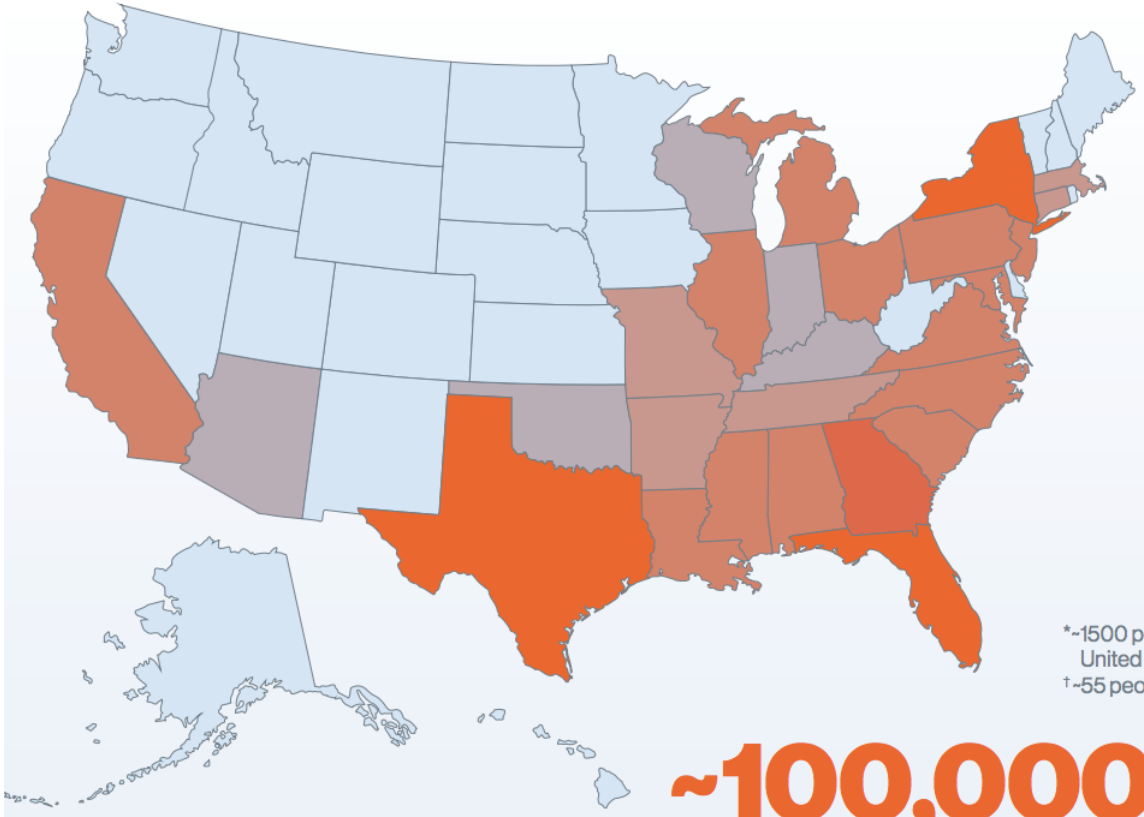


Centers for Disease Control and Prevention; World Health Organization; Piel et al. 2013. Lancet 381: 142-51.

The US demographics

FACTS ABOUT SICKLE CELL DISEASE

~100,000 People Are Affected by Sickle Cell Disease in the United States[1]



Incidence of Sickle Cell Disease[1]

~1:365 African American Births*

~1:16,300 Hispanic American Births†

Incidence of Sickle Cell Trait[1]

~1:13 African American Births

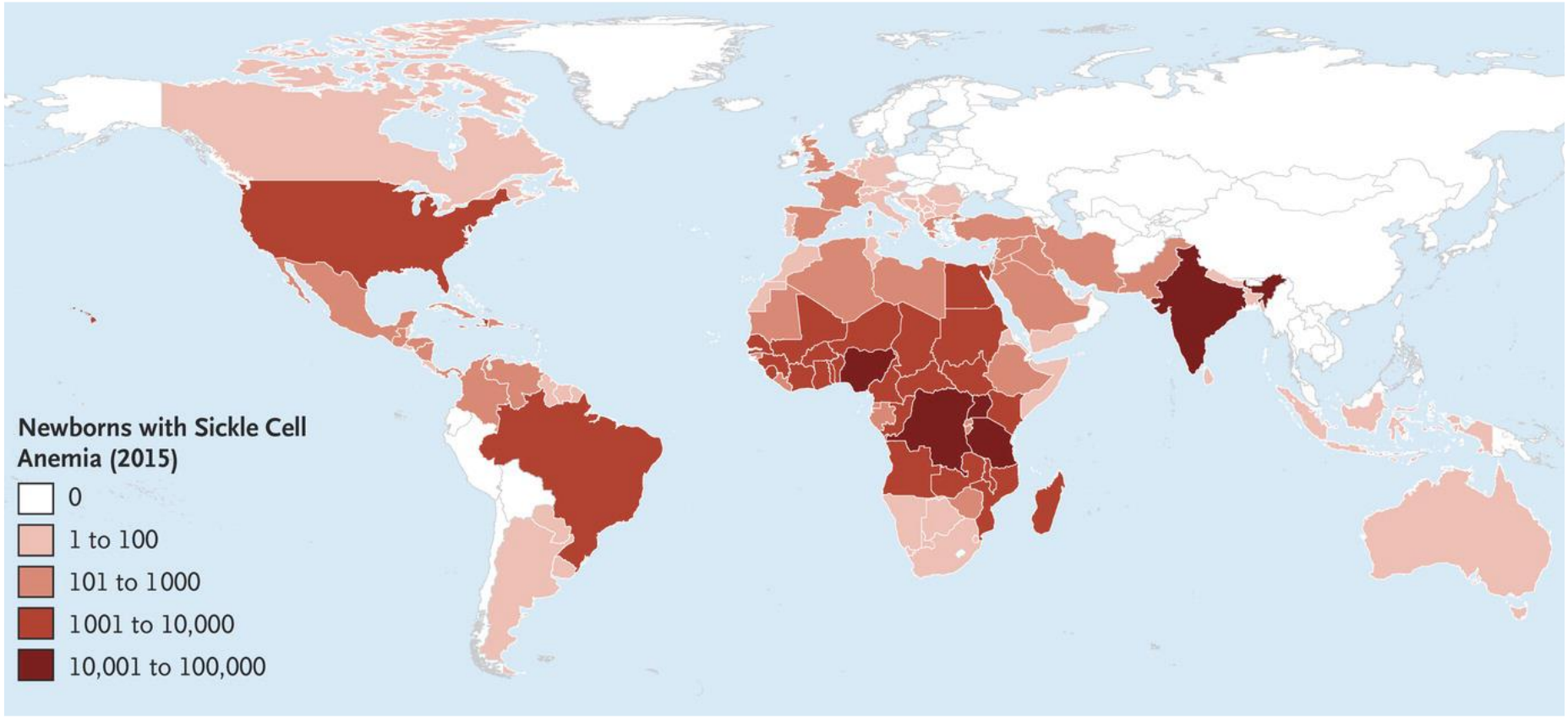
*~1500 people with sickle cell disease (SCD) per year based on the birth rates in United States, 2017.[2]

†~55 people with SCD per year based on the birth rates in United States, 2017.[2]

~100,000 PEOPLE IN THE UNITED STATES HAVE SICKLE CELL DISEASE[1]

