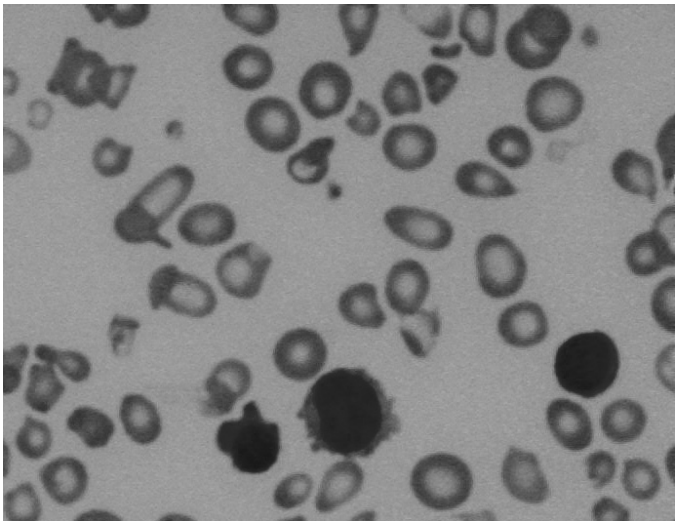
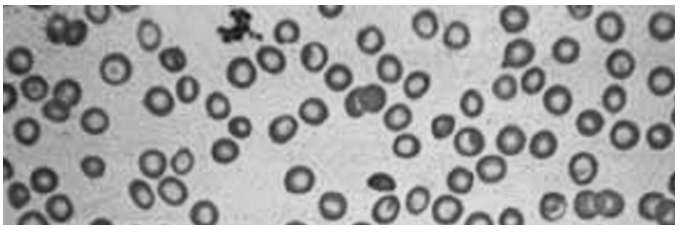
Standards of Care Guidelines for Thalassemia

2012





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1 Introduction

Thalassemia is a complex group of diseases that are relatively rare in the United States but common in Mediterranean regions and South and Southeast Asia. Worldwide, there are 350,000 births per year with serious hemoglobinopathies. In the United States, as a consequence of immigration patterns, occurrence of thalassemia disorders is increasing.

Treatment for thalassemia has dramatically improved. Patients should live full lives with careers and children of their own. Unfortunately, many patients die prematurely or develop morbid preventable complications. Outcomes are far better for patients whose care is coordinated by thalassemia centers (Modell, B., Khan, M., and Darlison, M. Survival in beta thalassaemia major in the UK: Data from the UK Thalassaemia Register. *Lancet* 355 [2000]: 2051–2052. Porter, J.B., and Davis, B.A. Monitoring chelation therapy to achieve optimal outcome in the treatment of thalassaemia. *Best Practice & Research: Clinical Haematology* 15 [2002]: 329–368). The majority of patients are managed in small programs which may not have access to recommended monitoring and treatments. Therefore, an established network of care between thalassemia centers, local providers, and patients is required for optimal treatment of thalassemia patients in North America. Each component of this network should follow the *Standards of Care Guidelines* and communicate frequently.

All patients should undergo at least an annual comprehensive assessment at a thalassemia center. During such an assessment, recommendations are summarized after consultation with multiple specialists and communicated directly to the primary provider and family. Verbal and written communication between the center and the primary provider should occur at least every six months following the formal annual visit and when there are changes in the patient's clinical and treatment plan.

A specialty center manages the regular care of at least 20 patients. A specialty program includes a team of thalassemia experts working closely together. This team includes a hematologist, a nurse specialist, a hepatologist, a cardiologist, an endocrinologist, a psychologist, a genetics counselor, a social worker, and a dietitian. A center includes linkage to a thalassemia-oriented bone marrow transplant and fertility service. Within the center, specialty laboratory support includes diagnostic imaging, a hemoglobinopathy reference laboratory, and a clinical research center.

The extent of services provided by a primary or regional program varies. Services may include supervising of regular transfusions and providing necessary medications according to the standards of care. Primary care, including monitoring of growth and general health and—for pediatric patients—liaison with the school, is centralized in the local program. Early recognition and stabilization of acute complications—i.e., sepsis, transfusion reactions, drug reactions, or cholecystitis—require close communication between the primary provider and the family. Twenty-four hour backup consultation should be available through the patient's designated thalassemia center.

In June 2000, a group of providers developed and finalized the first *Standards of Care Guidelines for Thalassemia,* with the goal of standardizing the management of care for thalassemia patients throughout the state of California. Since then, significant changes in technology and treatment have developed that required the original guidelines to be updated here.

1.1 Common Definitions Used in Thalassemia

Beta thalassemia disorders result from decreased production of beta globin chains, resulting in relative excess of alpha globin chains. The degree of excess nonfunctional alpha chains is the major predictor of disease severity. Beta^0 thalassemia refers to the absence of production of beta globin. When patients are homozygous for a beta^0 thalassemia gene, they cannot make any normal beta chains (hemoglobin A). Beta+ thalassemia indicates a mutation that presents decreased but not absent production of beta globin. Thalassemia patients in which one or both of their beta thalassemia mutations are beta+ mutations make some hemoglobin A, and the disorder may be less severe. Beta thalassemia major is a clinical diagnosis referring to a patient who has a severe form of the disease and requires chronic transfusions early in life. Beta thalassemia intermedia is a clinical diagnosis of a patient characterized by a less severe chronic anemia and a more variable clinical phenotype. Alpha thalassemia refers to a group of disorders characterized by inactivation of alpha globin genes. This results in a relative increase in nonfunctional beta globin or gamma globin tetramers and subsequent cell damage. Normally, there are four alpha genes. Absence or non-function of three alpha genes results in hemoglobin H disease, and the loss of all four alpha genes usually results in intrauterine death.

2 DNA Testing Prior to Treatment

Because of the enormous diversity in clinical severity of thalassemia patients, complete DNA testing prior to commencement of treatment is required to determine prognosis, appropriate therapy, and family counseling. Definitive diagnosis and family counseling should be done in conjunction with a thalassemia center.

3 Diagnosis of Thalassemia

Prior to consideration of transfusion therapy, it is critical to confirm the patient's diagnosis. In addition to complete blood count (CBC), hemoglobin electrophoresis is the first diagnostic test. Fractions of hemoglobin A, A_2, F, H, E, and other variants are measured. Hemoglobin analysis by hemoglobin electrophoresis or high performance liquid chromatography is used. Mutations may overlap on the screening test, resulting in incorrect diagnosis or a false negative. Therefore, genetic analysis for both beta-thalassemia and alpha-thalassemia mutations are necessary. In addition, parents and siblings should be screened. Occasionally (up to 20 percent of the time), only a single mutation will be found that is indicative of thalassemia trait. Some such cases result from an autosomal dominant form of thalassemia and others from inheriting a mutation that is not detected by the probes utilized in the DNA testing. Alpha-gene triplication is a common co-factor that may convert a thalassemia trait to a disease or worsen a benign mutation. Testing for co-mutations needs to be requested from the DNA laboratory—otherwise, it will not be performed.

Patients with thalassemia intermedia may have exaggerated anemia due to temporary nutritional deficiencies or infectious complications. It is important to complete a detailed medical history concerning factors that may temporarily lower hemoglobin, including viral illness, marrow-suppressing

medication, or exposure to environmental factors such as lead. Nutritional deficiencies in folic acid or iron may exaggerate anemia. Correcting these deficiencies may raise the hemoglobin level enough to obviate the need for transfusion.* Therefore, laboratory screening of patients is necessary to rule out other causes of anemia.

* Measurements should be taken of the G6PD level, serum ferritin, total iron-binding capacity, serum iron, and red cell folate. A brief therapeutic trial of iron (6 mg/kg/day for four to eight weeks) and folic acid (1 mg/day) are indicated if significant laboratory deficiencies are found.

4 Blood Transfusions

Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. The purpose of transfusion is twofold: to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. However, once started, the transfusion-related complications become a major source of morbidity. Standards must be developed and maintained to ensure a safe and rational approach to the use of blood transfusions in the management of these rare disorders.

Patients with ß+/ß+ thalassemia; hemoglobin E-ß thalassemia; hemoglobin H disease; and hemoglobin H–Constant Spring often have a thalassemia intermedia phenotype and do not necessarily require chronic transfusion. However, the DNA mutations do not reliably predict the clinical phenotype. $ß^0/ß+$ and even $ß^0/ß^0$ may occasionally have a thalassemia intermedia clinical phenotype. The clinical phenotype of thalassemia intermedia patients may change as they age and may require transfusion therapy. Ongoing assessment of transfusion requirements are necessary for both thalassemia major and intermedia.

The decision to start transfusions is based on inability to compensate for the low hemoglobin (signs of increased cardiac effort, tachycardia, sweating, poor feeding, and poor growth), or less commonly, on increasing symptoms of ineffective erythropoiesis (bone changes, massive splenomegaly). The decision to institute chronic transfusion should not be based exclusively on the presence of anemia.

The decision to initiate chronic transfusion therapy requires significant input from the patient, family, and medical team. Anemia alone is not an indication of the need for chronic transfusion. Anemia should be linked with a significant impairment in quality of life or associated morbidities. Factors to consider include: poor growth; inability to maintain daily routines and activities such as going to school and work; evidence of organ dysfunction; evidence of cardiac disease; pulmonary hypertension; and dysmorphic bone changes.

It may be necessary to initiate a six-month trial of blood transfusions in patients of families whose decision to transfuse is uncertain. After six months, transfusions can be stopped and the patient observed for a brief period of time to give the family and medical team information as to the clinical benefits and psychological impact of the transfusions.

4.1 Assessing the need for routine transfusions

The decision to start regular transfusions is clear when the initial hemoglobin level is well below 6 g/dL. To assess a child's need for routine transfusions due to thalassemia, anemia caused by sepsis or viral infection must be ruled out. Assessment may be accomplished by withholding transfusions and monitoring weekly hemoglobin level. If the hemoglobin drops under 7 g/dL on two occasions, two weeks apart, then regular transfusions should be commenced.

Patients with a hemoglobin level less than 7 g/dL may sometimes require regular transfusions in the presence of growth impairment, marked skeletal changes, or extramedullary hematopoiesis.

4.2 Baseline laboratory tests prior to regular transfusions

An extended red cell phenotype must be obtained to reduce the future probability of developing alloantibodies. If a child has already started transfusions, the red cell antigen genotype can be determined by DNA testing, and at the minimum, should include the C, E, and Kell alleles.

Although the hemoglobin level can define a patient's disease type, seldom does it alone determine the need for transfusion. Antibodies to hepatitis B, hepatitis C, and HIV should also be determined. Patients should demonstrate immunity to hepatitis B. The bilirubin, transaminase, and serum ferritin levels should be checked.

4.3 Transfusion administration and monitoring

The aim of transfusion therapy is to permit normal growth and activity level and to prevent skeletal changes associated with marrow hyperplasia. Adequate transfusion therapy will also reduce splenomegaly and hypersplenism and decrease absorption of dietary iron.

4.3.1 Transfusion facility

Transfusions should be administered in a designated outpatient clinical area by staff experienced with transfusion policies. Written transfusion policies—including maximum rate, volume of transfusion, and protocol for transfusion reactions—are required. The availability of access to outpatient transfusion services on weekdays, weekends, and evenings is important for school-aged children and working adults.

4.3.2 Type of blood product

The product of choice is packed red blood cells depleted of leucocytes and matched with the patient's red antigen phenotype for at least D, C, c, E, e, and Kell.

Whole blood or blood without leukodepletion is unsuitable for regular transfusions, since non-hemolytic transfusion reactions are common. When possible, large units less than two weeks of age are recommended.

Patients should be assessed for hemolytic reactions if any adverse event is noted during a transfusion. Febrile and allergic reactions may respond to acetaminophen and diphenhydramine before future transfusions.

Patients who develop allergic reactions should be given washed packed red blood cell units.

The development of alloantibodies can complicate transfusion therapy and may require the use of frozen packed red blood cell units of rare blood types. Some patients are transfused with irradiated red cells. This process is used to prevent graft-versus-host disease. It is largely unnecessary unless the patient is undergoing a bone marrow transplant or has an underlying immunodeficiency. Cytomegalovirus (CMV) infection is transmitted via transfusion. Leukocyte depletion of a red cell unit prevents its transmission. CMV negative units are usually unnecessary once the unit is leukocyte-depleted.

4.3.3 Target hemoglobin and frequency of transfusions

The goal of transfusion is to shut off erythropoiesis as much as possible. Transfusions should generally be given at an interval of three to four weeks. (With aging patients, a transfusion every two weeks may be necessary.) Transfusions should be scheduled in advance and maintained at a fixed schedule. This enables patients and families to establish routines and will improve quality of life.

The amount of blood received on transfusion day is determined by pre-transfusion hemoglobin levels. The target is to maintain the pre-transfusion hemoglobin level between 9 and 10 g/dL. Attempts to maintain pre-transfusion hemoglobin at above 10 g/dL increase transfusion requirements and the rate of iron loading. Transfusions should be given in an outpatient setting with an experienced transfusion team that uses proper safety precautions (patient/blood identification bracelets). Blood should be transfused at 5 mL/kg per hour, and the post-transfusion hemoglobin should not exceed 14 g/dL.

