Each year, an estimated 300,000 infants are born with either of the two most common hemoglobinopathies: the sickle cell diseases or the thalassemias. These inherited diseases are the most prevalent monogenetic disorders worldwide. Sickle cell disease makes up 85% of the total infants, and thalassemias the remaining 15%. It is increasingly apparent that sickle cell disease and thalassemia have become a major health challenge in emerging countries as more infants with hemoglobinopathies survive beyond infancy and into adulthood.

The prevalence of significant hemoglobin trait (Hb S, Hb C, Hb E, Hb D, etc., and β thalassemia and α thalassemia) varies from about 1% in all of Europe to as high as 18% in all of Africa; the prevalence in the American population is 3%. The presence of disease is 10.8/1000 in Africans, 0.6/1000 in Americans, and 0.2/1000 in all of Europe. Half of the people in the world with sickle cell disease live in three countries: Nigeria, Democratic Republic of Congo, and India. In West Africa, about 1,000 infants a day are born with sickle cell disease.

In the world’s population, 1.5% are β thalassemia mutation carriers. Hemoglobin E–β0 thalassemia (Hb E/β0 thalassemia) is the genotype responsible for approximately one-half of all severe β thalassemia worldwide. The distributions of the phenotype and genotype of North American thalassemia patients today—as well as their transfusion management—are dramatically different from those in the past decades. The majority of patients, previously of Mediterranean descent, are now largely of Asian, Indian, and Middle Eastern origin. In Thailand, about 3,000 affected children are born annually, with estimates of about 100,000 living patients. In southern China, the gene frequencies for β-thalassemia and for Hb E are over 4%, resulting in thousands of annual births of β thalassemia major and hemoglobin Hb E/β0 thalassemia. Due to the diaspora occurring in the past and present, sickle cell disease and thalassemia can now be found in areas that are free of malaria.

Sickle hemoglobin is a structural variant causing severe disease in the homozygous state and when in combination with other hemoglobin variants. The α and β thalassemias are genetically diverse with more than 200 mutations accounting for decreased production of hemoglobin in those affected. The thalassemia phenotype varies from mild to severe states of anemia. The heterozygote is mildly protective against malaria with increased prevalence in some areas of the world. Red cell transfusions are indicated for both of these hemoglobinopathies. In sickle cell disease, transfusions prevent and/or treat complications and ameliorate anemia. In the thalassemias, transfusion prevents the anemia associated with decreased or absent hemoglobin production.

### Malaria, blood groups, and hemoglobinopathy

Infections that are endemic and lethal in children are particularly effective for the selection of mutations that provide survival advantage. Malaria is a devastating parasitic disease with a very high mortality rate among children and pregnant women. Due to the high infection and mortality rates, malaria is an extremely strong force for selection. It is estimated that worldwide there are three billion people at risk for infection; there are 250 million clinical episodes of malaria and between one million and 500,000 deaths annually. Ninety percent of deaths occur in sub-Saharan Africa, where many of the hemoglobin polymorphisms and blood group variants are found. Mutations providing even a slight survival advantage are numerous, primarily changing the red cell membrane and hemoglobin. Without the genetic pressure from malaria, human history and the practice of hematology and transfusion medicine would be much different than they are today. An understanding of malaria and the mutations it has caused lays a foundation for understanding sickle cell disease, thalassemia, and transfusion therapy of the hemoglobinopathies.

In Africa between 50,000 and 300,000 years ago, a genetically similar species to *Plasmodium falciparum* infecting western gorillas jumped species and infected humans. It is thought that all of the *Plasmodium* species in sub-Saharan Africa jumped from chimpanzees, macaques, and gorillas to humans. However, the direction of transfer to New World monkeys cannot be determined for *Plasmodium malariae* or *Plasmodium vivax*; the parasite may have been transmitted from humans to monkeys. Currently, there are four species of malaria parasites infecting humans: *P. falciparum, P. vivax, Plasmodium ovale*, and *P. malariae*. *P. falciparum* is the most common of these species, occurring in about 40% of infections. It is
also the most lethal, accounting for the vast majority of deaths and severe disease. *P. vivax* may account for another 40% of cases, causing morbidity but not the mortality of *P. falciparum*. The most recent jump is the human populations in Southeast Asia. *P. knowlesi* has macaque monkeys as a reservoir, and is known to infect human populations in Southeast Asia. *P. knowlesi* infections are reported to be as severe as those of *P. falciparum*.

The association between hematological disease and malaria was first noted in the 1940s by Haldane in the Mediterranean and Beet in Africa. Six common diseases are associated with resistance to malaria, thalassemia (both α and β thalassemia), glucose-6-phosphate dehydrogenase deficiency, hemoglobin C, Southeast Asian ovalocytosis, and hemoglobin S. There are six blood groups with mutations associated with malarial disease: the Duffy blood group, Gerbich blood group, MNS blood group, Knops blood group, and possibly ABO and Lewis blood groups.

### Duffy blood group

The Duffy blood group gene locus, DARC, is an acronym for Duffy antigen receptor for chemokine. The gene resides on the long arm of chromosome 1 (1q21-q22). The gene notation for the blood group is FY. Polymorphisms are responsible for the FYa and FYb antigens. These antigens differ in only one amino acid at position 42: FYa glycine, FYb aspartic acid. There are four common Duffy phenotypes. Within the Duffy blood group system, there are six separate antigens. The Duffy antigen is the receptor for *P. vivax* and *P. knowlesi*. The Duffy antigen is also a nonspecific chemokine receptor. See Table 11.1.

The merozoite of *P. vivax* requires the Duffy-binding protein (PvDBP) in order to bind to the DARC on the red cell. *P. vivax* and *P. knowlesi* genes encode for only one binding protein; the absence of DARC on the red cell is protective against invasion by these parasites.

The Duffy negative allele in Africans is the result of a mutation in the erythroid-specific promoter at position 33 of the GATA-1 transcription factor region blocking the expression of the Duffy antigen on red cells. The mutation is in the FYb allele, designated erythroid silent: FYbS. The Duffy antigen remains present on somatic cells in the presence of the erythroid silent mutation.

### Gerbich blood group

The Gerbich blood group is expressed on glycophorin C and glycophorin D. There are 11 antigens in this group. The gene, GYPC, is located on chromosome 2, 2q14>2q21. Both glycophorins are encoded by this gene. There are two initiation codons; initiation at the first codon results in glycophorin C; initiation at the second codon results in glycophorin D. These glycophorins interact with the 4.1R protein, stabilizing the red cell membrane. A reduction of these antigens leads to hereditary elliptocytosis. Glycophorin C is one of the receptors of *P. falciparum* (EBA-140). There have been reports of increased Gerbich negativity in the coastal areas of Papua New Guinea, an area where malaria is endemic. There is evidence that the Gerbich phenotype is associated with malaria infection. There is no homology between this group and the glycophorins of the MNS system.

### MNS blood group system

The MNS blood group system includes three red cell antigens on two glycophorins. M and N are found on glycophorin A, and S on glycophorin B. These two glycophorins carry two receptors for *P. falciparum*: EBA-175 on glycophorin A and EBA-1 on glycophorin B. The glycophorins are encoded on chromosome 4, 4q28>4q31 in sequence GYPB, GYPB, GYPE. These are homologous genes probably arising from GYPB. There is no evidence of a glycophorin on the red cell membrane arising from GYPE. The MNS system is complex with unequal crossovers, deletions, gene conversions, and point mutations leading to 46 different antigens. It is second in complexity only to the Rh system. See Table 11.2.

### Knops blood group

The Knops blood group is found on the complement receptor 1 (CR1), a glycoprotein present on the red cell as well as other circulating blood cells. CR1 is one of a group of membrane proteins termed the regulators of complement activation; they include decay accelerating factor (DAF/CD55), membrane cofactor protein (CD46), and membrane inhibitor of reactive lysis (MIRL/CD59). CR1 also binds C4b/C3b immune complexes for transfer to the liver or spleen where the immune complexes are ingested by macrophages, returning the red cells to the circulation. CR1 has a binding site for *P. falciparum* entry into the host red cells. CR1 and a malaria red cell membrane protein are involved in red cell rosetting during cerebral malaria.

### ABO, Lewis blood groups

There is evidence that *P. falciparum* influenced the distribution of the ABO blood groups to favor group O in areas where *P. falciparum* was present. Group O decreases the adhesive properties of infected red cells relative to groups A and B. Empirically, there are higher rosette levels, increased size, and increased adhesion in groups A and AB. Group B patients have an intermediate...
level of rosettes, with the lowest level of rosette formation being seen in group O individuals. It is proposed that the distribution of blood group O should be highest in areas of malaria and lowest in areas without malaria, and that group A should be lower in these areas, which is indeed the case. Blood group O is common in equatorial regions, and group A is more common in northern latitudes. Infections with severe malaria are more common in group A1 versus group O, even though group O is much more common in the populations studied. Inhibition of this effect can be demonstrated in vitro using soluble A and B antigen, blocking the PfEMP-1 receptor. This could also occur in vivo due to the effect of the Lewis gene transferase, which increases the levels of A and B antigen in the serum.20 This would account for the increased Le (a−b−) seen in individuals with African ancestry.

Enzymopathy

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

G6PD is expressed in all cells. It is the first enzyme in the pentose phosphate pathway and is responsible for the production of the NADPH needed for the regeneration of reduced glutathione. Reduced glutathione converts hydrogen peroxide (H$_2$O$_2$) to water. It is the only NADPH source in the red blood cell protecting it from oxidative damage. It is located on the X chromosome (Xq28). G6PD is the most common enzympathy in humans. The disease affects males and females who are homozygotes; in some cases, G6PD can affect heterozygotes due to lyonization. The gene is polymorphic with 140 different variants. The normal allele is B. There are three alleles in Africa: B, A, A−. The two A alleles have 85% and 12% of normal activity; only the A− allele provides protection against malaria.21 The A allele differs from B by one amino acid, and the A− from A by one amino acid. The A− is always on an A background, which may be required for malaria protection. The most severe form of G6PD is the Mediterranean allele, also a one-amino-acid substitution, producing only 3% activity. It is found in the Mediterranean, India, and Indonesia.

Thalassemia

Alpha thalassemia

Alpha thalassemia is the most common single-gene disease in the world. Four common mutations lead to α thalassemia, and all are α globin gene deletions. In Africa, the most common deletion is −α3.7. The deletion types have not been studied in terms of their protective effect against malaria. It is assumed they are equally effective. Homozygous α+ thalassemia (−α/−α) has been found to be protective against severe malaria. In some malarial areas, such as parts of India and Asia, the incidence of homozygous α thalassemia is 80%. In sub-Saharan Africa, the incidence is 50% or less in spite of endemic severe malaria. This is thought to be due to the negative effect (negative epistasis) of the combination of hemoglobin AS and α thalassemia.22 In children with homozygous hemoglobin A, both the α thalassemia heterozygous23 and homozygous24 forms are protective. The protective effect is a decrease of disease progression from parasitemia to severe malaria. The actual biology of this effect has not been defined, but there is decreased rosette formation, increased phagocytosis,25 and increased immune recognition in α thalassemia red cells.

Beta thalassemia

Although β thalassemia is prevalent in malarial areas, the evidence for β thalassemia being protective against malaria is less convincing, primarily due to the fact that the areas around the Mediterranean where β thalassemia has been prevalent are now free of the malaria parasite. In Africa there are few, if any, published studies of the effect of the sickle β thalassemia phenotypes on survival in patients with malaria. The majority of β mutations in Africans are β plus mutations (−88 C>T and −29 A>G). In African Americans, there are 14 β mutations.26 The two most common β plus mutations are the same as noted. The most common β zero mutation is Codon 6 −A, also seen in Africans.

