THALASSEMIA MANAGEMENT CHECKLISTS

Monitoring of Iron Overload in Transfusion-Dependent Thalassemia (TDT)

Sujit Sheth, MD, NewYork-Presbyterian Hospital/Weill Cornell Medical Center

LEVEL OF IRON OVERLOAD	IRON OVERLOAD MEASUREMENTS	FREQUENCY OF MRI TESTING
Target	• LIC 2-5 mg/g DW • Ferritin <1,000 ng/mL • T2*>20 msecs	• Check LIC when chelation is first initiated and every year thereafter • Check cardiac T2* at age 10 and every 2 years thereafter
Moderately Elevated	• LIC 5-10 mg/g DW • Ferritin 1,000 to 2,500 ng/mL • T2*>20 msecs	• Check LIC when chelation is first initiated and every year thereafter • Check cardiac T2* at age 10 and every 1-2 years thereafter based on LIC trends
Seriously elevated	• LIC >10 mg/g DW • Ferritin >2,500 ng/mL • T2*<20 msecs	• Check LIC when chelation is first initiated and every 6 months thereafter, if on intensive chelation • Check cardiac T2* at age 10 and every year thereafter based on LIC trends
Mild cardiac iron overload with normal cardiac function	• T2* 10-20 msecs	• Check LIC and cardiac T2* when chelation is first initiated and every 6-12 months thereafter while on intensive chelation • Monitor cardiac function (MRI/ECHO) every 6 months
Severe cardiac iron overload with or without cardiac dysfunction	• T2* <10 msecs	• Check LIC and Cardiac T2*when chelation is first initiated and every 6 months thereafter on intensive chelation • Monitor cardiac function (MRI/ECHO) every 6 months with cardiac specialist

Caveats:

- Patients with pacemakers and mobile metal implants may not be able to undergo MRI testing. MRIs in patients with metal clips in areas under study may not be accurate because of artifacts caused by the metal.
- Children under the age of 5 may need sedation for MRI testing.
- Liver biopsy to evaluate iron overload in the liver may be necessary for patients who are not able to undergo MRI or magnetic susceptibility (SQUID) measurements for any reason. SQUID testing is only available at select centers in the US.

Guidelines for Monitoring of Iron Overload in Transfusion Dependent Thalassemia

- The gold standard for assessing iron burden is MRI testing of individual organs using a validated protocol. The Liver Iron Concentration (LIC) accurately reflects the total body iron stores.[1]
- MRI measurements of the liver by R2* or R2 have been validated to correlate well with actual liver tissue iron measurements.[2,3] There is some discussion as to the ideal LIC that patients on transfusion and chelation should maintain in order to prevent deposition in other tissues. An LIC of approximately 3 mg/g dry weight (twice the upper limit of normal) is a reasonable target. Maintaining LIC in the 2-5 mg/g range should ensure good iron balance with low risk of chelator toxicity. Overchelation may be a concern if LIC is <2 mg/g DW, and reduction in chelator dose may be considered.
- Liver Iron Concentration (LIC) should be measured by MRI when chelation is first initiated. If the LIC can be reasonably calculated based on the transfusion

volumes, this may be deferred if there is concern related to sedation for the MRI in young children. LIC should be measured annually to ensure that the patient's individual chelation regimen is accomplishing its goal and maintaining the liver iron in the desired range. More frequent measurements are necessary if:

  - The transfusion requirements change
  - The chelation regimen has to be changed because of side effects or poor compliance
  - Patients are heavily iron loaded and on intensive chelation
  - The serum ferritin shows a consistent upward trend.

- Cardiac MRI T2* measurement has been shown to accurately reflect myocardial iron deposition. In addition, there is correlation between myocardial T2* and cardiac function.[4,5] Cardiac T2* > 20ms is associated with very low risk of cardiac events. However, patients with historical cardiac iron deposition which has now cleared are at risk of cardiac complications and symptoms of failure or arrhythmia should be closely monitored.
- Cardiac T2* is usually not performed until 10 years of age in patients who have started chelation appropriately and who have not exhibited elevated LIC values for any significant length of time. Cardiac T2* should ideally be measured annually to ensure that the patient's individual chelation regimen is accomplishing its goal and maintaining the cardiac iron in the desired range. For compliant patients with a stable transfusion AND chelation regimen, with LIC and cardiac T2* in the optimal range, cardiac T2* may be measured every 2 years.
- Although serum ferritin levels provide a convenient method to approximate iron overload in thalassemia, this is not a reliable indicator of total body iron burden or liver or cardiac iron, since ferritin is an acute phase reactant and levels may change for a variety of non-iron related reasons. However, in individual patients, TRENDS in the ferritin are a reasonably good predictor of changes in the total body iron levels and may be helpful in avoiding over-chelation in patients with low LIC. To follow changes and look for consistent trends, ferritin levels are measured every 1-2 months for all patients on regular transfusions and chelation. Persistent trends may indicate need for an MRI to determine need for a change in chelation regimen.
- It is important to note that the correlation between LIC and myocardial T2* is not consistent. Iron loads AND unloads more rapidly in the liver as compared to the heart.[6] Thus, patients on intensified chelation will show a decline in LIC before an improvement in cardiac T2*.

References for this checklist can be found online at the Cooley's Anemia Foundation's website: ***www.thalassemia.org/checklists-references****.*
The Cooley's Anemia Foundation encourages doctors to utilize this information in treating thalassemia patients.

This project was supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) under grant number U1AMC28550 (Thalassemia). This information or content and conclusions are those of the author and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, HHS or the U.S. Government.