In patients with severe anemia (hemoglobin less than 5 g/dL) or cardiac compromise, the rate of transfusion should be reduced to 2 mL/kg per hour to avoid fluid overload. Diuretics such as furosemide (1 to 2 mg/kg) may be necessary for some patients.

If cardiac insufficiency is present, higher pre-transfusion hemoglobin levels (10 to 12 g/dL) should be maintained with smaller volume transfusions given every one to two weeks.

The patient's weight and pre-transfusion hemoglobin and the volume of transfusion should be recorded at each visit. These values should be periodically reviewed to assess the volume of blood required to maintain the desired pre-transfusion hemoglobin level. Annual blood transfusion requirement in patients without hypersplenism is usually below 200 mL packed red blood cells/kg per year.

4.4 Adverse reactions to transfusions

The very best practices for blood transfusion must be employed, since the need for lifelong transfusions leads to a cumulative increase in the risk of adverse reactions.

Alloimmunization is a frequent problem that can be prevented by transfusing blood matched for the patient's extended red blood cell phenotype (not just the ABO and RhD antigens). An alloantibody screen should be performed prior to each transfusion. An alloantibody is an antibody made by the patient against an antigen present on the transfused red cell. Once alloimmunized, patients may be at risk for developing an antibody against their own red cells (an autoantibody). Up to 10 percent of patients who develop alloantibodies will develop an autoantibody. The presence of an autoantibody does not always result in decreased red cell survival, but it may. An autoantibody will delay the patient's cross match and transfusion program. Autoantibodies can best be avoided by preventing alloantibodies.

If an autoantibody and/or alloantibody is detected, the specific antibodies causing the transfusion reaction should be determined by the blood bank or by a reference laboratory.

The management of patients who develop antibodies requires use of blood matched by extended red cell antigen phenotype.

The risk of transfusion-transmitted infections, while low, is still a concern for known and emerging pathogens, and annual monitoring for hepatitis B, hepatitis C, and HIV is necessary.

The risk of bacterial infection is small, but the transmission of parasitic infections (particularly malaria) is a significant threat in certain geographical areas.

The other complications of blood transfusion include the risk of mismatched transfusion, allergic reactions, and febrile, non-hemolytic reactions.

4.5 Splenectomy

The use of splenectomy in thalassemia has declined in recent years. This is partly due to a decreased prevalence of hypersplenism in adequately transfused patients. There is also an increased appreciation of the adverse effects of splenectomy on blood coagulation. In general, splenectomy should be avoided unless absolutely indicated.

Splenectomy is indicated in the transfusion-dependent patient when hypersplenism increases blood transfusion requirement and prevents adequate control of body iron with chelation therapy. An enlarged spleen—without an associated increase in transfusion requirement—is not necessarily an indication for surgery. Patients with hypersplenism may have moderate to enormous splenomegaly, and some degree of neutropenia or thrombocytopenia may be present.

Annual transfusion volume exceeding 225 to 250 mL/kg per year with packed red blood cells (hematocrit 75 percent) may indicate the presence of hypersplenism. The volume calculation should be corrected if the average hematocrit is less than 75 percent. The possible development of alloantibody should also be ruled out. Splenectomy should be avoided unless there is an inability to maintain iron balance with optimal chelation, or if there are clinically significant complications such as pancytopenia and marked enlargement. Often, hypersplenism develops because of a low pre-transfusion hemoglobin. Increasing the pre-transfusion hemoglobin to between 9.5 and 10 may reverse hypersplenism.

If a decision to perform surgery is made, partial or full splenectomy is the option. Partial splenectomy is a complicated surgery utilized to preserve some splenic function. It should be reserved for infants requiring splenectomy. Full splenectomy can usually be performed by laparoscopic technique. However, open procedure is necessary in cases of marked splenomegaly. The indications for splenectomy in hemoglobin H–Constant Spring patients are different than in beta-thalassemia disorders.

Transfusion-dependent infants with hemoglobin H–Constant Spring respond rapidly to splenectomy but require prophylactic anticoagulation because of a high incidence of serious thrombosis.

Patients must receive adequate immunization against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitides* prior to surgery. Splenectomy should be avoided in children younger than five years because of a greater risk of fulminant post-splenectomy sepsis.

After splenectomy, patients should receive oral penicillin prophylaxis (250 mg twice daily) and be instructed to seek urgent medical attention for a fever over 101º Fahrenheit.

Post-splenectomy thrombocytosis is common, and low-dose aspirin should be given during this time. Another complication following splenectomy is the development of a thrombophilic state. Venous thromboembolism, more common in thalassemia intermedia and hemoglobin H–Constant Spring, can develop following splenectomy.

Patients should have annual echocardiographic measurement of the pulmonary artery pressure to monitor for development of pulmonary hypertension.

4.6 Thromboembolic disease

People with thalassemia are at increased risk of thrombosis. Thrombotic events include pulmonary embolism, arterial occlusion, portal thrombosis, and deep vein thrombosis. Approximately 1 to 2 percent of thalassemia major patients and 5 percent of thalassemia intermedia patients experience a serious thrombosis. One of the most common and serious complications is stroke. Recent brain MRI studies suggest that thalassemia patients (particularly those with thalassemia intermedia) are at high risk for subclinical infarction or silent stroke. Splenectomy significantly increases the prevalence of thrombotic events. Inadequate transfusion may increase the risk of thrombosis secondary to increased release of procoagulant red cell particles. Many people recommend that all post-splenectomy patients should receive anti-platelet or anti-thrombosis therapy with aspirin or low dose warfarin.

5 Iron Overload and Chelation Therapy

Iron overload is the major cause of morbidity for thalassemia patients. Even nontransfused patients develop iron overload secondary to increased intestinal absorption of dietary iron. Iron overload is a leading cause of mortality and organ injury.

Iron overload occurs very rapidly in patients who are on chronic transfusion programs. Since humans have no mechanism other than sloughing of the mucosa of their gastrointestinal tracts or menstruation to excrete excess iron, patients who are being transfused every three or four weeks gain 0.5 mg/kg per day of iron in excess of natural losses. Patients who are not on a transfusion regimen are also prone to iron overload due to significantly increased intestinal absorption of iron secondary to ineffective erythropoiesis.

The only treatment options for removing excess iron are phlebotomy and chelation. While phlebotomy is a very effective way of removing iron, it is not appropriate for patients with thalassemia except after bone marrow transplantation. Thalassemia patients who are not transfusion dependent cannot maintain an adequate hemoglobin level and become symptomatic after phlebotomy. Outpatient exchange transfusion can be used in selected cases to decrease iron intake, but it is not effective by itself in rapidly reducing heavy iron loads and would not be appropriate by itself in the face of cardiac iron loading. The primary treatment for iron overload in thalassemia is chelation, which is described below.

Iron is very toxic to tissue. Under normal circumstances, in humans, iron is transported bound to a carrier protein called transferrin. Transferrin transports iron into certain tissues. Because the iron is bound to this protein, other tissues are protected from the toxic effects of free iron. Patients on chronic transfusion rapidly acquire much more iron than can be bound by transferrin, and free iron levels increase in the blood. This free iron, or so called non-transferrin bound iron, is directly toxic to the heart and other tissues.

There are two goals of iron chelation therapy: the binding of toxic non-transferrin bound iron in the plasma and the removal of iron from the body. Detoxification of excess iron is probably the most important function of chelation therapy. It is clear that certain symptoms of iron overload, such as cardiac arrhythmia and heart failure, can be improved well before local tissue levels of iron have decreased by the continual presence of a chelator in the plasma.

It is useful to think about the toxicity of iron according to the following relation:

Toxicity = [tissue iron] x [patient- and tissue-specific factors] x [time]

Generally, time is measured in years. Thus, it takes three to ten years of chronic exposure to high levels of iron before measurable organ dysfunction occurs. Fortunately, this means that there is time to implement treatment strategies to reduce iron loading. However, depending upon the organ, it can take a long time to significantly reduce iron, so the best strategy is acting early and, in fact, trying to prevent significant iron loading from the start.

New equipment—such as the quantitative MRI for iron and the ferritometer (SQUID)—has enabled providers to measure the amount of iron in the organs and also look at the relationship between excess iron, time, and patient- and tissue-specific factors. Such factors include transfusion regimen; weekly chelation; differences of transport of iron into various organs; genetic differences in antioxidant defense mechanisms; and disease-specific differences in inflammation and metabolism. It is now clear that there is a tremendous range of variability in end organ toxicity among patients who seemingly have the same amount of tissue iron. From a clinical standpoint, this means that end organ function, as well as tissue iron concentration, must be serially monitored during the management of chronic iron overload.

In general, significant iron loading of the liver can be detected after about six months of monthly transfusions, while cardiac loading takes about eight to ten years. The liver loads linearly with time, whereas the heart remains devoid of iron for years. However, once it starts, iron loading of the heart is very rapid. Evidence of liver

damage can occur after about four years of transfusions. The onset of cardiac dysfunction is more complex and less well understood. Quantitative cardiac iron, determined by MRI, is reported by T2*. The lower the number, the more the iron. A cardiac T2* greater than 20 ms is not associated with iron-induced cardiac dysfunction. A cardiac T2* between 10 and 20 ms indicates excess iron in the heart and represents a warning for potential cardiac dysfunction. If the T2* is less than 10 ms, the risk of cardiac dysfunction is high, and treatment should be considered emergent.

Under full chelation with deferoxamine, about 50 percent of liver iron can be removed in four to six months. It takes about 17 months to remove half of the heart iron.

5.1 Initiation of chelation

In general, chelation should be started as soon as the patient becomes significantly iron loaded. Since removal of iron from normal tissues can result in toxicity from over-chelation, it is important to delay the start of chelation until the patient is significantly iron loaded. Since iron loading occurs much faster than toxicity develops, this delay will not put the patient in danger.

General recommendations for treatment with iron chelation are presented in Table 5.1. The decision points are based on total amount of blood transfused, ferritin levels, and degree of iron loading based on liver iron concentration (LIC). Liver iron is measured by biopsy, MRI, or SQUID.

Chelation therapy should be started after about one year of chronic transfusions. This correlates with a serum ferritin of approximately 1,000 ng/mL. LIC is the best measure of total iron loading. LIC should be at least 3,000 µg/g dry weight before starting chelation. The general guidelines for iron chelation are gradually changing. Many experts are increasing the therapy in order to maintain a lower steady-state body iron store. While long-term prospective data is limited on these aggressive protocols, it is felt that more aggressive therapy may be more effective in preventing iron-induced organ injury. This needs to be balanced with the drug toxicity. While the standard recommendations have been to maintain a ferritin between 1,000 and 2,500 ng/mL, several programs are aiming to maintain serum ferritin at 500 ng/mL in adult patients.

Table 5.1: Guidelines for Iron Chelation Therapy and Monitoring

Liver iron concentration (LIC)	Ferritin	Recommended chelation	Monitoring	Comments
< 3,000 µg/g	< 1,000 ng/mL	Lower the dose at < 1,000 ng/mL and hold medication at < 500 ng/mL	Monitor ferritin monthly; start reduced-dose chelation when ferritin goes up to 500 ng/mL and full dose at 1,000 ng/mL, depending on age and risk factors	
3,000 to 7,000 µg/g	1,000 to 2,500 ng/mL	Maintain existing therapy	Monitor ferritin every 3 months	Note changes in trends. More aggressive therapy may be indicated, depending on organ dysfunction.
> 7,000 µg/g	> 2,500 ng/mL	Intensive chelation	Monitor ferritin every 2 to 3 months, and check LIC within 6 months	Note changes in trends. More aggressive therapy may be indicated, depending on organ dysfunction.
Excess cardiac iron without cardiac dysfunction; T2* < 20 ms		Intensive chelation	Monitor ferritin every 2 to 3 months, and check LIC within 6 months	Intensive chelation consists of at least 12 hours of deferoxamine per day, 7 days per week, or maximum tolerated deferasirox, as well as consideration of combination therapy.
Iron-induced cardiomyopathy, T2* < 20 ms; or T2* < 10 ms without cardiomyopathy		Maximum chelation: 24-hour deferoxamine therapy in combination with deferiprone (alternatively, in combination with deferasirox—limited combination data available)	Monitor ferritin every 2 to 3 months, and check LIC within 6 months; monitor cardiac function within 6 months	Intensive chelation consists of at least 12 hours of deferoxamine per day, 7 days per week. Combination therapy with deferiprone or maximum tolerated deferasirox is recommended.
Iron-induced cardiomyopathy, T2* < 20 ms; or T2* < 10 ms without cardiomyopathy		Maximum chelation: 24-hour deferoxamine therapy in combination with deferiprone (alternatively, in combination with deferasirox—limited combination data available)	Monitor intensively with cardiology consultation and iron chelation specialist	

Notes:

Ferritin may be a misleading measurement; liver iron is the much more accurate one. Young children may have more toxicity with chelators and may need dose adjustment.

