

A Guide to Living with Thalassemia



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Chapter 1

Introduction

You are reading this book because you or a member of your family has thalassemia. In this publication, we have assembled the most important information about thalassemia to help both patients and caregivers manage this condition.

Patients

A recent survey carried out by the Cooley's Anemia Foundation asked patients what specific topics they wanted to know more about. A few of the questions they asked were:

- What is the best way to manage the chronic condition of thalassemia?
- What are the latest treatments for thalassemia?
- What are the effects of thalassemia and its treatment on the heart and liver?
- Is there help for issues of financing and insurance for treatment?
- What is the latest information on clinical trials?
- How important is emotional support and how to find it?
- Where are the best places to get medical care?

This guide aims to answer questions like those and many more. We believe that patients want and need information so they can manage their condition in the best possible way.

Caregivers

Families who care for children and adolescents with thalassemia face many challenges. They need to coordinate medical care, oversee adherence to treatment, and help provide a supportive environment for their children. They also may need support for themselves and for members of their families, including siblings of children with thalassemia.



How to use the Guide

Some readers will find almost everything in this Guide to be new information. Others may have a strong background in thalassemia already but will benefit from having all the information in one place. Whatever a person's level of knowledge, the information in this book is crucial for everyone who is living with thalassemia.

Each chapter begins with “learning objectives.” These will be a preview of the chapter’s content and will help you know what information to expect.

The main part of each chapter will present the latest information about different aspects of thalassemia. (Look at the Table of Contents on page 1 for the specific chapter topics.) You can read the Guide through from beginning to end for a complete understanding of thalassemia. Or you may want to go first to specific chapters that hold the most interest for you.

We have made the Guide easy to read, but sometimes we use medical terms that may not be familiar to patients or caregivers, especially if they are new to the field of thalassemia. A glossary in the appendix of this book (page 89) will help you with many unfamiliar terms. The appendix also includes other additional information, including resources you might find helpful.

In the appendix, you will also find a questionnaire that we hope you will return to us. This will help us know what information to include in future updates of this publication. Those who return the questionnaire will be notified when we post updates to this Guide online.

Finally, a note about the photographs in this publication. Most of the people in these pictures are individuals with thalassemia or their family members. We are excited to share these examples of people living successfully with thalassemia.

Thalassemia is a very complicated disorder; the more that you, as a patient or caregiver, know about thalassemia and its treatment, the better you will be able to meet its challenges and to know what to do to live a healthier, fuller life. We think that this Guide will help you achieve that goal.



Chapter 2

Overview: The Basics of Thalassemia

Learning Objectives

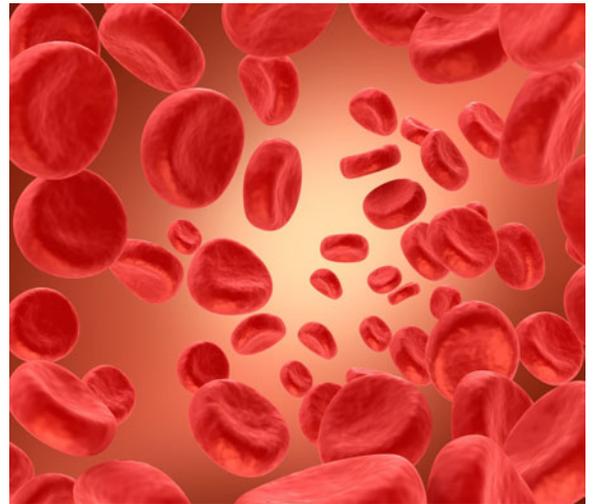
The purpose of this section is to give you some basic background information about thalassemia. At the end of this section, you will be able to:

- Identify the different types of thalassemia.
- Understand where to get treatment for thalassemia.

What is thalassemia?

Thalassemia is a group of inherited blood disorders. There are two important things you should know:

- Thalassemia is inherited. It is not something you “catch” by coming into contact with another person or from a virus. It is passed on to you through the genes of your parents.
 - If you have thalassemia, your body is not able to produce enough of the protein needed to form hemoglobin. You need hemoglobin to carry oxygen throughout your body. When you don’t get enough oxygen in your bloodstream, you may notice certain signs and symptoms, like fatigue and other health problems.



There are two kinds of proteins that produce hemoglobin, called alpha protein and beta protein. A person with alpha thalassemia doesn't have enough alpha protein; a person with beta thalassemia doesn't have enough beta protein.

What tests are used to determine if a patient has thalassemia?

There are several tests that are conducted to confirm a suspected case of thalassemia, including a *Complete Blood Count* (CBC) and a *hemoglobin electrophoreses*. These should be followed by a genetic analysis for both beta thalassemia and alpha thalassemia, even if initial results already indicate that either beta thalassemia or alpha thalassemia is a likely diagnosis.

There are numerous types of thalassemia, which depend on whether a person has defects in the alpha or beta protein chains. We will summarize the main types of thalassemia, grouping them together by their severity, in the chart on the next page.

You may notice that some forms of thalassemia appear in two categories of severity; that's because the severity associated with a particular form of thalassemia can vary widely from person to person, or the severity may change over time. This is especially true with beta thalassemia intermedia, Hemoglobin H - Constant Spring or E beta thalassemia. For example, one person with beta thalassemia intermedia may rarely need transfusions while another person with beta thalassemia intermedia may require a regular transfusion schedule.

The severity associated with a particular form of thalassemia can vary widely from person to person, or the severity may change over time.

Determining exactly what treatment is appropriate for each individual with thalassemia is very important. Your health care team will work with you to determine what transfusion and chelation regimen is best suited to you, and they may change that regimen as your needs change. See Chapter 3 on Transfusions (page 8) and Chapter 4 on Chelation (page 14) for more details.

Where can you get treatment?

Chapter 5 (page 22) will go into detail about what is involved in putting together your health care team; however, here is some basic information.

Because thalassemia is a blood disorder, a hematologist (doctor specializing in blood issues) should be in charge of your thalassemia care. Most patients are treated at a hospital, rather than a doctor's office.

Some hospitals have special Thalassemia Treatment Centers (TTC) which provide comprehensive care for people with thalassemia. In addition to the hematologist, the TTC team includes other doctors who can work on specific issues that may arise. The members of the TTC health care team generally have special experience working on thalassemia-related issues. (See

Thalassemia for Which No Treatment is Generally Needed:	Thalassemia for Which Transfusion Therapy May Be Infrequent and for Which Iron Chelation May Be Necessary:	Thalassemia for Which Regular Transfusion Therapy and Iron Chelation Therapy is Required:
<ul style="list-style-type: none"> • Thalassemia minor/ thalassemia trait 	<ul style="list-style-type: none"> • Beta thalassemia intermedia • Hemoglobin H disease (a kind of alpha thalassemia) <ul style="list-style-type: none"> • Hemoglobin H disease - Constant Spring (a kind of alpha thalassemia) • E beta thalassemia 	<ul style="list-style-type: none"> • Alpha thalassemia major • Beta thalassemia major • Beta thalassemia intermedia (in many cases) <ul style="list-style-type: none"> • Hemoglobin H disease - Constant Spring (in many cases) • E beta thalassemia (in many cases)
<p>People with thalassemia minor (also called thalassemia trait) are said to be “trait carriers.” This means they carry the trait for either alpha thalassemia or beta thalassemia. Aside from an occasional very mild anemia, there are no symptoms with thalassemia minor and no treatment is usually required.</p>	<p>In some cases, people with the above forms of thalassemia do not require transfusions as often as people with transfusion-dependent forms of thalassemia because their anemia may be more moderate than severe. However, many people with these forms of thalassemia may still experience iron overload due to other issues and will therefore require iron chelation therapy to remove that excess iron. Individuals with these forms of thalassemia should be monitored so that steps can be taken to prevent possible complications like bone expansion and weakening, spleen enlargement, and heart/liver damage.</p>	<p>Children who are diagnosed with alpha thalassemia major require transfusion treatments while they are in the womb and continue to need transfusion therapy after birth. Children with beta thalassemia major usually begin transfusion therapy six months - two years after birth. Iron chelation therapy is also required to remove excess iron, which results from transfusion therapy and other issues. Proper treatment helps to prevent possible complications such as bone expansion and weakening, spleen enlargement, and heart/liver damage.</p>

pages 26-27 for more details and a list of some of the larger TTCs throughout the country.)

Many people with thalassemia don't live near a TTC and so they receive their regular treatment through a local hematologist. These people should still try to go to a TTC once a year in order to receive a comprehensive care evaluation. In addition, it can be valuable for their doctor to establish a relationship with a hematologist at a TTC.

How has thalassemia changed over the years?

With improved screening programs, non-invasive iron measurement, better methods of measuring iron's impact, a safer blood supply and more drug treatment options, people with thalassemia are surviving into their fifth decade and beyond. The golden rule for survival is: **less iron is better and strict adherence to treatment is the most important predictor for survival.**



Chapter 3

Managing Thalassemia: Transfusions

Learning Objectives

The purpose of this section is to teach you about the kind of treatment that is usually involved with thalassemia. At the end of this section, you will be able to:

- Identify whether a specific form of thalassemia usually requires frequent blood transfusions.
- Determine the minimum hemoglobin level that a person with thalassemia should maintain.
- Identify the challenges that can be associated with transfusions.

Not every person with thalassemia requires regular blood transfusions. However, some people with thalassemia do depend on transfusions in order to survive and lead healthy, energetic lives.

This chapter explains some of the basics of transfusion.

Who needs transfusions?

Individuals with either alpha thalassemia major or beta thalassemia major will require regular transfusions, while a person with beta thalassemia intermedia or hemoglobin H disease may only need an occasional transfusion. In some cases, a person with thalassemia intermedia or hemoglobin H disease may never need a transfusion. Often a person with E beta thalassemia will fall somewhere in between, needing regular transfusions but not necessarily as often as a person with alpha thalassemia major or beta thalassemia major.



Sometimes, a patient's transfusion requirements may change. For example, people who once needed only an occasional transfusion may require regular transfusions as they age. In addition, the transfusion requirement may be affected by an illness or infection.

People with a severe form of thalassemia, such as beta thalassemia major, typically receive red blood cell transfusions about every two to four weeks. The amount of blood given to each patient is usually based on the patient's weight and pre-transfusion hemoglobin levels. Some patients may receive as many as 52 units of blood over the course of a year.

Your hematologist will determine when a transfusion is needed and if regular transfusions should be started.

What does the transfused blood do?

The hemoglobin of people with thalassemia lacks protein that is needed to carry oxygen throughout the body. Transfusion is a process where healthy red blood cells, which do contain the needed protein, are added into a person's veins. These transfused red blood cells help to more effectively carry oxygen and give the patient more energy. Regular transfusion enables the patient's blood-producing system to operate at a more normal level.

When should transfusions be started?

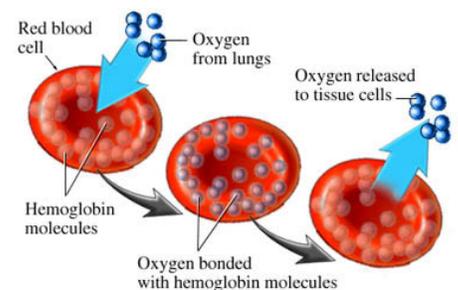


The best *age to begin transfusion varies with each patient*. Even patients who have the same type of thalassemia may start transfusion at different ages.

In general, children with alpha thalassemia major require transfusion while still in the womb and will continue transfusion after birth; those with beta thalassemia major will begin transfusions somewhere between six months and two years of age, assuming they have been diagnosed by this time. The doctor will advise about the best time to begin transfusion based on a number of factors, usually including the child's hemoglobin level and level of energy.

Red blood cells or blood?

Typically, a person with thalassemia who gets a transfusion receives red blood cells rather than “whole blood.” When we use the term “blood transfusion,” we’ll be referring to a transfusion of red blood cells.



Once transfusions begin in a child with thalassemia major, it is generally desirable to maintain pre-transfusion hemoglobin levels of between 8.5 and 10g/dL. (This means that the hemoglobin level when the patient is transfused will be between 8.5 and 10g/dL; after transfusion, it may be higher than this for some time but shouldn't usually exceed 14g/dL.) Targeting this level will determine how often transfusions are needed — again, usually about every two to four weeks. (Please note, however, that transfusion requirements are highly individualized and this target may be modified depending upon the needs of the patient and the policies of the treating doctor.)

For more moderate forms of thalassemia, such as beta thalassemia intermedia or hemoglobin H, there is no set age when transfusions begin. Some people with a moderate form of the disorder may not get transfused until they are adults, if ever.

The number of transfusions needed by people with less severe forms of thalassemia varies. Some may require four or five treatments a year; others can go for much longer periods between transfusions. Again, sometimes, patients who have been rarely transfused need more frequent transfusions as they grow older.

What tests are needed?

A Complete Blood Count (CBC) will measure your hemoglobin level. Your hematologist will use the results of this test to determine if you need transfusion and how many units of red blood cells are required. In addition, before being transfused, the blood sample will also be used for a “*cross and match*” test. This is done to check blood type and to check for possible substances in the donated blood that could potentially cause a transfusion reaction in the recipient.

Thalassemia patients most often receive packed red blood cells depleted of leukocytes (white blood cells). Some hospitals use red blood cells that have been “washed” with a saline solution; washed cells are most often used for patients who are potentially susceptible to transfusion reactions.

What are the challenges associated with transfusions?

Blood transfusions are a life-saving treatment for many people with thalassemia; however, transfusions do involve challenges, both medical and logistical. It's important to be aware of these issues — but also to keep in mind the essential role transfusions play in making a typical, healthy lifespan possible for you or your child.



Medical challenges

Iron overload

Iron overload is the major consequence of adding extra blood to your system. Excess iron can damage the heart, liver, and endocrine system (see chapter 6 for more on complications). Removing excess iron through chelation (iron removal) is a critical part of treatment. A detailed discussion of chelation follows in Chapter 4.

Bloodborne infections

Despite the high level of safety of blood in the United States, infections can sometimes result from bacteria, viruses, or parasites that have contaminated donated blood. The U.S. government monitors the potential transmission of diseases that may occur through transfused blood. The Centers for Disease Control and Prevention (CDC) has two programs that address this issue. First, through its established Universal Data Collection system, CDC screens for bloodborne pathogens like hepatitis and HIV. In addition, CDC developed the Thalassemia Data and Blood Specimen Collection system to help detect further known and emerging infections that may affect people who get frequent transfusions, such as those with severe forms of thalassemia.

Transfusion reactions

Patients may at times experience a transfusion reaction, a response to the blood that they are receiving. Usually this happens when the *donated blood contains a protein that the patient's body doesn't accept*. Some reactions occur while a person is being transfused; these can be observed and treated immediately by the doctor or nurse. Typical *symptoms include high fever, nausea, diarrhea, chills/shakes, or a sudden drop in blood pressure*. Vital signs taken during the transfusion process will alert nurses to a possible reaction.



Sometimes, reactions occur after the transfusion, up to two weeks later. One such reaction is a delayed hemolytic transfusion reaction involving the breakdown of red blood cells. The patient may become jaundiced and have a drop in hemoglobin levels. Fever and other symptoms like cola-colored urine may also occur. In such cases, the patient should return to the doctor to get hemoglobin levels checked and other tests to determine if more blood is needed. *If a patient at any time suspects they may be having a transfusion reaction, they should contact their doctor or nurse immediately to determine if any action needs to be taken.*

Allergic reactions also may occur during or after transfusion and should be treated with antihistamines, bronchodilators, a fluid bolus, steroids or epinephrine. If a patient has had previous reactions, a doctor may prescribe the use of pre-medications, such as Tylenol or Benadryl, in order to decrease the likelihood of a reaction.

Any transfusion reaction should get *immediate attention*. Alert your nurse or other health care provider right away if you or your child experiences any of the following:

- Fever
- Chills or shaking
- Hives or allergic symptoms
- Discomfort or anything unusual during the transfusion or a few days afterwards
- Dark urine

Logistical challenges

The transfusion process is time-consuming, both for the patient and the parent or caregiver. The process can take as much as an entire day, including getting to and from the clinic; having blood tested; waiting for results and for the blood to get moved from where it is stored to the transfusion center; and undergoing the actual transfusion.



The transfusion itself typically takes about 1½ to 2 hours per unit; babies and small children or patients with cardiac issues may require longer than the typical 1½ to 2 hours per unit. In some rare cases, transfusion time may be as high as 4 hours per unit.

For patients, parents or caregivers who work, the process means taking a whole day off every two to four weeks. Some parents may have the option of splitting up the process — for example taking the child in for the "cross and match" on one day and coming back another day for the actual transfusion. Although this is more time-consuming, it can ease the long clinic wait for a child.

Parents may also have additional issues to consider. For example, parents who have other children at home may need to find care for them while they accompany a child with thalassemia to the transfusion facility.

Many parents of children with thalassemia need to enlist the help of others in order to make sure their child is able to receive needed treatment. Having support from other family members or friends is an essential part of managing this aspect of thalassemia care.

Overall, managing the transfusion aspect of treatment can be challenging. However, it's important to remember that transfusions are vital for many patients with thalassemia. If a patient needs transfusions on a regular basis, they will benefit in terms of *better health and greater energy*.

Chapter 4

Managing Thalassemia: Iron Chelation

Learning Objectives

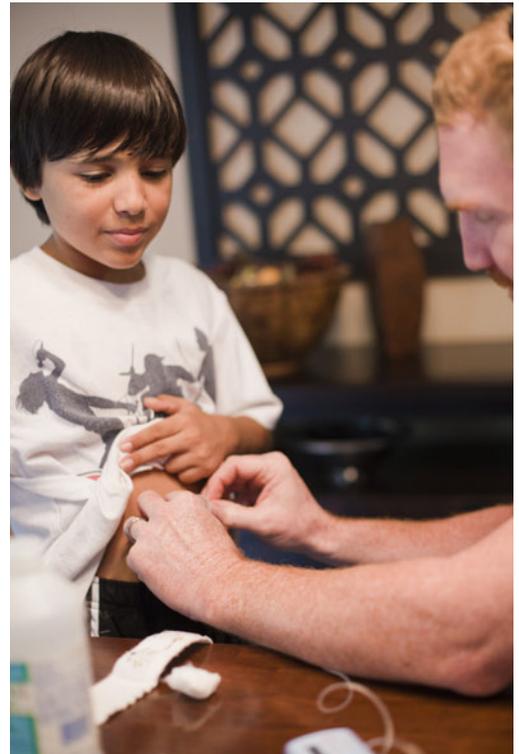
The purpose of this section is to teach you about iron overload in thalassemia and how it is treated. At the end of this section, you will be able to:

- Discuss in what ways iron overload can affect your health.
- Name the three iron chelators currently available in the United States.
- List ways in which iron is monitored.

The ability to survive with red blood cell transfusions makes thalassemia a chronic manageable disorder; however, red blood cell transfusions contain iron, and after being regularly transfused for a while, that iron builds up. If the excess iron (often called iron overload) is not removed, it can cause damage. Chelation drugs are used to help your body eliminate iron overload.

Even people with thalassemia who are not regularly transfused may also, over time, develop iron overload. This may come about, for example, when a person's hemoglobin is maintained at such a low level that a state called "ineffective erythropoiesis" occurs. In this situation, their body responds by over-producing red blood cells, which then add extra iron to the body.

This chapter will discuss some of the basics of iron chelation.



How does chelation work?

An iron chelator is a medicine that goes through the body and grabs on to iron particles. The chelator and the iron it grabs are removed from the body through urination or the stool.

Who needs chelation?

Again, anyone who has regular transfusions must have regular chelation to avoid iron overload and stay healthy.

In addition, chelation may be needed by people who don't depend on chronic transfusions, especially if their hemoglobin is maintained at low levels and causes their bodies to over-produce red blood cells. In these cases, a patient may require less frequent chelation or may require chelation at lower doses than a person who is regularly transfused.

In all cases, your health care team must monitor the iron levels in your body and determine what chelation dosage and schedule is best for maintaining your good health. There are numerous complications that can develop due to untreated iron overload. These include heart and liver problems, diabetes, low bone mass, growth and development issues and thyroid problems.

What are the chelation drugs that are available in the U.S.?

Three chelation drugs have currently been approved by the U.S. Food and Drug Administration (FDA).

Deferoxamine

Deferoxamine (brand name: Desferal™), sometimes called desferrioxamine, was the first chelation drug; it was approved by the U.S. Food and Drug Administration in 1968 and for many years was the only option.

Most of the time, deferoxamine is administered “*subcutaneously*,” which means “under the skin.” In other words, it is not a pill that is taken by mouth; instead, it is a medicine that gets into the body by inserting a small needle just under the skin (usually in the legs or stomach).

In most cases, a small battery-operated pump, called an *infusion pump*, is used to get the drug into the body. (Information on using an infusion pump can be found at the end of this chapter on page 20.) Some patients may use a “balloon” pump, which comes with pre-mixed, ready-to-use deferoxamine.

Another kind of pump, called a CADD® pump, generally is used when patients are getting deferoxamine for long periods of time, such as 24-hour

Pumps used for administering deferoxamine

- Infusion pump
- Balloon pump
- CADD pump

infusions. CADD pumps are typically used with a port or a PICC line, which are special implanted devices used in place of the usual needle.

