Contemporary insights on the management of sickle cell disease: Focus on complications and recent advances in therapy

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*
- *The presenting faculty have been advised by USF Health and touchIME to ensure that they disclose any such references made to unlabelled or unapproved use*
- *No endorsement by USF Health and touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in USF Health and touchIME activities*
- *USF Health and touchIME accept no responsibility for errors or omissions*

Expert panel

Prof. Biree Andemariam (Chair)

Professor of Medicine,
University of Connecticut Health,
Farmington, CT, USA

Prof. Mark C Walters

Professor of Pediatrics,
University of California San Francisco,
Oakland, CA, USA

Prof. Modupe Idowu

Professor of Medicine,
University of Texas Health
Science Center,
Houston, TX, USA

touch™ NEUROLOGY

Agenda

What are the various manifestations and complications of sickle cell disease?

What are the practical considerations for the multidisciplinary management of sickle cell disease complications?

What does the evidence for established and novel therapies tell us about the prospects for patients with sickle cell disease?

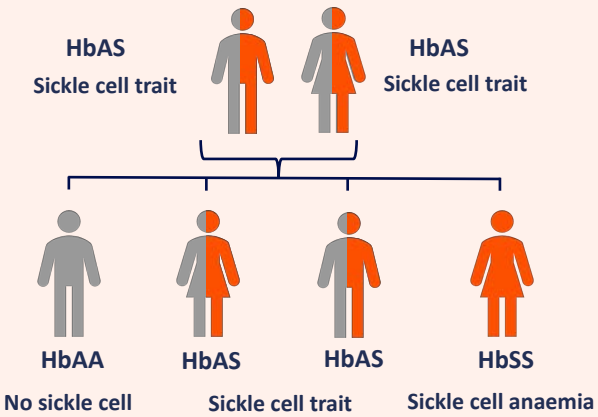
What are the various manifestations and complications of sickle cell disease?

Inheritance and epidemiology of sickle cell disease in the USA

SCD comprises a group of autosomal recessive disorders[1]

SCD affects ~100,000 people in the USA[2]

The most common SCD genotype is sickle cell anaemia (HbSS)[1]



- SCD occurs in ~1 out of every 365 Black or African-American births[2]
- SCD is particularly common among people whose ancestors came from regions where malaria is or was prevalent[2]

HbSC is another common genotype, but is associated with less severe disease[2]

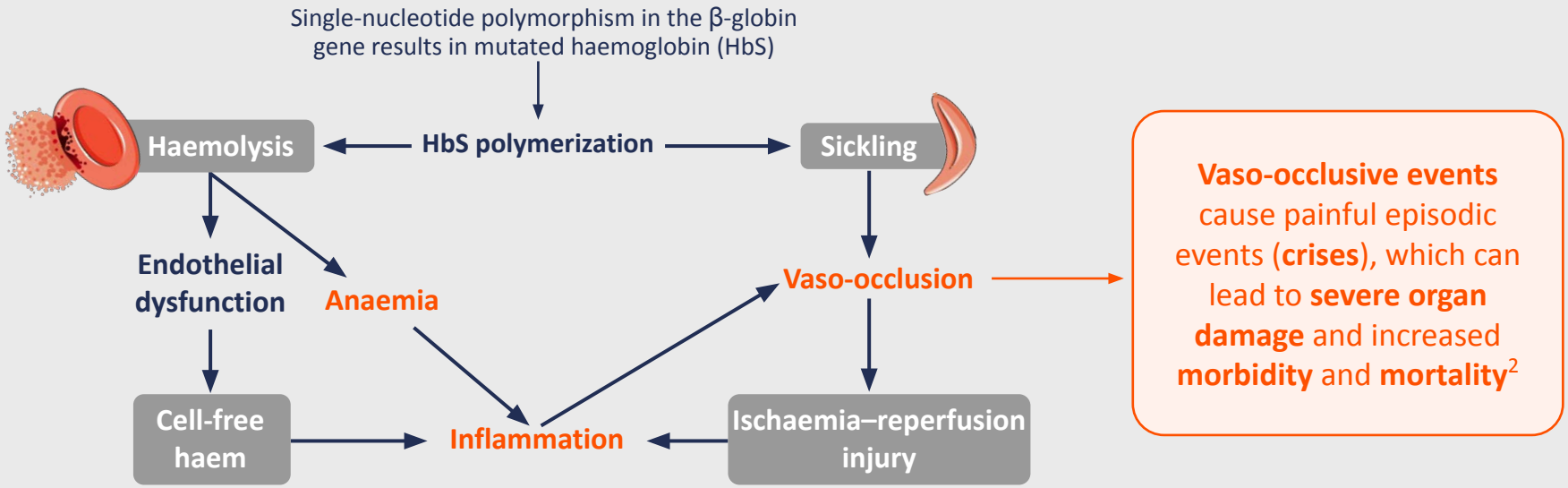
SCD, sickle cell disease.