Therapeutic index (TI) is often used in determining the deferoxamine dose when ferritin is analyzed. The therapeutic index is equal to the mean daily dose (mg/kg) / serum ferritin (mg/l). The target is to maintain the value of TI at under 0.025. The mean daily dose of deferoxamine is calculated by multiplying the dose administered in each treatment by the total number of doses administered per week, then dividing by seven—the number of days in a week. Ferritin measurements should be accompanied by periodic LIC measurements.

Consultation with thalassemia specialists should be considered in dose adjustments.

Nontransfused or intermittently transfused patients should receive chelation therapy and have their iron stores closely monitored. Their dosing should be modified on an individual basis with consultation.

LIC refers to dry weight, which is the standard method for reporting liver iron by liver biopsy and MRI. The wet weight conversion, which is a direct measurement determined by SQUID, is achieved using a divisor of 5 to 6.

In infants, chelation therapy may be delayed beyond the first year because of known toxicity of chelators in young children.

Starting a daily regimen of chelation therapy, whether oral or parenteral, represents a significant commitment and disruption of lifestyle. Before commencement of chelation, the patient and family should be taught about the reasons for the treatment, as well as how to prepare and take the medication. A continued education and support program involving the nurse practitioner, a child life specialist, and social workers can enhance acceptance and compliance with this kind of chronic therapy.

The adequate assessment of iron stores before the initiation of therapy is important; it allows determination of efficacy and appropriate dosing. Prior to the availability of MRI and SQUID, quantitative liver iron measurements were determined by liver biopsy. This method remains acceptable when MRI or SQUID is not accessible. However, noninvasive, quantitative liver iron assessments by MRI or SQUID performed at an experienced center are as accurate and less prone to measurement error and should be used in place of biopsy whenever possible. While most MRI machines are capable of making these measurements, they require special software modification and calibration to produce accurate and reliable results.

5.2 Treatment with iron chelators

The best iron chelation regimen is the one the patient is compliant with. Compliance with chelation therapy is the critical factor in treating iron overload. In the United States, there are three FDA-approved iron chelators: deferoxamine (Desferal), deferasirox (Exjade), and deferiprone (L1)

Table 5.2: Iron Chelator Properties

Agent	Route	Half-life of drug (hours)	Schedule	Clearance	Side effects and toxicity
Deferoxamine (Desferal)	Slow infusion: intravenous or subcutaneous	0.5	Eight to 24 hours per day, 5 to 7 days per week	Renal, hepatic	Dermatological, ocular, auditory
Deferasirox (Exjade)	Oral	12 to 16	Once daily	Hepatobiliary	Gastrointestinal, renal, hepatic
Deferiprone (L1)	Oral	2 to 3	Three times per day	Renal, cardiac	Hematological (neutropenia, agranulocytosis), arthropathic

5.2.1 Treatment with deferoxamine (Desferal)

Deferoxamine (Desferal, DFO) is the most studied iron chelator. It has an excellent safety and efficacy profile and has shown a dramatic effect on increasing survival rates and decreasing morbidity.

Deferoxamine has a poor oral bioavailability. It is administered subcutaneously, intravenously, or occasionally intramuscularly. It has a short half-life, necessitating administration at least eight to twelve hours daily, five to seven days per week. Generally, iron is removed much more efficiently when deferoxamine is infused over a longer period of time. It also can be given intravenously 24 hours per day when indicated. The primary—if not the only—reason deferoxamine is ineffective in some patients is poor compliance.

Deferoxamine is effective in chelating non-transferrin bound iron and can reverse cardiac arrhythmias and left-ventricular dysfunction, although, combination chelation therapy is usually recommended for patients with cardiac dysfunction.

The dosing of deferoxamine depends upon the weight of the patient, the degree of iron overload, and the presence of iron-related cardiotoxicity. Side effects of deferoxamine and chelators in general are greater in patients with limited iron stores and in children under two to three years of age. For this reason, deferoxamine treatment is usually withheld until after two years of age.

Ascorbic acid (vitamin C) increases the excretion of iron in the presence of deferoxamine. It is started after the initial month of deferoxamine therapy. It is given orally in the dose of 2 to 4 mg/kg per day (100 to 250 mg) and taken soon after the deferoxamine infusion has been initiated. Patients should be cautioned against excessive ascorbate intake when deferoxamine is not being infused. Ascorbate releases iron and has been associated with increased cardiac damage when taken in the absence of an iron chelator.

Subcutaneous deferoxamine should be administered at 30 to 60 mg/kg for eight to fifteen hours, five to seven days or nights per week. Deferoxamine should run over a minimum of six hours (or longer) at a maximum of 15 mg/kg per hour.

High doses of deferoxamine—more than 4 to 6 mg over 24 hours—should not be given. Increasing the dose beyond this point can cause deferoxamine toxicity. Overall survival is related to the number of hours per week that deferoxamine is infused. Deferoxamine is more effective when a lower dose is circulated through the body over a longer period of time than when a higher dose is circulated over a short period of time. Therefore, time of exposure is more important than total dose once doses of 60 mg/kg per day are being utilized.

Starting at a lower number of days per week and advancing to five to seven may help the family adapt to and accept the new therapy. Treatment seven days a week should be the goal.

A small-gauge needle in the thigh or abdomen is usually used. It is important that the needle be long enough to go through the dermis. Intradermal infusion is painful and results in blisters, swelling, and reactions. The sites should be rotated to prevent reaction and fat necrosis. (Also see Section 7.6, regarding treatment suggestions for local reactions.)

Additional intravenous deferoxamine can be given during each transfusion. However, its efficacy is limited, and toxicity is significant when given over a short period of time. By itself, this mode of administration is inadequate for control of iron overload, and additional daily dosing as described above is always necessary.

Deferoxamine at 60 mg/kg per day, 24 hours per day, 7 days per week, may be indicated with patients with severe hemosiderosis and vital organ dysfunction. Patients with a T2* less than 10 ms or a liver iron greater than 30 mg/g dry weight are candidates for this therapy. If the patient has cardiac arrhythmia or left-ventricular dysfunction, this therapy is mandatory and must be emergently started. Deferoxamine can be administered intravenously using a central line. The intravenous therapeutic dose is 60 mg/kg per day. In such high risk patients, combination therapy with deferiprone—or alternatively, deferasirox—should be utilized. If the patient has symptomatic cardiac disease due to iron, a cardiologist with special expertise in cardiac iron overload should be consulted. Certain standard cardiac treatments recommended by cardiologists unfamiliar with iron overload can be deleterious to a patient in heart failure due to iron overload.

5.2.2 Treatment with deferasirox (Exjade)

The oral iron chelator deferasirox (Exjade) is taken as a dispersible tablet once a day. It was approved in North America in November 2005 for the treatment of transfusional iron overload. The clinical experience is not as great as with deferoxamine. However, the drug has been used in thousands of patients and has been shown to be an effective iron chelator and to have an acceptable safety profile. It has become the most common iron chelator used in North America and many parts of the world because of its once-per-day oral dosage.

Deferasirox has good oral bioavailability and a long half-life suitable for once-daily dosing. In general, deferasirox appears similar to deferoxamine in lowering liver iron and serum ferritin levels in a dose-dependent manner. The starting dose is 20 mg/kg per day. The dose is often increased to 30 mg/kg per day, and in certain cases, to 40 mg/kg per day. After starting therapy, increase the dose by 5 to 10 mg/kg every three to six months based on iron stores. A dose of 20 mg/kg per day is effective in establishing negative iron balance in some patients. However, a higher dose of 30 to 35 mg/kg per day is usually required to establish negative iron balance. Recent data indicates that deferasirox in doses of at least 30 mg/kg per day significantly improves cardiac iron. Toxicities like skin rash, nausea, and diarrhea are dose-related, so starting at 20 mg/kg per day and working upward can help develop tolerance to the medication, even though the patient will likely require a higher dose at some later point. Ferritin is usually the most frequent parameter used to monitor efficacy. It is important to check ferritin with each transfusion and use the average change from three to five measurements to judge efficacy. (Also see Section 6, on monitoring iron overload.)

The safety profile of deferasirox is similar in pediatric and adult patients. In studies of deferasirox in children less than two years old, the medication appears to be safe, but the studies are limited. The most common side effects include gastrointestinal symptoms such as nausea and vomiting, diarrhea, and abdominal pain; mild skin rash is the second-most common side effect. These side effects often resolve with time and are dose-related. If gastrointestinal symptoms are significant, the dose can be lowered or stopped and then gradually increased. Dividing the same dose into twice-daily administration may decrease these side effects.

The most serious side effect with deferasirox is potential kidney damage; a mild nonprogressive rise in serum creatinine is seen in about one-third of patients. The dose should be lowered if there is an increase in serum creatinine that exceeds 33 percent of the baseline or greater than the upper limit of normal on two consecutive tests. Creatinine levels should be monitored monthly and repeated more frequently if rises are noted. Renal tubular problems, including severe renal tubular acidosis, have been seen.

Deferasirox is a dispersible tablet that can be suspended in water, apple juice, or orange juice. It should be taken on an empty stomach 30 minutes before or after eating. Recent data suggests that taking deferasirox with food is acceptable in patients who have difficulty with deferasirox on an empty stomach.

As with deferoxamine, deferasirox doesn't work if the patient does not take it. While there is improved quality of life with the oral chelator, compliance remains a problem. If a patient seems to not be responding, compliance should be the first issue addressed. Even though it is a once-daily dose, the preparation of the liquid takes time and planning. The drug is suspended in the liquid and has a chalky texture. Some patients let it settle before drinking, discarding the scum (the actual drug) at the bottom. Others describe forgetting to put the tablet in liquid in the morning before their shower so when they are ready for school or work, the drug is not ready, and they skip it. It may take some creativity on the part of the team to help the patient get past some of these barriers. As with deferoxamine, some patients have a serious psychological aversion to taking the medicine and may need professional counseling. Addressing compliance issues is probably one of the most important advantages of having a comprehensive team to help the patient with a chronic disease.

5.2.3 Treatment with deferiprone (L1/Ferriprox)

Deferiprone (L1, Ferriprox) has been approved for use in several countries for many years and recently received FDA approval for patients who are not effectively chelated with standard therapy. Deferiprone reduces or maintains total body iron stores in the majority of patients. Studies suggest that deferiprone may be more effective than deferoxamine in reducing cardiac iron. Deferiprone in combination with deferoxamine may decrease the risk of cardiac disease and improve cardiac function. Studies in Europe suggest that deferiprone, particularly in combination with deferoxamine, is beneficial in patients with iron cardiomyopathy and cardiac dysfunction. The standard therapeutic daily dose is 75 mg/kg given three times daily and may be increased to 100 mg/kg three times a day in high-risk patients.

The major side effects of deferiprone include gastrointestinal symptoms, joint pain, and neutropenia. Due to the risk of

agranulocytosis and associated rare deaths, weekly white blood cell counts are required for all patients receiving this drug. Zinc deficiency may occur particularly with deferiprone and require supplementation.

5.3 Patients with significant iron overload

Some patients have particularly high iron loads, a high presence of cardiac iron, or other organ toxicity that may require more aggressive treatment. There are many ways to approach these patients, and treatments need to be tailored to achieve reduction of iron in a way that is acceptable to each patient. With the availably of several chelators, a number of new approaches have been suggested. There is no extensive experience with any of them. Some are presented below.

5.3.1 High-dose, continuous deferoxamine

An aggressive chelation regimen is recommended when liver iron is greater than 20 mg/g dry weight, or cardiac T2* is less than 20. A higher—but not a toxic—dose of deferoxamine is recommended. Intensification of treatment can be accomplished by administering continuous intravenous deferoxamine (via a central intravenous line, if possible) in the hospital or in an outpatient/day unit. A minimum of 72 hours continuous, one to two times a month, *in addition to* regular use of subcutaneous deferoxamine has been recommended to increase iron removal. The continuous regimen alone may control liver iron concentration but will allow development of cardiac iron. Intravenous treatment is given at 50 to 100 mg/kg per day (with a maximum dose of 6 g per day). This regimen should be continued until the ferritin level is less than 2,000 ng/mL on two consecutive occasions. Alternative regimens include daily intravenous administration of deferoxamine, or continuous deferoxamine via percutaneous line or an indwelling venous access device. In all such treatment, high-dose, continuous treatments require careful monitoring for signs of toxicity.

5.3.2 Combination therapy: deferoxamine and deferasirox

Combination therapy of deferoxamine and deferasirox is presently being studied in North America. In over 30 patients followed for over one year, combination therapy appeared safe and effective in lowering body and cardiac iron. Larger multicenter trials are now underway.

5.3.3 Combination therapy: deferoxamine and deferiprone

Combination therapy with deferoxamine and deferiprone is increasingly being used worldwide. Treatment protocols include both sequential and simultaneous administration of both drugs. Pilot studies show that sequential therapy (for example, three days of deferoxamine and four days of deferiprone) appears to improve compliance and maintain iron levels. Simultaneous therapy (both drugs daily) improves cardiac function better than either drug alone. Careful monitoring for increased side effects is imperative.

