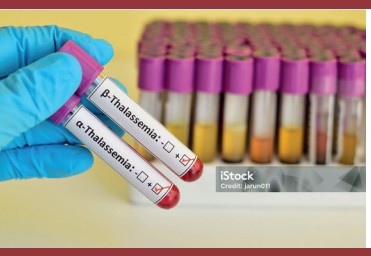
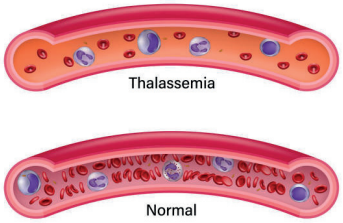
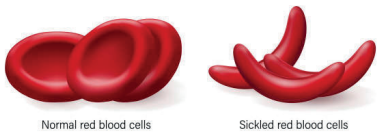
HNHCP
Haematology Nurses & Healthcare Professionals Group







Haematology Nurses and Healthcare Professionals (HNHCP)

Hemoglobinopathies:
Thalassemia's & Sickle Cell Disease:
Learning Progam

A Resource for Healthcare Professionals

Dear Colleague

It is with great pleasure that we present to you this learning program on Hemoglobinopathies: Thalassemia's and Sickle Cell Disease, developed on behalf of the Haematology Nurses and Healthcare Professionals Group.

Hemoglobinopathies are among the most common inherited blood disorders worldwide, with significant implications for patients, families, and healthcare systems. Thalassemia's and sickle cell disease represent the two most clinically relevant groups, each associated with lifelong challenges such as chronic anemia, organ complications, and complex treatment pathways.

This program has been created by a faculty of specialist nurses, haematologists/oncologists, and patient advocates, with the goal of providing healthcare professionals with the knowledge and tools necessary to support patients living with these conditions. Topics include:

- Understanding the pathophysiology and genetic basis of thalassemias and sickle cell disease.
- Evidence-based approaches to treatment, including transfusion support, iron chelation and new disease-modifying therapies.
- Curative and emerging options such as stem cell transplantation and gene therapy.

The crucial role of nurses and allied health professionals in education, monitoring, psychosocial support, and coordinated multidisciplinary care.

As with all our resources, this learning program emphasizes the multidisciplinary team approach to care.

Nurses, other allied health professionals, and patient organizations play an essential role in ensuring both immediate and long-term needs of patients and their families are addressed.

On behalf of the faculty and the Haematology Nurses and Healthcare Professionals Group who developed this program, we hope this resource will support you in your practice and enhance the care you provide to individuals and families affected by thalassemia and sickle cell disease.

Sincerely,

Erik Aerts

President

Haematology Nurses and Healthcare Professionals Group

The Haematology Nurses and Healthcare Professionals Group gratefully acknowledges the following individuals for their review and contributions to this learning program.

Faculty:

Erik Aerts (Zurich, Switzerland)

Maria-Domenica Cappellini (Milan, IT)

Lucia De Franceschi (Verona, IT)

Georgiadi Elpida (Athens, GR)

Giada Giuliani (Verona, IT)

Carol Krcmar (Germany)

Luhanga Musumadi (Riyadh, Saudi Arabia)

Nowell Ngwenya (Dublin, IRL)

Silvia Vitale (Verona, IT)

The timely completion of this Hemoglobinopathies Learning Program would not have been possible without the editorial support of Carol Krcmar (Medical Writer).

Haematology Nurses and Healthcare Professionals (HNHCP)

Hemoglobinopathies

Thalassemias & Sickle Cell Disease: A Resource for Healthcare Professionals is also available online at

www.hemcare.org

Date of preparation: 11.2025

Contents

Quick Facts

- Disorders of hemoglobin, hemoglobinopathies, are caused by a mutation in genes encoding for globins and can be categorized into two groups: defects in globin expression (i.e. pathologic hemoglobinopathies, sickle cell disease) or in globin quantity (i.e., the thalassemias).
- Hemoglobinopathies, including sickle cell (SCD), are not gender linked and are more prevalent in some parts of the world than in others: SCD is common in people of West African, Mediterranean, Middle Eastern, and South Asian descent, thalassemia is more common in Asia and in Mediterranean countries.
- In contrast to other genetic diseases, carriers of hemoglobinopathies can easily be detected using routine hematologic screening.
- Two types of strategies for screening are generally acknowledged: mass screening, which is appropriate in regions with a high disease frequency and is performed on the general population before or at childbearing age, and target screening, which is restricted to particular population groups and conducted before conception or in early pregnancy.

Module I: An Introduction to Hemoglobinopathies

Contents:

Introduction to Hemoglobinopathies

Hemoglobin (Hb) is the major component of red blood cells (RBCs), also known as erythrocytes, and its primary function is to transport oxygen from the lungs to tissues. In addition to oxygen transport, Hb also assists in the transportation of hydrogen ions and carbon dioxide back to the lungs. Hb is also responsible for the characteristic red color of blood, helps to maintain the shape and flexibility of red blood cells, helps to maintain the pH balance in the blood, and can affect the transport of other substances, such as drugs, to their target sites. Hb is an essential component of RBCs and accounts for a significant portion of their weight. Indeed, each RBC contains almost 250 million Hb molecules and the multifunctional nature of hemoglobin makes it a crucial protein for maintaining homeostasis in the body.

Overview of Hematopoiesis

Hemoglobin disorders (hemoglobinopathies) refer to a group of inherited blood disorders that affect the structure or production of hemoglobin. It is the most common type of inherited blood disorder, affecting millions of people worldwide. Approximately 600 types of hemoglobinopathy have been identified. RBCs are the end-product of erythropoiesis; 2 million RBCs are produced every second in the human body. RBC production is controlled by erythropoietin (EPO), which is produced by the kidneys. Specialized cells in the kidney sensing tissue hypoxia related to anemia produce EPO which subsequently targets hematopoietic stem cells towards commitment to erythroid progenitors and erythroblasts which then produce reticulocytes. There are 3 phases of erythroblast maturation and growth:1) production of ribosomes, 2) synthesis of Hb, 3) ejection of the nucleus and reduction in organelles (**Fig. 1**). Normoblasts leave the bone marrow as reticulocytes and mature in the peripheral blood system to become erythrocytes. The rate of RBC production is somewhat regulated by EPO to ensure an adequate but not an excessive number of RBCs in the body. This allows the body to maintain a Hb level of > 14 g/dL in males and > 12 g/dL in females, levels that correspond to those identified by the World Health Organization (WHO) to define anemia.

Ineffective erythropoiesis may result in:

- Hepatomegaly due initially to extramedullary hemopoiesis, but which can later be caused by heart failure or liver disease.
- Compensatory increase in RBC production through erythropoietin-induced stress
- Increased destruction of circulating abnormal RBCs by macrophages, mainly in the spleen, causing splenomegaly.
- Increased production of erythroid progenitor cells requires an increased iron supply causing suppression of hepcidin and increased iron absorption
- Organ dysfunction due to the accumulation of iron in endocrine glands and the liver. Endocrine dysfunction may cause poor growth (Fung 2023).

In erythropoiesis, iron is crucial for hemoglobinization but cytotoxic as free iron. In red cell disorders, such as SCD or thalassemia, free iron negatively affects erythropoiesis,

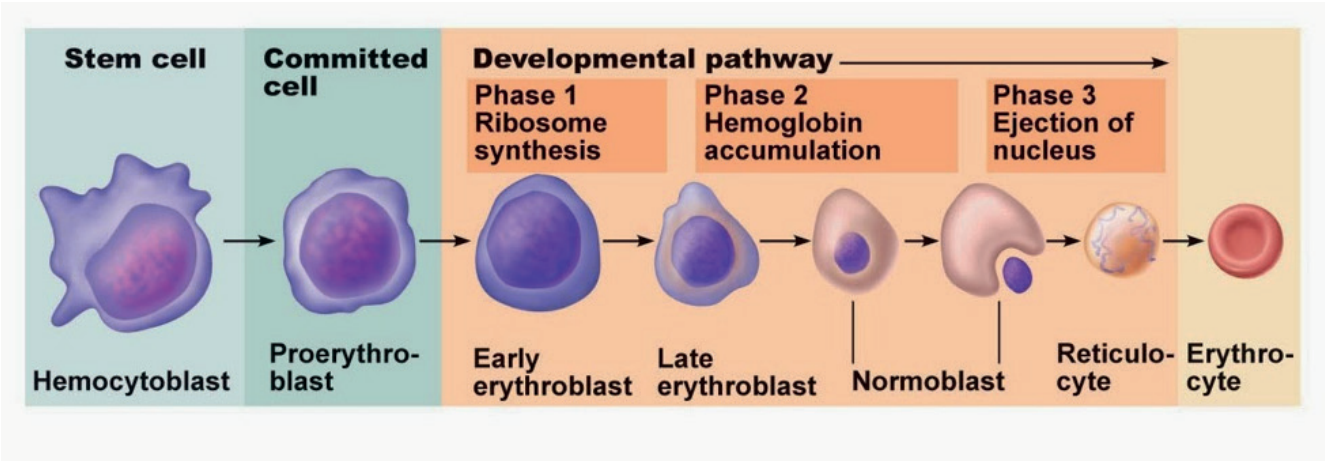


Figure 1. Erythropoiesis: the production of red blood cells (RBC) or erythrocytes. Normal erythropoiesis is dependent on EPO signaling, the iron "gateway" required for heme biosynthesis that needs to be harmonized with the α- and β-globin chain synthesis to develop adult Hb. Disruption of this process could cause ineffective erythropoiesis such as in thalassemia. Ineffective erythropoiesis is characterized by a block in maturation of erythroblasts, generally at the basophilic stage, associated with some erythroblasts undergoing programmed cell death.

red cell features, and red cell survival in the peripheral circulation. Thus, theoretically, modulation of iron homeostasis or heme biosynthesis might represent a useful treatment approach to improve anemia in these hereditary red cell disorders. Trials of molecules that modulate iron homeostasis are being explored as a treatment for SCD. Unfortunately, trials of using these molecules in thalassemia treatment have proven unsuccessful (Pinto 2024).

Types of Hemoglobinopathies

There are multiple forms of hemoglobin disorders, each associated with distinct genetic mutations and clinical manifestations.

Normal Hb is made up of different globin (polypeptide) chains and each Hb molecule is composed of four globin chains (**Fig. 2**). The globin chains combine to make different types of Hb. The structure of each globin chain in Hb is genetically determined. The different types of hemoglobin and their corresponding globin chains are:

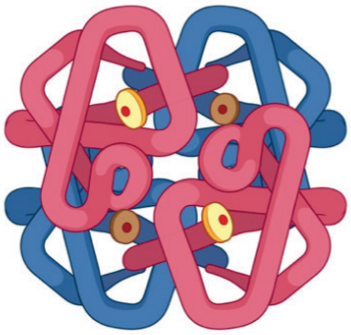


Figure 2. Schematic diagram showing the basic structure of a single hemoglobin A molecule, including two α-globin chains (blue), and two β-globin chains (red), each of which contain a heme-iron complex (blue). (Source: courtesy of L De Franceschi, generated by BioRender.)

1. Hemoglobin A: Hb A is the most common type of hemoglobin found in adults. It consists of two α globin chains and two b globin chains. Hb A is responsible for oxygen transport in adults.
2. Hemoglobin A2: A2 is a minor component of adult hemoglobin. It contains two α globin chains and two delta globin chains. Hb A2 helps maintain the stability and integrity of RBCs.
3. Hemoglobin F: Hb F, also called fetal hemoglobin, is predominant in newborns but decreases as an individual grows older. It is composed of two α globin chains and two gamma globin chains. Hb F aids in oxygen transfer in the fetus.
4. Hemoglobin H: Hb H is an abnormal type of hemoglobin that forms when there are deficiencies or mutations in the α globin genes. It consists of four β globin chains. Hb H is associated with certain genetic disorders affecting α globin production (α–thalassemia).

In adults, RBCs contain the following hemoglobin chain combinations:

- Hb A, >95%
- Hb A2, 2% to 3.4%
- fetal Hb F, <1%

Pathophysiology of Hemoglobin Disorders

Hemoglobinopathies, are caused by mutations in genes encoding for α- and β-globins. More than 1,000 mutations have been identified to date. These disorders can be roughly divided into two groups: defects in globin structure and quality (i.e., sickle cell disease) and defects in globin expression or quantity (i.e., the thalassemias) (Forget 2013). SCD is due to a mutation of the globin gene at the b7 position, leading to the production of hemoglobin S (HbS), which affects the biochemical characteristic of Hb resulting in polymerization of HbS with generation of rigid fibers causing the generation of sickle-shaped red blood cells. In thalassemias, the reduced/absent synthesis of either α or β globin chains results in the accumulation of either α- or β- free globin chain. The accumulation of either α- or β-free chains together with pathologic free iron/heme promotes a severe cell oxidation, contributing to the destruction of erythropoiesis and to reduced red cell survival in the peripheral circulation.

The interaction between thalassemia variants and various structural hemoglobin variants produces a wide range of disorders of varying clinical severity. The most severe categories of these are transfusion dependent thalassemia (or transfusion-dependent major [TDT]). Among the Hb variant, the most severe form is SCD. The clinical relevance of these disorders may differ among populations as the incidence is primarily population specific (Harteveld 2022).

Factors such as family history of the disorder, specific ethnic backgrounds, and certain geographic regions where these conditions are more prevalent can increase the risk of hemoglobinopathies within the general population. SCD, for example, is most common in people of West African, Mediterranean, Middle Eastern, and South Asian descent. Thalassemia major is more common in Asia and in Mediterranean countries.

Table 1: Overview of Characteristics of Cells in the Immune System

Disorder	Pathophysiology	Symptoms	Treatment	Complications
Sickle cel disease (SCD)	Inherited genetic abnormality of hemoglobin causing sickle-shaped red blood cells and chronic anemia.	Chronic hemolytic anemia, acute vaso-occlusive events causing tissue ischemia and infarction, increased risk of infections	Treatment of infection, analgesics, possibly transfusions in either acute or chronic settings; hydration; hydroxyurea, stem cell transplantation, gene therapy	Chronic spleen damage; organ dysfunction, ischemic stroke, chronic kidney disease, pulmonary hypertension. [see Modules 2 and 7].
Thalassemias	Inherited disorder of hemoglobin production. α - and b -thalassemia types.	α: usually none; mild to moderate chronic hemolytic anemia and low degree of ineffective erythropoiesis. b: asymptomatic to severe b globin deficiency with severe chronic hemolytic anemia and ineffective erythropoiesis.	α: no treatment or based on clinical presentation. HbH: treatment according to disease severity. β: blood transfusions, iron chelation, agents targeting erythropoiesis/red cells, allogeneic stem cell transplantation, gene therapy	Numerous caused by disorder and/or treatment [see Modules 4 and 7]
Hemoglobin C disease (Hb C) and Hemoglobin D disease (Hb D)	Caused by gene mutations. Hemoglobin C or hemoglobin D replaces normal hemoglobin. Hb D is rare.	Mild chronic hemolytic anemia, splenomegaly, jaundice, other symptoms consistent with anemia	Depends on severity of anemia	Cholelithiasis
Hemoglobin E disease	Hemoglobin E replaces normal hemoglobin	Mild hemolytic anemia	Not usually necessary, depends on disease severity	

The letters in the names of hemoglobin disorders represent different variants of the hemoglobin protein, and the order in which researchers discovered them. These letters provide information about the specific genetic variation responsible for abnormality.
RBC, red blood cell; SCD, sickle cell disease

Types of Hemoglobin Disorders (Hemoglobinopathies)

Table 1 summarizes the severe clinical forms of hemoglobinopathies. Carriers of either SCD or thalassemia α- or β- generally do not require treatment. Infants with severe hemoglobinopathies often have symptoms soon after birth; otherwise, symptoms do not appear until the first year of age when fetal Hb switches to adult Hb. Adults may experience disease flare-ups at which time symptoms become more severe. General features of hemoglobinopathies include:

- Chronic hemolytic anemia
- Sp[lenomegaly
- Frequent infections
- Organ damage
- Swelling in hands and feet

Screening for Hemoglobinopathies

The aim of screening is to identify carriers of hemoglobin disorders in order to assess the risk of a couple having a severely affected child and to provide options available to avoid this outcome. In contrast to other genetic diseases, carriers of hemoglobinopathies can easily be detected using routine hematologic screening (e.g., complete blood count, ferritin levels). Ideally, screening is performed before pregnancy. Several techniques are available for screening, depending on factors such as the frequency of the disease, heterogeneity of the genetic defects, resources available, and social, cultural and religious factors (Galanello 2013). Some screening methods detect multiple variants whereas others detect only the most common. Knowledge of the frequency and heterogeneity of hemoglobinopathy in a particular population is a critical prerequisite in planning an adequate strategy to identify carriers and subsequently selecting the appropriate laboratory method. Two types of screening are generally acknowledged:

Mass screening, which is appropriate where there is a high frequency and is performed on the general population before and at childbearing age.

Target screening, which is restricted to particular population groups, before conception or in early pregnancy.

Screening can be targeted at different age groups, such as newborn, adolescence, premarital, periconceptional, and antenatal. Inductive screening (also known as cascade screening or extended family testing) involves the testing of relatives of identified carriers and/or patients and is an effective means of improving the efficiency of carrier identification. Effective screening programs require coordination between laboratory services, multidisciplinary teams, and skilled genetic counseling services.

Individuals who undergo a screening test for hemoglobinopathy, and screen positive, should receive a definitive diagnosis in an expedient manner followed by the appropriate clinical management. Actions that must take place to ensure the achievement of these goals should include:

- Access to the newborn within days of birth or to no-newborns when possible
- Collection of adequate blood and prompt submission to a designated laboratory
- Performance of the actual screening test
- Correct interpretation of screening test results
- Referral to primary healthcare provider and/or specialist
- Initiation of penicillin prophylaxis for SCD or therapies appropriate for other hemoglobinopathies
- Diagnostic testing to confirm screening results
- Establishment of comprehensive care.

It is important to implement follow-up with parents whose child has screened positive for a hemoglobinopathy. Trait counseling of parents of heterozygous babies is an integral part of newborn screening programs. If an adult has a positive diagnosis for a hemoglobinopathy trait, proper follow-up should ensure that the individual understands what this means and is provided counseling if necessary.

References

Forget BG, Bunn HF. Classification of the disorders of hemoglobin. Cold Spring Harb Perspect Med 2013; 3(2):a011684.

Fung EB, Schryver T, Angastiniotis M. Nutrition in thalassemia & pyruvate kinase deficiency: a guide for clinicians. Thalassemia Internation Federation. 2023.

Galanello R. Screening and Diagnosis for Haemoglobin Disorders. In: Angastiniotis M, Eleftheriou A, Galanello R, et al., Prevention of Thalassaemias and Other Haemoglobin Disorders: Volume 1: Principles. 2nd edition. Nicosia (Cyprus): Thalassaemia International Federation; 2013. Chapter 4. Available at: Screening and Diagnosis for Hemoglobin Disorders - Prevention of Thalassemias and Other Hemoglobin Disorders - NCBI Bookshelf.

Harteveld CL, Achour A, Arkesteijn SJG, et al. The hemoglobinopathies, molecular disease mechanisms and diagnostics. International Journal of Laboratory Hematology 2022; 44(Suppl 1):28-36.

Pinto VM, Mazzi F, DeFranceschi L. Novel therapeutic approaches in thalassemias, sickle cell disease, and other red cell disorders. Blood 2024; 144:853-866

Summary Points

- Sickle cell disease (SCD) is due to a point mutation on the β-globin gene of Hb, resulting in the synthesis of pathologic HbS.
- The hallmark of sickle cell disease is the appearance of sickle-shaped red blood cells, which are dense and rigid with a reduced survival in the peripheral circulation when compared to healthy erythrocytes.
- The dense, rigid, sickled red cells with altered function cause an inflammatory cascade leading to acute and chronic organ damage at the cellular level, and acute pain, acute chest syndrome, and avascular necrosis.
- Universal screening for SCD on simple blood sample is performed in some countries.
- Persons with SCD may experience health-related stigmas such as exclusion, rejection, blame, or devaluation, which can have a detrimental effect on quality of life and on the attitude and behavior of the patient to access healthcare services.

Contents:

Introduction

Sickle cell disease (SCD) refers to a group of hereditary red cell disorders characterized by the presence of the pathologic sickle hemoglobin (HbS). Normally, red blood cells (RBCs) are disc-shaped and flexible, which allows them to easily move through blood vessels and microcirculation. Pathophysiological studies have shown that the dense, dehydrated red cells play a central role in acute and chronic clinical manifestations of SCD, in which intravascular sickling in capillaries and small vessels leads to vaso-occlusion and impaired blood flow. However, the persistent membrane damage associated with HbS polymerization also favors the generation of distorted rigid cells and further contributes to vaso-occlusive events and cell destruction in the peripheral circulation. The pathophysiologic changes in RBCs caused by HbS lead to two main clinical manifestation of SCD. Namely, chronic hemolytic anemia and acute vaso-occlusive events (VOCs).

It is estimated that about 300,000 people are born with SCD each year worldwide and that more than 100 million people worldwide live with sickle cell trait (National Academies of Sciences 2022). SCD particularly affects people living in sub-Saharan Africa, India, and the Caribbean. Unfortunately, the delivery of comprehensive quality care to pediatric and adult patients with SCD is in many countries adversely affected by racism, discrimination, socioeconomic disadvantage, and mistrust of the healthcare system on the part of patients and their families (National Academy of Sciences 2022). Although simple effective interventions to reduce mortality and morbidity of SCD are available, a main obstacle to achieving better outcomes is associated with inequalities impacting the patient populations (Piel 2023).

The average life expectancy of an individual with SCD is 20-25 years less than that of the general population. The implementation of screening programs for cerebrovascular disease, infection prophylaxis (i.e., penicillin) and early initiation of hydroxyurea therapy has significantly reduced pediatric mortality—but this strategy might not be sufficient to improve overall life expectancy. Treatments such as hydroxyurea and safe blood transfusion strategies, the two cornerstones of SCD care, have also positively affected survival and quality of life, but do not completely eliminate disease adverse events; progressive organ dysfunction remains a contributing factor to a shortened life expectancy.

Types of Sickle Cell Disease

The heading SCD includes sickle cell anemia (SCA), hemoglobin SC disease (HbSC), and hemoglobin sickle-β -thalassemia (β -thalassemia positive or b β eta-thalassemia negative) (Mangla 2023) (**Box 1**). The sickle cell trait (HbAS) carries a heterozygous mutation and is seldom expressed in clinical signs and symptoms. HbSS and HbSβ° (HbS-β thalassemia) tend to be the most clinically severe forms of SCD.

The prevalence of SCD varies within populations and across geographical regions (Piel 2017). In Africa, for example, prevalence ranges from 10% to 40% in certain areas. The epidemiology of SCD is influenced by genetic inheritance patterns, geographical location,and socioeconomic factors (Elendu 2023). Of interest, the prevalence of SCD is higher in populations with a historical association with malaria, as the sickle cell trait provides some protection against severe forms of malaria infection (Rees 2010).

Box 1. Genotypes responsible for SCD

SS	People with this form of SCD inherit two genes, one from each parent, that code for hemoglobin "S". Hemoglobin S is an abnormal form of hemoglobin that causes the RBCs to become rigid, and sickle shaped. This type is commonly referred to as sickle cell anemia and is often the most severe form of SCD.
SC	People who have this form of SCD inherit a hemoglobin S gene from one parent and a gene for a different type of abnormal hemoglobin ("C") from the other parent. People with HbSC usually experience milder anemia when compared to SS patients.
S-β-thalassemia	People with HbS thalassemia inherit a hemoglobin S gene from one parent and a gene for β thalassemia from the other. There are two types of β thalassemia: "zero" (HbS β) and "plus" (HbS β +). HbS β -thalassemia is generally a more severe form of SCD than HbS β +.
SD, SE, SO	These forms of SCD occur rarely. People who have these forms inherit one hemoglobin S gene and one gene that cods for another abnormal type of hemoglobin ("D", "E", or "O"). The severity of these rarer types varies.

Source: CDC 2017

Pathophysiology

SCD is an autosomal recessive hereditary red cell disorder. In sickle cell trait (SCT), a person inherits a mutated b-globin gene encoding for HbS from one parent and a normal βa-globin gene from the other. Generally, people with SCT are generally healthy; however, as they are carriers of hemoglobin S gene, they can pass it on to their children. If both parents have SCT, there is a 50% (or 1 in 2) chance that any child of theirs also will have SCT, if the child inherits the sickle cell gene from one of the parents. These children will not be symptomatic, but they can pass SCT on to their children (**Fig. 1**). When both parents have SCT, there is a 25% (1 in 4) chance that any child of theirs will have SCD. There is the same 25% (or 1 in 4) chance that the child will not have SCD or SCT. In summary, an individual must inherit 2 copies of the mutated gene (one from each parent) to develop SCD. Each time the couple has a child, the chances of that child having sickle cell disease remain the same. That is, if the first child has SCD, there is still a 25% chance that the second child will also have the disease. Both girls and boys can inherit sickle cell trait, SCD, or normal Hb. Thus, genetic counseling and carrier screening programs are essential to identify those at risk of having children with SCD and to support family planning decisions.

