Non-transfusion-dependent thalassemia (NTDT)

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Introduction
Spectrum of thalassemia:
Resulting from unbalanced $\alpha/\beta$ chains

**$\alpha$-thalassemias$^1$**
- $\alpha$-thalassemia silent carrier ($\alpha\alpha/\alpha-$)
- $\alpha$-thalassemia trait ($\alpha-/\alpha-$ or $\alpha\alpha/--$)
- Hb Constant Spring (homozygous $\alpha_2$-gene mutation)
- Hb H disease ($\alpha-/--$ or $\alpha\alpha^T/--$)
- Hb Barts-hydrops fetalis ($--/--$)

**$\beta$-thalassemias$^2$**
- $\beta$-thalassemia major
- $\beta$-thalassemia intermedia (TI)
- $\beta$-thalassemia minor
- Silent carrier
- $\beta$-thalassemia with associated Hb anomalies
  - HbC / $\beta$-thalassemia
  - HbE / $\beta$-thalassemia
  - HbS / $\beta$-thalassemia
- Hereditary persistence of fetal Hb and $\beta$-thalassemia

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Transfusion dependency in thalassemia

- **Transfusions seldom required**
  - α-thalassemia trait
  - β-thalassemia minor
  - HbC/β-thalassemia

- **Occasional transfusions required**
  - Mild HbE/β-thalassemia
  - β-thalassemia intermedia

- **Intermittent transfusions required**
  - Deletional HbH
  - Moderate HbE/β-thalassemia

- **Regular, life-long transfusions required**
  - Non-deletional HbH
  - β-thalassemia major
  - Severe HbE/β-thalassemia

Non-transfusion-dependent thalassemias

References:
- *Orphanet J Rare Dis* 2010;5:13;
- *Orphanet J Rare Dis* 2010;5:11;
- *Hematology Am Soc Hematol Educ Program* 2004;14–34
What is NTDT (non-transfusion-dependent thalassemia)?

• NTDT is a group of thalassemias where patients have limited or no requirement for regular blood transfusions
  – May require occasional transfusions for growth failure, pregnancy, infections and other specific situations

• 3 key NTDTs:
  – Hemoglobin H (HbH) disease
  – Hemoglobin E (HbE)/β-thalassemia
  – β-thalassemia intermedia (β-TI)
  – Hemoglobin S β-thalassemia .......... Sickle cell anemia-like
  – Hemoglobin C β-thalassemia .......... Milder

Weatherall DJ. Blood Rev 2012;26S:S3–6
Comparing NTDT with thalassemia major:
Taking β-thalassemia intermedia as an example

<table>
<thead>
<tr>
<th></th>
<th>β-TM more likely</th>
<th>β-TI more likely</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation (yrs)</td>
<td>&lt; 2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Hemoglobin (Hb) levels (g/dL)</td>
<td>6–7</td>
<td>8–10</td>
</tr>
<tr>
<td>Liver/spleen enlargement</td>
<td>Severe</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbF (%)</td>
<td>&gt; 50</td>
<td>10–50 (may be up to 100%)</td>
</tr>
<tr>
<td>HbA₂ (%)</td>
<td>&lt; 4</td>
<td>&gt; 4</td>
</tr>
<tr>
<td><strong>Genetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>Both carriers of high HbA₂ β-thalassemia</td>
<td>1 or both atypical carriers</td>
</tr>
<tr>
<td></td>
<td>High HbF β-thalassemia</td>
<td>Borderline HbA₂</td>
</tr>
<tr>
<td><strong>Molecular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of mutation</td>
<td>Severe</td>
<td>Mild/silent</td>
</tr>
<tr>
<td>Co-inheritance of α-thalassemia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hereditary persistence of HbF</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

TIF. Guidelines for the clinical management of thalassemia, 2nd Ed revised 2008
**Table 2 Characteristics and complications in NTDT patients**