Membrane mutation

Southeast Asian ovalocytosis

Southeast Asian ovalocytosis does not occur in Africa, but hereditary elliptocytosis has a prevalence of up to 1.5% in some populations.27 There is in vitro evidence that spectrin mutations may impede the entry of P. falciparum into red cells, but there is no published clinical evidence of an effect on survival.28

Structural hemoglobin mutations

Hemoglobin E

First described in 1954, hemoglobin E is a structural thalassemic mutation that is predominant in Southeast Asia. Hemoglobin E is the result of a point mutation at codon 26 of the β globin gene (Glu→Lys). Although this thalassemia is common in malarial areas, it is not clear how this mutation would protect against P. falciparum malaria. These red cells may be less susceptible to invasion.29

Hemoglobin C

Hemoglobin C occurs almost exclusively in West Africa, having a frequency of 50% in the Ivory Coast. Unlike hemoglobin S, where there is a disadvantage for the homozygote, there appears to be no selective disadvantage to the homozygote CC or the heterozygote AC. Hemoglobin C is not as effective in the prevention of severe malaria compared to hemoglobin S, which is probably why it is not more prevalent in sub-Saharan Africa. Both AC and CC are protective, with levels of protection differing depending upon reports.30,31 Protection from severe malaria is due to a decreased parasite survival in CC cells and changes in the red cell surface in CC and AC red cells, particularly PfEMP1, leading to decreased cyto-adherence and an increase in acquired immunity.32 This theory has been questioned33 in a report that there was no increase in antibody response between AS and AC children infected with malaria. The presence of hemoglobin C in the erythrocyte alters the red cell membrane as well as hindering the development of P. falciparum within the cell.34

Hemoglobin S

Hemoglobin S (β6 Glu→Val, GAG→GTG) is common in West and Central Africa where malaria is endemic. The more prevalent the malaria, the more prevalent is this hemoglobin mutation. Hemoglobin S also occurs in North Africa, the Mediterranean, and India. It is estimated that the hemoglobin S mutation occurred as recently as 250–700 years or as long ago as 1750 years. The mutation for
hemoglobin S occurred much more recently than the mutation for hemoglobin C, which is estimated to have occurred 3000 years ago. Hemoglobin S has become the dominant mutation due to superior protection against *P. falciparum* in the heterozygote.

Hemoglobin AS is highly protective against malaria. A recent study showed that hemoglobin AS was 90% effective in preventing malaria in 2591 children with severe malaria compared to a group of 2048 control children in Ghana. In this study, AC was only associated with a decrease in cerebral malaria. Although AS is clearly protective against severe malaria, it is not known how sickle hemoglobin provides this protection. There are several mechanisms that could account for the protection afforded by AS. Most of the research has been done in areas where *P. falciparum* is prevalent.

Red cells infected with *P. falciparum* have increased polymerization of hemoglobin and have an intracellular environment that decreases parasite growth. This could be due to high levels of potassium, elevated levels of hemoglobin, or microRNA that may reduce growth by inhibiting mRNA transcription in the parasite. There is also decreased rosetting of infected AS red cells in the circulation, likely due to a reduced expression of surface adherence proteins. The expression of these adherence proteins, such as a *P. falciparum* membrane protein-1 (PFWM1), leads to cycloadherence and increased endothelial activation in infected persons.

Recently, a murine model has shown that heme oxygenase I induction by hemolysis with the production of CO creates tolerance to malaria and could be another mechanism of protection provided by hemoglobin AS. The expression of the heme oxygenase I gene, Hmox1, is increased by plasma free hemoglobin. Heme oxygenase I has been shown to be protective in inflammatory disease. The protection against severe malaria is due to the effect of carbon monoxide on signal transduction by binding iron in the prosthetic groups’ effector molecules and the inhibition of heme release from hemoglobin. There is no decrease in parasitemia, but there is tolerance induced by heme oxygenase I production of CO. This mechanism could also explain the decrease in malaria mortality in the thalassemias and in G6PD deficiency.

**Hemoglobin SS pathophysiology**

Unlike homozygous hemoglobin C, which results in the crystallization of hemoglobin at normal oxygen tension, homozygous hemoglobin S results in hemoglobin polymerization at low oxygen tension. Polymerization can also occur at low pH and with temperature elevation. Hemoglobin S polymerization distorts the red cell membrane, disrupting the asymmetry found in the normal red cell membrane. When the red cell membrane loses its asymmetry, phosphatidylserine is exposed on the surface of the red cell. This exposure leads to a hypercoagulable state and activates the cellular elements of the blood and vascular endothelium. The distortion also leads to rigidity of the membrane and hemolysis. Hemolysis increases plasma red cell arginase and plasma free hemoglobin, depleting nitric oxide and decreasing cyclic guanosine monophosphate. Hemolysis and red cell membrane instability increases red cell membrane microparticles in the plasma. These changes in the red cell membrane and the activation of cellular elements and the vascular endothelium account for many of the clinical findings in sickle cell disease. Other modifiers of sickle cell disease include proteins S and C deficiency, α thalassemia, fetal hemoglobin production, nutritional factors, as well as others that influence the phenotypic expression of sickle cell disease.

Sickle cell disease is both a vasculopathy, with red cell adhesion to the vascular endothelium, and a hemolytic anemia with plasma free hemoglobin and microparticles. As each of these pathologies has a separate disease manifestation, there has been a proposed “phenotypic” model of sickle cell disease in which one or the other of these features predominates. See Figure 11.1.

Hemoglobin S can polymerize in the presence of other hemoglobin variants as well as hemoglobin A. These combinations are referred to as sickle cell disease if they cause clinical symptoms or have the potential to cause symptoms. Hemoglobin S combined with hemoglobin C, D*Los Angeles*, β thalassemia, O*Arab*, or CHORI cause symptomatic sickle cell disease. The only common hemoglobin-inhibiting polymerization is hemoglobin F. The sickle phenotype is affected by coinheritance of α thalassemia and by the level of hemoglobin F.

The most common sickle combinations are SS, SC, Sβ, and Sβ+ thalassemia. β refers to a thalassemia major mutation, and β+ refers to a mutation in which there is decreased hemoglobin A production, with S being the dominant hemoglobin. It would be expected that S β+ thalassemia would be a relatively benign combination, but this is not necessarily true. There are at least 14 β+ mutations commonly occurring in African Americans. The mutations produce a wide range of hemoglobin A concentrations in the red cell, determining the phenotypic expression of this combination.

Even though the genotype of homozygous S is the same, the phenotype is not. There are many variables that influence the phenotype, the level of fetal (F) hemoglobin and an α gene deletion being the two most common. However, there are biomarkers that could potentially change the phenotypic presentation of sickle cell disease. Biomarkers in sickle cell disease have been reviewed, and although there are over one hundred variables considered as possible biomarkers of severity, only the most commonly used laboratory tests are clinically relevant: complete blood count with reticulocyte count, renal and hepatic function testing, and urine albumin–creatinine ratios are the most useful. Initial steps have been taken in genome-wide surveys to find single nucleotide polymorphisms associated with severity, but clinical relevance has not been found to be associated with most of these single nucleotide polymorphisms.

It is usually not possible to predict the severity of a child’s course with sickle cell disease. In a review of the data from the Cooperative Study of Sickle Cell Disease, pain, persistent leukocytosis, and anemia in children under the age of 24 months were associated with poor outcome in the long term. Other predictors of poor outcome in sickle cell disease are an abnormal transcranial Doppler (TCD) velocity (predicting stroke in children homozygous for hemoglobin S or with Sβ thalassemia) or an elevated tricuspid jet velocity on an echocardiogram in adults.

**Clinical review of sickle cell disease/transfusion indications**

Red cell transfusion has been a therapy for sickle cell disease for decades, becoming more prevalent since the institution of nucleic acid amplification technology (NAT), leukoreduction, and routine red cell phenotyping for transfusion. There are numerous indications for transfusion in children and adults with sickle cell disease. Reviewed are the most common indications for transfusion and a brief description of each.
Cerebrovascular disease (stroke)

Cerebral vascular disease is the most common indication for the transfusion of children with sickle cell disease. Stroke and cerebral vascular disease can be prevented by transfusion in children who have an abnormal transcranial Doppler. Children who have preexisting cerebral vascular disease at diagnosis will likely have progressive cerebral vascular disease. There is an increased risk of progressive hemorrhagic stroke in adults who are treated with chronic transfusion therapy for stroke.

Stroke prevention

Stroke risk for children with homozygous hemoglobin S is 200 times that for children without sickle cell anemia. It is estimated that 10% of children will have a stroke before the age of 20 years. Stroke risk continues with age, with hemorrhagic stroke more common between the ages of 20 and 30 years.

The STOP I study revealed that TCD screening beginning between two and three years of age in children with homozygous hemoglobin S or S β0 thalassemia predicts increased risk of stroke. The institution of chronic red cell transfusion therapy for abnormal timed average mean maximum (TAMMv) can prevent brain injury. Children with abnormal transcranial velocity (TAMMv >200 cm/sec) frequently have normal brain magnetic resonance imaging and angiography (MRI–MRA), but this does not indicate they are at decreased risk of stroke. The elevation of the TAMM velocity is proportional to the risk of stroke. In the preliminary study leading to the STOP Study, there were strokes in children with TAMMv much less than 200 cm/sec. It would be prudent to evaluate patients with MRI–MRA–Perfusion scans and treat patients with persistently elevated conditional TCD TAMMv with either hydroxyurea (no findings on MR study) or chronic red cell transfusion (findings on MR study). Patients with cerebral vascular pathology should be transfused for life. Children who have normal TCD studies cannot be considered at no risk for stroke as MRI–MRA studies have shown ischemia and cerebral vascular disease in these children as well.

Once instituted, transfusion therapy should not be discontinued abruptly. The STOP II study was discontinued by the data safety monitoring board due to an increased rate of stroke and reversion to abnormal TCD in the non-transfused group.

Table 11.3

<table>
<thead>
<tr>
<th>TAMMv</th>
<th>Treatment</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal &lt;170 cm/sec</td>
<td>Screen annually</td>
<td>Follow2</td>
</tr>
<tr>
<td>Conditional ≥170 cm/sec</td>
<td>Institute transfusion therapy</td>
<td>Brain MRI–MRA– perfusion scan</td>
</tr>
<tr>
<td>Abnormal ≥200 cm/sec</td>
<td>Institute transfusion therapy</td>
<td>Brain MRI–MRA– perfusion scan</td>
</tr>
</tbody>
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1 Timed average mean maximum velocity per STOP I study.
2 Consider MRI–MRA at age five years to screen for occult ischemic or cerebral vascular disease per the SIT study.
this study may have been related to reticulocytosis following the discontinuation of transfusion, although this has not been documented. Children who appear normal on physical examination and by history are at risk for so-called silent stroke or occult cerebral infarct. Thirty percent of children with homozygous hemoglobin S will have evidence of occult infarct on MRI. There is an undefined increased risk of stroke or increased occult infarcts in these children, even if they have a normal TCD. The risk of stroke in children with preexisting occult cerebral ischemia was studied in the SIT Study (Silent Cerebral Infarct Multi-Center Clinical Trial). In this study, it was shown that the risk of a further increase in size (3 mm or more) of the initial area of ischemia, or of stroke, was reduced by 58% in the transfusion arm compared to the control arm. This would mean that 13 patients would have to be treated for three years to prevent one event. The optimum age and frequency for screening with MRI for occult ischemic injury are not known. By six years of age, the prevalence of brain ischemia is 27%. TCD as well as an MRI at age five years and further MRI–MRA–Perfusion scans if the child demonstrated soft neurologic signs or had decreased academic achievement at school. A preliminary study indicated there was an association between mildly elevated blood pressures, anemia, and silent infarct. Children who have abnormal sleep studies with obstructive or central apnea are at increased risk for stroke. Overall, children with hemoglobin SS have a cumulative risk of cerebral vascular disease of 49.9% by the age of 14 years. Stroke risk is increased for at least two weeks following an episode of acute chest syndrome. Posterior leukoencephalopathy has been reported with acute chest syndrome and is associated with blood transfusion, corticosteroid administration, and fluid overload with hypertension. Blood pressures for patients with sickle cell disease are lower than normal. Blood pressure should be closely monitored in patients who are receiving blood transfusion for acute chest syndrome or another catastrophic event requiring red cell transfusion. The STOP studies showed that stroke risk is decreased and acute strokes can be prevented by chronic red cell transfusion therapy. There is evidence that preexisting cerebral vascular disease is progressive in spite of appropriate chronic red cell transfusion therapy. The TWTCH Study revealed that, in selected patients, switching from transfusion to hydroxyurea did not lead to an increase in the TAMMv on transcranial Doppler compared to transfusion. The study did not show that there was equal protection from stroke with this change in therapy.