Deferoxamine is manufactured in a powder form, and is mixed with sterile water when it is ready to be used. (As noted above, balloon pumps come with the deferoxamine pre-mixed; some insurance plans have an option for pre-mixed Desferal for other pumps as well.) The maximum recommended dosage of deferoxamine is *40 mg per kg of weight*. That means for every kilogram (kg) that a person weighs, a maximum 40 milligrams (mg) of deferoxamine can be prescribed. One kg is equal to about 2 pounds, 3 ounces. So the maximum prescription for a person who weighs 140 pounds (approximately 63.5 kg) would be 2540 mg (63.5 x 40).

Deferoxamine has a *short half-life — about 30 minutes*; that means that after 30 minutes, it has lost about half of its strength. Therefore, it needs to be administered over a long period of time, typically between *8 and 12 hours*, and usually between five and seven nights per week, to effectively remove as much iron as possible. (The exact number of hours and days per week varies from patient to patient.) Many patients, or parents of young patients, choose to infuse the deferoxamine at night during sleep so the process won't interfere with normal activities like school or work.

If a patient is dangerously iron overloaded, deferoxamine may be administered 24 hours a day, until such time as the iron levels have returned to an acceptable level. In such cases, the drug may be administered "*intravenously*" rather than subcutaneously. This means that the drug is administered directly into a vein, rather than under the skin. As mentioned above, a port or PICC line may be used in these cases.

Deferasirox

Deferasirox (brand name: Exjade™) was approved by the FDA in 2005. Unlike deferoxamine, deferasirox is taken orally (by mouth). The medication is dissolved in a glass of water or juice, which the patient then drinks once a day. Deferasirox has a *much longer half-life* than deferoxamine, between *8 and 16 hours*, which is why it is generally prescribed to be taken

What is half-life?

Half-life is the amount of time it takes after a drug is administered for half of the dose to be metabolized or eliminated; if a drug has a half-life of one hour, that basically means that it uses up 50% of its effectiveness during the first hour after you take it.

Here are the half-lives of the three chelators used to treat iron overload:

Deferoxamine: 30 minutes

Deferasirox: 8 - 16 hours

Deferiprone: 2 - 3 hours

only once a day. The maximum recommended dosage of deferasirox is *40 mg per kg of weight*. (Information on preparing deferasirox can be found at the end of this chapter on page 21.)

Based on the results of one study, some doctors are allowing patients to try mixing their deferasirox in food; it should be noted, however, that this is an “*off label*” use of the drug and has not been submitted to the FDA for approval.

Deferiprone

Deferiprone (brand name: Ferriprox™) was approved by the FDA in 2011. This medication is also taken orally, usually in the form of a pill. Deferiprone’s *half-life* is between *2 to 3 hours*, so it is generally prescribed to be taken three times during a 24-hour period. The maximum recommended dose is *33 mg per kg of weight*, given three times a day, for a total of 99 mg per kg.

Combination therapy

Combination therapy refers to the use of two different iron chelators to treat a patient. For example, many people who take deferiprone also are prescribed deferoxamine; however, in most cases, the deferoxamine is prescribed to be taken less often than when deferoxamine is prescribed by itself. Combination therapy is prescribed when it is believed that the use of two chelators will do a more thorough or faster job of diminishing iron overload than the use of just one chelator.

What is “off label?”

A drug is used “off label” when it is prescribed by a physician for a use for which it has not been specifically approved by the U.S. Food and Drug Administration.

Several studies have examined combination therapy involving deferoxamine and deferiprone. There are also some initial clinical trials involving other combinations of iron chelators; however, at this time, no form of combination iron chelation therapy has been submitted for approval by the FDA and so its use is still “off label.”

All chelators should be taken as prescribed; *do not make any changes without first discussing them with your doctor*.

There are several things to consider when choosing a chelator, including the way it is administered (subcutaneously, dissolved in liquid, swallowed in pill form), possible side effects, your specific iron accumulation, and your ability to stick to the prescribed plan. In addition, some patients begin with one chelator but move to another during their course of treatment. You should talk with your health care team to determine what form of chelation therapy is best for you.

When should chelation therapy begin?

Typically, patients start chelation after one or two years of chronic transfusion; however, treatment may vary with each patient who has thalassemia, so the type, amount, and timing of chelation should be tailored for each individual. Again, you should talk with your doctor to determine the best regimen for your individual case.

How are iron overload and chelation therapy monitored?

Various tests monitor the amount of iron overload in a patient and help determine the impact of chelation therapy.

Ferritins

Ferritin is a protein in the body that binds to iron. A simple blood test to monitor the patient's ferritin level is an important way to check on the amount of iron in the blood. This test is used to provide a general picture of how effective chelation is on a day-to-day basis.

It should be noted that ferritins are most useful for monitoring changes in iron over a period of time. It's not unusual for ferritins to change significantly from one testing to the next, which may be due to a variety of factors; what is more important is whether over the period of several months there is a general trend of ferritins going up (indicating increasing iron) or down (indicating decreasing iron).

In general, most hematologists set a goal of a ferritin level of 1,000 or below for their thalassemia patients; some are even setting much lower goals. (The specific level will vary based on the individual patient and the treating hematologist.) Thanks to scientific advances and greater chelating options, the possibility of reaching lower ferritin levels has significantly increased.

Ferritins are most useful for monitoring changes in iron over a period of time. What is important is whether over the period of several months there is a general trend of ferritins going up (indicating increasing iron) or down (indicating decreasing iron).

Liver iron concentration: biopsy

Measuring the amount of liver iron concentration (LIC) in a patient is one way to estimate the total iron content of a patient's body. In the past, a liver biopsy had to be performed to measure iron in the liver, but this procedure has limitations. It can be a painful procedure and doesn't always provide an accurate gauge of the amount of iron in the liver; for example, if iron is not evenly distributed throughout the liver, taking a small sample from one part of the liver may not give an accurate picture of how much iron is present throughout the liver.

MRI for liver iron concentration and cardiac function

Although biopsy can be useful, there are new ways of monitoring iron that are less invasive and painful for patients. MRI imaging (utilizing specialized technology) can help doctors measure the amount of iron in the liver; at some centers, this special MRI-based technology can also measure iron in the pancreas. In addition, special MRI technology can measure cardiac function in a way that indicates if iron is affecting the heart. These techniques are typically done on an annual or bi-annual basis to provide a more complete picture of iron loading.

Note: The MRI machine requires people to hold their breath on command during the procedure, and children under 6 may not be able to lie still for the amount of time required for the testing. Many adult patients feel claustrophobic in the MRI scanner. If this is the case, sedation can be administered before the test. Also, *not all hospitals have the specific MRI technology necessary assess iron in the liver and the heart.* (If your hospital is unable to assess body iron non-invasively, contact the Cooley's Anemia Foundation to locate a center which possesses the specialized technology. You may want to have annual MRI scans performed at one of these centers while continuing to have your regular treatments at your local hospital.)

No one method of iron measurement gives a complete picture of iron loads in a person, so whenever possible it is best to utilize ferritins, LIC, and heart iron measurements together in order to get the fullest picture of iron levels.

Your health care team will use the information from these measurements to determine whether your chelation therapy needs to be increased or decreased. In addition, your team will consider information that they learn from giving you an annual comprehensive care exam and information that you provide about your general health, ability to stick to chelation, and any side effects from chelation you may be experiencing to determine if you need to make any changes to your chelation.

What's Better: Higher or Lower?

In general, the higher your heart function score (called T2*), the better; the lower your LIC, the better. A T2* above 20 is generally desirable; an LIC below 7 is generally desirable.

Are there any side effects from chelation therapy?

Any treatment has both benefits and risks — and that includes chelation. Some side effects of chelation therapy are minor, and some are more serious; a list of some possible side effects for each chelator is included in our Appendix. You should discuss any possible side effects with your health care team before starting therapy and make them aware if you encounter any side effects that could be related to the use of your chelation drug.

The U.S. Food and Drug Administration (FDA) requires the label of every drug to include

information on side effects. You should always carefully read the label for any drug you are prescribed and discuss any questions you may have about the information on the label with your doctor. If you do experience any serious side effects while on any drug, you and/or your doctor should report the side effects to the FDA. You can learn how to report the side effects by calling 1-800-FDA-1088 or visiting www.fda.gov/Safety/MedWatch/.

What are the main challenges to complying with chelation therapy?

Adherence to chelation therapy is critical, but many patients struggle with it for a variety of reasons, which researchers are just beginning to catalogue and understand.

However, it's important to remember that people with thalassemia today have many different options for chelation — and that chelation works. Your health care team can help tailor the best treatment for your specific needs. And both the Cooley's Anemia Foundation and many treatment centers also have a social worker who may be able to help you develop strategies to keep adherent to your prescribed therapy.

How to administer deferoxamine with an infusion pump

1. Gather all of your supplies (pump, needle, sterile water, etc.).
2. Make sure your pump is set correctly.
3. Attach needle to syringe and draw water for injection into syringe.
4. Clean rubber stopper of deferoxamine vial with alcohol; inject desired amount of water into vial.
5. Roll the vial in the palm of your hands or across the table in order to dissolve it or allow the vials to sit until the deferoxamine has dissolved. Do NOT shake the vials.
6. Draw the dissolved drug into the syringe. Remove the needle and dispose in sharps container.
7. Open the subcutaneous set. Take the extension tube and attach to the syringe. At the end of the tubing is the subcutaneous needle. Fill the empty tubing with liquid from the syringe just until it reaches the tip of the subcutaneous needle.
8. Place the syringe into the infusion pump.
9. Clean the skin thoroughly with alcohol before inserting the needle.
10. To begin infusion, insert the needle under the skin of the abdomen, buttocks, upper arm or thigh.
11. When inserting the needle into the skin, be sure to insert the needle into a fold of skin created by pushing your skin together.
12. Secure the needle in place by taping it down.
13. Turn the pump on.
14. Be sure to dispose of all needles and syringes in a sharps container.

Note: Some insurance plans will provide for a home health care representative to come to a patient's home to teach them how to use Desferal. Check with your insurance provider if this option interests you.

The recommended steps for preparing and taking deferasirox are as follows:

- Take on an empty stomach and do not eat until 30 minutes after you take it.
- Choose your drink (water, apple juice or orange juice).
- If you take 1 g or less, 3.5 oz of liquid is recommended. For all doses over 1 g, 7 oz of liquid is to be used.
- Fill the glass with your drink, drop the tablets in and mix with a spoon until dissolved. If the deferasirox starts to “settle” on the bottom of the glass mix it again to redistribute in the liquid.
- Drink immediately and finish all of the drink.

Chapter 5

Assembling Your Health Care Team

Learning Objectives

The purpose of this section is to introduce you to the importance of having a proper health care team to manage your thalassemia. At the end of this section, you will be able to:

- Identify the medical care providers you need for your ongoing care.
- Name the primary thalassemia treatment center(s) closest to you.

If you have thalassemia, you need to receive appropriate treatment in order to live a full and healthy life. Often, you will need several *different kinds of health care professionals who work as a team* to provide the best comprehensive treatment.

It's also important to remember that *YOU and your family are central members of the comprehensive care team*. You will interact with your health care providers, so you should make them aware of your needs, goals, and beliefs. All care plans should be developed with your input. If you provide input to your team and then follow through with the care plan, you are most likely to gain the full benefits of the thalassemia care team.



A key member of your health care team will be your *hematologist*.

It is important for your hematologist to be knowledgeable about the current state of treatment for thalassemia. If possible, you want to be under the care of a doctor who currently treats (or has recently treated) other patients with a severe form of thalassemia. If that is not

possible, be sure that your hematologist is up to date on the standard procedures for treating thalassemia and is willing to consult with a doctor who has more experience with thalassemia when necessary.

Although the hematologist may be the leading player on your health care team, proper treatment of thalassemia requires keeping an eye out for many complications that are in fields beyond hematology, it is important to assemble a team that can provide comprehensive care for a person with thalassemia.

Some hospitals have units that are referred to as *Thalassemia Treatment Centers (TTCs)*, which have in place a team of doctors, nurses, and other health professionals who have experience in treating people with thalassemia. Several of these TTCs have a relatively large number of patients and are generally recognized as providing exceptional care for people with thalassemia; you can find a list of some of these TTCs at the end of this chapter or at <http://cooleysanemia.org/updates/pdf/TTC2013.pdf>.

When you receive care at one of these TTCs, your health care team is already in place. On the other hand, if you are receiving care outside of one of these TTCs, you and your hematologist or nurse may need to put together a team.

There are many exceptional hematologists and other care providers who are not part of one of the larger TTC; however, if you are not seen at a TTC, it's generally a good idea for you to go to one of the larger TTCs on an annual or biannual basis for a *comprehensive care evaluation*. (See appendix C for a comprehensive care checklist.)

Who should be on your health care team?

The kind of thalassemia you have and the treatments you require will determine exactly who is needed on your team, but in general the thalassemia care team should include a range of specialists, possibly including those listed below.

Hematologist

We described the hematologist's important role in your care earlier. A hematologist has expertise in disorders that affect blood, and he or she is the doctor responsible for making the major decisions about your thalassemia care. These decisions include the diagnosis of thalassemia, when to start transfusions and how often they are needed, and the initiation or modification of chelation.

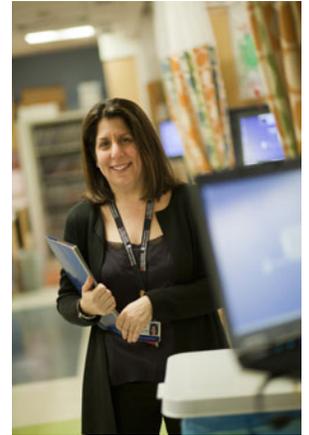
Thalassemia is a relatively rare blood disorder, so many hematologists may not have experience or familiarity with it. Hematologists at TTCs provide care for about half of the

thalassemia patients in the U.S. and so they have more opportunities to be exposed to the issues surrounding thalassemia care and to learn from the large number of patients they see.

Many hematologists who are not at a TTC are skilled and expert; however, some of them may not have had significant experience with thalassemia. A doctor who does not have significant direct experience in treating thalassemia can establish a relationship with a hematologist at a TTC to consult on any questions that might arise.

Nurse

Your nurse (or nurses) may be a nurse practitioner or a registered nurse who is responsible, with you, for the coordination of all your health care needs and may be referred to as your case manager. This is the person you will see and talk with most often. Any questions or concerns you have about yourself or your child with thalassemia should be directed to the nurse. If he or she is not able to answer your question or concern, the appropriate expert will be contacted to address your issue. Typically, the nurse coordinates the transfusion scheduling and annual comprehensive care evaluations. The nurse will also work with you in implementing the recommendations of the thalassemia team and support you and your family in managing thalassemia.



Endocrinologist

An endocrinologist is an expert in diseases affecting the *hormonal systems of the body*. They have an expertise in diagnosing and managing diabetes, growth delay, bone weaknesses, overactive or inactive thyroid, pubertal delay, and pituitary and adrenal gland insufficiencies. An endocrinologist is an important member of the thalassemia team because the endocrine glands can be easily damaged by iron.

Cardiologist

Cardiologists are experts in diseases affecting the *heart and blood vessels*. They can diagnose and manage heart failure, arrhythmias, pulmonary hypertension, and other heart-related issues.

Gastroenterologist (also known as a GI)

A gastroenterologist is an expert in diseases that affect your *digestive tract*, which includes the liver. Because the liver is one of the primary organs of iron overload, a gastroenterologist is often consulted on the impact of iron on liver functioning. The gastroenterologist will also make decisions about the diagnosis and treatment of hepatitis and gallstones.

Infectious Disease Specialist

This professional can help diagnose and treat acute and/or chronic infections that may occur due to thalassemia or its treatment.

Obstetrician/gynecologist

This specialist can advise people with thalassemia about women's reproductive health issues, including pregnancy.

Your own regular doctor

You may visit a pediatrician or internist for ordinary health issues, and it's valuable to keep that person involved in your health care team.



Social worker

A social worker is the professional on the thalassemia team who assists patients and families in managing the impact of thalassemia on the individual patient and their interactions with the outside world. Social workers can assist you and your family on topics such as *insurance, school performance, employment, and bills*. Many social workers also have training in providing counseling and can help families and patients cope with *balancing the demands of managing thalassemia* with other parts of their lives.

Psychologist/Psychiatrist

A psychologist is a PhD-level trained expert in providing counseling and psychotherapy. The psychologist can assist patients and family members in *coping with the challenges of thalassemia*. A psychiatrist, who is an MD, can also help with these challenges and can prescribe medications to help patients when this is needed.

Nutritionist

People who have thalassemia may benefit from nutritional counseling. A nutritionist is a registered dietician who can provide expert advice on managing your diet and using vitamin and mineral supplements to enhance your health.

Comprehensive Care and Standards of Care

Your health care team is going to help guide you through all aspects of your care. One of the most important components of effective thalassemia care is a comprehensive care

evaluation. This should be conducted annually (bi-annually, in cases of less severe thalassemia) and is a series of tests which will help your team know how well your treatment is going, what areas may need to be modified, etc. (You can see a list of all the recommended tests in a comprehensive care evaluation in the appendix on page 108 .)

Some of these tests require technology which is not readily available at most hospitals. If you are not being seen at a TTC, it's a good idea to visit a TTC annually for your comprehensive care evaluation.

A team of thalassemia specialists is in the process of devising new Standards of Care Guidelines for people with thalassemia. These will be valuable for both patients and doctors, as they will provide detailed information on the best practices for treating individuals with thalassemia. All patients should have a copy of these guidelines and be familiar with them so that they are able to better understand the treatment that they should be receiving.

CAF will post information about the Guidelines on the CAF website (www.thalassemia.org) when it is published. Please check the website periodically in order to learn more.

Major Thalassemia Treatment Centers

Here is a list of major TTCs throughout the country and a person to contact at each one:

Ann & Robert H. Lurie Children's Hospital (Chicago)

Director: Alexis Thompson, MD Contact: Janice Beatty, (312) 227-4813)

Children's Healthcare of Atlanta

Director: Jeanne Boudreaux, MD Contact: Laurie Thomas, (404) 785-3529

Children's Hospital of Boston

Director: Ellis Neufeld, MD Contact: Jennifer Eile, (617) 355-2457

Children's Hospital of Los Angeles

Director: Thomas Coates, MD Contact: Susan Carson, (323) 361-4132

Children's Hospital & Research Center at Oakland

Director: Elliott Vichinsky, MD Contact: Dru Foote, (510) 428-3342

Children's Hospital of Philadelphia

Director: Alan Cohen, MD Contact: Vanessa Nixon, (215) 590-3437

Children's Medical Center Dallas

Director: Zora R. Rogers, MD Contact: Deborah Boger, (214) 456-6102

Texas Children's Hospital

Director: Donald Mahoney, MD Contact: (832) 822-4213

Weill Medical College of Cornell University

Director: Patricia Giardina, MD Contact: Dorothy Kleinert, (212) 746-3404

Chapter 6

Complications

People with thalassemia who receive and maintain proper treatment — including blood transfusions and chelation for those who need it — can live long and productive lives. However, sometimes there are medical *complications that may be caused by the underlying anemia or by iron overload*. If you are a patient or parent of a child with thalassemia, it is important to know about these possible complications, how to recognize their signs and how to treat and prevent them. The information we present in the three sections of this chapter is meant to help you know what to do if these medical problems start develop.

Remember: it is always better to prevent complications, rather than to treat them. In general, prevention means sticking to your treatment (such as transfusions and chelation), scheduling appropriate tests to help identify any problems at an early stage, and maintaining a healthy lifestyle.

In this chapter, we will discuss complications of three major organs/systems: cardiac, liver, and endocrine. We start with cardiac (or heart) problems.

A. Cardiac

Section A Learning Objectives:

The purpose of this section is to look at complications from thalassemia and its treatment that can affect the heart. At the end of this section, you will be able to:

- Identify common causes of cardiac problems in thalassemia.
- List common symptoms of cardiac problems.
- Identify tests used to help diagnose cardiac problems.
- Identify how cardiac problems in thalassemia are treated.
- Identify what you can do to help prevent cardiac complications in thalassemia.
- Identify pulmonary hypertension and its treatment and prevention.

What causes cardiac (heart) problems for people with thalassemia?

There are two major causes of cardiac problems in thalassemia: (1) *iron overload* and (2) maintaining *hemoglobin at too low a level*. Every person with thalassemia is unique, but in general people with thalassemia who are transfused may be more likely to have cardiac issues associated with iron overload. And in general people with thalassemia who do not regularly receive transfusions may be more likely to have cardiac issues associated with low hemoglobin levels.

Iron overload can cause cardiac problems and is actually the most common cause of cardiac problems in thalassemia. If excess iron is deposited in the heart, it can interfere with the heart's ability to conduct electrical signals, causing *arrhythmia*. Arrhythmia is an irregular heart rhythm.

Tachycardia is one kind of arrhythmia — that's when the heartbeat is too fast (usually faster than 100 beats per minute in adults). Everyone's heart beats at different speeds at different times. For example, if you are feeling nervous or panicky, your heart may beat faster than normal. But if your heart beats faster than normal on an ongoing basis, that is unhealthy. It can "tire" the heart and also cause it to become enlarged.

Bradycardia is another kind of irregular heartbeat — that's when the heartbeat is too slow (usually slower than 60 beats per minute in adults). There are also irregular heartbeats that alternate between being normal and too fast or too slow. Any of these kinds of arrhythmias interfere with the heart's ability to pump blood around the body in the way it needs to do.

Iron overload can also interfere with the heart's ability to contract and pump blood. A significant decrease in the heart's ability to pump blood is called *congestive heart failure* and is very dangerous, although it can often be corrected by iron chelation if caught early enough.