6 The Use of Imaging to Monitor Iron Overload and Chelation Therapy

LIC is one way to determine total body iron content. While liver biopsy determination of LIC has been recommended for years, recent progress with MRI imaging provides an expedient and noninvasive way to directly measure LIC, as well as iron concentration in multiple organs. A FerriScan is a commercially available and validated system for quantitative MRI measurements of iron. The SQUID is also an effective way to noninvasively monitor LIC. The LIC is reported in wet weight and dry weight. The LIC in patients with thalassemia should always be maintained below 7,000 µg/g dry weight and 1,100 µg/g wet weight in order to avoid iron-induced organ damage.

Serum ferritin is a convenient way to monitor iron overload. The magnitude and direction of change in ferritin is a reasonable predictor of the magnitude and direction of change in total body iron. While there is about a 70 percent correlation of ferritin with LIC in population studies, there is tremendous scatter in the relation, so ferritin is a poor marker of absolute iron content in an individual patient.

The intermittent measurement of LIC by biopsy, MRI, or SQUID, in addition to measurement of ferritin with each transfusion, is the recommended way to follow change in iron burden in chronically transfused patients. It is important to use the average change of 3 to 5 ferritin measurements to determine the direction of change in iron. Because of the sensitivity of ferritin levels to inflammation, vitamin C, and iron, changes between two consecutive measures can be very misleading. If there seems to be little change in ferritin, in spite of good compliance with chelation, change in iron status should be verified by liver iron measurement before making drastic changes in chelation therapy.

The availability of noninvasive ways to directly measure iron in several organs has led to a better understanding of how iron is stored in the body and differences in iron storage among individual patients. It was once thought that liver iron correlated with heart iron, but due to further research, it is now clearly understood that iron transport into and removal from various organs occurs at different rates. We also know that ferritin levels can be misleading and that periodic direct measurement of liver iron can be of great benefit in monitoring patients. New iron measurement techniques have had a direct impact on management of iron overload. For example, it is now known that a patient can almost completely empty the liver of iron and reduce ferritin to very low levels even though significant amounts of iron may remain in the heart. This means that patients with such iron levels must cautiously proceed with chelation to empty the heart, when they might otherwise have considered stopping or reducing chelation treatment.

Recommendations for LIC goals are changing. The recommendations in Table 5.1 are based on previously published results and may need modification as new data is published. Some leading experts suggest that these recommendations should be modified and lower liver and ferritin levels should be used to increase dosing. In fact, there is emerging data that some complications such as endocrine dysfunction may respond to lowering iron levels to near normal. Since recommendations are evolving, we have included the standard accepted guidelines. Lower LIC and ferritin levels, as indicators for dose adjustment, should only be attempted by providers who are very familiar with the toxicities of over-chelation and can serially monitor liver tissue iron. Such levels should not be attempted using ferritin monitoring alone.

6.1 Monitoring the efficacy of chelation therapy in the presence of iron cardiomyopathy

Cardiomyopathy is the most life-threatening of the iron-related

complications. The heart often remains iron-free for many years. Once cardiac iron loading starts, it progresses very rapidly, since the presence of iron in the heart increases the rate of influx of iron. Removal of iron from the heart progresses very slowly with a half-life of approximately 17 months. Even though there is no linear correlation between LIC and cardiac iron, the heart often does not really began to unload until the LIC drops to very low levels. The cornerstone of effective treatment of iron cardiomyopathy is continual exposure to chelation. This can reduce cardiac arrhythmias and dysfunction even before the heart begins to unload iron. The actual dose of chelator depends primarily on the LIC and must be reduced as the LIC approaches normal in order to avoid symptoms of over-chelation. (Also see Section 7.7, on over-chelation.) However, in the presence of cardiac iron, and especially if there is cardiac dysfunction, chelation cannot be stopped.

In the presence of cardiac symptoms (arrhythmia or decreased left ventricular ejection fraction) the patient must be exposed to chelator 24 hours per day, 7 days per week. This treatment is considered to be emergent. Multiple drug therapy—in particular, therapy involving deferiprone—should be considered in this circumstance. Other cardiac medications may be recommended by the cardiologist. Patients whose cardiac T2* is less than 10 ms and who do not have cardiomyopathy should receive maximum therapy (see Table 5.1). Consultation with an iron chelation specialist is strongly recommended in the management of all patients with an abnormal cardiac T2*. Since several patients may have low body iron and high cardiac iron, iron chelation therapy decisions may be complex. Liver iron measurements should also be closely monitored with each cardiac T2*. It is very important to note that other things, such as myocarditis, vitamin B_1 deficiency, and vitamin D deficiency can also affect cardiac function and need to be explored, particularly if there is no cardiac iron and function remains abnormal.

7 Assessment of Chelator Side Effects and Toxicity

The primary signs of chelator toxicity are hearing loss, temporary loss of sight, cataracts, renal dysfunction, growth failure, and symptoms related to iron deficiency. Side effects from deferoxamine toxicity include auditory and visual changes, and may occur when total body iron is low but high doses of deferoxamine are still being used. The table below indicates toxicity-monitoring parameters. The following should be routinely monitored.

7.1 Audiology

A baseline formal audiology exam should be given prior to starting a chelator. Any history of hearing difficulty or tinnitus should prompt a physical exam of the tympanic membranes and formal audiology testing.

Inquire about hearing problems at each monthly visit. A screening audiogram should be performed in clinic every six months. Refer patients for formal audiogram assessment every 12 months, or more often if a patient is unable to undergo a screening test in clinic.

If there is new onset of hearing loss or tinnitus, the chelator should be stopped and the audiogram repeated. The testing should be confirmed within a month. The chelator can be restarted if the hearing changes have improved. Reevaluation of iron status may be necessary.

7.2 Ophthalmology

Inquire about decreased visual acuity at each visit—especially changes in color perception. Changes in color vision are often the first symptoms of over-chelation
An annual evaluation by an ophthalmologist should be performed to rule out cataracts, decreased acuity, night blindness, and decreased visual fields. Any vision change should be examined with causes unrelated to iron in mind, as well. A reevaluation of the chelation regimen should be done if any ophthalmologic abnormalities are found.

7.3 Nephrology

Creatinine and BUN with the serum chemistry, urine protein/creatinine, and microalbumin should be monitored monthly for patients on deferasirox and every three months for patients on deferoxamine.

7.4 Neutropenia

Neutropenia, or low neutrophil count, must be monitored weekly with a CBC for patients on deferiprone.

7.5 Growth

Evaluate patients for evidence of growth delay. Routinely record height and weight monthly and calculate annually growth velocity. Measure sitting height every six months to assess truncal shortening. Tibial and spinal radiographs should be evaluated for evidence of metaphyseal cartilaginous dysplasia in younger patients with evidence of growth delay.

7.6 Local and allergic reactions

Local reactions at the deferoxamine injection site that are urticarial in nature will usually respond to increased dilution of the deferoxamine by 25 to 30 percent. Hydrocortisone should be used only in severe cases and under the direction of the consulting hematologist. In some cases, treatment with antihistamines may be helpful.

Severe, life-threatening allergic reactions may occur. Patients who report systemic allergic symptoms should be observed and possibly challenged in clinic. Desensitization protocols have been used successfully on some patients. When desensitization has been accomplished, it is critical that the patient does not stop the medication, as it may necessitate reinstitution of the entire desensitization process. With the availability of alternative chelation drugs, changing chelators may be a better option than desensitization.

7.7 Over-chelation

Persistent low serum ferritin levels (below 500 ng/mL) in the face of regular chelation are not optimal due to the increased toxicity of deferoxamine, particularly in children, and presumably deferasirox, at low levels of total body iron. The chelation program should be modified and the LIC evaluated. In select high-risk patients, very low iron levels are maintained but consultation with experts in iron chelation is required due to toxicity. Low levels of zinc, copper, selenium, and ionized calcium can also be indicators of deferoxamine toxicity.

Table 7.7: Chelator Toxicity Monitoring

	Deferoxamine	Deferasirox	Deferiprone
Complete blood count (CBC); absolute neutrophil count (ANC)			Weekly
Liver function tests (LFTS)		Every 3 to 4 weeks	Every 3 months
Creatinine	Every 3 months	Every 3 to 4 weeks	Every 3 months
Urine protein/ creatinine	Every 3 months	Every 3 to 4 weeks	
Urine microalbumin/ Creatinine	Every 3 months	Every 3 to 4 weeks	
Urine glucose		Every 3 to 4 weeks	
Zinc, copper, calcium, and magnesium	Annually	Annually	Annually
Electrolytes		Every 3 to 4 weeks	
Eye exam	Annually	Annually	Annually
Audiogram	Annually	Annually	Annually
Sitting height	Biannually	Biannually	Biannually
Height/weight	Every 3 to 4 weeks	Every 3 to 4 weeks	Every 3 to 4 weeks
Clinical symptoms (nausea, diarrhea, color-vision change)	Every 3 to 4 weeks	Every 3 to 4 weeks	Every 3 to 4 weeks

8 Liver and Gall Bladder Diseases

Liver toxicity can occur as a direct consequence of iron toxicity, from transfusion-acquired hepatitis, and/or from other causes of liver disease such as medications, liver toxins, autoimmune reactions, or metabolic disease (Wilson's disease, alpha-1 antitrypsin). Liver function and hepatitis serology should be routinely screened in thalassemia patients on chronic transfusion as described below.

8.1 Screening for hepatic dysfunction

A hepatitis B surface antibody should be documented at the initial screening of the patient. Patients should have a positive hepatitis B antibody. This will usually occur following a vaccination or an infection. If it is negative, then a surface antigen and core antibody should be monitored annually until patients demonstrate surface antibody, either from resolved infection or vaccination.

Annual hepatitis C antibody should also be checked. If the hepatitis C antibody screen becomes positive, PCR for hepatitis C should be measured.

Every three months, bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase should be measured via a blood test. If the ALT is elevated, it should be repeated in two weeks. If the ALT remains elevated at two weeks or if it is intermittently elevated over a period of three months, a complete evaluation for causes of hepatitis should be performed. Suggested evaluation might include the following.

1. PT, PTT, albumin, albumin/globulin ratio
2. Hepatitis A IgM (if not previously positive or known to be immune)
3. Hepatitis B DNA quantification
4. Hepatitis C antibody (if the antibody screen is positive, viral RNA should be documented by qualitative TMA assay and load should be measured by quantitative PCR)
5. CMV titers (IgG, IgM), CMV PCR and/or urine culture for CMV
6. EBV titers (PCR for reactivation)
7. Baseline liver biopsy if PCR is positive for hepatitis C, to evaluate severity of disease and need for therapy
8. Autoimmune hepatitis, biliary obstruction, metabolic disease, and toxic hepatitis

8.2 Monitoring patients with documented hepatitis or hepatic dysfunction

Once hepatic dysfunction has been documented, hepatology consultation is important. The combination of hepatitis and iron overload increases the risk of liver damage. Rapid removal of iron and treatment of viral hepatitis should be considered.

All patients with hepatitis should be evaluated with a liver biopsy. Patients who have hepatitis B or C should be monitored for hepatocellular carcinoma with alfa-fetoprotein and have hepatic ultrasound evaluations biannually. This is particularly important if there is evidence of cirrhosis on the biopsy. Early treatment is recommended for newly acquired infection with hepatitis C.

Liver biopsy results showing moderate and/or progressing fibrosis are an indication for treatment.

8.3 Evaluation and treatment for hepatitis C

A decision on whether to recommend treatment of established hepatitis C depends on clinical status, severity, or progression of fibrosis. Treatment consists of pegylated interferon alfa given as a subcutaneous injection once a week and oral ribavirin twice daily for patients 18 years and older. (An interferon alfa and ribavirin combination is approved for children.) Recent data suggests the addition of protease inhibitors (such as boceprevir and telaprevir) may further improve cure rates.

Treatment with pegylated interferon alfa requires monitoring due to significant side effects, including

- neutropenia and thrombocytopenia
- evidence for hypothyroidism (antithyroid peroxidase antibody titer predicts complications of hypothyroidism)
- vision and hearing changes
- cardiac arrhythmia or failure
- depression

Liver enzymes and hepatitis C quantitative and qualitative (TMA) PCR should be monitored for response to treatment at one, two, three, six, twelve, and eighteen months. Ribavirin requires close monitoring of the hemoglobin because of increased risk of hemolysis. Patients on ribavirin require increased transfusions to avoid complications related to rapidly worsening anemia—particularly cardiac events. An increase in chelation is frequently necessary with an increase in blood requirement.

8.4 Evaluation and treatment for hepatitis B

A decision on whether to recommend treatment of established hepatitis B depends on clinical status. A liver biopsy should be obtained before initiating treatment. Patients with indices of active viral replication (HBV DNA), e-antigen status, liver injury (elevated transaminases and/or active hepatitis on biopsy), or family history of hepatocellular carcinoma are candidates for therapy.

Several drugs (interferon alfa, pegylated interferon alfa, lamivudine, adefovir, entecavir) are FDA-approved for use in adults. (Some are approved for children.) Consult with your hepatologist regarding treatment options.

8.5 Gall bladder disease

Chronic hemolytic anemias result in the development of bilirubin gallstones. Up to two-thirds of thalassemia patients develop gallstones. Thalassemia intermedia patients may be at greater risk. Most patients remain asymptomatic and do not have cholecystitis or cholangitis. Surgical removal of gallstones should be reserved for the symptomatic patient.