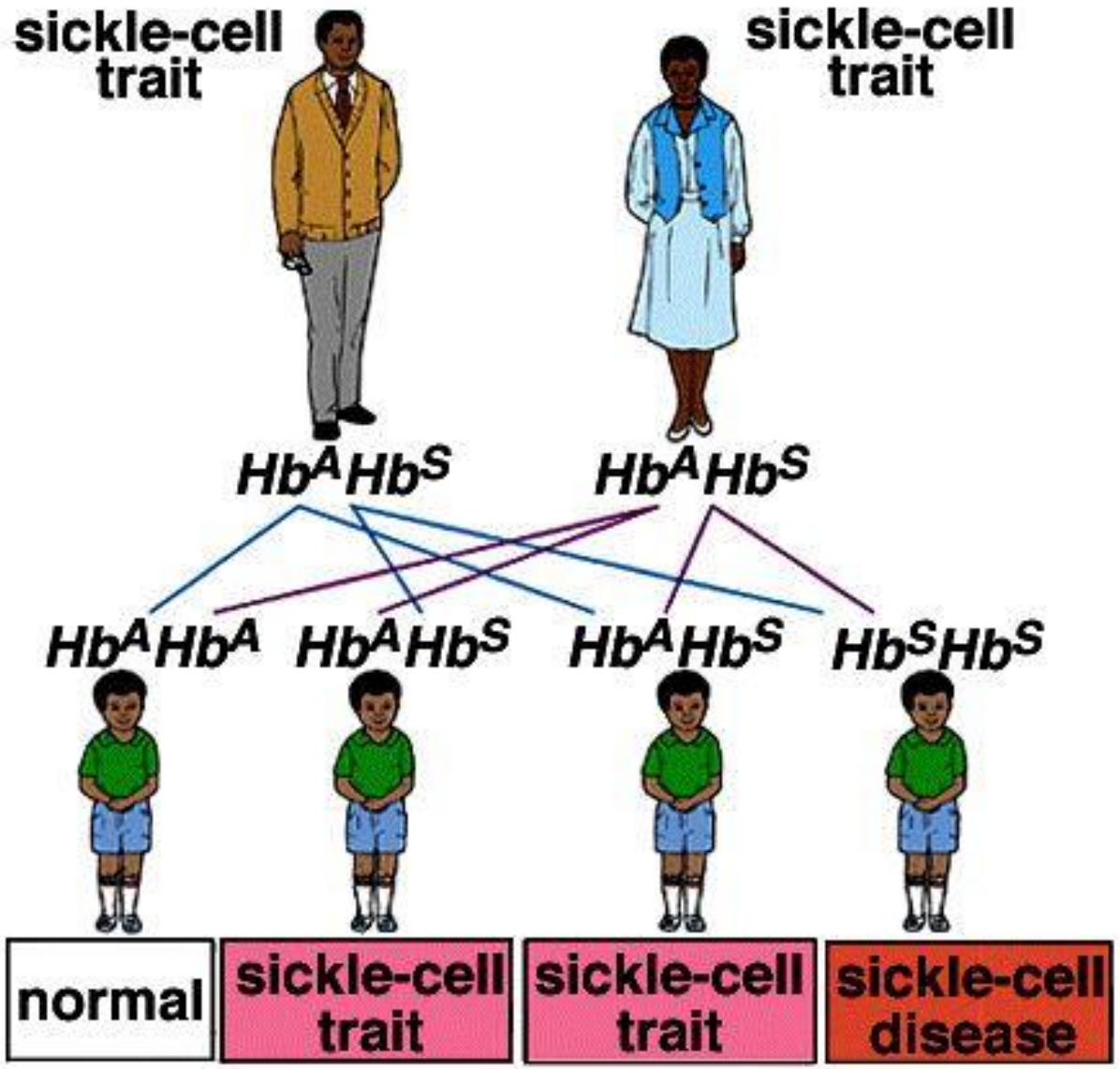
≥7000 | 5000-6999 | 2500-4999 | 1000-2499 | 500-999 | <500

Global Burden of SCD

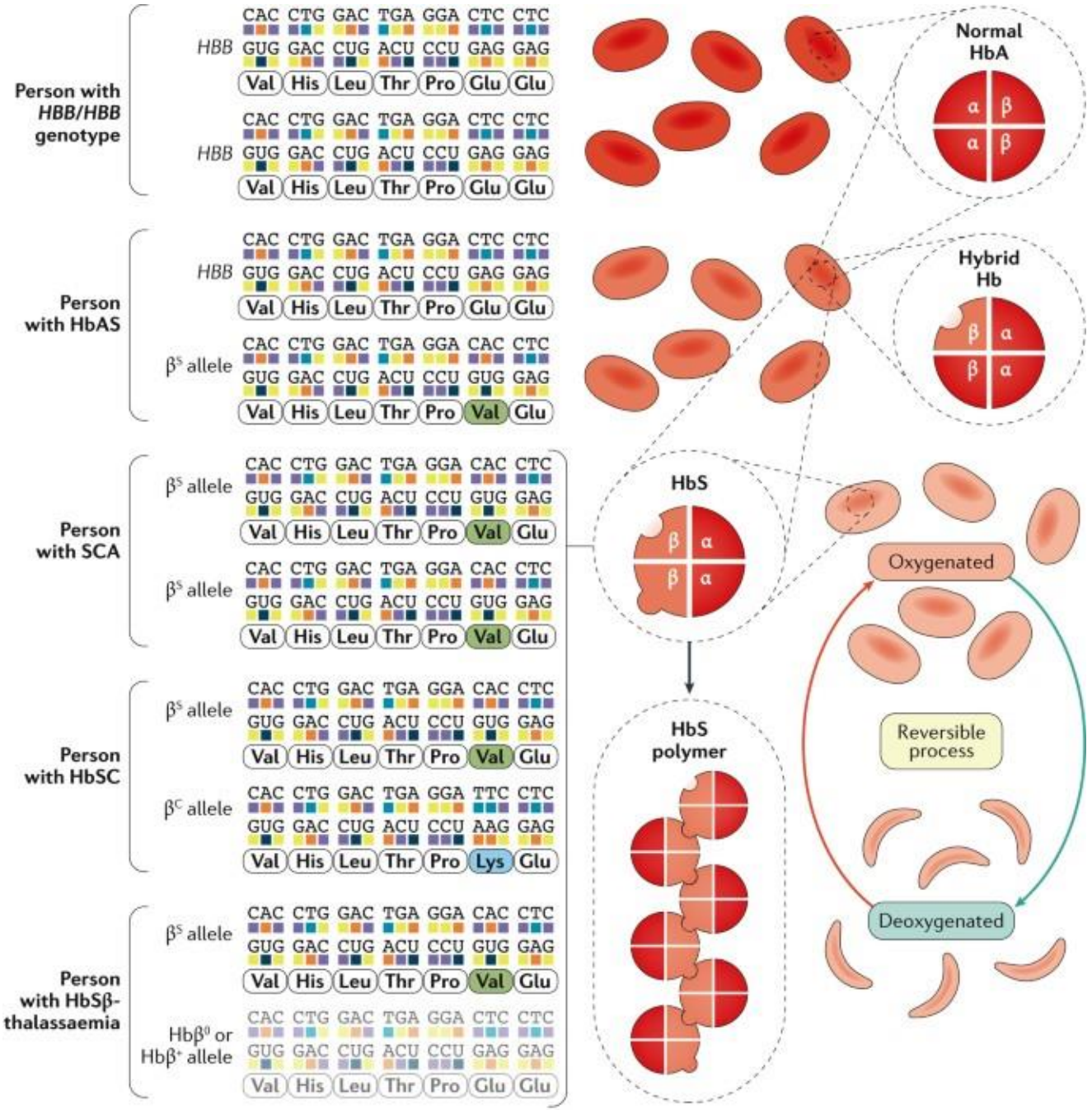


- Estimated Prevalence of 2%
- Africa – 2 million with sickle cell disease
- Nigeria – 300,000 newborns annually

