

1. Cardiac Complications

Principles

- To reduce cardiac morbidity and mortality by optimal iron chelation starting in childhood and continuing throughout adulthood.
- To monitor closely for cardiac dysfunction.
- To escalate chelation of cardiac iron if cardiac toxicity is identified.
- To treat urgently cardiac dysfunction according to standards of care.

Recommendation

- All thalassemia comprehensive care centers should have a cardiologist with expertise in managing cardiac complications and iron overload in thalassemia patients.
- The cardiologist should manage cardiac complications as heart failure or arrhythmias as per cardiology standard.
- All patients with thalassemia should have routine assessment for signs and symptoms of cardiac dysfunction and/or arrhythmias.
- Cardiac function and pulmonary artery pressure should be monitored routinely.
- Cardiac iron overload must be monitored routinely in patients with thalassemia.
- Cardiac iron overload should be lowered by iron chelation therapy to reduce complication and avoid mortality.
- In the presence of cardiac dysfunction or complication from iron overload, aggressive management with iron chelation must be used.

Background

Iron-induced heart failure and arrhythmias are one of the most common causes of death in patients with thalassemia major.^{199, 252} Deaths from cardiac disease are unusual before the age of 15 years. Appropriate iron chelation reduces the risk of cardiac disease and improves survival.^{198, 199} Effective chelation involves control of tissue iron levels as well as suppression of non-transferrin bound iron (NTBI) which cause free-radical mediated oxidative damage to organelles.²⁵³

Interventions

- Each thalassemia specialist centre should have a cardiologist with knowledge of managing cardiac complications in thalassemia patients.
- All patients should have routine clinical assessment for signs and symptoms of cardiac dysfunction.²⁰³
- Diabetic patients and males are at greater risk of cardiac related iron complications^{254, 255}
- Splenectomy status may also play a role^{256, 257, 267}
- Cardiac iron load and function should be measured routinely by MRI T2*.²⁰⁴
- Iron-overload should be reduced by chelation to lower the risk of iron associated cardiac complications and death.^{198, 199, 205, 227}
- In the presence of increased cardiac iron load and/or cardiac dysfunction, more aggressive iron chelation regimens should be initiated.²⁰⁵
- The specialist cardiologist should manage cardiac complication, including heart failure and arrhythmia, as per cardiology standards, but with appreciation of specific thalassemia-related considerations.

Monitoring for Cardiac Dysfunction and Iron Load

- All patients should be asked for symptoms of cardiac disease on each visit and have a cardiac physical examination every 6 months or if new symptoms present. Any abnormality should trigger specific cardiological evaluation.
- Cardiac function, including LVEF, can be measured by several techniques including echocardiography (ECHO), MUGA scan, and cardiac MRI. MUGA should be avoided due to cumulative radiation exposure. Since decreased LVEF is associated with subsequent development of symptomatic cardiac disease and death, cardiac function should be measured yearly starting at the age of 6 years.^{203, 258, 259}
- Assessment may be performed more frequently if clinically indicated or if compliance with chelation has been poor.
- If there is a suspicion of arrhythmias based on history or physical examination, an electrocardiogram (ECG) and Holter/event monitor should be performed.^{260, 261}
- NT-pro BNP may be helpful in the assessment of cardiac iron.²⁶²⁻²⁶⁴
- Vitamin D levels should be normalised as there may be a correlation with cardiac disease.²⁶⁵
- Baseline ECHO assessment should be ordered for pulmonary hypertension (PHT), though the prevalence is low in Thalassemia Major. In Thalassemia Intermedia, ECHO for PHT screen may be performed more frequently. LV non-compaction may be more prevalent in Thalassemia and can be screened with ECHO.²⁶⁶
- With the availability of Cardiac MRI T2* assessment, there is no role for using the serum ferritin or liver iron concentration as a marker of cardiac risk. Furthermore, particularly in chelation-exposed patients there can be discrepancy between these different markers.^{198, 267-271}
- Due to the major impact on outcomes, where cardiac MRI T2* is not available locally, there should be arrangement for patients to undergo cardiac MRI T2* analysis at another centre.²⁷²
- Each centre should have a radiologist with expertise in CMR T2* and the technique should be employed using a validated protocol.^{215, 273} A segmental approach to T2* analysis is controversial and is not required as a basic requirement of analysis (15, 84, 85)
- ECHO with strain analysis can be used as an interim assessment of iron related cardiomyopathy where it is difficult to obtain frequent MRI T2* or where there may be a contraindication to MRI.^{210, 276-278}
- Pancreatic MRI can predict those patients at risk of developing cardiac iron overload.²⁷⁹
- Cardiac MRI T2* values greater than 30ms are considered normal, and >20ms not usually associated with significant iron load.
- Cardiac MRI T2* less than 10ms correlates with a progressive and significant decline in LVEF.²⁰⁴
- CMR T2* should be repeated every 1 – 2 years in patients with high MRI T2* values (> 20 ms), and every 6 months in patients with low MRI T2* values <10ms. Additional imaging is recommended 6 months after changing chelation regimen or if there has been deterioration in compliance to chelation therapy. The timing and frequency of testing should be individualized to each patient.
- Detection of cardiac fibrosis is still at the experimental phase and results are controversial.