1. Egesa WI, et al. *Int J Pediatr.* 2022;3885979; 2. CDC. 2022. Available at: www.cdc.gov/ncbddd/sicklecell/data.html (accessed 7 June 2023).

Sickle cell disease pathophysiology

Vaso-occlusion leads to acute and chronic complications[1,2]

Pathophysiology of sickle cell disease[1]



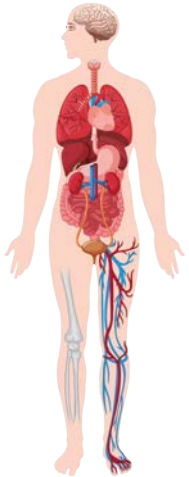
HbS, sickle haemoglobin.

1. Sundd P, et al. *Annu Rev Pathol.* 2019;14:263–92; 2. Piccin A, et al. *Eur J Haematol.* 2019;102:319–30.

Key manifestations of sickle cell disease

Symptoms and complications are unique to each individual, can affect every organ of the body and can range from mild to severe[1]

- Neurological[1,2]
- Oral[3]
- Respiratory[1]
- Cutaneous[1]
- Renal[1,3]
- Hepatic[1,4]
- Skeletal[1,3]



- Ocular[1,5,6]
- Endocrine*[7]
- Cardiovascular[1,8]
- Digestive[9]
- Reproductive system[1]
- Muscular[10]
- Haematological[1,11]

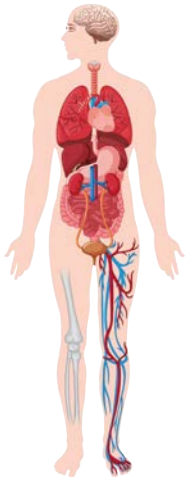
*Study in children and adolescents aged 3–18 years (N=52).[7]

1. CDC. 2022. Available at: www.cdc.gov/ncbddd/sicklecell/complications.html (accessed 7 June 2023); 2. Maduakor C, et al. *Front Neurol.* 2021;12:744118; 3. Chekroun M, et al. *Br Dent J.* 2019;226:27–31; 4. Suddle AR. *Hematology Am Soc Hematol Educ Program.* 2019;2019:345–50; 5. AlRyalat SA, et al. *Ophthalmic Epidemiol.* 2020;27:259–64; 6. Al-Jafar H, et al. *Open J Ophthalmol.* 2020;10:200–21; 7. Mandese V, et al. *BMC Pediatrics.* 2019;19:56; 8. Sachdev V, et al. *Trends Cardiovasc Med.* 2021;31:187–93; 9. Kinger NP, et al. *Curr Probl Diagn Radiol.* 2021;50:241–51; 10. Merlet AN, et al. *Med Sci Sports Exerc.* 2019;51:4–11; 11. Nardo-Marino A, Brousse V. *Haematologica.* 2023;108:954–5.