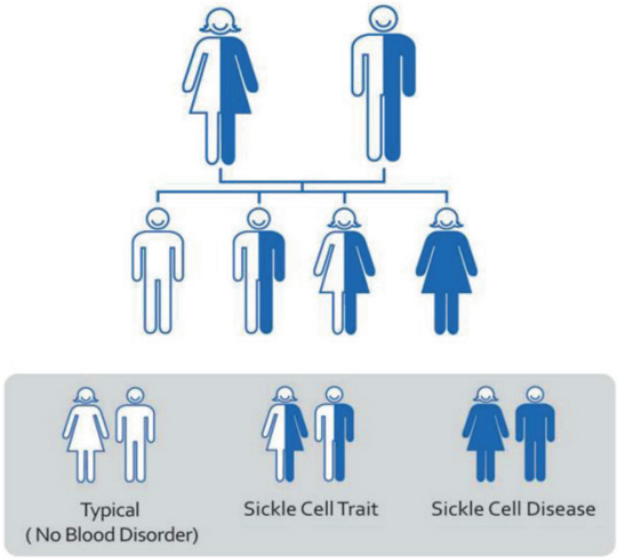


Figure 1. Sickle cell trait and sickle cell disease inheritance pattern (CDC 2017).

As stated above, SCD is a single-gene disorder in which 1 DNA base-pair alternation in the gene coding for hemoglobin produces sickle hemoglobin (HbS) when inherited in an autosomal recessive fashion with a second HbS or when combined with other hemoglobin variants, for example β -thalassemia (Piel 2017). RBCs that are misshapen into a sickle form are inefficient at transporting oxygen to tissues and vital organs. These cells break down rapidly, become very sticky, and tend to clump together causing them to become stuck within blood vessels and cause damage. This causes reduced blood flow to organs, which leads to physical symptoms of sometimes incapacitating pain, tissue and organ damage, and early death (National Academy of Sciences 2020).

Another result of the change in shape and function of the RBCs is an inflammatory cascade related to interactions with the endothelium, white blood cells, and platelets. The recurrence of RBC sickling and hemolysis, combined with endovascular inflammation, leads to acute and chronic organ damage at the cellular level, which is associated with acute, unpredictable, and potentially life-threatening complications [see Module 5]. Other sickle cell disease-related complications include acute pain, acute chest syndrome (ACS), and avascular necrosis, which are caused by vaso-occlusion (Kavanagh 2022).

Beyond genotype, other factors have been identified as contributing to the severity of SCD. These can be divided into genetic factors, such as the coinheritance of β-thalassemia or the level of HbF, and non-genetic factors such as weather, pollution, asthma, and stress (Kato 2018). Newer agents used to manage SCD increase HbF concentrations to prevent complications. More widespread availability of reliable biomarkers could be helpful in classifying individuals into subgroups and to predict disease severity and progression and possibly aid in developing tailored treatment plans (Kalpatthi 2018).

Screening and Diagnosis

Newborns

SCD and sickle cell trait status are currently identified at birth through universal newborn screening methods, such as those practiced in the United States (National Academy of Sciences 2020). The classical blood test is Hb electrophoresis, which identifies and measures different types of hemoglobin, including HbS. Electrophoresis is the cheapest method available, although it is time and labor intensive. Other tests used to screen for SCD, and sickle cell trait are isoelectric focusing, and high-performance liquid chromatography. All tests require dried blood spots or whole liquid blood from a heel prick and a check for red blood cell count or hemoglobin variants.

In many countries, screening is optional or performed selectively, potentially resulting in failure to diagnose SCD in some infants. Furthermore, test results are not necessarily available immediately requiring a return visit to the healthcare institution or confirmed results are not

communicated to parents.
There are numerous other tests that are easier to use, less expensive, rapid, and more suitable in specific situations or in specific populations. Methods to screen for SCD at the point-of-care using affordable and reliable methods are being evaluated in several studies in resource-poor regions of the world or in emergency departments of countries with adequate healthcare resources to identify SCD in recent refugees (De Franceschi 2019) . For example, HemoType SC is an immunoassay that has shown high sensitivity and specificity for sickle cell anemia in newborns in Ghana and Martinique (Steele 2019) and in newborns and adults in India (Mukherjee 2020).Most screening practices also identify newborns who are SCT carriers. Although it was previously thought that there were no clinical implications of carrier status beyond reproductive decision making, studies have shown that some individuals with SCT are at risk for a variety of clinical complications including muscle breakdown, cardiac dysfunction, sudden death, chronic renal disease, cancer, and splenic infarction (National Academy of Sciences 2022), and that SCT status is not always benign but may be a factor in the development of severe sickle cell complications under certain conditions such as altitude and dehydration (Xu 2019).

Prenatal screening

Genetic counseling in SCD is a cost-effective strategy to reduce the burden of the disease. The goals of genetic counseling are to provide an understanding of the inheritance of SCD and give people information to make family planning decisions (Piel 2023). Prenatal genetic counseling is designed to assist in decision making by providing objective information to individuals at risk of having a child with SCD to then be able to make informed decisions. A difficulty of prenatal diagnosis is that SCD is a variable condition, and it is difficult to predict clinical severity accurately. This increases the complexity of decision-making on the part of parents. Amniocentesis and chorionic villus sampling of fetal DNA, both invasive procedures, are used as part of prenatal screening and are conducted early in pregnancy. These invasive procedures are associated with minor risks of miscarriage or complications. Non-invasive tests in the prenatal period, such as cell-free fetal DNA tests, are also being used.
Counselling individuals with SCT relates to the risks and consequences of having a child with SCD. While these prospective parents are usually fit and healthy, counseling is necessary to increase their awareness of SCT to the level that they are able to make informed reproductive choices about pregnancy that conform to their cultural and religious beliefs (Piel 2023).Despite advances in and ease of administering screening methods, better universal communication of results to parents and follow-up care are still needed. Further, there is a lack of guidelines and policies to advise healthcare providers on how to effectively communicate disease or carrier status to families. Effective communication on testing results is extremely important because parents who discover that their child tested positive often experience mental distress, ranging from anxiety to depression (Farrell 2013).

Patients with Sickle Cell Disease and the Healthcare System

SCD is considered the most common, serious inherited disease in the world, and one of the top 50 most common causes of non-communicable death globally (Piel 2023). It has also been attributed to the most common contributor to death among children 5 to 14 years of age. Of interest, there are fewer than five effective disease-modifying agents available and considerably few individuals have access to these globally. Newer possibly curative treatment options, such as hematopoietic stem cell transplantation (HSCT) and gene therapy are only available to a very small minority of individuals due to challenges in terms of infrastructure and cost of these treatments [see Modules 3 and 6 on treatment options for SCD]. Even in wealthier countries, SCD occurs predominantly in low-income populations, who have little political influence.
For many years, SCD was considered a childhood disease because survival to adulthood was uncommon due to high rates of fatal infections in early childhood. Hence, the focus of managing SCD was primarily the pediatric population, which has subsequently led to improved survival into young adulthood (National Academy of Sciences 2022). There is, however, a lack of a standardized system to appropriately aid patients and their families during the transition process from pediatric to adult care [see Module 8].
Health-related stigma, experienced as exclusion, rejection, blame, or devaluation, may have health-related impacts if it results in limited access to beneficial services. People with SCD often face discrimination by healthcare providers due to the invisible nature of the acute pain they experience, and they may not receive the analgesic medications they require. The stigma associated with SCD can be related to racism, disease status, socioeconomic status, and pain episodes that require treatment with opioids and it can be expressed by family, friends, and healthcare professionals (National Academy of Sciences 2022). SCD-related stigma is a global problem.
Last but not least, there are significant disparities in the distribution of funding for research into SCD and its treatment as compared to other similar rare genetic disorders of childhood. The disparity in public and private funding between SCD and other genetic disorders is often attributed to the history of discrimination against

the racial and ethnic minority population most affected by SCD (Haywood 2014). Despite advances made in identifying and changing bias in healthcare, unconscious biases still pose barriers to achieving a diverse and equitable healthcare system (White 2011). Research confirms that unconscious bias in healthcare delivery has detrimental effects on patient health outcomes (IOM 2003).

In conclusion, improvements for people with SCD worldwide have been limited over the past few decades. Most individuals do not receive adequate healthcare and are victims of racism and stigmatization (Piel 2023). Furthermore, a vast majority of individuals with SCD have little access to proper sanitation, health education and health facilities, have nutritional deficits, and are regularly exposed to infectious diseases and toxic pollutants all of which impact on the course of SCD. To make the world a better place for individuals with SCD, an international, multidisciplinary commission therefore recommends:

- the initiation of newborn screening in every country with large numbers of people with SCD, increasing awareness of the disease and its sequelae within the general population,
- improve training and knowledge of SCD among healthcare professionals
- increase access to treatments for all people and develop and test new treatments that are affordable to all people and healthcare systems throughout the world (Piel 2023).

References

Centers for Disease Control and Prevention (CDC). What is sickle cell disease? https://www.cdc.gov/ncbddd/sicklecell/facts.html. Accessed April 2025.

De Franceschi L, Lux C, Piel FB, et al. Access to emergency department for acute events and identification of sickle cell disease in refugees. Blood. 2019; doi: 10.1182/blood-2018-09-876508

Elendu C, Amaechi DC, Alakwe-Ojimba CE, et al. Understanding sickle cell disease: causes, symptoms, and treatment options. Medicine 2023; 102:38.

Farrell MH, Christopher SA. Frequency of high-quality communication behaviors used by primary care providers of heterozygous infants after newborn screening. Patient Education and Counseling 2013; 90:226-232.

Haywood C, Diener-West J, Strouse CP, et al. Perceived discrimination in health care is associated with a greater burden of pain in sickle cell disease. Journal of Pain and Symptom Management 2014; 48:934-943.

Institute of Medicine (IOM). Unequal treatment: Confronting racial and ethnic disparities in health care. Washington, DC: The National Academies Press, 2003.

Kalpatthi R, Novelli EM. Measuring success: utility of biomarkers in sickle cell disease clinical trials and care. Hematology (American Society of Hematology Education Program) 2018. 2018:482-492.

Kato GJ, Piel FB, Vichinsky EP, et al. Sickle cell disease. Nature Reviews Disease Primers 2018; 4. https://doi-org.eaccess.tum.edu/10.1038/nrdp.2018.11

Kavanagh PL, Fasipe TA, Wun T. Sickle cell disease: a review. Journal of the American Medical Association 2022; 328:57-68.

Mangla A, Ehsan M, Agarwal N, et al. Sickle cell anemia (Nursing). In StatPearls [Internet]. StatPearls Publishing 2023.

Mukherjee MB, Colah RB, Mehta PR, et al. Multicenter evaluation of Hemo Type SC as a point-of-care sickle cell disease rapid diagnostic test for newborns and adults across India. American Journal of Clinical Pathology 2020; 153:82-87.

National Academies of Sciences, Engineering, and Medicine. Addressing sickle cell disease: A strategic plan and blueprint for action. Washington, DC: The National Academies Press 2022.

Piel FB, Rees DC, DeBaun MR, et al. Defining global strategies to improve outcomes in sickle cell disease: a Lancet Haematology Commission. Lancet Hematology 2023; 10:e633-686.

Piel FB, Steinberg MH, Rees DC. Sickle cell disease New England Journal of Medicine 2017; 376:1561-1573.

Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet 2010; 376:2018-2031.

Steele C, Sinski A, Asibey J, et al. Point-of-care screening for sickle cell disease in low-resource settings: A multi-center evaluation of HemoType SC, a novel rapid test. American Journal of Hematology 2019; 94:39-45.

White AA. Diagnosis and treatment: the subconscious at work. In: Seeing patients: Unconscious bias in health care. Cambridge, MA: Harvard University Press. 2011, pp. 199-210.

Xu JZ, Thein SL. The carrier state for sickle cell disease is not completly harmless. Haematologica 2019; 104:1106-1111

Summary Points

- Hydroxyurea was the first drug approved for treating sickle cell disease (SCD) and continues to be the gold standard treatment for children and adults
- Hydroxyurea decreases vaso-occlusive crisis, reduces stroke risk, and improves quality and length of life; it has not, however, shown universal effectiveness as a disease-modifying therapy
- The aims of transfusion therapy in SCD are to increase oxygen-carrying capacity by correcting anemia and to prevent or reverse complications of SCD related to vaso-occlusion and hemolysis

Module III: Treatment Strategies for Sickle Cell Disease

Contents:

Treatment of Individuals with Sickle Cell Disease

For almost 20 years, hydroxyurea was the mainstay of treatment for adults and children with SCD. While hydroxyurea remains front-line treatment, more recently, other drugs, including crizanlizumab, L-glutamine, and voxelotor have become available and are used as adjunctive or second-line treatment, mostly to alleviate or control symptoms (Cavazzana 2025; Kavanagh 2022). Hematopoietic stem cell transplant with a matched sibling donor and gene therapies are promising possibly curative treatments (Module 6). These therapy options are not, however, widely available or affordable for the majority of individuals with SCD, especially those living in sub-Saharan Africa and India.

Pharmacological Treatments

Hydroxyurea/ Hydroxycarbamide

Hydroxyurea was the first drug approved to treat the effects of SCD based on its effectiveness in decreasing the frequency of vaso-occlusive crisis (VOC), reducing the risk of stroke in some patients, and improving the quality and length of life in many affected individuals (Niihara 2018). However, hydroxyurea has not shown universal effectiveness as a disease-modifying therapy as many individuals continue to develop significant disease-related complications while taking the medication or adherence is low due to concerns about side effects, fertility, or drug tolerance (Kanter 2021).

Hydroxyurea is taken in oral form. It induces fetal hemoglobin production, which reduces the polymerization rate of sickle hemoglobin (HbS), with a beneficial impact on red cell features. Further, hydroxyurea reduces the frequency of painful attacks in most individuals and extends life expectancy. Hydroxyurea also increases nitric oxide (a potent vasodilator), decreases red cell adhesion, and decreases leukocytes, which contribute to vaso-occlusion. Children eligible for hydroxyurea should begin taking it at 9 months of age.

The major adverse effects of hydroxyurea are leukopenia, neutropenia, and thrombocytopenia, which are reversible with discontinuation or a decrease in dose (Wong 2014). Less frequent observed side effects include hyperpigmentation, skin and nail changes, leg ulcers, and gastrointestinal disturbances. Adjustments to dose might be required for individuals with known severe alteration of estimated glomerular filtration (eGFR), which could affect urinary clearance of hydroxyurea [see Module 7].

Of note, in low-income countries, critical barriers to the use of hydroxyurea for SCD have been identified. These include drug viability, distribution, the lack of sustainable payment models as well as the dissemination of knowledge on SCD and hydroxyurea treatment (Power-Hays 2020).

Other pharmaceutical treatments

L-glutamine

L-glutamine, an oral amino acid supplement, is able to cross the red blood cell (RBC) membrane and reduces sickling and RBC adhesivity (Kavanagh 2022). L-glutamine has been shown to reduce acute pain crises, hospitalization, and mean length of hospital stay from 11 to 7 days in adults and children over 5 years. Longer-term durability and utility of L-glutamine have not yet been demonstrated (Kantar 2021). Few data are available on L-glutamine kinetics and targets, reducing the attractiveness of L-glutamine in clinical practice. This pharmaceutical agent is not approved for treatment of SCD in Europe.

Voxelotor

Voxelotor is an oral potent and direct anti-sickling agent. Voxelator has been shown to increase Hb in patients with SCD independently from the affected genotype (Vichinsky 2019; Pinto 2024). However, although study results seemed promising, voxelotor was withdrawn from the market due to safety concerns several months after receiving governmental approval.

Crizanlizumab

Crizanlizumab is a humanized monoclonal antibody against P-selectin and acts by inhibiting the adhesion of RBCs and neutrophils to inflammatory activated vascular endothelial cells (Cavazzana 2025; Pinto 2024). Due to the failure of crizanlizumab to reach superiority over placebo in modifying pain crisis with VOC, the European Medicines Agency (EMA) suspended marketing authorization for its use in patients with SCD (Pinto 2024).

Transfusion Support

Transfusion of RBCs is a mainstay of supportive care for both acute and chronic life-threatening complications of SCD. Transfusions can be associated with adverse events, including alloimmunization, hyper-viscosity, and iron overload. Alloimmunization after transfusion is more common with patients with SCD than in other patient populations, resulting in morbidity and mortality (Chou 2025). Alloimmunization can result in both acute and delayed hemolytic reaction and may lead to broader, longer-term end-organ complications (Sathi 2020).

RBC transfusion in SCD may be necessary in the management of acute complications or electively to

prevent the development or progression of chronic complications. The aims of transfusion in SCD are to:

- Improve the oxygen-carrying capacity by correcting anemia
- Prevent or reverse complications of SCD related to vaso-occlusion and hemolysis (by decreasing the proportion of HbS in relation to HbA) (Davis 2017).

Alloimmunization is the formation of antibodies against non-self antigens on RBCs. May lead to delayed hemolytic or serologic transfusion reactions.

In SCD, potential curative therapies often require RBC transfusions to lower HbS before cellular therapy collections and infusions (Chou 2025) [see Module 6].

Transfusion strategies in SCD can be divided into simple transfusion and exchange transfusion, delivered as an automatic or manual procedure. These strategies can be used in both acute and chronic settings based on age, patient characteristics, and severity of organ damage. In children, simple transfusion might be used as a prophylactic approach to prevent stroke or to reduce sickle cell acute complications in a post-operative context.

Exchange transfusion is used to rapidly reduce the percentage of sickle cells in the circulation in individuals with severe vaso-occlusive crises events not responsive to hydration and analgesics, such as those experiencing rapidly progressive ACS who do not respond to simple transfusions (Chou 2020). The goal of the procedure is to reduce the percentage of HbS to < 30%.

There are two types of exchange transfusion.

Automated RBC exchange (red cell exchange, RCE) is performed using an apheresis device, while manual RBC exchange is based on sequential phlebotomies and isovolumic replacement. Compared to simple RBC transfusions, RCE offers advantages such as a lower risk for iron accumulation and efficient control of pathological erythrocyte populations. The cost of RCE is higher than simple RBC transfusions and the procedure requires special equipment and trained staff to ensure favorable outcomes (Stussi 2019). The higher cost, however, is balanced by preventing the costs of iron chelation therapy and of those related to iron-overload organ damage (Pinto 2025) [see Module 5].

The American Society of Hematology (ASH) developed evidence-based guidelines for transfusion support in SCD to support decision-making about RBC transfusions in this population (Table 1).

Detailed information on the administration of red blood cells including pre-transfusion activities and monitoring for transfusion reactions is provided in Module 5.

Newer treatments for SCD such as hematopoietic stem cell transplant and gene therapy are presented in Module 6.

Goal	Intervention
Provide support in individuals with chronically low hemoglobin	RCE preferred over simple transfusion taking into consideration target total hemoglobin and HbS %, age, preferences, iron overload status, iron chelation compliance, feasibility, availability of compatible RBCs.
Support healthy hemoglobin levels in pregnancy	Prophylactic transfusion at regular intervals at the onset of pregnancy should be considered in women with 1) a history of severe SCD-related complications; 2) in cases of a high-risk pregnancy; 3) in women who develop SCD-related complications during pregnancy who would benefit from transfusion
Support hemoglobin > 9 g/dL in individuals undergoing surgery	Individualized treatment according to genotype, risk level of surgery, baseline total hemoglobin, transfusion history, disease severity. RCE transfusion recommended for patients who require preoperative transfusion but have a high hemoglobin level

ASH, American Society of Hematology; RCE, red cell exchange; SCD, sickle cell disease
Source: Chou 2020

References

Cavazzana M, Corsia A, Brusson M, et al. Treating sickle cell disease: gene therapy approaches. Annual Review of Pharmacology and Toxicology 2025; 65:397-413.

Chou ST, Hendrickson JE. How I treat challenging transfusion cases in sickle cell disease. Blood 2025; 145:2257-2265

Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Advances 2020; 4:327-355.

Davis BA, Allard S, Qureshi A, et al. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. British Journal of Hematology 2017; 176:179-191

Kantar J, Falcon C. Gene therapy for sickle cell disease: where we are now? Hematology American Society Hematology Education Program 2021; (1):174-180. doi: 10.1182/hematology.2021000250.

Kavanagh PL, Fasipe TA, Wun T. Sickle cell disease: a review. Journal of the American Medical Association 2022; 328:57-68.

Niihara Y, Miller ST, Kanter J, et al. Investigators of the Phase 3 Trial of L-glutamine in sickle cell disease. A phase 3 trial of L-glutamine in sickle cell disease. New England Journal of Medicine 2018; 379:L226-235.

Pinto VM, Mazzi F, DeFranceschi L. Novel therapeutic approaches in thalassemias, sickle cell disease, and other red cell disorders. Blood 2024; 144:853-866

Power-Hays A, Ware RE. Effective use of hydroxyurea for sickle cell anemia in low-resource countries. Curr Opin Hematol 2020; 27:172-180

Sathi BK, Busken K, Coberly E, Gruner B. Alloimmunization is associated with increased indirect markers of hemolysis and distinct end-organ specific complications in sickle cell disease. Blood 2020; 136(Suppl 1):7-8

Stussi G, Buser A, Holbro A. Red blood cells: Exchange, Transfuse, or deplete. Transfus Med Hemother 2019; 46(6):407-416.

Vichinsky E, Hoppe CC, Ataga KI, et al. HOPE Trial Investigators. A phase 3 randomized trial of voxelator in sickle cell disease. New England Journal of Medicine 2019; 381:509-519.

Wong TE, Brandow AM, Lim W, Lottenberg R. Update on the use of hydroxyurea therapy in sickle cell disease. Blood 2014; 124:3850-3857.

Quick Facts

- Thalassemias are a heterogeneous grouping of genetic disorders that result from a decreased/absent synthesis of α or β globin chains of hemoglobin (Hb).
- There are two primary types of thalassemia: alpha (α) thalassemia, which is caused by a deletion or mutation of α-globin, which results in reduced or absent production of α globin chains, and beta (β) thalassemia, which is caused by a decreased production of β-polypeptide chains mainly due to point mutations, rarely to deletions in the β-globin gene.
- Thalassemia is almost exclusively diagnosed in infancy/early childhood and is a life-long condition.
- β-thalassemia has three phenotypes: minor, intermedia (or non-transfusion dependent thalassemia, NTDT), and major (transfusion dependent thalassemia, TDT), which is the most severe form. Patients with severe thalassemia require life-long transfusions and chelation therapy.
- National programs to prevent β-thalassemia via carrier screening, counseling, and prenatal diagnosis in at-risk populations in endemic countries have existed since the 1970s and include antenatal screening for the risk that a baby may be severely affected by thalassemia.
- Clinical manifestations of β-thalassemia become apparent after the change from fetal hemoglobin (HbF) to adult hemoglobin (HbA) at about 4 to 6 months of age.
- Carriers of thalassemia are often unaware that they carry gene mutations or deletions unless they undergo specific DNA testing.
- Nurses play an important role in supporting and educating parents whose infant has been diagnosed with transfusion-dependent thalassemia.

Contents:

Introduction

Geographically, the prevalence of thalassemia is highest in East Asia, followed by Southeast Asia, the Mediterranean region, and the Middle East. By contrast, high-income regions of the world (i.e., Australasia, Western Europe, North America) have significantly lower prevalence rates (Tuo 2024). Now, due to ever-changing migration patterns, thalassemia has become a global problem, spreading to areas of the world with previously low incidence rates. Approximately 80 to 90 million people are carriers of thalassemia, which is 1.5% of the global population (Origa 2017). Estimates place the number of infants born with thalassemia at 40,000 each year and the majority of these have β-thalassemia (Modell 2008). According to epidemiological study findings based on the global burden of thalassemia, age-standardized mortality rates have decreased globally, primarily due to the influence of health policies and significant public health interventions, such as prenatal screening, international practice guidelines, and the improvement of iron chelation therapy (Tuo 2024). Due to these efforts, there is now an increase in the number of elderly patients living with a diagnosis of thalassemia. Thalassemia is almost exclusively diagnosed in infancy/early childhood and is a life-long condition. Individuals with transfusion-dependent thalassemia (TDT) are at risk for secondary iron overload, which can accumulate in target organs like the heart, liver, and endocrine glands, leading to high rates of morbidity, mortality, and utilization of healthcare resources (Musallam 2023) [see Module 5]. The psychosocial and economic burden of chronic treatment can lead to poor treatment adherence and a diminished health-related quality of life. At present, there are two curative treatments for β-thalassemia: allogeneic hematopoietic stem cell transplant from a compatible donor and gene therapy.

Pathophysiology

Thalassemias are a heterogeneous grouping of genetic disorders that result from a decreased synthesis of α or β chains of hemoglobin (Hb). Hemoglobin, which carries oxygen to vital organs and tissues, consists of two proteins, an α, and a β. If the production of one or both of these two proteins is lowered, red blood cells do not form properly and cannot carry sufficient oxygen leading to anemia. In thalassemia, the resulting anemia begins in early childhood and lasts throughout life.

As an inherited disorder, at least one of the parents must be a carrier for thalassemia (**Fig. 1**). A primary genetic mutation reduces the rate at which α or β are produced. The chains themselves are normal, but their reduced production leads to an imbalance of chain pairs. The specific type of thalassemia depends on which globin chains are affected.