<table>
<thead>
<tr>
<th>Characteristics and complications</th>
<th>β-thalassaemia intermedia</th>
<th>HbE/β-thalassaemia</th>
<th>α-thalassaemia syndromes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting age (years)</td>
<td>Usually &gt;2</td>
<td>Usually &gt;2</td>
<td>Usually &gt;2</td>
</tr>
<tr>
<td>Presenting Hb level (g/dL)</td>
<td>7–10</td>
<td>6 –7 (moderately severe)</td>
<td>8–11</td>
</tr>
<tr>
<td>HbF(%)</td>
<td>3–50, but can be up to 100</td>
<td>3–50, but can be up to 100</td>
<td>Not raised, but HbH (βα) and Hb Barts (γα) present</td>
</tr>
<tr>
<td>HbA2/HbE(%)</td>
<td>&gt;3.5–4</td>
<td>30–40</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Jaundice</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Bone and skeletal abnormalities</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute haemolytic episodes</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Extramedullary haematopoiesis</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PHT</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Viprakasit V, unpublished data.

*α-thalassaemia syndromes include deletional HbH and non-deletional HbH disease.

Frequency of complications are expressed as:

- 0-10%: +
- 10-30%: ++
- 30-60%: +++
- 60-100%: ++++.
Pathophysiology and clinical consequences of NTDT

**Impaired α:β globin ratio**

- Red cell pathology
  - Ineffective erythropoiesis
  - Hemolysis

- Iron overload

- Anaemia
  - Tissue oxygenation
  - Erythroid marrow expansion

- Hypercoagulable state

- Gall stones

**Clinical Consequences**

- Diabetes mellitus
- Growth deficiency
- Hypothyroidism
- Hypoparathyroidism
- Hypogonadism
- Hepatic cancer
- Renal disease

- Leg ulcers
- Thrombotic events
- Pulmonary hypertension

- Bone deformities
- Osteoporosis

- Hepatosplenomegaly
- Extramedullary hematopoietic pseudotumors

TIF. Guidelines for the clinical management of NTDT, 2013
Common Complication of TM & NTDT

TDT | NTDT
---|---
Common complications found in both conditions
- Extramedullary hematopoiesis*
- Splenomegaly*
- Leg ulcers (rare)*
- Growth retardation*
- Skeletal abnormalities*
- Renal abnormalities†
- Iron overload complications
- Jaundice

Additional complications found in NTDT
- Ineffective erythropoiesis*
- Thrombosis*
- Pulmonary hypertension*
- Right heart failure*
- Gallstones*
- Infections*
- Hepatocellular carcinoma
- Folic acid deficiency
- Acute hemolytic episodes

A. Taher Vox Sanguin 2014
Complications in β-TI are different from β-TM:

<table>
<thead>
<tr>
<th>Complication (% of patients affected)</th>
<th>β-TI Lebanon (n=37)</th>
<th>Italy (n=63)</th>
<th>β-TI 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 hematopoiesis</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>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiopathy*</td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Pulmonary hypertension†</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>
Complications of NTDT from “OPTIMAL CARE” study:

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></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><strong>Male:female</strong></td>
<td>291 (49.8) : 293 (50.2)</td>
</tr>
<tr>
<td><strong>Splenectomized</strong></td>
<td>325 (55.7)</td>
</tr>
<tr>
<td><strong>Serum ferritin (ng/mL)</strong></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><strong>Complications</strong></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>Pulmonary hypertension</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>

EMH, extramedullary hematopoiesis

Blood 2010;115:1886–1892
Many complications increase with age

Complications in 120 treatment-naïve patients with β-TI

* Statistically significant trend.

Abbreviations: ALF, abnormal liver function; DM, diabetes mellitus; EMH, extramedullary haematopoiesis; HF, heart failure; PHT, pulmonary hypertension.