9 Endocrine Dysfunction

Endocrine dysfunction due to iron deposition and toxicity to the endocrine tissue is a common complication of iron overload, causing significant morbidity. Gonadal failure, sterility, and growth failure are common, as well as osteopenia and osteoporosis. Diabetes mellitus may also develop in patients with iron overload.

9.1 Routine endocrine screening

Height and weight should be measured accurately at each visit. Evaluate growth on CDC or WHO charts. Ethnic-specific charts are unnecessary. Sitting height should be measured semiannually.

Annual endocrinology consultation and screening should be started at five years of age, after three years of transfusions, or as otherwise clinically indicated. The following tests are recommended annually or semiannually.

1. TSH and free T4
2. Cosyntropin stimulation test (semiannually)
3. PTH
4. Serum calcium, ionized calcium, and vitamin D
5. Fasting glucose (semiannually)
6. Oral glucose tolerance testing as indicated by fasting glucose (see the following section)
7. IGF-1 and IGF BP-3 to screen for growth hormone deficiency
8. Bone density (DXA and CT)
9. Trace elements: zinc, copper, and selenium
10. Vitamins B_1, B_6, B_{12}, C, E, and A; also pyridoxine, carnitine, methylmalonic acid, and homocysteine.

9.2 Specific endocrinopathies: testing and evaluation

9.2.1 Diabetes mellitus

A two-hour oral glucose tolerance test should be performed at 10, 12, 14, and 16 years of age. The oral glucose tolerance test should be performed annually thereafter. If fasting serum glucose is greater than 110 mg/dL, an oral glucose tolerance test is indicated.

- A fasting glucose greater than 126 mg/dL is diagnostic of diabetes mellitus.
- A serum glucose at two hours over 200 mg/dL is diagnostic of diabetes mellitus.
- A serum glucose at two hours between 140 and 200 mg/dL indicates glucose intolerance.
- A casual blood glucose greater than 200 mg/dL with associated symptoms such as polyuria, polydipsia, or unexplained weight loss is diagnostic of diabetes mellitus.

The patient should be referred to endocrinology for management of diabetes mellitus or glucose intolerance. Patients diagnosed with glucose intolerance should have their chelation therapy reviewed and intensified.

9.2.2 Low bone mass (osteoporosis)

Initial bone-density assessment by dual-energy X-ray absorptiometry (DXA) or quantitative computerized tomography (QCT) should be performed at eight years of age and annually thereafter, as necessary. As low bone mass has been observed in all thalassemia syndromes, it is suggested that all patients with thalassemia have an initial bone mineral density assessment. The same method of bone-density measurement should be used for each evaluation. There is significant inter-method variability in bone-density measures. Therefore, different manufacturers of instruments (e.g., Hologic versus Lunar) or methods of assay (DXA versus QCT) are not acceptable for monitoring of a single patient over time.

Bone-density measurements are influenced by the trabecular bone density and the cortical thickness of the bone. Patients with thalassemia have been noted to have thinner bone cortex. Therefore, integral density measures (DXA) may provide different results than a true volumetric density test (QCT).

The current accepted definition of low bone mass for all patients under 50 years is a bone mineral density Z-score by DXA greater than – 2.0. Low bone mass for chronological age may be observed in the spine, the hip, or whole body regions. (The hip region should not be used for diagnosis in patients less than ten years old.)

Patients should have an annual evaluation of calcium metabolism and parathyroid function: nutritional history, 25-hydroxy vitamin D, PTH, and serum calcium should be measured. If the patient has achieved puberty or is pubertal, FSH, LH, and testosterone or estrogen should be examined.

Follow nutritional status and keep up adequate vitamin levels. Supplement with up to 1,300 mg calcium per day starting at nine years of age. Patients with low levels (25-hydroxy vitamin D less than 30ng/mL) or those at high risk to develop vitamin D deficiency should be supplemented with vitamin D (1,000 units per day). Nutrition referral is recommended. (Also see Section 14, on nutrition.)

Endocrine referral is recommended for older patients with established osteoporosis (DXA T-score of greater than – 2.5) prior to treatment with bisphosphonates. Serious thought should be given to the safety of bisphosphonate use in women with childbearing potential.

9.2.3 Growth hormone deficiency

Endocrine evaluation is required if there is a 5 percent or more falloff on the growth curve or poor growth velocity for the age. The evaluation should include the following.

1. A dietary assessment by a registered dietitian
2. Laboratory tests: serum calcium, PO4, albumin, urinalysis, urine culture T4, TSH, IGF-1, and IGF BP-3
3. A bone age assessment

Low IGF-1 or IGF BP-3 should prompt referral to an endocrinologist for determination and treatment of growth hormone deficiency. Early diagnosis, for successful treatment before completion of puberty, is recommended.

9.2.4 Hypogonadism

Tanner staging should be determined every six months. Girls without evidence of an advancing pubertal stage by 12 years and boys by 14 years require screening with LH-ICMA, FSH, and estradiol levels. Bone age films should be obtained.

Elevated LH-ICMA and FSH suggest primary hypogonadism. If LH-ICMA and FSH levels are low for the patient's age, suspect secondary or tertiary hypogonadism.

If LH-ICMA and/or FSH are abnormal, perform GnRH stimulation. Consider performing this treatment at age 12 in girls and age 14 in boys, then annually as clinically indicated. (This should to be done prior to a blood transfusion on a different day than the oral glucose tolerance test.)

Testosterone level should be checked annually in boys, starting in the early adolescent years (at approximately 12 years old). If a patient's testosterone level is low, obtain an endocrine consultation and start monthly testosterone treatment. The starting dose is usually 50 to 100 mg, given monthly as an intramuscular shot. The dose will need to be adjusted periodically for the patient's age and pubertal status, as well as for a sexually active man.

Estrogen replacement is recommended for amenorrheic adolescent girls and adult women: Premarin at a low dose (0.0375 µg per day for six months). The dose should be advanced after six months for an additional six to twelve months. Afterward, an oral contraceptive pill may replace Premarin. A gynecological consultation and fertility evaluation is recommended for women on estrogen therapy.

9.2.5 Hypothyroidism

TSH and free T4 should be measured at five years of age or after three years of transfusion. Elevated TSH and depressed T4 suggest primary hypothyroidism. Depressed TSH and depressed T4 suggest secondary or tertiary hypothyroidism. The patient should be referred for an endocrinology consultation and start replacement therapy as indicated.

9.2.6 Hypoparathyroidism

Parathyroid status should be evaluated annually with serum calcium. PTH, and 25-hydroxy vitamin D screening. A normal PTH with decreased calcium, or a decreased PTH with normal calcium, is diagnostic of hypoparathyroidism. The patient should be referred for an endocrinology consultation and start therapy with vitamin D (use an activated 1,25 OH vitamin D product) and calcium.

9.2.7 Adrenal insufficiency

Adrenal status should be checked biannually beginning at age five, using an ACTH stimulation test. The patient is given 1 µg of cosyntropin intravenously, and cortisol levels are then measured 30 and 60 minutes after dosing. A cortisol response of less than 17 mg/dL is diagnostic of adrenal insufficiency. The patient should be referred for an endocrinology consultation for further evaluation and replacement therapy. If a patient is acutely ill or at risk, the cortisol level is measured and a stress dose replacement is given.

10 Cardiac Dysfunction

Cardiac disease is the major cause of death in patients with iron overload. The liver and heart have different rates and mechanisms of iron uptake and elimination. As a result, measurements of ferritin and liver iron do not completely predict cardiac risk; high values are associated with future cardiac iron accumulation, but low values may not necessarily be reassuring. Recently, doctors and scientists using cardiac MRI T2* have developed a means to recognize preclinical cardiac iron accumulation. Although currently available only at a limited number of thalassemia centers, cardiac T2* measurements have transformed chelation and cardiac management in thalassemia.

Improved diagnosis of cardiac iron has led to improved chelation strategies. Deferoxamine does remove cardiac iron but is

significantly more effective when given six to seven days a week or continuously.

The oral chelator deferiprone, in combination with deferoxamine, has demonstrated excellent cardiac iron removal, as well as improvements in left ventricular function. It requires weekly ANC assessment to monitor for neutropenia and agranulocytosis.

There is less cardiac data for the oral chelator deferasirox, but available studies are promising and indicate that deferasirox does lower cardiac iron. Several clinical trials are ongoing. It is significant that patients now have many more options for therapy to control cardiac iron.

10.1 Cardiac evaluation

Prior to initiation of transfusions, a baseline evaluation should be made. This should include an echocardiogram, to evaluate pulmonary artery pressures, systolic function, and diastolic function, and a baseline electrocardiogram to monitor for ventricular hypertrophy and rhythm abnormalities.

Monthly evaluations should include a cardiac history (palpitations, irregular heart rate, chest pain, dyspnea, exercise intolerance, nocturnal cough, orthopnea, dependent edema, or unexplained fevers) and exam (systemic or pulmonary venous congestion, gallop, and edema). Any positive history of cardiac dysfunction requires evaluation by a cardiologist. Serum ferritin should also be checked monthly.

For patients over eight years of age, an annual evaluation should include an echocardiogram assessment of systolic and diastolic function, as well as pulmonary artery pressure (PI and TR jet velocity). Patients also should have an electrocardiogram—cardiac iron is associated with nonspecific ST-T wave changes, T-wave inversions, left ventricular hypertrophy, bradycardia, and PR prolongation. Readings from a Holter monitor need only be obtained if there is clinical suspicion of arrhythmias. Patients should have their cardiac T2* and left ventricular ejection fraction evaluated with a cardiac MRI, if available.

10.2 Echocardiography standards

The following parameters should be included in an echocardiographic evaluation.

1. M-mode: Left ventricular end diastolic and systolic dimensions, wall thickness, left ventricular mass and wall stress, shorting fraction, and corrected mean velocity of circumferential shorting
2. Pulse Doppler: mitral inflow peak velocities (E and A) and mitral deceleration time
3. Tissue Doppler: measurements of E, A, and S from the atrioventricular ring at the right ventricular free wall, left ventricular free wall, and interventricular septum
4. Color and continuous wave Doppler: severity and velocity of tricuspid and pulmonic regurgitant jets (estimation of right ventricular and pulmonary artery pressures)

10.3 Treatment of established heart failure

Heart failure is defined as a low ejection fraction with evidence of cardiomyopathy. All patients with heart failure should be assumed to have high levels of cardiac iron, regardless of their liver iron or ferritin, until proven otherwise by cardiac T2* assessment. A cardiac MRI should be performed, if possible, to evaluate the relative cardiac and liver iron loading. All patients with heart failure should be placed on continuous deferoxamine therapy (24 hours per day, 7 days per week) at 50 to 100 mg/kg over 24 hours, administered either intravenously or subcutaneously, depending on the patient's access and tolerance. Patients with low ferritin and/or low liver iron should still be managed with continuous deferoxamine to deplete intracardiac free iron, but the daily dose will have to be lowered to avoid over-chelation.

Combination therapy with deferiprone and continuous deferoxamine is recommended for patients in heart failure. There is less experience with combination therapy with deferasirox, but this is an alternative option. The introduction of any dual agent should occur after the initiation of continuous deferoxamine.

Patients in heart failure should be screened for thiamine and vitamin D deficiency, hypoparathyroidism, hypothyroidism, diabetes, and adrenal insufficiency. Empiric L-carnitine therapy at 50 mg/kg may be beneficial for cardiac function in some patients. Stress dose steroids should be administered empirically for patients in the intensive care unit.

Patients should be referred to a cardiologist who will generally manage their care with ACE inhibition, beta blockers, digoxin, and diuretics. Cardiac arrhythmias should be treated with amiodarone. Ablation is ineffective. Arrhythmias often reverse with iron chelation therapy.

The placement of automatic intracardiac defibrillators should be strongly discouraged because the cardiomyopathy is generally reversible. Heart transplantation should also be strongly discouraged unless the heart failure persists after cardiac iron depletion (verified by MRI), or the patient will not survive long enough for effective chelation.

Patients in heart failure require more frequent transfusions (at two-week intervals) to maintain a pre-transfusion hemoglobin of around 12.0 gm/dL. Diuretic therapy may be required during transfusions. Frequent evaluation of serum electrolytes, calcium, and magnesium while on diuretic therapy is required.

10.4 Pulmonary hypertension

Pulmonary hypertension is a progressive increase in the resistance of blood flow to the lungs. It is caused by the disruption of nitric oxide metabolism secondary to the intravascular release of hemoglobin from red blood cells, direct iron toxicity of the vascular endothelium, and back-pressure from the heart as it stiffens from iron and from aging.

Patients with thalassemia also have vasoactive fragments of platelets and red blood cells that appear to constrict pulmonary vessels. This circulating cellular debris is generally removed by the spleen—thus, patients who have undergone splenectomy appear to be at higher risk.

Unsplenectomized thalassemia major patients who are regularly transfused to maintain their pre-transfusion hemoglobin above 9 to 10 g/dL do not have much circulating free hemoglobin or

cellular fragments. Pulmonary hypertension is relatively rare in these patients (less than 10 percent) and is usually responsive to improved iron chelation strategies. In contrast, patients who have thalassemia intermedia or who allow their hemoglobin to fall to lower levels between transfusions are at much higher risk of pulmonary hypertension—nearly 50 to 60 percent in some studies.