Alpha (α) thalassemia is caused mainly by a deletion of α-globin, which results in reduced or absent production of α globin chains. α-globin gene has 4 alleles and disease severity ranges from mild to severe anemia depending on the number of deleted alleles (**Box 1**). In four allele deletion, the most severe form, no α-globins are produced and the excess gamma chains (present during the fetal stage of life) form tetramers. The tetramers are ineffective in delivering oxygen and are unstable; the four-allele deletion form of α-thalassemia is usually fatal. One allele deletion is the mildest form of α-thalassemia and is generally asymptomatic or presents mild anemia, requiring transfusion on demand in special conditions such as pregnancy. Deletion of 3-α genes causes HbH disease that has intermediate severity. α-thalassemias can also be due to point mutations in the α genes.

Beta (β) thalassemia is caused by a decreased or absent production of β-globin chains due to either mutations or occasionally to deletions in the β-globin gene. The gene defect leads to impaired production of hemoglobin in the bone marrow with consequent damage to RBC precursors (ineffective erythropoiesis). Gene mutations may result in partial loss or complete loss of β-globin synthesis. There are 2 β-globin genes, and patients may have heterozygous, homozygous, or compound heterozygous mutations (**Box 2**). βthalassemia is the most common form of thalassemia and is divided into three categories based on the zygosity of the β-gene mutation:

β-thalassemia minor, also referred to as carrier or trait thalassemia, is caused by a heterozygous status in which β chains are underproduced. It is mild and usually asymptomatic.

β-thalassemia intermedia, or non-transfusion dependent thalassemia (NTDT), is associated with mild to moderate clinical symptoms and encompasses a wide spectrum of genetic aberrations. Transfusions may be required in special conditions such as pregnancy or aging.

β-thalassemia major, or transfusion dependent thalassemia-TDT, (also referred to as Cooley's anemia and Mediterranean anemia) is caused by a homozygous severe mutation (usually β-zero thalassemia) of the β-globin gene causing a total absence of β chains. The clinical manifestations include severe anemia, jaundice, growth retardation, hepatosplenomegaly, and endocrine abnormalities (Needs 2023).

Box 1. Definition of allele

Allele: Any one of two or more genes that may occur alternatively at a given site (locus) on a chromosome. Alleles may occur in pairs, or there may be multiple alleles affecting the expression (phenotype) of a particular trait. The combination of alleles constitutes the genotype of an organism. If the paired alleles are the same, the genotype is homozygous for that trait; if they are different, the organism's genotype is heterozygous.

Box 2. Definitions of heterozygous and homozygous.

Heterozygous means that a person has inherited *different versions* of a genomic marker (i.e., the DNA sequence of a specific gene) from each biological parent.

Homozygous means that a person has inherited *identical versions* of a genomic marker from each biological parent.

Individuals with β-thalassemia and a coinheritance of α thalassemia experience a relatively mild clinical course due to less severe α-β chain imbalance. Conversely, individuals with β-thalassemia and sickle cell trait experience more severe disease and manifestations of sickle cell disease. Hence, there are great variations in genetic changes that lead to thalassemia and these alterations lead to variations in the clinical features observed in affected individuals.

As mentioned above, in clinical settings, the terminology used to describe thalassemia is transfusion requiring or transfusion dependent thalassemia (TDT) and non-transfusion requiring thalassemia (NTDT).

Clinical manifestations of thalassemia can range from the absence of any symptoms in carriers of the disorder to life-threatening, multi-system disturbances in individuals with severe TDT. Individuals with TDT require lifelong blood transfusions and iron chelation therapy to manage transfusional iron overload, a serious complication of TDT that can lead to impaired growth, disrupted endocrine homeostasis, and heart, liver, kidney and bone damage. The consequences of iron overload can seriously affect an individual's quality of life and increase health risks (Taher 2021; Taher 2025). Individuals with NTDT may not require regular transfusion but this situation can change later in childhood or in adulthood due to complications of thalassemia (Taher 2021).

Thalassemia is an inherited autosomal recessive disorder. If one parent has the autosomal recessive trait, children do not show symptoms. If both parents have the autosomal recessive gene, each of their children has a 25% chance (1 in 4) of getting that gene. (**Fig. 1**). Because thalassemia most often occurs among people of Italian, Greek, Middle Eastern, Southern Asian, and African descent, ancestry plays a role as a risk factor for thalassemia. Hence, family history of thalassemia and ancestry are the two risk factors for inheriting the disorder.

Screening

National programs to prevent β-thalassemia via carrier screening, counseling, and prenatal diagnosis in at-risk populations in endemic countries have existed since the 1970s. This includes antenatal screening for the risk that a baby may be severely affected by thalassemia. If a woman is identified as a potential carrier of β-thalassemia or a high-risk type of α-thalassemia, screening of the biological father is recommended. Antenatal screening and diagnosis should be managed in a manner sensitive to the individual's needs and beliefs. Routine screening of all newborn babies (using the heel-prick test) is not specifically performed to identify babies affected by thalassemia but can detect most cases of severe β- thalassemia, allowing early referral to specialized teams for further assessment (UKTS 2023).

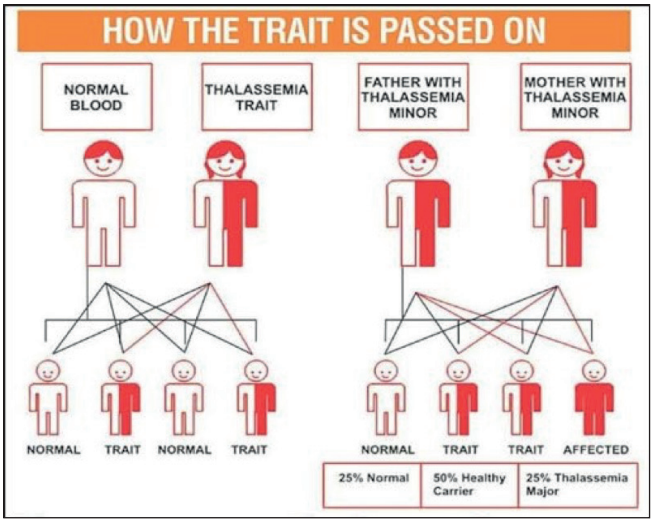


Figure 1. Inheritance of an autosomal recessive disease. For an autosomal recessive disease to be transmitted, both parents must be at least heterozygotes for each of them to transmit one affected gene to their child. In this case, the child has a 25% chance to inherit both affected genes and thus express the disease. There is a 50% chance that the child gets only one affected gene from one of the parents, which means the child becomes a heterozygote (carrier) and a 25% chance that the child will not inherit any affected gene from either parent. In this case, the child does not inherit the disease, is not a carrier of the gene, and cannot transmit the disease any further.

Prevention programs that not only include population screening and prenatal diagnosis for thalassemia, but also include public education to remove any stigma associated with detection of thalassemia genes have resulted in a reduction in the number of children born with thalassemia (Weatherall 2011). In Italy, where β-thalassemia is endemic, policies to reduce the incidence of hemoglobinopathies with free carrier screening and genetic diagnostics have been in practice. The preventative measures have led to a reduction in the number of children born with thalassemia, particularly in Sicily and the Ferrara region, where there has been an 85% decrease in the incidence of β-thalassemia over the last 30 years (Giambona 2015). To be impactful in countries where thalassemia is prevalent, screening programs should take into account the culture and beliefs of the involved population.

Screening for thalassemia may be appropriate at other time points. For example, premarital screening, where results may be taken into account in the process of considering a marriage partner, or preconceptual screening to allow couples to be counseled regarding the risk of having an affected child and provide alternative reproductive options if both are carriers of thalassemia.

The milder forms of thalassemia intermedia, or NTDT, may be diagnosed later in life, when individuals exhibit symptoms of anemia or when evidence of anemia is identified from blood count results. The content of counseling services should be based on international standards and provided by trained counselors.

Clinical presentation

The clinical features of thalassemia are driven by:

- decreased Hb production with consequent ineffective hematopoiesis
- reduced RBC survival (chronic hemolysis) due to the accumulation of excess unaffected globin chains that precipitate and damage erythrocytes
- expansion of hematopoietic tissues in an attempt to compensate (UKTS 2023).

In β-thalassemia, the clinical processes relevant to the disease begin and symptoms become apparent after the change from fetal hemoglobin (HbF) to adult hemoglobin (HbA), which occurs at about 4 to 6 months of age. The clinical presentation of untreated thalassemia varies greatly depending primarily on the extent of the inherited defects in the affected globin genes as well as coinherited changes in other globin areas. Some of the clinical manifestations of untreated thalassemia include

- progressive anemia that can present as failure to thrive, poor feeding, irritability, jaundice, and reduced activity in infants; if left untreated, cardiopulmonary failure and death may occur within a few years.
- hyperplasia of erythroid marrow causing deformities of the skull and face, i.e., a particularly prominent forehead known as frontal bossing
- extramedullary erythropoietic tissue masses with splenomegaly
- pulmonary hypertension due to nitric oxide depletion and endothelial damage due to chronic hemolysisincreased intestinal iron absorption leading to iron overload even without blood transfusions (Cappellini 2021; Taher 2021).

Complications from thalassemia and its treatment are frequent and those with moderate or severe forms must closely follow treatment plans, which include supportive care with the administration of regular blood transfusions and iron chelation therapy for transfusion-related iron overload (Taher 2025; Borgna-Pignatti 2004) [see Module 5].

Genetic counseling and pregnancy planning

In addition to abnormalities in pubertal development, growth, and endocrine function, both women and men with TDT can experience issues related to fertility. Patients desiring to conceive should be referred to a fertility/endocrine/assisted conception clinic with experience in treating patients with thalassemia for evaluation and to discuss options. [For a complete description of sexual health including reproductive health in women and men, the reader is referred to professional practice guidelines such as those from the Thalassemia International Foundation (Taher 2025) and those by the UK Thalassemia Society (2023)]. The following section will focus on genetic counseling and pre-pregnancy planning.

Genetic counseling

Often, carriers of thalassemia are unaware that they carry mutations or deletion of the hemoglobin genes and of their risk for conceiving a child with thalassemia unless they undergo specific testing. Therefore, DNA testing should be offered to both partners (ideally before pregnancy) to identify the precise mutations they carry and to enable genotype-phenotype correlations. A child with β-thalassemia received two mutated β-globin genes from the parents, one from the father and one from the mother (**Fig. 1**). In this scenario, each parent has one of the two β-globin genes (which are always present in

pairs) and is commonly referred to as a "carrier" of the disease. Ideally, carrier screening occurs preconception or with the initial prenatal labs by hemoglobin electrophoresis. While Hb electrophoresis is a reliable indicator of whether a person has the β-thalassemia trait, it is only available in specialized centers. Careful genetic counseling is needed when one parent has the thalassemia minor trait and the other parent has another β-globin-related disease, such as sickle cell disease.

If both partners carry the β-thalassemia gene, there is a 25% (1:4) chance in each pregnancy that the child will inherit a defective gene from both parents (**Fig. 1**). At-risk couples should be referred to a genetic specialist with expertise in the genetic aspects of hemoglobinopathies to ensure the couple fully understand the risks of having an affected child.

Pre-pregnancy planning for patients with TDT

Advances in treatment leading to improved survival and QoL mean that individuals with TDT are now more likely to want to conceive and start a family. Although spontaneous fertility can occur in well-transfused and well-chelated patients, the majority are sub-fertile mainly due to hypogonadotropic hypogonadism, a consequence of iron overload from repeated transfusions.

The goal of pre-pregnancy care is to evaluate and optimize the woman's current health status. Pubertal development, growth and endocrine function should be closely monitored in girls with thalassemia and referral to a specialist made if there is a suspicion of problems or deficiencies. Regular monitoring with attention to overall health can aid in recognizing and managing general as well as thalassemia-related problems early. Medications should be reviewed to identify those requiring adjustment. Both partners should undertake a full fertility workup prior to initiation of any fertility support for conception. Evidence is lacking regarding the effect of iron overload on ovarian function. For example, markers of ovarian reserve were found to be significantly lower in women with TDT compared with age-matched healthy controls (Talaulikar 2019) and it may be that chronic iron-induced oxidative damage can cause earlier or accelerated follicular ageing, which may contribute to reduced fertility and early menopause (Taher 2025; UKTS 2023).

Nursing Supportive Measures at Diagnosis

The diagnosis of thalassemia in an infant or young child may come as a complete surprise–perhaps shock –to some parents. The impact of hearing words such as treatment with regular blood transfusions, chronic, and incurable may be devastating to them. Parents will, understandably, have numerous questions and concerns. Some examples of frequently asked questions following diagnosis include:

1. What are the characteristics and consequences of this disease?
2. How is the disease treated, including medications and care?
3. Can thalassemia be cured?
4. How does the disease impact life, growth, physical appearance, educational achievements?
5. How does the disorder affect daily activities, employment, marriage, fertility, and social life?
6. What are the treatment costs and are they typically covered by healthcare problems or issues they may be trying to sort out?
7. How do I tell family and close friends about the diagnosis?

Making time to provide answers to these questions, actively listening to what the parent is saying, and referring parents to reliable sources of information and support are important nursing actions during the phase of diagnosis and treatment decision-making. Parents need to know that supportive services and assistance are available and that the nurse is there to provide help and act in the capacity of advocate. Empowering parents through education and accurate information can help them navigate the very critical time after diagnosis.

Examples of nursing interventions after diagnosis include

- Encouraging patients/caregivers to share their feelings with others, even if those feelings are of a negative kind.
- Encouraging parents of infants/young children, to seek support from others with a similar experience. This may help them to feel less isolated and/or help them to find solutions to the questions, problems, and emotions they are experiencing

Providing support to parents/caregivers:

- Assure parents and family members that thalassemia is a genetic disorder -it is not the result of anything a parent may have done.
- Help and support parents through education and active listening to their questions and concerns

- Encourage parents to model positive emotional attitudes.
- Stress opportunities rather than limitations associated with thalassemia.

Some patients diagnosed with thalassemia may not live near a specialty thalassemia treatment center at which multidisciplinary healthcare services and modern treatment services are available. It is advisable that these people try to go to a thalassemia-specialized clinic at least once a year to receive a comprehensive care evaluation.

References

Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004; 89(10):1187-1193.

Cappellini MD, Farmakis D, Porter J, Taher A. 2021 Guidelines for the management of transfusion dependent thalassemia (TDT) (4th edition). Thalassaemia International Federation, 2021.

Giambona A, Damiani G, Vinciguerra M, Jakil C, Cannata M, Cassara F, et al. Incidence of haemoglobinopathies in Sicily: the impact of screening and prenatal diagnosis. International Journal of Clinical Practice 2015; 69(10):1129–38.

Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull. World Health Organ (2008) 86(6):480–7. doi: 10.2471/blt.06.036673

Musallam KIM, Lombard L, Kistler KD, et al. Epidemiology of clinically significant forms of alpha- and beta-thalassemia: a global map of evidence and gaps. American Journal of Hematology 2023; 98:1436-1451.

Needs T, Gonzalex-Mosquera LF, Lynch DT. Beta Thalassemia. 2023 May 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. PMID: 30285376

Origa R. -Thalassemia. Genetics in Medicine 2017; 19:609-619

Taher AT, Farmakis D, Porter JB, Cappellini MD, Musallam KM. Guidelines for the Management of Transfusion-Dependent -Thalassaemia (5th edition). Thalassaemia International Federation 2025. Available at: Guidelines for the Management of Transfusion-Dependent -Thalassaemia (5th edition – 2025) – TIF

Taher AT, Musallam KM, Cappellini MD. Beta Thalassemias. NEJM 2021; 384:727-743

Talaulikar VS, Bajoria R, Ehidiamhen AJ, et al. A 10-year longitudinal study of evaluation of ovarian reserve in women with transfusion-dependent beta thalassaemia major. European Journal of Obstetrics and Gynecology Reproductive Biology 2019; 238:38-43

Tuo Y, Li Y, Ma J, et al. Global, regional, and national burden of thalassemia, 1990-2021: a systematic analysis for the global burden of disease study 2021. eClinicalMedicine (The Lancet) 2024; 72: https://doi.org/10. 1016/j. eclinm.2024. 102619.

United Kingdom Thalassemia Society (UKTS). Standards for the Clinical Care of Children and Adults Living with Thalassaemia in the UK. 4th Edition, 2023. Available at Standards-for-the-Clinical-Care-of-Children-and-Adults-Living-with-Thalassaemia-in-the-UK-4th-Edition-2023.pdf. Accessed May 2025.

Weatherall DJ. The challenge of hemoglobinopathies in resource-poor countries. British Journal of Hematology 2011; 156(6):736-744.

Quick Facts

- Individuals with transfusion-dependent thalassemia (TDT) require lifelong transfusion due to severe anemia present since infancy.
- The aim of blood transfusions should be to deliver effective and safe treatment while minimizing the burden of transfusion therapy on daily life activities of the individual.
- Transfusion reactions are adverse events that are directly related to the transfusion and range from mild to life-threatening. Their onset may occur during the transfusion or in days/weeks following the transfusion.
- Iron overload is a serious complication of regular blood transfusions. If left untreated, it can cause numerous complications related to iron accumulation in organs leading to liver and heart disease as well as endocrine gland dysfunction.
- Iron chelation therapy is used to remove excess iron. This therapy must be taken regularly and is associated with unpleasant side effects making adherence challenging; non-adherence is a major cause of morbidity and early mortality.
- Initiating and maintaining shared decision-making may be helpful in supporting adherence.
- Novel treatment targeting erythropoiesis to reduce transfusion burden is now available for TDT and non-transfusion-dependent thalassemia.

Module V: Treatment Strategies for Transfusion-Dependent Thalassemia

Contents:

Treatment Strategies for Transfusion-dependent Thalassemia

As is similar to sickle cell disease (SCD), the provision of services to individuals with thalassemia is not available equally and to the same standards globally. Even within resource-rich countries, health inequities exist and can affect health outcomes (Pearce 2019). Healthcare providers in countries with low incidences of thalassemia may lack clinical experience to care for these patients, which means a possible delay in establishing a diagnosis or possibly arriving at an incorrect diagnosis.

Although individuals with transfusion-dependent thalassemia (TDT) require lifelong transfusions, with adequate supportive care, the life expectancy of these individuals has dramatically improved since the 1970s. The introduction of orally active chelators and increasing use of magnetic resonance imaging to detect presymptomatic liver and cardiac iron overload have improved the prevention of both mortality and morbidity (Modell 2008).

Transfusion Support

The aim of blood transfusions in TDT should be to deliver effective and safe treatment while minimizing the burden of transfusion therapy on the everyday life of the individual (Farmakis 2022). The decision to initiate transfusions is an attempt to balance possible consequences of anemia and ineffective erythropoiesis against the complications of chronic transfusion therapy (i.e., iron overload). Due to the potential for the occurrence of complications in almost all organ systems, patients should be ideally managed by a multidisciplinary team comprising hematologists, hepatologists, cardiologists, hematologists, endocrinologists, pediatricians, specialized nurses, and psychosocial support services (Taher 2025).

The benefits of transfusions include

- Improved oxygen transport
- Control of ineffective erythropoiesis, which can cause bone marrow expansion, elevated basal metabolism, extra-medullary erythropoietic masses, and skeletal deformities of face and skull.

Prevention of red cell alloimmunization is important in the transfusion management of individuals with TDT. It is recommended that red blood cell (RBC) genotyping is performed once the decision to initiate regular transfusions is made. The results of this typing determine the risk for developing alloantibodies and/or autoantibodies and determine the extent to which antigen-matched blood is required.

The initiation of regular transfusions is recommended if either of the following conditions are met:

1. Hemoglobin < 7g/dL on 2 occasions at least 2 weeks apart

   - TDT: < 7g/dL on 2 occasions, with or without severe symptoms

   - HbE β -thalassemia: < 7g/dL on 2 occasions AND one or more severe symptoms

2. Hemoglobin ≥ 7g/dL, with one or more severe symptoms (Taher 2025; Lal 2021).

> Alloimmunization is the formation of antibodies against non-self antigens on RBCs. It may lead to delayed hemolytic or serologic transfusion reactions.

After a decision has been made to initiate regular transfusions, a transfusion plan to determine the rate, frequency, and volume of transfusion required to maintain a target pretransfusion hemoglobin level (the level at which the next transfusion should be administered) should be established. The transfusion plan (frequency, volume of blood transfused, transfusion rate) should be individualized to meet the individual's needs and may need to be adjusted over time.

Regular transfusions are indicated even if the hemoglobin level is > 7g/dL if there are complications such as

- Growth problems, failure to thrive, or delayed puberty
- Complications from excessive intramedullary erythropoiesis such as pathological fractures and facial changes
- Clinically significant extramedullary erythropoiesis
- Stroke
- Thrombotic events
- Pulmonary hypertension (Lal 2021).

Ideally, the target pretransfusion hemoglobin level is

- 9.5-10.5 g/dL (95 to 105 g/L) for people with TDT
- 9.0-10.0 g/dL for people with HbE β -thalassemia.

Maintaining these levels may be beneficial to ensure normal growth, prevent fatigue, suppress splenomegaly and marrow hyperactivity, improve quality of life and increase life expectancy (Taher 2025; Musallam 2024). Higher hemoglobin targets (11–12 g/dL) may be indicated in cases of clinically significant heart disease, extramedullary erythropoiesis, pregnancy, and prior to hematopoietic stem cell transplant or cell therapies (Boudreax 2023).

Pre-transfusion evaluation

Prior to the initiation of each transfusion, the following points and recommendations should be addressed:

- Obtain an informed consent for blood transfusion therapy
- Follow institutional policies for transfusion administration and reporting of adverse events
- Perform blood group antigen typing: ABO system; Rh system and subgroups
- Obtain and have available: complete blood count (CBC) including hemoglobin; indices; nucleated red cells; platelet count; hemoglobin fractionation; HLA (human leukocyte antigen) typing
- Screen for new antibodies and perform an IAT crossmatch, or perform an electronic crossmatch where allowed
- Molecular mapping: alpha-globin gene cluster; β -globin gene cluster, if possible
- G6PD quantification (test to check levels of glucose-6-phosphate dehydrogenase (G6PD), a protein that supports red blood cell function).

Transfusion procedure

Individual institutions and clinics should establish policies and procedures for safe blood transfusion, and these should be strictly followed to prevent complications. Therefore, the following is a brief overview of the transfusion procedure for RBCs and readers are urged to follow their specific institutional policies.

Prior to transfusion, an indirect antiglobulin test (IAT) crossmatch is performed in order to select compatible units. New clinically significant antibodies must be identified so that blood lacking the corresponding antigen(s) is selected.

A complete and detailed record of antigen typing, current and historical RBC antibodies, and transfusion reactions should be maintained for each patient and should be available if the patient is transfused at a different center. If a centralized record system is not available, patients should receive and have available information to reduce or prevent a transfusion reaction including personalized information on their antibody status (i.e., antibodies they may have had, antibodies they may have received).

Leucocyte-depleted packed red cells should be transfused where available and red blood cells that are less than 2 weeks old should be used when possible. The blood product should be filtrated pretransfusion (pre-storage filtration is strongly recommended). Washed red cells should be used for patients who experience severe, recurrent allergic reactions to plasma.

Rate of transfusion:

The time to complete a transfusion safely may differ between individuals. In general, units of blood (i.e., packed RBC units with a mean volume of 260 mL) can be infused over 90 minutes; the clinical state of the patient should be assessed to see whether this rate is suitable. Slower rates of transfusion may be indicated in children and patients with cardiac failure or very low initial hemoglobin levels (UKTS 2023).

Frequency:

In general, individuals with β -thalassemia need transfusions

- Every 3 weeks for most older children and adults
- Every 4 weeks for younger children with TDT.

While a shorter interval between transfusions reduces hemoglobin level variability, it requires more frequent visits to the infusion center.

Volume:

In general, the volume of blood transfused for individuals with β -thalassemia major is

- 4 ml/kg per gram increase in hemoglobin desired, up to 20 ml/kg at a single visit for children
- 2, 3, or 4 units of blood per transfusion for adults. A common regimen would be 3 units if the pretransfusion hemoglobin level is < 10 g/dL; 2 units if the pretransfusion hemoglobin level is ≥ 10 g/dL (Lal 2021).

Monitoring the patient during transfusion administration

Institutional policies and procedures for the administration of blood transfusions should be in place and strictly followed. At a minimum, nursing responsibilities for safe handling and administration of RBC infusion should include:

- Accurate identification of the patient at all stages of the transfusion process, cross check with information on blood bag
- Insertion of an appropriate-sized cannula following institution standards of care; connection of the cannula should be visible and secured
- Set-up of gravity blood infusion set or infusion pump following institutional guidelines

- Start infusion at a slow rate per agency policy
- Take and record baseline temperature, pulse, respiration rate, blood pressure
- Take and record vital signs every 15 minutes at start of infusion
- If vital signs are stable, increase infusion rate to prescribed rate; ensure transfusion completion with 4 hours
- Perform identity check of patient and blood product according to institutional procedures
- Have the patient report any potential adverse events including shivering, rashes, flushing, shortness of breath, pain in the extremities or loins
- Continue to assess and monitor the patient for 4 – 6 hours after the transfusion (Oxford University Hospitals 2012).

Preventing, recognizing and managing transfusion reactions and complications

Transfusion reactions are adverse events that are directly related to the transfusion of blood products and may range from mild to life-threatening. The onset of reactions may occur during the transfusion or in days or weeks following the transfusion. Allergic reactions are usually due to plasma proteins and can range from mild (urticaria, itching and flushing) to severe (difficulty breathing, bronchospasm, hypotension or other symptoms of anaphylaxis) (Suddock 2023). Some mild reactions may resolve without treatment, but those that are severe may require emergency interventions (**Table 1**). Delayed reactions due to alloimmunization usually occur 5 to 14 days after transfusion and are characterized by an unexpected drop in Hb (at least 2 g/dL), reticulocytosis, hemoglobinuria, malaise and jaundice. These reactions may be due to an alloantibody that was not detectable at the time of transfusion or to the development of a new antibody.