Thromboembolic events: β-TI vs. β-TM

- Patients (n=8860) in Mediterranean area and Iran
  - 6670 with β-TM
  - 2190 with β-TI

- Longitudinal FU results

- 146 (1.65%) thrombotic events
  - 61 (0.9%) with β-TM
  - 85 (3.9%) with β-TI

- Risk factors for developing thrombosis in β-TI were:
  - Age (> 20 years)
  - Previous thromboembolic event
  - Family history
  - Splenectomy

DVT, deep vein thrombosis; PE, pulmonary embolism; PVT, portal vein thrombosis; STP, superficial thrombophlebitis

*Thromb Haemost* 2006;96:488–491
Pulmonary hypertension (PHT): Higher incidences in β-TI

- Rate of PHT reported in β-TI are 22-59%
- Comparative study on 131 β-TM (iron-chelated) vs 74 β-TI (not chelated)
  By echocardiogram
  CHF rate 3.8% vs 2.7%
  LV dysfunction rate 8.4% vs 0%
  PHT rate is high for β-TI, in all age group

<table>
<thead>
<tr>
<th>Variables</th>
<th>≤ 25 yr</th>
<th>&gt; 25 yr</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricuspid gradient, mm Hg</td>
<td>22.9 ± 4.9</td>
<td>27.3 ± 7.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Pulmonary acceleration time, ms</td>
<td>128.8 ± 16.9</td>
<td>116.8 ± 22.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>17.6 ± 6.1</td>
<td>22.3 ± 8.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Total pulmonary vascular resistance, dyne · s · cm$^{-5}$</td>
<td>234.3 ± 119.1</td>
<td>380.9 ± 225.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Increased systolic pulmonary artery pressure†</td>
<td>1 (2.3)</td>
<td>13 (43.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Considerable pulmonary hypertension‡</td>
<td>0 (0)</td>
<td>4 (13.3)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Chest 2005;127:1523–1530
Blood 2001;97:3411–3416
Pediatr Hematol Oncol 2011;28:497–508
Pediatr Cardiol 2011;32:154–159
Hepatic cancer: Potentially linked but not confirmed

Hepatocellular carcinoma in thalassemia

Patients are living longer, hence more likely to develop HCC

Iron overload is often under-recognised and under-treated

β-TI patients may be at higher risk of developing HCC than β-TM patients

Why are we now discussing HCC in β-TI patients?

Patients are living longer, hence more likely to develop HCC

Iron overload is often under-recognised and under-treated

β-TI patients may be at higher risk of developing HCC than β-TM patients

Patients are diagnosed and started on transfusion therapy later in life, resulting in increased risk of developing chronic hepatitis, leading to end-stage liver disease if infected with HCV

References:

1. Haematologica 2004;89:1187–1193;
Health-related-QoL (HR-QoL): β-TI is worse than β-TM patients !(?)

• 32 β-TI vs 48 β-TM in Lebanon, single center

*P<0.05
Conclusions

• NTDT is NOT JUST a milder form of thalassemia major.
  – High clinical variabilities
  – Different clinical sequelae
  – HR-QoL can be worse!

• A different management is required for these patients.
Diagnosis
Diagnosis Workups

Figure 2: Diagnostic algorithm for NTDT. *α-thalassaemia traits and related disorders include δ² and δ⁴⁺-thalassaemia by deletions and non-deletional α-thalassaemia mutations. †There are two main types of HbH disease: 1) deletional HbH due to deletions (-α) and; 2) non-deletional HbH disease caused by δ²-thalassaemia and non-deletional mutation (-/αTq). ‡The common disorders associated with Hb variants include homozygous HbE, HbE/βthalassaemia and HbE with other variants such as HbE/Hbs or HbE/HbC or HbE/HbD, HbS (Sickle), Hbs/β-thalassaemia, homozygous HbC and HbC/βthalassaemia. These diagnoses can be confirmed using appropriate globin genotyping.
Clinic Follow Up