Inheritance of sickle-cell disease



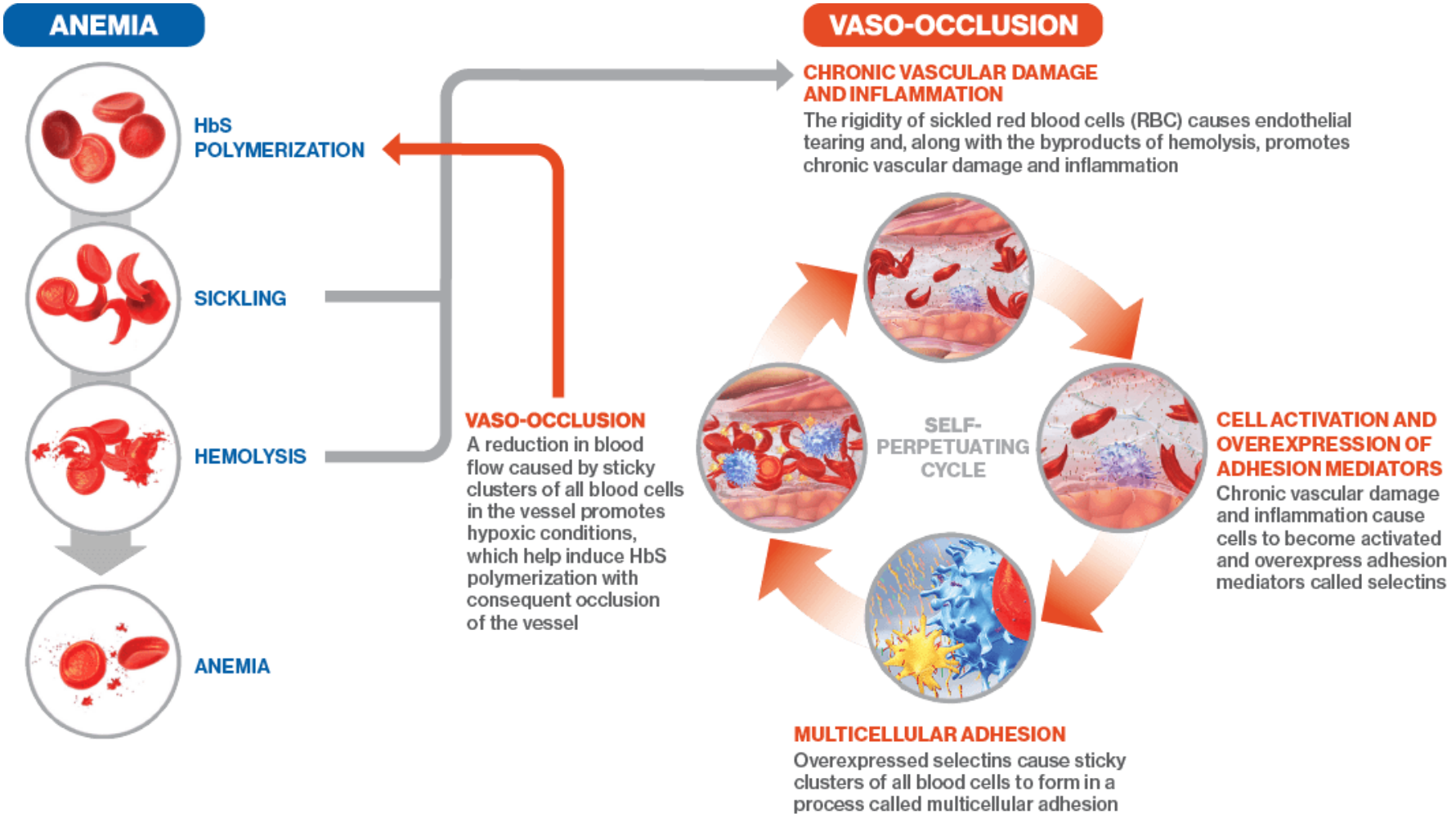
a.



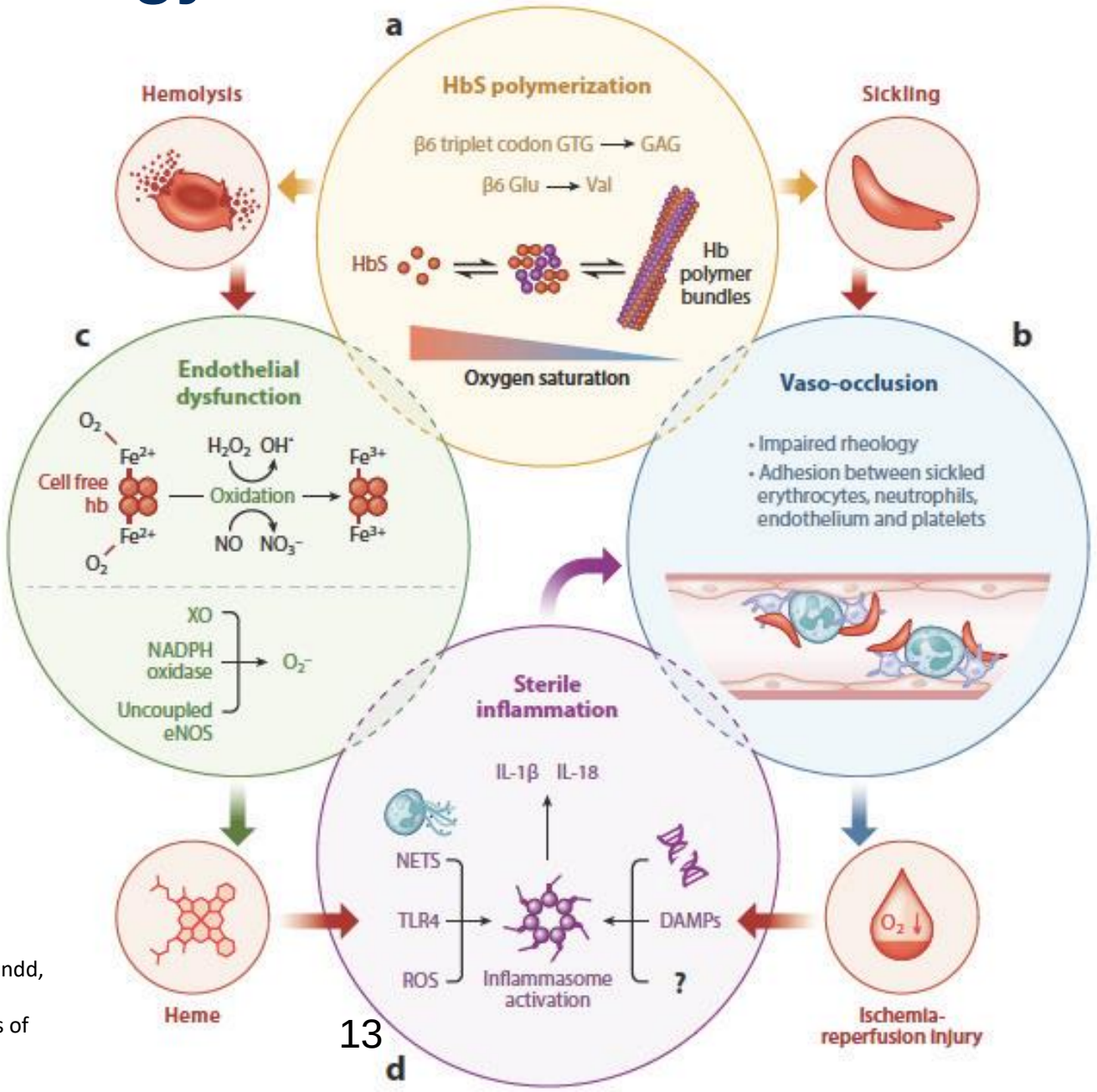
Kato, G. J. et al. (2018) Sickle cell disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2018.10

