Beta-thalassemia: clinical findings, molecular defects and genotype/phenotype relationships

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Disclosure

Member of Advisory Board:
- Novartis
- Genzyme/Sanofi
- Celgene
- Shire
- Merganser Biotech
- Isis
DIAGNOSIS ACCORDING TO TRANSFUSION REQUIREMENTS IN THALASSAEMIA

Non-transfusion-dependent thalassaemias (NTDT)
- β-Thalassaemia intermedia
- Mild/moderate haemoglobin E/β-thalassaemia
- α-Thalassaemia intermedia (haemoglobin H disease)

Transfusions seldom required
Occasional transfusions required (e.g. surgery, pregnancy, infection)
Intermittent transfusions required (e.g. poor growth and development, specific morbidities)
Regular, lifelong transfusions required for survival

- α-thalassemia trait
- β-thalassemia minor

- β-thalassemia major
- Severe haemoglobin E/β-Thalassaemia
- A-Thalassaemia major (hemoglobin Bart’s hydrops fetalis)

Defining transfusion-dependent thalassemias (TDT)

- Inherited from two carrier parents
- Severe anemia accompanied by failure to thrive or grow without transfusional support, resulting from:
  - severe homozygous β thalassemia (β thalassemia major)
  - or severe compound heterozygous (severe Hb E/β thalassemia)
  - or severe α thalassemia (α thalassemia major)
- Usually presents before 2 years of age
Non-transfusion-dependent thalassemia syndromes

- Non-transfusion-dependent thalassemia (NTDT) is a group of thalassemias where patients require no or occasional regular red blood cell transfusions \(^1\)\(^-\)\(^4\)

  - May require occasional transfusions for growth failure, pregnancy, infections and other specific situations

\(^1\)Taher AT et al. Br J Haematol 2011;152:512–523; \(^2\)Galanello R & Origa R. Orphanet Journal of Rare Diseases 2010;5:11; 
PATHOPHYSIOLOGY OF β-THAL.

- Chronic anaemia & haemolysis
- Ineffective erythropoiesis
- Iron overload

- Increased erythropoietin synthesis
- Reduced tissue oxygenation
- Increased Iron absorption
- Formation of heme and hemichromes
- Iron-mediated toxicity
- Removal of damaged red cells
- Excess free α-globin chains
- Denaturation Degradation
- Erythroid marrow expansion
- Iron overload
- Splenomegaly
- Skeletal deformities, osteopenia
- Reduced tissue oxygenation
- Increased Iron absorption

Alpha/beta+gamma normal ratio

α globine

β + γ globine
β Thalassemia

γ genes → α2γ2 → Hb F

α genes → α2 β2 → Hb A

increase Hb F

Anemia and hemolysis

Bones → Iron overload → Jaundice → Infections

VDR, ESR1, Collagen → HFE → UGT1 → HLA-DR, TNF, ICAM1

Primary modifiers

Secondary modifiers

Tertiary modifiers
β Thalassemias

α globine

β + γ globine

β^0
β^+
β^{++}
Beta-Thalassemia

- Deletion forms
- Non-deletion forms: point mutations
- Dominant forms
Hemoglobin E (Hb E) syndromes

- Hb E is a result of Glu→Lys mutation at position 26 of β globin chain and can be present in various states
  - Heterozygous (Hb E trait)
  - Homozygous Hb E
  - Compound heterozygous (eg Hb E/β thalassemia)

- Hb E/β thalassemia is associated with a highly variable clinical phenotype

<table>
<thead>
<tr>
<th>Hb E/β thalassemia category</th>
<th>Clinical phenotype</th>
</tr>
</thead>
</table>
| **Mild**                    | • Hb levels between 8 and 12 g/dL  
                              | • Usually do not develop clinically significant problems |
| **Moderately severe**       | • Hb levels between 6 and 7 g/dL  
                              | • Clinical symptoms similar to β thalassemia intermedia |
| **Severe**                  | • Hb level as low as 4 to 6 g/dL  
                              | • Clinical symptoms similar to β thalassemia major |

