

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

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Expert panel



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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

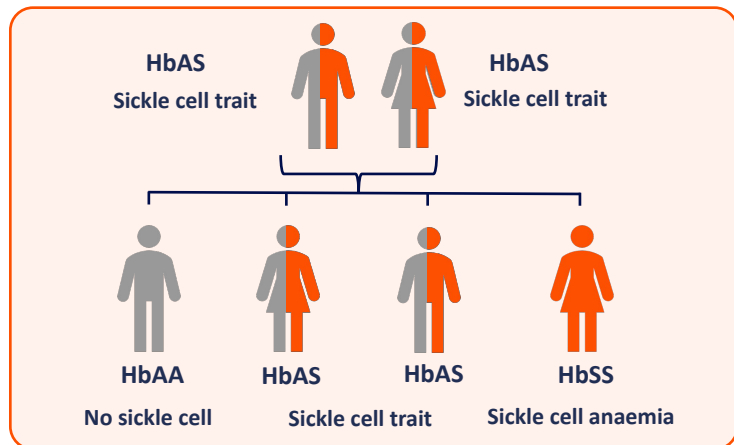


SCD comprises a group of autosomal recessive disorders¹



SCD affects ~100,000 people in the USA²

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



- SCD occurs in ~1 out of every 365 Black or African-American births²
- SCD is particularly common among people whose ancestors came from regions where malaria is or was prevalent²

HbSC is another common genotype, but is associated with less severe disease²

SCD, sickle cell disease.

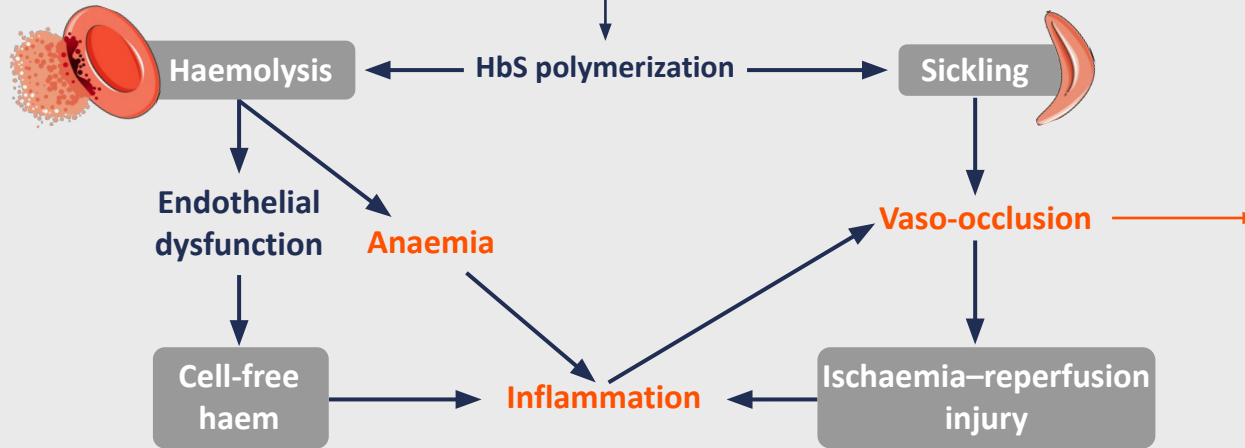
1. Egesa WI, et al. *Int J Pediatr.* 2022;3885979; 2. CDC. 2022. Available at: www.cdc.gov/ncbddd/sicklecell/data.html (accessed 7 June 2023).