Secondary stroke prevention
Overt stroke has become less common in children and young adults since the institution of transcranial Doppler screening. Chronic transfusion therapy is not completely protective for progressive cerebral vascular disease and stroke, that is present when transfusion therapy is initiated. Children and adults who have severe brain injury following a completed stroke should be placed on transfusion for life. Red cell exchange can eliminate or decrease iron burden in patients with overt stroke on chronic transfusion. It should be the preferred method for chronic transfusion therapy for secondary prevention of stroke. The SWITCH study would suggest that patients who have overt stroke or cerebral vascular disease are more likely to have a good outcome with transfusion and chelation versus hydroxyurea and phlebotomy.

Transfusion
The goal of transfusion therapy is to decrease hemoglobin S by dilution in simple transfusion and by removal of affected cells and replacement in red cell exchange. For acute events, the post-transfusion percentage of hemoglobin S is optimally less than 30%. During chronic transfusion, the goal for the pretransfusion hemoglobin S is between 30 and 35%. The hemoglobin should not be above 11 g/dl with simple transfusion. With red cell exchange, the goal for hemoglobin should be 9 g/dl, which in some patients will lead to a reduction in iron overload. Red cell exchange is the preferred initial treatment for acute stroke.

Ophthalmologic complications
Transfusion is indicated for retinal arterial occlusion with visual loss, particularly if blindness is a possibility. Transfusion for invasive retinal surgery is indicated. Laser therapy for routine management of sickle cell vascular retinopathy does not require transfusion, although patients with severe sickle retinopathy with visual loss should be considered for transfusion. Hemoglobin SC patients would require red cell exchange transfusion.

The incidence of retinopathy is the greatest in hemoglobin SC disease (33%) and Sβ thalassemia (13%), and lowest in homozygous S (3%). Over the age of 30 years, 43% of SC patients and 13% of SS patients will have retinopathy. Hyphemia is a medical emergency in both sickle cell disease and sickle cell trait causing glaucoma and blindness. Retinal artery occlusion, suspected or confirmed, is an indication for transfusion.

Transfusion
Transfusion is initiated until a definitive diagnosis is determined and a long-term care plan made. Retinal arterial occlusion is an indication for chronic transfusion therapy. Patients with hemoglobin SC or SS with elevated hemoglobin are transfused by red cell exchange. The percentage of hemoglobin S should be less than 40%, and for SC it is convenient to use a goal of hemoglobin A greater than 60%.

Respiratory disease
There is no indication for transfusion for obstructive or restrictive lung disease in patients with sickle cell disease. Severely anemic adults who have restrictive lung disease may benefit from transfusion to improve oxygenation. Obstructive or central sleep apnea are risk factors for stroke. Transfusion for central sleep apnea depends on the clinical assessment. Echocardiography should be performed to evaluate for pulmonary hypertension, and nighttime oxygen administration should be considered.

Children and adults with sickle cell disease are at increased risk for obstructive restrictive lung disease and asthma. Asthma is a risk factor for acute chest syndrome and for stroke. Children frequently present with both restrictive and obstructive disease on pulmonary function testing without symptoms. Nitric oxide depletion occurs in both sickle cell disease and asthma. Treatment for asthma is recommended for children with sickle cell disease who have a history of acute chest syndrome and abnormal pulmonary function testing. Children and adults with respiratory disease would benefit from hydroxyurea therapy to reduce the incidence of acute chest syndrome. Tonsillectomy and adenoidectomy for sleep apnea with hypoxia are considered high-risk surgeries, and preoperative transfusion is...
Pulmonary hypertension has been a known complication of sickle cell disease for over 30 years. It is only recently that pulmonary hypertension has become a major focus in the treatment of sickle cell disease. The interest has increased as the pathophysiology of pulmonary hypertension has become understood and there are therapies for pulmonary hypertension that were not available previously. Screening by cardiac echocardiogram beginning at the age of 10–15 years is recommended. Adults who have pulmonary artery pressures estimated to be ≥25 mmHg (Transthoracic 2.5 m/sec.) have an increased risk of morbidity and mortality. Patients with pulmonary artery pressures of ≥30 mmHg or higher should be considered for cardiac catheterization to determine true pulmonary hypertension. If it is determined that a patient has elevated pulmonary pressures with increased pulmonary artery vascular resistance, they are considered for treatment. Sildenafil (a phosphodiesterase type 5 inhibitor) was shown to increase pain episodes in patients with sickle cell disease during the Walk PHaSST Study, which was terminated by the US National Institutes of Health. Treatment has not been studied beyond sildenafil alone. One study of bosentan showed that this therapy was well tolerated in sickle cell disease. A recent study has shown that the incidence of cardiac catheterization-proven pulmonary hypertension is much less frequent than estimated by echocardiogram. In this study, those patients who were diagnosed as having pulmonary hypertension were older, had increased six-minute walk, increased N-terminal pro brain natriuretic peptide, and evidence of increased hemolysis. Only 1.5% of 398 patients had increased pulmonary arterial resistance, and only 24 had evidence of pulmonary hypertension by capillary wedge pressure. It is not known what significance elevated echocardiographic tricuspid-regurgitation jet velocity is in pediatric patients. In adult patients, it is a risk factor for morbidity and mortality.

**Transfusion**

For documented pulmonary artery hypertension, transfusion alone has been successful in reducing pulmonary artery pressures in some cases. Sildenafil could be added to transfusion if transfusion therapy was not effective. In pediatric patients, hydroxyurea has been found to be effective in a small study. There is no consensus as to the optimal therapy for documented pulmonary hypertension. Aspirin has been recommended for splenectomized patients to prevent pulmonary hypertension due to platelet aggregation in the lungs. There have been no studies of the effectiveness of aspirin for this indication.

**Acute chest syndrome**

Acute chest syndrome accounts for about 25% of hospital admissions and is a leading cause of death in sickle cell disease. Recurrent episodes of acute chest syndrome can cause lung scarring leading to restrictive lung disease in children and adults with sickle cell disease. Obstructive pulmonary disease is common when pulmonary function is formally evaluated. Children and adolescents may not have symptoms of obstructive disease. Asthma is a risk factor for acute chest syndrome. Acute chest syndrome is a risk factor for encephalopathy and stroke. Acute chest syndrome can develop within 72 hours of a painful event in adults. Elevated phospholipase A2, in conjunction with fever and respiratory symptoms, predicts acute chest syndrome, and expectant transfusion may arrest its development.

The National Acute Chest Syndrome Study Group reviewed the common features and evaluation of acute chest syndrome in sickle cell disease. Patients should be continuously monitored, and transfusion should be considered if there is a new infiltrate and oxygen saturation is less than 90–95%. Chest pain and low oxygen saturation, without infiltrate, should be the threshold for considering pulmonary emboli as a cause of these symptoms.

**Transfusion**

For patients who present with acute chest syndrome and severe anemia, simple transfusion may be sufficient to increase oxygenation and reduce risk of more severe disease. Hyperviscosity and hypervolemia can complicate simple transfusion. Patients who present with an elevated hemoglobin (8 g/dl or higher) should receive an exchange transfusion as the initial therapy. Neurologic changes during acute chest syndrome are more frequent in adults and are an indication for exchange transfusion as stroke risk is increased during, as well as following, an episode of acute chest syndrome. There is an association between blood transfusion, corticosteroid use, and stroke/posterior leukoencephalopathy, usually precipitated by hypertension.

**Red cell exchange transfusion**

Red cell exchange transfusion is the safest and most effective method of transfusion for severe acute chest syndrome. It provides for isovolumetric red cell exchange without changes in viscosity. The end hematocrit and percentage of hemoglobin S are predictably obtained. The transfusion goal should be a reduction in the percentage of hemoglobin S to 30% or less with an end hematocrit of 9–10 g/dl. Ventilated patients should have an end hematocrit of 10 g/dl.

Chronic transfusion for six months following a severe episode of acute chest syndrome is reasonable therapy. Hydroxyurea should be considered for all patients who have had an episode of acute chest syndrome, particularly if they have obstructive lung disease.

**Immune dysfunction/sepsis risk**

Children and adults who are septic frequently have a precipitous drop in their hemoglobin. Patients who appear septic should have a type and screen at presentation in the event they need an emergent transfusion.
Acute renal failure can occur in sickle cell disease during episodes of sepsis and multiorgan failure. Rhabdomyolysis can occur with much higher Pitt counts. The incidence of infection is greatest in infancy and early childhood, then decreases with age. The effect of pneumococcal vaccine and penicillin prophylaxis has decreased the incidence of death from overwhelming pneumococcal sepsis in sickle cell disease. Children with sickle cell disease are more likely to have bacteremia with acute chest syndrome, they are at risk for pyelonephritis and urosepsis, and they have an increased incidence of osteomyelitis with salmonella. Children with sickle cell disease can appear deceptively nontoxic with infections that prove fatal.

Transfusion
In the absence of multiorgan failure, simple transfusion to maintain the hemoglobin between 9 and 10 g/dl is recommended. Severe sepsis with multiorgan failure would be an indication for red cell exchange to decrease the percentage of hemoglobin S to 30% with an end hemoglobin of 9 to 10 g/dl.

Renal disease
Transfusion for renal disease would include patients with declining renal function and anemia and patients with a kidney transplant. Priapism has not been reported to respond to transfusion.

Renal disease is common in children and adults with sickle cell disease. Total renal blood flow is increased in sickle cell disease due to anemia, with hyperfiltration present in infants by about one year of age. Microalbuminuria is present in about 30% of adolescents. The inability to concentrate urine (hypostenuria) is extremely common in sickle cell disease, and it has been reported to be reversed in childhood with chronic transfusion therapy. Both proximal and distal tubular disease is present in patients with sickle cell disease. Distal tubule dysfunction causes a mild renal tubular acidosis. Proximal tubular disease causes an increase in tubular secretion making creatinine a poor indicator of glomerular filtration rate. Microscopic hematuria is common, frank bleeding can follow renal papillary necrosis. Blood loss from renal papillary necrosis may appear to be severe, but it generally does not require transfusion. An uncommon complication of papillary necrosis is hypernephrosis due to ureter obstruction.

Renal findings in sickle cell disease include:
- Decreased ability to concentrate urine;
- Decreased ability to excrete potassium;
- Inability to lower urine pH; and
- Hematuria/papillary necrosis.

Risk factors for renal failure include:
- Anemia, proteinuria, and hematuria.

Acute renal failure can occur in sickle cell disease during episodes of sepsis and multiorgan failure. Rhabdomyolysis can occur with dehydration and has been described during acute painful episodes. Exchange transfusion and dialysis are lifesaving.

Priapism
Priapism is a common symptom in sickle cell disease. It is estimated that as many as 40% of males will have an episode of priapism during childhood and adolescence, but the actual incidence is unknown. Priapism leads to permanent ischemic damage and impotence. Severe priapism prognosticates a more severe course of sickle cell disease. Priapism may be induced by hemolysis. There are no reports of priapism in the setting of delayed hemolytic transfusion reactions (DHTRs) or other settings of hemolysis.