β Thalassemia

γ genes → α genes → α2γ2 → Hb F

β genes

α genes → α2 β2 → Hb A

increase Hb F

Anemia and hemolysis

Bones → Iron overload → Jaundice → Infections

Primary modifiers

Secondary modifiers

Tertiary modifiers

VDR ESR1 Collagen

HFE

UGT1

HLA-DR TNF ICAM1
β Thalassemias

αααα/αα
ααα/αα
αα/αα
−−/αα
−α/αα

α globine

β + γ globine

β0
β+
β++
β Thalassemias

- $\beta^0$
- $\beta^+$
- $\beta^{++}$

$\alpha$ globine

$\beta + \gamma$ globine

$\gamma$
## Helpful clues to differentiate TM from TI

<table>
<thead>
<tr>
<th></th>
<th>TM more likely</th>
<th>TI more likely</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation (years)</td>
<td>&lt; 2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Hb levels (g/dL)</td>
<td>6–7</td>
<td>8–10</td>
</tr>
<tr>
<td>Liver/spleen</td>
<td>Severe</td>
<td>Moderate to severe</td>
</tr>
</tbody>
</table>

| **Haematologic**     |                |                |
| HbF (%)              | > 50           | 10–50 (may be up to 100%) |
| HbA2 (%)             | < 4            | > 4            |

| **Genetic**          |                |                |
| Parents              | Both carriers of high HbA2 | 1 or both atypical carriers: |
|                      | β -thalassaemia | - high HbF β -thalassaemia |
|                      |                | - borderline HbA2 |

| **Molecular**        |                |                |
| Type of mutation     | Severe         | Mild/silent    |
| Co-inheritance of α-thalassaemia | No | Yes |
| Hereditary persistence of | No | Yes |
| fetal haemoglobin    | No             | Yes            |
| δ δ-thalassaemia     | No             | Yes            |
| Gγ Xmnl polymorphism | No             | Yes            |

Multiple mutations in the $\beta$ globin gene lead to the $\beta$ thalassemias, with $\beta$ thalassemia intermedia having mild-to-moderate clinical severity\(^1\)

- More than 300 known mutations\(^2\)
- Insertions, substitutions or deletions of single nucleotides or small oligonucleotides leading to frameshift\(^3\)
- Range from mild promoter mutations that cause a slight reduction in $\beta$ globin chain production to a complete absence of $\beta$-globin product (mild $\beta^+$, $\beta^+$ or $\beta^0$)\(^4\)
- Deletions of the $\beta$ globin gene are uncommon\(^2\)

\[\begin{align*}
\text{Normal} & \quad \text{Trait} & \quad \text{Major} \\
\text{mild $\beta^+/\beta^N$} & \quad \text{severe $\beta^+/\beta^N$} & \quad \text{mild $\beta^+/\beta^0$} \\
\beta^0/\beta^N & \quad \beta^+\text{severe $\beta^+$} & \quad \beta^0/\beta^0
\end{align*}\]

$\beta$ thalassemia intermedia

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Distinct genetic modifiers can contribute to the phenotypic diversity of β-thalassemia intermedia

- Inheritance of two mutated β genes
  - One severe (β₀ or β⁺) and one mild (mild β⁺) mutations
  - Two mild (mild β⁺) mutations
- Two severe (β₀ or β⁺) mutations plus co-inheritance of α thalassemia or determinants of increased Hb F production
  - Inheritance of one mutated β gene
  - β₀, β⁺ or mild β⁺ plus α duplications
  - Dominantly inherited β thalassemia (inclusion body β thalassemia intermedia)
- Gγ XMN1 polymorphism
- α/β chain ratio
  - Homozygous β₀ + 2–3 α deletion (--/−α)
  - Heterozygous β₀ + extra α genes (ααα/αα)
- Deletions/rearrangement of β cluster
  - δβ thalassemia
  - HPFH
  - Hb Lepore

HPFH, hereditary persistence of fetal hemoglobin

Non-transfusion-dependent thalassemias (NTDT)

β-Thalassaemia major (regularly transfused)

- Silent cerebral ischaemia
- PHT
- Right-sided heart failure
- Extramedullary haemopoietic pseudotumours
- Hepatic fibrosis, cirrhosis, and cancer
- Gallstones
- Splenomegaly
- Osteoporosis
- Venous thrombosis
- Leg ulcers