• History
• Physical Examination
• Laboratory studies
• Image Studies
History

- LMP/Menopause
- Splenectomy
- Renal stone
- Gallbladder stone
- Bone fracture, cause
- Transfusion history: never occasional regular
- Medication history: hydroxyurea, folate, iron chelation therapy
- Hepatitis B/C history
- HBV vaccination
- Thromboembolic event: VTE, CVA
- Heart failure symptoms: NYHA Congestive Heart Failure classification
- Arrhythmia
- Otitis media
- Chronic sinusitis
- back pain
Physical exam

- Dental malocclusion
- Bone change (Cooley face)
- Hepatomegaly (below costal margin)
- Splenomegaly (below costal margin)
- Leg ulcer
- Heart failure sign
Laboratory studies

- CBC+DC reticulocyte normoblast
- Alb Bil (T/D) GOT GPT ALP rGT Cre uric acid
- Na K Ca P
- AC sugar
- Ferritin
- HBV/HCV profiles: anti-HBs Ab, anti-HBc Ab, HBsAg, anti-HCV Ab if no previous results
- TSH, T4
- FSH LH E2/testosterone for hypogonadism
- EKG
## Image studies

<table>
<thead>
<tr>
<th>Image study</th>
<th>Indication</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X ray</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal echo</td>
<td>Jaundice, hepatosplenomegaly</td>
<td>1 year</td>
</tr>
<tr>
<td>Cardioechography for LVEF and TRV</td>
<td>Heart failure sign</td>
<td>1 year</td>
</tr>
<tr>
<td>Spine X ray</td>
<td>Back pain</td>
<td></td>
</tr>
<tr>
<td>DEXA</td>
<td>osteoporosis</td>
<td></td>
</tr>
<tr>
<td>Bone age</td>
<td>growth delay</td>
<td></td>
</tr>
<tr>
<td>MRI liver R2</td>
<td>optional</td>
<td>1 year</td>
</tr>
</tbody>
</table>
General and Specific Treatment
Practical Recommendation

CONSIDER SPLENECTOMY
- Worsening anemia leading to poor growth and development
  - When transfusion therapy is not possible or iron chelation therapy is unavailable
- Hypersplenism
  - Leading to worsening anemia, leucopenia or thrombocytopenia and causing clinical problems such as recurrent bacterial infections or bleeding
- Splenomegaly
  - Accompanied by symptoms such as left upper quadrant pain or early satiety
  - Massive splenomegaly (largest dimension >20 cm) with concern about possible splenic rupture

CONSIDER HYDROXYUREA
- β-Thalassemia intermedia homozygous for the Xmn1 polymorphism
  - Patients with Lepore or δβ-thalassemia
  - Patients for which a transfusion course is required but are alloimmunized
  - Patients with the following clinical morbidities
    - Pulmonary hypertension
    - Extramedullary hematopoietic pseudotumors
    - Leg ulcers

Older than 5 years

Characteristics or complications

Evaluate response (if yes, hemoglobin, function, quality of life, complications)
Monitor safety

FOLLOW UP AND CLOSE OBSERVATION

Acute stress
- Hemoglobin decline <5 g/dl
- Surgery
- Infection
- Pregnancy

Progressive changes from childhood
- Persistently severely low or declining hemoglobin level in parallel with profound enlargement of the spleen (at a rate exceeding 3 cm/year in periods of maximal growth and development)
- Growth failure (height is more indicative of growth pattern than weight)
- Poor performance at school
- Diminished exercise tolerance
- Failure of secondary sexual development in parallel with bone age
- Signs of bony changes
- Declining quality of life

Complications
- Thrombotic or cerebrovascular disease
- Pulmonary hypertension with or without secondary heart failure
- Extramedullary hematopoietic pseudotumors
- Leg ulcers
- Frequent hemolytic crisis (hemoglobin H disease)