The risk of real and potential transfusion reactions points to the importance of taking steps to ensure that the patient receives the blood product intended for her or him, initiating and maintaining a full transfusion history for each patient, informing patients about their blood type and, antigen status, and making patients aware of the signs/symptoms of transfusion reactions.

Under-utilization of blood transfusions

Negative outcomes may occur, such as symptomatic anemia and increased ineffective erythropoiesis with extra-medullar erythropoiesis, if the targets for Hb are not consistently maintained. Transfusion of RBCS can sustain normal physical appearance, growth, and activity in children through the reversal of anemia and bone marrow hyperplasia (Piomelli 1985). Similarly, regular transfusions can help adults achieve normal functioning in their personal and professional lives (Sobota 2011).

Iron Overload and Management

Iron overload has several causes in people with thalassemia. The body responds to anemia by increasing absorption of iron from the gut. This situation is exacerbated by iron released through the breakdown of red cells in transfused blood. The extra iron from transfusions is stored in the liver. Once liver stores are consistently above 7 mg/g/dw, the iron begins to accumulate in endocrine glands causing hypogonadotropic hypogonadism, hypothyroidism, hypoparathyroidism, adrenal and growth hormone insufficiency. If liver iron exceeds 15 mg/g/dw there is a high risk of cardiac iron deposition which may lead to the development of heart failure if chelation therapy is not intensified (Taher 2021; Toumba 2007; Belhoul 2013). Hence, the diagnosis, monitoring and effective treatment of iron overload are crucial for individuals with TDT as a means of regulating and personalizing the iron chelation program.

Iron overload also occurs in NTDT , although to a much smaller extent. These patients may require less frequent chelation or may start chelation later compared to TDT patients, for example as soon as ferritin levels are higher than 800 or the amount of transfused RBCs is more than 10 RBCs units.

In children and young adults, iron overload causes pituitary damage, leading to hypogonadism, growth retardation and delayed puberty. Other manifestations include endocrine complications, such as diabetes mellitus, hypothyroidism and hypoparathyroidism. Children receiving transfusion therapy without iron chelation eventually exhibit iron overload symptoms in early adolescence, starting with lack of pubertal maturation. If left untreated, iron overload can cause major complications including organ failure (i.e., of the heart, endocrine glands and liver) and death and is the major cause of ill-health in people with TDT, even in those with milder forms of the disease (**Fig. 1**).

Table 1. Transfusion Reactions and Related Nursing Interventions

Transfusion reaction	Cause	Onset	Manifestations	Prevention	Intervention
Mild/moderate allergic reaction	Hypersensitivity to a foreign protein in the donor product	During transfusion, up to 24h post-transfusion	Pruritus erythema, local hives, urticaria, bronchospasm	Administer antihistamine prior to infusion if history of allergic reaction	Stop transfusion, notify physician. Administer antihistamine, monitor for new or symptom progression. Assess VS every 15 min
Anaphylactic	Recipient allergy to donor antigen (most often IgA)	Within 5-15 min of transfusion	As above but more severe with N/V, SOB, cough, wheezing, hypotension, loss of consciousness. May lead to cardiac arrest	If known history of allergic reaction, use leukocyte-depleted RBCs	Stop transfusion, notify physician. Administer epinephrine, antihistamines, and corticosteroids. Monitor VS frequently until stable.
Febrile, non-hemolytic	Release of cytokines from donor leukocytes or platelets	30 min after start of infusion to 6h post infusion	↑ temperature > 1 degree above baseline; flushing, chills, muscle pain, headache. Tachycardia, tachypnea, hypotension may occur.	If known history of allergic reaction, use leukocyte-depleted RBCs	Stop transfusion, notify physician. Administer antipyretics. Monitor temp every 4h
Acute hemolytic	ABO and Rh incompatibility causes RBC destruction	Within 15 min of transfusion	Flank, chest, low back pain; ↑ heart rate, chills, ↑ temperature; headache, dyspnea, bronchospasm, anxiety, hypotension, pain at insertion site	Considered a hospital-acquired condition preventable by diligent patient identification & blood product verification.	Stop transfusion, remove blood product & tubing, maintain access with 0.9% NS. Notify physician, monitor VS every 15 min. Obtain blood & urine specimens, send to lab.
Septic	Contamination of blood product with bacterial microorganisms	During transfusion, up to 2h post infusion	High fever, skin flushing, hypotension, back pain, abdominal cramping, N/V, diarrhea	Complete transfusion within 4h to avoid bacterial growth.	Stop transfusion, remove blood product & tubing, maintain access with 0.9% NS. Notify physician, monitor VS, obtain blood cultures, administer fluids, administer antimicrobials.
Transfusion-associated circulatory overload	Volume of transfusion causes volume overload from an overly rapid administration rate.	At anytime during transfusion, within 1-2h post-transfusion	Dyspnea, tachycardia, hypertension, jugular vein distension, headache	Follow prescribed rate of infusion. Use caution when administering blood to older adults, adults with cardiac & renal disorders	Reduce rate or stop infusion, notify physician. Monitor/ manage patient symptoms, elevate head of bed, administer diuretic.
Transfusion-related acute lung injury	Antibodies in donor blood react with antigens in recipient leading to pulmonary edema	Within 6-72h of products rich in plasma	Cyanosis, dyspnea, fever, hypoxemia, hypotension, pulmonary edema not cardiac related	Assess patients before infusion for risk factors including infection, inflammation and recent surgery.	Stop transfusion, notify physician. Administer treatment to support BP, administer O_2.

BP, blood pressure; h, hours; N/V, nausea/vomiting; NS, normal saline; RBCs, red blood cells; SOB, shortness of breath; VS, vital signs
Adapted from: Suddock 2023; Open RN 2023

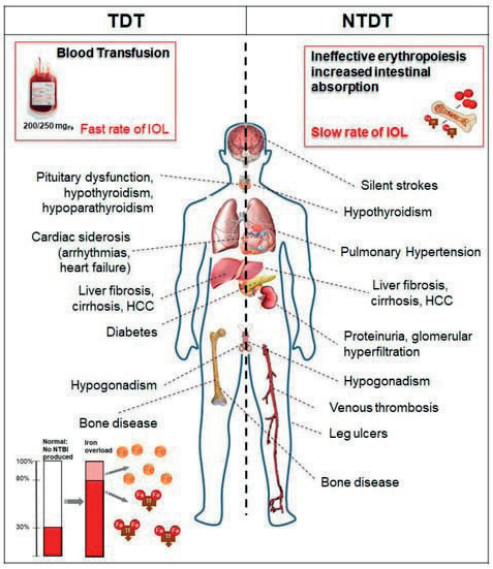


Figure 1. Complications of iron overload in transfusion-dependent and non-transfusion dependent thalassemia. HCC, hepatocellular carcinoma; IOL, iron overload; NTDT, non-transfusion dependent thalassemia. Adapted from: Pinto 2020

Monitoring iron overload

Monitoring of iron overload is important in identifying existing complications, and for quantifying the risk of and therefore preventing future complications from developing (Taher 2025; UKTS 2023).

Serum ferritin broadly correlates with total body iron loading and is therefore used to diagnose and monitor levels of iron in the body (**Table 2**). Measurements are performed at least every 3 months, and the target value is between 500 and 1000 µg/L. Measuring trends in serum ferritin levels is a more reliable indicator for adjusting therapy than just a single value (Farmakis 2022).

Table 2. Serum Ferritin Monitoring of Iron Overload

Advantages	Disadvantages	Usefulness of results
Easy & inexpensive to perform. Useful for dose adjustment as iron levels fall.	Indirect estimate of iron burden. Should be performed in a laboratory with knowledge of the process of diluting blood sample to provide accurate results. Relationship to iron load varies with chelator.	Decreased values indicate decreasing body iron. Increased values indicate increasing iron burden but may indicate inflammation or tissue damage. Longer-term monitoring can identify risk of complications of iron overload.

Myocardial tissue concentrations of iron increase with the severity of liver iron burden and the duration of higher levels of iron. Higher levels of cardiac iron can result from short but frequent episodes of not taking chelation or as a consequence of an imbalance between transfusion rate and iron chelation. In thalassemia, magnetic resonance imaging (MRI) is part of standard of care to diagnose and monitor organ iron concentrations in the liver and heart. MRI scanning is non-invasive, allows averaging of liver iron concentration over a large volume of liver tissue, and is suitable for sequential assessment. It is recommended to perform a MRI examination on a routine basis (at least every 14 to16 months) with the frequency dependent on the severity of iron burden, the intensity of chelation, and the concordance with iron chelation therapy (Taher 2025).

Medical management: chelation therapy

The recommendation is to start chelation therapy once serum ferritin reaches 1000 µg/L on at least 2 measurements, after 10 to 12 transfusions, or after significant liver iron loading (UKTS 2023). Iron overload is generally diagnosed late in NTDT patients because iron accumulation is much slower, and monitoring occurs less frequently (Eleftheriou 2021). Removal of stored iron is slow and inefficient because only a small proportion of body iron is available for chelation. Once iron has been deposited in some tissues the damage is often irreversible. Prevention, therefore, is preferable to rescue.

Three agents are currently used for the treatment of iron overload: deferoxamine (also known as desferrioxamine) (DFO), deferiprone (DFP), and deferasirox (DFX). These agents act to:

- bind iron and to excrete the iron-chelate complex at a rate equal to or greater than the iron accumulation rate
- decrease free radical-mediated tissue damage while the process is taking place.

The goal is to personalize iron chelation therapy, which might involve combining two agents with different pharmacologic profiles such as deferoxamine (DFO) + deferiprone (DFP), a combination that has been largely used in severe iron loaded patients especially when cardiac iron load is very high. (Borgna Pignatti 2014). DFP + deferasirox (DFX) has been shown to reduce serum ferritin and liver iron concentration without significant treatment toxicities (Origa 2022). Doses of agents require adjustments to changing circumstances; that is, tailoring

Chelation therapy should be initiated before cytotoxic levels of iron are reached.

dosing to the current needs of the patient, which are identified by careful monitoring of body iron and its distribution.

Monitoring is important to avoid:

- Under-chelation with increased iron toxicity
- Over-chelation with subsequent increased chelator toxicity (**Table 3**).

Intensification of chelation treatment may become necessary when liver iron concentration levels increase to abnormal levels. Emergency intensification is required when there is evidence of cardiac decompensation or there is a high risk of this occurring (Taher 2025; UKTS 2023). At this point, it is imperative to assess the patient's adherence with the chelation regimen as complete or partial non-adherence could be the cause of ineffective chelation therapy. Oral agents can be initiated once the child is older than 2 years.

Monitoring and improving adherence: nursing role

Patients with TDT must take iron chelation therapy, which requires lifelong adherence to prevent end organ damage from developing (Eziefula 2022). The major obstacle to achieving desired treatment goals remains adherence to the prescribed chelation regimen (Origa 2013). As expected, patients who are non-adherent are more likely to experience worsening of their medical condition, complications, and higher rates of morbidity and mortality. A systematic review showed that reported adherence to iron chelation therapy varies greatly (range: 42.0% – 99.97%) (Locke 2022). Adherence to oral chelators, such as deferiprone (DFP) and deferasirox (DFX), compared to subcutaneous deferoxamine (DFO) is generally higher, and adherence is often lower in adolescents than in other age groups.

Taking chelation agents can have an impact on quality of life and result in low levels of personal satisfaction due to the intensive demands and uncomfortable side effects of the therapy. Non-adherence can be both intentional and unintentional;

Intentional non-adherence is influenced by poor communication, adverse effects of the medication or treatment, personal preferences or beliefs, and disagreement with the need for treatment. Unintentional non-adherence is influenced by factors generally beyond the patient's control such as forgetfulness or difficulty understanding instructions (Fortin 2018) (**Box 1**).

Chelation monitoring, which goes hand-in-hand with monitoring adherence, is often delegated to specialist nurses. However, getting patients to take their prescribed medications can be challenging. Interventions such as promoting self-management, changing health behaviors, providing education on medications, developing strategies for delivering daily reminders, and involving other members of the healthcare multidisciplinary team may be effective interventions, but to be effective, interventions need to be tailored to the patient's individual situation (**Table 5**).

Monitoring of chelation is a continuous process because it assesses safety as well as efficacy of treatment. Recommendations are to perform monitoring for complications as well as efficacy every 3 months (UKTS 2023). However, monitoring should not be confined to clinic visits only and it is advisable that healthcare

Table 3. Chelating Agents

Agent	Route	Dose/Duration	Known adverse effects	Caution/Notes
Deferoxamine (DFO)	SQ or IV	SQ: 30-60 mg/kg/d IV: over 8 – 12 hours, 5-6 times/week	Pain or skin reactions at injection site; bone effects (damage to growth plates of long bones, especially spine in growing children); retinal toxicity; hearing loss; zinc deficiency; Adherence is a major challenge	Retinal, auditory, bone growth toxicities more likely if storage iron levels are low, close monitoring advised. Ascorbic acid (vitamin C) may enhance iron mobilization and increase efficacy of DFO.
Deferiprone (DFP)	Oral	75mg/kg/day, maximum 100mg/kg/day taken 3x /day or 4 x/day	Gastrointestinal disturbances; joint disease; elevated liver enzymes; neutropenia; agranulocytosis; zinc deficiency; increased appetite	Neutropenia may be life threatening
Deferasirox (DFX)	Oral	14mg/kg/day escalated to 28mg/kg/day if needed taken once daily	Skin rashes; gastroenteritis; increase in liver enzymes; reduced kidney function; zinc deficiency	Monitor renal & liver function; Once daily dosing supports adherence

IV, intravenous; SQ, subcutaneous
Adapted from: Khandros 2019

Box 1. Factors that influence adherence

- Patient-related factors: patient knowledge, patient/caregiver education, psychological factors, attitudes, beliefs, perceptions of severity of disease, treatment expectations, treatment intolerance
- Therapy-related factors: frequency of dosage, complexity of regimen, preparation time
- Modifiable factors: underlying psychological problems (depression, negative beliefs and assumptions)
- Other factors: patient/healthcare professional relationship, positive & effective communication

professionals continuously be on alert for complications of iron overload and suspect issues with adherence if they occur. Adjustments in dose should be made if neutrophil count decreases, or if there are changes in liver or renal function.

Luspatercept: A Novel Treatment for β-thalassemia

Luspatercept, an erythroid maturation agent, works by specifically targeting and blocking molecules that prevent RBCs from maturing, allowing them to mature properly, thereby increasing the number of RBCs in the plasma and reducing the transfusion burden in TDT (Cappellini 2021). It received approval in 2020 by the EMA and FDA for use in patients with TDT.

Transient adverse events of bone pain, arthralgia, dizziness, hypertension, and hyperuricemia were manageable, as reported in clinical trials (Cappellini 2020). Real-world and long-term clinical trials are on-going.

Table 5. Strategies to Improve Adherence

Action	Intervention
Assessment	Explore with patient/caregiver their perceptions about the importance, effectiveness and need for chelation and other medications
Education	Provide information on chelation and other prescribed medications, their side effects, mechanism of action, and consequences of non-adherence; provide clear verbal and written instructions on how to take medications; explore ways to provide the taking of medications that suits the patient's overall state of health and lifestyle; assess patient/caregiver understanding of provided information.
Psychological/ psychosocial support	Ensure that patients/caregivers are included in decision-making Work with patients to identify support groups, peer groups or social contacts that could be helpful Recognize and address mental health problems by facilitating access to psychological interventions and/or treatment
Medication	Identify and correct any medication issues such as dosing and scheduling; identify any financial issues that may interfere with taking medications/chelation agents. As much as possible, provide patient-centered strategies to facilitate personal preferences or decrease side effects Explore with healthcare team possibilities to simplify treatment regimen if this is an issue for the patient/caregiver
Nursing interventions	Recognize and implement interventions for disease- and transfusion-related complications to improve tolerance and acceptance. Integrate and collaborate with other members of the multidisciplinary team to support adherence interventions. Use a non-judgemental approach when providing education/ acknowledging patient-report of problems/circumstances imposing on adherence; the plan for taking chelation should be tailored to meet patient-specific situation; interactions with the patient/family should demonstrate support and empathy. Provide the patient the opportunity to participate in decision-making regarding chelation therapy.

Adapted from: Fortin 2018; Wang 2025

References

Belhoul KM, Bakir ML, Kadhim AM, Dewedar HE, Eldin MS, Alkhaja FA. Prevalence of iron overload complications among patients with b-thalassemia major treated at Dubai Thalassemia Centre. Ann Saudi Med. 2013;33(1):18–21. doi:10.5144/0256-4947.2013.18.

Cappellini MD, Taher AT. The use of luspatercept for thalassemia in adults. Blood Advances 2021; 5:326-333.

Cappellini MD, Viprakasit V, Taher AT, et al; BELIEVE Investigators. A phase 3 trial of luspatercept in patients with transfusion-dependent b-thalassemia. N Engl J Med. 2020; 382:1219-1231.

Eleftheriou A, Angastiniotis M. Global thalassaemia review 2021. Thalassaemia International Federation's Perspective. Available at: Global Thalassaemia Review 2021 – TIF. Accessed May 2025.

Farmakis D, Porter J, Taher A, et al. 2021 Thalassaemia International Federation Guidelines for the management of transfusion-dependent thalassemia. Hemasphere 2022; 6(8):e732.

Fortin PM, Fisher SA, Madgwick KV, Trivella M, Hopewell S, Doree C, Estcourt LJ. Interventions for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia. Cochrane Database of Systematic Reviews 2018; 5:CD012349.

Khandros E, Kwiatkowski JL. Beta thalassemia: monitoring and new treatment approaches. Hematol Oncol Clin North America 2019. https://doi.org/10.1016/j.hoc.2019.01.003

Lal A, Wong T, Keel S, et al. The transfusion management of beta thalassemia in the United States. Transfusion 2021; 61:3027-3039.

Locke M, Reddy PS, Badawy SM. Adherence to Iron Chelation Therapy among Adults with Thalassemia: A Systematic Review. Hemoglobin. 2022; 46(4):201-213. doi: 10.1080/03630269.2022.2072320.

Modell B, Khan M, Darlison M, et al. Improved survival of thalassemia major in the UK and relation to T2* cardiovascular magnetic resonance. Journal of Cardiovascular Magnetic Resonance 2008; 10:42.

Musallam KIM, Lombard L, Kistler KD, et al. Epidemiology of clinically significant forms of alpha- and beta-thalassemia: a global map of evidence and gaps. American Journal of Hematology 2023; 98:1436-1451.

Open Resources for Nursing (Open RN); Ernstmeyer K, Christman E, editors. Nursing Advanced Skills. Eau Claire (WI): Chippewa Valley Technical College; 2023. Chapter 3 Administer Blood Products. Available from: https://www.ncbi.nlm.nih.gov/books/NBK594497/.

Origa R, Cinus M, Pilia MP, et al. Safety and efficacy of the new combination iron chelation regimens in patients with transfusion-dependent thalassemia and severe iron overload. J Clin Med 2022; 11(7):2010.

Origa R, Danjou F, Cossa S, et al. Impact of heart magnetic resonance imaging on chelation choices, compliance with treatment and risk of heart disease in patients with thalassemia major. Br J Haematol 2013; 163:400-403

Oxford University Hospitals. National Health Service. Blood Transfusion Policy, version 4.0, June 2012

Pearce A, Dundas R, Whitehead M, et al. Pathways to inequities in child health. Arch Dis Child 2019; 104:998-1003.

Piomelli S, Hart D, Graziano J, et al. Current strategies in the management of Cooley's anemia. Ann N Y Acad Sci. 1985; 445: 256–67.

Pinto VM, Forni GL. Management of iron overload in beta-thalassemia patients: clinical practice update based on case series. Int J Molecular Sci 2020; 21(22):8771

Sobota A, Yamashita R, Xu Y, Trachtenberg F, et al. Quality of life in thalassemia: a comparison of SF-36 results from the thalassemia longitudinal cohort to reported literature and the US norms. Am. J. Hematol. 2011; 86: 92–5.381:509-519.

Suddock JT, Crookston KP. Transfusion Reactions. [Updated 2023 Aug 8]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482202/. Accessed September 2024

Taher AT, Farmakis D, Porter JB, Cappellini MD, Musallam KM. Guidelines for the Management of Transfusion-Dependent -Thalassaemia (5th edition). Thalassaemia International Federation 2025. Available at: Guidelines for the Management of Transfusion-Dependent -Thalassaemia (5th edition – 2025) – TIF

Taher AT, Musallam KM, Cappellini MD. Beta Thalassemias. NEJM 2021; 384:727-743

Toumba M, Sergis A, Kanaris C, Skordis N. Endocrine complications in patients with Thalassaemia Major. Pediatric Endocrinol Rev. 2007; 5(2):642–648.

United Kingdom Thalassemia Society (UKTS). Standards for the Clinical Care of Children and Adults Living with Thalassaemia in the UK. 4th Edition, 2023. Available at Standards-for-the-Clinical-Care-of-Children-and-Adults-Living-with-Thalassaemia-in-the-UK-4th-Edition-2023.pdf. Accessed May 2025.

Wang LE, Muttar S, Badawy SM. The challenges of iron chelation therapy in thalassemia: how do we overcome them? Expert Rev Hematol 2025;18(5):351-357.

Quick Facts

- Although matched donor hematopoietic stem cell transplantation represents a curative treatment in sickle cell disease and transfusion-dependent thalassemia, especially in children, any benefit should be weighed against possible risks and difficulties of the procedure.
- The harms of hematopoietic stem cell transplantation are exacerbated by underlying morbidities common to sickle cell disease (SCD) and transfusion-dependent thalassemia (TDT).
- Whereas in SCD complications such as chronic pain or silent cerebral infarct may continue to affect the patient after transplantation, in thalassemia, complications such as iron overload may be more easily managed, sometimes leading to recovery of damaged organs.
- Results thus far for gene therapy technologies applied to SCD and TDT are encouraging; the high price and limited access to these treatments are hinderances to most patients who would benefit from them.

Module VI: New Treatment Strategies for SCD and TDT

Contents:

Hematopoietic Stem Cell Transplantation

There are two types of hematopoietic stem cell transplantation (HSCT): allogeneic and autologous. Allogeneic stem cell transplantation involves the use of stem cells donated by someone related or not related to the patient. In autologous stem cell transplantation, the patient's own stem cells are used for the transplant. They are collected or harvested in advance and frozen. The stem cells from either the patient or a donor are reinfused in the patient after the administration of high doses of chemotherapy, either with or without radiation therapy. The conditioning treatment causes a weakening of the immune system to prevent rejection of the donor cells. The infused cells move to the bone marrow where they grow and produce new blood cells. Allogenic HSCT is most often used in hemoglobinopathies.

Matched family donor HSCT is the only proven treatment modality that can establish long-term normal hematopoiesis, avoiding the need for pharmaceutical agents or transfusions and chelation, in SCD and TDT (Cappelli 2024), respectively. Hence, for those individuals and families for whom the possible risks and benefits are acceptable, who have a related donor, and who are looking for a permanent cure, HSCT is now considered standard of care. Further, considering improvements in supportive care, transplant conditioning regimens, and strategies to prevent graft rejection and graft-vs-host-disease (GvHD), allogeneic HSCT is an increasingly feasible treatment option. Quality of life (QoL) studies have demonstrated great improvements, especially in the areas of role, pain, and social functioning in patients transplanted for TDT (La Nasa 2013). Of course, any benefit of HSCT needs to be weighed against the possible risks and difficulties of the procedures. The main limitations of HSCT include:

- The length and intensity of treatment (i.e., hospitalization, frequent clinic visits for monitoring of immunosuppression, inability to attend school/work while immunocompromised).
- The risk of transplant-related mortality
- Long-term effects of transplantation caused by conditioning regimens (i.e., infertility) and chronic GvHD (Kanter 2021).

Hematopoietic stem cell transplantation in sickle cell disease

The use of HSCT continues to evolve as a curative treatment for SCD, with new conditioning regimens, alternative donor sources and methods of cell harvesting, and strategies for GvHD prevention (Kanter 2021). It is the first-choice treatment when a matched sibling donor is available; results of transplants using matched donors show an overall survival of 92.9% (Gluckman 2017). The optimal goal of HSCT is to replace the patient's marrow with donor stem cells prior to major organ dysfunction and irreversible damage (Cappelli 2024).

The procedure is potentially curative in patients with SCD but is associated with mortality risks with most deaths occurring within 2 years after transplantation (St Martin 2022). Despite stable donor engraftment, chronic pain lingers in those who were significantly affected by it before the transplant, and it is unknown if organ damage is reversed by transplantation (Taher 2025). Emphasis is now being placed on improving results from unrelated stem cell donors as outcomes with partial mismatched donors have been encouraging.

HSCT in SCD is used to correct the pathophysiological abnormality by replacing abnormal HbS with more functional HbA. That is, new hematopoietic stem cells are used as the vehicle to deliver healthy hemoglobin and therefore eliminate erythrocyte sickling and the secondary effects of this pathological process (Al-Khabori 2015). The American Hematology Society (ASH) has put forth guidelines for the use of HSCT in SCD considering when to use HSCT based on patient and family values and preferences, and real and potential harms (Kanter 2021). It is recognized that HSCT is not globally available or feasible, and that there is few evidence in the scientific literature to support its widespread use in this population.