- Hypothyroidism
- Hypoparathyroidism
- Cardiac siderosis
- Left-sided heart failure
- Hepatic failure
- Viral hepatitis
- Diabetes mellitus
- Hypogonadism
- Osteoporosis

Changing causes of death in TDT

Mortality rates

- Hepatitis C complications
- Other/unknown
- Malignancy
- Infection
- BMT complication
- Anaemia
- Iron overload

Patients, %

1950-1959
1960-1969
1970-1979
1980-1989
1990-1999
2000-2003
This cohort

London

The incidence of myocardial iron overload is decreasing

The proportion of β thalassaemia patients with myocardial iron overload decreased 3-fold in a decade.

Use of modern iron chelation therapy and regular CMR monitoring has dramatically reduced myocardial iron overload-related mortality.

- Baseline (1999/2000)
- Follow-up (≥ 7 years)

<table>
<thead>
<tr>
<th>Category</th>
<th>Baseline (1999/2000)</th>
<th>Follow-up (≥ 7 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-to-moderate iron overload</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>Severe iron overload</td>
<td>17</td>
<td>7</td>
</tr>
</tbody>
</table>

CMR, cardiovascular magnetic resonance

Liver complications are becoming more prominent

The number of deaths due to cardiac problems has decreased, while the number of deaths due to liver disorders has increased over the last decade.
The prevalence of non-cardiac complications is rising

Patients with thalassaemia major are living longer, resulting in an increase in the prevalence of age-related complications

Mortality rates per cohort

Liver involvement in the deaths due to: HCV complications, malignancy (incl. 2 hematomas) and other causes (incl. 3 cases of liver disease)

BMT, bone marrow transplantation; HCV, hepatitis C virus

Adapted from UK Thalassaemia Registry data from Modell B et al.

J Cardiovasc Magn Reson 2008;10:42.Thomas
Disease complications may progress with age, presenting new challenges

- **Long-term disease exacerbates**
  - Hepatic complications
    - Cirrhosis
    - HCC
  - Cardiac complications
    - Pulmonary hypertension
  - Renal dysfunction
  - Endocrine problems
  - Osteoporosis

- **Progression of these complications has a multifactorial pathogenesis**
  - Physiological aging
  - Chronic anemia
  - Chronic haemolysis
  - Iron toxicity
  - Adverse events from the therapy
  - Chronic infections
  - Environmental changes
Treatment for patients with TDT

- Transfusion + chelation
  - transfusion
  - iron chelation therapy
  - supportive management
    - splenectomy
    - infection prophylaxis
    - osteoporosis management
    - viral hepatitis therapy
    - monitoring

- Stem cell transplantation
- Reduction of Ineffective Erythropoiesis (Luspatercept)
- Gene Therapy?
Summary

- Patients with TDT (β-thalassaemia major) require regular transfusions in order to prevent sequelae resulting from anaemia, including growth retardation.

- Patients undergoing chronic blood transfusions develop secondary iron overload that leads to many complications, including cardiopathy, liver pathology, and endocrinopathy.

- Iron chelation results in a decrease in serum ferritin levels, improvement in cardiac function and improvement in liver pathology.
β-Thalassaemia major (regularly transfused)

- Hypothyroidism
- Hypoparathyroidism
- Cardiac siderosis
- Left-sided heart failure
- Hepatic failure
- Viral hepatitis
- Diabetes mellitus
- Hypogonadism
- Osteoporosis

Non-transfusion-dependent thalassemias (NTDT)

- Silent cerebral ischaemia
- PHT
- Right-sided heart failure
- Extramedullary haemopoietic pseudotumours
- Hepatic fibrosis, cirrhosis, and cancer
- Gallstones
- Splenomegaly
- Osteoporosis
- Venous thrombosis
- Leg ulcers