A significant decrease in the heart's ability to pump blood is called *congestive heart failure*.

If you have thalassemia and your hemoglobin levels are too low, your body won't get enough oxygen. Your heart may try to make up for this lack of oxygen by beating faster, causing tachycardia and possibly an enlarged heart. Other serious cardiac issues can develop over time.

The most important ways to *prevent cardiac problems* are to *maintain the appropriate treatment* that has been prescribed for you by a thalassemia expert so that you stick to chelation therapy and make sure your hemoglobin levels are high enough.

What are symptoms of possible cardiac complications?

The following common symptoms often (but not always) accompany a cardiac complication:

- Shortness of breath or difficulty in breathing (sometimes, even when you are resting)
- Inability to lie down flat (needing to sleep in a chair or need to be propped up with pillows)
- Palpitations (an awareness that your heart is beating in a way that is not typical)
- Chest pain
- Fainting
- Getting tired very easily
- Swelling in the legs or around the ankles
- Weight gain
- Nausea and sometimes vomiting (may indicate congestive heart failure)

However, sometimes a person may have cardiac issues but *not have any symptoms* or they may not show up until the complication is already far along. That's why it's very important for people with thalassemia to have regular tests that can help alert your doctor to any "warning signs" of a problem that may be developing. Your doctor can then recommend a way to prevent or treat the complication (see below for more on treatment and prevention).

Regular tests can help alert doctors to any "warning signs" of a problem that may be developing.

What diagnostic tests help identify cardiac complications?

The following tests help identify potential cardiac problems and should be performed during your annual comprehensive care evaluation:

Echocardiogram (sometimes referred to as an "echo")

An echocardiogram is an ultrasound device that produces sound waves used to create a picture of the heart. This information helps your doctor to get an idea of the size of each of the heart's chambers and how well the parts of the heart are functioning.

Cardiac MRI

Magnetic resonance imaging (MRI) uses an electromagnetic field to get a picture of a part of the body. T2* refers to a measurement that lets the doctor know about the amount of iron in your heart and how that may be affecting your heart's function. In general, the desired T2* score for an individual with thalassemia is 20 milliseconds or greater. A T2* score between 10 and 20 may be indicative of moderate



cardiac iron loading; below 10 may be indicative of severe cardiac iron loading. (For more information, see our publication, “What to expect when you go for an MRI for iron” (URL inserted here). Please note that, at this time, only certain TTCs have the technology to perform cardiac T2* testing.

Electrocardiogram (sometimes called ECG or EKG)

This is a test that records electrical activity of the heart. It is useful in detecting arrhythmias and assessing heart function. When this test is done, several electrodes are placed around the chest and attached to a machine that gathers information over a short period of time (usually just a few minutes)

Cardiac exercise stress test and/or 6-minute walk test

This may be ordered in some cases, as needed. Typically, electrodes are attached to the patient and to an ECG machine, after which the patient is asked to undergo some form of physical exercise, such as running on a treadmill. In addition, a blood pressure cuff is used to monitor blood pressure during the test. The length of the test may vary from a few minutes to perhaps half an hour, depending upon your physical condition and the kind of information your doctor requires. The cardiac stress test helps to determine if your heart is getting the oxygen that it needs.

Chest X-ray

This may be used to determine if the heart is enlarged.

LVEF

Among the information that doctors look for when assessing cardiac function is your ejection fraction, which is the percentage of blood that is pumped from your large heart chamber (the ventricle) with each beat. Because heart failure more often occurs in the left side of the heart, doctors tend to pay attention to the *LVEF (Left Ventricular Ejection Fraction)*. In a typical healthy individual, a normal LVEF is between 55 and 75.

How are cardiac complications treated?

Getting treatment for iron overload is the main way to treat cardiac problems. Doctors usually prescribe chelation therapy such as 24-hour deferoxamine treatment or combination therapy, involving deferoxamine and the oral chelator deferiprone. Other treatments may include dietary changes and other medications.

How can cardiac problems be prevented?

It is better to prevent cardiac problems than to treat them after they occur. The two most important ways to *prevent cardiac problems are sticking to chelation therapy and making sure*

your hemoglobin levels are high enough.

Another big factor in preventing cardiac problems is through getting an appropriate amount of exercise. Check with your doctor to determine an exercise program that provides the best benefit for you, but realize that small changes can make a big difference. Even a mild amount of exercise can have an impact.

Other important ways to help prevent cardiac problems include the following:

- Not smoking
- Eating healthy foods and maintaining an appropriate weight
- Limiting alcohol
- Treating complications such as diabetes and thyroid issues
- Avoiding stress
- Keeping a positive outlook



What is pulmonary hypertension and how does it affect people with thalassemia?

Pulmonary hypertension is a special kind of high blood pressure that affects the arteries that lead to the lungs. If the pulmonary arteries narrow, blood pressure rises. This can make the heart work too hard and possibly lead to heart failure.

People with thalassemia who have low levels of hemoglobin and don't get enough transfused blood are at greatest risk of getting pulmonary hypertension. Patients who have had their spleens removed also appear to be at greater risk. In addition, smoking may increase risk of this complication. Pulmonary hypertension can be worsened by iron overload.

Symptoms of pulmonary hypertension may include shortness of breath when you have only minimal exertion, fatigue, chest pain, dizzy spells, and fainting. But sometimes, people with thalassemia and pulmonary hypertension have no symptoms at all. For that reason, it's important to include certain screening tests, such as an echocardiogram, at your annual comprehensive care exam so that your *doctor can detect the condition early* and treat it right away.

Various medications can help treat pulmonary hypertension. These include blood thinners, calcium channel blockers, blood vessel dilators, and drugs used to open and widen blood vessels.

You can help prevent development of pulmonary hypertension in several ways. The most important way is by keeping an adequate hemoglobin level and by controlling iron overload. It's

also helpful to simply stay healthy by not smoking, maintaining a healthy weight and keeping active.

Whether working to prevent pulmonary hypertension or receiving treatments for the condition, it's important to discuss any plans with your doctor and to determine how changes will be monitored and measured.

Remember:
The two most important ways to *prevent cardiac problems are sticking to chelation therapy and making sure your hemoglobin levels are high enough.*

Chapter 6

Complications

B. Liver

Section B Learning Objectives

The purpose of this section is to look at complications from thalassemia and its treatment that can affect the liver. At the end of this section, you will be able to:

- Identify common causes of liver problems in thalassemia.
- List common symptoms of hepatitis and liver cirrhosis.
- Identify how liver problems in thalassemia are treated.
- Identify what you can do to help prevent liver complications in thalassemia.

The liver is another important organ that can be affected by problems related to thalassemia.

One of the liver's functions is to store iron for when the body needs it. But if a person has too much iron — “iron overload” — because of frequent blood transfusions and/or inadequate chelation, that's a problem. Too much iron can settle in the liver and begin to damage it, leading to scars known as *fibrosis*. Too much scarring leads to *cirrhosis*, a serious condition that can result in liver failure.

Patients with thalassemia also may have liver problems related to viral infections from hepatitis B or C. In very rare occasions, blood received in transfusions may contain a hepatitis virus. However, the blood supply in the United States is very safe, and the benefits of blood transfusions for people with thalassemia *greatly outweigh* the small risk of becoming infected with a virus from the transfused blood.

Hepatitis is basically an inflammation of the liver. If it is not treated, it can lead to scarring

(fibrosis) and cirrhosis. A person who is infected with a hepatitis virus may not always have symptoms. That's why it's important to have regular screening tests to detect any possible liver problems.

Some drugs may also have an impact on the health of the liver and so require monitoring. In some cases, this may include iron chelating drugs.

What are the symptoms of liver problems?

The most common symptoms of hepatitis include the following:

- Low-grade fever
- Headache
- Fatigue
- Nausea/vomiting
- Diarrhea
- Loss of appetite
- Stomach pain and bloating
- Muscle aches
- Joint pain
- Itchy skin
- Dark urine
- Pale stool
- Jaundice (yellowing of eyes and/or skin)
- Mood swings
- Night sweats

The most common symptoms of cirrhosis include the following:

- Redness on the palms of hands
- Red, spider-like rash on the chest, shoulders, or face
- Swelling of the stomach, legs, or feet (due to fluid build-up)
- Muscle loss
- Weight loss
- Frequent infections
- Fatigue
- Tendency to bruise easily
- Itching
- Frequent nosebleeds
- Blood in urine or stool
- Confusion or memory problems
- Jaundice

What tests can help identify liver problems?

There are a number of tests that can help assess the health of the patient's liver. Your doctor can help determine which ones will be right for you.

Quarterly tests

Liver enzyme screening (ALT/GGT) are blood tests that act as an "early warning system" to alert your doctor about any liver problems. They check for inflammation and damage to the liver, as well as determine if the liver is working properly. Typically, you have this screening every

three months, unless your ALT levels are higher than they should be. If your ALT levels are high, your doctor may want to check your levels every month. (Fluctuations in levels from one measurement to another can occur, so it's important to look at the long-term trend — if your levels going generally up or generally down — rather than concentrating strictly on one “bump” up or down.)

Annual tests

Certain tests related to liver complications may be included in your annual comprehensive care evaluation. Most of these are blood tests that can detect viruses like hepatitis A, B, and C. Other tests might include the following:

Abdominal ultrasound — a non-invasive procedure that examines your internal organs.

T2 MRI or R2/FerriScan — a non-invasive procedure that uses magnetic resonance imaging (MRI) to non-invasively measure iron in the liver. Another MRI-based technology known as **SQUID** (Superconducting Quantum Interference Device) is sometimes used to non-invasively measure liver iron. Please note that only a few TTCs have the specific technology required to measure liver iron via these methods.

Liver biopsy — a procedure in which a small portion of the liver is removed and examined for evidence of scarring related to iron overload or other problems. In general, liver biopsy is used when the specific MRI technologies for measuring liver iron are unavailable.

The T2 MRI, R2/FerriScan, SQUID and liver biopsy methods all provide information on a patient's liver iron concentration (LIC). In thalassemia, maintaining an LIC of 7 or lower is desirable; LICs above 15 are indicative of serious iron overloading in the liver.

How can liver complications be treated?

If tests indicate liver complications, your doctor may recommend changes to iron chelation therapy to remove as much iron as possible. Antiviral medications may help if you also have hepatitis B or C infection.

If your condition has progressed to fibrosis (scarring) or even cirrhosis, it is difficult to

What do these letters mean?

ALT: alanine transaminase

GGT: Gamma-glutamyl transpeptidase

Normal ranges for these measurements are affected by the lab that examines the samples. Your doctor can tell you what is considered normal for the lab service they use.

reverse the damage; but you can do a number of things to prevent further damage. In addition to chelation therapy, people with thalassemia can stop all alcohol intake, make healthy lifestyle and dietary changes, and possibly consider some medications, as appropriate.

Can liver complications be prevented?

The two most important things to prevent liver complications are maintaining adherence with chelation therapy and undergoing regular testing to identify early warning signs of potential problems.

In addition, all people with thalassemia can take certain lifestyle steps that can impact the health of the liver:

- Limit alcohol intake, especially if you have hepatitis C (too much alcohol damages the liver)
- Maintain a healthy diet (ask your hematologist or nutritionist for help with this)
- Drink plenty of water

Chapter 6

Complications

C. Endocrine

Section C Learning Objectives

The purpose of this section is to look at complications from thalassemia and its treatment that can affect the endocrine system and other parts of the body. At the end of this section, you will be able to:

- Identify common endocrine system issues, such as diabetes and low bone mass.
- Identify fertility and pregnancy complications that may arise in thalassemia.
- Understand the role of appropriate treatment in preventing these complications.

The endocrine system is a system of glands that release *hormones* into the bloodstream. Hormones are chemicals produced by our bodies and are used to regulate almost every organ and function of our bodies. Iron overload affects the endocrine system (just as it does the heart and liver) and can cause harm to health and growth.

Here are a few of the issues related to problems of the endocrine system:

Diabetes and glucose intolerance

The pancreas secretes the hormone *insulin*, which helps control blood sugar (also called *glucose*). Sometimes the insulin is out of balance and causes too much sugar to remain in the bloodstream.

Remember:

- Although there are treatments for all the endocrine problems described below, it is better to prevent them from developing in the first place.
- It is important to get proper testing for endocrine problems and to maintain the proper therapies, especially chelation. (You can find a list of recommended annual endocrine tests in the Comprehensive Care Checklist in our Appendix.)

When blood sugar levels are higher than normal but not high enough to meet the definition of diabetes, a person is said to have *glucose intolerance*; even higher levels of blood result in a diagnosis of *diabetes*, which may be classified as either Type 1 or Type 2. In Type 1, the body does not produce insulin; in Type 2, it produces insulin but doesn't use it properly. (See the box below for specific levels that designate glucose intolerance and diabetes.)



A glucometer measures blood sugar

While glucose intolerance is less severe than diabetes, both are serious conditions. Eye damage and blindness, kidney disease, diseases of the nerves (numbness or tingling in the feet and hands), heart attack, stroke and other problems in the heart and blood vessels, and other major problems are associated with diabetes.

Many people have some form of glucose intolerance or diabetes, but it is a special burden for people who are trying to manage their thalassemia. People with thalassemia need to have an annual glucose tolerance test, a blood test that measures the body's ability to handle glucose. While genetic factors and/or obesity can contribute to blood sugar issues, in thalassemia iron overload is usually the problem. As with other complications, *being consistent with chelation therapy is essential*.

Treatment for diabetes or glucose intolerance can include lifestyle changes (healthy eating, exercise, losing weight) and medication (often insulin injections for diabetes). Management is tailored to each person's specific needs, so your doctor can discuss this with you.

Glucose levels

A "normal" glucose level depends on a number of things, including how long it has been since a person ate. Most of the time, a normal blood glucose level is below 125; if a person has not eaten for at least 8 hours, a normal blood glucose level is usually between 70 and 100.

Tests used to identify blood sugar issues include a fasting blood glucose test and an oral glucose tolerance test.

For a fasting blood glucose test, a normal level is below 100; a level of 100 to 125 indicates glucose intolerance; and a level of 126 or over indicates diabetes.

For an oral glucose tolerance test, a level of 139 or lower is normal; a level of 140 - 199 indicates glucose intolerance; and a level of 200 or over indicates diabetes.

Low bone mass (osteoporosis)

Patients with thalassemia frequently have low bone mass due to anemia and/or iron overload. Individuals with low bone mass have bones that are not as strong as they should be. A test called a *DEXA scan* is used to measure bone density. A bone density test should be performed by the time a patient is 8 years old and repeated every year after that.

The DEXA scan enables your doctor to determine a *T-score*. A T-score is a mathematical measure of your bone mineral density (BMD) as compared to that of a healthy, typical 30-year-old. A score of “0” means your BMD is the same as the healthy, typical individual. A score between -1 and -2.5 indicates moderate low bone mass (sometimes called osteopenia); below -2.5 indicates more severe low bone mass (sometimes called osteoporosis).

A doctor may also obtain a *Z-score* when assessing BMD. A Z-score measures your BMD, comparing it with a healthy, typical person of the same age, race and gender.

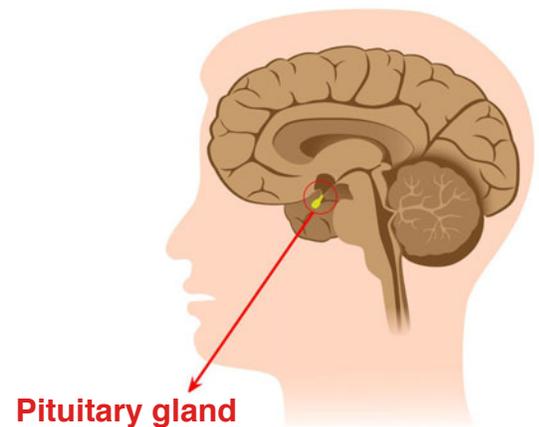
Good nutrition and vitamin supplements like calcium and vitamin D can help maintain bone density and treat milder forms of low bone mass. Adults with established osteoporosis can consider taking bisphosphonates to slow bone loss. Adjusting iron chelation therapy may be required. Again, your health care team will play a significant role in determining what treatment will be most effective.

Growth hormone deficiency

Some people with thalassemia may have slower or decreased growth due to issues with the pituitary gland.

The pituitary gland helps to manage the rate of a person's growth by secreting growth hormones. Sometimes, low hemoglobin levels and/or iron overload problems keep the pituitary gland from properly producing this growth hormone. With low hemoglobin, pituitary gland becomes "underactive," so it doesn't operate efficiently; with iron overload, iron settles in the gland and damages it, keeping it from functioning properly.

When any factor keeps the pituitary gland from producing enough growth hormone, slower or decreased growth results. Treating low hemoglobin levels may require *adjusting the rate of transfusions and/or altering chelation treatment* or making sure the patient is sticking with chelation as prescribed. In addition regular growth hormone injections may be used until



appropriate results are achieved. The length of time for treatment is likely to vary from patient to patient. Growth can only be expected prior to the time that the ends of the bones fuse, which occurs shortly after puberty ends.

Delayed puberty or hypogonadism

The pituitary gland also helps create sex hormones: It tells the testes to make testosterone in males and the ovaries to produce estradiol and progesterone in females. These sex hormones play an important role as children mature into puberty. When iron overload or anemia keeps the pituitary gland from signaling the development of these sex hormones, normal sexual development can be delayed. Girls who have no sign of sexual development by age 13 and boys with no sign of sexual development by age 14 are said to have *delayed puberty*. If they have no sexual development by age 16, they are said to have *hypogonadism*. In addition to making adjustments to iron chelation therapy, treatment may include the prescription of sex steroids.

Problems with fertility

People with serious forms of thalassemia may have problems becoming pregnant. The cause may be problems related to hormone deficiency such as delayed puberty, hypogonadism, and lack of menses (amenorrhea). Women with these problems may not ovulate (produce eggs). And men with those problems may not produce enough sperm to fertilize an egg.

These problems are often the result of iron overload or low hemoglobin levels. Maintaining adherence to transfusion and chelation therapies can help prevent fertility issues.

Couples planning for a pregnancy should discuss plans with their doctor. If they have these types of fertility problems, they can consider *hormone replacement therapy, other fertility treatments, or in vitro fertilization*. A doctor who specializes in the endocrine system can help advise couples with fertility problems who want to become pregnant.



Problems in pregnancy

Any pregnancy involves *certain risks*, and the risks may increase for a woman with thalassemia. The physical stress of pregnancy can worsen existing problems related to the heart, liver, and endocrine system. In particular, pregnancy can trigger a form of diabetes, which may be harmful to both mother and infant. In addition, chelation therapy may have to be modified or stopped altogether during pregnancy, due to uncertainty about the possible effects of chelating drugs on the fetus; the possible effects of stopping chelation therapy need to be considered and discussed.

That said, as treatment for thalassemia has improved and lengthened the lives of patients, an increasing number of women have chosen to become pregnant and many have had *successful pregnancies and births*. It is possible for many women with thalassemia to have a healthy pregnancy, as long as they take good care of their general health; discuss with their doctors the possibility of pregnancy and what it would entail for them; and maintain consistent treatment with transfusions prior to and throughout pregnancy and with chelation prior to pregnancy.

Thyroid problems

Iron overload also affects the thyroid and parathyroid glands. The thyroid gland produces the hormone *thyroxin*, which is required for body metabolism and helps boost a person's *energy level*. Too much iron can result in *hypothyroidism*. A person with that condition may feel drowsy and cold and possibly gain weight. In severe cases, hypothyroidism can harm the heart. The replacement hormone L-thyroxin is used for patients with hypothyroidism.

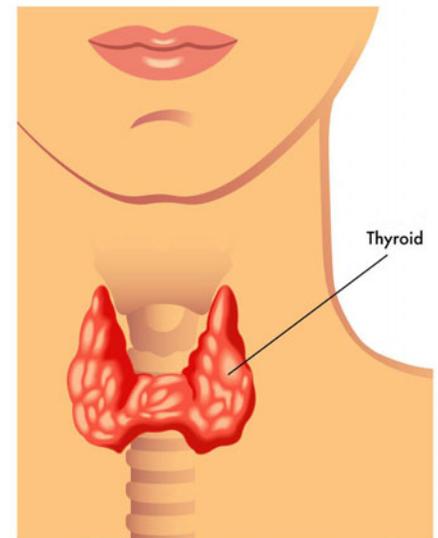
Iron overload or anemia can keep the parathyroid glands from doing their job. These small glands within or next to the thyroid in the neck regulate calcium metabolism. When the glands malfunction due to iron overload, *hypoparathyroidism*, results, leading to decreasing calcium and phosphorous in the body. This can lead to cramps and muscles spasms and, in advanced cases, seizure and cardiac impairment.

An annual comprehensive care evaluation should include tests (called TSH, Free T4, and Parathyroid Hormone Level tests) that assess the health of the thyroid and parathyroid glands.

Adrenal insufficiency

The adrenal glands produce several important hormones, including some which affect blood pressure, stress levels, metabolism and testosterone levels. Iron overload can reduce the production of these hormones and result in symptoms like fatigue, body aches, unexplained weight loss, and other problems.

A Fasting A.M. Cortisol test ("A.M." refers to the test being administered in the morning), performed as part of a patient's annual comprehensive care evaluation, can help detect adrenal insufficiency. The desired level for this test is between 5 and 23 mcg/dL.



Although complications to the endocrine system, as well as to the heart and liver, frequently occur in thalassemia, it is important to remember that the more adherent you are to your prescribed treatments, especially appropriate transfusions and chelation, the less likely you are to develop complications. Adherence can be difficult and time consuming, but the results are worth it.