Prior to the decision to initiate HSCT, the risk of harms associated with transplantation must be considered, especially when there are approved targeted therapies, (e.g., hydroxyurea and L-glutamine) and new potentially curative therapies (e.g., gene therapy) under development.

Side effects and risks

The side effects and risks of allogeneic stem cell transplant are similar to those observed in other diseases, but they are made more complex by SCD-specific factors. The toxicity of conditioning regimens, for example, may be more intense due to a compromised physiologic function of vital organs. The immune reactivity of the transplant recipient is also affected by chronic transfusion regimens, which may result in HLA and RBC alloimmunization and alterations in the bone marrow microenvironment.

The major risk with HSCT is graft vs host disease (GvHD), which increases with age at transplantation independently from the source of the transplanted stem cells (Gluckman 2017; Walters 2000). With the exception of severe forms of SCD, existing and developing disease-modifying treatments offer patients long-term survival with tolerable morbidity and acceptable QoL. In this light, the side effects

of HSCT need to be balanced with the individual patient's experience with SCD and projected disease course; this is especially the case when considering longer-term side effects such as the risk of myelodysplastic syndrome and secondary malignancies following myeloablative conditioning (Lawal 2022).

Conditioning regimens

Myeloablative condition is recommended for identical match HCST in children and adults with SCD (**Table 1**). The historically recommended regimen is

busulfan + cyclophosphamide or fludarabine + ATG (anti-thymocyte globulin) (Cappelli 2024).

Currently, the recommended regimen is

fludarabine, treosulfan, and thiotepa as this combination is better tolerated with less endothelial toxicity and less blood-brain barrier passage, and better preserves fertility (Faraci 2019). Conditioning regimens should be tailored to preserve fertility in children and reduce toxicity in adults.

Table 1. Common Conditioning Regimens used in Pediatric Patients with Sickle Cell Disease

Purpose	Regimen
Myeloablative	• Busulfan > 7l.2 mg/kg IV • Busulfan > 300 mg/m2 IV • Melphalan > 150 mg/ m2 • Thiotepa > 10 mg/kg • Treosulfan > 30,000 mg/ m2
Reduced intensity and non-myeloablative	• TBI single or fractionated • Cyclophosphamide +/- ATG +/- fludarabine • Busulfan ≤ 7 .2 mg/kg IV or ≤ 9.0 mg/kg PO • Busulfan ≤ 300 mg/ m2 IV or ≤ 375 mg/ m2 PO • Melphalan ≤ 150 mg/ m2 +/- fludarabine • Treosulfan ≤ 30 gm/ m2 +/- fludarabine • Thiotepa ≤ 150 mg/kg

ATG, anti-thymocyte globulin; PO, per mouth; IV, intravenous
Adapted from: Limerick 2022

Hematopoietic stem cell transplantation in transplant-dependent thalassemia

An HSCT replaces the diseased, ineffective erythropoiesis with an allogeneic, effective erythropoietic process. However, HSCT replaces the entire hemopoietic system and not just the defective process. Newer conditioning regimens, improved prevention of GvHD, more effective infection prophylaxis and significant improvements in the care of individuals undergoing HSCT have led to substantial improvement in outcomes in patients with TDT (Angelucci 2017). In fact, the survival of HSCT recipients with TDT is similar to that of those who are conventionally treated and the vast majority of long-term HSCT survivors are cured of thalassemia (Caocci 2017).

It has become clear that the outcomes for children receiving fully matched unrelated donor transplants are now comparative to those for children who receive matched related donors. While an optimal timing of transplantation in children is unknown, evidence supports implementing the procedure in patients younger than 14 years to achieve the best outcome (Baronciani 2016). Favorable outcomes are seen in those with low iron load at the beginning of the procedure (UKTS 2023). Results of a large study in which the median age of patients was 7 years showed an overall survival of 91% and thalassemia-free survival was 83% (Baronciani 2016). According to real-world data, favorable outcomes seem to be achieved in those transplanted up to 12 years of age (Baronciani 2024), and for any patient transplanted at a designated center with experience in HSCT (Yesilipek 2022).

Side effects and risks

A major obstacle to successful HSCT in children with TDT is the limited number of HLA-matched related donors within families. More than 60% of patients do not have a suitable sibling donor. However, updated high resolution molecular typing techniques can identify suitable matched unrelated donors leading to outcomes similar to those for matched related donors.

Experience with HSCT in adults is limited. The incidences of organ toxicity due to iron overload have decreased thanks to newer chelation agents, an advancement that may positively influence future outcomes in adult patients. However, to reduce risk it is important to conduct accurate iron studies using MRI analysis to evaluate liver and cardiac iron load and function, and studies of endocrine function to also assess iron-related damage pre-transplant.

Conditioning regimens

Myeloablative busulfan + cyclophosphamide was the standard conditioning regimen for HSCT for TDT. However, this regimen is associated with hepatic and cardiac toxicity. Currently used myeloablative regimens include

busulfan + fludarabine or

fludarabine + treosulfan.

ATG has a favorable effect on engraftment and is therefore frequently added to these two regimens.

Post-transplant follow-up

Regular and comprehensive post-transplant follow-up is important. Within the first year, monitoring of hematologic and engraftment parameters, infectious complications, and signs/symptoms indicating GvHD is essential to identify impending complications. Longer-

term follow-up should focus on monitoring the onset of disease-related problems (Table 2).

In thalassemia it may be possible to manage complications such as iron overload, chronic hepatitis, cardiac function, and endocrine deficiencies more easily after transplantation, sometimes leading to recovery of damaged organs. Iron-overload may persist after transplant leading to progressive organ damage and possibly life-threatening organ failure, particularly when associated with other morbidities (Angelucci 2002). Excess iron should be deleted from the blood system using phlebotomy or systemically removed using chelation therapy.

newest treatment options for individuals with SCD and TDT and may represent an alternative to HSCT in patients who do not have a compatible donor. In SCD, these novel therapies induce the replacement of HbS with non-sickling hemoglobin. In TDT, gene therapy aims to either restore beta-globin production during erythropoiesis (using gene addition) or to reactivate the production of fetal-globin (using gene editing techniques).

Gene therapy works by altering the genetic code in cells to recover the functions of critical proteins. The instructions for making proteins are contained in genetic code, and variants (or mutations) in this code can impact the production or function of proteins that may be critical

Table 2. Selected Follow-up Recommendations after HSCT for Sickle Cell Disease and Transfusion-dependent Thalassemia

Organ system	SCD or TDT
Immune functions	Monitor at 6 months, 1 year, then every 6 months until recovery; include post-vaccination-specific antibody titers; continue PCN prophylaxis; administration of immunizations; infection prophylaxis as necessary for bacterial & fungal infections.
Iron overload	Monitor iron load with serum ferritin and transferrin saturation, if abnormal start iron depletion; avoid deferasirox and calcineurin inhibitors due to nephrotoxicity risk.
Heart	Consider cardiac MRI to monitor iron load; consider lipid profile; monitor BP
Liver	Assess LFT every month through 1st year; consider liver biopsy in patients with pre-transplant fibrosis or hepatitis B; refer to gastroenterologist/infectious disease specialist for possible antiviral therapy.
Diabetes mellitus	Monitor fasting glucose and GTT if there is significant iron overload or after discontinuation of steroid therapy if indicated
Growth	Evaluate height, weight, BMI at 6 months and yearly thereafter; assess hormone levels for short stature and bone age; refer patients with growth retardation to endocrinologist to discuss growth hormone supplementation.
Gonads	Track Tanner progression, gonadal hormones, gonadotropin levels as age appropriate; consider total and free testosterone and other hormonal indexes; refer patients with pubertal delay, low testosterone levels, or primary/secondary amenorrhea to endocrinologist.
Chronic GvHD	Evaluate monthly while receiving immunosuppression
Quality of life	Evaluate QoL in age-appropriate manner at 1 year and as needed (i.e., education, social life, activities, employment, earning capacity, independence)
Other	Consider tracking hospital admissions before during, and after HSCT recovery; screening for malignancies; perform nutritional assessment if indicated.

BMI, body mass index; BP, blood pressure; HSCT, hematopoietic stem cell transplantation; LFT, liver function test; PCN, penicillin; QoL, quality of life
Adapted from: Shenoy 2018

Gene Therapies for Hemoglobinopathies

Types and techniques

Gene therapies, or beta globin replacement, are the

to bodily functions, in the case of hemoglobinopathies, the production of normal hemoglobin in red blood cells. By fixing or compensating for disease-causing genetic changes, gene therapy may recover or repair the role of essential proteins.

Two approaches to gene therapy are used in hemoglobinopathies.

- Gene addition therapy introduces new genetic material into cells that provides instructions for the cell to make more of the specific protein needed. Vectors, such as lentivirus, are used to deliver the working gene to the cell's nucleus where the DNA is stored. This gene is now in the cell nucleus and should become permanent. Some therapies are designed for the new gene to insert itself into the main DNA storage while in other designs it remains next to the main DNA storage. The viral vector is then delivered directly to the body (in-vivo therapy) or to cells (ex-vivo therapy) to deliver the therapeutic genetic material to the nucleus of the cell. In-vivo viral vector therapies are frequently limited to a one-time delivery due to the innate immune response to the virus that often prevents re-administration (American Society of Gene and Cell Therapy 2024).
- Gene editing corrects pieces of DNA by changing or deleting the information within the affected gene. Genetic material is sent to directly edit or change pieces of DNA already located within a cell to correct the protein being made by that DNA. Gene editing uses technology that is highly precise to make these types of changes. For example, a CRISPR-Cas9 system that consists of a guide RNA complementary to the target genomic DNA sequence and a Cas9 nuclease. In hemoglobinopathies, regulators of HbF synthesis such as BCL11A are the target of CRISPR-Cas9 action, resulting in increased HbF expression and reduction of pathologic Hb such as HbF in SCD or correction of the imbalance α/β globin towards α/γ globin in TDT.

Several gene therapies have received FDA and EMA approval and are in current use as treatments for SDC and/or TDT.

Exagamglogene autotemcel (Casgevy®): Approved in several countries for the treatment of SDC in patients who have recurrent vaso-occlusive events and are 12 years and older and in TDT in patients 12 years and older. Casgevy is a CRISPR/Cas9-based, one-time cell-based gene therapy.

Lovotibeglogene autotemcel (Lyfgenia®): Approved in several countries for the treatment of SCD in patients 4 years and older who have a history of vaso-occlusive events. Lyfgenia is a cell-based gene therapy. It uses a lentiviral vector as a gene delivery vehicle for genetic modification.

Betibeglogene autotemcel (Zenteglo®): Approved in several countries for the treatment of TDT in patients 12 years and older.

Procedures and precautions

Gene therapies, like other treatments, are associated with adverse events. A high number of CD34+ cells are required for the procedure. Aging represents an additional challenge for obtaining enough stem cells for gene therapy drug production (De Franceschi 2025). The procedure of collecting stem cells, administering conditioning agents, and infusing the modified cells should be taken into consideration when selecting patients for the procedure (**Table 3**).

It is imperative that genetically modified stem cells are administered at a healthcare facility adequately prepared to formulate, administer, and monitor this therapy. For example, healthcare providers at the facility should be educated to properly monitor patients for side effects, specially trained laboratory and pharmaceutical services should be available, and emergency personnel should be located in or at nearby facilities (De Franceschi 2025).

Table 3. Preparation before Gene Therapy Infusion

Product	Precautions
Exagamglogene autotemcel (Casgevy®)	Discontinue disease modifying agents (hydroxyurea, crizanlizumab, voxelotor) 8 weeks before the planned start of mobilization and conditioning. Discontinue iron chelation therapy at least 7 days prior to myeloablative conditioning.
Lovotibeglogene autotemcel (Lyfgenia®)	Discontinue hydroxyurea for at least 2 months prior to mobilization and until all cycles of apheresis are completed, discontinue hydroxyurea 2 days prior to initiation of conditioning. Discontinue iron chelators at least 7 days prior to initiation of mobilization or conditioning. Specific manufacturer instructions should be followed for resumption of iron chelators.
Betibeglogene autotemcel (Zenteglo®)	Discontinue iron chelation at least 7 days prior to myeloablative conditioning. Administer prophylaxis for hepatic veno-occlusive disease (recommended).

The procedure for collecting, modifying, and administering gene therapy is depicted in Figure 1.

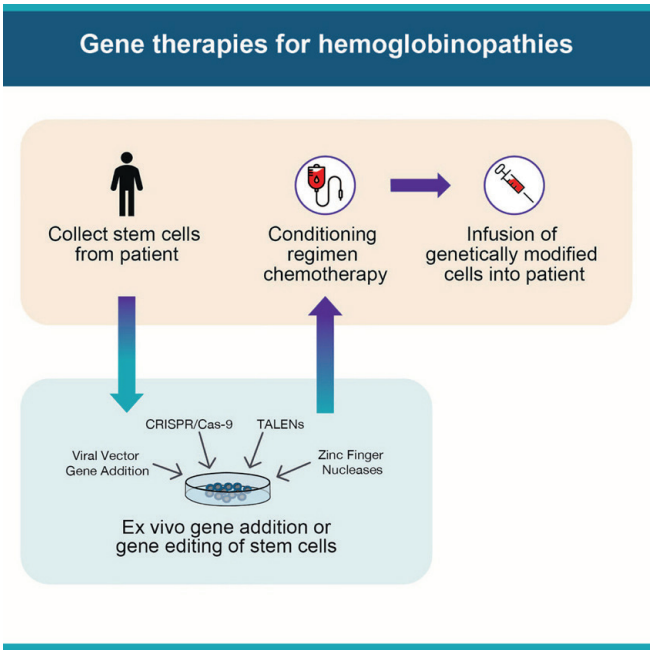


Figure 1. Gene therapies for hemoglobinopathies. Before stem cells are collected, the patient is treated with granulocyte colony-stimulating factor (G-CSF) to mobilize hematopoietic stem cells into the peripheral blood. Then, stem cells are collected from the patient. The collected stem cells undergo gene editing or gene addition (4 techniques are currently in use). Prior to re-infusion of the altered stem cells the patient receives moderate, non-ablative myelosuppression treatment to improve the proliferation of the altered stem cells. Adapted from: Locatelli 2024.

Side effects and known treatment risks

Gene therapies used in SCD and TDT are known to have side effect or reactions that occur during or shortly after administration, and side effects that can occur weeks to months later (**Table 4**).

All of the side effects and medium to longer-term risks of gene therapy are currently unknown. However, as gene editing makes changes directly to the DNA, there are unique risks that could change the intended effects of the therapy such as:

- Unintended gene modifications: when editing a DNA sequence, unintended gene modifications or chromosome rearrangements may possibly occur, especially if multiple edits are being made at the same time.
- Off-target editing events: depending on the guide sequences, there is a risk of modifying DNA locations that are not the desired target site.

Similar to HSCT, gene therapy requires a conditioning regimen, which poses risks of infertility and secondary malignancies, particularly when myeloablative regimens are used. The reported short-term side effects of gene therapy in both diseases are related primarily to busulfan pretreatment used for myeloablation such as febrile neutropenia, and not to the cell therapy product (i.e., exa-cel [Casgevy]) based on a systematic review of clinical trials (Ahmed 2025).

All 3 gene therapies carry a risk of not achieving neutrophil engraftment and, a prolonged time to platelet engraftment.

Lyfgenia has received a boxed warning regarding the risk of hematologic malignancy occurring in some patients. For this reason, the manufacturer advises that patients are followed and complete blood counts are taken at months

6, 12, and as warranted.

Future perspectives

A dominant disadvantage of gene therapies is their price: approximately € 1.6 million ($1.8 million) for a treatment course. The steep price of gene therapy may be burdensome for patients and national healthcare providers seeking alternative treatment options. Other disadvantages are

Table 4. Gene Therapies for SCF and TDT and their Reported Side Effects

Product	Side effects (immediate)	Side effects (up to 6 months)
Exagamglogene autotemcel (Casgevy®)	Hypersensitivity reactions	↓ platelet and ↓WBC levels, mucositis, febrile neutropenia, nausea, musculoskeletal pain, abdominal pain, vomiting, headache, itching
Lovotibeglogene autotemcel (Lyfgenia®)	Hypersensitivity BP, hot flushes	Stomatitis; ↓ platelet and ↓WBC levels, febrile neutropenia, anemia Secondary hematologic malignancy
Betibeglogene autotemcel (Zenteglo®)	Hypersensitivity reactions; ↑ heart rate, abdominal pain	↓ platelet and ↓WBC levels; mucositis, febrile neutropenia; vomiting, fever, alopecia, epistaxis, abdominal pain; musculoskeletal pain, diarrhea, rash, constipation, decreased appetite, pruritis
Sources: Package Insert - LYFGENIA; Package Insert - CASGEVY; Package Insert - ZYNTEGLO		

the length of time required for the manufacturing of gene therapy as it is generated from the patient's own cells, and that patients should receive treatment in specialized clinics.

Because the number of participants in clinical trials is still small, it is still too early to have conclusive evidence of the efficacy and safety of these novel treatments and to gain a better understanding of what, if any, longer term side effects could occur. It can be assumed, however, that especially CRISPR gene editing holds promise for successful, and possibly curative treatment of SCD and TDT. Other issues to be addressed include further research and further exploration of associated ethical issues, the provision of wider and less expensive access to this therapy, and the need for specialized facilities.

Shared Decision-Making

Both HSCT and novel treatments, such as gene therapy, represent hope for a normal life but are associated with known and unknown risks. Patients and their caregivers (primarily parents) may wish for a "normal" life that includes a good QoL and favorable perspectives for the future when considering standard supportive treatment versus HSCT or a novel treatment for thalassemia (Mekelenkamp 2024). The decision-making process is made more difficult by the risks and uncertainties of treatment versus the impact of the hemoglobinopathy being treated.

Shared decision making is a collaborative process that involves a person/patient and their healthcare team working together to reach a joint decision about care (NICE 2021). Shared decision-making has been described as involving 4 steps:

Shared decision-making is an important aspect of patient-centered healthcare. Nurses play a crucial role in helping patients/caregivers navigate and understand the key decisions they may be facing. Their broad base of knowledge and clinical experience combined with their close relationship with patients and families helps nurses to provide insights into treatment preferences and values to support the decision-making process.

Box 1. Steps in shared decision-making process

Step	How to optimize
1. Provide explanations of the choice	Informing the patient that a decision is to be made, and that the patient's/ caregiver's opinion is important
2. Inform patients/ caregivers about the options	Explaining the pros and cons or risks and benefits of the treatment options
3. Explore with the patient/ caregiver their preferences	Identifying with the patient/caregiver their preferences and supporting the patient/ caregiver in their decision-making process
4. Make a decision	Discussion of the decision, whether it is to proceed or delay the treatment.

Adapted from: Stiggelbout 2015

References

Ahmed R, Alghamadi WN, Alharbi RF, et al. CRISPR/Cas 9 system as a promising therapy in thalassemia and sickle cell disease: a systematic review of clinical trials. Molecular 2025; https://doi.org/10.1007/s12033-025-01368-x.

Al-Khabori M, Al Ghafri F, AlKindi S, et al. Safety of stem cell mobilization in donors with sickle cell trait. Bone Marrow Transplant 2015; 50:310311.

American Society of Gene and Cell Therapy. 2024. Available at: Different Approaches | ASGCT - American Society of Gene & Cell Therapy |. Accessed June 2025.

Angelucci E, Pilo F, Coates TD. Transplantation in thalassemia: revisiting the Pesaro risk factors 25 years later. American Journal of Hematology 2017; 92:411-413.

Angelucci E, Muretto P, Nicolucci A, et al. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. Blood 2002; 100:17-21.

Baronciani D, de la Fuente J, Galimard JE, et al. Age is a crucial determinant of GFRS with incidence of sever chronic GVHD reducing over time in haemopoietic cell transplantation for transfusion dependent thalassemia: Real world data from 2010-2021. An analysis of the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Working Party. Blood 2024; 144:2136

Baronciani D, Angelucci E, Potschger U, et al. Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000-2010. Bone Marrow Transplant 2016; 51:536-541.

Caocci G, Orofino MG, Vacca A, et al. Long-term survival of beta thalassemia major patients treated with hematopoietic stem cello transplantation compared with survival with conventional treatment. American Journal of Hematology 2017; 92:1303-1310

Cappelli B, Gluckman E, Corbacioglu S, et al. Hemoglobinopathies (sickle cell disease and thalassemia). In: The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies. Sureda A, Corbacioglu, Greco R, et al (ed). 2024. Available at: The EBMT Handbook - NCBI Bookshelf. Accessed June 2025

De Franceschi L, Locatelli F, Rees D, et al. Selecting patients with sickle cell disease for gene addition or gene editing-based therapeutic approaches: Report on behalf of a joint EHA Specialized Working Group and EBMT Hemoglobinopathies Working Party consensus conference. HemaSphere 2025;9:e70089

Faraci M, Dioesch T, Labopin M, et al. Gonodal function after busulfan compared with treofsulfan in children and adolescents undergoing allogeneic hematopoietic stem cell transplant. Biol Blood Marrow Transplant 2019; 25:1786-91.

Gluckman EB, Cappelli B, Bernaudin F, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood 2017; 129:1548-1556.

Kanter J, Falcon C. Gene therapy for sickle cell disease: where we are now? Hematology American Society Hematology Education Program 2021; (1):174-180. doi: 10.1182/hematology.2021000250.

La Nasa G, Caocci G, Efficace F, et al. Long-term health-related quality of life evaluated more than 20 years after hematopoietic stem cell transplantation for thalassemia. Blood 2013; 122:2262-2267

Lawal RA, Walters MC, Fitzhugh CD. Allogeneic transplant and gene therapy: evolving toward a cure. Hematol Oncol Clin North Am 2022; 36:1313-1335

Limerick E, Abraham A. Across the myeloablative spectrum: hematopoietic cell transplant conditioning regimens for pediatric patients with sickle cell disease. Journal of Clinical Medicine 2022; 11:3856.

Locatelli F, Cavazzana M, Frangoul H, et al. Autologous gene therapy for hemoglobinopathies: from bench to patient's bedside. Molecular Therapy 2024; 32:1202-1218.

Mekelenkamp H,m de Vries M, Saalmink I, et al. Hoping for a normal life: decision-making on hematopoietic stem cell transplantation by patients with a hemoglobinopathy and their caregivers. Pediatric Blood Cancer 2024; 71:e30808.

National Institute for Health and Care Excellence (NICE). Sharede decision making 2021. Available at: Shared decision making. Accessed September 2025.

Shenoy S, Gaziev J, Angel;ucci E, et al. Late effects screening guidelines after hematopoietic cell transplantation (HCT) for hemoglobinopathy: Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium Internation Conference on Late Effects after Pediatric HCT. Biology of Blood and Marrow Transplantation 2018; 24:1313-1321.

Stiggelbout AM, Pieterse AH, De Haes JC. Shared decision making: concepts, evidence, and practice. Patient Education Couns 2015; 98:1172-1179.

St Martin A, Hebert KM, Serret-Larmande A, et al. Long-term survival after hematopoietic cell transplant for sickle cell disease compared to the United States population. Transplant Cell Therapy 2022; 28:325.e1-325.e7.

Taher AT, Farmakis D, Porter JB, Cappellini MD, Musallam KM. Guidelines for the Management of Transfusion-

Dependent -Thalassaemia (5th edition). Thalassaemia International Federation 2025. Available at: Guidelines for the Management of Transfusion-Dependent -Thalassaemia (5th edition – 2025) – TIF

United Kingdom Thalassemia Society. Standards of the Clinical Care of Children and Adults living with Thalassemia in the United Kingdom, 4th Edition. 2023. Available at Standards-for-the-Clinical-Care-of-Children-and-Adults-Living-with-Thalassaemia-in-the-UK-4th-Edition-2023.pdf

Walters MC, Storb R, Patience M, et al. Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. Blood 2000; 15:1918-1924

Yesilipek MA, Uygun V, Kupesiz A, et al. Thalassemia-free and graft-versus-host-free survival: outcomes of hematopoietic stem cell transplantation for thalassemia major, Turkish experience. Bone Marrow Transplant 2022; 57:760-767

Quick Facts

- Individuals with SCD experience recurrent but unpredictable episodes of debilitating acute pain that, over time, evolves into daily chronic pain.
- In addition to pain, the complications of SCD are numerous, can affect almost all organ systems, and can be acute or chronic in nature.
- Children and adults with SCD are at higher risk for cerebrovascular accidents than the healthy population.
- Cardiac complications are common in patients with TDT and require a multidisciplinary approach to identify and manage these complications early.
- Hepatic complications in TDT may be exacerbated by viral infections such as HCV, which might become a risk factor for the development of hepatocellular carcinoma.

Contents:

Sickle Cell Disease: Common Complications and their Management

In sickle cell disease (SCD), the sickled, dense red blood cells (RBCs) observed are more rigid than normal RBCs. This rigidity may cause them to become trapped in small blood cells together with neutrophils, triggering acute painful events (Tanabe 2019). Painful events may be further complicated by local organ changes generating a clinical condition known as vaso-occlusive crisis (VOC). Sluggish circulation, high levels of oxygen extraction and low pH result from changes in organs and systems affected by SCD. The recurrent and unpredictable nature of sickle cell-related VOCs means that SCD is a monogenic disorder with multi-organ effects (**Fig. 1**). Therefore, managing SCD requires attention to its complex pathophysiology and its effects on general medical comorbidities.