10.5 Treatment of pulmonary hypertension

Liver iron and ferritin values do not really help discriminate the mechanisms of pulmonary hypertension. Physicians must decide whether the pulmonary hypertension is primary or secondary to iron-mediated cardiomyopathy. The former condition will have elevated circulating free hemoglobin, low haptoglobin, low arginine, elevated platelets, and platelet adhesion markers. Treatment consists of initiating transfusion therapy if the patient is not already on regular transfusions and maintaining pre-transfusion hemoglobin above 9.5 g/dL. The latter condition will exhibit left ventricular systolic and diastolic dysfunction, abnormal cardiac T2*, and cardiac arrhythmias. Treatment of the latter condition consists of treating iron cardiomyopathy.

For patients with pulmonary hypertension, optimize their transfusion program to maximize suppression of all marrow activity. All patients with severe pulmonary hypertension (TR jet greater than 3 m per second) should undergo diagnostic catheterization to assess pulmonary vascular resistance and its responsiveness to nitric oxide and oxygen. Patients should be evaluated for oxygen desaturation, particularly at night. Supplemental oxygen should be administered, as needed, to maintain saturations greater than 95 percent. A complete coagulopathy workup should be performed.

Warfarin should be initiated for patients having persistent pulmonary hypertension. The INR target is 1.5 to 2.0. Patients failing to respond to hematologic management should be started on sildenafil as the first line of therapy.

11 Pulmonary Care

Pulmonary disease is an uncommon phenomenon in thalassemia, although a body of data exists regarding pulmonary disease in thalassemia patients. In addition, the pulmonary disease which has been described is generally asymptomatic.

The most common disorder is a restrictive pulmonary condition which appears to be associated with iron overload. The restrictive pulmonary condition is seen in 30 to 60 percent of patients. However, most of these restrictive findings are asymptomatic, and there is little therapy for this condition. This emphasizes the need for aggressive chelation and monitoring of transfusion-related hemosiderosis. Hypoxia is rarely encountered.

The most easily treatable condition that may affect the lungs is pulmonary embolism. Patients with thalassemia are known to be hypercoaguable, which leads to a higher risk for developing thromboembolic events. Splenectomy may be an additional thrombophilic risk factor. The thrombophilia of thalassemia patients may contribute to the pathophysiology of pulmonary hypertension, and as this phenomenon may present with the respiratory symptoms of dyspnea or exercise intolerance, attention to the pulmonary system is important. (Also see Sections 10.4 and 10.5, on pulmonary hypertension.)

Recommendations for pulmonary care include the following:

1. An annual review of respiratory symptoms and a lung exam
2. An annual pulse-oximetry
3. Aggressive iron chelation if transfusion-related hemosiderosis is present
4. An echocardiogram to evaluate for pulmonary hypertension, if symptomatic
5. A pulmonary function test or high-resolution CT, if symptomatic
6. A referral to pulmonology in the case of restrictive disease
7. An anticoagulation treatment if thromboembolism is present; ASA may be considered if the patient is splenectomized

12 Pain Syndrome in Thalassemia

Chronic pain has not been noted as a major component of the symptoms of thalassemia. However, in the last decade, as prognosis has improved, cumulative tissue injury appears to be resulting in chronic pain syndrome. A recent study utilizing the Brief Pain Inventory (BPI) assessed pain in 250 thalassemia patients in North America. Two-thirds of the patients reported repeated pain episodes each month, and 20 percent reported daily pain. The prevalence and severity of pain correlated with age of the patient. As patients age, pain becomes a more prominent problem in their lives. Most patients have back pain. Three-quarters of the patients were taking non-steroidal analgesics for pain relief. In addition, 24 percent were receiving short-acting narcotic analgesics, and another 11 percent were receiving long-acting narcotic analgesics.

Pain assessment on a regular basis is recommended for all patients. While transfusion therapy may decrease the pain in thalassemia intermedia, this has not been prospectively evaluated. All patients should undergo assessment for causes of pain, including extramedullary masses, osteoporosis, and spinal fractures, as well as other less common problems, such as secondary gout and thrombosis.

13 Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is the only treatment that offers a potential cure for thalassemia at this time. HCT relies on high-dose chemotherapy to eliminate thalassemia-producing cells in the marrow and replaces them with healthy donor cells from bone marrow or umbilical cord blood, usually taken from a human-leukocyte antigen (HLA) match: an identical sibling. This therapy should be considered for all patients who have a suitable donor. Early referral to a transplant center is recommended, as HCT has a better outcome in younger patients.

Patients are classified before HCT as Class 1, 2 or 3 patients on the basis of risk factors that influence outcome after HCT. These risk factors include:

- age of the patient
- adequacy of chelation
- the presence or absence of liver fibrosis
- the presence or absence of hepatomegaly

The overall thalassemia-free survival of low-risk, HLA-matched sibling stem cell transplantation patients is 85 to 90 percent, with a 95 percent overall survival. While not as effective, new approaches to Class 2 and 3 patients have significantly improved their overall survival. The problems of rejection and engraftment in these patients are improving with the use of more intensified immunosuppressive therapy.

If HCT is considered, patients should be referred to the nearest transplant center with experience in HCT for genetic diseases. The liver, lungs, heart, and skeleton are particular targets of complications of thalassemia and chronic transfusion. The following studies must be done before HCT:

1. A staging of liver fibrosis and inflammatory lesions by liver biopsy, as per the Knodell numerical scoring system (Knodell, R.G., et al. *Hepatology* 1 [1981]: 431.), with measurement of LIC
2. A measurement of hepatic, cardiac, endocrine, renal, and pulmonary function
3. A dental evaluation and restoration

13.1 Iron overload after HCT

After a successful HCT, continuous treatment of preexisting iron overload is indicated.

After an HCT, a phlebotomy of 5 cc/kg per month should be performed until liver iron is less than 7.5 mg/g dry weight. For patients on whom phlebotomy cannot be performed, iron chelation therapy using deferoxamine is also effective, but more cumbersome and expensive than phlebotomy.

If the pre-transplantation liver biopsy was performed more than two years before starting phlebotomy, consider repeating a measurement of the LIC by noninvasive methods or by liver biopsy to confirm the baseline liver iron level. Measurement of LIC by noninvasive methods or by liver biopsy should be continued every 12 to 24 months to monitor the response to the phlebotomy. A post-HCT phlebotomy should be performed if hepatic iron before the HCT exceeds 7 mg/g dry weight, or if ferritin is greater than 2,000 ng/mL.

13.2 Experimental HCT

Since HLA-matched sibling transplantation in healthy thalassemia patients offers a very high cure rate, stem cell options for families without matched siblings are being studied. Most patients do not have an HLA-matched sibling. Experimental trials with unrelated, matched umbilical cord blood or stem cell transplantation are being conducted. Alternative immunosuppressive preparations and therapy are being studied to decrease graft-versus-host disease and improve graft survival. Pregnant mothers of affected children are more frequently undergoing prenatal diagnosis for thalassemia and determining a fetal HLA typing on the prenatal sample. If there is a match with the sibling, the umbilical cord blood cells can be stored for transplantation. An experimental procedure called pre-implantation genetic diagnosis is an option available for preselected HLA-compatible donors of affected siblings.

13.3 Experimental drug therapy to increase fetal hemoglobin

The amount of fetal hemoglobin within each red cell plays a major role in determining the severity of thalassemia. The increase in gamma globin chain synthesis decreases the alpha chain imbalance and improves the anemia. Multiple drugs have been studied to increase hemoglobin F. Histone deacetylase (HDAC) inhibitors such as butyrate and short-chain fatty acids have had benefit in select patients, but most responses have been modest and unpredictable. New HDAC drugs are under study. The first successful drug therapy for fetal hemoglobin in thalassemia was 5-azacytidine. This was abandoned because of toxicity. Recent pilot studies evaluating a safer analog (decitabine) are ongoing; however, the long-term benefit and toxicity are unknown. Erythropoietin has increased fetal hemoglobin and total hemoglobin, particularly in patients with relatively low levels of erythropoietin. However, the long-term benefit is unknown, and the risk of marrow expansion is a cause for concern.

The most successful fetal hemoglobin agent to date is oral hydroxyurea. Hydroxyurea is a cytotoxic drug that is short-acting and relatively easy to monitor. It is FDA-approved for the treatment of severe sickle cell disease. However, it is less effective and predictable in thalassemia and more likely to be beneficial in thalassemia intermedia. Approximately 40 percent of patients will have a modest increase in hemoglobin and a decrease in measurement of hemolysis. Baseline hemoglobin F is the strongest predictor of response. Splenectomy and baseline erythropoietin levels may also influence its benefit. The dosage of hydroxyurea is lower in thalassemia than in sickle cell disease. Often, the drug is started at 5 to 10 mg/kg per day and slowly escalated as tolerated to 20 mg/kg per day. While modest responses can be observed, hydroxyurea is not usually successful in preventing eventual transfusion therapy.

14 Acute Infection

Acute infection remains a major cause of death in thalassemia patients. A vigilant approach to recognizing and treating serious infections will prevent unnecessary mortality. Patients should be educated on management of fever and acute symptoms, with advanced understanding of who to call and where to seek care. Easy access to medical records can assist in the rapid assessment and treatment of patients. This can be facilitated by patients carrying health records listing diagnosis, complications, and treatments.

Prophylactic antibiotics for splenectomized patients do lower the risk of pneumococcal infections. However, gram-negative organisms are the major cause of bacteria in thalassemia patients. Prompt treatment with broad spectrum antibiotics should start before the results of blood cultures are indicated. Patients with central venous catheters may have staphylococcus epidermidis and require vancomycin therapy. Thalassemia patients have an increased risk of *Yersinia enterocolitica.* This iron-avid organism may present clinically with fever, abdominal pain, and diarrhea. Antibiotics should be started before stool and blood culture results are available. In general, all chelation therapy should be stopped until the febrile illness is adequately treated.

15 Dental Evaluation

The teeth can be significantly affected in patients with thalassemia, but proper transfusion therapy can prevent many of the changes. However, close dental and orthodontic monitoring is crucial. In addition to regular annual dental care, thalassemia patients should be evaluated by a dentist to determine if bony changes requiring orthodontic treatments have developed. If orthodontics are recommended, they will be covered by insurance, since their necessity is disease-related.

Furthermore, splenectomy can complicate dental care due to increased risk of infection. Prior to dental work, which is likely to cause bleeding of the gums, splenectomized patients should receive dental prophylaxis. Recommended treatment is 50 mg/kg of amoxicillin (to a maximum dose of 2 g) one hour prior to dental work. If the patient is allergic to penicillin, 20 mg/

kg of clindamycin (to a maximum dose of 600 mg) should be administered one hour prior to procedure.

16 Nutrition

Nutritional deficiencies are common in thalassemia, due to hemolytic anemia, increased nutritional requirements, and morbidities such as iron overload, diabetes, and chelator use.

Patients should be evaluated annually by a registered dietitian regarding adequate dietary intake of calcium, vitamin D, folate, trace minerals (copper, zinc, and selenium) and antioxidant vitamins (E and C). Annual nutritional laboratory testing should include albumin, 25-hydroxy vitamin D, fasting glucose, fasting plasma zinc, serum copper, ceruloplasmin, serum selenium, alpha and gamma tocopherol, plasma ascorbate, and serum folate. (See nutrition table below.)

Recommendations for dietary supplementation should be made as indicated by nutritional history, complications of the disease, and, in children, growth status. Typically multivitamin supplementation without iron is suggested (e.g., Centrum Silver in tablet or chewable form is now available).

For nontransfused thalassemia patients, folate supplementation (1 mg daily) is recommended, and consuming a moderately low-iron diet is encouraged—that is, avoiding iron-fortified cereals and other products and excessive consumption of red meat. Drinking black tea with meals is recommended to reduce iron absorption from food.

For transfused patients on chelation therapy, a low-iron diet is unnecessary and may decrease the quality of life for some patients. The amount of iron obtained from just one unit of packed red cells (200 mg) far outweighs the amount of iron obtained from a 3-ounce steak (5 mg).

Vitamin D supplementation (50,000 IU once a week until levels normalize) is recommended for patients with a 25-hydroxy vitamin D less than 20 ng/dL. Calcium supplementation should be encouraged if dietary intake is insufficient.

Counseling should be offered for patients with special dietary needs. These include patients with diabetes or lactose intolerance, those who practice vegetarianism, those who are pregnant, or those on oral chelators or bisphosphonate medications.

Alcohol consumption and cigarette smoking are to be discouraged. Alcohol potentiates the oxidative damage of iron and aggravates the effect of hepatitis B and C on liver tissue. Cigarette smoking affects bone remodeling and is associated with osteoporosis.