Clinical Manifestation

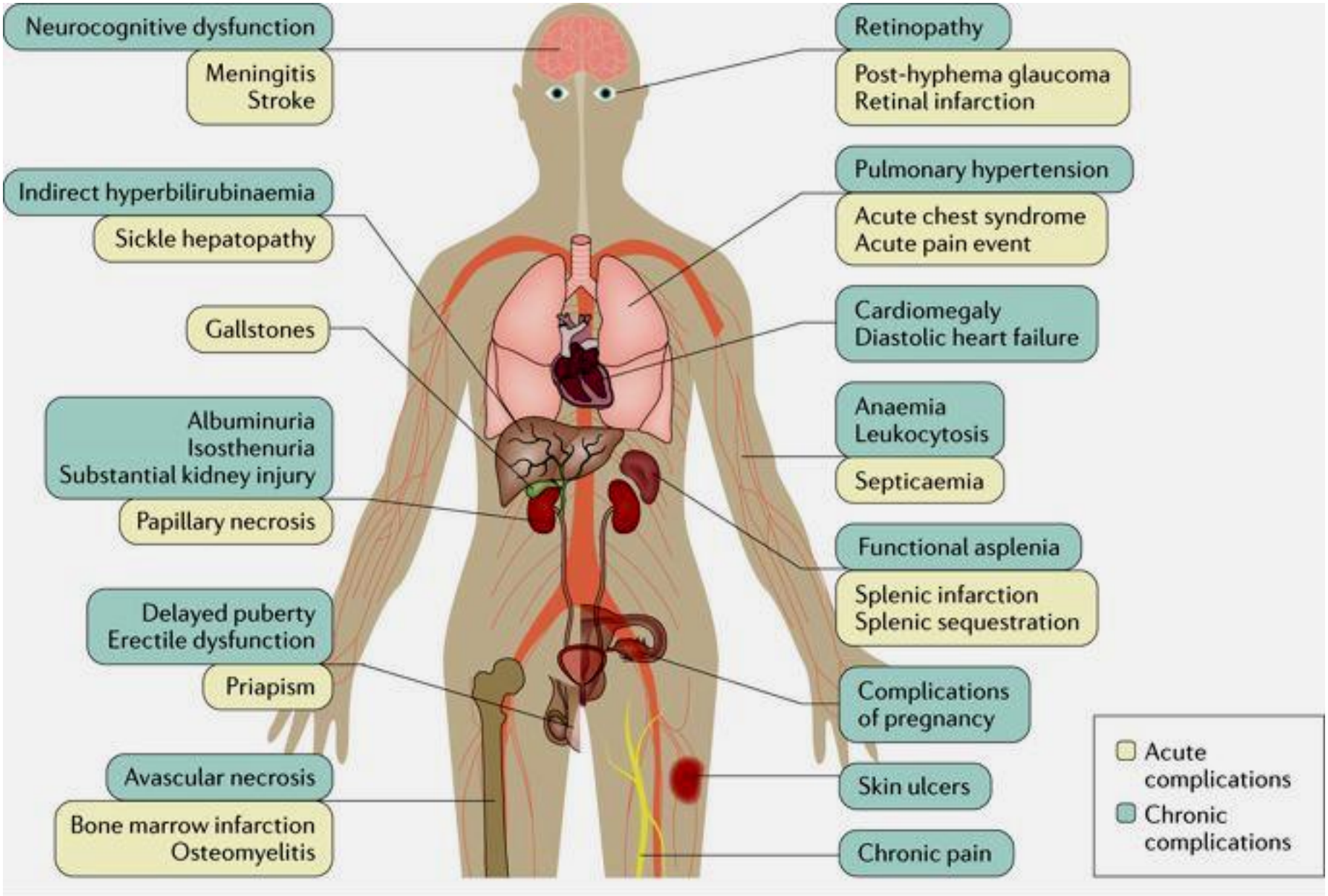
Pathophysiology



Pathophysiology of Sickle Cell Disease



Pathology of Sickle Cell Disease, Prithu Sundd, Mark T. Gladwin, Enrico M. Novelli
Annual Review of Pathology: Mechanisms of Disease 2019 14:1



Kato GJ et al. *Nature Reviews Disease Primers.* V4: 18010 (2018).
https://media.nature.com/m685/nature-assets/nrdp/2018/nrdp201810/images_hires/nrdp201810-f5.jpg.

Management

EVIDENCE REPORT

Evidence-Based Management of Sickle Cell Disease

Expert Panel Report, 2014

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines

Expert Panel

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[a] These individuals contributed to the development of these guidelines during their tenure with the NHLBI Division for the Application of Research Discoveries.
[b] These individuals contributed to the development of these guidelines during their tenure with American Institutes for Research (AIR).

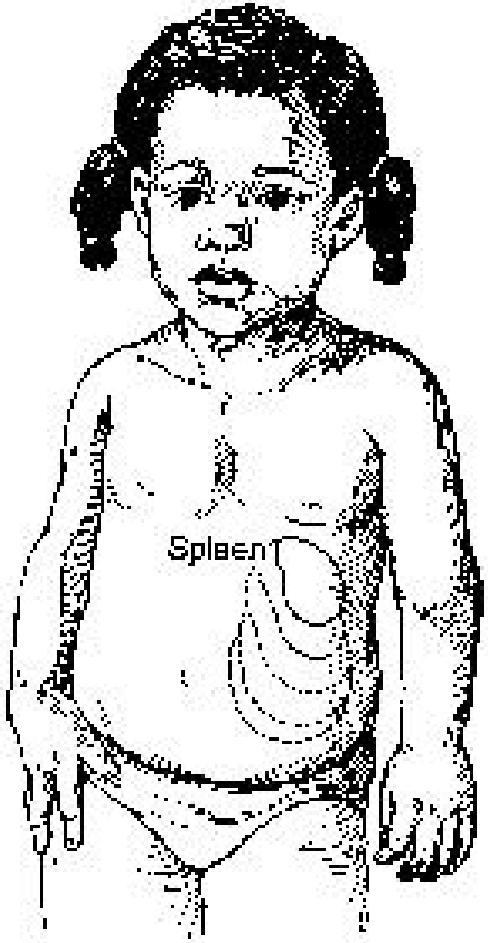
Fever in SCD

Fever in patients with SCD

- Panel used Consensus Process for triaging and management of fever

Recommendations
1. Temperature ≥101.3˚ F (38.5˚ C), evaluate with history and physical examination, complete blood count with differential, reticulocyte count, blood culture. ***(Consensus–Panel Expertise)***
2. Temperature ≥101.3 ˚ F (38.5 ˚ C), administer empiric parenteral antibiotics that provide coverage against *Streptococcus pneumoniae* and gram-negative enteric organisms. Subsequent outpatient management using an oral antibiotic is feasible in people who do not appear ill. ***(Consensus–Panel Expertise)***
3. Hospitalize if temperature ≥103.1 ˚ F (39.5 ˚ C) and who appear ill for close observation and intravenous antibiotic therapy. ***(Consensus–Panel Expertise)***
4. Febrile illness accompanied by shortness of breath, tachypnea, cough, and/or rales, add a chest x ray to investigate for acute chest syndrome. ***(Consensus–Panel Expertise)***

Spleen in SCD



Acute Splenic Sequestration Crisis

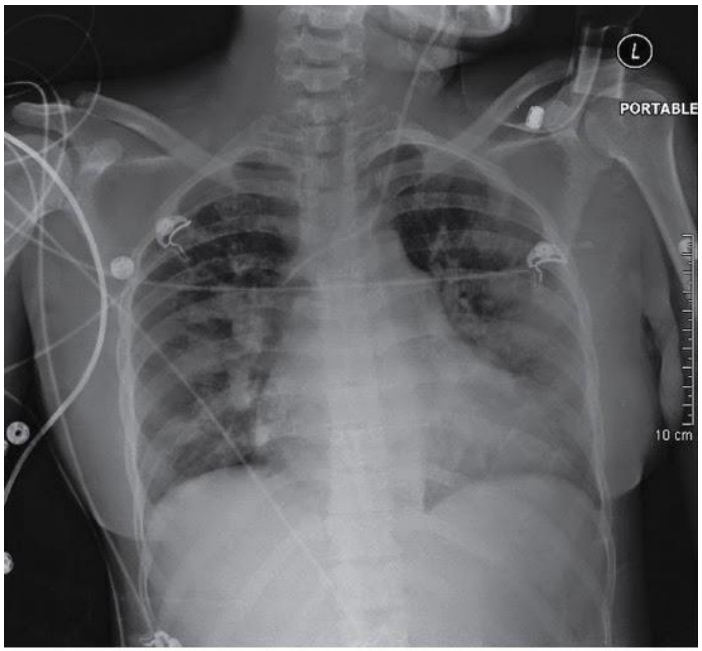
- Definition of ASSC—Hb > 2 gm less than baseline, large or enlarging spleen, evidence of active marrow
- As well as the anemia, usual features:
  - higher than baseline retic ct
  - platelets less than baseline and often < 150 K
  - often marked leukocytosis
- Age 1-4 with highest prevalence (70% is SS).
- HbSC and HbSb+ can occur later in childhood or adult years
- ASSC is usually progressive until transfused

ASSC Management

- Once diagnosis is confirmed or strongly suspected, transfusion is needed
- Should be begun as soon as possible. Usually would not wait for transfer to another facility
- Begin with 10 cc/kg. Rapidity of infusion depends on illness of child. Anticipate that spleen will release some cells, don't want to overshoot.

Recommendations
1. In people with hypovolemia due to severe acute splenic sequestration, immediately provide IV fluid resuscitation. **(*Strong Recommendation, Low-Quality Evidence*)**
2. Transfuse people who have acute splenic sequestration and severe anemia to raise the hemoglobin to stable level, avoid over-transfusion. ***(Strong Recommendation, Low Quality Evidence)***
3. Address the performance and timing of splenectomy in people with recurrent acute splenic sequestration **(*Moderate Recommendation, Low-Quality Evidence*)**

Acute Chest Syndrome



Source: Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology, 8th Edition:* http://www.accessmedicine.com

Acute Chest Syndrome

- Common and serious acute complication of SCD
- Second most frequent reason for hospitalization in children and adults with SCD and the most common cause of death
- Resembles pneumonia and can develop suddenly or insidiously, during hospitalization for a pain crisis or after a surgical procedure
- Increased frequency in people with asthma or prior acute chest events

ACS - Management

Recommendations

1. Evaluate for ACS if development of acute onset of lower respiratory tract disease signs and/or symptoms with or without fever for ACS. Chest x ray and measurement of oxygen saturation by pulse oximetry. ***(Consensus–Panel Expertise)***