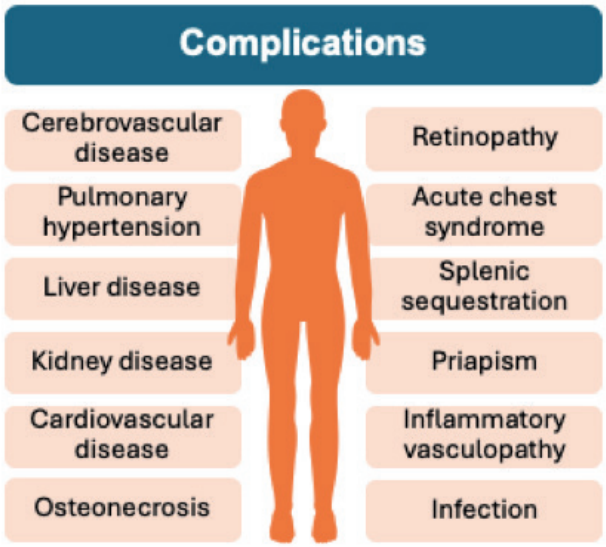


Figure 1. Schematic diagram summarizing sickle cell related to acute and chronic organ complications. (Figure courtesy of L. De Franceschi)

Common problems associated with the pathophysiology of SCD are progressive throughout the life span (**Fig. 2**). As most individuals with SCD living in developed nations now survive into adulthood, the current challenge in disease management is the treatment and prevention of end-organ disease (Liem 2019). In infancy and childhood, most complications occur in acute recurrent episodes. Growth and puberty are delayed due to increased metabolic demands secondary to ongoing hemolytic anemia. Later, in adulthood, organ damage as well as acute complications are prominent. Acute pain episodes, acute chest syndrome, and ischemic stroke can occur at any stage in the life cycle.

Current management of complications is frequently based on clinical experience and expert opinion, which highlight the need for prospective research to generate high quality evidence (Piel 2023). While prompt and appropriate management of complications is important, the prevention of these events is an equally important goal. Study results indicate that, individuals with hemoglobinopathies cared for in centers with specialists seem to have an increased survival rate compared to those followed by non-specialists (Forni 2023), highlighting the value of specialist care of these patients.

As mentioned in Module 2, the severity of SCD is variable. However, even individuals with milder forms of SCD, such as HbSC and HbS+-beta thalassemia, commonly experience acute painful events and serious complications including acute chest syndrome (ACS), silent cerebral infarction, avascular necrosis (AVN), priapism, and kidney failure throughout life (**Fig. 1**).

Two challenges face healthcare professionals when managing individuals with SCD. The first is a lack of evidence-based practice guidelines due to the paucity of data from large, randomized controlled trials involving SCD patients, which most likely stems from discrimination within healthcare systems and society in general against individuals with SCD. The second challenge is the underuse of hydroxyurea as a disease-modifying therapy available for SCD (Yawn 2014).

Major health complications in sickle cell disease and their management

Pain

Recurring and relapsing pain in patients with SCD can start as early as six months of age. The pain can be acute intermittent pain or chronic daily pain, or a mixture of these two (**Box 1**).

Needless to say, pain has a profound negative impact on the patient's health-related quality of life (HRQoL). The various biological mechanisms involved in sickle cell-related pain as well as sociological and psychological factors may be the cause or contribute to the pain experience (**Box 2**).

Socioeconomic factors relating to race and social circumstances that are characteristic of the affected population can complicate the experience and treatment of pain. Individuals with SCD report higher levels of pain compared with cancer patients of either the same or a different race (Ezenwa 2018). Individuals who perceive

Product	Infancy and childhood	Adolescence	Adulthood
During a specific life stage	Delayed growth	Delayed puberty	Hemorrhagic stroke/ischemic stroke Leg ulcers Pulmonary hypertension Reproduction complications
During multiple life stages	Aplastic crisis Sepsis Osteomyelitis Splenic sequestration Splenic infarction	Avascular necrosis Cognitive dysfunction Chronic pain Gallstones	Priapism Sickle retinopathy Sickle renal disease Venous thromboembolism
During all life stages	Acute pain	Acute chest syndrome	Ischemic stroke

Figure 2. Complications occurring during the life span of a patient with sickle cell disease. (Adapted from: Kavanagh 2022).

Box 1. Mechanisms of pain in SCD

Type of pain	Mechanisms
Nociceptive pain	• Tissue injury-inflammation (VOC) • Vasospasms • Release of prof-inflammatory cytokines • Release of pain producing molecules (prostaglandin-2, serotonin)
Neuropathic pain	Damage of nerve system (nerve ischemia from VOC, nerve compression, nerve injury)
Idiopathic pain	Pain due to unknown causes

VOC, vaso-occlusive crisis

Box 2. Sociological and psychological factors that impact pain events

Sociological factors	Psychological factors
Negative provider attitudes Disease stigma Environmental stressors Traumatic life events Disparities in care	Depression Anxiety Learned helplessness Sleep disorders

Source: Brandow 2018

discrimination from healthcare team members due to their race or socioeconomic status experience more intense stress and pain (Ezenwa 2015, Haywood 2014).

Pain is the most common reason for patients to seek emergency care. An individualized, multidisciplinary approach that encompasses pharmacological, nonpharmacological, and integrative therapeutic interventions is necessary to manage pain due to its complexity.

Acute pain episodes (pain crisis)

An acute vaso-occlusive crisis (VOC), also referred to as vaso-occlusive episodes (VOE), is a new onset of severe, acute pain that persists for at least four hours for which there is no explanation other than vaso-occlusion (Tanabe 2019). VOCs are the primary underlying cause of acute pain and for most instances of pain that requires medical attention in patients with SCD. They are also considered the hallmark complication of SCD.

Often, pain episodes are preceded by an early recognition phase that manifests as fatigue and diffuse body aches occurring 1- to 2-days before pain onset. As patients grow older, they are often able to develop self-care and coping mechanisms to manage VOC. Still, VOCs are the most common reason for patients to seek emergency medical attention (Lanzkron 2010). Risk factors for the development of VOCs include extreme temperature changes, dehydration, menstrual cycle changes, alcohol, or stress. Pain episodes are often, however, unprovoked and begin with little warning (Brosseau 2010; Carroll 2009).

Infants and young children often experience dactylitis, which is pain and swelling in the digits of the hands and feet.

Multidisciplinary team management

The focus on acute pain management is the rapid assessment of pain and initiation of analgesic medications. Pain management should be initiated within 1 hour of arrival at the healthcare center. Nurses act as patient advocate to ensure the patient receives adequate analgesia.

Chronic pain

Chronic pain occurs with increasing patient age and approximately 30% to 40% of adolescents and adults with SCD experience chronic pain (Brandow 2020). The American Society of Hematology (ASH) defines chronic pain in this population as a report of ongoing pain present

on most days over the past 6 months in either a single location or multiple locations (Brandow 2020).

Three subtypes of chronic pain have been identified in SCD:

- Chronic pain without associated SCD complications, such as leg ulcers
- Chronic pain with contributing SCD complications
- Mixed presentation; evidence of chronic pain from SCD complications but also apparently unrelated persistent pain (Dampier 2017).

In comparison to acute pain, chronic pain often has no identifiable associated pathology except for the underlying SCD. Chronic pain can manifest as general discomfort, mood changes, emotional disturbance, and behavioral dysfunction and evidence suggests that patients who have greater levels of chronic pain have associated increases in acute pain (Smith 2008). Chronic pain is often treated with opioid and nonopioid analgesic medications in combination with anti-depressive and low-dose neuroleptic agents.

Multidisciplinary team management

Nursing management of chronic pain involves working with the individual to identify which types of chronic pain respond to which interventions and how to use both medications and nonpharmacological interventions most effectively (**Table 1**). A consultation with a pain management expert may be beneficial in developing an effective analgesic plan.

Acute chest syndrome

Acute chest syndrome (ACS) is a life-threatening complication of SCD. It is caused by increased adhesion of sickled RBCs and neutrophils to pulmonary microvasculature in the presence of hypoxia, Commonly associated etiologies include:

- Pulmonary fat embolism
- Pulmonary infarction
- Hypoventilation (Friend 2023)

And possibly:

- Atelectasis
- Capillary leakage/edema
- Bronchospasm (Jain 2017)

Symptoms common to ACS include:

- Chest pain
- Temperature > 38.5oC
- Tachypnea, wheezing, the appearance of an increased work of breathing

The syndrome can progress quickly and is a leading cause of death in patients with SCD (Day 2018). Approximately 50% of patients with SCD will experience more than 1 episode of ACS and it is the most common cause of death in patients with SCD, accounting for almost 25% of all deaths (Friend 2023). ACS incidence is highest in children ages two to four years, but severity is higher in adults. Risk factors include low fetal hemoglobin, young age, presence of asthma or other hyperreactive lung disorder, smoking, recent trauma or surgery.

Multidisciplinary team management

Because of the potential severity of ACS, early recognition and treatment are crucial – all patients with ACS should be hospitalized. Therefore, individuals should be given information on signs/symptoms of ACS and when to seek medical treatment.

In addition to ACS, individuals with SCD may experience other acute and chronic pulmonary problems (**Table 1**). Asthma and airway hyperreactivity are significant comorbidities in SCD, particularly in children, and are associated with worse disease outcomes (Field 2011).

Stroke

Children and adults with SCD are at risk for cerebrovascular accidents such as ischemic stroke, hemorrhagic stroke, and silent stroke. Stroke risk increases over 100-fold in children with SCD compared to children without the disease (Baker 2015). Most commonly, children with SCD experience silent strokes to the brain, which may occur in up to 39% of children by age 18 and occur without typical outward physical signs of stroke such as arm or leg weakness but are visible on an MRI of the brain (American Stroke Association 2024). Silent strokes in children, which are small infarctions detectable only using MRI, may lead to problems in thinking, learning, and decision-making and are a risk factor for future strokes.

Whereas the previous incidence of stroke in patients younger than 20 years with SCD was about 11%, this number has significantly decreased due to screening and stroke prevention therapies in high-risk patients. ASH recommends regular blood transfusion to substantially reduce the incidence of new stroke, silent infarct recurrence, or both in children with silent stroke (DeBaun 2020).

Parents of children with SCD should be taught to recognize the signs of stroke (using the acronym FAST) and to know who or where to call should they observe these signs:

F = Face drooping

A = Arm weakness

S = Speech difficulty

T = Time to call for emergency assistance

Other signs and symptoms include numbness or weakness especially on one side of the body, trouble seeing in one or both eyes, trouble walking, dizziness loss of balance, or lack of coordination, severe headaches with no known cause.

Stroke should be suspected in individuals who exhibit altered neurologic signs or symptoms. Acute changes in neurological status, including altered mental status, should be immediately reported to the primary care provider. Parents should be advised that poor academic performance or a change in performance is a red flag for potential neurocognitive deficits and should be called to the attention of the child's healthcare team (**Table 2**).

Infection

Individuals with SCD are at risk of developing severe infection, particularly invasive bacterial infection, throughout their life. Infection is primarily due to splenic pathologies characteristic of SCD. Clinical manifestations of infection can occur as acute episodes or as chronic conditions. Acute manifestations include bacteremia/sepsis, meningitis, hepatitis, osteomyelitis, and urinary/renal infection.

Prophylaxis with penicillin and immunizations early in life in children have reduced the incidence and severity of infection in children in countries that practice prophylaxis. Fever requires rapid assessment with complete blood count, reticulocyte count, blood culture, and empirical administration of broad-spectrum antibiotics.

Parents/caregivers should be taught to closely monitor temperature and to seek medical attention if temperature is ≥ 38.5oC: a temperature above 38.5oC is typically managed aggressively (**Box 3**). Adult patients with SCD should not receive prophylactic antibiotics (Forni 2023) to avoid a risk of developing antimicrobial resistance (Opoku-Asare 2025). Patients should be instructed to maintain a vaccination record and receive vaccinations against Meningococcus, Pneumococcus, and Hemophilus infections, among others.

Box 3: Interventions in response to temperature greater than 38.5 oC

- Full blood count
- Blood and other relevant cultures
- Chest x-ray for any respiratory symptoms
- Empirical antibiotics covering pneumococcus

Source: Piel 2023

Avascular necrosis

Periodic disruption of the blood supply to bone tissue due to SCD promotes ischemic/reperfusion damage, causing bone edema and subsequent avascular necrosis (AVN) (De Silva 2012). AVN affects about 10% of patients with SCD, as identified in one study (Alshurafa 2023) and may be associated with eventual bone collapse. It typically involves the hips, shoulders, and spine (Kavanagh 2022).

Risk factors for AVN may be the severity of SCD and a history of acute chest syndrome (ACS). AVN occurs in adults as well as children as young as five years and is common in the bone marrow of the head of the femur (thigh bone) or head of the humerus (upper arm bone). AVN is painful and may have significant function-limiting effects. Management of AVN is often challenging and includes conservative and surgical options; if severe, joint replacement surgery may become necessary (Box 4).

Box 4: Nursing interventions: avascular necrosis

- Perform a comprehensive pain assessment to identify the presence of AVN.
- If AVN is suspected, discuss findings with primary care provider to initiate referral to orthopedic specialist.
- Help individuals and family to understand the condition and the various procedures that may be considered to alleviate related pain and possible disability.

Source: Tanabe 2019

Priapism

Priapism is defined as a painful erection of more than 4 hours. It may lead to erectile dysfunction and subsequently affect QoL. It is a common complication among boys and men with SCD: incidences of up to 48% of males with SCD have been reported with a peak incidence during puberty and young adulthood (Arduini 2018). Stuttering or intermittent priapism (lasting < 3 hours) is a risk factor for more severe ischemic priapism. Priapism can be an embarrassing problem for men, and it may be a difficult problem for them to discuss with a partner or with a healthcare professional.

Some preventative measures include the use of analgesia, hydration, exercise/walking, frequent voiding, and warm baths to prevent episodes (Tanabe 2019).

Sickle cell-related kidney disease and organ failure

Renal and multi-organ failure are common complications of acute and severe VOCs related to SCD. Alterations of renal function appear early in SCD subjects, presenting with age-dependent non-selective proteinuria, reported in approximately 50% of patients between 36 and 45 years. Various markers of kidney function may be used including microalbuminuria, which occurs in approximately 16% of children and in approximately 33% of adults with SCD, and ACR (albuminuria/creatinuria ration) and PCR (proteinuria/creatinuria ratio) (Ruffo 2023). The presence of end stage kidney disease (ESKD) in patients is a risk factor

for premature death. Risk factors for the development of renal disease include the following:

- age (young adult)
- hemolysis (LDH)
- anemia - hypoxia (Hb)
- transfusion needs
- hypertension
- proteinuria
- microhematuria

Individuals with significantly elevated albuminuria should be referred to a nephrologist for evaluation and all individuals with SCD should undergo annual assessment of albumin levels starting at age 10 years (Kavanagh 2022).

Multi-system organ failure is characterized by dysfunction of at least two or three major organ systems and often develops after several days of hospital treatment for a VOC, when pain is improving. Deterioration of organ function is often rapid and is often signaled by significant changes in respiratory status or renal function.

Box 5: Nursing interventions: multi-system organ failure

- Further assess any elevation in respiratory rate or reduction in oxygen saturation as this could a potential early sign of ACS; report significant changes to primary care provider
- Monitor renal function and IV fluid administration, especially in individuals with a history of renal failure

Source: Tanabe 2019

Other health complications

Anemia

Chronic hemolytic anemia is a hallmark characteristic of SCD. The symptoms of anemia include pallor, fatigue, decreased exercise tolerance, shortness of breath, and decreased cognitive function. Severe anemia is associated with serious complications such as stroke in children with SCD. The severity of hemolysis is associated with severe complications including pulmonary hypertension and chronic kidney disease (Kato 2017).

Reproductive issues

The reproductive and sexual consequences of SCD have been poorly studied. Pregnancy is considered high-risk, and these women should be followed closely, especially for indications of medical complications (i.e., urinary infection, deep vein thrombosis), complications of pregnancy (i.e., placenta ischemia, poor fetal growth), and worsening of SCD.

Newborns of mothers with SCD can be affected by problems such as being small for gestational age and prematurity; the consequences of these complications are not fully understood.

Some of the SCD complications that are not confined to a particular organ system include

- Nutritional deficits due to anorexia, deficiencies in vitamins D, E, and A, zinc deficiencies, increased caloric demand (see Module 8).
- Constitutional complications such as fatigue, exercise intolerance.
- Sleep disturbances, lethargy, chronic insomnia, hypersomnia.

Psychosocial issues

In addition to disease- and treatment related factors, there are numerous sociocultural, environmental, individual, and economic factors that influence outcomes across the life span for people living with SCD. The psychosocial implications of living with SCD are presented in Module 8.

Transfusion-dependent Thalassemia: Common Complications of TDT and their Management

The pathophysiology of thalassemia, independent of any treatments administered, can cause disease-related problems. In 2021, the UK Thalassemia Society surveyed its members to collect data on the incidence of secondary conditions and the impact of these on their QoL. Of 106 respondents, 97% reported having acquired more than one secondary condition, 63% of respondents having five or more secondary conditions, and 32% reported having 10 or more secondary conditions. Chronic bone and joint pain, previously underreported in publications and undertreated in most situations, were experienced by 83% of patients and reported in children as young as 3 years of age (UKTS 2023).

Major health complications

Metabolic

While advances have been made in understanding and treating transfusion-dependent thalassemia (TDT), the complications caused by the underlying pathophysiology of the condition means that morbidities continue to occur and do occur at higher incidences in individuals with

Table 1. Major Complications of Sickle Cell Disease and their Management

Problem	Management strategies	Possible complications
Acute pain (acute VOC or VOE)	Comprehensive and early pain assessment that includes location, intensity, duration of the pain; identification of actions that normally relieve pain and assessment if pain is typical of VOC or due to another complication; Provide rapid and tailored analgesia with frequent re-assessment of effect on pain relief; Mild to moderate pain can be managed at home with paracetamol, non-steroidal anti-inflammatory drugs, and weak oral opioids; if pain relief is not achieved, opioid treatment may be an option. Work with patient/family to identify helpful nonpharmacologic therapies to ↓ pain (i.e., heat to site, cognitive behavioral therapy, relaxation, acupuncture, herbal therapies). Work with patient/family to identify triggering mechanisms. Encourage adequate hydration, movement to prevent blood clots and pulmonary complications.	Acute multisystem failure, death; younger age at death.
Chronic pain	Determine type and location of pain and initiate appropriate interventions; obtain thorough medication history, including opioid and non- opioid pain medications; assess patient understanding of how to take analgesics effectively. Cognitive behavioral therapy, mindfulness therapy, and guided imagery may be helpful.	Depression and anxiety, insomnia, sleep disorders
AVN	Comprehensive pain assessment, especially when patient complains of hip or upper arm pain; follow appropriate channels to obtain orthopedic consultation	If untreated, permanent gait abnormalities and limb-length discrepancies that can significantly impair mobility
ACS	Key management includes pain control, cautious administration of IV fluids, antibiotics, supplemental oxygen, and blood transfusions. Aggressive incentive spirometer and respiratory therapy every 2 hours to improve lung function. Conduct a comprehensive respiratory assessment, noting even subtle changes in respiratory status. Monitor oxygen saturation and/or hemoglobin status: a significant decline can indicate more severe ACS. Administration of antibiotics, oxygen, invasive and non-invasive respiratory support, bronchodilators, nitric oxide, and corticosteroids may be prescribed Evidence is lacking to support the use of simple or exchange transfusions to improve outcomes.	Recurrent episodes of ACS, interstitial lung disease, pulmonary hypertension; death
Stroke	RBC transfusion, hydroxyurea administration. Follow institutional protocols for the management of stroke. Alert parents of the necessity to seek immediate care for any emerging neurologic symptoms, provide education on the importance of yearly transcranial doppler ultrasound screening of children between ages 2-16 and MRI of the brain every 2 years after age 5.	Progression of cerebral infarcts and cerebral vasculopathy; cognitive decline; Complications related to blood transfusions; hypertension leading to poorer outcomes

ACS, acute chest syndrome; AVN, avascular necrosis; VOC, vaso-occlusive crisis; VOE, vaso-occlusive episode;
Sources: Brandow 2020; Chou 2020; Howard 2015; Kavanagh 2022; Tanabe 2019

numerous risk factors and in older aged individuals (**Table 3**). These complications can significantly impair physical, mental and psychosocial areas of HR-QoL.

Complications due to treatment (i.e., transfusions) may occur because of low reliability of blood and blood products in some regions of the world, inadequate blood transfusion therapy, chronic iron deposition, or inadequate use of chelation therapy (Tarim 2022). [Management of iron overload (i.e., chelation therapy) is presented in detail in Module 5]. Secondary iron overload from regular transfusion therapy can lead to organ damage due to the toxic effects of iron accumulation in the heart, liver, and endocrine glands. Hence, the care of patients requiring regular transfusions is optimized to each patient's clinical course and profile and is primarily focused on the improvement of anemia and the regulation of iron overload and its complications (Taher 2025; Makis 2021).

Endocrine and growth disorders

Endocrine disorders comprise the four leading causes of complications in patients with TDT, which are manifested as growth retardation due to hypogonadism hypogonadotropic disease, abnormalities in glucose profile, hypothyroidism and hypoparathyroidism, and bone disease (with associated low bone mineral density

Table 2. Common and Chronic Complications of Sickle Cell Disease

Organ system	Complication	Chronic complication	Comorbid conditions
Cardiovascular	Sudden death, fatigue, dyspnea syncope, MI.	Sickle cardiomyopathy, diastolic dysfunction, iron-induced cardiomyopathy/dysrhythmias, endothelial dysfunction, pulmonary hypertension	Cardiac iron toxicity, methadone-related QT changes, hyperlipidemia, venous thromboembolism
Central nervous	Headache, stroke, ruptured aneurysms	Chronic headaches, poor executive functioning, memory deficits, increased cerebral blood flow, cerebral aneurysms	Posterior reversible encephalopathy syndrome, pre-/post eclampsia, cerebral aneurysms
Dental	Abscess, dental crown fracture, dental pulp fracture	Dental caries, gingivitis, cracked teeth, early dental loss, misaligned teeth	
Endocrine	Pain at time of menses, pregnancy, and menopause	Growth hormone deficiency, delayed puberty, hypogonadism	Diabetes and thyroid disease from iron overload, hypo/hyperthyroidism
Gallbladder/ pancreas	Cholelithiasis, cholecystitis, common bile duct obstruction, acute pancreatitis	Dyspepsia, cholecystitis, pancreatitis	Pancreatitis with comorbid alcohol misuse
Gastrointestinal	Mesenteric infarcts	Abdominal pain, constipation, IBS, GERD, ↑ abdominal girth	Ileus, cyclic vomiting syndrome, drug-induced nausea and vomiting
Hematopoietic	Anemia, aplastic crisis, scleral icterus	Hemolysis, anemia, extramedullary hematopoiesis, thrombocytosis, leukocytosis, splenomegaly	Delayed hemolytic transfusion reactions, hypoplastic anemia from CKD
Hepatic	Hyperbilirubinemia, hepatic sequestration, hepatitis, transaminitis	Hepatomegaly, hepatic congestion, porta hypertension	Hepatic fibrosis, infectious hepatitis, hepatorenal syndrome
Immune	Bacteremia/sepsis, meningitis, osteomyelitis	Dental abscess, gingivitis, leg ulcer super infection	Transfusion-associated infection, salmonella osteomyelitis
Musculoskeletal	Bony infarction, dactylitis	Vertebral compression fractures, maxillary hyperplasia, gout, osteoporosis	Orbital bone infarction, osteonecrosis/ avascular jaw necrosis, ↑ risk pathological fractures
Ophthalmic	Retinal detachment, retinal artery occlusion, macular infarction	Sickle retinopathy, maculopathy	Early cataracts/glaucoma, ↑ intraocular pressure
Pulmonary	Pulmonary fat embolism syndrome, atelectasis from hypoventilation, pulmonary embolism	Lung disease, hypoxemia/ hypoxia, nocturnal hypoxemia	In situ pulmonary thrombosis, asthma, obstructive sleep apnea, right middle lobe syndrome
Reproductive	Spontaneous abortion/miscarriage, intrauterine growth retardation	Low sperm counts/poor sperm function	Hypospermia from hydroxyurea, infertility
Spleen	Acute splenic infarction, splenic abscess	Hypersplenism	Risk of splenic rupture

CKD, chronic kidney disease; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; MI, myocardial infarction
Source: National Academies of Sciences 2022

high fracture risk, abnormalities of bone turnover markers and vitamin D deficiency The primary cause of endocrine disorders is early toxicity of iron accumulation on endocrine glands.

Growth impairment

Growth failure is common in young patients with TDT and is due to several factors including chronic anemia, hypoxia, iron overload, nutritional deficiencies, and chronic liver disease (UKTS 2023).