Transfusion
Transfusions, both simple and exchange, have not been shown to have an effect on acute priapism. There have been reports of neurologic events when treating priapism with exchange transfusion due to increased viscosity and fluid overload. Patients with a renal allograft should have either simple or exchange transfusion for graft protection. The hemoglobin should be kept between 9 and 10 g/dl with a percentage of hemoglobin S between 30 and 40%.

Gastrointestinal
There is no indication for transfusion as nutritional support for patients who have growth or pubertal delay. Transfusion for children or adults who have hepatic disease may be indicated.

Common gastrointestinal complications in sickle cell disease are cholelithiasis, choledocholithiasis, hepatic sequestration, and intestinal ischemia. Surgical emergencies occur as frequently in sickle cell disease as in other populations. Hepatic disease is relatively common in sickle cell disease. The pathology includes viral hepatitis, hepatic sequestration, hepatic iron injury, and intrahepatic cholestasis. During hepatic sequestration, the transaminases are elevated as well as the bilirubin, and the ALT (alanine aminotransferase) can remain elevated for several weeks. Overtransfusion in hepatic sequestration has led to hyper-viscosity morbidity. Intrahepatic cholestasis is a rare complication of sickle cell disease. Exchange transfusion has been successful in some cases. Liver biopsy is contraindicated in the presence of hepatic congestion and coagulopathy. Elevation of bilirubin above 13 mg/dl with a predominantly direct component can be a sign of intrahepatic cholestasis, a sometimes fatal complication of sickle cell disease. Bilirubin levels greater than 30 mg/dl or higher can lead to hepatorenal syndrome and death.

Transfusion
The most common surgical diagnosis in patients with sickle cell disease is cholelithiasis. The complications of this surgery have been reported. Red cell exchange transfusion may be effective for intrahepatic cholestasis.

Skeletal (avascular necrosis/osteomyelitis)
There is no indication for transfusion for avascular necrosis of bone. Hyper-viscosity occurring during simple transfusion could, theoretically, contribute to avascular necrosis. Microparticle formation has been implicated in avascular necrosis.

Bone in sickle cell disease is a major area of pathology. Bone infarcts are perhaps the most common source of severe acute pain in
patients with sickle cell disease. Infarcts can cause nerve compression, digital shortening following dactylitis, and avascular necrosis of both the shoulders and the hips. Rib infarcts are thought to contribute to acute chest syndrome, sternal infarcts are common, and the vertebral bodies in sickle cell disease owe their peculiar shape to damage from necrosis.

**Transfusion**

Hip replacement is the most common orthopedic surgery in sickle cell disease. Shoulder replacement is much less common. Simple transfusion is recommended in the absence of elevated hemoglobin, in which case a red cell exchange could be considered.

**Integument (skin ulcers)**

Transfusion has been used to increase oxygenation for patients with chronic skin ulcers. There is better therapy for treatment, although transfusion following skin grafting could be helpful to decrease microvascular occlusion.

The most common problem in the skin in sickle cell disease is skin ulcers. They are usually due to skin trauma, not recalled by the patient. There may be a relationship between skin ulceration and hydroxyurea in adult patients.

**Transfusion**

Blood transfusion has been used in the treatment of skin ulceration. There are anecdotal reports of other therapies: vascular flaps, special dressings, and arginine butyrate.

**Hematologic (severe anemia)**

Children and adults with anemia and a low reticulocyte count due to infection or other cause may benefit from transfusion. Children with parvovirus infection require transfusion if they have severe anemia with an inadequate reticulocyte count. Spleenic and hepatic sequestration require transfusion.

Sickle cell anemia and sickle β-thalassemia can have significant anemia. Patients with sickle β thalassemia have microcytosis, making the diagnosis of iron deficiency problematic. A one or two α gene deletion (always trans in African Americans) will lead to microcytosis. Patients with severe anemia (hemoglobin of 5 g/dl or less) should be transfused to improve oxygen delivery and prevent complications of anemia. Chronic anemia results in a vascular overloaded state, and transfusion should be performed cautiously. Patients otherwise well with a brisk reticulocyte count and safe hemoglobin can be monitored. Other etiologies of anemia should be considered.

A child presenting with an enlarged spleen or liver is diagnostic of splenic or hepatic sequestration. Both are life-threatening. Parvovirus is the next most common etiology of acute anemia in children.

Overtransfusion can lead to hyperviscosity and morbidity when treating sequestration; blood may be released from the congested organ, increasing the hematocrit to dangerously high levels. Children who have life-threatening splenic sequestration should be transfused on a monthly basis to prevent recurrence and should have a laparoscopic splenectomy as soon as they have been fully immunized. There is significant morbidity in children who have hepatic sequestration. Hepatorenal syndrome should be entertained as a possible complication.

**Transfusion**

Simple transfusion is indicated for anemia due to parvovirus aplastic anemia. Cautious transfusion for sequestration with a target hemoglobin of 8–9 g/dl is the safest approach to these patients.

**Surgery**

It has been shown in a prospective randomized trial that transfusion prior to surgery decreases morbidity and mortality.

Surgery is common in sickle cell disease. Cholelithiasis and osteonecrosis are the most common indications for surgery. Patients with sickle cell disease have many risk factors for morbidity during surgery: Acute chest syndrome is the most common, and some patients may have stroke risk, although stroke as a complication of surgery is uncommon. Hypoventilation can lead to dehydration in the sickle cell patients awaiting surgery. Rhabdomyolysis can occur due to dehydration and prolonged positioning during surgery. Pain management is not usually a problem following surgery. Transfusion is the standard of care for surgery with a prolonged anesthesia time. Surgery that has a long anesthesia time leads to atelectasis, increasing the risk of acute chest syndrome postoperatively.

**Preoperative**:

- **Hemoglobin** of greater than 10 g/dl is recommended for medium and high-risk surgeries to prevent complications. For hemoglobin SC or other sickle cell disease patients with hemoglobin 10 g/dl or higher, exchange transfusion should be considered, particularly in patients with hemoglobin SS, S/β0 thalassemia, and SC who are to have high-risk or prolonged procedures.

**Intraoperative**:

- Warm room, warm blood, and meticulous fluid management.

**Postoperatively**:

- Pain management, fluid management, and evaluation of any respiratory or neurologic symptoms. Incentive spirometry every 2 hours, and oxygen therapy to maintain oxygen saturation over 95%.

Common postoperative complications of surgery include:

- **Acute chest syndrome**;
- **Fluid overload**;
- **Allergic reaction**;
- **Rhabdomyolysis**;
- **Neurolologic complications**;

**Pain**

Transfusion as an intervention for an acute, uncomplicated, pain episode has not been studied. For patients who have chronic pain, a trial of transfusion may allow patients to be pain free while they are withdrawn from pain medications and learning other coping skills. It is not recommended that patients be maintained on both transfusion and opioid medications for pain unless there is a physiologic indication such as avascular necrosis.
Pain is the pathognomonic symptom of sickle cell disease. Pain in sickle cell disease is not necessarily sickle cell vaso-occlusive pain.

Acute pain that is sickle cell related includes:
- Acute painful episodes;
- Acute chest syndrome;
- Priapism;
- Cholecystitis (ascending cholangitis);
- Dactylitis;
- Left upper quadrant pain: splenic sequestration/infarct;
- Right upper quadrant pain: hepatic sequestration;
- Skin ulcer (even before skin breakdown);
- Pain with internal rotation of the hip: early avascular necrosis of hip; and
- Pain with arm extension: shoulder avascular necrosis.

Chronic pain that is sickle cell related includes:
- Avascular (osteo) necrosis (non-acute);
- Arthropathies (vertebral infarcts/collapse);
- Leg ulcers (chronic);
- Chronic osteomyelitis;
- Intractable chronic pain; and
- Neuropathic pain.

Transfusion
A fall in hemoglobin and hyperhemolysis can occur during painful events in patients with sickle cell disease. Transfusion should be judiciously used in the event of anemia occurring during a painful episode. Transfusion can be used during a period of weaning from chronic pain medication. It is not recommended to treat chronic pain with both transfusion and opioid.

Pregnancy

There is controversy concerning transfusion during pregnancy. Studies have shown there is little to no benefit to the fetus, but that mothers have less painful events when transfused during the latter half of pregnancy compared to nontransfused women with sickle cell disease. Pregnancy carries a high risk for the mother and fetus compared to normal women. Maternal complications occur even in the chronically transfused patient. Chronic transfusion should be considered for all women during pregnancy.

Some young women do relatively well with pregnancy, but generally there is an increase in morbidity. Pregnancy-related complications occur more frequently in women with hemoglobin SS. Transfusion has been offered to women in the last trimester of pregnancy, but should be offered early if there is any comorbidity. There is no indication that this improves fetal outcome, but it does decrease complications for the mother. A recent study of partial exchange transfusions during pregnancy revealed that, even with transfusion, there is still an increase in morbidity for women with sickle cell disease during pregnancy. Some studies have shown that red cell exchange transfusion significantly decreases morbidity and mortality during pregnancy.

Transfusion
Transfusions for complications of pregnancy are indicated to prevent morbidity and mortality. Consider prophylactic simple red cell transfusion during pregnancy. Red cell exchange may provide an additional benefit. See Table 11.4.

### Table 11.4 Sickle Cell Disease Indications for Transfusion

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Vascular</td>
<td>Transfusion by simple or red cell exchange for cerebral vascular disease, occult brain ischemia, abnormal TCD</td>
</tr>
<tr>
<td>Stroke prevention</td>
<td></td>
</tr>
<tr>
<td>Secondary stroke</td>
<td>Transfusion by simple or red cell exchange for stroke</td>
</tr>
<tr>
<td>prevention</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Transfusion for arterial infarct</td>
</tr>
<tr>
<td>complications</td>
<td></td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>No indication for transfusion</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Red cell exchange for catheterization proven</td>
</tr>
<tr>
<td>hypertension</td>
<td>pulmonary hypertension</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>Simple transfusion for low hemoglobin, red cell</td>
</tr>
<tr>
<td></td>
<td>syndrome exchange if clinically severe or for elevated</td>
</tr>
<tr>
<td></td>
<td>hemoglobin at presentation</td>
</tr>
<tr>
<td>Immune</td>
<td>Simple transfusion for severe anemia</td>
</tr>
<tr>
<td>dysfunction sepsis</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td>Consider transfusion for severe anemia</td>
</tr>
<tr>
<td>Priapism</td>
<td>Transfusion not proven effective</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Transfusion not effective</td>
</tr>
<tr>
<td>Integument</td>
<td></td>
</tr>
<tr>
<td>Severe anemia</td>
<td>Consider transfusion for severe anemia</td>
</tr>
<tr>
<td>Parvoviral infection</td>
<td>Simple transfusion for anemia</td>
</tr>
<tr>
<td>Splenic sequestration</td>
<td>Simple transfusion</td>
</tr>
<tr>
<td>Hyperhemolysis</td>
<td>Avoid transfusion if possible</td>
</tr>
<tr>
<td>Surgery</td>
<td>Transfusion to hemoglobin of 10 g/dl</td>
</tr>
<tr>
<td>Pain</td>
<td>Transfusion not proven to be effective</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Role for transfusion, red cell exchange may be beneficial</td>
</tr>
</tbody>
</table>

Thalassemia
The thalassemias are the most common monogenic diseases worldwide. These syndromes are classified according to whether the mutation causing the defect affects the α globin gene cluster or the β globin gene cluster. There is one β globin gene cluster on each chromosome 11 (β/β). Duplicated α gene clusters occur on chromosome 16 (αα/αα). Mutations in the globin genes reduce or eliminate the synthesis of the respective globin molecule. The majority of α gene mutations are deletional, although structural mutations occur. There are about 100 α gene mutations reported. β globin mutations are primarily point mutations leading to absent β globin synthesis (β0 mutations) or decreased β globin synthesis (β+ mutations). There are well over 200 β globin gene mutations. Structural variants of the globin genes can lead to thalassemic gene combinations. There are also deletions of β globin regulatory elements and of the other genes in the β globin cluster that lead to changes in expression of the gamma globin gene (HPFH). The β globin gene cluster is also regulated by genes on distant chromosomes such as BCL11A, KLF1, and others.

