Standards of Care in Thalassemia

Thalassemia Support group

Thomas D Coates, MD
Childrens Hospital Los Angeles

What is Thalassemia?

Thalassemia is an inherited disorder due to a DNA mutation that causes either inefficient or no production of hemoglobin. Patients have anemia and small red cells.

Hemoglobin level
- Normal: 12.5 to 16
- Trait: 10.5 to 14
- Intermedia: 6.5 to 10
- Severe: less than 6

Over 250 different mutations

Each cell in the body has two complete sets of DNA-encoded instructions
How to Make the Diagnosis

Newborn Screen
CBC, reticulocytes
Iron Studies
Hb Electrophoresis
Quantitative Hb A2
Quantitative Hb F

All thalassemia patients should have alpha and beta gene testing done by DNA
- Confirm diagnosis
- Prenatal diagnosis

What is thalassemia?

• An inherited problem with the genes that tell you body how to make the red chemical in your blood called hemoglobin that carries oxygen from your lungs to your body. There are several hundred known gene defects so there are lots of different severities of thalassemia.
• Patients with severe gene defects cannot keep their hemoglobin levels over 6 gm/dl. This is called thalassemia major:
  - They require transfusions every three weeks to keep their pre-transfusion hemoglobin level greater than 9.5 g/dl.
  - Their bone marrow, which makes blood, is much more active than normal because it is not able to make hemoglobin. It is like running on ice. You run like crazy but never get anywhere. This causes many problems see in thalassemia like bone deformity and fractures and pulmonary hypertension (high blood pressure in the lungs). The transfusions are given to shut off all marrow activity. That is why it is important to keep the hemoglobin above 9.5 and not wait for it to drop before transfusing again.
  - Transfusion causes severe iron overload which is fatal if not treated. We treat iron overload with drugs called chelators, NOT by restricting transfusion.
• Patients with milder gene defects who can keep their hemoglobin levels over 6 gm/dl are called thalassemia intermedia.
  - These patients may or may not require chronic transfusion. They are the most difficult to manage because it requires a lot of experience to know when to transfuse.
  - Even if you are not transfused a lot, you still have increased iron absorption and get iron overload.
  - Thal intermedia patients develop pulmonary hypertension in their 30’s and 40’s if they are not transfused.
  - They can develop osteoporosis and bone deformity as well.
  - We are inclined to put these patients on chronic transfusion unless their hemoglobins are very good.
Why and when to transfuse

• We transfuse to suppress the increased marrow activity that characterizes thalassemia and to help carry oxygen.
  — Causes bone damage
  — Bone pain
  — Enlarged spleen
  — High blood pressure in the lungs (Pulmonary hypertension)

• Need to transfuse every three weeks to keep pre-transfusion hemoglobin over 9 to 11 in order to turn off the ineffective marrow activity that causes these complications.

Thalassemia major patients (Hb < 6) need transfusion to support normal growth and prevent heart failure.

Thalassemia intermedia (Hb > 6) patients may not develop so much heart failure but can have growth problems, bone disease, pulmonary hypertension and iron overload.

Many thalassemia intermedia patients require transfusion to prevent complications of over active marrow.

Severe iron toxicity from transfusion causes heart, endocrine and liver damage.
Transfusion therapy results in iron overload

- 1 blood unit contains 200–250 mg iron
- Iron overload occurs after ~20 transfusions leading to ferritin levels of about 1,000 µg/L
- Transfusion every 3 weeks leads to net iron gain of 0.5 mg/kg/day
- Humans have no way to excrete excess iron

Whole blood: 0.47 mg iron/mL
“Pure” red cells: 1.08 mg iron/mL

Iron loading in thalassemia

Transferrin binds toxic iron and blocks damage

Non-transferrin-bound iron (NTBI) is very toxic and is the main kind that enters the heart and endocrine organs.

Uncontrolled iron loading of organs
- Pituitary
- Parathyroid
- Thyroid
- Heart
- Liver
- Pancreas
- Gonads

Chelators immediately bind NTBI

Heart failure
Growth failure
Diabetes
Delayed puberty
Endocrine failure

High transferrin saturation (NTBI) and early death in the general population


So it is really important to have chelator circulating as much of the time as possible because it protects from the damage from iron.