Treatment Based on Cardiac Dysfunction and Iron Load Assessment

- Chelation therapy to reduce high iron load lowers the likelihood of developing cardiac dysfunction. However, longstanding iron deposition in the heart can lead to late cardiac events such as restrictive cardiomyopathy and arrhythmia, even if successfully chelated. For this reason, current T2* value does not predict for longterm morbidity from prior iron accumulation, and vigilance should be maintained in old patients with a prior history of sustained non-adherence or suboptimal chelation.⁴⁷⁴
- Lack of compliance with chelation therapy should be identified and importance of chelation stressed.²³⁷
- Cardiac MRI T2* values between 10 and 20 ms indicate cardiac iron deposition with a risk of eventual cardiac decompensation.
- A more aggressive chelation program should be implemented in patients with T2* <10ms or a drop in LVEF by 7-10% or to below the normal range.
- Conversion to an aggressive chelation program in patients with heart failure can improve LVEF and myocardial MRI T2* measurements.²⁰⁵
- Cardiac MRI T2* values < 10 ms indicate significantly increased iron loading and are associated with significant risk of more immediate cardiac decompensation without aggressive intervention.^{237, 266} Aggressive chelation therapy

should be started immediately and cardiac function monitored at least every 6 months.

- A cardiologist with knowledge of thalassemia and iron-related cardiotoxicity should be involved in every affected patient's care and be consulted when problems arise.
- Cardiologic intervention and management for heart failure and arrhythmia should follow cardiology standards and should include medications such as ACE inhibitors, beta-blockers, diuretics, digoxin, and anti-arrhythmic agents, pacemakers with or without cardioversion capacity, and ablation of arrhythmogenic tissue. Amiodarone should be avoided due to risk of thyroid and liver disease in Thalassemia.
- Ablation may be unsuccessful due to widespread fibrosis and should be undertaken by an experienced Electrophysiologist cardiologist, ideally in cooperation with a thalassemia specialist cardiologist.
- Implantable cardiac devices should be considered in the setting of cardiogenic shock as a bridge to effective chelation.
- If heart transplantation is being considered, a panel reactive antibody should be requested early on to determine likelihood of successful engraftment and blood transfusions limited to reduce further sensitisation.
- Deferiprone has been shown to increase both T2* and RVEF & LVEF in patients with severe cardiac iron overload and cardiac dysfunction²⁵⁰
- Deferasirox has been shown to increase both T2* and LVEF in patients with moderate-severe cardiac iron overload and normal cardiac function.²⁴¹⁻²⁴⁵ It has not yet been determined if liver iron concentration affects the efficacy of Deferasirox to chelate the myocardium²³⁹
- Continuous infusion of Deferoxamine can effectively chelate non-transferrin bound iron and improve iron and cardiac dysfunction.
- First line management of a T2* < 10ms with reduced LVEF should be high dose CIV Deferoxamine with Deferiprone tid.^{233, 234, 237, 238, 247}
- Second line management of a T2* < 10ms with reduced LVEF should be Deferiprone tid at 100mg/kg/d with or without intermittent Deferoxamine, especially in the presence of significant liver iron overload^{238, 247}
- For patients with a low T2* and normal LVEF Deferiprone and Deferasirox have both been shown to be effective.
- Combination of Deferoxamine and Deferasirox for severe myocardial iron is limited but efficacious for those with normal LVEF.²⁶³
- There is insufficient data at present to recommend combination therapy with Deferasirox and Deferiprone for cardiac iron overload.
- Intermittent Deferoxamine should not be used as chelation monotherapy in patients with significant cardiac iron overload.²³⁴
- At present, use of Calcium Channel Antagonists as an adjuvant to chelation is experimental and should be limited to clinical trials.²⁶⁶

Pulmonary Hypertension (PHT)

- Markers of platelet and endothelial activation as well as hemolysis and splenectomy status have been associated with pulmonary hypertension (PHT) in non-transfused thalassemia patients. The prevalence of PHT (overall ~2% - 33% depending on diagnostic criteria) in TDT and deletional HbH disease is very low compared to NTDT.²⁶⁷⁻²⁷⁶ ECHO has a high positive predictive value when TRJV > 3.2.
- Chronic blood transfusion was found in one study to reduce ECHO – defined pressures and improve six minute walk test in a group of Hb/Ebeta thal patients.²⁷⁷
- The OPTIMAL study showed benefit of Hydroxyurea or transfusion in reducing risk of PHT.²⁷⁸
- At the current time there is insufficient evidence to support the use of sildenafil for improving TRJV in thalassemia syndromes. A pilot study demonstrated safety but with no improvement in 6MW.²⁷⁹
- There is limited data to suggest possible benefit from L-carnitine in reducing TRJV.²⁸⁰