β Thalassemia presents with a diverse phenotype. Among this group are individuals who do not require regular transfusion but do require intermittent transfusion during illness, and individuals who require lifelong chronic transfusion therapy. The goal of transfusion is normal growth and development and the prevention of complications of ineffective erythropoiesis. Iron accumulation from transfusion and/or ineffective erythropoiesis is a major problem for patients with β thalassemia.

The major predictor of the β thalassemic phenotype is the α/β-globin chain imbalance with more severe disease in those
genotypes with excess α globin and decreased β globin production. A β-gene heterozygote predicted not to require transfusion might require transfusions due to duplicated or triplicated α-genes leading to a greater α/β gene imbalance than expected.

The β thalassemias can be classified into four general categories: silent carrier, trait/thalassemia minor, thalassemia intermedia, and thalassemia major. β thalassemia carriers have no hematologic abnormalities, but do have elevated hemoglobin A2 on hemoglobin electrophoresis. Those with β thalassemia trait (β thalassemia minor) have elevated A2 as well as mild anemia and microcytosis. They do not require red cell transfusion. β thalassemia intermedia presents late with variable levels of anemia and is of the non-transfusion-dependent-thalassemia (NTDT) phenotype. Some mutations with this phenotype will go on to chronic transfusions due to the severity of their anemia or complications of their disease. β thalassemia major presents early and is transfusion dependent.

A common structural mutation occurring in combination with β0 mutations is hemoglobin E.148 Hemoglobin E is structurally abnormal, and the mutation causes abnormal RNA processing leading to decreased hemoglobin production. Hemoglobin E/β0 thalassemia can be grouped into three types: severe with very low hemoglobin production (4–5 g/dl), moderate (hemoglobin 6–7 g/dl), and mild with hemoglobin levels in the 9–12 g/dl range. These phenotypes are influenced by the β+ mutation, the production of fetal hemoglobin and α-gene. Patients with the most severe phenotype require lifelong chronic transfusion.

Regularly transfused patients with thalassemia have complications that are primarily due to the increased absorption of iron from the gastrointestinal tract and iron derived from chronic transfusion.149 The NTDT group has morbidity associated with ineffective erythropoiesis and splenectomy. The decision to begin transfusion should be considered after careful assessment of the genotype and the presentation over several months. Transfusion may not be necessary in some NTDT patients in childhood, but a transfusion requirement may develop in adulthood. Due to gastrointestinal absorption of iron, many NTDT patients will require chelation in the absence of transfusion.

**Transfusion goals for β thalassemia**

Even with identical genotypes, the baseline hemoglobin for the β thalassemia syndromes is not predictable. The baseline hemoglobin should be established for each child prior to the initiation of transfusion therapy. If the baseline is below 6 or 7 g/dl, chronic transfusion therapy should be initiated. The goal for transfusion-dependent β thalassemia is a pretransfusion hemoglobin of 9 to 10 g/dl, which requires transfusion every month in infants and young children, increasing to every three weeks in adults.150 Patients who have an annual transfusion requirement of greater than 200 ml/kg/year should be evaluated to determine if their transfusion requirement can be reduced. If not splenectomized, they may have hypersplenism or be overtreated to hemoglobin levels higher than necessary. Chelation becomes increasingly difficult with intensive transfusion therapy. (See Table 11.5.)

<table>
<thead>
<tr>
<th>Complications due to transfusion or dietary hemosiderosis and thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-gene deletions (−α/αα) are not detectable without α gene mapping. Alpha gene mutations that occur in trans (−α/−αα) or cis (−α/−αα) are indistinguishable hematologically and are frequently referred to as a thalassemia traits. Single mutations on the same gene are αα thalassemia mutations. Two common mutations are the 3.7 and 4.2 deletions. The case in which both genes are deleted on the same chromosome is the αα thalassemia mutations. A common α+ thalassemia mutation is the SEA deletion, −αα/αα. Nondetection mutations may occur as single mutations or in combination (−α/α−αα). These combinations can be detected on the complete blood count with microcytosis and occasionally mild anemia. The combinations by themselves do not require transfusion and are referred to as the α thalassemia trait.</td>
</tr>
<tr>
<td>Combinations of α/αα thalassemia and α+ thalassemia can lead to a phenotype requiring red cell transfusions on an intermittent basis or chronically. Hemoglobin H disease (−α/−αα) is the most common α/αα thalassemia–α+ thalassemia combination.152 It is rare that patients with hemoglobin H require transfusions, but transfusion may be needed during illness. Hemoglobin H disease manifests with a mild anemia and splenomegaly. In contrast, hemoglobin H constant spring (−α/−αα) is a much more severe disease with anemia, requiring intermittent or chronic transfusion and occasionally occurring early in life. Most patients will develop hypersplenism and thrombophilia. Thrombosis following splenectomy is common in this nondeletional form of hemoglobin H disease. Later in life, cholelithiasis and skin ulcers can occur. Both hemoglobin H disease and H constant spring are in the NTDT group of thalassemias, although some H constant spring patients will require frequent or chronic transfusions later in life.153</td>
</tr>
<tr>
<td>The most severe form of α thalassemia is Bart’s hydrops fetalis (−α α/−α α). The affected embryo develops severe hypoxia in the third trimester and will not survive without intrauterine transfusions or exchange transfusion at birth. Other α+ thalassemia mutations may cause fetal demise earlier in gestation. These infants require chronic transfusion therapy or progenitor cell transplantation if they survive.</td>
</tr>
<tr>
<td>Monitoring during acute illness and simple red cell transfusion for severe anemia is needed in patients with hemoglobin H disease and hemoglobin H constant spring. For those patients requiring chronic transfusion, the goal should be a pretransfusion hemoglobin of between 9 and 10 g/dl. (See Table 11.6.)</td>
</tr>
</tbody>
</table>

**Table 11.5 Simple Transfusion versus Non-transfusion-Dependent Thalassemia (NTDT)**

<table>
<thead>
<tr>
<th>Chronic Transfusion</th>
<th>NTDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Silent cerebral infarct</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Left heart failure: cardiac hemosiderosis</td>
<td>Hepatic fibrosis and cirrhosis</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Thrombophilia</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Extramedullary hematopoiesis</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Skin ulcers</td>
<td></td>
</tr>
</tbody>
</table>

**Transfusion methods**

**Red cell product**

A red cell antigen phenotype and/or genotype is obtained prior to transfusion with the purpose of identifying absent red cell antigens.
in order to provide antigen-negative red cells for transfusion; this is done as soon as possible before the first transfusion. Common antigens causing alloimmunization are: D, E, c, C, c, K, jK\(^b\), Fy\(^a\), Fy\(^b\), s, S, m, N, Le\(^a\), and Le\(^b\).\(^{154}\) It is recommended these antigens be phenotyped at a minimum. Genotype is predetermined by the platform used. This information will guide investigations when an alloantibody is suspected. Using partially phenotypically matched red cells for Rh (D, C, c, E, e) and Kell antigen significantly decreases incidence of alloimmunization.\(^{155}\) Alloimmunization is reduced in sickle cell disease from 30% to less than 3%. For thalassemia, the age of beginning transfusion influences the rate of alloimmunization, with children beginning transfusion before one year of age having less alloimmunization (11% vs. 30%).\(^{2}\) An antigen common in the Chinese thalassemia population is Mi\(^\ast\), accounting for 30% of alloimmunization in Chinese thalassemia patients.\(^{2}\) Other less common antigens can be involved in DHTRs, particularly in patients with sickle cell disease.

Sickle cell trait-negative blood products are recommended for sickle cell disease, although a patient with a rare phenotype could receive sickle trait-positive units when necessary.\(^{154}\) Genotyping for the GATA box mutation seen in Fyb can somewhat simplify the provision of phenotypically matched blood products. Silencing will preclude the need to honor this antigen. There may be a higher risk of Rh alloimmunization if using only African-American donors for sickle cell patients.\(^{156}\) The blood provider should confirm phenotypes for chronically transfused patients rather than relying on historically antigen-negative units. Confirmation of the partial phenotype at the blood bank prior to being issued for transfusion is optional.

Testing for HIV, hepatitis A, B, and C, and liver function provides baseline prior to initiation of transfusion, particularly in older children, adults, and patients who have been previously transfused. Transfusion-transmitted disease testing should be repeated annually. Hepatitis screening should be repeated if there is a rise in transaminases. Immunize patients who do not have serologic evidence of infection or immunity for hepatitis B and hepatitis A. Patients with positive serology for hepatitis B or C infections should be followed for hepatocellular carcinoma.\(^{157}\)

Leukoreduced products are indicated for all sickle cell and thalassemia patients. Red cells do not require irradiation for either thalassemia or sickle cell disease. Radiation damages the red cell membrane and shortens red cell survival. The only indication for irradiation is for patients who are immune suppressed or who will possibly have a progenitor cell transplant.\(^{158}\) Cytomegalovirus (CMV) infections should be prevented in CMV seronegative patients, particularly those likely to receive a progenitor cell transplant and women who are pregnant. Units that have been leukocyte-reduced by the blood supplier are widely accepted to be efficacious; there is no demonstrated need to combine with seronegative units shown to lack antibody. There are extremely rare cases of window-period CMV donations from newly infected donors that can transmit CMV infection.\(^{159}\) Red cells are not required to be washed unless the recipient has had a urticarial or other transfusion reaction that could conceivably be ameliorated by washed units. Transfusion of CMV negative units is recommended for transfusion during pregnancy.\(^{160}\) Patients considered for a progenitor cell transplant and who are CMV negative should receive CMV-negative red cells. When a referred patient is recommended for transfusion therapy and the indication for transfusion is unclear, reassess the need for chronic transfusion in both sickle cell disease and thalassemia patients. Sickle cell disease patients may be able to be weaned to hydroxyurea, and thalassemia patients may fit the category of NTDT.