Discontinue when outcome achieved
Observe for alloimmunization and iron overload

CONSIDER TAILORED TRANSFUSION THERAPY
Outlines

- General care
  - Transfusion
  - Splenectomy
  - Iron Overload Assessment and Management

- Managing specific complications
  - Thrombosis, PHT, liver problems, leg ulcer, and others
Transfusion
Pathophysiology and clinical consequences of NTDT

Impaired α:β globin ratio

Red cell pathology

Ineffective erythropoiesis  Hemolysis  Gall stones

Iron overload  Anaemia  Tissue oxygenation  Erythroid marrow expansion  Hypercoagulable state

- Diabetes mellitus
- Growth deficiency
- Hypothyroidism
- Hypoparathyroidism
- Hypogonadism
- Hepatic cancer
- Renal disease

- Leg ulcers
- Thrombotic events
- Pulmonary hypertension

- Bone deformities
- Osteoporosis

- Hepatosplenomegaly
- Extramedullary hematopoietic pseudotumors

TIF. Guidelines for the clinical management of NTDT, 2013
Transfusion reduced the risk of thromboembolism:

• For β-TI cases in OPTIMAL CARE study:

Iron chelation
Hydroxyurea
Transfusion
Splenectomy
SF ≥ 1000 ng/mL
Hb ≥ 9 g/dL
Female
Age > 35 years

Adjusted odds ratio for thrombosis

SF, serum ferritin

1Musallam KM, Taher AT. Hemoglobin 2011;35:503–510
Transfusion naivety is associated with PHT:

- OPTIMAL CARE cohort
- Case-control study for β-TI (age and sex matched, by echo, no LV disease)
- N=64 for Gr I (PHT+) and GR II (PHT-)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group II Referent</th>
<th>Group I AOR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomized</td>
<td>1.00</td>
<td>4.90</td>
<td>1.90–8.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nucleated red blood cell count</td>
<td>1.00</td>
<td>2.59</td>
<td>1.69–6.05</td>
<td>0.010</td>
</tr>
<tr>
<td>≥300×10^6/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenectomized</td>
<td>1.00</td>
<td>3.21</td>
<td>1.29–6.55</td>
<td>0.007</td>
</tr>
<tr>
<td>Non-splenectomized</td>
<td>1.00</td>
<td>1.13</td>
<td>1.09–2.05</td>
<td>0.047</td>
</tr>
<tr>
<td>Previous thromboembolic events</td>
<td>1.00</td>
<td>3.69</td>
<td>2.38–7.05</td>
<td>0.020</td>
</tr>
<tr>
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</table>

AOR, adjusted odds ratio

Transfusion therapy may be protective for other complications:

<table>
<thead>
<tr>
<th>Complication</th>
<th>Parameter</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Leg ulcers</td>
<td>Age &gt; 35 years</td>
<td>2.09</td>
<td>1.05–4.16</td>
<td>0.036</td>
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<tr>
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<td>Splenectomy</td>
<td>3.98</td>
<td>1.68–9.39</td>
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<td></td>
<td><strong>Transfusion</strong></td>
<td><strong>0.39</strong></td>
<td><strong>0.20–0.76</strong></td>
<td><strong>0.006</strong></td>
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<td>Hydroxyurea</td>
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<td>Serum ferritin ≥ 1,000 µg/L</td>
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<td>1.48–4.26</td>
<td>0.001</td>
</tr>
</tbody>
</table>

In the OPTIMAL CARE study, 445/584 patients had transfusions

Recommendation (1):

- No prospective evaluation about the role of transfusion in NTDT now.

- Transfusion requirement of NTDT patients should not be determined solely by Hb level, but will be tailored individually by activities, growth/development requirement, patients’ willing, and so on.