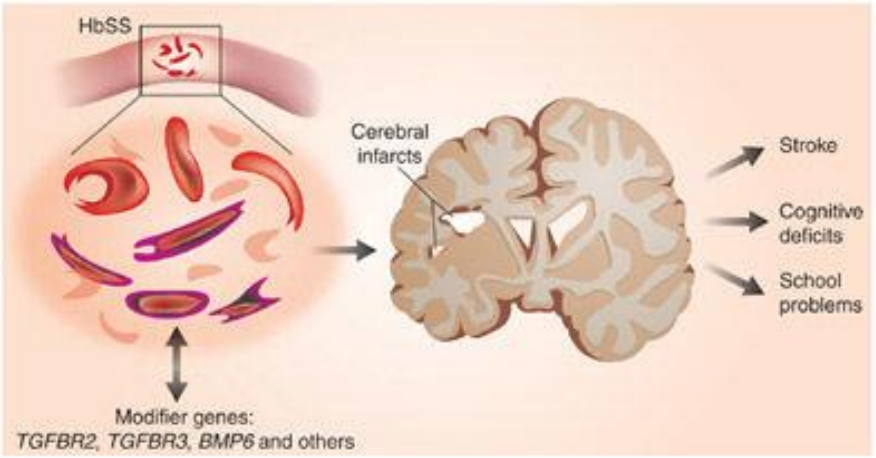
2. Hospitalize people with ACS. ***(Consensus–Panel Expertise)***

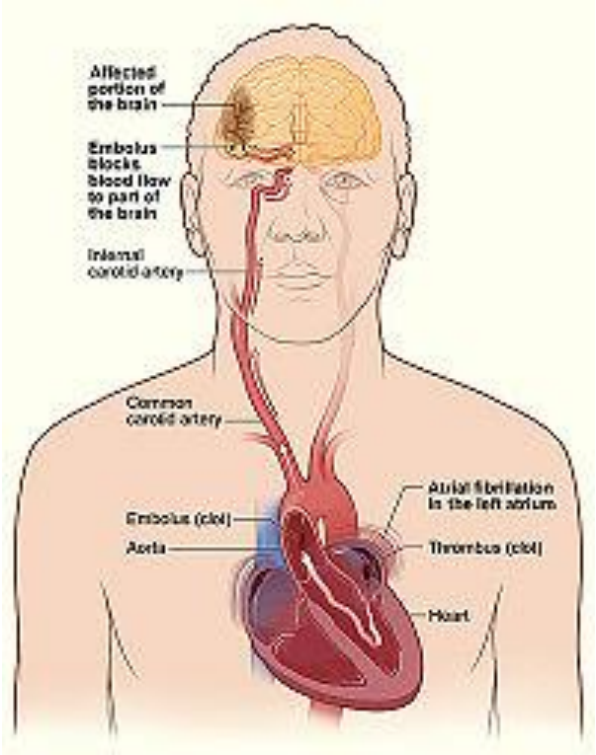
3. Treat ACS with an intravenous cephalosporin, an oral macrolide antibiotic, supplemental oxygen (maintain oxygen saturation >95%). ***(Strong Recommendation, Low-Quality Evidence)***

4. Simple blood transfusion (10 mL/kg red blood cells) to improve oxygen carrying capacity if hemoglobin concentration is >1.0 g/dL below baseline. ***(Weak Recommendation, Low-Quality Evidence)***

5. Urgent exchange transfusion when there is rapid progression of ACS as manifested by oxygen saturation below 90% despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, decline in hemoglobin level despite simple transfusion. ***(Strong Recommendation, Low-Quality Evidence)***

Stroke in SCD





Primary Stroke Prevention - Management

Recommendations
1. In children with SCA, screen annually with TCD, beginning at age 2 and continuing until age 16. **(*Strong Recommendation, Moderate-Quality Evidence*)** 2. In children with conditional (170–199 cm/sec) or elevated (>200 cm/sec) TCD results, refer to a specialist with expertise in chronic transfusion therapy aimed at preventing stroke. **(*Strong Recommendation, High-Quality Evidence*)** 3. In children with genotypes other than SCA (HbS β+-thalassemia or HbSC), do not perform screening with TCD. **(*Strong Recommendation, Low-Quality Evidence*)**

2019 ASH Guidelines

- Five ASH Sickle Cell Disease Guidelines covering cardiopulmonary and kidney disease, cerebrovascular disease, transfusion, transplantation, and pain management.
- www.hematology.org/SCDGuidelines

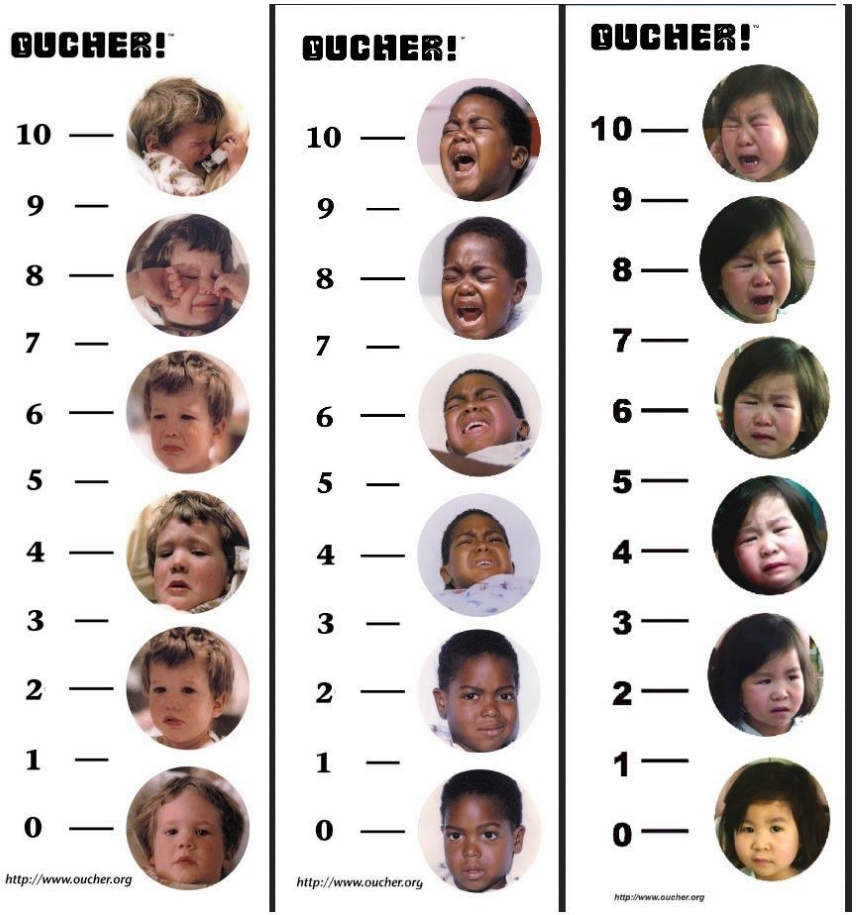
Cardiopulmonary – Screening Recommendations

Topic	Panel Recommendation	Strength of Recommendation	Notes
Screening ECHO	**Suggests *against*** screening ECHO in asymptomatic patients to identify PH	Conditional	Comprehensive review of systems may identify indications for diagnostic study
Screening PFT	**Suggests *against*** screening PFT in asymptomatic patients	Conditional	Comprehensive review of systems may identify indications for diagnostic study
Screening Sleep Study	**Suggests *against*** screening sleep study in asymptomatic patients	Conditional	Comprehensive review of systems may identify indications for diagnostic study

Cardiopulmonary – Management Recommendations

Topic	Panel Recommendation	Strength of Recommendation	Notes
Managing abnormal ECHO	**Suggests *against*** RHC for patients with isolated peak TRJV of ≥ 2.5 to 2.9 m/s	Conditional	• Need for RHC should be based on ECHOs done at steady state • ECHOs showing elevated peak TRJV should be repeated • NT-BNP and 6MWD may improve diagnostic accuracy of elevated peak TRJV for PH
	Suggests RHC for patients with peak TRJV ≥ 2.5 m/s and also reduced 6MWD and/or elevated NT-BNP	Conditional	
Treatment of PAH	**Recommends *against*** PAH-specific therapies for patients without PAH confirmed by RHC	Strong	• Disease-modifying therapies should be initiated or optimized • Patients receiving PAH-specific therapies should also be under care of PH specialist
	Suggests PAH-specific therapies for patients with PAH confirmed by RHC	Conditional	

Pain in SCD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Pain in SCD

- **Acute pain**: Pain should be assessed, and medication administered within one hour of their arrival at the acute care facility.
  - Individuals should then be frequently reassessed every 30-60 minutes for consideration of additional doses of pain medication to optimize their pain control.
- **Chronic pain**: Individuals who experience chronic pain may benefit from a tailored treatment plan when starting or ending chronic opioid therapy.
  - Treatment decisions should balance the risks and benefits of opioids and consider the individual's function, goals, and durability of benefit over time.
  - Medications that treat pain that are not opioids can be considered for individuals who experience chronic pain as part of a comprehensive pain treatment plan.