HLA-type full siblings of patients with chronically transfused sickle cell anemia and transfusion-dependent thalassemia all are candidates for progenitor cell transplantation.\(^{161}\)

### Simple transfusion

Simple transfusion is the only method of transfusion in thalassemia. Simple transfusion can be performed with a minimal amount of infrastructure. The volume for simple transfusion should be calculated for pediatric patients, and transfusion should not be by whole units. A simple method of calculating red cell requirement is: the transfusion factor

\[
\text{Transfusion factor} = \frac{3}{\text{Hematocrit}}
\]

\[
\times \text{Hct}, \text{and then by the weight of the patient in kilograms:}
\]

\[
(\text{Hgb}^{d} - \text{Hgb}^{b})(3/\text{Hct})(\text{Wt. in Kg})
\]

= milliliters of red cells to transfuse.\(^{162}\)

Red cell units can be “split” by the blood bank to conserve the blood supply. Overtransfusion can lead to hyperviscosity in patients with thalassemia or sickle cell disease, and has led to morbidity in both. Simple transfusion in patients with anemia leads to a mild volume overload that is tolerated by most patients, but it can lead to cardiac overload in older patients or those with cardiomyopathy that requires monitoring.\(^{163}\) Diuretics should be considered if the transfused volume is greater than 20 ml/kg. The pretransfusion goal for chronically transfused thalassemia and sickle cell patients should be a hemoglobin of 9–10 g/dl. The goal for simple transfusion should be a posttransfusion hemoglobin of 11 g/dl for sickle cell anemia and of 12–13 g/dl for thalassemia. In sickle cell disease, the

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype</th>
<th>Clinical Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Thalassemia</td>
<td>(\beta^{0}/\beta^{0})</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Silent carrier</td>
<td>(\beta^{0}/\beta^{0})</td>
<td>Microcytosis</td>
</tr>
<tr>
<td>Trait/thalassemia minor</td>
<td>Combinations of (\beta^{0}/\beta^{0}) alone or in combination with gene duplications, deletional forms of (\delta^{+}) thalassemia, increased (\delta^{0}) production, or (\delta^{+}) thalassemia and HPH and E(^{b}) thalassemia</td>
<td>Late presentation, Mild to moderate anemia May be transfusion dependent or independent</td>
</tr>
<tr>
<td>Intermedia</td>
<td>Early presentation</td>
<td>Severe</td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>(\beta^{+}/\beta^{0}), (\beta^{+}/\beta^{+}), (\beta^{+}/\beta^{+}), (\beta^{+}/\beta^{0})</td>
<td>Late presentation</td>
</tr>
<tr>
<td>Alpha Thalassemia</td>
<td>(\alpha^{+}/\alpha^{+})</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Silent carrier</td>
<td>(\alpha^{+}/\alpha^{+})</td>
<td>Microcytic, hypochromic</td>
</tr>
<tr>
<td>Trait/minor</td>
<td>(-/-\alpha^{+})</td>
<td>Mild to moderate anemia</td>
</tr>
<tr>
<td>Hemoglobin H:</td>
<td>(-/-\alpha^{+})</td>
<td>Variable severity</td>
</tr>
<tr>
<td>Deletional</td>
<td></td>
<td>Usually moderate severity</td>
</tr>
<tr>
<td>Hemoglobin H:</td>
<td>(-/-\alpha^{+})</td>
<td>Transfusions possible</td>
</tr>
<tr>
<td>Nondeletional</td>
<td>Moderate severity</td>
<td>Possibly nonviable</td>
</tr>
<tr>
<td>Major (Bart’s hydrops fetalis)</td>
<td></td>
<td>Chronic transfusion</td>
</tr>
</tbody>
</table>
pretransfusion hemoglobin S should be <30% for patients who have cerebral vascular disease and <40% if transfusion is for other indications. Thalassemia major patients may require monthly transfusions as infants and children, whereas adult patients usually require transfusions at three-week intervals. Patients with sickle cell disease should be transfused on a monthly basis.

**Red cell exchange**

Red cell exchange is the preferred method of transfusion for sickle cell disease for chronic transfusion as well as emergent situations in which the percentage of hemoglobin S must be reduced rapidly and the patient is not severely anemic. Exchange transfusion is isovolumetric to avoid fluid overload, and can decrease iron accumulation in some patients. Exchange can be performed manually as phlebotomy and infusion with red cells diluted to a predetermined hematocrit or as an automated procedure using erythrocytapheresis.

**Erythrocytapheresis**

Automated red cell exchange is the preferred method for transfusion where it is available. The posttransfusion hematocrit and percentage of hemoglobin S can be predictably achieved, and the procedure provides for a continuous isovolumetric red cell transfusion. For emergent situations, the percentage of hemoglobin S should be 30% with a hemoglobin between 9 and 10 g/dl. The procedure is safe, and very few adverse events have been reported. The barriers to automated red cell exchange are the infrastructure required, intravenous access, and the expertise of the medical staff to perform the procedure. Alloimmunization has been shown to be equal to or less than that of simple transfusion. Hypocalcemia is a problem that is easily corrected with infusions of calcium gluconate.

Central intravenous access is necessary for acute procedures. Double lumen dialysis catheters are used and placed in either the femoral vein or the internal jugular vein. Intravenous access is the major barrier to chronic transfusion by automated red cell exchange. Young children generally do not have venous access for red cell exchange and are not developmentally able to tolerate the procedure. Most children who are five years of age or older are able to cooperate with the procedure, and many will have peripheral intravenous access. Access by angiocatheter is preferable with an 18 gauge for adults and a 22 gauge for children. The flow rates recommended by the manufacturer should be used for the procedure.

In the absence of peripheral access, an implantable dialysis catheter is required for chronic transfusion. Currently, these catheters are not available in a size for pediatric patients until they weigh between 30 and 40 kg. The current catheter requires a large noncoring needle, and the placement should be done as a sterile/clean procedure to prevent infection. Ideally, the catheter should only be used by the apheresis staff for red cell exchange. It is recommended to use 1000 u/ml heparin for heparin lock and to use TPA if there are any problems related to flow during a procedure.

Hypocalcemia can be avoided with the use of calcium gluconate infusion. Calcium gluconate diluted to 50 mg/ml is infused at 0.25–0.5 mg/kg/minute. Ionized calcium monitoring is to provide the optimum infusion rate initially and less frequently once a rate is established. A bolus of calcium gluconate for symptomatic hypocalcemia can be given: 250 mg over five minutes for adults and 5 mg/kg for children over five minutes.

The transfusion goal for erythrocytapheresis should be an end hematocrit of 27%. This will reduce the iron burden of patients who come to transfusion with higher hematocrits. Many patients will not need chelation, and the postexchange transfusion hematocrit can eventually be equal to the pretransfusion hematocrit. This is a practical goal for chronic transfusion where whole units are used and end hematocrit is easily obtained.

Transfusion using percentage of hemoglobin S (fraction of cells remaining [FCR]) should be used in acute situations where the initial percentage of hemoglobin S is estimated to be close to 100% and the percentage of hemoglobin S is required to be a low level, such as 30%. Large-volume exchanges should be done with monitoring of the ionized calcium and replacement with calcium gluconate.

**Manual exchange transfusion**

There is no universal standard for the performance of manual exchange transfusions. This method is used in developed, resource-rich countries as well as resource-poor countries. Partial exchange transfusions have used a predetermined phlebotomy followed with simple transfusion or successive aliquots of whole blood being removed and replaced by whole blood diluted to a desired hematocrit with albumin or normal saline. Hypocalcemia can be a problem due to the citrate in the red cell preservation solution. It is recommended that the exchange transfusion be accomplished by exchanging 25–50% total blood volume and repeating if necessary to reach the desired percentage of hemoglobin S and hematocrit.

**Transfusion monitoring**

Although alloimmunization is reduced in patients who are transfused with partially phenotypically matched blood products, alloimmunization is not prevented. Suspected transfusion reactions should be pursued to determine whether alloimmunization has occurred. Autoantibodies are relatively common and are not prevented by providing phenotypically matched products. Autoantibodies are known to mask alloantibodies.

For sickle cell disease, it has been shown that a dedicated pool of African-American donors for patients requiring chronic transfusion may increase the rate of Rh alloimmunization. Both the donors and recipients are likely to have Rh variant genes leading to a high rate of Rh alloimmunization. Almost 60% of patients transfused from African-American donors were alloimmunized in a recent study. The rate of Rh alloimmunization in chronically transfused patients was 45% versus 12% in the episodically transfused patients. High-resolution genotyping of donors and recipients may resolve this problem.

The mean pretransfusion hemoglobin for chronically transfused sickle cell disease should ideally be 9–9.5 g/dl. The hemoglobin posttransfusion should not exceed 12 g/dl. Hemoglobin levels higher than 12 g/dl increase blood viscosity with the potential for increased morbidity. Sickle cell patients receiving simple transfusions should be transfused at four-week intervals with the goal of a hemoglobin S percentage as close to 30% as possible prior to transfusion for stroke or stroke risk. The optimal hemoglobin S percentage for other complications is not defined, but a goal of less than 45% hemoglobin S would be reasonable. If the pretransfusion hemoglobin S is higher than the target hemoglobin S, the patient may need an increased frequency of transfusions or increased volume of transfusion, and this is more easily accomplished with erythrocytapheresis. The administration of hydroxyurea (25 mg/kg/d) to patients who are chronically transfused may increase fetal
hemoglobin and reduce erythropoiesis, increasing control of the patient’s hemoglobin S.\textsuperscript{169}

During transfusing by erythrocytapheresis, the goal for the end hematocrit should be 27%. A higher end hematocrit will lead to increased iron accumulation. An end hematocrit of 27% will slow iron accumulation in some patients and can eliminate iron overload in others.\textsuperscript{170} Increasing the numbers of units exchanged can reduce the hemoglobin S (FCR), although a large number of units will lead to removal of the donor red cells near the end of the red cell exchange with only minor decreases in the FCR. The use of an end hematocrit higher than the pretransfusion hematocrit cannot be avoided in all patients, such as those who have a high rate of hemolysis. The goal of exchange transfusion should not be narrow suppression but a low percentage of hemoglobin S with an adequate hematocrit in order to avoid iron overload. Patients who come to transfusion with a high hematocrit may benefit from a depletion exchange procedure. A depletion exchange is a two-stage exchange with a phlebotomy to a predetermined hematocrit in the first stage and an exchange transfusion to a higher hematocrit in the second stage. Depletion exchange can lead to less blood exposure in some patients. There may be a slightly higher incidence of adverse events, primarily hypocalcemia.

For sickle cell patients treated with simple transfusion, the goal should be the suppression of erythropoiesis by increasing the hemoglobin at the end of the transfusion to between 11 and 12 g/dl. During simple transfusion, evaluate total blood requirement every 12 months, and calculate all blood given to the patient (total volume) divided by an average weight over the past six months (cc/kg/year). If transfusion requirement is greater than 200 cc/kg/year, the cause for such a high transfusion requirement should be explored. There is a point at which chelation becomes difficult or impossible with high annual transfusion requirements.

The transfusion goal for thalassemia is higher than that for sickle cell disease. The pretransfusion hemoglobin should be between 9 and 10 g/dl. This may require monthly transfusion in infants and young children, with transfusions every three weeks in adolescent and adult patients. The posttransfusion hemoglobin should be 12–13 g/dl. Splenomegaly can lead to significant hyper-splenism with an increase in blood requirement. Splenectomy should be considered if the annual blood requirement is over 200 ml/kg/year. Splenectomy can reduce the annual red cell requirement. Prior to splenectomy, patients should be fully immunized. Treatment with aspirin following splenectomy can decrease the risk of pulmonary hypertension.\textsuperscript{171} Aspirin is not an effective treatment once pulmonary hypertension is established.\textsuperscript{172} See Table 11.7.

### Hyperviscosity

Overtransfusion should be avoided in the hemoglobinopathies. Hyperviscosity can lead to complications in patients with thalassemia as well as sickle cell disease. The level of hematocrit that may cause morbidity in thalassemia is higher than in sickle cell disease. A hematocrit of greater than 36% in sickle cell disease following a simple transfusion can lead to hypertension and posterior leukoencephalopathy or stroke. Patients who have thalassemia can have morbidity with hematocrits of over 45%.