Overview on Practices in Thalassemia Intermedia Management Aiming for Lowering Complication-rates Across a Region of Endemicity: the OPTIMAL CARE study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt; 18</td>
<td>172 (29.5)</td>
</tr>
<tr>
<td>18–35</td>
<td>288 (49.3)</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>124 (21.2)</td>
</tr>
<tr>
<td>Male:female</td>
<td>291 (49.8) : 293 (50.2)</td>
</tr>
<tr>
<td>Splenectomized</td>
<td>325 (55.7)</td>
</tr>
<tr>
<td>Serum ferritin (µg/L)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1,000</td>
<td>376 (64.4)</td>
</tr>
<tr>
<td>1,000–2,500</td>
<td>179 (30.6)</td>
</tr>
<tr>
<td>&gt; 2,500</td>
<td>29 (5)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>134 (22.9)</td>
</tr>
<tr>
<td>EMH</td>
<td>124 (21.2)</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>101 (17.3)</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>100 (17.1)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>82 (14)</td>
</tr>
<tr>
<td>PHT</td>
<td>64 (11)</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>57 (9.8)</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>46 (7.9)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>33 (5.7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25 (4.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (1.7)</td>
</tr>
</tbody>
</table>

Cross-sectional study of 584 β-TI patients from 6 comprehensive care centres in the Middle East and Italy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Frequency n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea</td>
<td>202 (34.6)</td>
</tr>
<tr>
<td>Transfusion</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>139 (23.8)</td>
</tr>
<tr>
<td>Occasional</td>
<td>143 (24.5)</td>
</tr>
<tr>
<td>Regular</td>
<td>302 (51.7)</td>
</tr>
<tr>
<td>Iron chelation</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>248 (42.5)</td>
</tr>
<tr>
<td>Deferoxamine</td>
<td>300 (51.4)</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>12 (2.1)</td>
</tr>
<tr>
<td>Deferiprone + deferoxamine</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>21 (3.6)</td>
</tr>
</tbody>
</table>

EMH, extramedullary haemopoiesis.

## Complications of NTDT

<table>
<thead>
<tr>
<th>Complication</th>
<th>β-TI Lebanon (n = 37)</th>
<th>Italy (n = 63)</th>
<th>β-TM Lebanon (n = 40)</th>
<th>Italy (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>90</td>
<td>67</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>85</td>
<td>68</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Gallstones</td>
<td>55</td>
<td>63</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Extramedullary haemopoiesis</td>
<td>20</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>20</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>28</td>
<td>22</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Cardiopathy(^a)</td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>PHT(^b)</td>
<td>50</td>
<td>17</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Abnormal liver enzymes</td>
<td>20</td>
<td>22</td>
<td>55</td>
<td>68</td>
</tr>
<tr>
<td>HCV infection</td>
<td>7</td>
<td>33</td>
<td>7</td>
<td>98</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>5</td>
<td>3</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>2</td>
<td>12.5</td>
<td>10</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3</td>
<td>2</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

\(^a\)Fractional shortening < 35%.

\(^b\)Defined as pulmonary artery systolic pressure > 30 mmHg; a well-enveloped tricuspid regurgitant jet velocity could be detected in only 20 patients, so frequency was assessed in these patients only.

HCV, hepatitis C virus.

Complications of β-thalassaemia intermedia increase with age

ALF, abnormal liver function; DM, diabetes mellitus; HF, heart failure.

NTDT-related complications: thromboembolic events

- 146 (1.65%) thrombotic events
  - β-TM: 61/6,670 (0.9%)
  - β-TI: 85/2,190 (3.9%)

Risk factors for developing thrombosis in β-TI
- age (> 20 years)
- previous thromboembolic event
- family history
- splenectomy

DVT, deep vein thrombosis; PE, pulmonary embolism; PVT, portal vein thrombosis; SF, serum ferritin; STP, superficial thrombophlebitis.

Serum ferritin underestimates iron burden by MRI in NTDT

LIC values in β-TI were similar to those in β-TM, but serum ferritin levels were significantly lower.


LIC, liver iron concentration.
On multivariate analysis, a 1 mg Fe/g dry wt increase in LIC was significantly associated with higher odds of thrombosis, PHT, hypothyroidism, osteoporosis, and hypogonadism. Adjusted for age, gender, splenectomy status, transfusion history, total haemoglobin level, fetal haemoglobin level, platelet count, nucleated RBC count, and serum ferritin level.

Iron overload and the liver

Several case reports and case series suggest an association between iron overload and hepatocellular carcinoma in hepatitis C-negative patients with β-TI.

Leg ulcers are more common in older than in younger patients.