Key manifestations of sickle cell disease

Symptoms and complications are unique to each individual, can affect every organ of the body and can range from mild to severe[1]

- **Neurological**[1,2]: Stroke; Cerebrovascular disease; Neuropsychological condition; Peripheral neuropathy
- Oral[3]
- **Respiratory**[1]: Acute chest syndrome; Pulmonary embolism; Pulmonary hypertension; Sleep apnoea
- Cutaneous[1]
- Renal[1,3]
- **Hepatic**[1,4]: Acute sickle hepatic crisis; Sickle intrahepatic cholestasis; Hepatic sequestration; Acute/chronic cholelithiasis; Acute/chronic viral hepatitis; Biliary-type cirrhosis; Iron overload
- Skeletal[1,3]



- Ocular[1,5,6]
- **Endocrine***[7]: Vitamin D deficiency; Insulin resistance; Growth hormone deficiency; Subclinical hypothyroidism; Hypergonadotropic hypogonadism
- Cardiovascular[1,8]
- **Digestive**[9]: Bowel infarction, which can result in necrosis and perforation
- Reproductive system[1]
- **Muscular**[10]: Muscle atrophy; Contractures; Fibrosis; Myonecrosis
- Haematological[1,11]

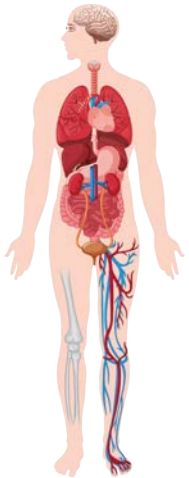
*Study in children and adolescents aged 3–18 years (N=52).[7]

1. CDC. 2022. Available at: www.cdc.gov/ncbddd/sicklecell/complications.html (accessed 7 June 2023); 2. Maduakor C, et al. *Front Neurol.* 2021;12:744118; 3. Chekroun M, et al. *Br Dent J.* 2019;226:27–31; 4. Suddle AR. *Hematology Am Soc Hematol Educ Program.* 2019;2019:345–50; 5. AlRyalat SA, et al. *Ophthalmic Epidemiol.* 2020;27:259–64; 6. Al-Jafar H, et al. *Open J Ophthalmol.* 2020;10:200–21; 7. Mandese V, et al. *BMC Pediatrics.* 2019;19:56; 8. Sachdev V, et al. *Trends Cardiovasc Med.* 2021;31:187–93; 9. Kinger NP, et al. *Curr Probl Diagn Radiol.* 2021;50:241–51; 10. Merlet AN, et al. *Med Sci Sports Exerc.* 2019;51:4–11; 11. Nardo-Marino A, Brousse V. *Haematologica.* 2023;108:954–5.

Key manifestations of sickle cell disease

Symptoms and complications are unique to each individual, can affect every organ of the body and can range from mild to severe[1]

- **Neurological**[1,2]
- **Oral**[3]: Delayed tooth eruption; Papillary atrophy of the tongue; Mandibular osteomyelitis; Orofacial pain; Necrosis of healthy teeth; Pale oral mucosa
- **Respiratory**[1]
- **Cutaneous**[1]: Leg ulcers
- **Renal**[1,3]: Chronic kidney disease; Glomerulopathies; Haematuria; Proteinuria
- **Hepatic**[1,4]
- **Skeletal**[1,3]: Avascular necrosis; Chronic bone pain



- **Ocular**[1,5,6]: Peripheral retinal artery occlusion; Sickle cell retinopathy
- **Endocrine***[7]
- **Cardiovascular**[1,8]: Thrombosis; Cardiomyopathy; Diastolic dysfunction; Sudden cardiac death
- **Digestive**[9]
- **Reproductive system**[1]: Priapism
- **Muscular**[10]
- **Haematological**[1,11]: Anaemia; Acute splenic sequestration; Dactylitis; Vaso-occlusive crisis

*Study in children and adolescents aged 3–18 years (N=52).[7]