Transfusion to a hematocrit greater than 36% can lead to morbidity in sickle cell anemia, particularly if the percentage of hemoglobin S is not reduced to below 50%. Red cell transfusion to a hematocrit between 30% and 33% is adequate for all indications. Erythrocytapheresis\textsuperscript{173} enables an isovolumetric transfusion, but hyperviscosity\textsuperscript{174} remains an issue if not carefully monitored by the apheresis physician. The goal for end hematocrit during erythrocytapheresis should reduce an elevated hematocrit to 33% to avoid the complications of hyperviscosity in some patients with sickle cell anemia and thalassemia, those with SC disease, or others presenting with elevated hematocrit.\textsuperscript{175} Transfusion to increase the hemoglobin to above 33% only can be detrimental.\textsuperscript{176} Transfusion to a hematocrit greater than 38% has resulted in increases in blood pressure, congestive heart failure, stupor, coma, intracerebral infarct, or hemorrhage.\textsuperscript{177}

At a hematocrit of 25%, patients with homozygous S have a blood viscosity slightly less than homozygous A with a hematocrit of 45%.\textsuperscript{178} Above a hematocrit of 45%, hemoglobin A blood becomes more viscous and oxygen transport declines.\textsuperscript{174} Oxygen delivery with hemoglobin S begins to decline with a hematocrit of 30–35%. During hypoxia, these effects are increased if the percent hemoglobin S is greater than 30%.\textsuperscript{167}

### Alloantibodies and autoantibodies

Autoimmunization\textsuperscript{179} or alloimmunization\textsuperscript{180} should be considered if the pretransfusion hemoglobin in a chronically transfused patient is less than 7.0–7.5 g/dl or is significantly less than usual following a transfusion. In sickle cell disease, it should be assumed that there is new antibody formation if the percentage of hemoglobin S and the reticulocyte count are both elevated. The indirect antiglobin test (IAT) and the direct antiglobin test (DAT) may be negative due to consumption of the antibody and antibody-coated red cells during hemolysis. An investigation for a new antibody should be undertaken prior to transfusion. Even micropositive IAT results should prompt a consideration of alloimmunization, as this could be the first indication of a new antibody. If an antibody is suspected after the initial screening, the specificity of the antibody must be determined by the blood bank reference laboratory or by a regional reference laboratory prior to transfusion.

Autoantibodies are known to obscure alloantibodies.\textsuperscript{181} A high index of suspicion is needed to prevent severe delayed transfusion reactions in patients who have an autoantibody obscuring an alloantibody. The management of antibodies in patients who require chronic transfusions and develop alloimmunization is not straightforward.\textsuperscript{182} If extended antigen typing is necessary, finding compatible units can be difficult or even impossible.

Autoantibodies are common in chronically transfused patients with sickle cell disease, and they may lead to increased transfusion requirements due to shortened red cell survival.\textsuperscript{183} It is not clear why autoantibodies appear to be so prevalent in this group of patients.\textsuperscript{184} Occasionally, the specificity of the autoantibody is an
antigen occurring on the patient’s red cells. Anti-e is the most common specificity in cases of autoimmunization when an antibody type can be identified. The term least incompatible is occasionally used by blood bank technicians, but has no meaning in transfusion medicine and is discouraged. When an autoantibody is detected, the patient’s phenotype or genotype can be used to help determine if an underlying alloantibody exists. Safe blood can be provided if alloantibodies have been ruled out and the appropriate units are available for transfusion.185

The use of phenotypically or genotypically matched red cells for major antigens (D, C, c, E, e, and Kell) from the beginning of a chronic transfusion regimen can prevent alloimmunization to a significant degree.186 Increased red cell exposure during erythrocytapheresis has been shown not to increase alloimmunization.187 The safest units are those tested prior to transfusion for antigen negativity, rather than historically negative units.

Delayed hemolytic transfusion reaction
Acute hemolytic transfusion reactions are rare in sickle cell disease and thalassemia. DHTRs are much more common than would be expected for the general population. Some studies report up to 11% of patients will have DHTRs.180 Many of these DHTRs will go unnoticed if they are not severe. A complete blood count with a reticulocyte count and a percentage of hemoglobin S prior to transfusion will be pathognomonic for a DHTR. The hemoglobin will be lower than baseline, the reticulocyte count will be higher, and the percentage of hemoglobin S will be higher than usual. The indirect antiglobin test may not be positive due to consumption of the offending antibody. The crossmatch may be compatible due to the absence of antibody in the recipient's plasma. With this presentation prior to a transfusion, the patient should not be transfused, and an investigation for the antibody should be undertaken. Occasionally, patients will present 10–14 days following a transfusion with symptoms that can be mistaken for a vaso-occlusive episode. If they have hematuria, they may be suspected of having papillary necrosis. If fever is present, they may be suspected of having infection.188 A complete blood count with a reticulocyte count will contribute to the diagnosis in a patient who has been recently transfused. Some patients will have hyperhemolysis with no red cell antibody found on investigation. The anemia can be severe, requiring immune suppression and support.

Hyperhemolysis
Patients who have sickle cell disease can have dramatically decreased hemoglobin levels or other complications during vaso-occlusive episodes. These events have been termed hyperhemolytic episodes.136,180,190 They may or may not be associated with a recent transfusion. They are not isolated to sickle cell disease.191

Hyperhemolytic transfusion reactions related to transfusion can be life-threatening and are similar to, but distinct from, other types of hyperhemolytic episodes. Continuing to transfuse in the face of falling hemoglobin during an immune-mediated hyperhemolytic transfusion reaction can exacerbate the hemolysis leading to life-threatening anemia. There have been no prospective studies to guide therapy. Immune suppression is often used with steroids, immunoglobulin, and rituximab, generally in that order. High-dose erythropoietin has also been recommended.192 Transfusions should be reserved as a lifesaving measure. Apheresis has been used as an adjunct to treat hyperhemolysis with serial plasmapheresis followed by red cell exchange or by plasma to red cell exchange.193 Frequently, no inciting antibody will be found, so patients can be successfully transfused once the event has resolved.

There is a relationship between transfusion, corticosteroid use, hypertension, intracranial hemorrhage, and stroke.194 Patients should be monitored for hypertension and fluid overload when they are receiving intensive therapy for hyperhemolysis.

Iron overload and chelation therapy
Iron is regulated by absorption because there is no mechanism for excretion. Nonheme iron is absorbed from the intestinal lumen as ferrous iron (Fe2+) by divalent metal transporter 1.195 The iron can be stored in the enterocyte and returned to the villi surface or transported from the enterocyte to the circulation. The membrane transporter for iron entry to the circulation is ferroportin. Cellular expression of ferroportin is controlled by intracellular iron, iron-responsive elements, and heme. Ferroportin is regulated in a negative manner by hepcidin, a peptide hormone produced by the hepatocytes. Hepcidin is regulated by iron via elements of the bone morphogenetic protein pathway and in an unknown manner by erythropoiesis. Hepcidin is also regulated by inflammation, increasing production with increasing levels of IL6 and possibly other cytokines. The physiology and regulation of hepcidin are complex.196

Hepcidin regulation is partly responsible for the decreased effects of iron loading in sickle cell disease compared to thalassemia. Most of the disparity between hemosiderosis in thalassemia versus sickle cell disease is due to the ineffective erythropoiesis of thalassemia, which significantly decreases hepcidin production in the liver, increasing iron absorption and increasing the release of iron from the enterocytes, as well as from macrophages and hepatocytes. Patients with sickle cell disease do not have the degree of ineffective erythropoiesis and have a chronic inflammatory state with the absorption of half as much iron from the diet compared to patients with thalassemia.198 Due to decreased iron absorption and effective erythropoiesis, there are less transferrin saturation and less non-transferrin-bound iron (NTBI) in sickle cell disease compared to thalassemia. Increases in NTBI are associated with tissue damage, particularly in the endocrine organs. Increases in cardiac iron from NTBI are associated with cardiac disease in thalassemia.199 Morbidity and mortality from other causes are amplified in adult patients with transfusion-induced hemosiderosis.200

Monitoring iron overload
Serum ferritin is a routinely available laboratory test, but it results in inaccurate determination of iron loading when used alone.202 Serial trends are more important than single results. The chronic pro-inflammatory state of sickle cell disease makes serum ferritin levels a suboptimal method in making major iron chelator dose adjustments.202 Measurement of hepatic iron by liver biopsy has been replaced by noninvasive, reliable imaging techniques such as the superconducting quantum interference device (SQUID, or ferriometry) or MRI.203 Specialized software is needed for MRI iron determination. In addition to evaluation of hepatic hemosiderosis, which reflects total body iron stores, T2* cardiac MRI quantitates cardiac iron.205 Due to differences in iron loading, T2* MRI rarely shows cardiac dysfunction in patients with sickle cell disease who have been transfused for less than 10 consecutive years.206 Cardiac
iron is much more significant for patients with thalassemia.\textsuperscript{207} In thalassemia, there is a relationship between iron, pancreatic function,\textsuperscript{208} and pituitary function.\textsuperscript{209}

**Initiation of chelation**

Chelation should be considered after 1–2 years of transfusion therapy, when the serum ferritin is approximately 1500 ng/ml, or when the hepatic iron is greater than 7 mg/gram dry weight.\textsuperscript{210} Optimal iron chelation should maintain serum ferritin between 500 and 1000 ng/ml. Because ferritin underestimates iron in sickle cell disease, it is important to have a quantitative measurement as a baseline for future evaluation. Compliance with chelation therapy is probably the most important factor in reducing the morbidity of chronic transfusion therapy.\textsuperscript{211} Frequent evaluation of compliance and counseling is necessary in most patients for effective therapy.

**Treatment with deferoxamine (desferal)**

Iron is removed much more efficiently when deferoxamine is infused over a long period at a relatively low dose. The dose depends upon the age of the patient and the degree of iron overload. Side effects of deferoxamine are greater with lower levels of iron and in children under 2–3 years of age.

Subcutaneous deferoxamine should be administered at 30–50 mg/kg. Eight to 12 hours, 5–7 days per week is the standard dose for home therapy. Starting at fewer days per week may help the family adapt to and accept the new therapy. Ascorbic acid (vitamin C) 2-mg/kg/day (100–250 mg maximum) orally after infusion has been initiated increases iron excretion, but without deferoxamine, it will increase oral iron absorption.\textsuperscript{212}

**Oral iron chelators**

**Ferriprox (L-1, deferiprone)**

Deferiprone has been used in Europe and in other countries and found to be relatively safe and effective in removing iron. Deferiprone has a short half-life requiring three-times-a-day dosing. The daily dose is 75 mg/kg per day. It may be used as a monotherapy, but it is the novel effect of this drug to remove cardiac iron that has made it attractive in combination chemotherapy in patients with cardiac hemosiderosis. One of the side effects, agranulocytosis (1.7%), is serious. This is a rare complication that requires monitoring of the leukocyte count while this drug is being administered. Neutropenia (6.2%) can precede agranulocytosis; neutrophil counts are monitored weekly. Some patients also experience joint swelling and pain during therapy with this chelator.

**Exjade (deferasirox)**

Deferasirox is the most recently developed iron chelators and has been extensively studied.\textsuperscript{213} It is an oral iron chelator with a relatively long half-life. This allows for once-daily dosing. It has become the most-used iron chelator in the United States. The starting dose is 20 mg/kg per day. It generally maintains a negative iron balance when used at 30 mg/kg. A tablet is available. Renal function should be closely monitored.

**Patients with significant iron overload**

Deferoxamine combined with deferasirox or deferiprone is an effective chelation approach for severe hemosiderosis.\textsuperscript{214} A physician familiar with the toxicity of these drugs should oversee their administration.

**Assessment and monitoring of iron overload**

Annual assessment of endocrine function including thyroid, parathyroid, pancreas, adrenal, pituitary gland, and bone density should be performed.

Evaluate serum ferritin level quarterly. Ferritin levels greater than 3000 ng/ml (in the absence of hepatitis or other inflammatory process) and hepatic iron greater than 7 mg/gm dry liver weight are considered evidence of iron burden in thalassemia. Signs of elevated iron should prompt an evaluation of compliance, the chelation protocol, the annual and semiannual transfusion requirement, as well as hepatitis status and liver function.

**Assessment of side effects and toxicity of iron chelators**

Patients require ongoing monitoring for chelator toxicity. All patients should have hearing and vision screening, and monitoring of growth, renal, and liver functions. Patients treated with deferasirox require monthly renal function testing. Deferiprone use requires weekly monitoring of white cell count.