Chapter 7

Healthy Living

Learning Objectives

The purpose of this chapter is to discuss some things that you need to do to stay healthy, in addition to regular blood transfusions and chelation therapy. At the end of this chapter, you will be able to:

- Understand the importance of preventing infections and list several things you can do to help avoid infections.
- Identify the two kinds of iron found in food and how each can affect you.
- Understand how to plan trips so your ongoing care needs aren't neglected

Don't forget: **thalassemia is a treatable disorder that can be well managed with transfusions and chelation therapy** to reduce iron overload. Although you may find it challenging to stick to treatment, you can live a full and satisfying life if you manage your disorder.

“Management” also involves paying attention to other aspects of your daily life in order to stay healthy.

Daily “maintenance”

As you know, if you are prescribed chelation therapy, the most important thing on your stay healthy “to-do” list is to take your chelation medicine.

In addition, you should be alert to other issues, like these listed below.

Most Important Rule:
If you are prescribed chelation, do not miss a day of it!

Recognizing acute infections and keeping vaccinations up to date

Acute infections can be a serious problem for people with thalassemia. You should always be alert to fever or any symptoms that suggest infection and seek medical help right away. It is *important to get on antibiotics quickly if you have an infection.*

Immunizations can help protect against many infections. This is especially important for people on chronic transfusion and those who have had their spleens removed, which can make people more susceptible to infections. Children should have the routine pediatric set of immunizations and also should start on pneumococcal vaccine at 2 months, followed by boosters at appropriate ages. Splenectomized patients should have a Meningococcal vaccine. People with thalassemia also should be vaccinated against hepatitis A and B.

In addition, there are several “common sense” things you can do to help prevent “every day” infections:

- Wash your hands frequently.
- Cover your mouth when sneezing or coughing.
- Tend to cuts, scratches and other injuries by washing, disinfecting and bandaging.
- Try to stay away from sick people.
- Wipe down surfaces with antibacterial wipes at the gym or in shared work spaces.
- Don't share personal items (toothbrushes, towels, nail clippers, etc.)
- If traveling to other countries, drink bottled water.

Recognizing and managing pain



As thalassemia patients gain a longer lifespan due to transfusion treatment and chelation therapy, they may begin to develop pain that affects the quality of their lives.

Until recently, clinicians had not studied the issue of pain and thalassemia. However, a recent study at the Children's Hospital and Research Center at Oakland found that pain was a significant issue for thalassemia patients and was correlated with increased age. A second, multi-center study of 252 thalassemia patients found that *82% had experienced pain in the last 7 days*. Many said that the pain affected their ability to work and enjoy life. About half took medication like Advil or Tylenol for pain relief.

Doctors and researchers are continuing to explore the question of pain related to thalassemia. They don't have all the answers yet, but they do offer some advice for those who do experience pain.

- When you visit your health care provider, speak up and be honest about your pain.
- Work with your health care provider and consider a multi-pronged approach to manage pain. This might include medication or alternative therapies.
- Try to stay appropriately active. You don't want to do anything to cause pain or increase it, but physical activity often helps.

Maintaining good dental hygiene and health

Make regular visits to the dentist. He or she will look for any problems, including changes in the jaw or other nearby bony structures. In addition, thorough cleaning at your dentist will complement your own daily brushing and flossing.

Be aware that some types of dental work result in *bleeding of the gums*. This can result in infections, which can be a hazard to some people with thalassemia. Your dentist should be aware that you have thalassemia and you should discuss whether to take antibiotics in advance (which is referred to as "*prophylaxis*") to help prevent infections.

Nutrition

Good nutrition is especially important for people with thalassemia. Your diet needs to provide you with the essential nutrients, but some people may need to avoid some foods that contain too much iron. (See box.)

When discussing with your doctor whether you need to modify your diet, ask if you should seek the advice of a nutritionist. If so, ask your doctor (1) if s/he can recommend a nutritionist who has

Dietary Iron and Thalassemia

The impact of dietary iron in thalassemia depends upon the individual patient; however, in general, this is a rule to follow:

1. If you are a transfused patient who is adherent to an appropriate chelation regimen, the dietary iron you absorb is likely to have little effect; however, you may still want to discuss with your doctor if you should modify your diet.
2. If you are a non-transfused patient who is adherent to an appropriate chelation regimen, your dietary iron intake may have more of an impact; you, too should discuss with your doctor if you should modify your diet.
3. If you are a non-transfused patient who is not prescribed (or is not adherent to) an appropriate chelation regimen, dietary iron intake has the potential to have a more significant impact on you. Follow the suggestions in this chapter and definitely discuss with your doctor how you should modify your diet.

experience with thalassemia, or (2) if not, can s/he advise you on what you should tell the nutritionist about thalassemia.

Types of iron in your diet

There are two forms of iron in food:

- *Heme*— found in animal food, like meat and some fish
- *Non-heme*— found in plant foods

In general, *heme iron is more easily absorbed by the body than non-heme iron*; therefore, those who are concerned about controlling iron from their diet (such as non-transfused patients who are not chelating) should limit the animal sources of food (such as red meat). They should also be aware that the *absorption of non-heme iron is enhanced by foods that are rich in vitamin C*. Therefore, they might avoid eating foods with those combinations at the same time, such as iron-fortified cereal and orange juice. Drinking tea with your meal also helps limit the absorption of non-heme iron. (Be sure to watch the amount of sugar you put in your tea.)

Balance is important

The challenge comes in balancing iron intake with the need for essential vitamins and nutrients. Everyone should include healthy foods in their diet, such as dairy products, fruits and vegetables. Spinach is an excellent source of many nutrients (fiber, vitamin A, folate, calcium) and is also high in anti-oxidants. But it is also high in non-heme iron. So, what should you do: consume spinach or avoid it?



One possibility is to eat spinach in moderation and avoid eating food high in vitamin C at the same time. You might also drink tea with your spinach.

What about patients who receive regular transfusions? They get so much iron from the transfusions that iron from food is generally not as great a concern (as long as they are chelating appropriately). The best *nutrition advice for transfused patients is to strive for an overall healthy diet high in anti-oxidants that is rich in fruits and vegetables*. If they are following a low-calorie diet, it's extra important to avoid "empty calories" like sodas and highly refined carbohydrates like cookies and alcohol. It's a challenge to meet all your nutritional needs within a low-calorie diet, but it can be done if you plan carefully.

Supplements

Both transfused and non-transfused patients can also benefit from the following daily supplements to boost nutrition:

- A multivitamin and mineral supplement (that contains no iron)
- Vitamin D, 2,000 IU/day
- Calcium, 1,000 mg/day

Again, working with a qualified nutritionist who understands the challenges involved with thalassemia can be a good way of determining a diet plan that works for you.



Exercise and sports

Getting an appropriate amount of exercise is important for everyone. Research suggests that some people with more severe forms of thalassemia may have trouble with more vigorous kinds of exercise. But many people with thalassemia are able to engage in significant physical activity, even running marathons. As with so many things in thalassemia, there is a great deal of variation between one person's physical ability and another's.

Your best strategy is to ask your health care provider about an appropriate level of physical activity. There are numerous kinds of activities to choose from, including those that are easier on the joints (swimming, water aerobics) or are more gentle (t'ai chi, some forms of yoga). For some, the more traditional kinds of aerobic activity — walking, jogging, and bicycling — can be combined with weight training for even better results. You may be able to do more than you imagine; discuss these options with your health care provider.

Remember: physical activity can lengthen your life and add to the quality of life as well.

Relationships and sexual health

Having good relationships is central to good health for everyone. These relationships can encompass social friends, work colleagues, and family members. A web of good relationships can offer you support and pleasure.

Good relationships include those that are romantic or sexual in nature. If you do develop a sexual relationship, it's important to pay attention to the same kinds of issues as people without thalassemia. That is, be sure to know your potential partner and learn their sexual history,

especially in terms of sexually transmitted diseases. Be sure to use contraceptives, if you don't want to get pregnant; condoms should also be used to limit the risk of contracting or spreading sexually transmitted diseases. And remember that mutual respect is the cornerstone of any relationship.

Managing stress

Managing a chronic disorder like thalassemia can be stressful. You need to keep up with medications and appointments, take care of daily health needs, and deal with emotional issues. You will learn more about managing stress in the next chapter.

Keeping healthy while you travel

Thalassemia shouldn't prevent you from traveling, whether to visit friends and relatives or just to take a vacation. However, with thalassemia, you need to think in advance about certain issues, especially if your travel will last more than a few days:

- Will you need to be transfused while you are away? If so, do you know of a facility where you can go?
- If you travel out of state, will your insurance still cover you?
- Do you have a sufficient supply of chelation drugs to carry you through the trip?
- Do you have a list of providers who specialize in thalassemia in the location to which you are traveling? This will help you find someone quickly, in case of a medical problem or emergency.
- Are there medical records you need to travel with, in case you need medical care?
- If you are traveling to another country, make sure well in advance that there will be no problem locating a hospital that is able to treat you; that coverage or payment issues have been discussed and decided; and, if you will be getting transfused, that the country's blood collection policies provide sufficient and appropriate safeguards.

In addition, it's important to maintain overall healthy habits when you travel: stick to a healthy diet, exercise as appropriate, and avoid situations that might lead to infections. And, of course, keep up with transfusions and chelator drugs.



Chapter 8

Thoughts, Feelings and Behavior

Learning Objectives

The purpose of this chapter is to learn some ways to recognize and manage your emotional reactions in order to help to increase your own and your family's quality of life and management of thalassemia.

At the end of the section you should be able to:

- Identify the thoughts, feelings, and behaviors that help (or get in the way of) successfully coping/managing with your own or your child's thalassemia.
- List coping techniques to use to manage emotional obstacles.
- Describe ways to access support and help

When people talk about managing their thalassemia, they are often referring to issues like transfusions, chelation, doctor visits, etc. But there's another aspect of managing your thalassemia that can be just as important: managing the feelings, thoughts, and behaviors associated with having and treating your condition.

Everyone reacts to thalassemia (and the challenges that come with it) in different ways — and those reactions vary at different times. The reactions can also be different depending on whether you are a person with thalassemia or are related to a person with thalassemia.

Emotions

Some people may have very little difficulty in dealing with the emotions and thoughts that accompany their experience with thalassemia. Other people may find that they have very strong reactions.

Some of these reactions may involve what are usually thought of as “unpleasant” or “difficult” feelings, such as:

- Anger
- Guilt or shame
- Worry or anxiety
- Fear
- Sadness

There’s nothing wrong with any of these feelings, which happen to everyone. But sometimes a feeling can create an obstacle for you and keep you from taking care of important things in your life (such as keeping up with your treatment). If that happens, it is very important that you find a way to handle that feeling so that it will no longer create an obstacle to your care.

Many times, people are able to find their way around these obstacles on their own by properly managing their feelings, but other times they may need help. Following are some ways to manage difficult emotions, as well as some resources for getting help.

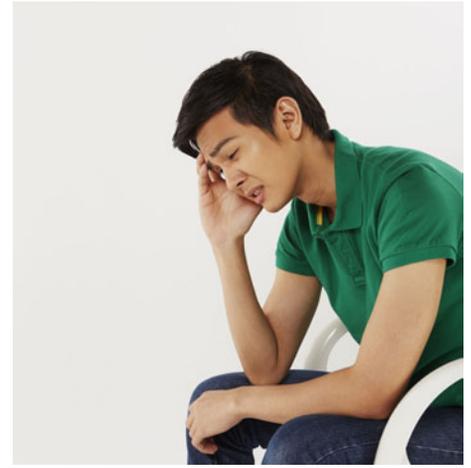
Managing Thoughts, Feelings, and Behaviors — and Solving Problems

It’s important to learn to recognize what triggers your emotions, especially those that cause problems for you, so that you can develop ways of coping. Here are some suggestions on ways to better cope:

Communicate with others about how you feel

Sharing your feelings with others is very important — and how you share your feelings can make a difference. For example, if you tell someone, “You make me so angry” it lets them know how you feel, but it doesn’t let them know why you are angry. It also may also make them feel defensive.

Instead of expressing your anger that way, try *using an “I” statement*, such as “I feel angry,” and then explain why. For example, you might say “I feel angry when you tell me I have to chelate.” It’s even better if you can explain a little more: “I feel angry when you tell me I have to chelate because chelating is boring” or “...because I think I’m old enough to take care of myself.” It’s better to acknowledge and share negative feelings than to deny them. Sharing your feelings also lets others know about the problem and offers the possibility of working together to solve the problem.



Some families have an unstated “rule” that it’s better not to express negative emotions. If your family is not accepting of negative emotions, you may want to find resources that allow you to express these feelings: close friends, a support group, a social worker (at your hospital or CAF's on-staff social worker), a psychotherapist, a trusted member of a religious or community-based organization, etc.

Reach out to others with a similar experience

Many times the most helpful person to share your feelings with is someone who has been through a similar experience (for example, another parent who has worried about their child's health). It’s therapeutic to hear “I know exactly how you feel,” especially when you have been struggling to find someone who really understands. This makes you feel less alone; in addition, another person’s experience may provide a solution to a problem you have. (The [Cooley’s Anemia Foundation’s Facebook](https://www.facebook.com/cooleysanemiafoundation) page at www.facebook.com/cooleysanemiafoundation is a good place to connect online with others who have thalassemia or who have a family member with thalassemia.)



Engage in activities that you enjoy

When you’re feeling weighed down by unpleasant feelings, try to force yourself to do things that you like to do. It could be a “physical” thing like playing your favorite outdoor sport or a “relaxing” thing like reading a good book. Focusing on pleasurable activities can make a big difference. You will almost always feel better afterwards. When you are in a more positive frame of mind, you are also more *open to seeing possible solutions* to problems.

Learn to be empathetic

Empathy is feeling what someone else feels. When you “put yourself in the shoes of someone else,” you can better understand why others act the way they do. For example, if you experience your parents as nagging you to keep up your treatment, take a moment to try to feel what they are feeling when they “nag” you. If your child doesn't want to bring their chelator with them on a sleepover, try to imagine what it means to explain to another child why they need this medicine. This may help you to see something that you or they can do differently to solve this problem.

Resources: Enlisting Support

No one single person in your life can help you and support you all of the time with every type of problem. The more people or resources you can rely on for support, the stronger you will feel.

The Cooley's Anemia Foundation (www.thalassemia.org; info@thalassemia.org) is a resource for support. In addition to supplying you with up-to-date information, CAF's patient services department (including its on-staff Social Worker) can also assist you in your search for solutions to issues you are facing. The Foundation's annual *Patient-Family Conference* is also a valuable experience for both gathering medical information and meeting other members of the community who can understand what you may be going through. And, as mentioned earlier, the *Foundation's Facebook page* (www.facebook.com/cooleysanemiafoundation) is a helpful online resource for connecting with others in the thalassemia community.

Transfusion centers can be another excellent place for education and support for patients who receive their treatment there. The doctors and nurses can answer specific questions, and in larger transfusion centers, you can meet other families and patients.

Also, many *online support groups, blogs, and chat rooms* are available to connect with others about issues related to thalassemia. However, it's *advisable to discuss any medical information you find online with your health care team*, for a number of reasons: not all patients are equally well informed about medical issues; the severity of thalassemia can vary from patient to patient; and sometimes commercial representatives can post information online that presents misinformation about a particular product.

Sometimes, you can benefit from getting *professional help*. If you feel that things are too difficult for you to manage on your own, seek help from a family counselor, therapist, or social worker. Every hospital has a social worker in the department who can help you or refer you to professionals in the community. You can also call your insurance carrier and ask for a referral or contact the Cooley's Anemia Foundation if you would like to work with the Foundation's social worker.

Life can be demanding and challenging. However, every time you get through something difficult and solve a problem, you gain strength, confidence, and competence. These qualities will give you strength to manage future difficulties that may arise.

Chapter 9

Advice for Parents and Caregivers

Learning Objectives

This chapter discusses the special role and responsibilities of parents/caregivers of a child with thalassemia. At the end of this chapter, you will:

- Know the importance of being a strong and supportive family member for someone with thalassemia.
- Know some sources you can turn to for advice and information.
- Understand how thalassemia trait affects future family planning choices.

As the parent or caregiver of a child with thalassemia, you will be making decisions that have a huge impact on your child's well being, both now and throughout their life. Although the doctors and nurses who treat your child are important, you and other family members really set the tone for how your child thinks about thalassemia and its treatment. Here are some guidelines to help you help your child.

Model positive emotional attitudes

Thalassemia is a genetic disorder. It is not the result of anything wrong you did, so you should not feel guilty or ashamed that you passed on this condition to your child. If you feel shame or guilt because your child has thalassemia, he or she is likely to pick up on that attitude and feel the same way.





Instead, emphasize a *positive attitude*. Advances in treatment mean that children born in this era can live a long and productive life, with proper treatment. Tell your child you are proud that they are managing a disorder and encourage them to feel pride, too. Stress the *opportunities your child can explore, rather than the limitations* associated with thalassemia.

Your child will look to you for cues about how to respond to life’s challenges. If you are resilient and have a sense of optimism, chances are good that your child will feel positive, too. It’s not realistic to expect that you can “put on a happy face” all the time. It’s normal to feel discouraged or fearful; however, there is a great benefit to helping your child develop a positive approach to managing thalassemia.

Seek support and expertise

Thalassemia is a very complicated condition, and you can’t be expected to know everything about it. Be prepared to ask for help from health care professionals and others who know about thalassemia. You can get different kinds of help from different people and groups.

Your child will look to you for cues about how to respond to life’s challenges.

Doctors and nurses

Your medical team are key allies in helping your child with thalassemia. The team will be your guide to treatment, chelation options, necessary tests, and general health care concerns. The hematologist and nurse who specializes in thalassemia care should keep current on all the developments and latest research about this disorder. They can then recommend adjustments to treatment and answer all your medically related questions.

If your child is being treated outside of a Thalassemia Treatment Center (TTC), or by a doctor who does not have experience with thalassemia, we encourage you to ask your doctor to establish a *consulting relationship* with a thalassemia doctor at a TTC . This will ensure that your doctor can provide the best care for your child.

You should feel comfortable talking to your doctor, and if you have any questions about any specific treatment or approach, ask them to explain what is involved or why it is recommended. Be persistent if answers are still unclear to you or leave you with a sense of or uncertainty or concern. As mentioned in an earlier chapter, *new Guidelines for Standards of Care for thalassemia are being prepared*; when these are available, read them and discuss as needed with your child’s doctor.

Social workers

Most hospitals have social workers who can be major supporters for you. They can help you with emotional aspects of living with thalassemia, refer you to community resources, and provide guidance on insurance and financial matters or on being a caregiver for a person living with thalassemia. If your hospital does not provide this service or if you would like to speak with CAF's on-staff social worker, please contact the Foundation (212-279-8090; info@thalassemia.org).

Cooley's Anemia Foundation

CAF is all about helping parents. It offers a rich array of publications, on both general and specific topics, and sponsors conferences where families can meet and share concerns and ideas. CAF raises money to support important medical research and publicizes key findings in its newsletter. The Foundation also lobbies for better awareness of and support for thalassemia. And CAF provides practical, down-to-earth help for parents through its Patient Services Manager and its Social Worker via phone (212-279-8090) or email (info@thalassemia.org). See the website for all this information and more: www.thalassemia.org.

Other parents/patients/families

Sometimes it's a huge relief to talk with other people whose children have thalassemia. You can compare notes, share ideas and tips for coping, and learn about community resources. Most of all, you can get — and give — emotional support from others who understand your situation. CAF can put you in touch with other families in your area. Just call or email the Patient Services Manager (212-279-8090; info@thalassemia.org.) Remember, of course, that you should check any medical advice you get from other people with your own doctor.



Websites/social media

The Internet can be a great resource for finding out more information about thalassemia. However, be sure to consult with your doctor about any medical information or advice you see on the Internet. Information on some websites is not supported by good science, so beware. (For a list of some website and social media sites you may wish to explore, see Appendix D: Resources.) Medical information from CAF is vetted by a doctor with appropriate expertise.

Establish (and stick to) a treatment plan

Once you and your child’s health care team have established the best treatment routine, it’s very important to stick with it. Consistent, proper treatment is essential to your child’s long term health.

If you have a young child, you may be completely responsible for making sure that all medical appointments are kept and that your child takes all the required medications. At some point — perhaps as your child approaches adolescence — you will need to encourage your child to progressively take responsibility for their treatment. You will then take on more of an “oversight” role. In this way, you can *promote your child’s growing independence*. As they grow up, they have to become responsible for their own health; you will need to find the best way to prepare your child for that responsibility.

Be supportive — and firm

Listen to your child and empathize when they feel frustrated with demands of treatment or worried about the future. But don’t let your empathy affect the *treatment requirements*. That is, even if your child fusses about treatment, don’t give in and say it’s all right to skip transfusions or chelation. Giving in may make your child happier in the short term, but in the long term, it will harm them. Instead of caving in, stay firm and encourage your child to keep up with treatment and work with the health care team to develop ways to keep your child adherent. Remember that for children who are prescribed chelation, their *long-term complication-free survival depends upon strict adherence* to their chelation regime.



Encourage physical activity

Don’t emphasize the limitations of thalassemia, but instead *encourage your child to engage in play, sports, and physical activities*, assuming that health permits. If your child is getting regular transfusions (if that is required) and sticking to the recommended chelation therapy regimen, they probably have the energy to do active things. Being physically active may help your child to see themselves as “normal.” (As always, it’s best to check with your child’s doctor first. Children with low bone mass may want to take extra care.)