DFO = deferoxamine; NTBI = non-transferrin-bound iron.
Iron loading and damage is not the same in all tissues

- **Organ damage** = (tissue iron) x (TIME) x (environment) x (genetic factors)
  - It usually takes years (3 to 10 years) to have measurable damage to an organ, even if the iron in that organ is high.
  - Removing free iron (NTBI) from the blood can significantly improve heart failure and rhythm problems in a few weeks, long before you can get iron out of the heart itself.
  - High iron over many 30-40 years can cause liver cancer.

- **MRI allows measurement of Fe in tissues**
  - Liver loads very quickly
  - Heart delayed loading for years, then really fast loading
  - Pancreas loads slowly and predicts future iron in heart
  - Pituitary loads fairly quickly
  - Adrenal rate of loading not well known

Liver iron does not directly correlate with cardiac iron

Black means high iron. In the MRI between A and B, the cardiac iron was high and the patient became adherent to chelation. Panel B shows the liver clears before the heart. (Image courtesy of Dr J Wood)
Cardiac T2* and risk for cardiac dysfunction

Figure 1

- Cardiac T2* less than 6 ms means very very high heart iron
  - High risk of heart failure
  - High risk of heart rhythm disturbances including sudden death
- High cardiac iron and presence of arrhythmia or heart failure is a medical emergency.
  - Very few heart specialists know how to manage this.
  - They do not know that even very severe cases can almost always be reversed with proper treatment.
  - You need to speak to an experience thalassemia doctor immediately.
- If there is no heart failure or arrhythmia, the iron overload can always be reversed using current treatments.
Iron Induced Cardiac Disease in Patients with Thalassemia Major - Main Cause of Death in Patients in the UK up to 1999


Prevalence of Endocrine Dysfunction

<table>
<thead>
<tr>
<th>Endocrinopathy</th>
<th>Borgna-Pignatti 2004</th>
<th>Vogiatzi et al 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low sex hormones</td>
<td>54.7</td>
<td>51.3</td>
</tr>
<tr>
<td>Low thyroid hormone</td>
<td>10.8</td>
<td>12</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.4</td>
<td>14.1</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>--</td>
<td>2.1</td>
</tr>
</tbody>
</table>
Improvement in endocrine function with clearance of iron overload

![Graph showing improvement in endocrine function](image)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Glucose metabolism</td>
<td>44</td>
<td>22%</td>
<td>66%</td>
</tr>
<tr>
<td>Testosterone replacement</td>
<td>24</td>
<td>58%</td>
<td>30%</td>
</tr>
<tr>
<td>Thyroid replacement</td>
<td>51</td>
<td>36%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Farmaki et al, BrJ Hematol, 2010;148(3):466-75

Chelation works if you take it..

![Graph showing liver iron levels](image)

T. D. Coates, M.D.

DFO Started 24/7
Iron Toxicity in SCD and Thalassemia

IRON TOXICITY = TISSUE IRON X ENVIRONMENTAL FACTORS X GENETICS X TIME

CERTAIN NUTRIENTS ARE IMPORTANT FOR PROTECTION AGAINST IRON TOXICITY

% of patient with abnormal levels

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Reference range</th>
<th>Sickle cell patients</th>
<th>Thalassemia patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (ug/dl)</td>
<td>36-96</td>
<td>34.4 ± 8.5</td>
<td>34.9 ± 12.2</td>
</tr>
<tr>
<td>B12 (ug/ml)</td>
<td>2.4-11.7</td>
<td>3.3 ± 1.6</td>
<td>33.5% ± 4.1</td>
</tr>
<tr>
<td>B12 (ug/ml)</td>
<td>3.9-28</td>
<td>8.1 ± 7.7</td>
<td>34.2% ± 7.0</td>
</tr>
<tr>
<td>B12 (pg/ml)</td>
<td>200-1100</td>
<td>6644 ± 399.2</td>
<td>4.7% ± 528</td>
</tr>
<tr>
<td>Ferritin (ug/ml)</td>
<td>38</td>
<td>15.5 ± 6.0</td>
<td>32.6% ± 11.8</td>
</tr>
<tr>
<td>C (mg/dl)</td>
<td>0.2-1.9</td>
<td>0.28 ± 0.20</td>
<td>52.7% ± 0.92</td>
</tr>
<tr>
<td>D25 (pg/ml)</td>
<td>20-100</td>
<td>16.8 ± 6.2</td>
<td>74.4% ± 17.1</td>
</tr>
<tr>
<td>D25 (pg/ml)</td>
<td>15-60</td>
<td>61.1 ± 18.2</td>
<td>48.6% ± 99.9</td>
</tr>
<tr>
<td>E-alpha (mg/dl)</td>
<td>5.7-19.9</td>
<td>8.7 ± 4.7</td>
<td>10.5% ± 7.5</td>
</tr>
<tr>
<td>Selenium (ug/ml)</td>
<td>110-160</td>
<td>107.1 ± 13.3</td>
<td>67.5% ± 99.5</td>
</tr>
<tr>
<td>Zinc (ug/dl)</td>
<td>65-124</td>
<td>81.0 ± 17.8</td>
<td>24.3% ± 93.0</td>
</tr>
<tr>
<td>Copper (ug/l)</td>
<td>580-1100</td>
<td>1092.1 ± 221.1</td>
<td>34.8% ± 801</td>
</tr>
</tbody>
</table>