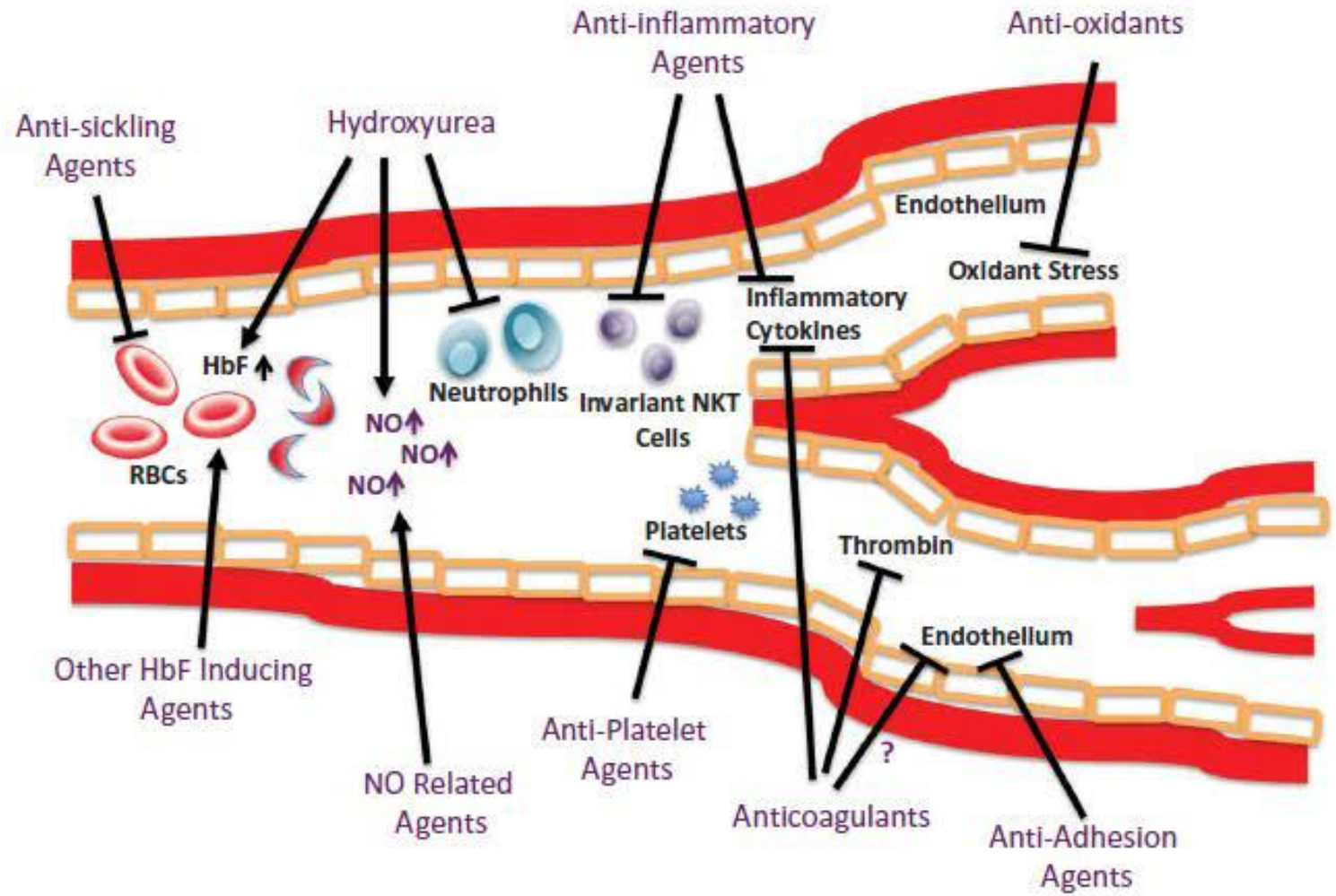
Pain Management

- Pain management approaches beyond and in addition to prescription medicines:
  - Approaches such as massage, yoga, virtual reality, and guided audiovisual relaxation in addition to medications (e.g., opioids, NSAIDs).
  - Cognitive Behavioral Therapy and other integrative approaches (e.g., acupuncture, massage therapy) in addition to medications as part of a comprehensive disease and pain management plan.
- Transfusion: Individuals living with SCD who have recurrent acute pain may not benefit from chronic monthly transfusions as a first-line strategy to prevent or reduce future acute pain episodes

Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. Blood Adv. 2020;4(12):2656-2701

Treatment Options

Advances in New Drug Therapies



Ataga et al. 2018 Advances in New Drug Therapies for the Management of Sickle Cell Disease

Treatment options for SCD

- Penicillin
- Transfusions
- **Hydroxyurea**
- **L-Glutamine**
- **Crizanlizumab**
- **Voxelotor**
- Stem Cell transplant
- Gene Therapy

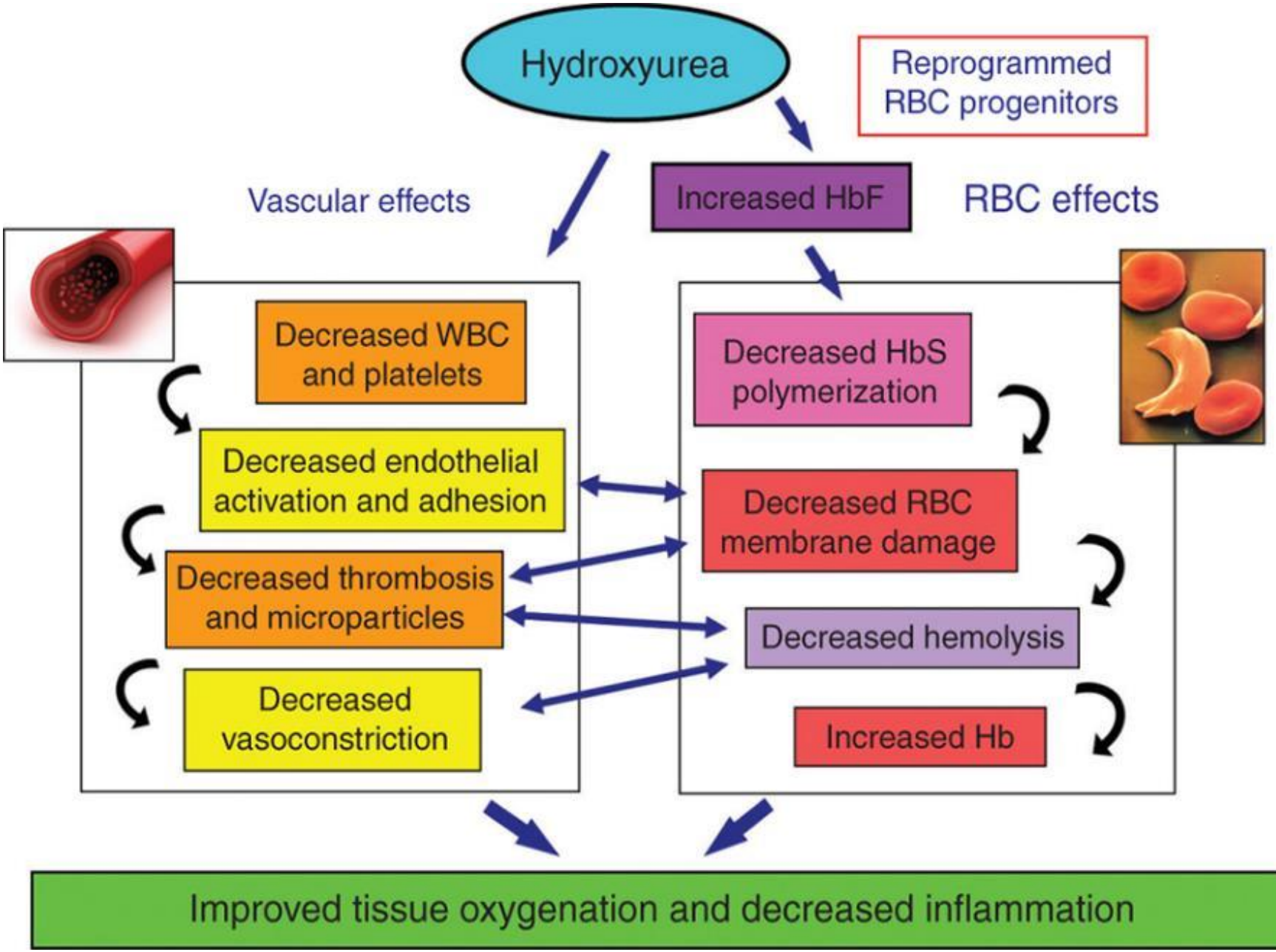
Drug options and mechanisms

- Inhibiting HbS Polymerization
- Blocking intermolecular contacts in the sickle Fiber
- Induction of HbF synthesis
- Reduction of intracellular HbS concentrations
- Increase in Oxygen Affinity
- Reduction of the concentration of 2, 3 diphosphoglycerate

William A Eaton[1], H Franklin Bunn[2] **Treating sickle cell disease by targeting HbS polymerization**
2017 May 18;129(20):2719-2726. doi: 10.1182/blood-2017-02-765891. Epub 2017 Apr 6.