Build strong relationships with your child and all family members

Naturally, you want to develop a strong, trusting relationship with any child. It may be extra important to do this with a child who has thalassemia. A good relationship will help both of you navigate the challenges of managing the disorder.

It's also important to build relationships with others who can provide support to you when you are having difficulty. How can you do this? Learn to ask for help. Learn to articulate your concerns and share them with family and friends. Many people will be glad to help out, whether it's providing transportation to a medical appointment, babysitting siblings, or just providing emotional support.

Pay attention to other siblings in the family

Understand that siblings can play a big role in helping a child with thalassemia. They may be a support who can help encourage a brother or sister to adhere to treatment, may be able to accompany a sibling to transfusions, or may just be there to listen to the sibling when he or she feels frustrated. The bond between siblings is different than the bond between parent and child; in some situations, some children may respond better to their siblings than to their parents. It's important for parents to *acknowledge siblings' good work* when they help your child with thalassemia and make sure they know that they play an important part in their sibling's life.



Understand also that siblings *may feel neglected or jealous* of the extra attention that a child with thalassemia may receive. Do your best to give siblings attention, making time for one-on-one outings or just special times alone with them.

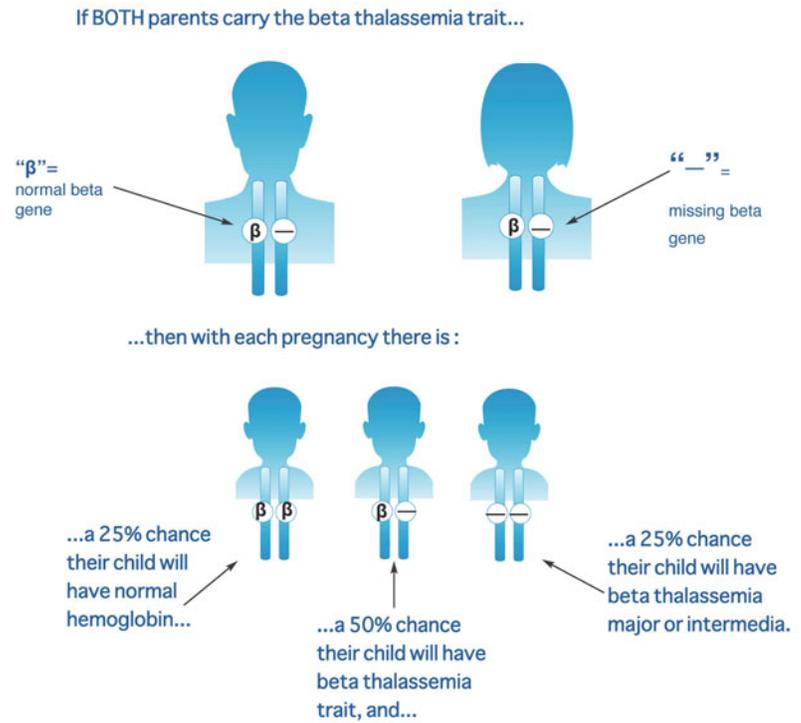
Educate all your children about thalassemia so they feel included in family issues. When the siblings are old enough to understand the basic genetics, explain to them what thalassemia trait is and what it means for them. It's also a good idea to have them tested so you know about their trait status.

Learn about your family planning choices

If you have a child with thalassemia, you may wonder about the chance of another child also having the condition.

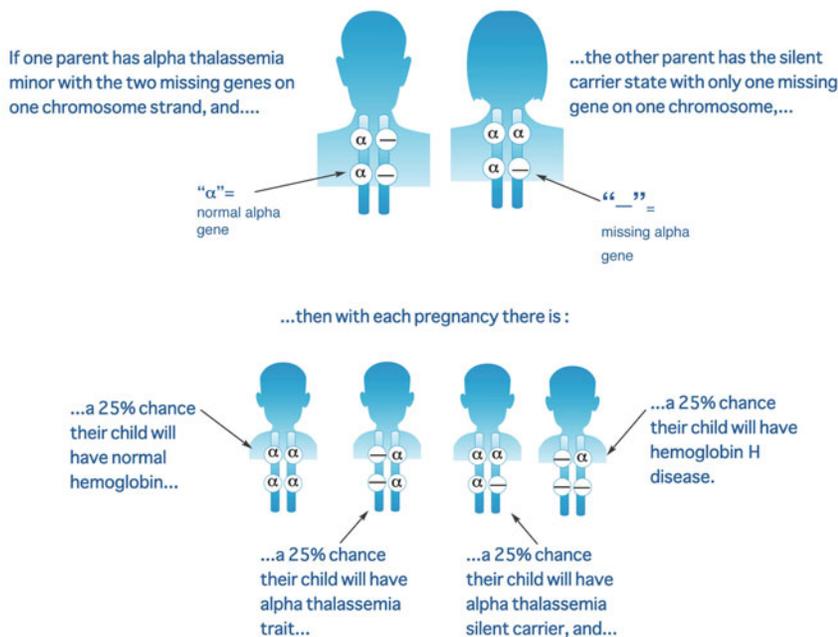
You probably already know that your child has thalassemia because both you and the other parent of your child carry thalassemia trait (or else have another form of thalassemia).

For example, if you and your partner both carry the trait for beta thalassemia, there is a 1-in-4 chance with EACH pregnancy that the child will be born with a severe form of thalassemia:



With alpha thalassemia, the chances of a child having severe thalassemia vary; because alpha genes are carried on two strands of chromosomes rather than on one, there are greater possible combinations. However, if two individuals with either the trait or mild forms of alpha thalassemia have a child together, there is a chance that their child will have a severe form of thalassemia.

For example:



Remember that *the chances of having a child with thalassemia DO NOT CHANGE with subsequent pregnancies if both parents carry thalassemia trait*; just because a person has had one child with thalassemia does NOT mean that any future children will NOT be born with thalassemia.

However, it is also possible that subsequent children of parents who carry the trait born without thalassemia may qualify as *donors for a bone marrow transplant* to help cure a sibling with thalassemia. This is an option that some patients and parents may wish to consider. Some parents use a process called Pre-implantation Genetic Diagnosis (PGD), which screens an embryo in the very early stages of pregnancy to try to determine its genetic composition (such as whether it has a severe form of thalassemia) and whether it might be a potential match for a bone marrow transplant. (See next chapter for more on PGD.)

Making these family planning decisions is complicated. Seek help so you can better understand the genetics and how to weigh your choices. You can ask your social worker or the CAF Patient Services Manager to help you. They may refer you to a genetics counselor who specializes in advising couples with concerns like yours.



Chapter 10

Curative Approaches

Learning Objectives

The purpose of this section is to explain several approaches to curing thalassemia or ensuring a child is born without thalassemia. At the end of this section, you will be able to:

- List the kinds of curative methods currently being used.
- Briefly explain the process involved in stem cell transplantation and gene therapy.
- State how pre-implementation genetic diagnosis may be used by couples with thalassemia trait.

Serious forms of thalassemia, like beta thalassemia major, are a chronic condition. People with these serious forms of thalassemia can manage their condition through blood transfusions and chelation therapy. Many people live relatively healthy and productive lives if they adhere to the recommended treatments.



However, transfusions and chelation therapy do not cure the condition. A cure means that the genetic defect that causes the anemia has been corrected and that patient's body begins producing healthy blood cells.

There are some curative approaches available. Stem cell transplantation has a history of success but is not possible for many patients. Gene therapy holds promise but is still new and experimental. And pre-implantation genetic diagnosis (PGD) can be used to determine if an embryo has thalassemia or if the embryo might be a potential donor for a stem cell transplantation.

There can be risks associated with stem cell transplantation or gene therapy, as discussed below. Because stem cell transplantations have been performed many times in thalassemia, more is known about the risks and benefits for this kind of therapy than for gene therapy. *Families considering a curative approach should take into consideration all of the possible factors and known risks involved*, just as when they consider any treatment option. These curative approaches are not for everyone, but they do represent a new frontier of treatment for people with thalassemia.

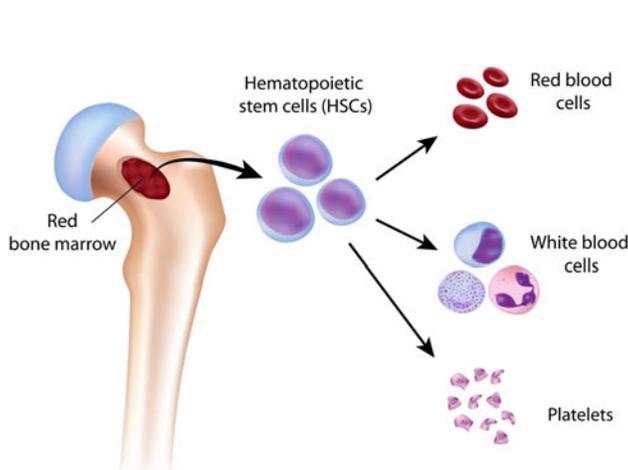
Stem cell transplantation

In both stem cell transplantation and gene therapy, the idea is to find a way to get the patient's body to make "good" red blood cells — the kind with the protein that the patient is currently missing. In stem cell transplantation, that happens by *giving the patient new stem cells*.

These stem cells are special cells that, in this case, are in charge of creating the blood cells. So, when a person has a stem cell transplantation, it's like they're making a change in their body that will help them make healthy red blood cells.

It might help for a minute to think about a factory. Let's say there's a factory that puts soda in bottles. One day they decide they're going to put milk in bottles instead. They'd have to make changes: The machines would need to be scrubbed clean of any old soda, they would need new bottles, they might need a refrigerating system to keep the milk cold. And, of course, they'd need a good source of milk.

It's a little bit like that with a person with thalassemia having a stem cell transplant. They have to make some changes in their body to make it ready for the new stem cells and they have to have a *source for the stem cells*.



The doctors make the changes in the body by removing some of the patient's cells (some blood-forming stem cells and immune cells) and replacing them with new blood-forming stem cells. They do this both to make room for the new cells and to take care of immune cells that might cause complications. The immune cells' job is to get rid of things that shouldn't be there; they might think that the new stem cells are "invading" and try to get rid of them, which is why they have to be removed.

The source for the stem cells is a *donor*, someone who gives up some of their stem cells. These donated stem cells sometimes come from the bone marrow (which is the stuff inside the bones); in those cases, the stem cell transplantation is called a *bone marrow transplantation (BMT)*. In other cases, the stem cells may come from umbilical cord tissue; then the process is called an *umbilical cord blood transplant (UCB)*.

Unfortunately, finding the right donor can be a challenge. The healthy cells used in these procedures must be a near-perfect match for what is called the human-leukocyte antigen (HLA) type of the patient. The *closer the match, the more likely that the transplant will be successful* and not have any complications.

The most likely donor is the full sibling of the patient; there is a *1 in 4 chance that any full sibling's HLA type will be the same as the patient's*. Since the first bone marrow transplant for beta thalassemia was performed in 1981, almost all patients undergoing BMT received complete HLA-matched sibling bone marrow transplants. However, in recent years, some doctors have been experimenting with transplanted tissue from *partially matched (called "haplo-identical")* related donors and also unrelated donors — that is, donors who are not a sibling.

The transplantation process requires a hospital stay to allow recovery after the cells are transplanted. After that, the patient will have outpatient care with frequent clinic visits, which focus on monitoring for any problems, such as infections, graft rejections, and chronic graft versus host disease (GvHD).

Generally, children are the best candidates for transplantation. Adults and children older than 16 years have less success with transplants.

Gene therapy

Although the process is still very much experimental, there is growing interest in the use of gene therapy to cure thalassemia. Several studies involving gene therapy for thalassemia in animals have been successful, but human studies of gene therapy for thalassemia are only now beginning. There is a great deal still to be learned, including how safe and effective this therapy is. It is important to realize that *a clear picture of the value of gene therapy to the thalassemia community may not be available for many years*.

In gene therapy, the defective gene that cause thalassemia is removed and replaced with a healthy, non-thalassemic gene. If effective, the new gene starts creating enough healthy red blood cells to reduce or eliminate the need for transfusions.

There are several ways to accomplish this, but all techniques use a virus as a “*vector*,” or way to transport the new genes into a patient’s body. (The virus is first “gutted” of the viral machinery that can cause infections.)

The first human clinical trial in gene therapy for thalassemia began in recent years, and several other trials are in preparation. In the first trial, an 18-year-old boy in France who had been diagnosed with α -beta thalassemia was treated and subsequently was able to stop transfusions and, at this writing, has had no adverse effects from the treatment. The trial was on hold for a period of time after transplant to monitor the patient's progress and health.

At this writing, two human gene therapy trials in thalassemia in the United States have been approved by the U.S. Food and Drug Administration. The results of these trials and the ongoing France-based trial will be watched and studied carefully; vital information is likely to come from these efforts, which will advance the knowledge in this promising field.

One of the key concerns with gene therapy trials is to make sure that the new genes do not in some way activate other processes, such as encouraging the growth of potentially cancerous cells.

Another gene therapy approach attempts to reactivate or stimulate the patient’s own genes that produce *fetal hemoglobin*. Fetal hemoglobin is the hemoglobin that functions inside the child in the womb but is largely replaced with regular hemoglobin after birth. This gene therapy approach hopes to cause the patient's body to create enough fetal hemoglobin so that the need for transfusions can be reduced or eliminated.

These gene therapy approaches hold promise as a cure for thalassemia, and exciting research advances give reason for cautious optimism.

Simplified Gene Therapy

Gene therapy is very complicated, but this is a “bare bones basics” approach to kind of understanding how it works.

1. Scientists take out some stem cells from a patient.
2. They pull out the gene in the stem cells that doesn’t work right and causes the thalassemia.
3. They take a working gene and put it back in the stem cells.
4. They put the stem cells with the new gene back into the patient.
5. If all goes well, those cells make many, many more healthy cells that raise the patient’s hemoglobin so that they don’t have to have transfusions.

Pre-implantation genetic diagnosis

Pre-implantation genetic diagnosis (PGD) is a process which determines whether an embryo has the genetic marker for thalassemia. This can reduce the chance of a baby being born with thalassemia and can also be used to identify an HLA-matched sibling for bone marrow transplant.

Couples who are at risk for having a child with beta thalassemia (because both parents are thalassemia trait carriers or are suspected of being carriers) can undergo this early diagnosis. The egg is extracted from the woman. It is fertilized and the embryo is tested by a single cell genetic analysis for a variety of genetic conditions, including thalassemia. If the embryo is healthy, it then can be transplanted into the woman's uterus. This increases the chance for a normal, healthy pregnancy and baby.

As mentioned, PGD can also be used to determine whether an embryo is an HLA-match for an existing child with thalassemia. In such cases, the younger sibling could then be considered as a possible donor for a bone marrow transplantation for the sibling with thalassemia.

Chapter 11

Finances and Insurance

Learning Objectives

The purpose of this chapter is to help you understand the impact that financial issues can have on thalassemia care, to suggest ways to help pay for health care, and to encourage thoughtful financial planning. At the end of this chapter, you will be able to:

- Identify different types of health insurance plans.
- Describe the steps to take if you are denied coverage for treatment.
- Determine what medicines are covered in a prescription plan.
- List basic financial planning steps.

If you have a child with thalassemia — or if you have the condition yourself — financial issues may worry you. You may be wondering about such questions as:

- Do I have enough health care insurance to cover treatment, tests, and drugs?
 - What are alternative ways of paying for treatment if I don't have traditional insurance or if the co-pay is too high?
 - Will there be a problem with my employer if I have to take off too many days for treatment for myself or my child?
 - What happens to health care coverage if I lose my job?
 - How can I best plan for my child's future?



These are all realistic concerns and important to think about. But there are ways to manage your finances so that you or your child can be assured of the best possible treatment and care. You can cope with financial concerns if you are realistic about your situation, if you

organize and maintain your paperwork, if you are persistent with insurance companies, and if you seek help when you need it.

Let's start with health insurance.

The Affordable Care Act and Health Insurance

The *Affordable Care Act* (known as the ACA or health care reform) was signed into law on March 23, 2010. Among its goals are to expand Americans' access to health care and provide new options for health care insurance.



Various sections of the law are being phased in, and by 2014, all Americans will have access to affordable health insurance options. Even currently, the law has provisions that are important to families with thalassemia. Here are two examples:

The new law will help people who have been denied health insurance coverage because of a "*pre-existing condition*" (such as thalassemia). Currently, insurance plans cannot deny health insurance coverage for children under the age of 18 because of a pre-existing condition, including disability. Starting in 2014, people of any age cannot be denied coverage because of a pre-existing condition or disability.

Also, the Affordable Care Act extends the *maximum age of coverage for young people* under their parents' health insurance plan from age 19 to age 26.

There are many other ways that the Affordable Care Act will help people with thalassemia meet the financial challenges of high-cost health care. The government website www.healthcare.gov highlights aspects of the law that pertain to people with disabilities and families with children; much of this information is relevant for people with thalassemia. Check the website to learn more about this.

Many of the changes will vary by state, so it's important to learn about the *specific options in your state*. Your hospital social worker may be able to help you or you can talk to the Patients Services Manager at Cooley's Anemia Foundation (info@thalassemia.org; 212-279-8090).

Types of health insurance plans

Following are the current ways that people can get coverage for health and medical expenses.

Employee health insurance

You and your child may be eligible for health insurance coverage through your job or your spouse's or partner's job. If the employer offers health insurance coverage to employees, you cannot be denied coverage because you or your child has a "pre-existing condition" such as thalassemia. (However, you may have to wait 12 - 18 months before coverage of a pre-existing condition goes into effect.)

Employee benefits
Employee benefits are provided to employees in salaries. In instances where wages for some other form as a 'salary sacrifice' or 's

Private health insurance plans for individuals and families

Some people who are not employed or who work for a company that doesn't offer health insurance can purchase insurance on their own. It may be worth it for you because of regular expenses associated with thalassemia care. Individuals need to balance the cost of premiums against the potential cost of health services over time. Health insurance that covers more services may have higher premiums, but it can save you money if you need to use it.

Like employer-sponsored insurance, private health plans may require a waiting period to cover a pre-existing condition. The government website www.healthcare.gov has much valuable information about things to consider when looking at private health insurance. The website offers this general advice:

When you review your insurance choices, look at both the price charged (monthly premium) for a policy and the level of protection it offers (for example, what services are covered, and what you have to pay when you receive covered services).

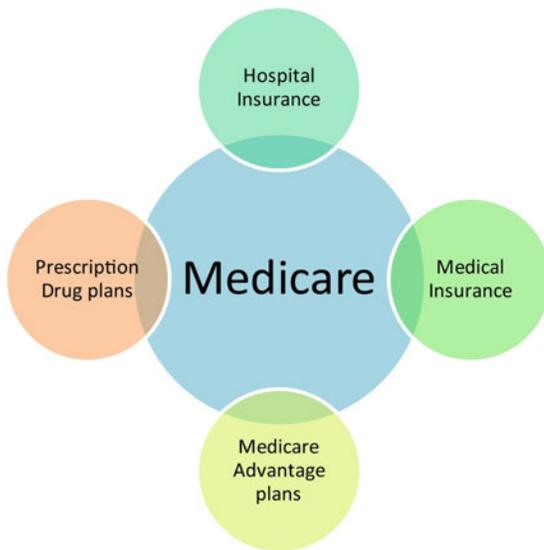
COBRA

This is a way to continue your employer insurance policy coverage when you leave a job. It can provide security for a period of time up to 18 months until you get another health insurance policy through a new employer or some other program. COBRA can be a good solution to ensure that your medical expenses are paid after you leave your job. But you will have to pay monthly premiums, which equal *the total cost of your policy* to the company (not just the portion which you paid as an employee), which can be expensive.

The Children's Health Insurance Program (CHIP)

This program provides low-cost health insurance coverage for children in families who earn too much to qualify for Medicaid but who can't afford private health insurance. The different states manage this program and the rules about eligibility vary. The CHIP program is likely to continue for the next several years, until the Affordable Care Act is fully phased in.

Visit this website for more details on CHIP: <http://www.medicaid.gov/medicaid-chip-program-information/by-topics/childrens-health-insurance-program-chip/childrens-health-insurance-program-chip.html>



Medicare and Medicaid

These programs are both administered through the Social Security Administration. Here is basic information who is eligible for these programs.

Medicare

This program guarantees access to health insurance for Americans ages 65 and older and younger people with disabilities; many individuals with thalassemia receive Medicare due to a *disability classification*. The website www.medicare.gov provides details on the programs' coverage, costs, and how to apply.

Medicaid

This program serves people with low incomes. The website www.medicaid.gov gives a great deal of useful information about the Medicaid program, including news about how it relates to the Affordable Care Act.

Things to consider when choosing insurance

Whatever type of coverage you have, it's important to understand the full scope of your coverage. You can ask your company's human resources manager or a representative from the insurance provider you are considering to help you examine all aspects of the coverage. For example, you will want to know what doctors and specialists you can have access to, which drugs are covered, which tests are covered, what your co-pay may be, and so on.

You will want to make sure that all of your *thalassemia-related medical expenses are adequately covered* by the policy you choose. If there are any gaps or "shortfalls" in your coverage, it's best to know about them in advance, so you can plan for supplemental help.

Until recently, it was a problem when young people who were covered under a parent's health insurance policy "aged out" as they turned 19 or graduated from college. As mentioned above, under the Affordable Care Act, young people may continue to be eligible for coverage under their parents' policy until age 26.