- More frequent transfusion will be considered in:
  - Growth failure or signs of bone change
  - Poor performance at school
  - Diminished exercise tolerance or poor QoL
  - Frequent hemolytic crisis
Recommendation (2):

- Transfusion can be used as 2nd-prevention of 1st-prevention in high-risk patients for the following complications:
  - Thrombotic events
  - PHT
  - Pseudotumor formation (extramedullary hematopoiesis)
  - Leg ulcers

- The complications of transfusion, such as allo-immunization, infection or iron overload, should be carefully monitored in NTDT patients.
Splenectomy
Splenectomy is associated with thromboembolism:

- For β-TI cases in OPTIMAL CARE study:

<table>
<thead>
<tr>
<th>Adjusted odds ratio for thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron chelation</td>
</tr>
<tr>
<td>0.97</td>
</tr>
<tr>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>0.56</td>
</tr>
<tr>
<td>Transfusion</td>
</tr>
<tr>
<td>0.28</td>
</tr>
<tr>
<td>Splenectomy</td>
</tr>
<tr>
<td>6.59</td>
</tr>
<tr>
<td>SF ≥ 1000 ng/mL</td>
</tr>
<tr>
<td>1.86</td>
</tr>
<tr>
<td>Hb ≥ 9 g/dL</td>
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<td>0.41</td>
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<tr>
<td>Female</td>
</tr>
<tr>
<td>1.27</td>
</tr>
<tr>
<td>Age &gt; 35 years</td>
</tr>
<tr>
<td>2.59</td>
</tr>
</tbody>
</table>

SF, serum ferritin

1Musallam KM, Taher AT. *Hemoglobin* 2011;35:503–510
Splenectomy is associated with increased PHT:

- OPTIMAL CARE cohort
- Case-control study for β-TI (age and sex matched, by echo, no LV disease)
- N=64 for Gr I (PHT+) and GR II (PHT-)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group II Referent</th>
<th>Group I AOR</th>
<th>95% CI</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Splenectomized</td>
<td>1.00</td>
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<tr>
<td>Nucleated red blood cell count ≥ 300 × 10⁶/l</td>
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<td>2.59</td>
<td>1.69–6.05</td>
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<tr>
<td>Previous thromboembolic events</td>
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<td>2.38–7.05</td>
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AOR, adjusted odds ratio

Splenectomy is associated with increased risk of other complications:

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In the OPTIMAL CARE study, 325/584 patients had splenectomy

Recommendation (1): Indications

- Splenectomy should be generally avoided in patients under the age of 5.

- Due to observed association with various complications in NTDT patients, splenectomy should be reserved in:
  - Worsening anemia leading to poor growth/development, when frequent transfusion is not possible.
  - Hypersplenism with leukopenia or thrombocytopenia, leading to frequent bleeding or infection complications
  - Massive splenomegaly, with symptoms or concerns on splenic rupture

- More frequent transfusion will be considered in:
  - Growth failure or signs of bone change
  - Poor performance at school
  - Diminished exercise tolerance or poor QoL
  - Frequent hemolytic crisis
Recommendation (2):

- Laparoscopic procedure is preferred to the open one, unless otherwise indicated by the responsible surgeon.

- Post-splenectomy sepsis is a risk with concern, therefore a detailed evaluation should be done for febrile splenectomized NTDT patients.

- The following vaccination will be helpful in splenectomized NTDT patients:
  - Pneumococcal vaccine (23-valent polysaccharide)
  - H. influenzae vaccine
  - Meningococcal polysaccharide vaccine (?)
Iron Overload Assessment and Management
Serum ferritin increases with age in patients with NTDT

Increased GI absorption of iron
(primary source of iron)
• Ineffective erythropoiesis

Episodic transfusion
(secondary source of iron)
• Surgeries
• Pregnancy
• Infections

OPTIMAL CARE cohort:
Age versus serum ferritin level
(R=0.653; P<0.001)

Iron overload is present in HbH, HbE/β-thalassemia and β-TI

1Br J Haematol 2010;150:486–489;
4Blood 2004;104:1504–1510
LIC is correlated with morbidity in β-TI.