1. CDC. 2022. Available at: www.cdc.gov/ncbddd/sicklecell/complications.html (accessed 7 June 2023); 2. Maduakor C, et al. *Front Neurol.* 2021;12:744118; 3. Chekroun M, et al. *Br Dent J.* 2019;226:27–31; 4. Suddle AR. *Hematology Am Soc Hematol Educ Program.* 2019;2019:345–50; 5. AlRyalat SA, et al. *Ophthalmic Epidemiol.* 2020;27:259–64; 6. Al-Jafar H, et al. *Open J Ophthalmol.* 2020;10:200–21; 7. Mandese V, et al. *BMC Pediatrics.* 2019;19:56; 8. Sachdev V, et al. *Trends Cardiovasc Med.* 2021;31:187–93; 9. Kinger NP, et al. *Curr Probl Diagn Radiol.* 2021;50:241–51; 10. Merlet AN, et al. *Med Sci Sports Exerc.* 2019;51:4–11; 11. Nardo-Marino A, Brousse V. *Haematologica.* 2023;108:954–5.

What are the practical considerations for the multidisciplinary management of sickle cell disease complications?

Dedicated team effort can have positive outcomes

- Co-ordination between primary care and subspecialities is essential for greatest impact[1–4]
- Regular screening for complications[5]

CORE TEAM

- Haematologist[1]/paediatric haematologist[2]
- Primary care physician[1]/paediatrician[3]
- Emergency medicine physician[1,3]
- Nurse practitioner[1,3]
- Social worker[1,3]
- Pharmacist[3]

EXTENDED TEAM

- Neurologist[3]
- Pulmonologist[3]
- Nephrologist[3]
- Cardiologist[3,5]
- Hepatologist[3,5]
- Gynaecologist[3]
- Endocrinologist[3,5]
- Psychiatrist[3]
- Ophthalmologist[3]
- Dentist[3]

1. Powell RE, et al. *Am J Med Qual*. 2018;33:127–31; 2. Balsamo L, et al. *Pediatrics*. 2019;143:e20182218; 3. Martinez RM, et al. (eds). *Addressing Sickle Cell Disease: A Strategic Plan and Blueprint for Action*. Washington, DC, USA: The National Academies Press, 2020; 4. Terry CM, et al. *Blood*. 2018;132 (Suppl.1):4931; 5. Houwing ME, et al. *Blood Rev*. 2019;37:100580.

touch™ NEUROLOGY

What does the evidence for established and novel therapies tell us about the prospects for patients with sickle cell disease?

Established therapies for sickle cell disease

Mechanisms of action and therapeutic goals

Blood transfusion[1]

Treats anaemia and other complications[2]

First used in 1960s[3]

MoA: Dilutes circulating sickled RBCs with unaffected RBCs to increase oxygen carrying capacity of blood[1]

Deferoxamine[4]/Deferasirox[5]

Reduces iron overload due to transfusion[4,5]

Approved 1968[4]**/2005**[5]

MoA: Iron chelation[4,5]

Hydroxyurea[6]

Prevents painful crises[7]

Approved for SCD in 1998[3]

MoA: Ribonucleotide reductase inhibitor.[8] Modulates HbS polymerization by increasing HbF[8]

Allogeneic haematopoietic stem cell transplantation[9]

Curative therapy

First transplant in 1984

MoA: Stem cells from HLA-matched donor produce healthy RBCs

HbF, foetal haemoglobin; HbS, sickle haemoglobin; HLA, human leukocyte antigen; MoA, mechanism of action; RBC, red blood cell; VOC, vaso-occlusive crises.