Sickle cell disease pathophysiology

Vaso-occlusion leads to acute and chronic complications^{1,2}

Pathophysiology of sickle cell disease¹

Single-nucleotide polymorphism in the β -globin gene results in mutated haemoglobin (HbS)



Vaso-occlusive events cause painful episodic events (**crises**), which can lead to **severe organ damage** and increased **morbidity and mortality²**

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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 severe¹

Neurological^{1,2}

Oral³

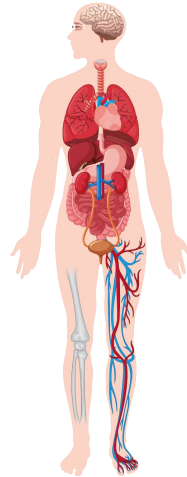
Respiratory¹

Cutaneous¹

Renal^{1,3}

Hepatic^{1,4}

Skeletal^{1,3}



Ocular^{1,5,6}

Endocrine^{*7}

Cardiovascular^{1,8}

Digestive⁹

Reproductive system¹

Muscular¹⁰

Haematological^{1,11}

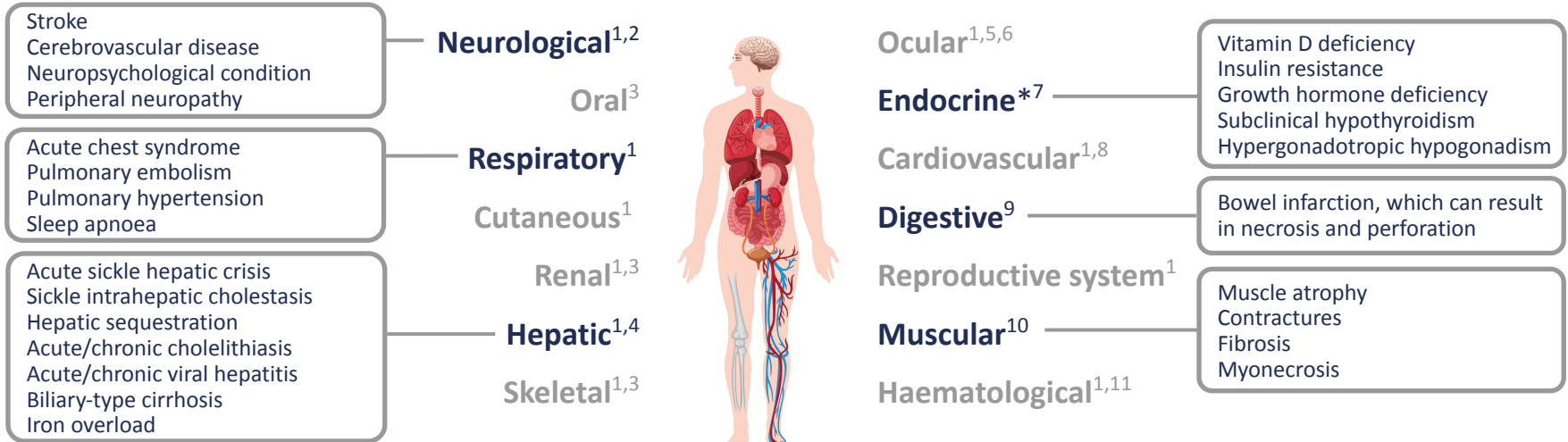
*Study in children and adolescents aged 3–18 years (N=52).⁷

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. Kingler 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