Hydroxyurea

- Hydroxyurea, a ribonucleotide reductase inhibitor, was identified as a promising drug candidate to increase HbF levels in people with SCD
- Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH) a randomized, double-blind, placebo-controlled trial; 299 adults with SCA
- MSH trial demonstrated that hydroxyurea reduced the frequency of painful episodes and ACS events, and need for RBC transfusions and hospitalizations
- 1998, the U.S. FDA approved hydroxyurea for the treatment of clinically severe SCA in adults


Hydroxyurea
Reprogrammed RBC progenitors
Vascular effects
Increased HbF
RBC effects
Decreased WBC and platelets
Decreased endothelial activation and adhesion
Decreased thrombosis and microparticles
Decreased vasoconstriction
Decreased HbS polymerization
Decreased RBC membrane damage
Decreased hemolysis
Increased Hb
Improved tissue oxygenation and decreased inflammation

- Double-blind, randomized
- Pt's with SS or $S\beta^0$thalassemia
- 299 patients with history of 3 or more crises/year
- Decrease in number of crises/yr (2.5 v. 4.5 $p < 0.001$)
- Decrease in ACS (25 v. 51 $p < 0.001$))
- Decrease in no. of patients undergoing transfusion (48 v. 73 ($p = 0.001$)
- Higher hemoglobin levels, mean corpuscular volumes, fetal hemoglobin levels
- Lower white-cell, platelet, reticulocyte, and dense-cell counts

NEJM 1995 May 18;332(20):1317-22

Hydroxyurea in Children

Recommendations

1. Infants 9 months of age and older, children, and adolescents with SCA, **offer treatment with hydroxyurea regardless of clinical severity** to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia). ***(Strong Recommendation, High-Quality Evidence*** **for ages 9–42 months**

Note: The panel intentionally used the term “offer” realizing that patients’ values and preferences may differ particularly considering treatment burden, availability of drug in a liquid form, and cost.

Hydroxyurea

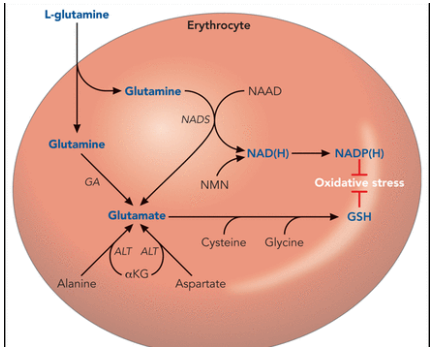
- Comes in many formulations
  - Capsules: Hydroxyurea (500mg)
    - (200, 300, 400mg),
  - Tablets: (100mg, 1000mg)
  - Can be compounded to liquid as well
- Dosing: Starting dose is 20mg/kg to max of 35mg/kg
- Monitor for Myelotoxicities (Neutropenia, Thrombocytopenia)

L- Glutamine

- L Glutamine (GLN) is an essential nutrient that helps in cell functions
- Gln has been first isolated in beet juice in 1883 and subsequently found in protein hydrolase of gliadin in 1932
- L Glutamine was found to significantly reduce endothelial cell adhesion in sickled red cells
- Oral therapy with pharmaceutical-grade L-glutamine has been shown to increase the proportion of the reduced form of nicotinamide adenine dinucleotides (NADPH) in sickle cell erythrocytes, which probably reduces oxidative stress and hemolysis.

Niihara*, N Engl J Med,* 2018

L-Glutamine



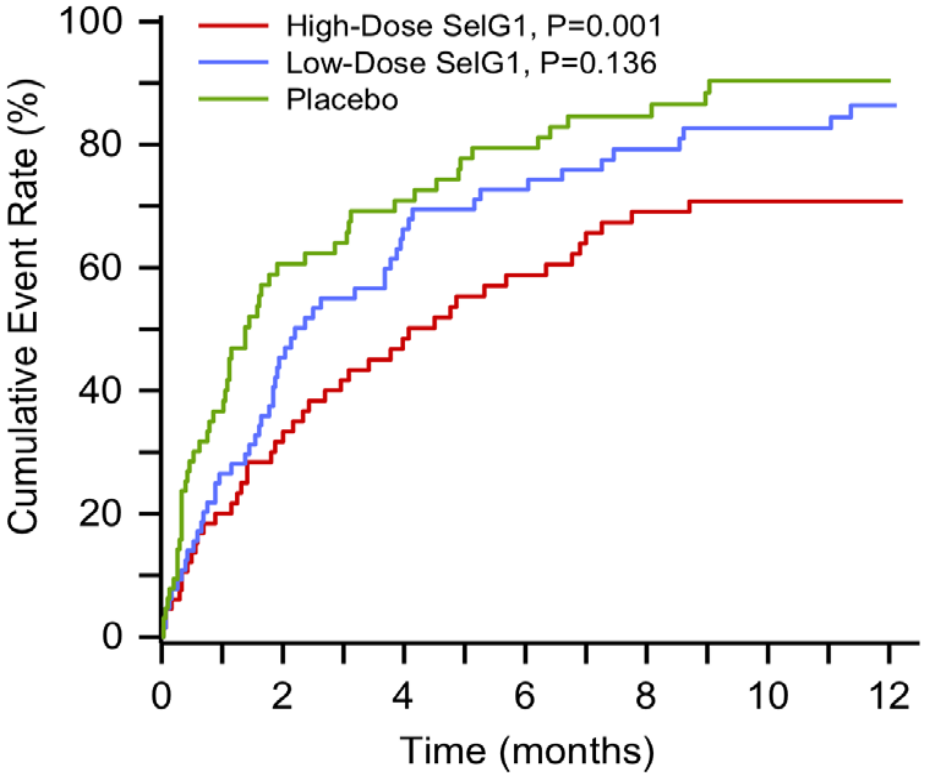
- FDA approved in July 7th, 2017
- January 2018, available in the formulary
- 2nd FDA Approved Drug in SCD in 2017
  - Reduces Pain Crisis
  - Reduces Acute Chest Syndrome
- Powder
- Needs to be mixed in Cold Food or Fluid
- Taken Twice Daily
- Dose is weight based

Crizanlizumab

- Humanized monoclonal antibody that binds to P-selectin and blocks its interaction with P-selectin glycoprotein ligand 1
- Double-blind, randomized, placebo-controlled, phase 2 trial,
- Compared crizanlizumab (2.5 mg/kg) and 5.0 mg/kg, or placebo, administered intravenously 14 times over a period of 52 weeks

Crizanlizumab

- P- selectin Inhibition
- Decrease median time to the first crisis
- Approved in 2019
- 5mg/kg IV 30 minutes monthly infusion
- For children 16 and up

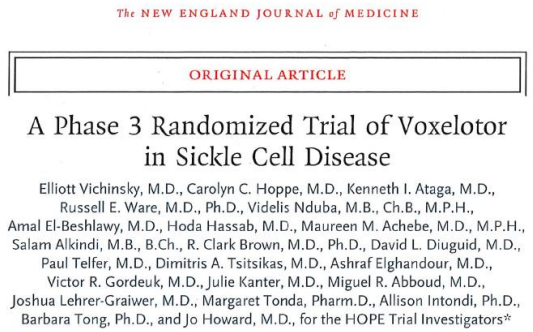


Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

K.I. Ataga, A. Kutlar, J. Kanter, D. Liles, R. Cancado, J. Friedrisch, T.H. Guthrie, J. Knight-Madden, O.A. Alvarez, V.R. Gordeuk, S. Gualandro, M.P. Colella, W.R. Smith, S.A. Rollins, J.W. Stocker, and R.P. Rother

