Non-transfusion-dependent thalassemia (NTDT)

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Introduction
Transfusion dependency in thalassemia

- **Transfusions seldom required**: α-thalassemia trait, β-thalassemia minor, HbC/β-thalassemia
- **Occasional transfusions required**: Mild HbE/β-thalassemia
- **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;5:11
- Orphanet J Rare Dis 2010;5:13
- 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
<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 (β₄) and Hb Barts (γ₄) 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%: ++++.
Common Complication of TM & NTDT

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

- NTDT
  - 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
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.

Diagnosis
Diagnosis Workups

Figure 2 Diagnostic algorithm for NTDT. *α-thalassaemia traits and related disorders include d0 and α-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 δ-thalassaemia and non-deletional mutation (-/αT). ‡The common disorders associated with Hb variants include homozygous HbE, HbE/β-thalassaemia and HbE with other variants such as HbE/Hbs or HbE/HbC or HbE/HbD, HbS (Sickle), Hbs/β-thalassaemia, homozygous HbC and HbC/β-thalassaemia. 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>Year</th>
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<tbody>
<tr>
<td>Chest X-ray</td>
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<td></td>
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<tr>
<td>Abdominal echo</td>
<td>Jaundice, hepatosplenomegaly</td>
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<tr>
<td>Cardioechography for LVEF and TRV</td>
<td>Heart failure sign</td>
<td>1</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>
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</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 αβ-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

Characteristics or complications
- Evaluate response Q6 months (hemoglobin, function, quality of life, complications)
- Monitor safety

Older than 5 years

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)

Consider tailored transfusion therapy

Discontinue when outcome achieved
- Observe for alloimmunization and iron overload
Outlines

• General care
  – Transfusion
  – Splenectomy
  – Iron Overload Assessment and Management

• Managing specific complications
  – Thrombosis, PHT, liver problems, leg ulcer, and others
Transfusion
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
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
Recommendations of ICT in NTDT by TIF 2013 guidelines

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 Q3 mo
  - SF ≥800 ng/ml
  - SF ≤300 ng/ml
- SF >300 to <800 ng/ml
  - MRI
    - LIC <5 mg/g
    - LIC ≥5 mg/g
  - MRI unavailable
    - Other measures supportive of iron overload state
    - 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: 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
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
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?