Treatment of iron overload

• Almost all the complications of thalassemia now come from iron overload due to transfusion.
• Humans have no way to get rid of excess iron
• Chelators are drugs that help remove iron from the body.
• If you effectively remove iron from your body you will have very few complications of thalassemia and a near normal life expectancy
• You should have some chelator in your circulation all the time to optimize protection and block iron entry into the heart and endocrine organs.

Overview of iron chelators

<table>
<thead>
<tr>
<th>Property</th>
<th>Deferoxamine (DFO)</th>
<th>Deferiprone (DFP) (Feriprox)</th>
<th>Deferasirox (Exjade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dose</td>
<td>25–60 mg/kg/day</td>
<td>75 mg/kg/day</td>
<td>20–30 mg/kg/day</td>
</tr>
<tr>
<td>Route</td>
<td>s.c., i.v.</td>
<td>p.o.</td>
<td>p.o.</td>
</tr>
<tr>
<td></td>
<td>8–12 h, 5 days/week</td>
<td>3 times daily</td>
<td>once daily</td>
</tr>
<tr>
<td>Half-life</td>
<td>20–30 min</td>
<td>3–4 h</td>
<td>8–16 h</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, faecal</td>
<td>Urinary</td>
<td>Faecal</td>
</tr>
<tr>
<td>Approved indications</td>
<td>Treatment of chronic iron overload due to transfusion-dependent anaemias</td>
<td>Thalassaemia major</td>
<td>Treatment of chronic iron overload due to frequent blood transfusions</td>
</tr>
</tbody>
</table>

Monitoring for iron toxicity and effect of treatment

- Liver iron concentration (LIC) is the most accurate measure of total body iron
  - Normal is less than 1.2 mg / g liver
  - Over 5 to 10 is really bad
  - 40 is as high as we can measure
  - Liver MRI for iron requires special software. Any MRI can make the measurement, but very few centers have the software and can do it correctly.
  - This test should be done every 1 to 1.5 years as a standard measure. More frequently under certain conditions.
  - You can reduce your LIC by 50% in 4 to 6 months with intense chelation.
- Ferritin should be measured with each transfusion.
  - It is a poor but convenient marker of iron overload
- Transferrin saturation is the only test that measures the dangerous kind of iron
  - Because it changes so fast, it is not generally a good test to monitor chelation
  - It can drop within minutes of taking you chelator, showing the chelator is binding the free, dangerous kind of iron
Relation of serum ferritin to LIC in populations of iron loaded patients

1. 527 observations in 117 patients
2. $r = 0.8 \ (p<0.0001)$

Ferritin is useful when it makes sense!

**In our opinion:**
- Ferritin should be monitored with each transfusion to establish useful trends
- LIC should be measured every 12 to 18 months or when the ferritin trend doesn’t make sense.
Monitoring for iron toxicity and effect of treatment

- Cardiac MRI should be done once every year to 1.5 years
  - The cardiac T2* needs to be measured
  - This required special software. All machines have a drop down menu that had T2*. However, if the iron version of the protocol isn’t there, you will get an incorrect result. Most radiologists do not know the difference
  - You cannot predict the heart iron accurately any other way and iron in the heart is the most dangerous toxicity for thalassemia patients.
- Cardiac contractility very one to 1.5 years
  - This is most accurately measured by MRI
  - Echocardiogram can estimate this as well
- Test for high pressure in the arteries to the lung (pulmonary hypertension) every year or two after age 12
  - This is done by echocardiogram

What about combination chelation?

- Offers the possibility of intensified Rx.
- May be able to avoid or reduce toxicity.
- However, unknown toxicities may exist.
- May tailor treatment to lifestyle.
- Little controlled data yet.