Voxelotor

- Small molecule that binds to alpha globin chain and creates higher affinity for oxygen binding; thus, causing small delay in oxygen delivery and Hb polymerization (slows down delay time).
- Inhibitor of Hb S polymerization
- Phase 3, double-blind, randomized, placebo-controlled trial, comparing two dose levels of voxelotor (1500 mg and 900 mg, administered orally once daily) with placebo



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

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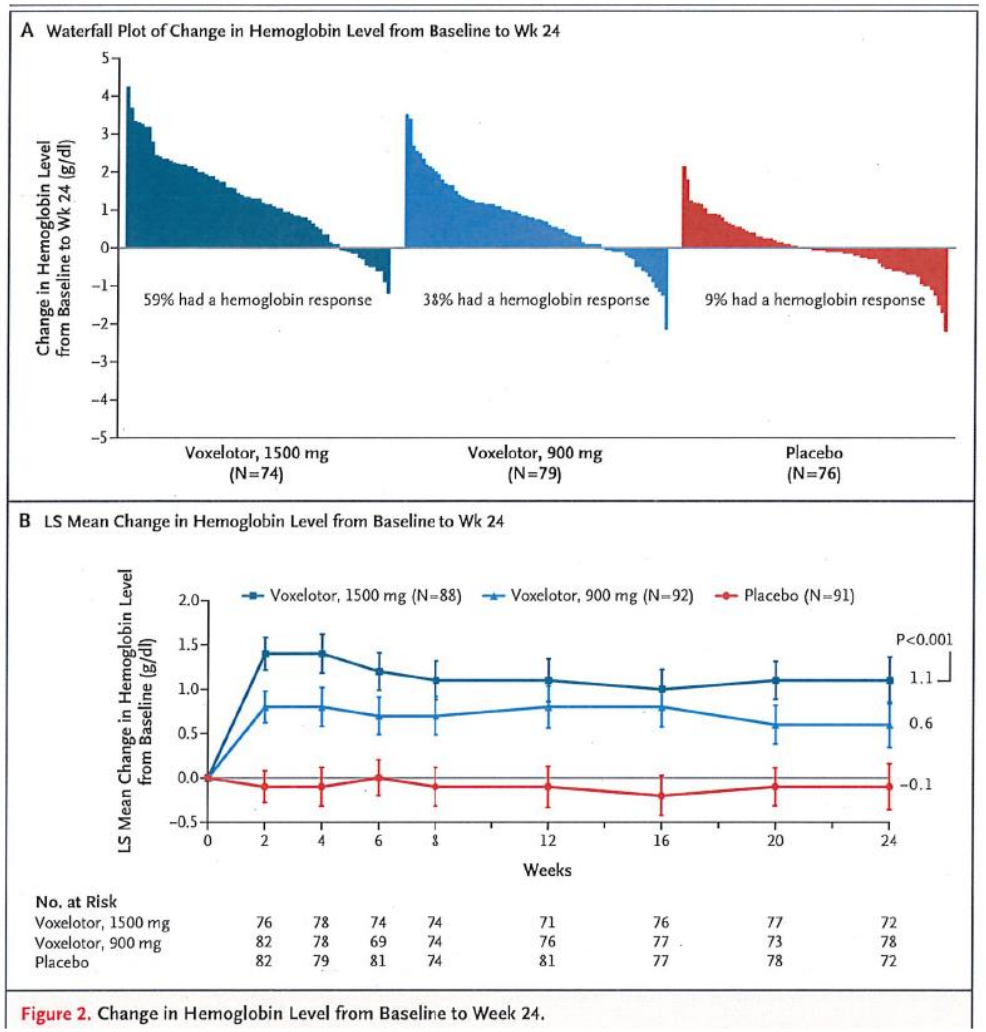
Volexotor

- At 1500mg there is a 50% hemoglobin response
- Approved in 2019
- 1500 mg tablet po daily
- For children 12 and up

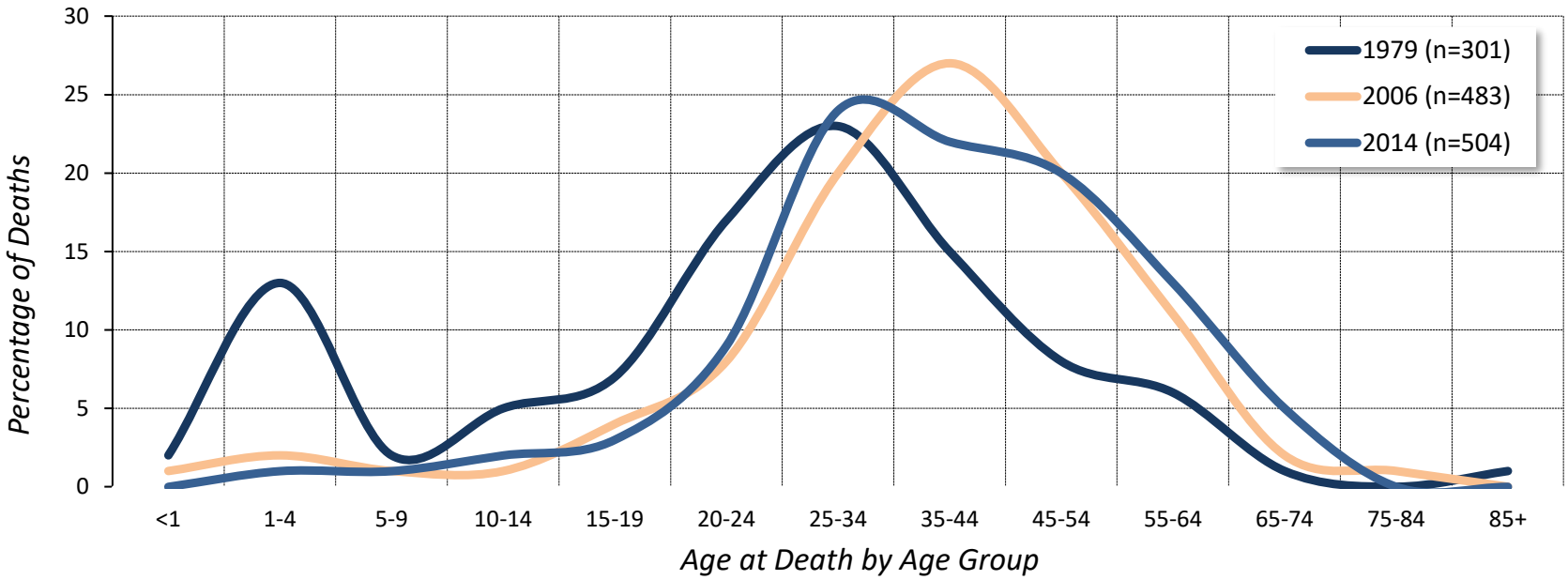


Vichinsky, *N Engl J Med*, 2019

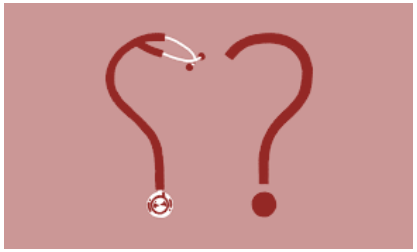
Selected New Drugs Under Investigation

Investigational Drug	NCT/Trial Name	Recruiting Ongoing	Route	Effect Being Studied
VIT 2763	04817670	Yes	PO	Hemolysis
Arginine	04839354/**STArT**	Yes	IV	Pain Crisis Resolution
Riociguat	02633397/**STERIO SCD**	Yes	PO	Adverse Events (AE)
Etavopivat (FT 4202)	04624659/**HIBISCUS**	Yes	PO	Hemoglobin & Pain Crises
Mitapivat (AG-348)	05031780	No	PO	Hemoglobin, AE & Pain Crises
GBT 021601-012	04983264	Yes	PO	Safety
CSL 889	04285827	Yes	IV	Safety
SCD-101	02380079	Yes	PO	Adverse Events
Crovalimab	04912869/**CROSSWALK-a**	Yes	IV	AE, Pain Crisis Resolution
Inclacumab	04935879	Yes	IV	Pain Crisis
L-citrulline (Turnobi)	04852172	Yes	IV	Pain Crisis Resolution
Intravenous Immunoglobin (IVIG)	01757418	Yes	IV	Pain Crisis Resolution

SCD Mortality



- In all genotype Childhood survival over 95%
- In 2014, most deaths (66%) occured at ages 25-54 years
- Recent surveillance data from Georgia and California showed mean age at death was 43 years for women, 41 years for men



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