**Congenital hemolytic anemia (see Table 11.8)**

**Red cell enzymopathies**

**Glucose-6-phosphate dehydrogenase deficiency**

Glucose-6-phosphate dehydrogenase deficiency (G6PD) is the most common enzymopathy in humans.\textsuperscript{215} G6PD is the first enzyme in the pentose phosphate pathway providing reducing power for the red cell. Without mitochondria, the pentose phosphate pathway is the only source of NADPH available to the red cell, which provides for a high level of reduced glutathione. In the absence of NADPH production, there is no protection against cellular oxidative damage through the regeneration of reduced glutathione by glutathione reductase. Without this reduction potential in the red cell, oxidative membrane damage and hemolysis occur when the cells are presented with excessive oxidative stress.

G6PD has classical X-linked inheritance with the deficiency primarily affecting males, although females homozygous for the deletion or heterozygous with lyonization can be symptomatic with the disease. There are over 160 mutations leading to inactivation of the G6PD enzyme; most are single base mutations leading to amino acid substitutions and inactivation.\textsuperscript{216}

The G6PD mutation has been most common in areas were malaria is prevalent as there is restricted parasite growth in the affected red cells.\textsuperscript{217} As would be expected, the highest prevalence is in Africa, the Mediterranean, the Middle East, Southeast Asia, and the Pacific Islands. Although there are numerous mutations leading to the inactivation of G6PD, two common mutations are found: one in African and in areas of the African Diaspora, and one in the countries surrounding the Mediterranean, Israel, India, and Indonesia. The African variant is G6PDA-, the other second most common variant is G6PD Mediterranean. In the absence of oxidative stress, these mutations do not cause hemolysis. The presence of the mutation does not appear to have an effect on growth, development, or life expectancy.\textsuperscript{218} There is evidence that there may be a reduction in coronary artery disease in males with this deficiency.\textsuperscript{219}

Infection is the most common cause of acute hemolysis in G6PD deficiency. Viral hepatitis can be complicated by renal failure. The severity of the hemolysis depends on the type of infection and other compounding factors, but it can be severe. Numerous drugs have been implicated with hemolysis in G6PD deficiency; the degree of
hemolysis can vary between individuals and with re-exposure in the same individual.220 Favism is thought to be associated with the Mediterranean mutation and leading to severe hemolysis, particularly if fresh fava beans are ingested.

**Pyruvate kinase deficiency**

Pyruvate kinase deficiency (PKD) is much less common than G6PD, but is the most common cause of hemolytic anemia due to an enzyme abnormality of the glycolytic pathway. It is a more common cause of nonspherocytic hemolytic anemia than Class I G6PD. There are four isoenzymes (M1, M2, L, and R) found on two chromosomes: the gene for the L and R isoenzymes (PK-LR) on chromosome 1 (1q21) using different promoters to produce the two isoenzymes.222 The R isoenzyme is expressed exclusively in red cells. The deficiency is autosomal recessive. The prevalence is unknown, but mutations have been reported in European and Asian populations.223 One hundred and fifty-eight mutations are known to cause nonspherocytic hemolytic anemia.

**Congenital nonpherocytic hemolytic anemia**

Congenital nonpherocytic hemolytic anemia includes Class I variants of G6PH and PKD. There are 61 Class I variants of G6PD that lead to a severe chronic hemolytic anemia.221 These patients present younger, at a median age of 4 years versus 22.5 years for other mutations. There are three mutations that seem to be the most common worldwide: G6PD Guadalajara 1159 C>T, G6PD Beverly Hills 1160 G>A, and G6PD Nashville 1178 G>A. These patients present with neonatal hyperbilirubinemia, chronic hemolytic anemia, jaundice, hyperbilirubinemia, moderate splenomegaly and reticulocytosis, and cholelithiasis. They require chronic red cell transfusion and may not respond to splenectomy. (See Table 11.9.)

Red cells are dependent on glycolysis for the production of adenosine triphosphate (ATP). Pyruvate kinase catalyzes two steps in the production of ATP. Deficiency results in ATP depletion and loss of red cell integrity. Upstream intermediates are increased in the red cell, including 2,3-diphosphoglycerate, which inhibits hexokinase, exacerbating the defect in the enzyme pathway. Due to this increase in 2,3 DPG, transfusion should not be determined by the hemoglobin, but by clinical symptoms of hypoxia.

The degree of anemia can be predicted by the neonatal jaundice and the need for exchange transfusion. Most of these infants will go on to require chronic red cell transfusions during infancy until they have had a splenectomy. The effect of splenectomy cannot be predicted, but it can raise the hemoglobin 2–3 g/dl, alleviating the need for transfusion.

Two missense mutations are associated with severe PKD (994A and 1529A). The most severe disease is found in “null” mutations with intrauterine growth retardation, severe anemia at birth requiring exchange transfusion, and transfusion dependence until splenectomy. Death has occurred in the neonatal period in infants with this severe genotype.225 Hemosiderosis may occur without transfusion therapy or as a complication of chronic transfusion therapy in these patients. The transfusion requirement can decrease with age.

**Disorders of the red cell membrane**

The red cell membrane has a unique structure that is elastic, deformable without fragmentation, and rapidly responsive to changes in stress.225 These properties are due to the structure of the lipid bilayer membrane and the underlying cytoskeleton. The lipid bilayer has an asymmetric distribution of phospholipids with phosphatidylserine (PS) localized to the inner layer. Both PS and internally located phosphoinositides interact with the spectrin and protein 4.1R anchoring the membrane to the cytoskeleton. Loss of this asymmetry, with PS translocated to the outer membrane, leads to phagocytosis and the membrane destruction seen in sickle cell disease and thalassemia. Key components of the membrane include band 3, glycophrin C, RhAG, α and β spectrin, actin, and ankyrin.

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**Table 11.8 Inherited Hemolytic Disorders**

<table>
<thead>
<tr>
<th>Membrane Defects</th>
<th>Mutation</th>
<th>Inheritance</th>
<th>Prevalence in disease population</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherocytosis (HS) prevalence: 1/2000-3000</td>
<td>Ankyrin-1</td>
<td>AD, AR, de novo</td>
<td>60% in the HS population</td>
<td>Mild to Moderate</td>
</tr>
<tr>
<td>Spherocytosis (severe)</td>
<td>α spectrin</td>
<td>AR (Homozygote)</td>
<td>&lt;5% in HS population</td>
<td>Severe</td>
</tr>
<tr>
<td>Elliptocytosis (HE) Prevalence: 3–5/10,000 (US)</td>
<td>α, β spectrin</td>
<td>AD</td>
<td>Asian American</td>
<td>Severe</td>
</tr>
<tr>
<td>Severe HE</td>
<td>α, β spectrin</td>
<td>AR (Homozygote)</td>
<td>African descent predominates</td>
<td>Severe in childhood</td>
</tr>
<tr>
<td>Pyropoikilocytosis</td>
<td>α, β spectrin</td>
<td>AR (Homozygote)</td>
<td>Southeast Asian descent</td>
<td>Mild</td>
</tr>
<tr>
<td>SEA ovalocytosis</td>
<td>Band 3</td>
<td>AD</td>
<td>Rare</td>
<td>Severe</td>
</tr>
<tr>
<td>Stomatocytosis dehydrated (DSHS)</td>
<td>RhAG Mutation</td>
<td>AD</td>
<td>Rare</td>
<td>Less severe</td>
</tr>
<tr>
<td>Stomatocytosis hydrated (DSHS1)</td>
<td>PIEZO1 (North America)</td>
<td>AD</td>
<td>Rare</td>
<td>Severe</td>
</tr>
<tr>
<td>Enzymopathy</td>
<td>Class I</td>
<td>X chromosome: numerous variants</td>
<td>X-linked recessive</td>
<td>Common</td>
</tr>
<tr>
<td>G6PD deficiency prevalence: common in African descent, Sardinian, Greek, others</td>
<td>Class UUII</td>
<td>AR</td>
<td>Most common of the related glycolytic enzymopathies</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Pyruvate kinase deficiency prevalence: rare</td>
<td>47 mutations leading to deficiency</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Table 11.9 Classes of G6PD Deficiency**

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Severely deficient; chronic nonpherocytic hemolytic anemia</td>
</tr>
<tr>
<td>Class II</td>
<td>Severely deficient; (1–10% activity) acute hemolytic episodes</td>
</tr>
<tr>
<td>Class III</td>
<td>Moderately deficient; (10–60%) mild</td>
</tr>
<tr>
<td>Class IV</td>
<td>Normal activity (60–150%) mild</td>
</tr>
<tr>
<td>Class V</td>
<td>Increased activity (&gt;150%) mild</td>
</tr>
</tbody>
</table>
Hereditary spherocytosis
This membrane disorder occurs in all racial groups, but it is particularly common in northern Europeans where the prevalence is one in 3000. The inheritance is dominant in 75% and recessive in 25%. Spherocytosis is recognized as mild with compensated hemolysis in about 6% of cases, although many patients may go unrecognized; moderate in 60% with hemoglobin of 8–10 g/dl and reticulocytosis of >8%; moderately severe (10% of total patients) with hemoglobin in the range of 6–8 g/dl, higher reticulocyte counts, splenomegaly, and intermittent transfusion requirement; and a small number (<5% of total patients) who have severe disease and a transfusion requirement. The most severe cases have autosomal recessive inheritance.

Loss of membrane determines the severity of this disease, leading to sequestration of defective red cells in the spleen. The most common defects are inherited abnormalities in ankyrin (50%), spectrin (20%), and band 3 (15–20%). Splenectomy will significantly decrease the severity of anemia in this disease. Rh-deficient cells or Rh-null cells have decreased or absent RhAG leading to stomatocytosis; this is less than 1% of the total cases.226

Hereditary elliptocytosis
Hereditary elliptocytosis (HE) has a worldwide distribution, but it is more common in malarial areas. The majority of mutations are related to α-spectrin, occurring in about 65% of cases. In 30% of cases, the mutation is β-spectrin; homozygotes have severe anemia. A small number, 5%, of mutations are in the 4.1R protein. Most mutations are missense mutations; notable is Arg28His, which is seen in African Americans and leads to severe hemolytic anemia. Hereditary pyropoikilocytosis is not a distinct membrane disorder; it is a HE variant that is either homozygous or a compound heterozygote for a spectrin mutation.227

Hereditary ovalocytosis
Hereditary ovalocytosis is common in malarial regions of Southeast Asia and the Philippines. The inheritance is autosomal dominant; only heterozygotes have been seen, with the assumption that homozygosity is incompatible with life. Only one mutation has been identified, a 27 base pair deletion of band 3. This membrane disorder is relatively benign with no or minimal hemolysis.

Hereditary stomatocytoses
These disorders lead to overhydrated hereditary stomatocytosis (OHSt) or dehydrated stomatocytosis (DHSSt). Southeast Asian ovalocytosis is included in this group, a benign disorder.228 DHSSt may occur with pseudohyperkalemia, with perinatal fluid effusions, or as a single finding. DHSSt is dominantly inherited. The precise mutation causing DHSSt is not known. There is a compensated mild to moderate hemolytic anemia. OHSt has been characterized as having dominant inheritance of mutations in the RHAG gene in some cases. Other mutations have not been characterized. Hemolytic anemia can be mild to moderate. There have been case reports of thromboembolic events following splenectomy for hemolytic anemia in stomatocytosis.229

The congenital hemolytic anemias are a diverse group of blood diseases that generally do not require red cell transfusion. In the few severe presentations, patients will require red cell transfusions on a chronic basis or intermittently with viral illness and fever. In the case of G6PD deficiency, acute anemia due to exposure to inciting drugs, foods, or chemicals can require emergent transfusion.

Key references
A full reference list for this chapter is available at: http://www.wiley.com/go/simon/transfusion

68 Ware RE, Helms RW. Stroke with transfusions changing to hydroxyurea (SWiTCH). Blood 2012;119 (17): 3925–32.