The skin at the extremities of elderly patients can be thin due to reduced tissue oxygenation; this makes the subcutaneous tissue fragile and increases the risk of lesions.

A role for local iron overload is suggested.

Extramedullary haemopoietic pseudotumours in β-thalassaemia intermedia

- Chronic anaemia and hypoxia
- Increased bone marrow haemopoietic activity and expansion
- Formation of erythropoietic tissue masses around the body
- Symptoms develop due to pressure on surrounding structures
- Spinal cord compression and possible irreversible neurological damage most serious

Management options for NTDT patients

- Splenectomy
- Transfusion therapy
- Hydroxyurea and other fetal haemoglobin inducers
- Iron chelation therapy

Splenectomy in NTDT

- Indicated for increased transfusion demand, hypersplenism, and splenomegaly
- Associated with increased risk of most disease-related complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMH</td>
<td>0.44</td>
<td>0.26–0.73</td>
<td>0.001</td>
</tr>
<tr>
<td>PHT</td>
<td>4.11</td>
<td>1.99–8.47</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>6.59</td>
<td>3.09–14.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>5.19</td>
<td>2.72–9.90</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>4.73</td>
<td>2.72–8.24</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>3.98</td>
<td>1.68–9.39</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6.04</td>
<td>2.03–17.92</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.88</td>
<td>0.99–8.32</td>
<td>0.051</td>
</tr>
</tbody>
</table>

*The OPTIMAL CARE study*

*Splenectomized patients with β-TI: 325/584*
Hydroxyurea treatment in NTDT

- Can increase Hb and decrease transfusion requirement via induction of HbF
- Beneficial effects appear to be transient
- Protective for EMH, PHT, leg ulcers, hypothyroidism, and osteoporosis

The OPTIMAL CARE study*

<table>
<thead>
<tr>
<th>Complication</th>
<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMH</td>
<td>0.52</td>
<td>0.30–0.91</td>
<td>0.022</td>
</tr>
<tr>
<td>PHT</td>
<td>0.42</td>
<td>0.20–0.90</td>
<td>0.025</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>0.10</td>
<td>0.02–0.43</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.05</td>
<td>0.01–0.45</td>
<td>0.003</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.02</td>
<td>0.01–0.09</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>4.32</td>
<td>2.49–7.49</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Patients with β-TI treated with hydroxyurea: 202/584

Iron chelation therapy was protective against PHT, cholelithiasis, and osteoporosis

The OPTIMAL CARE study*

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<th>RR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>0.53</td>
<td>0.29–0.95</td>
<td>0.032</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>0.30</td>
<td>0.18–0.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>2.51</td>
<td>1.48–4.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.40</td>
<td>0.24–0.68</td>
<td>0.001</td>
</tr>
</tbody>
</table>

THALASSA: Deferasirox continues to reduce iron burden over 2 years

**Core study**
- Placebo/deferasirox: median dose = 14.0 mg/kg/day

**Deferasirox extension**
- Median dose = 10.8 mg/kg/day

**Deferasirox core+extension**
- Median dose = 9.5 mg/kg/day

<table>
<thead>
<tr>
<th>Time, months</th>
<th>Deferasirox</th>
<th>Placebo/deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>110</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>94</td>
<td>51</td>
</tr>
<tr>
<td>12</td>
<td>93</td>
<td>51</td>
</tr>
<tr>
<td>18</td>
<td>82</td>
<td>47</td>
</tr>
<tr>
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Proposed Algorithm for Iron Overload Assessment and Chelation Therapy in NTDT

- **NTDT ≥ 10 years** (≥ 15 years in deletional HbH disease)
  - LIC Q 1–2 years
    - SF Q 3 months
  - LIC ≥ 5 mg Fe/g dry wt (SF ≥ 800 µg/L)
    - Yes
    - DFX 10 mg/kg/day
    - LIC Q 6–12 months (SF Q 3 months)
      - LIC ≤ 3 mg Fe/g dry wt (SF ≤ 300 µg/L)
        - Discontinue DFX
    - LIC after 6 months > 7 mg Fe/g dry wt (SF > 1 500–2,000 µg/L) and < 15% decrease from baseline
      - DFX 20 mg/kg/day
  - No

Thank you