In the past, some insurance plans had "lifetime limits" or "annual caps" on coverage of

certain medical services. These put a limit on the expenses that a policy would cover, either over the life of the policy or per year. Under the Affordable Care Act, these *limits and caps are eliminated as of January 1, 2014*.

It's also important to be aware of open enrollment periods and consider if you want to make to make a change of insurers. "*Open enrollment*" refers to a period of time during which members are given the opportunity to enroll in a group insurance plan; it is usually held once a year. You want to be alert to any policy changes that might affect you, such as a change in co-payment or a change in the specialists you are able to see.

Consult with your doctor's office to learn more about the insurance plans that your hospital takes and which options are best for you, including which ones cover specialists you may need, such as an endocrinologist and cardiologist. If you are working, it's also a good idea to get to know your company's human resources manager, who can help you understand the different insurance plans that your company offers and any other options you might consider, eg, Medicaid.

Denial of coverage and denial of claims

In the past, insurance companies could deny coverage for people with certain conditions (like thalassemia), disability, or illnesses — or would make coverage very costly. Now, under the Affordable Care Act, children cannot be denied, and as of 2014, no one of any age can be denied coverage because of a medical condition or disability.



However, even if you have health insurance, your plan *may reject a claim for a specific kind of treatment or drug*. You may not understand why your claim has been denied. It's important not to accept this denial if you think you have the right to be paid for treatment or drugs. You can *appeal the denial of your claim*. Your insurance plan's summary description will explain the specific steps to take, but here are general guidelines (according to the U.S. Department of Labor's Employee Benefits Security Administration):

- Be sure that you filed the claim correctly.
- If your claim is denied, you can file an appeal within a certain time period. Be sure to include any extra information that can support your claim.
- If your appeal is denied, you can follow up in several ways. Your health insurance plan administrator can explain the options to you.
- You may be protected by "external review," which allows you to ask an independent, expert third party to help resolve the dispute with your health plan.

One thing to remember: *sometimes claims are denied purely due to human error*. Your doctor’s administrative office may have incorrectly coded a procedure or information may have been mistyped when being entered into the insurance records. It’s a good idea to check records for potential errors such as this. It’s also advisable to be familiar with your plan’s Explanation of Benefits (EOB), which provides information on what your plan covers.

Dealing with a claims denial can be frustrating and confusing. Remember that you are not alone and you have resources to help you. The Cooley’s Anemia Foundation offers practical help for this kind of problem. Contact the Patient Services Department (info@thalassemia.org; 212-279-8090) for assistance.



Understanding your drug prescription plan

It’s important for everyone to understand what drugs are covered under his or her insurance plan. This understanding of drug coverage is even more important for people with thalassemia, as the chelation drugs are vital to life and health. These drugs — Desferal, Exjade, and Ferriprox — are expensive. So you need to know if your insurance plan will cover at least some of their costs and if so, how much. Most insurance plans place different drugs on different “*tiers*” or categories and base the amount of coverage on what category an individual drug falls under.

You may also have options that can help cover costs of your drugs that are not covered by your insurance. For example, you can ask the pharmaceutical company that manufactures the drug if it has an *assistance plan*. Each company has different eligibility criteria for assistance with drug costs, so it’s best to check with the companies individually. See below for specifics on the programs recommended by the companies that manufacture specific chelator drugs.

For Exjade (deferasirox) (Company: Novartis)

EPASS (Exjade Patient Assistance and Support Services)

Phone: 888-903-7277

Patients can contact EPASS, a service that Novartis has set up to provide information to individuals who are prescribed Exjade: that is the first step in getting information related to Exjade. Novartis is familiar with Exjade-related insurance issues and should be able to give you information about co-pay assistance programs, if needed.

Sometimes the programs change or “fill up” so they are not available, but EPASS is up-to-date on all the latest information. The most common co-pay assistance programs — and those that EPASS is most likely to direct you to — are listed below. (Please note that all of these programs have various criteria that patients must meet and a formal application process which can take a period of time to process. Specific information is available from each of the individual programs.)

Exjade CoPay Card Program (Scriptassist)

Phone: 888-903-7277

Scriptassist is a co-payment assistance program offered by Novartis for individuals needing assistance covering costs associated with Exjade. Originally it was established for a period of one year (to end on May 2010); however, Novartis has extended the program and as of this date is still enrolling eligible patients.

Other Co-pay Assistance

Chronic Disease Fund

Phone: 877-968-7233

Fax: 214-570-3621

www.cdfund.org

Healthwell Foundation

(Note: As of this writing, Healthwell Foundation is not currently accepting new patients; we include it in the hope that it may enroll new patients in the future)

Phone: 800-675-8416

Fax: 800-282-7692

www.healthwellfoundation.com

For Desferal (deferroxamine) (Company: Novartis)

Desferal is also made by Novartis. At this time, no Desferal-specific programs are available (as ScriptAssist is for Exjade), but Novartis will consider patients for assistance if they meet the required criteria. Patients should contact the Novartis Patient Assistance Program for more information. Patients on Desferal also may be able to get assistance with co-pays from the Chronic Disease Fund.

Novartis Patient Assistance Program

Phone: 866-884-5906

www.pap.novartis.com

Chronic Disease Fund

Phone: 877-968-7233

Fax: 214-570-3621

www.cdfund.org

For Ferriprox (deferiprone) (Company: ApoPharma)

For assistance with Ferriprox , contact:

Ferriprox Total Care

Phone: (866) 758-7071

If your insurance plan does not at all cover the chelator which is recommended for you, *find out why*. It may be that the company does not understand the different needs of thalassemia patients and the intricacies of chelation; in such an instance, contact your doctor and the Cooley's Anemia Foundation and ask them to write letters to your insurance company explaining why you need a particular chelator. This sometimes gets results and is an option worth trying.

Remember, for general help and assistance with insurance issues, check with your company's human resources manager, your doctor's office, or the Cooley Anemia Foundation's Patient Services Department.

Financial planning

Thalassemia is challenging enough, even without the burden of managing all aspects of your finances — but if you are proactive and plan well, you can overcome many obstacles. You may need to ask for help, but at the same time, take responsibility for yourself and/or your child. You will be empowered by the process.

Here are a few guidelines to help you get started.

Make a plan

Develop a plan for managing your finances. You may benefit from help from a professional financial planner or from a friend who is skilled in the area of finance. In any case, take a broad view of your finances, asking questions such as these:



- What are my overall assets? Overall debts?
- What is my income and how secure is my job?
- What plan is in place for my child's education and training?
- What plan is in place for care of my child if something should happen to me?
- What kind of insurance coverage do I have and what do I need?
- How can I find a job or profession that provides the necessary flexibility to take time for doctor's appointments or transfusion therapy?
 - How will I know if I need to go on disability and how do I apply for it? (See separate section below)
- What are the most effective ways to save and invest to be sure that my financial needs are met?
- Where can I find resources to help me with financial and insurance issues?

Get organized and stay organized

You will be dealing with reams of paperwork and it may seem overwhelming. But it's important to keep good records.

- Keep *copies of your medical records*, as well as notes on conversations with insurers and employers, especially if you are dealing with a claims denial.
- Be aware of all *important dates*, and don't wait until the last minute to file an appeal or apply for new assistance. Missing a key deadline can cause problems.
- Also, be sure to *review your medical bills* as they come in.
- Learn the diagnostic codes and procedure codes to ensure that you are being *billed correctly*. If you see errors, it is your responsibility to raise the issue with the provider or insurer.

Learn about your health care options and plans: review the section in this chapter about types of insurance plans. If you have insurance, take the time to study your plan and know what your coverage is. Does it cover the specialists you need to see, such as an endocrinologist? What about possible emergency room or hospital stays? What is the procedure for dealing with a claims denial? Are all medications, including newer ones like Ferriprox, covered? If your child is on

your insurance plan, will he or she be able to get continued coverage if he or she goes to college out of state? If you have any questions, consult with your company's human resources or benefits specialist.

If you do not have coverage — or if it is inadequate — *what are your alternatives?* Can you go on Medicaid? Is your child eligible for a state-based CHIP program? Talk with your hospital's social worker or Cooley's Anemia Foundation Patient Services Manager to learn about possible ways to help cover some of your health care costs.



Clarify issues relating to your employment

If you have thalassemia and have a job, you know that it can be difficult to get enough time off for transfusions. If you miss too much work, you might be endangering your job security. You cannot be fired for having a disability or condition like thalassemia, and your employer must make reasonable accommodations to help you do your job. But if you cannot do your job successfully because you need to take so much time off, *it can have an impact on your employment*; if you work in a large company, you should work with the benefits department of your company to find out what paperwork you may need to complete in order make sure you do not face disciplinary action due to work missed due to treatment.

Some patients may want to see if taking advantage of the *Family and Medical Leave Act (FMLA)* might be an option. Employees eligible for FMLA can take up to 12 workweeks of unpaid leave per year; the leave can be “intermittent,” so it may be used as a way of reducing work hours and expectations during weekw in which a patient receives transfusions. For more information, including requirements for qualifying for FMLA, visit: <http://www.dol.gov/whd/fmla/fmla-faqs.htm#1>.

It also may be worth finding out if *evening or weekend transfusion options*, so you don't have to miss too much work during the week. If you are the caregiver for a child with thalassemia and you work, you may need to ask a family member or friend to take your child to some transfusion appointments.

If necessary, think about going on disability

What if you and your employer try all possible ways for you to continue in your job, but it's just not working out? Some people's experience with thalassemia is such that maintaining a job is not an option. In this instance, you can consider applying for disability — that is, apply to receive monthly cash payments to help you when you cannot work.

Disability is a complicated topic and your own individual situation will determine whether or not you can receive disability payment. A few basic facts are listed below, and the website <http://www.ssa.gov/disability/> will provide much more detailed information. The Social Security Administration oversees several programs, including the Social Security Disability Insurance program.

To qualify, you must have a physical or mental impairment (or combination of impairments) that prevents you from working and that has lasted or can be expected to last at least one year. Thalassemia qualifies as such an impairment.

To apply, go in person to a Social Security field office or apply online. It's important to have documentation that describes your medical, work, and education/training history. The more information you have about how thalassemia interferes with your ability to work, the better.

Typically, you will hear if you qualify for disability within *4-5 months*. Fewer than half of all applicants receive a positive response on their first try. If your application is denied, you should request (in writing) a hearing at which you or your advocate can argue your case. Many people are awarded disability after appealing an initial denial.

Find out about resources and ask for help

Throughout this chapter, we have mentioned people who can help you with issues related to insurance and finances. It makes sense to cultivate a good relationship with your hospital social worker. He or she will be familiar with many of your concerns and will be able to direct you to different sources of help. The Patient Services Department at Cooley's Anemia Foundation (212-279-8090; info@thalassemia.org) is a great resource in this area also, and can provide practical help, as well.

Do your homework and find out about websites of government agencies, pharmaceutical companies, and organizations that offer additional information about financial aspects of living with thalassemia.

The more informed you are about your finance and insurance requirements and options, the better you will be able to plan for you or your family's needs.

Chapter 12

Clinical Trials

Learning objectives

This chapter explains research studies, such as clinical trials, and describes the role and value of clinical trials in improving the care of people with thalassemia. At the end of this chapter, you will be able to:

- Describe how research can help people with thalassemia and why it is important for people to take part in research.
- Name different kinds of clinical trials.
- Know what types of questions to ask and things to consider before giving informed consent to participate in a clinical trial.

Disclosure: The Cooley's Anemia Foundation funds medical research, including some clinical trials.

What is a clinical trial?

Advances in the treatment of people who have thalassemia are the result of what is learned from research studies. For example, people with thalassemia today can use oral chelation drugs to treat iron overload because the drugs first went through clinical research studies.

A clinical trial is a type of research study of a drug, medical device, or procedure. Clinical trials can be designed to study a new treatment or a new use of an existing treatment or compare different treatment approaches.

Researchers begin with an idea to be tested, called a *hypothesis*. They then decide which

outcomes the experimental treatment should affect and record their observations about those outcomes after treatment. Examples of such outcomes are extending a patient's life or improving symptoms. In a clinical trial, researchers test whether or not a treatment has a positive effect.

Clinical research studies can be carried out by a *government health agency* such as the National Institutes of Health (NIH); a *hospital or university*; *private industry*, such as a drug company; or by researchers and doctors working *on their own*.



The U.S. Food and Drug Administration (FDA) uses information from clinical trials to decide whether to approve a new treatment and make it available to the public.

If you take part in a clinical trial, you are part of a process aimed at making thalassemia treatment better and helping future generations of people with thalassemia. It should be noted, however, that *not all participants benefit from a clinical trial* and in some instances there may be negative results. A clinical trial will be stopped if there are adverse effects to subjects, and any individual has the *right to withdraw* from a trial whenever they wish.

As we learn more from research, new information is used to develop and approve new treatment options and to improve education for people with thalassemia and their families.

What are the different kind of trials?

Clinical trials can be either observational or interventional.

Observational

Observational studies are those in which people are observed and the data are measured; a participant may answer questions or otherwise provide information, but the participant's *treatment is not changed during an observational trial*. Information obtained through observational trials helps to guide further research, identify or define community needs, and develop universal standards of care. Observational studies can be either prospective (meaning information is gathered in the future as it occurs) or retrospective (meaning information is gathered from the past, usually by reviewing a patient's chart).

Interventional

Interventional studies are trials in which the research subjects are assigned to a treatment or other intervention, and the results are measured. Examples of these are treatment, prevention, diagnostic, and screening trials:

- **Treatment trials** test new drugs, combinations of drugs, or new approaches to surgery or other therapies.
- **Prevention trials** look for better ways to prevent disease in people who have never had it, prevent disease from worsening, or prevent disease from returning.
- **Diagnostic trials** are conducted to find better tests or procedures for diagnosing a particular disease or condition.
- **Screening trials** test the best way to detect certain diseases or health conditions.

Who benefits from participating in a clinical trial?

Deciding to participate in a clinical trial is a *personal decision*. You need to understand what will happen during and after the trial and how it may affect your quality of life. Make sure you have as much information as possible about the *benefits and risks* of a clinical trial. Risks can differ, depending on the trial, with some having very few risks and others having more significant risks. For example, you may experience unpleasant, serious, or even life-threatening short- or long-term side effects that result from taking a drug or treatment being tested. The benefits may differ, too. It may turn out that the treatment being tested has no effect.

However, many people believe that the benefits outweigh the risks and find reward in being a part of a clinical trial, even if they do not get an immediate health benefit. They know that future generations might benefit from the knowledge gained from the trial.

Who can participate in a clinical trial?

Before you can join a clinical trial, you must first qualify to be eligible. All clinical trials have guidelines, called inclusion and exclusion criteria, that define who can take part. These guidelines are put in place to make sure that people who participate will be safe and that the results will be reliable. These guidelines are based on many factors, which may include:

- Age
- Gender
- Type of disorder or condition the person has
- Severity of the disorder or condition
- Laboratory results
- Other medical conditions
- Other factors that are important for the individual trial

What should you know before you decide to participate in a trial?

You have the right to know as much as possible about what to expect with any trial you or your child are being asked to take part in. During your first meeting with the research staff, you will be given a great deal of information at one time. You may find it helpful to *have someone come with you* to take notes as you learn more about what is expected and what will happen during a clinical trial.

Here are some questions you might want to ask during an initial meeting about enrolling in a clinical trial:

- How might this research help me directly or benefit others in the future?
- How many other people will be enrolled in the trial? How am I like these other people?
- Why do the researchers think the drug or treatment being studied might help? Has it been studied before?
 - What kinds of tests and experimental treatments will be used? What will I be asked to do?
 - How do any risks, side effects, and benefits of the drug or treatment being tested compare with my current treatment regimen?
 - How might my participation in this research affect my daily life?
 - How long will this research study last? How long will I be expected to take part?
 - Will I have to stay in a hospital during this time?
 - Who will pay for experimental treatment — the organization conducting the research, my insurance, or me? If I am paying, what will the costs be? If others are paying, will they pay for all or part of the treatment?
 - Will I be paid for other expenses, such as transportation and parking?
 - Is any long-term follow-up care a part of this study?
 - How will I know that the experimental treatment is working? Will results of the research study be provided to me?
 - If there is an unexpected side effect, who will be responsible for treating this and who will bear the cost of treatment?
 - What is my right to privacy of my medical information?
 - Who will be in charge of my care during this time?
 - If I want to quit the study, what will I need to do?



And of course you may have other questions. It's a good idea to write down any questions you might want to ask so that you don't forget them.

Take the time you need to make your decision about participating and review carefully the information provided by the researchers. You should never be made to feel pressured to participate in a research study.

How is my safety protected if I have if I decide to participate in a clinical trial?

Federal law requires that every research project is reviewed by at least one institutional review board (IRB). An IRB is an independent group of people, such as doctors, statisticians, researchers, and community advocates, who work together to ensure the following objectives:

- The research is *ethical and confidential*.
- Study participants (sometimes called human subjects) are protected in many ways through conditions of *informed consent and confidentiality agreements*. (More information on protections for participants can be found at <http://www.hhs.gov/ohrp/policy/populations/index.html>)
- *Known risks are as low as possible* and worth the potential benefits to the patient population.

The IRB committee must approve the research study before anyone can be asked to participate. The IRB committee will review research as it is being conducted to make sure that the research process is still safe and that data are collected, submitted, and reported in a way that protects your confidentiality.

What is informed consent and why is it so important?

Once you decide to take part in a research study, you will be asked to give your informed consent. Informed consent is a term used to refer to the voluntary consent process and to the form you will sign indicating that you agree to participate in a research study. *Voluntary informed consent is required before anyone can participate.*

The informed consent process is intended to protect people who participate in research. Through the process of informed consent, you confirm that you understand what will happen during this research study and that you agree to participate. Before you sign an informed consent form, you must first have all your questions answered and have talked with your health care provider about taking part in this research study. A signed consent form should summarize everything that was discussed during a patient interview. You will receive a copy of the consent form. You may need to refer to information on this form during your participation in the research study.

You may also consider taking the consent form home to read over and discuss with your family and loved ones. This will help them better understand the process of the clinical trial and learn more about how best to support you during this time.

The consent process involves more than gaining your signature. During the entire consent process you should have a participatory role in the following activities:

- Receive adequate information about the clinical trial.
- Have adequate opportunity to consider all options in a clinical trial.
- Have all your questions responded to your satisfaction.
- Understand the information provided to you.
- Provide your voluntary agreement to participate.
- Continue to receive ongoing information as required during the clinical trial.

Can children give informed consent?

Generally, children *older than 7 years of age* also must be asked for informed consent. The information they receive must be provided in language they can understand. The research team will make sure that the child is comfortable with taking part in the research planned. The child will be given every opportunity to ask questions and have them answered. *If a child does not want to take part in research, even if a parent consents, the child will not be allowed to participate.*

What should you expect in a clinical trial?

After you give informed consent, the research team will check on your health status and provide specific information on your role and what is expected of you during the clinical trial. A research protocol describes the proposed study and includes information on tests, recordkeeping, and medical appointments. Review this protocol carefully to learn as much as you can about the research. Keep in close contact with the research team and follow the protocol closely. This will help ensure that your participation is successful and that the information being collected is as accurate as possible.

To have the best experience possible in a clinical trial, here are some tips:

- Make sure the research doctor has your medical records and has contact information on your other doctors. Confirm that the research doctor is communicating with them about what is happening to you during the clinical trial.
 - Keep in close contact with the research team and follow the protocol to the best of your ability. Make sure you understand what is being expected of you during this time.
 - If any side effects occur, report them immediately to the research team and also to your regular doctor.

- Let someone on the research team know if you have done anything that the protocol said not to do. It is important that the researchers know as soon as possible so that your health and safety can be protected. Write down what happened and when so that you can remember to tell the research team. Remember, clinical trials also find out how easy or difficult it is for patients to follow a treatment regimen. If many patients have the same difficulty in following a treatment regimen, the researchers will have information that may result in revising some aspect of the treatment or the instructions about the treatment regimen. This is why it is beneficial to be *completely honest* about how well you are able to comply with what is being asked of you.

How can you find out more information about clinical trials?

If you would like to learn more about current clinical trials, talk directly with your doctor or visit these resources:

- National Institutes of Health (www.clinicaltrials.gov): This registry has general information on clinical research as well as information about federal regulations. You can find information on both federally and privately funded clinical trials. You can also search for information in multiple ways, such as location of trial, type, and phase.

- Cooley's Anemia Foundation (www.thalassemia.org): CAF lists information on clinical trials for research on thalassemia.

- CenterWatch (www.centerwatch.com): This for-profit company provides information on clinical trials and lists more than 41,000 industry- and government-sponsored clinical trials. It also provides information on new drug therapies recently approved by the U.S. Food and Drug Administration (FDA). This site is a resource for patients interested in participating in clinical trials as well as research professionals.

If think you would like to participate in a clinical trial, first discuss your interest with your doctor.

Clinical trials play an important role in the development of new therapies for thalassemia. The new treatments of tomorrow begin with the clinical trials of today.

Chapter 13

Advocacy

Learning Objectives

- List ways in which you can advocate for yourself.
- Name steps you can take to become an effective advocate.

Thalassemia is a condition that can be managed. But it's not always easy, as you know.

Sometimes, you can't find a transfusion center with convenient hours. Or you may find it difficult to obtain and pay for the latest chelator drugs. Or maybe you are frustrated because people in your life don't seem to understand the challenges you face with thalassemia. The solution to these problems is to advocate — to speak up for yourself and your family, your peers, and the wider thalassemia community.