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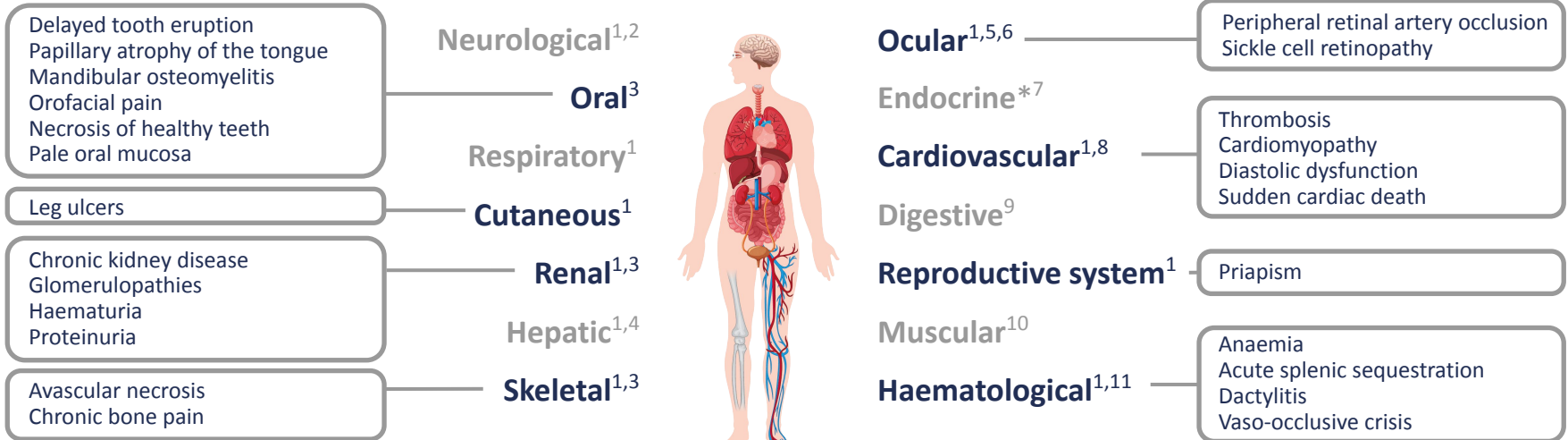
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1. CDC. 2022. Available at: www.cdc.gov/ncbddd/sicklecell/complications.html (accessed 7 June 2023); 2. Maduakor C, et al. *Front Neurol.* 2021;12:744118; 3. Chekroun M, et al. *Br Dent J.* 2019;226:27–31; 4. Suddle AR. *Hematology Am Soc Hematol Educ 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.

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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 subspecialties is essential for greatest impact¹⁻⁴
- Regular screening for complications⁵


CORE TEAM

-  Haematologist¹/paediatric haematologist²
-  Primary care physician¹/paediatrician³
-  Emergency medicine physician^{1,3}
-  Nurse practitioner^{1,3}
-  Social worker^{1,3}
-  Pharmacist³




EXTENDED TEAM

-  Neurologist³
-  Nephrologist³
-  Hepatologist^{3,5}
-  Endocrinologist^{3,5}
-  Ophthalmologist³
-  Pulmonologist³
-  Cardiologist^{3,5}
-  Gynaecologist³
-  Psychiatrist³
-  Dentist³



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 transfusion¹

Treats anaemia and other complications²
First used in 1960s³

MoA: Dilutes circulating sickled RBCs with unaffected RBCs to increase oxygen carrying capacity of blood¹



Deferoxamine⁴/Deferasirox⁵

Reduces iron overload due to transfusion^{4,5}
Approved 1968⁴/2005⁵

MoA: Iron chelation^{4,5}



Hydroxyurea⁶

Prevents painful crises⁷
Approved for SCD in 1998³

MoA: Ribonucleotide reductase inhibitor.⁸ Modulates HbS polymerization by increasing HbF⁸



Allogeneic haematopoietic stem cell transplantation⁹

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 crises²

Approved 2017²

MoA: Possible reduction in NAD redox potential and in cell adhesion¹

Voxelotor (age ≥ 4 years)⁴

Improves anaemia and reduces haemolysis⁴

Approved 2019⁴

MoA: Increases Hb–oxygen affinity^{1,4}
Reduces HbS polymerization^{1,4}

Crizanlizumab (age ≥ 16 years)^{1,3}

Reduces pain crises³

Approved 2019³

MoA: Anti P-selectin inhibitor; reduces RBC and WBC adhesion to endothelium¹

Deferiprone (age ≥ 3 years)⁵

Reduces iron overload due to transfusion⁵

Approved for SCD 2021⁶

MoA: Iron chelation⁵



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/44AZnI9> (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 modifying¹⁻³ or curative⁴

Gene therapies⁴⁻⁶

Gene addition approach⁴

- Lovotibeglogene autotemcel (lovo-cel)⁵
Adds functional β -globin gene⁵

Gene editing approach⁴

- Exagamglogene autotemcel (exa-cel)⁶
Edits *BCL11A*, an HbF repressor^{4,6}



Pyruvate kinase activators^{1,2}

Increases ATP in RBCs
Reduces HbS polymerization

- Etavopivat¹
- Mitapivat²

DNA methyltransferase inhibitor⁷

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.