1. Howard J. *Hematology Am Soc Hematol Educ Program.*2016;2016:625–31; 2. Chou ST, et al. *Blood Adv*. 2020;4:327–55; 3. American Red Cross. 2023. Available at https://rcblood.org/44mWKn7 (accessed 26 June 2023); 4. FDA. Deferoxamine PI. Available at: https://bit.ly/3XFQ1CF (accessed 22 June 2023); 5. FDA. Deferasirox PI. Available at: http://bit.ly/43Wr4VJ (accessed 22 June 2023); 6. FDA. Hydroxyurea PI. Available at: https://bit.ly/3CK0ovk (accessed 26 June 2023); 7. Charache S, et al. *N Engl J Med*. 1995;332:1317–22; 8. Carden MA, Little J. *Haematologica.* 2019;104:1710–19; 9. Bhalla N, et al. *Front Med (Lausanne)* 2023;10:1036939.

Recently approved therapies for sickle cell disease

Mechanisms of action and therapeutic goals

L-Glutamine (age ≥5 years)[1,2]

Reduces pain crises[2]

Approved 2017[2]

MoA: Possible reduction in NAD redox potential and in cell adhesion[1]

Crizanlizumab (age ≥16 years)[1,3]

Reduces pain crises[3]

Approved 2019[3]

MoA: Anti P-selectin inhibitor; reduces RBC and WBC adhesion to endothelium[1]

Voxelotor (age ≥4 years)[4]

Improves anaemia and reduces haemolysis[4]

Approved 2019[4]

MoA: Increases Hb–oxygen affinity[1,4]
Reduces HbS polymerization[1,4]

Deferiprone (age ≥3 years)[5]

Reduces iron overload due to transfusion[5]

Approved for SCD 2021[6]

MoA: Iron chelation[5]

Hb, haemoglobin; HbS, sickle haemoglobin; MoA, mechanism of action; NAD, nicotinamide adenine dinucleotide; RBC, red blood cell; VOC, vaso-occlusive crises; WBC, white blood cell.

1. Rai P, Ataga KI. *F1000Res.* 2020;9:F1000 Faculty Rev-592; 2. FDA. L-Glutamine PI. Available at: https://bit.ly/3CKB9cm (accessed 22 June 2023); 3. FDA. Crizanlizumab PI. Available at: https://bit.ly/44dfLs2 (accessed 22 June 2023); 4. FDA. Voxelotor PI. Available at: https://bit.ly/3rejcR5 (accessed 05 July 2023); 5. FDA. Deferiprone PI. Available at: https://bit.ly/44AZnl9 (accessed 10 July 2023); 6. FDA. Orphan Drug Designations and Approvals. Available at: https://bit.ly/3PMUcue (accessed 5 July 2023).

Investigational therapies for sickle cell disease

Mechanisms of action and therapeutic goals

The goals of emerging treatments are disease modifying[1–3] or curative[4]

Gene therapies[4–6]

Gene addition approach[4]

- Lovotibeglogene autotemcel (lovo-cel)[5]

Adds functional β-globin gene[5]

Gene editing approach[4]

- Exagamglogene autotemcel (exa-cel)[6]

Edits *BCL11A*, an HbF repressor[4,6]

Pyruvate kinase activators[1,2]

Increases ATP in RBCs
Reduces HbS polymerization

- Etavopivat[1]
- Mitapivat[2]

DNA methyltransferase inhibitor[7]

Increases HbF expression via gene reactivation

- NDec

ATP, adenosine triphosphate; HbF, foetal haemoglobin; HbS, sickle haemoglobin; NDec, decitabine + tetrahydrouridine combination; RBC, red blood cell.

1. Telen M, et al. *HemaSphere.* 2022;6:2–3; 2. van Dijk MJ, et al. *Am J Hematol.* 2022;97:E226–29; 3. Carden MA, Little J. *Haematologica.* 2019;104:1710–19; 4. White SL, et al. *Annu Rev Med.* 2023;74:473–87; 5. Kanter J, et al. *Am J Hematol.* 2023;98:11–22; 6. de la Fuente J, et al. *HemaSphere.* 2023;7:2–3; 7. Andemariam B, et al. *Blood.* 2022;140:5420–21.