Advocate for yourself or your child

Who is the most important person to advocate for? You! (Or your child!)

Is that selfish? Absolutely not. In fact, advocating for yourself or your child is one of the healthiest things you can do. When you speak up for your needs (or the needs of your child), you have the potential to help bring about positive change both on a personal level and for all people living with thalassemia.

Here are a few examples of how you can advocate for yourself:

- Develop *good relationships* with your health care providers— hematologist, nurse, social workers. Be courteous and patient, but speak up about getting the help you need.
- Learn to *clearly detail* your medical history and your medical needs so that you can more effectively communicate these with your health care team. Being adherent to your treatment

increases your knowledge of whether treatment is working for you and enables your health care team to more clearly determine how to best manage your care.

- If job or school schedules make it hard to get to a transfusion center during weekdays, talk to the administrator about adding evening or weekend hours.

- If you have trouble paying for life-saving drugs, contact the Patient Services Manager at the Cooley's Anemia Foundation (212-279-8090; info@thalassemia.org) and discuss ways to reduce costs.

- Be responsible about all the *financial and insurance* aspects of dealing with thalassemia. Most people don't enjoy doing all the paperwork and record keeping that's necessary. But if you stay on top of this, you will make life easier for yourself and make it easier for others, like providers and insurance companies, to work more quickly and efficiently with you.

- *Stay informed* about thalassemia. Keep up with the CAF newsletter and website to learn about the latest scientific advances related to thalassemia.

- Know and understand the *standards of care for thalassemia* and make sure your doctor is adhering to these guidelines.

Emergency Room Advocacy

One time when you may be called upon to be an advocate for yourself or for your child is during an Emergency Room visit. Often the staff at an Emergency Room may not have knowledge of or experience with thalassemia. In such cases, it is important to make the staff and doctors aware of this condition and how it may have an impact on treatment.

Thalassemia patients and caregivers should have the following information written down to give to staff in the event of an Emergency Room visit:

- The patient's name, diagnosis, date of birth and treatment schedule (such as transfusions every x weeks, etc.) and specific blood requirements;
- contact information for the patient's hematologist;
- a list of medications;
- a list of any allergies;
- any information on liver or cardiac iron burden;
- a list of current complications.

In addition, you should be prepared to discuss how thalassemia may affect the patient's hemoglobin level.

More information on Emergency Room advocacy will be forthcoming from CAF in a future publication.

Advocate for your peers

Do you know other families who face the challenge of thalassemia? Do you connect with them regularly to give support and share ideas? You can help yourself and others if you participate in a community of people with similar issues. You will feel less isolated and you can help others.



You or your child can join regular groups of thalassemia patients and families who get together to share stories. If you can't find an actual face-to-face group, maybe you can find an online site or participate in CAF's Facebook page, where you can "meet" others to talk about problems and successes related to thalassemia. And you can interact with peers at the annual CAF conferences.

Your best sources for finding out about how to connect with others in the thalassemia community are CAF or a Thalassemia Treatment Center (for those patients treated at a center).

Advocate for the wider thalassemia community

All the advantages you now enjoy — chelation drugs, the Cooley's Anemia Foundation, funding for research into thalassemia — came about because *someone advocated for them*. Many of those people were parents whose children suffered from serious forms of thalassemia before there was a good understanding of the condition. These advocates spoke up. They educated themselves about thalassemia — and then they educated the public. They started the Cooley's Anemia Foundation. They talked to legislators, policymakers, and pharmaceutical companies. They held events to raise money for the cause.

All of these efforts took time and energy. Sometimes, when you or your child have thalassemia, it's hard enough to manage your day-to-day concerns without attempting to do more for the wider community. And that is fine — you should never feel guilty about not doing enough advocacy work. However, if you feel the call to volunteer, there are countless ways to advance care by working with CAF. Contact the CAF staff (info@thalassemia.org; 212-279-8090) to learn more.

Tips for becoming an effective advocate

If you want to be a good advocate — for yourself or for thalassemia in general—it helps to develop skills to be effective. Here are a few suggestions.

- Learn the facts about thalassemia from reliable sources like CAF or your Thalassemia Treatment Center. They have good educational materials based on sound science and expert advice from their experience
- Remember that your own story is powerful. Help people understand the challenges of thalassemia by telling your family’s story in a clear way.
- When you speak to people in authority (an administrator, a politician, a pharmaceutical company representative), be courteous and focused about what you want. Respect their time limitations by preparing for your conversation.
- Be clear in your own mind about what change you hope to bring about. Then practice asking for what you want. Is it better hours at the transfusion center? Funds to help thalassemia patients pay for needed drugs? Support for important research in the field of thalassemia? Whatever it is, practice asking — whether in person or in writing — in a clear and positive way.
- Participate in Facebook discussions and respond to requests for your opinions on thalassemia issues.
- Don’t let your lack of knowledge stop you from speaking up. Asking questions is an important aspect of advocacy.

Chapter 14

A Last Word

We hope that this Guide to Living with Thalassemia has been helpful to you. If you have any questions or comments, please contact us at info@thalassemia.org or (212) 279-8090, or return the questionnaire in the Appendix.

Living with thalassemia presents many challenges; however, recent advances in care have had a profound impact on the lives of those in the thalassemia community. Individuals with thalassemia who are able to properly manage their care are in a position to live long and full lives.

There is a great deal of information in this book, but the single most important message is this:

**Sticking to your prescribed treatment
(especially transfusions and chelation) can
make a world of difference in your life.**



Stay well.

The Cooley's Anemia Foundation

Appendix A

Glossary

arrhythmia: a problem with the rate or rhythm of the heartbeat; it can be too fast, too slow, or irregular.

biopsy: a medical test involving the removal of cells or tissues for examination. In a liver biopsy, a small sample of liver tissue is removed.

bradycardia: a slower than normal heart beat. In an adult at rest, this would be a heartbeat below 60 beats per minute.

chelation: A method for removing metals from the bloodstream. In thalassemia, iron is the metal which is being removed (or chelated).

cirrhosis: a disease in which normal liver cells are damaged and replaced by scar tissue.

comprehensive care evaluation: an annual examination of an individual with thalassemia which is intended to provide a complete picture of the individual's health status. A comprehensive care evaluation enables doctors to spot potential issues before they develop and to suggest strategies for preventing them. In addition, they enable doctors to determine how effective current treatments have been and whether any changes are needed.

congestive heart failure: a condition marked by weakness, fluid accumulation and shortness of breath due to the heart not being able to maintain adequate blood circulation.

fibrosis: a disease in which an excessive amount of fibrous tissue (fibers) forms in an organ.

glucose: a simple sugar.

half-life: the time required for half the quantity of a drug to be eliminated in the body.

hemoglobin: an iron-containing protein in the blood that carries oxygen from the lungs to other parts of the body.

insulin: a hormone that helps to control the level of sugar in the blood.

intravenous: administered into a vein. Often called “IV.”

in vitro fertilization: a process by which eggs are removed from a woman’s ovary, fertilized and then returned to the woman’s uterus.

leukocyte: a white blood cell.

MRI: short for “magnetic resonance imaging.” This is the use of nuclear magnetic resonance to create images of parts of the body, such as the heart and liver.

off label: the use of a drug approved by the FDA for a purpose for which it has not been approved.

osteopenia: a condition in which bone mineral density is lower than normal; in terms of a DEXA scan score, it is one which lies between -1.0 and -2.5 .

osteoporosis: a condition in which bone mineral density is significantly lower than normal; in terms of a DEXA scan score, it is one which measure -2.5 or lower.

saline solution: a mixture involving salt and liquid, usually distilled water.

sterile: free from germs.

subcutaneous: under the skin.

tachycardia: a faster than normal heart beat. In an adult at rest, this would be a heartbeat above 100 beats per minute.

Appendix B

Possible Chelation Side Effects

The following information on warnings and potential adverse effects from chelators is excerpted from the labels for the chelators Desferal, Exjade and Ferriprox. For more complete information, you should read the label in full for each drug. You should consult your doctor if you have any questions or concerns related to possible side effects from chelation medicines.

Desferal

WARNINGS

Ocular and auditory disturbances have been reported when Desferal was administered over prolonged periods of time, at high doses, or in patients with low ferritin levels. The ocular disturbances observed have been blurring of vision; cataracts after prolonged administration in chronic iron overload; decreased visual acuity including visual loss, visual defects, scotoma; impaired peripheral, color, and night vision; optic neuritis, cataracts, corneal opacities, and retinal pigmentary abnormalities. The auditory abnormalities reported have been tinnitus and hearing loss including high frequency sensorineural hearing loss. In most cases, both ocular and auditory disturbances were reversible upon immediate cessation of treatment (see PRECAUTIONS/Information for Patients and ADVERSE REACTIONS/Special Senses).

Visual acuity tests, slit-lamp examinations, funduscopy and audiometry are recommended periodically in patients treated for prolonged periods of time. Toxicity is more likely to be reversed if symptoms or test abnormalities are detected early.

Increases in serum creatinine (possibly dose-related), acute renal failure and renal tubular disorders, associated with the administration of deferoxamine, have been reported in postmarketing experience (see ADVERSE REACTIONS). Monitor patients for changes in renal function.

High doses of Desferal and concomitant low ferritin levels have also been associated with growth retardation. After reduction of Desferal dose, growth velocity may partially resume to pretreatment rates (see PRECAUTIONS/Pediatric Use).

Adult respiratory distress syndrome, also reported in children, has been described following treatment with excessively high intravenous doses of Desferal in patients with acute iron intoxication or thalassemia.

PRECAUTIONS

General

Flushing of the skin, urticaria, hypotension, and shock have occurred in a few patients when Desferal was administered by rapid intravenous injection. THEREFORE, DESFERAL SHOULD BE GIVEN INTRAMUSCULARLY OR BY SLOW SUBCUTANEOUS OR INTRAVENOUS INFUSION.

Iron overload increases susceptibility of patients to *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* infections. In some rare cases, treatment with Desferal has enhanced this susceptibility, resulting in generalized infections by providing these bacteria with a siderophore otherwise missing. In such cases, Desferal treatment should be discontinued until the infection is resolved.

In patients receiving Desferal, rare cases of mucormycosis, some with a fatal outcome, have been reported. If any of the suspected signs or symptoms occur, Desferal should be discontinued, mycological tests carried out and appropriate treatment instituted immediately.

In patients with severe chronic iron overload, impairment of cardiac function has been reported following concomitant treatment with Desferal and high doses of vitamin C (more than 500 mg daily in adults). The cardiac dysfunction was reversible when vitamin C was discontinued. The following precautions should be taken when vitamin C and Desferal are to be used concomitantly:

- Vitamin C supplements should not be given to patients with cardiac failure.
- Start supplemental vitamin C only after an initial month of regular treatment with Desferal.
- Give vitamin C only if the patient is receiving Desferal regularly, ideally soon after setting up the infusion pump.
- Do not exceed a daily vitamin C dose of 200 mg in adults, given in divided doses.
- Clinical monitoring of cardiac function is advisable during such combined therapy.

In patients with aluminum-related encephalopathy and receiving dialysis, Desferal may cause

neurological dysfunction (seizures), possibly due to an acute increase in circulating aluminum (see ADVERSE REACTIONS). Desferal may precipitate the onset of dialysis dementia. Treatment with Desferal in the presence of aluminum overload may result in decreased serum calcium and aggravation of hyperparathyroidism.

Drug Interactions

Vitamin C: Patients with iron overload usually become vitamin C deficient, probably because iron oxidizes the vitamin. As an adjuvant to iron chelation therapy, vitamin C in doses up to 200 mg for adults may be given in divided doses, starting after an initial month of regular treatment with Desferal (see PRECAUTIONS). Vitamin C increases availability of iron for chelation. In general, 50 mg daily suffices for children under 10 years old and 100 mg daily for older children. Larger doses of vitamin C fail to produce any additional increase in excretion of iron complex.

Prochlorperazine: Concurrent treatment with Desferal and prochlorperazine, a phenothiazine derivative, may lead to temporary impairment of consciousness.

Gallium-67: Imaging results may be distorted because of the rapid urinary excretion of Desferal-bound gallium-67. Discontinuation of Desferal 48 hours prior to scintigraphy is advisable.

Information from Patients

Patients experiencing dizziness or other nervous system disturbances, or impairment of vision or hearing, should refrain from driving or operating potentially hazardous machines (see ADVERSE REACTIONS).

Patients should be informed that occasionally their urine may show a reddish discoloration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been performed with Desferal.

Cytotoxicity may occur, since Desferal has been shown to inhibit DNA synthesis in vitro.

Pregnancy Category C

Delayed ossification in mice and skeletal anomalies in rabbits were observed after Desferal was administered in daily doses up to 4.5 times the maximum daily human dose. No adverse effects were observed in similar studies in rats.

There are no adequate and well-controlled studies in pregnant women. Desferal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Desferal is administered to a nursing woman.

Pediatric Use

Pediatric patients receiving Desferal should be monitored for body weight and growth every 3 months.

Safety and effectiveness in pediatric patients under the age of 3 years have not been established (see INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS/Drug Interactions/Vitamin C, and ADVERSE REACTIONS).

Geriatric Use

Clinical Studies of Desferal did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from the younger subjects. Postmarketing reports suggest a possible trend for an increased risk of eye disorders in the geriatric population, specifically the occurrence of color blindness, maculopathy, and scotoma. However, it is unclear if these eye disorders were dose related. Although the number of reports was very small, certain elderly patients may be predisposed to eye disorders when taking Desferal. Postmarketing reports also suggest that there may be an increased risk of deafness and hearing loss in the geriatric population. (see ADVERSE REACTIONS). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No studies have been performed in patients with hepatic impairment.

ADVERSE REACTIONS

The following adverse reactions have been observed, but there are not enough data to support an estimate of their frequency.

At the Injection Site: Localized irritation, pain, burning, swelling, induration, infiltration, pruritus, erythema, wheal formation, eschar, crust, vesicles, local edema. Injection site reactions may be associated with systemic allergic reactions (see Body as a Whole, below).

Hypersensitivity Reactions and Systemic Allergic Reactions: Generalized rash, urticaria, anaphylactic reaction with or without shock, angioedema.

Body as a Whole: Local injection site reactions may be accompanied by systemic reactions like arthralgia, fever, headache, myalgia, nausea, vomiting, abdominal pain, or asthma.

Infections with *Yersinia* and Mucormycosis have been reported in association with Desferal use (see PRECAUTIONS).

Cardiovascular: Tachycardia, hypotension, shock.

Digestive: Abdominal discomfort, diarrhea, nausea, vomiting.

Hematologic: Blood dyscrasia (thrombocytopenia, leucopenia).

Hepatic: Increased transaminases, hepatic dysfunction.

Musculoskeletal: Muscle spasms. Growth retardation and bone changes (e.g., metaphyseal dysplasia) are common in chelated patients given doses above 60 mg/kg, especially those who begin iron chelation in the first three years of life. If doses are kept to 40 mg/kg or below, the risk may be reduced (see WARNINGS, PRECAUTIONS/Pediatric Use).

Nervous System: Neurological disturbances including dizziness, peripheral sensory, motor, or mixed neuropathy, paresthesias, seizures; exacerbation or precipitation of aluminum-related dialysis encephalopathy (see PRECAUTIONS/Information for Patients).

Special Senses: High-frequency sensorineural hearing loss and/or tinnitus are uncommon if dosage guidelines are not exceeded and if dose is reduced when ferritin levels decline. Visual disturbances are rare if dosage guidelines are not exceeded. These may include decreased acuity, blurred vision, loss of vision, dyschromatopsia, night blindness, visual field defects, scotoma, retinopathy (pigmentary degeneration), optic neuritis, and cataracts (see WARNINGS).

Respiratory: Acute respiratory distress syndrome (with dyspnea, cyanosis, and/or interstitial infiltrates) (see WARNINGS).

Skin: Very rare generalized rash.

Urogenital: Dysuria, acute renal failure, increased serum creatinine and renal tubular disorders (see CONTRAINDICATIONS and WARNINGS).

Postmarketing Reports

There are postmarketing reports of deferoxamine-associated renal dysfunction, including renal failure. Monitor patients for changes in renal function (e.g., increased serum creatinine).

Exjade

WARNING: RENAL, HEPATIC FAILURE AND/OR GASTROINTESTINAL HEMORRHAGE

Exjade may cause:

- renal impairment, including failure
- hepatic impairment, including failure
- gastrointestinal hemorrhage

In some reported cases, these reactions were fatal. These reactions were more frequently observed in patients with advanced age, high risk myelodysplastic syndromes (MDS), underlying renal or hepatic impairment or low platelet counts ($<50 \times 10^9/L$) [see Contraindications (4), Warnings and Precautions (5.1 - 5.7)]. Exjade therapy requires close patient monitoring, including measurement of:

- serum creatinine and/or creatinine clearance prior to initiation of therapy and monthly thereafter; in patients with underlying renal impairment or risk factors for renal impairment, monitor creatinine and/or creatinine clearance weekly for the first month, then monthly thereafter;
- serum transaminases and bilirubin prior to initiation of therapy, every two weeks during the first month and monthly thereafter.

5 WARNINGS AND PRECAUTIONS

5.1 Renal

Acute renal failure, fatal in some patients and requiring dialysis in others, has been reported following the postmarketing use of Exjade (deferasirox). Most fatalities occurred in patients with multiple comorbidities and who were in advanced stages of their hematological disorders. Monitor serum creatinine and/or creatinine clearance in patients who: are at increased risk of complications, have preexisting renal conditions, are elderly, have comorbid conditions, or are

receiving medicinal products that depress renal function. Closely monitor the renal function of patients with creatinine clearances between 40 and less than 60 mL/min, particularly in situations where patients have additional risk factors that may further impair renal function such as concomitant medications, dehydration, or severe infections.

Assess serum creatinine and/or creatinine clearance in duplicate before initiating therapy to establish a reliable pretreatment baseline, due to variations in measurements. Monitor serum creatinine and/or creatinine clearance monthly thereafter. In patients with additional renal risk factors (see above), monitor serum creatinine and/or creatinine clearance weekly during the first month after initiation or modification of therapy and monthly thereafter.

Consider dose reduction, interruption, or discontinuation for increases in serum creatinine. If there is a progressive increase in serum creatinine beyond the age-appropriate upper limit of normal, interrupt Exjade use. Once the creatinine has returned to within the normal range, therapy with Exjade may be reinitiated at a lower dose followed by gradual dose escalation, if the clinical benefit is expected to outweigh potential risks [see Dose Modifications (2.2)].

In the clinical studies, for increases of serum creatinine on 2 consecutive measures (>33% in patients >15 years of age or >33% and greater than the age-appropriate upper limit of normal in patients <15 years of age), the daily dose of Exjade was reduced by 10 mg/kg. Patients with baseline serum creatinine above the upper limit of normal were excluded from clinical studies.

In the clinical studies, Exjade-treated patients experienced dose-dependent increases in serum creatinine. These increases occurred at a greater frequency compared to deferoxamine-treated patients (38% vs. 14%, respectively, in Study 1 and 36% vs 22%, respectively, in Study 3). Most of the creatinine elevations remained within the normal range [see Adverse Reactions (6.1)]. There have also been reports of renal tubulopathy in patients treated with Exjade. The majority of these patients were children and adolescents with β -thalassemia and serum ferritin levels <1500 mcg/L.

5.2 Hepatic Dysfunction and Failure

In Study 1, 4 patients discontinued Exjade because of hepatic abnormalities (drug-induced hepatitis in 2 patients and increased serum transaminases in 2 additional patients). There have been postmarketing reports of hepatic failure, some with a fatal outcome, in patients treated with Exjade. Most of these events occurred in patients greater than 55 years of age. Most reports of hepatic failure involved patients with significant comorbidities, including liver cirrhosis and multiorgan failure. Serum transaminases and bilirubin should be monitored before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. Consider dose modifications or interruption of treatment for severe or persistent elevations.

5.3 Gastrointestinal

Fatal GI hemorrhages, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts, have been reported. Non-fatal upper GI irritation, ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving Exjade [see Adverse Reactions (6.1)]. Physicians and patients should remain alert for signs and symptoms of GI ulceration and hemorrhage during Exjade therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. Use caution when administering Exjade in combination with drugs that have ulcerogenic or hemorrhagic potential, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants.

5.4 Cytopenias

There have been postmarketing reports (both spontaneous and from clinical trials) of cytopenias, including agranulocytosis, neutropenia and thrombocytopenia, in patients treated with Exjade. Some of these patients died. The relationship of these episodes to treatment with Exjade is uncertain. Most of these patients had preexisting hematologic disorders that are frequently associated with bone marrow failure [see Adverse Reactions (6.2)]. Monitor blood counts regularly. Consider interrupting treatment with Exjade in patients who develop unexplained cytopenia. Reintroduction of therapy with Exjade may be considered, once the cause of the cytopenia has been elucidated.

5.5 Hypersensitivity

Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving Exjade, with the onset of the reaction occurring in the majority of cases within the first month of treatment [see Adverse Reactions (6.2)]. If reactions are severe, discontinue Exjade and institute appropriate medical intervention.

5.6 Rash

Rashes may occur during Exjade (deferasirox) treatment. For rashes of mild to moderate severity, Exjade may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, Exjade may be interrupted. Reintroduction at a lower dose with escalation may be considered in combination with a short period of oral steroid administration. Erythema multiforme has been reported during Exjade treatment.