Multidisciplinary team management

- The primary treatment of growth impairment is the optimization of the transfusion regimen using a pre-transfusion Hb of 10 g/dL, personalized iron chelation therapy, and early identification and treatment of endocrinopathies such as hypothyroidism (Walker 2025).
- Starting at the time of presentation and at 6-month intervals thereafter, measure height, weight, body

Table 3. Metabolic Problems related to the Pathophysiology of Thalassemia

Problem	Cause	Consequences
Chronic hemolytic nemia	Low hemoglobin, ineffective RBCs, destruction of RBCs	Tissue hypoxia causing ↓ energy level, ↓ exercise tolerance; slowed growth. Untreated anemia can cause heart failure
Destruction of RBCs	Ineffective erythropoiesis causing destruction of WBC precursors leading to ↓ capacity of immune system to recognize & fight infection	Inflammation, ↑ infection risk
Folic acid deficiency	RBC destruction, ↑ folate requirement to support RBC metabolism, ↑ erythropoiesis	Fatigue, weakness, mouth sores, neurologic issues (memory loss, difficulty concentrating)
Increased iron absorption	Suppression of hepcidin (a hormone produced in the liver, which reduces iron absorption and availability) by erythroid factors secreted by destroyed erythroid cells; iron overload adversely affects the binding and detoxification of iron	Joint pain, abdominal pain, weakness, heart/liver failure
Disruption of bone micro-architecture	Expansion of erythropoietic tissue leads to mechanical damage of bone tissue, ↑ bone resorption, bone disease	Increased risk of bone fractures, bone deformities, bone pain

RBC, red blood cells; WBC, white blood cells
Adapted from: Fung 2023

mass index, height when sitting, growth rate, and Tanner stage measurements to assess growth using standardized growth velocity charts based on age and sex.

- Continue screening until achievement of adult height and completion of pubertal development (Casale 2025). Measurements should be charted, and height velocity calculated, to ensure prompt detection of any abnormality.
- If short stature is determined, perform laboratory tests to determine causes such as low hemoglobin (anemia), iron overload, inflammation, deficiencies in liver and kidney function, abnormal electrolytes and/or nutritional deficits.
- Deficiencies in growth hormone can generally be avoided in children who have been sufficiently treated from early childhood on.
- Treatment with recombinant human growth hormone; treatment of growth hormone deficiency followed by treatment of hypogonadism may be beneficial in children. Recombinant human growth hormone is administered as subcutaneous injection at bedtime, which is intended to mimic the metabolic effects of normal growth hormone secretion as closely as possible.
- In adults, growth hormone deficiency is associated with an adverse lipid profile, increased cardiovascular and cerebrovascular events, and decreased bone mineral density, muscle strength, exercise capacity, cognitive function, and QoL (UKTS 2023). There is currently no strong evidence to support supplementing growth hormones in adults.

Hypogonadism

Hypogonadism is primarily due to iron overload in the gonads or in the pituitary gland resulting in primary gonadal failure or gonadotrophin failure, respectively. In adolescents, hypogonadism presents as delayed or incomplete puberty, which is defined as a lack of breast development in girls by the age of 13 or primary amenorrhea by age 15, and as a lack of testicular development in boys by the age of 14 years (Palmert 2012).

Multidisciplinary team management

- Utilize Tanner staging starting at age 10 to assess pubertal development at 6-monthly intervals. Evidence of slowing of growth is often apparent around the age of 8 to 12 years.
- The timing of initiation of hormone replacement therapy is difficult to know. Those individuals with delayed puberty may still experience substantial growth potential. Hence, careful assessment and monitoring by a specialist pediatric endocrinology team is advisable.
- Initiate discussions with patient/family on effects of slowed puberty and assess their understanding of possible causes and treatments.

Glucose metabolism disorders

Impaired glucose regulation and diabetes mellitus are common and significant complications of thalassemia (UKTS 2023). The main cause of these disorders is iron accumulation in the pancreas which damages pancreatic beta cells reducing insulin secretion. Liver disease and HCV may also cause impaired glucose regulation. Sarcopenia

Table 4. Common Cardiovascular Problems in Patients with TDT, their Cause and Management

Problem	Cause	Consequences
Acute heart failure	Iron overload in the heart	Prompt administration of chelation therapy with DFO or combination DFO + DFP; cardio & hemodynamic monitoring; administration of medications appropriate for acute heart failure
Arrythmia: 1) Ventricular tachycardia 2) Atrial fibrillation	Accumulation of iron in the heart, incidence ↑ with age	Initiate chelation with DFO as management for both problems. 1) Insertion of pacemaker 2) Cardioversion

DFP, deferiprone; DFO, deferoxamine;TDT, transfusion-dependent thalassemia
Source: Walker 2025

in adults may also contribute to insulin resistance, accelerating the onset of diabetes.

Multidisciplinary team management: Screening

- Perform OGTT and fructosamine testing annually at about 10 years of age, earlier if there is a family history.
- Intensify/re-evaluate iron chelation therapy, considering combining agents, to normalize iron load evaluated using cardiac and hepatic MRI.
- Measure fructosamine levels every 6 months to identify trends in glycemic control; HbA1c and glycated Hb testing are unreliable in TDT.
- Individuals with symptoms of hyperglycemia (thirst, polyuria, polydipsia or Candida infections) should have plasma glucose and fructosamine levels measurements done immediately.

Multidisciplinary team management: Treatment

- Instruct patient/family how to test blood glucose at home to monitor glycemic control and how to identify hypoglycemia or severe hyperglycemia.
- If glucose metabolism disorder is diagnosed, provide patient/family with information on healthy lifestyle initiatives (appropriate diet, regular activity, weight control, high fiber diet).
- Manage patient according to treatment targets and recommendations for type 1 and type 2 diabetes.

Cardiovascular

Hypertrophic cardiomyopathy and heart failure remain a common cause of death in patients with TDT and are caused by both disease and treatments such as the accumulation of iron in the heart resulting from frequent blood transfusions, hemolysis, increased iron absorption in the intestines, and a lack of iron excretion mechanisms in the body (Ali 2021; Taher 2021). Cardiac arrythmias such as chronic atrial fibrillation are also common cardiac manifestations of SCD. Today, the widespread use of iron chelation to prevent excessive iron loading has allowed patients to survive into older age, although the considerable cardiovascular issues they experience require continued monitoring and treatment (Walker 2025).

Generally speaking, cardiovascular complications are primarily associated with iron stores and chronic anemia (**Table 4**).

Multidisciplinary team management: Monitoring

- Routine clinical checkups involving a multidisciplinary team and assessment of overall cardiac function to identify and treat problems early.
- Children should be referred for their first extensive cardiac evaluation between ages 6 and 8; assessments thereafter should be at intervals according to symptoms and adequacy of chelation
- Monitor iron concentration in the heart to establish cardiovascular problems. MRI is recommended to assess cardiac iron load, but may not be widely available, especially in resource-poor countries. Serum ferritin measurements are more readily available in most clinics.
- Echocardiogram (ECG)
- 24-hour Holter or exercise test
- Right heart catheterization
- CT scan angiography
- Screening and treatment of endocrine and metabolic comorbidities to prevent and manage cardiovascular disorders
- Multidisciplinary team management: Prevention

- Maintain a pre-transfusion hemoglobin value of 10 g/dL and
- Regular administration of an effective iron chelation therapy regimen.
- Multidisciplinary team management: Treatment
- Iron chelators are efficient at lowering iron load. Therefore, it is important to assess adherence to this therapy if serum ferritin levels are increasing or at high levels.
- Instruct and encourage patients to undergo routine cardiovascular examinations and to report any symptoms of cardiovascular disease (i.e., shortness of breath, sensation of a "racing" heart rate, chest pain, chest tightness, dizziness, pain or numbness in the legs or arms) to healthcare staff and to discuss any concerns with healthcare staff.
- Reassure patient/family that cardiac dysfunction may be reversible through the implementation of timely therapy and the importance of consulting healthcare services in the event of symptoms
- Discuss preventative measures with patient/family including

o Management of comorbid conditions

o Lifestyle adaptations such as regular physical activity, maintaining a normal body weight, eliminating the intake of alcohol, smoking abstinence.

Liver/hepatic diseases and hepatocellular carcinoma

Liver disease is one of the major causes of mortality in TDT. Chronic deposits of iron in the liver promote liver fibrogenesis and chronic liver disease leads to cirrhosis. Cirrhosis may also be caused or exacerbated by viral hepatitis B (HBV) and C (HCV) infections (Taher 2018; Fung 2023). Hepatic iron overload and chronic hepatitis C virus infection may synergize to worsen liver damage, and both are risk factors for the development of hepatocellular carcinoma.

Hepatocellular carcinoma

Hepatocellular carcinoma is the most prevalent malignancy in TDT and death from hepatocellular carcinoma has become more prevalent and has surpassed deaths from cardiac disease in these patients (Origa 2025; Walker 2025).

The treatment of hepatocellular carcinoma in this population is the same as that for the general population. A diagnosis of TDT is no longer considered a contraindication to liver transplant as a treatment option in patients without severe pulmonary hypertension or subclinical heart failure.

Multidisciplinary team management: Monitoring

- Monitor liver function tests every 3 months or every month if results are > 5 times the upper limit of normal
- Liver ultrasound every year or every 6 months if abnormal
- Perform physical examination to assess signs of iron excess such as skin pigmentation and hepatomegaly or ascites in later stages of liver disease
- Laboratory tests: aminotransferases, aspartate transaminase (AST), alanine transaminase (ALT). Prolonged prothrombin time, low albumin, high serum bilirubin in severe hepatic impairment.
- Early diagnosis of hepatocellular carcinoma is key to achieving favorable outcomes; screening using ultrasound, fibroscan, and alpha fetoprotein (AFP) evaluation should be performed every 6 months.

Multidisciplinary team management: Treatment

- Consultation with hepatologist
- Optimize iron chelation
- Optimize administration of antiviral agents in the presence of viral hepatitis
- Assess patient adherence to chelation
- Educate patient/family on the importance of regular screening for hepatocellular carcinoma and provide information on centers where this can be performed.

Bone disease

Bone disease greatly contributes to morbidity in individuals with thalassemia and can be caused by inadequate transfusion, deferoxamine (DFO) use, failure to reach peak bone mass and progressive bone thinning in adults. Inadequate transfusion can lead to deformities of the skull and face. Reduced bone mass density can be caused by bone marrow expansion and iron overload, effects of thalassemia, and by secondary factors such as endocrine, liver, and renal disorders, or by nutritional deficits and a lack of physical activity (Casale 2025). Sarcopenia leading to bone fragility and fractures may be an underrepresented risk factor for bone disease.

Multidisciplinary team management

- Educate patient/family on need for adequate dietary calcium intake; dietary modification should be explored as the first option to achieve target intake, zinc supplementation (Piga 2017).
- Educate patient/family on following healthy lifestyle changes that promote achievement of peak bone mass and maintenance of bone mass density: smoking cessation, avoid excessive alcohol consumption,

undertake weight-bearing exercises (UKTS 2023), sunlight exposure.

- Timely administration of blood transfusions to prevent irreversible deformities associated with bone marrow expansion
- Monitor DFO to maintain doses at a safe range to minimize risk of bone toxicity
- Timely diagnosis and treatment of hypogonadism and other endocrinopathies
- Consider bisphosphonates and other bone specific agents in patients with deteriorating bone mass density/osteoporosis
- Monitor vitamin D levels after age 2 every 3 to 6 months and provide supplements if needed
- Initiate fracture prevention interventions in individuals at risk of falling such as older patients (i.e., education on establishing a safe home environment, exercises/therapy to improve muscle strength/mass).

Bone pain

Bone pain is a common complaint that adversely affects HRQoL in individuals with thalassemia. Sites of pain include the lower back, mid-back, legs and head, and may be localized or of a more generalized nature (Oliveros 2013).

Pain may be acute or chronic, may be underrecognized by healthcare professionals, and severity may increase with age.

Multidisciplinary team management

- Assessment of pain to identify cause, if possible.
- Assess the severity and frequency of pain and its interference in daily activities.
- Administration of analgesics in a stepwise method beginning with non-opioid drugs and nonsteroidal anti-inflammatory drugs and progressing to strong opioids as required for pain relief. Instruction on and initiation of non-pharmacological and cognitive methods may be beneficial in some patients.

Dental complications

Most dental manifestations of thalassemia are manageable and may be preventable through monitoring and early recognition. Unfortunately, awareness of dental complications among dental practitioners is limited in many areas of the world. Hence, within the scope of providing quality of care, it is essential that dental practitioners consult with or refer patients to hematology specialists when extensive dental procedures are required.

Numerous orofacial manifestations of thalassemia, although rare nowadays, may occur (**Box 6**). While these changes are not necessarily life-threatening, they are closely linked to overall health and HR-QoL.

Medication-related osteonecrosis of the jaw is associated with anti-resorption therapy (such as bisphosphonates) used in TDT and can develop spontaneously or following oral surgery. Before starting antiresorptive therapy, patients should undergo dental screening with extraction of teeth in poor condition, adjustment of any oral prostheses and receive advice on oral hygiene and smoking cessation. There is no conclusive evidence for the efficacy of any intervention to manage medication-related osteonecrosis of the jaw.

Box 6. Orofacial manifestations

Changes in facial/jaw bones: enlargement of the upper jaw, maxillary sinus reduction/nasal obstruction, medication-related osteonecrosis of the jaw
Teeth: delayed dental development; changes in dental morphology, teeth discoloration, varying degrees of malocclusion (i.e., overbite), dental caries, migration and spacing of upper anterior teeth, dental decay
Soft tissues: pale gingivae and oral mucosa, discolored gingivae, painful swelling of salivary glands and dry mouth, sore/burning tongue
Sources: Kumar 2025; UKTS 2023

Multidisciplinary team management

- Involve healthcare professionals from multiple disciplines including hematologists and pediatricians in the patient's care.
- Perform a risk assessment prior to invasive dental intervention followed by appropriate individualized treatment interventions.
- Encourage patient/parents to seek out and maintain regular, preventive dental care.
- Advise patients to report any adverse symptoms such as loose teeth, pain or swelling as soon as possible.
- Reinforce oral care including the use of fluoride toothpaste.
- Initiate urgent care measures including antimicrobial therapy in individuals with acute dental infections/ abscesses (UKTS 2023; Kumar 2025).

Other health-related complications

TDT is a complex disease with numerous long-term effects on various bodily systems (**Table 5**). These problems are primarily attributed to suboptimal anemia and/or iron overload management or to the side effects of treatments (El-Beshlawy 2024). The list of real and potential co-morbidities and complications in TDT is long -- and too

lengthy to adequately address in this module. Readers are referred to the UK Standards for the Clinical Care of Children and Adults Living with Thalassemia in the UK and the Guidelines for the Management of Transfusion-Dependent Beta-Thalassemia (TDT) from the Thalassemia International Federation for a full list of disease- and treatment-related complications of TDT.

Table 5. Common Complications of TDT

Complication	Etiology and risk factors	Management strategies
Gall stones	Infection/inflammation of the gallbladder and biliary duct; increasing age	Removal of the gall bladder via laparoscopy
Leg ulcers	Increasing age, iron overload, hypercoagulability, splenectomy	Regular inspection/screening for dermatological manifestations or leg ulcers; Good wound hygiene, compression therapy if appropriate, management of complications such as pain and infections. Administration of CSGF. Provide advice on lifestyle changes to promote healing and ↓ recurrence such as regular walking, avoiding leg trauma, use of emollients. Referral to dermatology or plastic surgery for skin grafting if needed.
Ophthalmological manifestations	Manifestations include ocular surface changes (i.e., dry eyes), lens opacification, DFO retinopathy (i.e., night blindness). Etiologies include underlying disease, iron overload/iron chelation therapy	Referral to ophthalmologist, close ophthalmological monitoring in patients on continuous IV DFO,
Renal disease	Renal stones caused by increased risk of hypercalciuria. Renal glomerular dysfunction due to underlying disease/iron overload. Iron chelation can cause renal injury.	Routine assessment of renal function, monthly in patients on DFX. Consultation with renal specialist
Extramedullary hematopoiesis	Suboptimal transfusional support. Symptoms correspond to site of the mass and its effect on adjacent organs.	↑ blood transfusions to suppress ineffective erythropoiesis. Administration of hydroxyurea, low-dose radiation therapy, decompressive surgery or paraspinal masses.
Infectious disease	HCV and associated liver disease. Great variability of types of infection depending on geographic location & accessibility to healthcare. Other causes: iron overload, ineffective erythropoiesis, hemolysis, anemia, splenectomy, blood transfusions, stem cell transplantation.	Leucodepletion of packed red blood cell units. Educate splenectomized patients on increased risk of infections, how to avoid them, and actions to take in case of infection. Vaccination against HBV, influenza, pneumococcal and meningococcal infections. Prophylactic antibiotic therapy in patients undergoing splenectomy. Good personal hygiene, phlebotomy site disinfection.
Fatigue	Oral chelation treatment, anemia, psychosocial causes.	Encourage regular physical activity, advise patients to plan and prioritize daily activities, and drink plenty of water/tea. Pharmaceutical agents: luspatercept

CSGF, colony stimulating growth factor; DFO, deferoxamine; DFX, deferasirox; HBV, hepatitis B virus; HCV, hepatitis C virus; IV, intravenous

References

Ali S, Mumtaz S, Shakir, HA, et al. Current status of beta-thalassemia and its treatment strategies. Mol Genet Genom Med 2021; 9:e1788.

Alshurafa A, Soliman AT, DeSanctis V, et al. Clinical and epidemiological features and therapeutic options of avascular necrosis in patients with sickle cell disease (SCD): a cross-sectional study. Acta Biomed 2023; 94(5). DOI: 10.23750/abm.v94i5.14603.

American Stroke Association. Sickle cell disease and pediatric stroke risk. 2024. Available at: Sickle Cell Disease and Stroke | American Stroke Association. Accessed March 2025.

Arduini GAO, Trovo de Marqui AB. Prevalence and characteristics of priapism in sickle cell disease. Hemoglobin 2018; 42:73-77.

Baker C, Grant AM, George MG, et al. Contribution of sickle cell disease to the pediatric stroke burden among hospital discharges of African Americans 1997-2012. Pediatric Blood Cancer 2015; 62:2076-2081.

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 Advances 2020; 4(12):2656-2702.

Brandow AM, DeBaun MR. Key components of pain management for children and adults with sickle cell disease. Hematology/Oncology Clinics of North America 2018; 32:535-550

Brousseau DC, Owens PL, Mosso AL, et al. Acute care utilization and rehospitalizations for sickle cell disease. JAMA 2010; 303:1288-1294

Carroll CP, Haywood C, Fagan P, Lanzkron S. The course and correlates of high hospital utilization in sickle cell disease: evidence from a large, urban Medicaid managed care organization. Am J Hematology 2009; 84:666-670

Casale M, Baldini M, Giusti A, et al. Growth Abnormalities, Endocrine, and Bone Disease. In: Guidelines for the Management of Transfusion-Dependent β-Thalassemia (TDT), 5th Edition, 2025. Taher AT, et al (ed). Thalassemia International Federation, Cyprus.

Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Advances 2020; 4:327-355.

Dampier C, et al. AAPT diagnostic criteria for chronic sickle cell disease pain. Journal of Pain 2017; 18(5):490-498.

Day ME, Rodeghier M, DeBaun MR. Children with HbSβ^0 thalassemia have higher hemoglobin levels and lower incidence rate of acute chest syndrome compared to children with HbSS. Pediatr Blood Cancer. 2018; 65(11):e27352.

DeBaun MR Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Advances 2020; 4(8):1554-1588.

De Silva Junior GB, et al. Osteoarticular involvement in sickle cell disease. Revista Brasileira de Hematologia e Hemoterapia Journal 2012; 34(2):156-164.

El-Beshlawy A, Dewedar H, Hindawi S, et al. Management of transfusion-dependent beta-thalassemia (TDT): expert insights and practical overview from the Middle East. Blood Review 2024; 63:101138.

Ezenwa MO, Molokie RE, Wang ZJ, et al. Differences in sensory pain, expectation, and satisfaction reported by outpatients with cancer or sickle cell disease. Pain Management Nursing 2018; 19:322-332.

Ezenwa MO, Molokie RE, Wilkie DJ, et al. Perceived injustice predicts stress and pain in adults with sickle cell disease. Pain Management Nursing 2015; 16:294-306.

Field JJ, Stocks J, Kirkham FJ, et al. Airway hyperresponsiveness in children with sickle cell anemia. Chest 2011; 139:563-568.

Forni GL, Giansin B, Musallam KM, et al. Overall and complication-free survival in a large cohort of patients with beta-thalassemia major followed over 50 years. American Journmal of Hematology 2023; 98:381-387

Friend A, Settelmeyer TP, Girzadas D. Acute Chest Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. PMID: 28722902.

Fung EB, Schryver T, Angastiniotis M. Nutrition in thalassemia & pyruvate kinase deficiency: a guideline for clinicians. Thalassemia International Federation 2023

Haywood C, Diener-West M, Strouse J, et al. Perceived discrimination in health care is associated with a greater burden of pain in sickle cell disease. Journal of Pain and Symptom Management 2014; 48:934-943.

Howard J, et al. Guideline on the management of acute chest syndrome in sickle cell disease. British Journal of Hematology 2015; 169(4):492-505.

Jain S, Bakshi N, Krishnamurti L. Acute chest syndrome in children with sickle cell disease. Pediatric Allergy, Immunology, and Pulmonology, 2017;30:191–201.

Kato G, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. Journal of Clinical Investigation 2017; 127:750-760.

Kavanagh PL, Fasipe TA, Wun T. Sickle cell disease: a

review. JAMA 2022; 328:57-68.

Kumar N, Hattab FN. Oral and Dental Care. In: Guidelines for the Management of Transfusion-Dependent β-Thalassemia (TDT), 5th Edition, 2025. Taher AT, et al (ed). Thalassemia International Federation, Cyprus.

Lanzkron S, et al. The burden of emergency department use for sickle-cell disease: an analysis of the national emergency department sample database. American Journal of Hematology 2010; 85(10):797-799.

Liem RI, Lanzkron S, Coates D, et al. American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease. Blood Advances 2019; 3:3867-3897.

Makis A, Voskaridou E, Papassotiriou I, Hatzimichael E. Novel therapeutic advances in beta-thalassemia. Biology (Basel) 2021; 10:546. doi: 10.3390/biology10060546.

National Academies of Sciences, Engineering, and Medicine. Addressing sickle cell disease: A strategic plan and blueprint for action. Washington, DC: The National Academies Press, 2022.

Oliveros O, Trachtenberg F, Haines D, et al. Pain over time and its effects on life in thalassemia. American Journal of Hematology 2013 88. doi: 10.1002/ajh.23565.

Opoku-Asare B, Ntim OK, Awere-Duodu A, Donkor ES. Sickle cell disease and antimicrobial resistance: a systematic review and meta-analysis. Infec Dis Rep 2025; 17:32

Origa R, Gianesin B, Zappu A, et al. Luspatercept for transfusion-dependent beta-thalassemia: real-world experience in a large cohort of patients from Italy. Am J Hematol 2025; 100:1651-1655

Palmert MR, Dunkel L. Clinical practice. Delayed puberty. New England Journal of Medicine 2012; 366:443-453.

Piel FB, Rees DC, DeBaun MR, et al. Defining global strategies to improve outcomes in sickle cell disease: a Lancet Haematology Commission. Lancet Haematolog 2023; 10:e633-686.

Piga A. Impact of bone disease and pain in thalassemia. Hematology Am Soc Hematol Educ Program. 2017; 2017(1):272-277.

Ruffo GB, Russo R, Casini T, et al. Nephrological complications in hemoglobinopathies : SITE Good Practice. J Clinical Medicine 2023; 12:7476

Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. Annals of Internal Medicine 2008; 148(2):94-101

Taher AT, Farmakis D, Porter JB, Cappellini MD, Musallam KM. Guidelines for the Management of Transfusion-Dependent β-Thalassaemia (5th edition). Thalassaemia International Federation 2025. Available at: Guidelines for the Management of Transfusion-Dependent β-Thalassaemia (5th edition – 2025) – TIF

Taher AT, Musallam KM, Cappellini MD. Beta Thalassemias. NEJM 2021; 384:727-743

Taher AT, Cappellini MD. How I manage medical complications of beta-thalassemia in adults. Blood 2018; 132:1781-1791.

Tanabe P, Spratling R. Smith D, et al. Understanding the complications of sickle cell disease. American Journal of Nursing 2019; 119(6):26-35.

Tarim HS, Öz F. Thalassemia major and associated psychosocial problems: a narrative review. Iran Journal of Public Health 2022; 51:12-18.

United Kingdom Thalassemia Society (UKTS). Standards of the Clinical Care of Children and Adults living with Thalassemia in the United Kingdom, 4th Edition. 2023. Available at Standards-for-the-Clinical-Care-of-Children-and-Adults-Living-with-Thalassaemia-in-the-UK-4th-Edition-2023.pdf.

Walker JM, Farmakis D. Cardiovascular Disease. In: Guidelines for the Management of Transfusion-Dependent β-Thalassemia (TDT) 5th Edition, 2025. Taher AT, et al (Ed). Thalassemia International Federation, Cyprus.

Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 10:1033-1048.