- Cross-sectional study for β-TI
- N=168, in Lebanon and Italy
- LIC by MRI

*Haematologica*. 2011;96:1605–1612
Rationales for using LIC 5mg/g dw as the cutting point for iron chelation:

Am J Hematol 2010;85:288–290
ICT is protective for PHT, hypogonadism, osteoporosis and cholelithiasis:

<table>
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<tr>
<th>Complication</th>
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<th>P-value</th>
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</thead>
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<td>Transfusion</td>
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<td>Cholelithiasis</td>
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<td>1.56–4.87</td>
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</tr>
</tbody>
</table>

Investigational use of deferasirox versus placebo: THALASSA study design

Efficacy and safety of deferasirox versus placebo in NTDT patients

Inclusion
- Male/female
- Aged ≥10 years with NTDT
- LIC ≥5 mg Fe/g dw
- Serum ferritin >300 ng/mL

Exclusion
- Regular transfusion requirement
- Chelation therapy prior to entry
- HbS thalassemia variants
- Impaired renal/liver function

Change in LIC from baseline after 1 year of treatment compared with placebo-treated patients

Blood 2011;118(21);abst 902; Blood 2012 epub ahead of print
Effect of deferasirox in THALASSA
Recommendations of ICT in NTDT by TIF 2013 guidelines

1. **NTDT ≥ 10 YEARS** *(≥15 years in deletional hemoglobin H disease)*
   - LIC Q 1-2 years
   - SF Q 3 months
   - LIC ≥5
     - (SF ≥800)

2. **Yes**
   - DFX
     - 10 mg/kg/day

3. **No**
   - LIC Q 6-12 months
     - (SF Q 3 months)

4. **LIC ≤3** *(SF ≤300)*
   - Discontinue DFX

5. **LIC ≥5** *(SF ≥800)*
   - LIC after 6 months >7
     - (SF >1500-2000) and <15% decrease from baseline
     - DFX
     - 20 mg/kg/day

---

TIF. Guidelines for the clinical management of NTDT, 2013
Practical Recommendation in Iron Overload Assessment and Management

NTDT in patients ≥10 years (≥15 years for deletional HbH)

- SF ≥800 ng/ml
- SF ≤300 ng/ml

SF >300 to <800 ng/ml

- Q1 yr MRI
- LIC <5 mg/g
- LIC ≥5 mg/g
- Other measures supportive of iron overload state
- MRI unavailable
- No other measure supportive of iron overload

Initiate iron chelation therapy with Deferasiroxat 10 mg/kg/d
Monitor LIC Q6-12 mo or SF Q3 mo
Escalate dose to 20 mg/kg/d after 6 months if LIC >7 mg/g or SF >1500-2000 ng/ml
Interrupt dose if LIC is 3 mg/g or SF is 300 ng/ml and monitor LIC Q1-2 yr or SF Q3 mo

Ali Taher Drug 2014
Recommendation:

- Regular monitoring of body iron contents is suggested in NTDT patients
  - Serum ferritin every 3 months
  - Liver iron contents (by MRI or biopsy) if indicated
- Iron chelation therapy can effectively reduce body iron contents in NTDT patients, especially with deferasirox:
  - Both LIC and serum ferritin can be reduced
  - The initiation of ICT is suggested to be 5 mg/g dw (LIC) or 800 ng/ml (serum ferritin)
  - The initial dose of DFX is 10 mg/Kg/d, and can be escalated to 20 mg/Kg/d
- ICT may be protective against some complications in NTDT, but its impact on survival are uncertain and require further investigation
Managing specific complications
Thrombosis, PHT, liver problems, leg ulcer, and others
Thrombosis: Pathophysiology

- **Transfusion**
  - Pathological RBC
    - ↑ Thrombin generation (phosphatidyl serine exposure)
    - ↑ Rigidito, deformability, and aggregation
  - >> Circulating microparticles
  - ↓ Antithrombin III
  - ↓ Protein C
  - ↓ Protein S