- Exjade + DFO appears to be very effective.
- ExJade + Deferiprone very little data.
- Desferal + Deferiprone there is considerable data
At the Children’s Hospital Los Angeles, we attempt to normalize the liver iron concentration and clear all cardiac iron LIC target of 0.8 to 1.5 mg/G

You need to be able to accurately measure LIC if you are going to try to do this without danger of over-chelation.

There is no published large series of data on this aggressive approach. The Greek data is very supportive, but the numbers are small. Most centers do not aim for LIC that is this low.

Ferritin by itself is TOTALLY inadequate for the diagnosis and monitoring of transfusional iron overload but remains a useful adjunct to routine assessment of liver iron concentration (LIC).

Routine assessment of LIC and cardiac iron by T2* is critical for proper management of patients with iron overload.

It is critical to monitor endocrine function and other organ functions as well as micronutrient status in iron loaded patients.

Cardiac T2* < 10 ms is a very serious problem and requires aggressive treatment.

Presence of cardiac iron, especially a T2* < 10 ms in conjunction with arrhythmia or decreased cardiac contraction is an emergency.
Routine Monitoring

- Round 1 (Veggie Panel)
  - Vit B1 (thiamine)
  - Vit B6 (pyridoxine)
  - Vit B12
  - 25-OH-vit D
  - Vit C (ascorbate)
  - Vit A
  - Vit E
  - Carnitine
  - Zn, Se, Cu, Ceruloplasmin
  - Methylmalonic Acid
  - Homocystine

- Endocrine functions
  - FBS, 2HPPG, insulin
  - PTH
  - Ca, PO4, alk phos
  - Osteocalcin, Urine N-telopeptide
  - TSH, T3 T4
  - Testosterone, FSH, LH
  - Progesterone, estradiol
  - IGF1, IGFBP3
  - Cortisol, ACTH
  - Bone density
  - Growth velocity

Demands are much greater in iron loaded patients so you need to follow levels and adjust doses accordingly.

Take home messages

- It takes several years for the heart to load with iron.
- If cardiac T2* is less than 10 ms or there is evidence weak contraction of the heart or abnormal heart rhythm, you are in great danger and intensive chelation is needed.
- You can remove half the liver iron in four to six months.
- The heart doesn’t start to really unload until the liver iron is below 18 mg/G.
- It takes about 17 months to remove half the iron in the heart.
- Any time you do not have a chelator in your blood, free iron is present and is entering your heart and endocrine organs.
- Just having a chelator in your blood binding free iron protects your heart, even though there may be still a lot of iron in the heart muscle itself.

So don’t get discouraged, you are protected if you have chelator present in your blood. Your heart and liver will clear.
Survival in thalassemia is directly related to compliance with chelation therapy (1).
Projected survival is markedly improved with 100% compliance (2).
Even though once a day oral therapy is much more convenient (3), compliance remains a major issue with effectiveness of treatment.


Treatment of thalassemia:

• Blood transfusion every three weeks and iron chelation therapy
  – This is a very safe and effective treatment and compatible with long term survival and almost normal life expectancy if iron chelation treatment is followed properly.
  – It is important to use regular transfusions and not “on demand” transfusion.
  – There are patients in their 60’s now who are doing reasonably well.
  – If you are compliant with iron chelation, you can avoid most if not all of the complications of thalassemia and expect to live a fairly normal life.

• Bone marrow stimulants and hemoglobin F inducing drugs
  – Not a practical option now
  – However, there is good research ongoing so our opinions may change.

• Sotateracet
  – Treats ineffective red cell production through a new mechanisms.
  – Very promising

• Bone marrow transplantation.
  – If you have a matched sibling donor, this is curative and the recommended therapy.
  – Currently transplant data for people over 16 yo is not so good. However, this is old data from an era when control of iron was not as good.
  – Un-related donor transplant is not standard first line treatment for most cases, in our opinion. This is changing as well as progress in matching and preparation regimens advances.

• Gene therapy.
  – Eight patients treated by Bluebird Bio. Results are promising
  – New Gene editing approach trial with a different approach than BlueBird may open in a year.
You need to be in contact with a center that has significant experience managing thalassemia and iron overload. This means more than 20 to 30 patients on transfusion and that has immediate access to MRI measures of iron.

Importantly, your physician needs to be willing to interact with a major center.

Thalassemia Support Foundation or Cooley’s Anemia Foundation can help make these connections.

The Task

How do you get your local physician to follow the recommendations of your comprehensive thalassemia center or published guidelines.

... So, talking about this topic and making suggestions is easy.