Quick Facts

- Acknowledging the challenges faced by those with sickle cell disease and transfusion-dependent thalassemia can help to improve quality of life and emotional wellbeing of these patients.
- Patients and their caregivers need education and support so that they can manage their health alongside their normal lives.
- Young people should be supported and encouraged to take responsibility for their self-care management and healthcare choices.
- A quality-of-life (QoL) assessment should form part of the regular evaluation of each patient's progress and may be useful to highlight actual and potential problems
- Helping patients to define a personal "healthy lifestyle" includes exploring with them what makes her/him feel good and what brings her/him happiness
- Older patients, regardless how mild their disease- and treatment-related symptoms may be, continuously experience some degree of chronic end-organ deterioration, the rate of which is determined by the genotype of their disease, genetic background, lifestyle, healthcare access, and environment

Module VIII: Providing Support for Patients and their Caregivers

Contents:

Effects of Disease and Treatment on Health-related Quality of Life

While patients with optimally treated sickle cell disease (SCD) and transfusion-dependent thalassemia (TDT) can now expect to live a near-normal life and lifestyle, globally, treatment and care are suboptimal in many countries. The lives of affected individuals are impacted by sociocultural and socioeconomic factors, which can exacerbate the disease's impact, especially for those from racial and ethnic minority groups (National Academy of Sciences 2022). The complications associated with disease and treatment may impact the mental health of individuals living with SCD or TDT by increasing the risk of depression and profoundly challenging coping skills. In children and adolescents, educational achievement may be compromised, and for adults, employment prospects and maintaining employment. Hence, the provision of psychosocial care is an essential component of holistic care for individuals with a hemoglobin disorder. It can help individuals and caregivers to cope with the emotional impact of their disorder, reduce anxiety and depression, and improve quality of life (QoL) (UKTS 2023).

All members of the multidisciplinary team should consider the psychosocial, anthropologic, and supportive needs of these patients. Further, when providing care, the family context and developmental/life stage of the individual should be taken into consideration to ensure that care and treatment recommendations are individually tailored to and appropriate for each patient. In addition to the physical, the psychosocial symptoms of the disorder and its impact on family, relationships, emotional wellbeing and QoL, the child or adult must also cope with invasive, complex and demanding treatments, frequent hospital visits, and a lifelong reliance on healthcare services.

The diagnosis of SCD combined with lower socioeconomic status may negatively affect outcomes. Disease-related complications may affect the mental health of individuals with SCD by increasing the risk of depression and overwhelming available coping resources. Depressive disorders in adolescents and adults with SCD range from 20% to 57% and 6% to 29% report anxiety disorders, rates that are higher than in the general population (Treadwell 2023). Children and adolescents may have difficulty achieving their academic goals and adults may find it difficult to maintain employment. For some, living with SCD is similar to experiencing recurrent episodes of psychological trauma (Wilson 2023).

Not surprisingly, thalassemia, especially TDT, and treatments for thalassemia (i.e., transfusions and chelation therapy) can have a considerable impact on the QoL of adults. Compared with the general population, adults with TDT were found to have worse physical, emotional, and social function health-related quality of life (HRQoL) scores (Gan 2016; Scalone 2008). Furthermore, anxiety, depression and perceived barriers to treatment, including the difficulties and expenses associated with ongoing treatment, are significant negative predictors of the level of HRQoL in adult patients (Maheri 2020).

Children and adolescents

Children are vulnerable to emotional and behavioral problems due to the stressful conditions they experience. For example, school-aged children may miss school due to treatment schedules or disease side effects, which leads to behavioral health complications. An often-overlooked psychosocial issue that affects QoL in children and adolescents is the stigma of having SCD or TDT. Fear of being discriminated against may interfere with a child's wish to be a part of a school or social group.

Some strategies to improve QoL and decrease feelings of depression and isolation in children and adolescents include providing relatively simple psychological interventions such as

- teaching children about the disorder and treatment in an age-appropriate manner,
- demonstrating techniques for managing stress and promoting relaxation exercises,
- providing help to control negative emotions,
- encouraging interactions and communication with friends and peers,
- helping with scheduling of medical visits and transfusions so as not to interfere with school and social activities.

Self-help programs available on the internet may also be valuable in helping young patients better cope with their situation.

Adolescents and young adults may experience a lowered health-related quality of life (HRQoL) related to delayed growth and puberty or social isolation. If cognitive or developmental problems are suspected, a referral should be made to clinical psychology and a further referral made, if necessary, to a specialist neuropsychologist.

Adults

In adults, anxiety, depression and perceived barriers to treatment, including the difficulties and expenses associated with ongoing treatment, are significant negative predictors of the level of QoL (Maheri 2020).

Interventions to help adults cope with their situation include:

- Routine screening and questioning about feelings of depression, anxiety, and other social and behavioral determinants of health.
- Inquire about possible financial challenges including payment for medications and refer to financial resources as appropriate.
- Refer to social worker or case manager for assistance with health insurance, arranging travel, housing, and employment issues.

A QoL assessment should be a part of the regular evaluation of each patient's progress. Various tools that are easy to administer and have been validated in clinical studies are available to assess QoL. Results of the assessment should be shared with members of the multidisciplinary team to identify real and potential problems and develop appropriate interventions. Examples of tools are:

- TranQoL (Transfusion-dependent Quality of Life Questionnaire)
- PedsQL TM (Pediatric Quality of Life Inventory TM)
- World Health Organization Quality of Life Tool
- SF-36 (Short Form Survey Instrument to measure health-related quality of life).

Individuals and their caregivers face continued physical and psychosocial challenges, some of which deal with these individuals reclaiming their responsibility to improve and maintain their health and to attain and maintain an equal partnership in their care. Patient empowerment is defined as a process through which people gain greater control over decisions and actions affecting their health'(World Health Organization). Empowering patients through tailored educational interventions, establishing open two-way communication in which listening rather than doing on the part of the healthcare professional is emphasized, actively engaging patients in their care, acknowledging patient preferences and values are examples of supporting patient empowerment (Wakefield 2018). In this light, also recognizing when patients do not desire complete honesty in the context of life-limiting illness is also important in terms of empowerment (**Fig.1**). Empowering patients and their caregivers to be actively involved in decision-making and health management is crucial to reinforce their self-identity and to support them on their journey.

Parents and caregivers

The diagnosis of a child with SCD or TDT is a challenging time for families and appropriate support should be available to enable the family to discuss any issues or problems they may be experiencing.

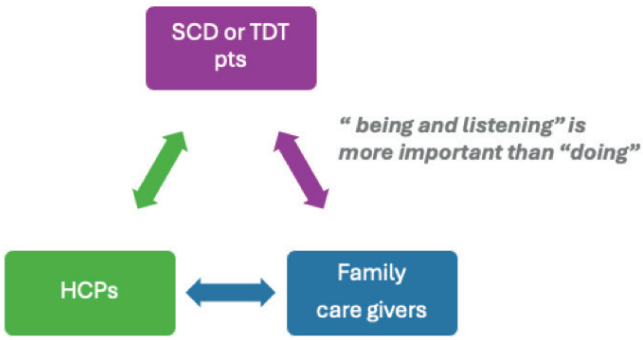


Figure 1. Empowering patients during their patients' journey, maintaining functional communication between patients, health care providers (HCPs) and family/care givers (Wakefield 2018).

The mental health challenges experienced by caregivers for children living with SCD or TDT have not been extensively studied. Some of these challenges are:

- Watching a child be uncomfortable, in pain, or suffering in any way
- Financial and psychological problems
- Chronic nature of SCD and TDT
- Schedules and complications of treatments
- Lack of social support network/social contacts
- Lack of sufficient healthcare services
- Uncertainty of the patient's future
- Overcoming the stigma of SCD and TDT present in some cultures
- Feelings of guilt caring for a sick child and not spending sufficient time with other family members (Punaglom 2019; Yousuf 2022).

Strategies to support parents and caregivers:

- Work to establish a strong and trusting relationship with parents/caregivers
- Ensure that parents/caregivers have an adequate understanding of SCD and TDT
- Refer parents/caregivers to support groups and encourage them to practice spirituality and religiosity if these activities are important to them
- Refer parents/caregivers to sources for information about financial assistance

Box 1. Strategies to help patients, family, and caregivers live better with SDC and TDT

- Members of the multidisciplinary team should be aware of the importance of cultural influences on health.
- The psychosocial needs and challenges faced by affected individuals across their lifespans should be prioritized to provide comprehensive and effective care
- Specialist psychological support should be made available at critical milestones including initial diagnosis, first transfusion, puberty, transition to adult care, and at other major life events such as university entrance, first employment, marriage, pregnancy and parenthood.
- The opportunity for patients to meet one another at specialist facilitated support groups should be provided.
- Changes in treatment should be discussed with the patient/caregiver in full providing rationale and reasons for any change made. Information on treatment options, including benefits or disadvantages, should also be discussed in full.
- Support networks should be present and involved when presenting difficult news to the individual. The multidisciplinary team should be aware of and prepared for the possibility of depression, suicidal thoughts, and self-harm in response to bad news.

Fostering a Healthy Lifestyle

A healthy lifestyle is important: a healthy lifestyle for individuals with SCD or TDT also means managing the disorder. Both disorders can be well-managed when the patient/caregiver understands the importance of receiving regular medical care and adhering to medication and transfusion schedules to lower their risk of developing complications. Other aspects of a healthy lifestyle are keeping vaccinations up-to-date, eating a well-balanced diet (see next section), exercising, and connecting and interacting with people and contributing to society (Angastiniotis 2025).

Vaccinations: Young children, older children and adolescents should receive scheduled vaccinations and any other vaccines as recommended by their primary healthcare provider. Adults should regularly receive influenza vaccinations.

Exercise: Regular physical activity is part of an overall healthy lifestyle and helps lead to better health outcomes. Some types of vigorous forms of exercise may not be possible, but most children and adults can participate in moderate physical activities including biking, running, walking, yoga, and swimming.

Relationships: Adolescents and young adults may not enter into intimate relationships because of the fear of being viewed differently. However, having and participating in supportive relationships is an important part of life. Friends, including co-workers, classmates, and family members can offer help in managing SCD and TDT and with coping with the stress of daily life.

Education: Attending school or university is a useful step towards social integration. Family support and a sound clinical state help the patient to be a successful student. Some countries provide financial assistance for educational expenses for students with SCD or TDT.

Feeling good about oneself (i.e., being happy, content, having a sense of purpose, and having self-esteem) and being integrated socially are important components of an overall sense of wellbeing. Social isolation, marginalization, and discrimination, either perceived or real, are associated with poor psychosocial and mental health outcomes.

Other actions to support patients in choosing a healthy lifestyle:

- Encourage the patient to assume responsibility for their own health status (i.e., taking medications as prescribed, taking measures to avoid infections)
- Encourage the patient to seek out activities that strengthen their spiritual growth
- Work with the patient to identify stress-causing events and actions that may help to reduce stress in their daily life (i.e., identifying and pursuing activities that bring them joy, deep breathing relaxation techniques, listening to relaxing audio tapes, talking with a counselor)
- Help patient to define a personal "healthy lifestyle": what makes her/him feel good and what brings her/him happiness -- and to enjoy a treat occasionally.

Nutrition

The importance of a nutritionally sound dietary intake is largely under-recognized in SCD and TDT and nutritional deficit can occur in a considerable number of patients Malnutrition in these populations varies greatly by country of origin with low- and middle-income countries having the highest prevalence of malnutrition (Fung 2023). There are numerous and serious consequences of malnutrition such as growth failure, delayed pubertal development, inadequate immune function and insulin secretion, and altered lipid profiles (Fung 2023). In SCD, micronutrient deficiencies have been linked to an increase in acute pain episodes (Darbari 2020). An adequate diet, in terms of both caloric intake and dietary quality (i.e., micronutrient content) is a prerequisite to adequate growth and the maintenance of optimal health. Nutritional deficit, on the other hand, is multifactorial and may include cultural and economic factors as well as individual preferences and tolerances.

An improved strategy for nutritional support should

be part of the broader commitment to enhancing the general well-being of these individuals. First and foremost, dieticians should be active members of the multidisciplinary team providing care.

Box 2. Recommendations to achieve adequate nutritional intake

- Routine screening of patients for malnutrition/risk of malnutrition by healthcare professionals with appropriate skills and training
- Patients identified as at high risk for developing nutritional deficits should be offered nutritional assessment by a dietician or nutritionist and a nutritional management care plan should be developed
    - o Variables that may impact nutritional status such as infection risk, dehydration, frailty, gastrointestinal disturbances, and medical treatments (transfusion treatment, iron overload) should be considered when developing a dietary plan
- Routinely measure parameters related to growth and nutrition.
- Educate patients/caregivers on the importance of a varied, nutrient-dense diet rich in antioxidants (fruits and vegetables).
- Zinc supplementation for patients with zinc deficiency, poor growth, reduced bone mass
- Vitamin D supplements for patients with vitamin D deficiency
- A daily multivitamin/mineral supplement may be beneficial in some patients but should not replace a well-balanced, healthy, nutrient-dense dietary intake.

A note of caution for individuals with TDT. Some foods are naturally high in iron while others may be fortified with iron. Iron can be found in meat, fish, and some vegetables (e.g., spinach). Other products, like cereal and orange juice, may contain extra iron.

Transitioning from Pediatric to Adult Healthcare Services

Transition is defined as the purposeful, planned process that addresses the medical, psychosocial, educational, and vocational needs of adolescents and young adults with chronic medical and physical conditions as they move from child-centered to adult oriented healthcare systems (Blum 1993). This time of transition can be a high-risk time for non-engagement with services and non-adherence to therapy. In most cases, transition corresponds to physical, biological, developmental and psychosocial changes related to adolescence.

The transition from pediatric to adult care is a difficult and inconsistent process for young people with a hemoglobinopathy. Often the transition is accompanied by obstacles such as a lack of support and resistance on the part of the young person. Subsequently, the young person often does not keep follow-up appointments with the new healthcare service and may return to pediatric providers or turn to emergency care services. Missed appointments can lead to irreversible, preventable complications and even death (Bell 2007).

Young people may experience concerns about facing the transition to adult care. Some of these concerns are associated with leaving the pediatric healthcare provider, meeting new providers, the competence and expertise of the new providers, continuity of care, and flexibility of the transition process, including adequate preparation from providers (Bryant 2011). The study conducted by Bryant revealed that youth experienced feelings of sadness and fear of the unknown about transitioning into an unfamiliar adult environment. Some youth acknowledged that they felt pushed into transitioning to adult care without proper transitional preparation (Bryant 2011). On the other hand, parents may be reluctant to release control over the youth's medical care and have concerns over the youth's medication adherence after transition to adult care.

To ease the transition process, Bryant (2011) recommends beginning a conversation with the young adult long before the transfer to adult care actually takes place, as early as age 12 (UKTS 2023). Because of feelings of isolation during the transition process, peer mentoring, where an older peer with experience provides support and guidance, can be helpful.The advance practice nurse is in an ideal position to initiate consistent care and education in this setting. To achieve best outcomes, the multidisciplinary team should invest time and be committed to patients and families during transition.

The "Got Transition" program (White 2020) recommends the following interventions to support young adults and their parents/caregivers transitioning to an adult healthcare provider. Suggestions for implementing an individualized and comprehensive transition are provided in Table 1

Suggestions from the nursing literature on assisting young patients to adjust to adult care include:

- Scheduling a portion of a medical visit without the parent/caregiver present to build healthcare autonomy
- Encouraging the expression of fears and anxieties related to transitioning
- Providing education on diagnosis, treatment, and preventative measures directly to the young adult to encourage responsibility for self-care
- Encouraging the participation of the young adult in discussions related to treatment decisions (Bryant 2011).

Table 1. Recommendations to Facilitate Transition from Pediatric to Adult Care	
Stage of transition	**Actions**
Assessment of transition readiness	Conduct regular transition readiness assessments, beginning at about age 14 to 16, to identify and discuss with young person and parent/caregiver their needs for self-care and how to use healthcare services. Offer education and resources on needed skills identified through the transition readiness assessment.
Transition planning	Develop and regularly update the plan of care including readiness assessment findings, youth's goals and prioritized actions, nursing care plan, medical summary and emergency care plan. Individualize plan to reflect personal and cultural preferences. Prepare youth and parent/caregiver for an adult approach to care including legal changes in decision-making and privacy and consent, self-advocacy, and access to information. Determine need for decision-making support, make referral to legal resources if needed. Plan with youth optimal timing of transfer to adult services. Take cultural preferences into account throughout transition planning.
Transfer of care	Prepare documents for transfer, including final transition readiness assessment, plan of care with transition goals, medical and nursing reports, and legal documents (if needed). Confirm role of pediatrician for care until young person is seen by an adult care provider.
Transition follow-up	Contact youth and/or parent/caregiver to confirm attendance at first adult appointment. Confirm completion of transfer with adult care provider.
Adapted from: White 2020	

Challenges in Older Adults with Sickle Cell Disease and Transfusion-Dependent Thalassemia

Because of well-established standardized treatment and advancements in understanding SCD and TDT, significant improvement has been seen in the survival of patients with these disorders of hemoglobin. However, age-related complications associated with both SCD and TDT, which were uncommon in the past, are now emerging and presenting challenges for healthcare providers as well as the affected individuals and their caregivers (**Table 2**). A longitudinal study of patients with SCD showed that approximately one-half of patients in their fifth decade had some form of irreversible damage of lungs, kidneys, brain, retina, or bones significantly affecting their QoL (Powars 2005). This indicates that patients with these disorders, regardless how mild their disease- and treatment-related symptoms may be, continuously experience some degree of chronic end-organ deterioration, the rate of which is determined by the genotype of their disease, genetic background, lifestyle, healthcare access, and environment (Shet 2019). Similarly, as the population of individuals with TDT grows older, previously not well described complications, such as hepatocellular carcinoma and atrial fibrillation (Taher 2018) as well as liver fibrosis and cirrhosis (UKTS 2023) are now increasing in frequency.

Older patients with SCD and TDT require greater support to address the many disease-related complications emerging as they age, in addition to conditions common to physiologic aging (Thein 2018). Not only patient-centered challenges, but also a lag in recognition of the growing population of older adults with hemoglobinopathies and insufficient resources available to manage these individuals means that they do not consistently receive recommended adequate, appropriate care (Shet 2019).

Older patients should be closely monitored at regular intervals. Patients who are stable and then present with worsening of their disease should be astutely assessed for the presence of new comorbidities. Coexistence of other chronic diseases, especially if poorly controlled, may lead to worsening of SCD or TDT. As is the case for older individuals without a hemoglobinopathy, medications should be reviewed routinely and dose adjustments made as appropriate, and their social environment regularly assessed.

Table 2. Complications in Older Patients	
Age-related complications	**Management**
Any clinical complication	Close, regular monitoring of older patients to achieve early detection and intervention. Referral to specialists.
Cardiovascular disease remains a significant cause of morbidity; arrhythmias are becoming more prevalent in adults who have exhibited iron overload in the past.	Provide education on signs/symptoms of cardiovascular disease and when to seek medical attention. Treatment of arrhythmias according to standard practice in the general population.
Bone disease is caused by numerous factors and is related to a significant decrease in a patient's QoL due to pain and limitations in mobility.	Vitamin D, calcium, bisphosphonates supplementation. Physical therapy. Assessment of pain and impact on activities of daily living; help patients to prioritize activities, take analgesics as prescribed
Risk of cancer (hepatocellular carcinoma, other solid and hematologic tumors)	Provide patient/caregiver with information on risk; advise to get regular check-ups and cancer screening/early detection tests. Treatment as in general population.
Renal dysfunction	Assess for comorbidities such as hypertension and diabetes. Early recognition is essential⟶ regularly monitor renal function; monitor dose & type of chelation. Referral to nephrology team. Renal replacement therapy may be necessary.
Anemia	Assess hemoglobin levels; assess for underlying causes excluding primary diagnosis. vitamin B12 supplementation; assess nutritional intake and correct deficiencies;
Pulmonary	Assess for impaired exercise tolerance, ask about sleep-disordered breathing. Pulmonary function tests, screening for other causes (i.e., lung cancer).
Stroke, transient ischemic attacks	Evaluate for underlying risk factors (diabetes, hyperlipidemia, hypertension, atrial fibrillation); exchange blood transfusion (SCD).
Chronic pain	Assess for type, intensity, location, current use of analgesics and effect. Consult with pain specialist. Adjust/add analgesics, opioids to achieve relief/restore QoL.
Adapted from: Motta 2020; Shet 2019	

Box 3. Recommended health maintenance and outpatient management of older adults with hemoglobin disorders

- Provide age-appropriate education for patients and caregivers.
- Administration of appropriate immunizations
- Annual screening for blood borne diseases (hepatitis C, HIV) in transfusion-dependent patients
- Screening and prevention of chronic complications (iron overload, cerebrovascular disease, pulmonary hypertension)
- Annual ophthalmology evaluation for retinopathy
- Assessment of bone health and leg ulcers
- Assessment of stress and depression
- Assessment of pain and narcotic use
- Assessment of steady-state blood parameters and physiological measurements (oxygen saturation, blood pressure)

Source: Thein 2017

References

Angastiniotis M, Fung EB. Lifestyle and Quality of Life. In: Guidelines for the Management of Transfusion-Dependent -Thalassemia (TDT) 5th Edition, 2025. Taher AT, et al (ed). Thalassemia International Federation, Cyprus.

Bell L. Adolescents' dialysis patient transition to adult care: a cross-sectional survey. Pediatric Nephrology 2007; 22:720-726.

Blum RW, Garell DM. Hodgman CH, et al. Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. Journal of Adolescent Health 1993; 14:570-576.

Bryant R, Young A, Cesarioo S, Binder B. Transition of chronically ill youth to adult health care: experience of youth with hemoglobinopathy. Journal of Pediatric Health Care 2011; 25:275-283.

Darbari DS, Sheehan VA, Ballas SK. The vaso-occlusive pain crisis in sickle cell disease: definition, pathophysiology, and management. European Journal of Haematology 2020; 105;237-246.

Fung EB, Angastiniotis M. Nutrition. In: Guidelines for the Management of Transfusion-Dependent -Thalassemia (TDT) 5th Edition, 2025. Taher AT, et al (ed). Thalassemia International Federation, Cyprus.

Gan GG, Hue YL, Sathar J. Factors affecting quality of life in adult patients with thalassaemia major and intermedia. Ann Acad Med Singapore. 2016; 45: 520-523.

Maheri M, Rohban A, Sadeghi R, Joveini H. Predictors of quality of life in transfusion-dependent thalassemia patients based on the PRECEDE model: a structural equation modeling approach. J Epidemiol Glob Health. 2020; 10(2): 157-163.

Motta I. Mancarella M, Macron A, Vicenzi M, Cappellini MD. Management of age-associated medical complications in patients with -thalassemia. Expert Review in Hematology 2020; 13:85-94.

National Academies of Sciences, Engineering, and Medicine. Addressing sickle cell disease: A strategic plan and blueprint for action. Washington, DC: The National Academies Press 2022.

Powars DR, Chan LS, Hiti A, et al. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine 2005; 84:363-376.

Punaglom N, Kongvattananon P, Somprasert C. Experience of parents caring for their children with thalassemia: challenges and issues for integrative review. The Bangkok Medical Journal 2019; 15(1):100-106

Scalone L, Mantovani LG, Krol M, et al. Costs, quality of life, treatment satisfaction and compliance in patients with beta-thalassemia major undergoing iron chelation therapy: the ITHACA study. Curr Med Res Opin. 2008; 24: 1905-1917.

Shet AS, Thein SL. A growing population of older adults with sickle cell disease. Clinical Geriatric Medicine 2019; 35:349-367.

Taher AT. Thalassemia. Lancet 2018; 391:155-167.

Thein SL, Tisdale J. Sickle cell disease—unanswered questions and future directions in therapy. Seminars in Hematology 2018; 55:51-52.

Thein MS, Igbineweka NE, Thein SL. Sickle cell disease in the older adult. Pathology 2017; 49:1-9.

Treadwell MJ. Mental health and psychological resilience in sickle cell disease. The Lancet Hematology 2023; 10:E569-E571.

United Kingdom Thalassemia Society (UKTS). Standards for the Clinical Care of Children and Adults Living with Thalassaemia in the UK. 4th Edition, 2023. Available at Standards-for-the-Clinical-Care-of-Children-and-Adults-Living-with-Thalassaemia-in-the-UK-4th-Edition-2023.pdf. Accessed May 2025.

Yousuf R, Akter S, Wasek SM, et al. Thalassemia: a review of the challenges to the families and caregivers. Cureus 2022; 14(12):e32491.

Wakefield D, Bayly J, Selman LE, et al. Patient empowerment, what does it mean for adults in the advanced stages of a life-limiting illness: a systematic review using critical interpretive synthesis. Palliative Medicine 2018; 32:1288-1304

White P, Schmidt A, Shorr J, et al. Six Core Elements of Health Care Transition™ 3.0. Washington, DC: Got Transition, The National Alliance to Advance Adolescent Health, July 2020. Available at: Six Core Elements - Transitioning Youth to an Adult Health Care Clinician Package. Accessed: June 2025.

Wilson SR. Mental health disorders are prevalent and influence outcomes in patients with sickle cell disease. Hematologist 2023; 20. doi.org/10.1182/hem.V20.6.202366

HNHCP
Haematology Nurses & Healthcare Professionals Group

Faculty:

Erik Aerts (Zurich, Switzerland)

Maria-Domenica Cappellini (Milan, IT)

Lucia De Franceschi (Verona, IT)

Georgiadi Elpida (Athens, GR)

Giada Giuliani (Verona, IT)

Carol Krcmar (Germany)

Luhanga Musumadi (Riyadh, Saudi Arabia)

Nowell Ngwenya (Dublin, IRL)

Silvia Vitale (Verona, IT)

Date of preparation: 11.2025.