Table 16: Nutrition Table Recommended for Patients

Nutrient	Diagnosis of adequacy	U.S. dietary recommended intake	Tolerable upper limit
Calcium	Serum calcium not informative as it is buffered.	19 to 50 years—1,000 mg/day 9 to 18 years—1,300 mg/day 4 to 8 years—800 mg/day	2,500 mg/day
Vitamin D	Serum 25-hydroxy vitamin D > 30 ng/mL	400 IU per day	10,000 IU/day for adults; unknown for children
Folate	Serum or plasma folate > 3 ng/mL	1 mg per day for nontransfused patients	Unknown for thalassemia patients; for general population, suggested upper limit is 1 mg/day
Zinc	Fasting morning plasma zinc > 70 µg/dL	Women/girls: 8 mg/day men/boys: 11 mg/day 4 to 8 years: 5 mg/day	Over 19 years—40 mg/day 14 to 18 years—34 mg/day 9 to 13 years—23 mg/day
Copper	Serum copper > 70 µg/dL	19 to 50 years—900 µg/day 14 to 18 years—890 µg/day 9 to 13 years—700 µg/day 4 to 8 years—440 µg/day	Over 19 years—10 mg/day 14 to 18 years—8 mg/day 9 to 13 years—5 mg/day
Ceruloplasmin	Ceruloplasmin > 17 mg/dL	N/A	N/A
Selenium	Serum selenium > 45 µg/L	19 to 50 years—55 µg/day 9 to 18 years—40 µg/day 4 to 8 years—30 µg/day	400 µg/day
Vitamin C	Plasma or serum ascorbate > 0.4 mg/dL (avoid hemolysis)	75 to 90 mg/day If on chelation, 100 to 250 mg/day recommended	Unknown for thalassemia patients; for general population, suggested upper limit is 2,000 mg/day
Vitamin E	Serum or plasma fasting alpha and gamma tocopherol (see local lab for normal for age and gender)	Adults: 100 IU/day	Unknown for thalassemia patients; for general population, suggested upper limit is 1,000 mg/day

Notes: All trace elements (zinc, copper, selenium) need to be collected into trace element–free vacutainers.

Normative values may be somewhat different depending upon the reference lab. The upper limit for vitamin D is 10,000 IU when taken daily; much higher doses (e.g., 200,000 IU) have been used in vitamin D–deficient patients when taken weekly or monthly.

1 mg vitamin E = 0.45 to 0.67 IU vitamin D, depending upon the form of vitamin E.

17 Vaccinations

Optimal immunization is critical for all patients with thalassemia, especially transfused patients and individuals who have been splenectomized. Prior to splenectomy patients should receive the meningococcal conjugate vaccine and should be up to date for Hib and pneumococcal vaccines.

Routine pediatric immunizations should be current and vaccination records should be checked annually. Beginning at two months of age, patients should be given 7-valent conjugate pneumococcal vaccine as recommended. A booster with 23-valent vaccine should be administered at 24 months. Pnuemovax boosters should be considered every five to ten years. Check the pneumococcal titers following immunization. Severe local reactions can indicate high titer.

Patients need to be immunized against hepatitis A and B, especially patients on chronic transfusions. Annual monitoring of titers and booster immunizations, when indicated, will ensure patients are well protected. Individuals who are HIV positive or undergoing treatment for hepatitis C should not receive live virus vaccines. An annual influenza vaccination and annual PPD should also be administered. Particular attention should be given to the H1N1 virus, as this pathogen may cause more severe symptoms in patients with thalassemia.

18 Fertility and Pregnancy in Thalassemia

Delayed puberty and primary or secondary amenorrhea due to iron overload are common complications in transfused thalassemic females. Iron can cause damage to the hypothalamic-pituitary axis and possibly to the ovaries and testes. As with prevention of other endocrinopathies, it is important to ensure adequate chelation starting in early childhood and through adolescence. (Also see Section 9.2.4, regarding evaluation of adolescent females and males with delayed puberty due to endocrinopathy.)

Adult fertility status in both genders may be assessed by testing LH, FSH, and estradiol in females (can be tested at any time if females are menstruating) and LH, FSH, and testosterone in males. Obtain free T4, TSH, ACTH, and cortisol stimulation tests to assess central hypothalamic-pituitary axis function. In females with amenorrhea, obtain prolactin levels.

If gonadotropins (LH, FSH) are elevated, there has been primary testicular or ovarian failure. If LH, FSH, and estradiol or testosterone are low, there is likely a hypothalamic-pituitary axis failure or secondary failure. However, in this situation, the presence of ovarian or testicular failure cannot be ruled out in addition to the pituitary failure. If pregnancy is sought, additional evaluation and treatment require referral to a reproductive center.

18.1 Pregnancy

In the past, pregnancy was uncommon and often discouraged because of risk. Now, with improved treatment including transfusion and chelation, pregnancies are relatively common. Both spontaneous pregnancies and in vitro fertilization have been successful. Pregnancy even in patients who develop amenorrhea is being observed. Pregnancy in a patient with thalassemia is high-risk and requires multidisciplinary management. Deaths due to cardiac failure occur. Patients with cardiac disease and significant cardiac iron are at particular risk. Optimal transfusion therapy and iron control should be established before pregnancy.

There is limited data on iron chelators administered during the first trimester, and risks do exist. While iron chelation during pregnancy should generally be avoided, normal births have occurred in mothers on chelation.

19 Thalassemia Intermedia

Thalassemia intermedia is a severe disease, and special care needs to be made to assure proper treatment and care. Thalassemia intermedia is difficult to diagnose, and there are many variants which need to be considered.

Thalassemia intermedia is a more serious thalassemia syndrome than previously thought and frequently does not receive the attention it deserves. It is vital that people with thalassemia intermedia be monitored closely throughout life. Unlike thalassemia major, where the level of anemia makes transfusion mandatory, thalassemia intermedia patients may not have hemoglobin levels low enough to warrant mandatory blood transfusion and regular care. However, progression of both the anemia and ineffective erythropoiesis may eventually result in serious complications. This important group of patients suffers immeasurably due to an unpredictable degree of anemia and course of treatment; therefore, following standards of care is of utmost importance.

Many of the complications noted in thalassemia major occur in thalassemia intermedia. These complications result from ineffective erythropoiesis, anemia, dietary iron absorption, and inadequate transfusion. Patients with thalassemia intermedia experience bone changes, endocrinopathies, osteoporosis, cardiac disease, pulmonary hypertension, and chronic bone and joint pain. The extent of these complications affects intervention and initiation of treatment. Beyond supportive treatment, treatment modalities involve transfusions, splenectomy, and medications that increase hemoglobin F synthesis. Occasionally, attention should be given to treatment of specific complications, including iron overload, pulmonary hypertension, osteoporosis, and gallstones.

19.1 Nontransfused thalassemia intermedia

A baseline red blood cell phenotype should be obtained from patients, who should then be seen at a thalassemia center every three to six months, with attention to overall clinical well-being, anthropometrics as described for thalassemia major, changes in exercise tolerance, complaints of pain and/or shortness of breath, CBC, reticulocyte count, and ferritin levels.

A low-iron diet and drinking tea with meals to decrease absorption of iron is recommended. If zinc level is low, patients should be put on supplementation. Daily supplementation of 1 mg folic acid should also be taken. Patients should receive immunizations as outlined for thalassemia major patients.

19.1.1 Growth and development

Look for changes in facial bone structure. For growing children, obtain biannual skull X-rays and facial photographs: anterior/posterior and lateral. Pay attention to growth velocity, especially in young children and in adolescents. Patients should have annual dental and orthodontic evaluations and be observed for delayed or arrested puberty. Some patients have excessive growth of their heads even with only mild anemia. This in itself could be an indicator for transfusion therapy. Therefore, close monitoring of the head circumference is necessary.

19.1.2 Extramedullary erythropoiesis
Tumor masses of extramedullary erythropoietic tissue are a common complication of the nontransfused thalassemia patient. These often occur in the paraspinal areas, and are asymptomatic. However, some cases lead to spinal cord compression and acute neurologic complications. Transfusion therapy often decreases their size and prevents further growth. Rarely, emergency intervention is necessary.

19.1.3 Endocrinopathies
Osteopenia and osteoporosis should be assessed annually or every two years via DXA scan. Bone pain and fractures should be an emphasis.

Fertility should be assessed on an individual basis. Transfusion support during pregnancy should also be considered.

19.1.4 Cardiopulmonary assessment
Adults should have an annual echocardiogram for early detection of left heart decompression, and TR jet, which detects pulmonary hypertension. Those with existing pulmonary hypertension should have an annual pulmonary function test and a six-minute walk test.

19.1.5 Considerations for transfusions
The decision to start regular transfusions depends on clinical and laboratory assessment. This decision is not necessarily a permanent commitment to lifelong transfusion. Such decisions are difficult and best made at a thalassemia center.

Indications that might be considered before starting chronic transfusion include the following:
- In childhood, growth failure, delayed puberty, or poor school performance
- Symptomatic anemia
- Skeletal malformation or bone disease
- Pulmonary hypertension with or without left heart decompression

Transient transfusions may also be considered during pregnancy or times of infection.

19.1.6 Considerations for splenectomy
Splenectomy is reserved for cases of massive splenomegaly or hypersplenism, or instances where patients are unable to be transfused. The benefits and complications of transfusions and splenectomy need to be discussed with the family.

The general recommendations for endocrine and iron-status monitoring outlined for thalassemia major should be applied to patients with thalassemia intermedia. After the initial evaluations, the frequency of monitoring can be modified based on the degree of iron loading or growth failure.

19.1.7 Assessment of iron overload
Ferritin and iron saturation levels should be monitored annually. If the ferritin levels are persistently greater than 1,000 ng/mL or the iron saturation is greater than 60 percent, obtain a quantitative assessment of liver iron. Use the guidelines in Section 5 for the administration of deferasirox or deferoxamine. When a thalassemia intermedia patient does not get transfused, the iron burden develops from increased gastrointestinal absorption only, so drug dosing may need to be modified. Consultation with an iron chelation specialist is recommended.

20 Hemoglobin H Disease and Its Variants
The gene frequencies of alpha-thalassemia exceed those of beta-thalassemia. The loss of alpha-gene function may be secondary to a deletional or nondeletional mutation. Nondeletional mutations are more severe. The inactivation of one alpha-globin gene is insignificant. The inactivation of two alpha-globin genes causes a very mild microcytic, hypochromic anemia. The loss of function of three alpha-globin genes is called hemoglobin H disease. People with hemoglobin H disease have a variable phenotype that can range from mild symptoms to those similar to thalassemia major. Due to phenotypic variability or in utero intervention, more patients with this disorder are being reported.

Hemoglobin H disease is a serious health problem in Southeast Asia and southern China. Thousands of affected patients live in the Middle East, the Mediterranean region, and North America. Many patients require intermittent transfusions. The clinical severity is strongly influenced by the type of mutation. Deletions on chromosome 16 are responsible for 75 percent of hemoglobin H mutations, and these deletions cause a milder form of the disorder. The remaining 25 percent of patients with hemoglobin H disease have two deletions plus a point mutation or insertion in the alpha-globin gene. Nondeletional hemoglobin H is often severe and likely to require transfusions. In both groups, however, there is marked phenotypic variability.

20.1 Diagnosis
The diagnosis of hemoglobin H may be difficult. Hemoglobin H and hemoglobin Barts are fast-moving hemoglobins that may appear on electrophoresis. However, they are unstable and often go undetected. Patients with hemoglobin H disease have greater than 20 percent hemoglobin Barts at birth. Hemoglobin Barts rapidly disappears on electrophoresis after birth. Since hemoglobin H and hemoglobin Barts are unstable, electrophoresis may fail to detect these abnormalities.

The state of California screens newborns for hemoglobin H disease utilizing high performance liquid chromatography to measure hemoglobin Barts. Newborns with greater than 20 percent hemoglobin Barts undergo DNA testing to distinguish more severe, nondeletional hemoglobin H, such as hemoglobin H–Constant Spring from deletional hemoglobin H disease. High performance liquid chromatography or hemoglobin electrophoresis cannot reliably detect nondeletional mutations.

20.2 Hemoglobin H deletion
After the newborn period, the diagnosis of deletional hemoglobin H disease is often made only after the detection of complications such as cholelithiasis, exacerbation of the anemia induced by infection, or the findings of splenomegaly and growth failure. The mean hemoglobin in deletional hemoglobin H is quite variable but averages 9.5 g/dL. Twenty-nine to 50 percent of patients with deletional hemoglobin H require intermittent transfusion therapy, but the need for chronic transfusion therapy is uncommon. Pregnancy is often associated with an increased severity of anemia, as well as pre-eclampsia, and may necessitate transfusion. Iron overload and iron-induced heart failure are increasingly being noted in adult patients not receiving intermittent transfusions.

Serum ferritin levels usually underestimate the magnitude of iron overload. Iron deposits in nontransfused patients are in the ferrihydride form, which causes more damage than the goethite iron that results from transfusion. Earlier therapeutic intervention for iron overload in nontransfused hemoglobin H disease is indicated.