... Establishing an effective collaboration between the patient, your local physician and your thalassemia center takes work and is not necessarily so easy.
The Frustration

In the worst case scenario, no bone marrow transplantation, no hope of gene therapy, by using “standard” adequate transfusions and effective chelation to normalize iron load, a relatively normal life expectancy can be achieved with minimal complications of thalassemia.

This can be accomplished by following some relatively simple general guidelines and achieving a couple of treatment goals.

What doesn’t work is writing down a recipe for an inexperienced provider to follow on his own doesn’t work.

(Look, I know there are barriers, but the medical part is not rocket science or neurosurgery. But then “… Just getting along with each other” and world peace would seem to be simple concepts as well.)

Transfuse regularly to maintain pre-transfusion hemoglobin levels sufficient to suppress excessive marrow activity. This usually means a hemoglobin over 10 gm and transfusions every three weeks.

An effective iron chelation program to keep free iron suppressed at all times and normalize iron levels.

Appropriate monitoring of efficacy of the transfusion program, normalization of iron loading, and side effects of medications.
To start with, it's on your back

- You need to educate yourself about thalassemia, iron overload and management of thalassemia.
- You have a very focused and specific interest in this disorder and really only one patient to take care of.
- You do not need an MD or other fancy degree to understand the important things about thalassemia. Maybe not the detailed biochemistry, but the important concepts are easily within reach of anyone.
- You must advocate for yourself. There are plenty of folks at this meeting, at Cooley's and other places who can help you.
- It is quite likely you will become more knowledgeable about the concepts of thalassemia care than most physicians, including hematologists.

Just the facts

- Just because you have “hematologist” on your calling card doesn’t mean you know about rare disease. Similarly, just because you are thalassemia center director doesn’t mean you have a lot of experience.
- If your local physician or hematologist isn’t active in the thalassemia community or doesn’t have a significant focus in the area, he will not likely know the names of your center physicians.
- It is not reasonable to expect a local practitioner to try to develop the same level of expertise as the folks at a center. The easiest way for him to develop expertise is to collaborate with your thalassemia center. Handing them a guideline book to follow probably isn’t a great introduction.
- You don’t necessarily need a local expert thalassemiologist. A reasonable family physician would work depending on their interest and willingness to work with the center.
What you need

“I don’t care how much you know
I want to know how much you care”

Zimbalist Chalk, 2014

A physician who may not have experience but who is willing to work with some one do does and really wants to help manage your thalassemia.

Your job in facilitating the center connection is to get to know the local physician and determine if he really means it when he says he will work with the center and if he really cares about participating in the management.

This will require direct communication between the local physician and the center physician and a concerted effort to many the local physician feel like part of the team. If this happens,

A few suggestions

• Call TSF or Cooley’s anemia first. They can communicate with folks who are in the know and really find out if the way you are being managed is really bad or not and do it such as way as not to threaten your provider or cause any legal issues.

• Even if your provider is not doing things correctly, you really don’t know if things can be changed until there has been some communication with your center.

• There really needs to be a conversation, on the phone not by letter or email by a politically savvy center physician who wants to develop relationships and your provider.

• (if you are not followed in a center ... TSF or Cooleys can help you there regarding who are really experienced centers ... Then you need to be).
A few suggestions

How you present your concerns to your local physician probably makes a lot of difference:

• “I just got back from a national family conference on thalassemia and everyone was getting regularly transfused to a hemoglobin of 10 or above. The speakers from centers said ..... 

• Rather than “I told a thalassemia PooBah in Chicago that I was getting transfused randomly whenever my hemoglobin is less than 7 and he said you didn’t know what you were doing and you should change ..... 

Playing dumb is often effective .. Being dumb, not so much ..

A few more suggestions

• Have your center contact your new provider before you see them. “Doctor Jones, I have a 20 yo thalassemia patient I have been following for years I am hoping that you will be willing to help me with her care ........

• We (Sue Carson) has had success by speaking with local hematologists and saying …"I know it’s a ton of work to management these patients in a busy private practice, how can we help with ....
The take-home Messages

• There is tremendous hope for patients with thalassemia and other severe chronic anemias.
• Thanks to significant advances in the past 10 years, the therapy available in 2015 can reverse iron related cardiac disease and prevent most if not all complications of iron overload.
• Some survival predictions approach normal for patients who are compliant with chelation.
• There is hope for curative treatments for thalassemia in the fairly near future. Eight patients have been treated as of Dec 2014 by gene therapy.

Quaerite Veritatem:

Seek the Truth

(And stay as far away as possible from those who think they have found it ...