- **Splenectomy**
  - Endothelial injury
    - Expression of adhesion molecules and tissue factor
  - ↑ Circulating microparticles

- **Iron overload**
  - Platelet abnormalities
    - Thrombocytosis
    - Chronic activation
    - ↑ Adhesion and aggregation
  - Endocrine & hepatic dysfunction
  - ? ↑ Atherosclerosis

TIF. Guidelines for the clinical management of NTDT, 2013
Thrombosis: High-risk patients

- β-thalassemia intermediate
- Adults
- Post-splenectomy
- Transfusion-naive
- High PLT count (>500K/uL)
- High nucleated RBCs (>300/uL)
- Hb < 9 gm/dL

- Hx of PHT
- Iron overload
- Pregnant
- FHx of thrombosis
- Other conventional risk factors for thrombosis
Thrombosis:

• No clinical trials available about prophylactic interventions for thrombosis in NTDT

• Aspirin for high-PLT, splenectomized pts
• Awareness of thrombosis and early intervention are encouraged
• Conventional thrombotic risk factors should be controlled if presented
• No evidences now for fetal hemoglobin induction or iron chelation on thrombosis
### Risk factors for PHT

- OPTIMAL CARE cohort
- Case-control study for β-TI (age and sex matched, by echo, no LV disease)
- N=64 for Gr I (PHT+) and GR II (PHT-)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group II Referent</th>
<th>Group I AOR</th>
<th>95% CI</th>
<th>P-value</th>
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<td>1.00</td>
<td>4.90</td>
<td>1.90–8.50</td>
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<td>2.26</td>
<td>1.33–3.67</td>
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</table>

AOR, adjusted odds ratio
Pulmonary hypertension (PHT):

- Risk groups as thrombosis
- Routine echocardiography exam suggested in high-risk patients
  - TRV (TV regurgitant jet velocity) >2.5 m/s: possible
  - TRV >2.5 m/s, symptomatic or with other echo criteria: likely
  - TRV > 3.2 m/s: likely
- For “possible”, “likely” or confirmed PHT, the following treatment will be considered:
  - Blood transfusion
  - Hydroxyurea
  - Anti-coagulants
  - ICT
  - PHT-specific treatment
Hepatic cancer: Potentially linked but not confirmed

Hepatocellular carcinoma in thalassemia

- Patients are living longer, hence more likely to develop HCC\(^1\)
- Iron overload is often under-recognised and under-treated\(^2\)
- Patients are diagnosed and started on transfusion therapy later in life, resulting in increased risk of developing chronic hepatitis, leading to end-stage liver disease if infected with HCV\(^3\)
- \(\beta\)-TI patients may be at higher risk of developing HCC than \(\beta\)-TM patients\(^{3,4}\)

Liver problems:

- In NTDT patients, the following liver-related complications should be paid attention to:
  - Hepatitis (iron, virus)
  - Liver cirrhosis
  - HCC
  - GB problems

- Vaccination against HBV/HAV if acceptable
- Regular FU of liver functions, AFP or sonography is recommended.
Leg ulcers:

• No evidences for prophylactic intervention

• Awareness on physical exam
• Keeping leg raised may be beneficial
• Topical management, in collaboration with plastic surgeons/dermatologists

• Treatment opinions
  – Blood transfusion
  – Hydroxyurea
  – Vasodilators
  – Oxygen chamber
  – Graft
Other problems:

• Extramedullary hematopoiesis:
  – Spinal cord compression by pseudotumors are potential complications for NTDT patients and should be aware.

• Endocrinopathy
  – Endocrine functions can be surveyed in NTDT pt >10y/o
  – Bone mineral density can be tested. If osteoporosis is presented, specific management is required.

• Pregnancy
  – High-risk, consultation required
  – FU for maternal liver/heart/Hb/endocrine status, fetal growth is important.
  – Low-dose anti-coagulants is encouraged?