Hemoglobin H–Constant Spring is the most common nondeletional alpha-thalassemia mutation associated with hemoglobin H disease. Hemoglobin H–Constant Spring disease has significantly more ineffective erythropoiesis. The laboratory and clinical course of hemoglobin H–Constant Spring disease is more severe than hemoglobin H disease. The average hemoglobin is 2 g/dL less than in deletional hemoglobin H disease. The mean corpuscular volume is a near-normal 72 fL, compared to 59 fL for deletional hemoglobin H disease. Most patients have moderately severe splenomegaly, and over 50 percent require splenectomy. Splenectomy often results in improved hemoglobin levels but is associated with a high rate of portal vein thrombosis. Ninety percent of patients with hemoglobin H–Constant Spring disease have been intermittently transfused, and up to 40 percent have required repeated transfusions, particularly in early infancy and in later adulthood. Iron overload occurs in 75 percent of patients by adulthood. Rarely, hemoglobin H–Constant Spring disease and other nondeletional hemoglobin H disorders have caused fatal hydrops fetalis syndrome.

Homozygous alpha-thalassemia, caused by a deletion of all four alpha-globin genes, leads to the formation of high levels of hemoglobin Barts in utero. Hemoglobin Barts has an extremely high oxygen affinity, and therefore delivers little oxygen to fetal tissues. The severe hypoxia results in cardiac failure, massive ascites, and intrauterine death. Congenital malformations associated with homozygous alpha-thalassemia include hypospadias, other genitourinary defects, and limb malformations. Infants surviving to delivery without prenatal intervention are usually hydropic and commonly have neurological impairment. Intrauterine transfusions following early detection of homozygous alpha-thalassemia have resulted in the birth of several nonhydropic infants, some but not all of whom have no significant neurological abnormalities or congenital anomalies. Affected infants who survive gestation and the neonatal period subsequently require chronic transfusion therapy or may be appropriate candidates for hematopoietic stem cell transplantation.

Occasionally, infants with homozygous alpha-thalassemia are born without hydrops, even in the absence of intrauterine transfusions. Nondeletional, highly unstable alpha-globin gene mutations may result in a hemoglobin H genotype, causing hydrops fetalis. In pregnancies known to be at risk, chorionic villous sampling with molecular analysis identifies homozygous alpha-thalassemia within the first months.

The ethical issues of managing a fetus known to have homozygous alpha-thalassemia are complex. Obstetric complications and the necessity for long-term transfusion therapy are serious considerations. Increased risk of both maternal and fetal morbidity should be included in counseling families at risk for an affected fetus. Education, screening, and counseling of the family are essential.

20.3 Recommendations for care

Often the patient with hemoglobin H is asymptomatic and is unprepared for the acute complications that occur during infection, pregnancy, and drug exposure. In particular, these include hemolytic and aplastic anemic episodes. Folic acid supplements and avoidance of oxidative compounds and medications are recommended. In mild cases, biannual visits are adequate. In more severe cases, more frequent visits are indicated. At routine visits, growth, development, facial bone deformity, dental status, and hepatosplenomegaly should be monitored. Routine monitoring of hemoglobin levels is required.

Patients with hemoglobin H disorders develop neonatal anemia. Splenomegaly and hypersplenism are relatively common. Splenectomy usually ameliorates the severe anemia noted in nondeletional hemoglobin H cases. Splenectomy may be required at a very young age in transfusion-dependent cases. Prophylactic antibiotics and infection precautions are similar to other splenectomy patients. Thrombosis prevention is indicated in cases requiring splenectomy. Low-dose aspirin or other anticoagulants may be used.

Ongoing monitoring of iron stores with quantitative imaging of the liver is indicated because of the unreliability of serum ferritin tests. In nontransfused patients, imaging should be initiated in early adolescence. Cardiac function monitoring is indicated. The frequency is determined by the anemia and the iron-overload status. Gallstones frequently occur in hemoglobin H disease, and cholecystectomy is indicated in symptomatic patients. Bone-density measurement should be initiated in early adolescence. Pregnancy requires more frequent monitoring because of the risk of severe anemia and pre-eclampsia.

21 Thalassemia Research

Research and clinical teams in comprehensive thalassemia centers work together to provide the highest-quality, integrated health care possible. Research is an important component of comprehensive care for patients with thalassemia. Research allows doctors to offer patients and families the most up-to-date and innovative therapies. In recent years, research has led to many advances in thalassemia treatment.

As part of thalassemia patients' care, they should be informed about studies that they might be eligible to participate in. Patients are never obligated to join any study, and if they choose not to participate, they should be assured that they will still receive high-quality health care.

There are a variety of long-term projects, funded by different sources—the National Institutes of Health (NIH), the Center for Disease Control (CDC)—that are available for patients. The Thalassemia Clinical Research Network (TCRN) was funded in 1998 by the National Heart, Lung, and Blood Institute (NHLBI) to provide a national structure to conduct clinical studies in thalassemia. The TCRN has been successfully funded by the NHLBI for two five-year cycles, based on the previous successful studies that have been done.

The CDC also funds a national study to monitor the safety of the nation's blood supply. The CDC is collecting blood samples from patients with thalassemia to screen for disease (HIV, hepatitis A,

B, and C). This study is also collecting an annual visit form to evaluate care for patients with thalassemia at various sites around the country.

22 Psychosocial Support

Thalassemia imposes a significant intrusion in the lives of patients and their families. The effects are many, sweeping from financial hardships and absence from school and work to significant problems with self-image and self-esteem. All of these issues have a tremendous impact of the effectiveness of therapy and on the quality of life of patients. These challenges are further complicated by normal stages of development incurred from infancy to adulthood and by vast cultural differences. This latter point cannot be emphasized enough. Because of the ethnic predilection of thalassemia, the patients come from diverse cultural backgrounds which are usually different from those of their health-care providers.

Thus, all professionals who provide care and support to these patients must be aware of the cultural, social, developmental, and behavioral issues that affect this diverse population. Behavioral problems have great bearing on compliance with therapy, and thus with medical outcome, as well as with quality of life for patients with chronic disease. Medical and psychosocial professionals must also collaborate closely with each other in order to provide optimal care to their patients. Referral to outside providers who have no knowledge or understanding of the medical problems is generally ineffective.

22.1 Child life services

Culturally sensitive child life services are an integral part of comprehensive care. Child life services assure that care is family-centered and developmentally appropriate for the patient. It is imperative that patients with thalassemia understand their disease and treatment in order to follow their prescribed medical regiments. Child life programs in health-care settings minimize psychological trauma and promote optimal development of children and their families.

Through observation and discussion, assess the response of the patient and family to health-care experiences, and develop a plan to meet their needs and facilitate coping. Provide opportunities for gaining a sense of mastery, for play, for learning, for self-expression, for family involvement, and for peer interaction. This can be achieved in many ways, including medical play and art therapy.

Provide a positive growth experience for patients. Minimize stress and anxiety for the patient, parents, and siblings. Provide continual teaching to patients to help them understand all aspects of thalassemia, including blood type and transfusion, chelation, and general health and wellness.

Prepare children and families for health-care experiences. For example, conduct a medical preparation prior to a patient's liver biopsy/SQUID and splenectomy. This increases overall understanding of the procedure, reduces anxiety, and enables patients to gain mastery over their health-care experiences.

During hospitalizations, provide essential life experiences such as play, school, peer interaction, community events. These activities commonly take place in the hospital playroom or schoolroom. Also create opportunities that strengthen self-esteem and independence.

Child life specialists are an integral part of the health-care team. They can work to empower patients and families, as well as teach them to be proactive members in their own health care. Child life can also assist with transitional issues as patients get older and new issues and challenges arise.

22.2 Psychological services

Culturally sensitive psychological services make up a critical part of all comprehensive care plans for patients with thalassemia. Thalassemia requires time-intensive, lifelong medical treatment. Therefore, ongoing therapeutic services are needed to help patients cope with issues related to chronic illness and mortality. Psychologists providing support should be experienced and consistent. Student interns are not recommended to give psychological counseling for people with chronic illness due to a high rate of turnover and the inability to establish long relationships needed to build trust.

Patients should have an evaluation of general functioning and adaptation to chronic illness and hospital culture. In addition, assess patients' ability to comply and cope with medical regimen. Assistance and intervention with issues of compliance and coping styles should be considered for every patient. Evaluate and refer patients to a psychiatrist for administration of psychotropic medication. In addition, therapeutic groups for adolescents and adults must be organized and directed.

22.3 Social services

Social services that meet the needs of the patients in a culturally sensitive way are critical for patients with a chronic disease that requires an inordinate amount of resources. Social services should:

- evaluate functioning in the community and at school/work
- provide for adequate social and medical services
- assess the need for financial assistance and make referrals to community services/resources
- make it a priority to obtain health insurance for patients (children and adults) and families with thalassemia

22.4 Genetic counseling

Genetic counseling is the communication process of providing information and support to individuals and families with a diagnosis and/or risk of occurrence of an inherited disorder. Culturally sensitive genetic counseling, with an emphasis on reproductive issues, is an integral and necessary component of comprehensive care for patients and parents affected by all forms of thalassemia disease and trait. Services should be provided by a licensed genetic counselor in states with licensure legislation and by an ABGC board-certified or board-eligible genetic counselor in all other states.

Genetic counseling is needed:

- at diagnosis
- during adolescence
- prior to and after any genetic testing
- prior to pregnancy and/or as early in pregnancy as possible

Annual follow-ups are needed to reinforce teaching.

Critical components of genetic counseling include:

- obtaining a three-generation genetic family history (pedigree)
- assessing risk for thalassemia in family members
- identifying risk factors impacting medical management (e.g., family history of other hemoglobin traits or diseases, hereditary hemochromatosis, G6PD deficiency, inherited thrombophilia, cardiovascular disease or its risk factors, cardiac conduction defects, diabetes, renal disease, ophthalmologic disorders, hearing loss, allergies, ethnicity, consanguinity)
- incorporating psychosocial information impacting the family system and relationships (e.g., location of residence, disclosure/nondisclosure of diagnosis, reliable source of emotional/social support)
- assisting patients in conveying information about genetic risk to other family members
- providing informed consent, pre-, and post-counseling for all genetic testing
- alpha-globin genotyping: hemoglobin H–Constant Spring and other structural alpha-globin variants, possible modifying effects of alpha-globin deletions/triplications on beta-thalassemia
- beta-globin genotyping: beta0/beta+, S, D, E, O, and other structural variants

The limitations of drawing genotype/phenotype correlations include:

- developmentally appropriate consent/education for minors
- reproductive genotype post–stem cell transplant or bone marrow transplant
- the possibility of revealing undisclosed adoption or alternative paternity
- discussing/facilitating appropriate screening and diagnostic tests for relatives

23 Genetic Testing

If HLA typing is performed when stem cell transplant or bone marrow transplant is an option, genetic counseling and education is vital due to ethical implications. A genetic counselor should provide initial and ongoing teaching regarding natural history and clinical manifestations; signs and symptoms of disease that warrant immediate medical attention; and available emotional and social support services. Genetic counselors should also provide available resources in collaboration with outreach coordinators and social workers (e.g., research studies, support groups, advocacy organizations, and patient-to-patient or parent-to-parent connections).

24 General Timetable for Clinical and Laboratory Evaluation

Category	Measurement	Check after this number of months					As clinically indicated	Initially	Comments
		1	3	6	12	24			
Growth and development	Height	X							
	Sitting height		X						
	Weight								
	Growth velocity				X				
	Tanner Stage			X					
	Head circumference								This should be checked every other month.
Hematology	CBC, reticulocytes	X							
	T+C Coombs (indirect)	X							
	Coombs (direct)						X		
	Serum transferrin receptor						X		
General	HLA typing							X	
	DNA mapping (alpha and beta)							X	
	Red blood cell phenotype							X	
	Volume of packed red blood cells transfused			X	X				
Iron and toxicity	Ferritin		X						
	Liver iron				X		X		If there is evidence of hepatitis, histology is necessary.
	Audiology evaluation				X		X		
	Vision screen			X		X			
	Ophthalmology evaluation				X				
	Iron, TIBC						X		
	Transferrin saturation						X		
Liver function and disease	AST, ALT		X						
	Bilirubin (total)		X						
	Bilirubin (direct)		X						
	Hepatitis A serology				X				
	Hepatitis B serology				X				
	Hepatitis B PCR				X		X		When hepatitis is active, do this test annually. With undiagnosed hepatitis, this may be monitored.
	Hepatitis C serology				X				
	Hepatitis C PCR						X		Evaluation of positive serology or undiagnosed hepatitis.
	PT, PTT							X	Have this before a liver biopsy. Patients with active hepatitis should have the test annually.
	Albumin				X				
Periodic	Chemistry panel		X						
	Urinalysis			X					
	Dental				X				

24 General Timetable for Clinical and Laboratory Evaluation (continued)

Category	Measurement	Check after this number of months					As clinically indicated	Initially	Comments
		1	3	6	12	24			
Endocrine	T3, free T4, TSH				X				Start at 5 years.
	PTH				X				Start at 5 years.
	Calcium, ionized calcium				X				Start at 5 years.
	Fasting glucose				X				Start at 5 years.
	Glucose tolerance test						X		Perform at 10, 12, 14, and 16 years.
	IGF-1, IGF BP-3						X		Perform at noted growth delay.
	LH-ICMA						X		Perform at noted delay in puberty: 12 years for girls and 14 years for boys.
	FSH						X		Perform at noted delay in puberty: 12 years for girls and 14 years for boys.
	Estradiol						X		Perform at noted delay in puberty: 12 years for girls and 14 years for boys.

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