5.7 Co-morbidities

Clinical trials to demonstrate increased survival or to confirm clinical benefit have not been completed. Exjade has been shown to decrease serum ferritin and liver iron concentration in clinical trials. Consider the importance of these factors as well as individual patient factors and

the prognosis associated with any underlying conditions before initiation of Exjade therapy [see Contraindications (4)].

In postmarketing experience, there have been reports of serious adverse reactions, some with a fatal outcome, in patients taking Exjade therapy, predominantly when the drug was administered to patients with advanced age, complications from underlying conditions or very advanced disease. Most of these deaths occurred within six months of Exjade initiation and generally involved worsening of the underlying condition. The reports do not rule out the possibility that Exjade may have contributed to the deaths.

5.8 Special Senses

Auditory disturbances (high frequency hearing loss, decreased hearing), and ocular disturbances (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) have been reported at a frequency of <1% with Exjade therapy in the clinical studies. Auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) are recommended before starting Exjade treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, consider dose reduction or interruption.

5.9 Laboratory Tests

Measure serum ferritin monthly to assess response to therapy and to evaluate for the possibility of overchelation of iron. If the serum ferritin falls consistently below 500 mcg/L, consider temporarily interrupting therapy with Exjade [see Dosage and Administration (2.2)]. In the clinical studies, the correlation coefficient between the serum ferritin and LIC was 0.63. Therefore, changes in serum ferritin levels may not always reliably reflect changes in LIC. Perform laboratory monitoring of renal and hepatic function [see Warnings and Precautions (5.1, 5.3)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following adverse reactions are also discussed in other sections of the labeling:

Renal Failure [see Warnings and Precautions (5.1)]. Hepatic Failure [see Warnings and Precautions (5.2)]. Fatal and non-fatal Gastrointestinal Bleedings [see Warnings and Precautions (5.3)]. Cytopenias [see Warnings and Precautions (5.4)].

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 700 adult and pediatric patients were treated with Exjade (deferasirox) for 48 weeks in premarketing studies. These included 469 patients with β -thalassemia, 99 with rare anemias, and 132 with sickle cell disease. Of these patients, 45% were male, 70% were Caucasian and 292 patients were < 16 years of age. In the sickle cell disease population, 89% of patients were Black. Median treatment duration among the sickle cell patients was 51 weeks. Of the 700 patients treated, 469 (403 β -thalassemia and 66 rare anemias) were entered into extensions of the original clinical protocols. In ongoing extension studies, median durations of treatment were 88-205 weeks.

Table 1 displays adverse reactions occurring in >5% of Exjade-treated β -thalassemia patients (Study 1) and sickle cell disease patients (Study 3) with a suspected relationship to study drug. Abdominal pain, nausea, vomiting, diarrhea, skin rashes, and increases in serum creatinine were the most frequent adverse reactions reported with a suspected relationship to Exjade. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related.

Table 1. Adverse Reactions Occurring in >5% of Exjade-treated Patients in Study 1 and Study 3*

Preferred Term	Study 1 (β -Thalassemia)		Study 3 (Sickle Cell Disease)	
	EXJADE N=296 n (%)	Deferoxamine N=290 n (%)	EXJADE N=132 n (%)	Deferoxamine N=63 n (%)
Abdominal Pain**	63 (21.3)	41 (14.1)	37 (28.0)	9 (14.3)
Diarrhea	35 (11.8)	21 (7.2)	26 (19.7)	3 (4.8)
Creatinine Increased***	33 (11.1)	0 (0)	9 (6.8)	0
Nausea	31 (10.5)	14 (4.8)	30 (22.7)	7 (11.1)
Vomiting	30 (10.1)	28 (9.7)	28 (21.2)	10 (15.9)
Rash	25 (8.4)	9 (3.1)	14 (10.6)	3 (4.8)

*Adverse reaction frequencies are based on adverse events reported regardless of relationship to study drug.

** Includes 'abdominal pain', 'abdominal pain lower', and 'abdominal pain upper' which were reported as adverse events.

*** Includes 'blood creatinine increased' and 'blood creatinine abnormal' which were reported as adverse events. Also see Table 2.

In Study 1, a total of 113 (38%) patients treated with Exjade had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2) and 25 (8%) patients required dose reductions. Increases in serum creatinine appeared to be dose related [see Warnings and Precautions (5.1)]. In this study, 17 (6%) patients treated with Exjade developed elevations in SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits. Of these, 2 patients had liver biopsy proven drug-induced hepatitis and both discontinued Exjade therapy [see Warnings and Precautions (5.2)]. An additional 2 patients, who did not have elevations in SGPT/ALT >5 times the upper limit of normal, discontinued Exjade because of increased SGPT/ALT. Increases in transaminases did not appear to be dose related. Adverse reactions that led to discontinuations included abnormal liver function tests (2 patients) and drug-induced hepatitis (2 patients), skin rash,

glycosuria/proteinuria, Henoch Schönlein purpura, hyperactivity/insomnia, drug fever, and cataract (1 patient each).

In Study 3, a total of 48 (36%) patients treated with Exjade had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2) [see Warnings and Precautions (5.1)]. Of the patients who experienced creatinine increases in Study 3, 8 Exjade-treated patients required dose reductions. In this study, 5 patients in the Exjade group developed elevations in SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits and 1 patient subsequently had Exjade permanently discontinued. Four additional patients discontinued Exjade due to adverse reactions with a suspected relationship to study drug, including diarrhea, pancreatitis associated with gallstones, atypical tuberculosis, and skin rash.

Table 2. Number (%) of Patients with Increases in Serum Creatinine or SGPT/ALT in Study 1 and Study 3

Laboratory Parameter	Study 1 (β-Thalassemia)		Study 3 (Sickle Cell Disease)	
	EXJADE N=296 n (%)	Deferoxamine N=290 n (%)	EXJADE N=132 n (%)	Deferoxamine N=63 n (%)
Serum Creatinine				
Creatinine increase >33% and <ULN at 2 consecutive postbaseline visits	113 (38.2)	41 (14.1)	48 (36.4)	14 (22.2)
Creatinine increase >33% and >ULN at 2 consecutive postbaseline visits	7 (2.4)	1 (0.3)	3 (2.3)	2 (3.2)
SGPT/ALT				
SGPT/ALT >5 x ULN at 2 postbaseline visits	25 (8.4)	7 (2.4)	2 (1.5)	0
SGPT/ALT >5 x ULN at 2 consecutive postbaseline visits	17 (5.7)	5 (1.7)	5 (3.8)	0

Proteinuria

In clinical studies, urine protein was measured monthly. Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) occurred in 18.6% of Exjade-treated patients compared to 7.2% of deferoxamine-treated patients in Study 1. Although no patients were discontinued from Exjade in clinical studies up to 1 year due to proteinuria, monthly monitoring is recommended. The mechanism and clinical significance of the proteinuria are uncertain.

Other Adverse Reactions

In the population of more than 5,000 patients who have been treated with Exjade during clinical trials, adverse reactions occurring in 0.1% to 1% of patients included gastritis, edema, sleep disorder, pigmentation disorder, dizziness, anxiety, maculopathy, cholelithiasis, pyrexia, fatigue, pharyngolaryngeal pain, early cataract, hearing loss, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, and renal tubulopathy (Fanconi's syndrome). Adverse reactions occurring in 0.01% to 0.1% of patients included optic neuritis,

esophagitis, and erythema multiforme. Adverse reactions which most frequently led to dose interruption or dose adjustment during clinical trials were rash, gastrointestinal disorders, infections, increased serum creatinine, and increased serum transaminases.

6.2 Postmarketing Experience

The following adverse reactions have been spontaneously reported during postapproval use of Exjade. Because these reactions are reported voluntarily from a population of uncertain size, in which patients may have received concomitant medication, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: leukocytoclastic vasculitis, urticaria, alopecia

Immune system disorders: hypersensitivity reactions (including anaphylaxis and angioedema).

Ferriprox

WARNING: AGRANULOCYTOSIS/ NEUTROPENIA

- Ferriprox can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. [see Warnings and Precautions (5.1)]
- Measure the absolute neutrophil count (ANC) before starting Ferriprox therapy and monitor the ANC weekly on therapy. Interrupt Ferriprox therapy if neutropenia develops. [see Warnings and Precautions (5.1)]
- Interrupt Ferriprox if infection develops, and monitor the ANC more frequently. [see Warnings and Precautions (5.1)]
- Advise patients taking Ferriprox to report immediately any symptoms indicative of infection. [see Warnings and Precautions (5.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Agranulocytosis/Neutropenia

Fatal agranulocytosis can occur with Ferriprox use. (Ferriprox can also cause neutropenia, which may foreshadow agranulocytosis. Measure the absolute neutrophil count (ANC) before starting Ferriprox therapy and monitor the ANC weekly on therapy [see Boxed Warning].

Interrupt Ferriprox therapy if neutropenia develops (ANC < 1.5 x 10⁹/L).

Interrupt Ferriprox if infection develops, and monitor the ANC more frequently.

Advise patients taking Ferriprox to immediately interrupt therapy and report to their physician if they experience any symptoms indicative of infection.

In pooled clinical trials, the incidence of agranulocytosis was 1.7% of patients. The mechanism of Ferriprox-associated agranulocytosis is unknown. Agranulocytosis and neutropenia usually resolve upon discontinuation of Ferriprox, but there have been reports of agranulocytosis leading to death.

Implement a plan to monitor for and to manage agranulocytosis/neutropenia prior to initiating Ferriprox treatment.

For neutropenia (ANC < 1.5 x 10⁹/L and > 0.5 x 10⁹/L):

Instruct the patient to immediately discontinue Ferriprox and all other medications with a potential to cause neutropenia.

Obtain a complete blood cell (CBC) count, including a white blood cell (WBC) count corrected for the presence of nucleated red blood cells, an absolute neutrophil count (ANC), and a platelet count daily until recovery (ANC ≥ 1.5 x 10⁹/L).

For agranulocytosis (ANC < 0.5 x 10⁹/L):

Consider hospitalization and other management as clinically appropriate.

Do not resume Ferriprox in patients who have developed agranulocytosis unless potential benefits outweigh potential risks. Do not rechallenge patients who develop neutropenia with Ferriprox unless potential benefits outweigh potential risks.

5.2 Cardiac QT Syndrome

A thorough QT study has not been conducted with Ferriprox. One patient with a history of QT prolongation experienced Torsades de Pointes during therapy with Ferriprox. Administer Ferriprox with caution to patients who may be at increased risk of prolongation of the cardiac QT interval (e.g., those with congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia or hypomagnesemia). Instruct any patient taking Ferriprox who experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizures) to seek medical attention immediately.

5.3 Embryofetal toxicity

Based on evidence of genotoxicity and developmental toxicity in animal studies, Ferriprox can

cause fetal harm when administered to a pregnant woman. In animal studies, administration of deferiprone during the period of organogenesis resulted in embryofetal death and malformations at doses lower than equivalent human clinical doses. If Ferriprox is used during pregnancy or if the patient becomes pregnant while taking Ferriprox, the patient should be apprised of the potential hazard to the fetus. Women of reproductive potential should be advised to avoid pregnancy when taking Ferriprox [see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)].

5.4 Laboratory Tests

Serum liver enzyme activities

In clinical studies, 7.5% of 642 subjects treated with Ferriprox developed increased ALT values. Four (0.62%) Ferriprox-treated subjects discontinued the drug due to increased serum ALT levels and 1 (0.16%) due to an increase in both ALT and AST.

Monitor serum ALT values monthly during therapy with Ferriprox, and consider interruption of therapy if there is a persistent increase in the serum transaminase levels.

Plasma Zinc concentration

Decreased plasma zinc concentrations have been observed on Ferriprox therapy. Monitor plasma zinc, and supplement in the event of a deficiency.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

The following adverse reactions are also discussed in other sections of the labeling:

Agranulocytosis/Neutropenia [see Warnings and Precautions (5.1)]. Elevated ALT (5.4), Torsades de Pointes (5.2), Decreased plasma zinc concentrations (5.4).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reaction information for Ferriprox represents the pooled data collected from 642 patients who participated in single arm or active-controlled clinical studies.

The most serious adverse reaction reported in clinical trials with Ferriprox was agranulocytosis [see Warnings and Precautions (5.1)].

The most common adverse reactions reported during clinical trials were chromaturia, nausea, vomiting, abdominal pain, alanine aminotransferase increased, arthralgia and neutropenia.

The table below lists the adverse drug reactions that occurred in at least 1% of patients treated with Ferriprox in clinical trials.

Table 2: Adverse drug reactions occurring in $\geq 1\%$ of 642 Ferriprox-treated patients

Body System Preferred Term	% Subjects
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Neutropenia	6.2
Agranulocytosis	1.7
GASTROINTESTINAL DISORDERS	
Nausea	12.6
Abdominal pain/discomfort	10.4
Vomiting	9.8
Diarrhea	3.0
Dyspepsia	2.0
INVESTIGATIONS	
Alanine Aminotransferase increased	7.5
Neutrophil count decreased	7.3
Weight increased	1.9
Aspartate Aminotransferase increased	1.2
METABOLISM AND NUTRITION DISORDERS	
Increased appetite	4.0
Decreased appetite	1.1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Arthralgia	9.8
Back pain	2.0
Pain in extremity	1.9
Arthropathy	1.4
NERVOUS SYSTEM DISORDERS	
Headache	2.5
URINARY DISORDERS	
Chromaturia	14.6

Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain were the most frequent adverse reactions reported by patients participating in clinical trials and led to the discontinuation of Ferriprox therapy in 1.6% of patients.

Chromaturia (reddish/brown discoloration of the urine) is a result of the excretion of the iron in the urine.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in patients receiving Ferriprox. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: thrombocytosis, pancytopenia.

Cardiac disorders: atrial fibrillation, cardiac failure.

Congenital, familial and genetic disorders: hypospadias.

Eye disorders: diplopia, papilledema, retinal toxicity.

Gastrointestinal disorders: enterocolitis, rectal hemorrhage, gastric ulcer, pancreatitis, parotid gland enlargement.

General disorders and administration site conditions: chills, pyrexia, edema peripheral, multi-organ failure.

Hepatobiliary disorders: jaundice, hepatomegaly.

Immune system disorders: anaphylactic shock, hypersensitivity.

Infections and infestations: cryptococcal cutaneous infection, enteroviral encephalitis, pharyngitis, pneumonia, sepsis, furuncle, infectious hepatitis, rash pustular, subcutaneous abscess.

Investigations: blood bilirubin increased, blood creatinine phosphokinase increased.

Metabolism and nutrition disorders: metabolic acidosis, dehydration.

Musculoskeletal and connective tissue disorders: myositis, chondropathy, trismus.

Nervous system disorders: cerebellar syndrome, cerebral hemorrhage, convulsion, gait disturbance, intracranial pressure increased, psychomotor skills impaired, pyramidal tract syndrome, somnolence.

Psychiatric disorders: bruxism, depression, obsessive-compulsive disorder.

Renal disorders: glycosuria, hemoglobinuria.

Respiratory, thoracic and mediastinal disorders: acute respiratory distress syndrome, epistaxis, hemoptysis, pulmonary embolism.

Skin, subcutaneous tissue disorders: hyperhidrosis, periorbital edema, photosensitivity reaction, pruritis, urticaria, rash, Henoch-Schönlein purpura.

Vascular disorders: hypotension, hypertension.

Appendix C

Comprehensive Care Evaluation Checklist

The following tests are recommended for most patients with thalassemia on an annual basis. However, since each patient's case is unique, your doctor may recommend some of these tests be done more or less frequently. While each test result is important, their trends over time must also be analyzed to detect early problems.

These are tests that are recommended in addition to monthly CBC's and quarterly chemistry panels and ferritin measurements.

Cardiac Evaluation

The following tests should be performed at least once per year.

- Assessment by a cardiologist knowledgeable in problems of iron overload and thalassemia.
- Echocardiogram (with assessment of tricuspid regurgitant jet velocity after age 10 to diagnose pulmonary hypertension, and left ventricular ejection fraction to diagnose cardiomyopathy. Functional MRI of heart and MUGA scanning are useful assessments)
- T2* MRI of heart for cardiac iron
- 24 Hour Holter Monitor or event recorder to diagnose cardiac arrhythmia (after age 12)
- ECG (electrocardiogram)

Liver and Infection Evaluation

Annual testing for hepatitis, transfusion associated infections and response to vaccines are recommended.

- Annual Hepatitis C Antibody test if previously negative
- Annual hepatitis C RNA viral load (if not previously treated and antibody +)
- Liver Function Enzyme Screening (AST/SGOT, ALT/SGPT) every three months

If you have an elevated ALT, it is recommended you repeat the test every month. If ALT is persistently elevated for 6 months or more, a liver biopsy or MRI for iron should be considered. All thalassemia patients should consider a MRI to evaluate liver iron (or a liver biopsy) every two years.

- Hepatitis B Panel
- Hepatitis A Panel (if not vaccinated or if hep A + in past)
- Annual HIV
- Serum AFP and abdominal ultrasound are annual screening tests for early liver cancer for patients with chronic hepatitis.

Iron Stores:

- Annual or bi-annual quantitative liver iron assessment by liver biopsy or noninvasive measurement is recommended. As of this writing, the specialized Ferriscan technique is the only FDA approved non-invasive measure for hepatic iron; others are in development. SQUID (Superconducting Quantum Interference Device) is another non-invasive alternative but its availability to patients is limited.

Endocrine Function Evaluation

Annual assessment in growing children should include growth and height velocity and puberty status. A bone age exam should be included every few years until puberty if low bone mass or slow growth is noted. After puberty, annual assessment should also include studies of gonadal function, fertility, impotence.

- TSH, Free T4, Parathyroid Hormone Level
- Fasting AM Cortisol
- Glucose Tolerance Test (for patients older than 10 yrs of age)
- Bone Density (for patients older than 8 years of age)
- Testosterone, FSH, LH, Estradiol and endocrinology consult recommended

Ophthalmology Evaluation

- Annual evaluation by an ophthalmologist (for cataracts, night blindness, decreased visual field). (Especially recommended for patients on Desferal or with diabetes.)

Audiological Evaluation

- Annual Audiological Evaluation for evaluation of hearing changes and Tinnitus (ringing in the ears)

Transfusion Monitoring

- Annual assessment of number of red cell units transfused
- Review of transfusion complications (red cell antibodies, transfusion reactions)
- Review of the pre-transfusion hemoglobin values and frequency of transfusions

Iron chelation

□ Annual assessment of the effectiveness of the chelation program, including discussion of heart, endocrine and other organ dysfunction. Review of chelation options, dosing, and evidence of adequacy of chelation on the present regimen.

NON-ANNUAL OR OTHER

Immunizations

- Influenza annually
- Pneumococcal (Prevnar and pneumovax) (for splenectomized patients)
- Meningococcal (Menactra) (for splenectomized patients)

Pulmonary function studies - post splenectomy

□ E very three years or as indicated.

Genetics

- Globin genotype (once)
- HLA typing (once)
- HLA typing for new siblings after birth
- Genetic counseling

Appendix D

Resources

Organizations and websites:

Affordable Care Act information

www.healthcare.gov

Center Watch

www.centerwatch.com

Centers for Disease Control and Prevention

www.cdc.gov/ncbddd/hbd/thalassemia.htm

Clinical Trials

www.clinicaltrials.gov

Cooley's Anemia Foundation

www.thalassemia.org

www.facebook.com/cooleysanemiafoundation

Disability: Social Security

<http://www.ssa.gov/disability>

Family and Medical Leave Act (FMLA)

<http://www.dol.gov/whd/fmla/fmla-faqs.htm#1>

Medicaid

www.medicaid.gov

Medicare
www.medicare.gov

National Heart, Lung and Blood Institute
www.nhlbi.nih.gov/

National Institutes of Health
www.nih.gov

Thalassaemia International Federation
www.thalassaemia.org/cy

U.S. Food and Drug Administration: To report adverse events of a drug
www.fda.gov/Safety/MedWatch

Appendix E

Questionnaire

Thank you for supplying us with feedback on this **Guide to Living with Thalassemia**. Please return this form via fax (212-279-5999), email (info@thalassemia.org) or mail (Cooley's Anemia Foundation, 330 Seventh Avenue #200, New York, NY 10001). Your feedback will help us improve this book when we make revisions in the future. Please feel free to use additional sheets of paper if you need more room.

1. How helpful did you find this publication, based on a scale of 1 (not very helpful) to 10 (very helpful)? (Please circle your answer.)

1 2 3 4 5 6 7 8 9 10

2. How informative did you find this publication, based on a scale of 1 (not very informative) to 10 (very informative)? (Please circle your answer.)

1 2 3 4 5 6 7 8 9 10

3. How easy to read did you find this publication, based on a scale of 1 (not very easy) to 10 (very easy)? (Please circle your answer.)

1 2 3 4 5 6 7 8 9 10

4. What part(s) of the Guide, if any, did you find the most valuable?

5. What parts(s) of the Guide, if any, did you find least valuable?

6. Were there any parts of the Guide where you wished we had included more information? If so, which parts, and what kind of additional information would you have liked?

7. Were there any parts of the Guide that you found unnecessary? If so, which parts?

8. I am: (circle one)

- a. An adult patient with thalassemia
- b. A thalassemia patient who is under 18 years of age
- c. The parent or guardian of a child with thalassemia
- d. The sibling of a person with thalassemia
- e. Other: _____

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For more information about thalassemia:

Cooley's Anemia Foundation

www.thalassemia.org

212-279-8090

800-522-7222

info@thalassemia.org

Centers for Disease Control and Prevention

www.cdc.gov/ncbddd/thalassemia

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