General insights and current management of Thalassemia Intermedia

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Disclosures

- Novartis advisory board
- Celgene advisory board
- Sanofi advisory board
- Shire advisory board
Established and emerging management options

- Transfusion
- Modulator of HbF
- Iron chelation therapy
- Splenectomy
- Vitamins and supplements
- Targeting ineffective erythropoiesis
- Stem cell transplantation
- Gene therapy
Management of NTDT patients is a continuous lifelong cycle

1. Understand the pathophysiology of NTDT*
2. Recognize and manage possible complications†
3. Correct the factors that lead to complications
   - Anemia
     - Transfusion therapy
     - Hydroxyurea and other Hb F inducers
     - Exploratory molecules targeting ineffective erythropoiesis
   - Iron overload
     - Iron chelation therapy
       - Splenectomy
       - Vitamins and supplements
4. Investigate curative treatment strategies

Hb, hemoglobin
Screening and disease prevention programs are being implemented worldwide resulting in decreased incidence of thalassemia

Iran:

Sardinia:
Rate declined from 1/250 to 1/4000 births

Lebanon:
20 cases/year for 8 years before 1994; reduced to 5.5 cases/year during 2006–2011

Turkey:
Number of affected births declined from 272 in 2002, to 23 in 2008 (90% reduction)

Saudi Arabia:
Prevalence decreased from 32.9 to 9.0/1000

Global prevention strategies are being implemented

Early recognition of disease type via screening is vital in order for appropriate management strategies to be applied

• To prevent placing children on life-long transfusion therapy it is essential to recognize the disease type early

• Diagnosis of NTDT remains largely a clinical decision

• Screening families in high frequency areas offers clinical value by allowing prenatal advice to be given

• Screening protocol uses complete blood cell count with erythrocyte indices using an automated blood cell counter

  • Patients with low MCV (<80 fl) and MCH (<27 pg) are usually investigated further using electrophoresis, HPLC or DNA analysis to identify thalassemia type


HPLC, high-performance liquid chromatography
MCV, mean corpuscular volume;
MCH, mean corpuscular hemoglobin
Before embarking on any treatment modality, observation and careful follow-up is crucial

Assess the patient carefully over the first few months after a diagnosis is established

Do not embark on any treatment modality, especially transfusion therapy, too hurriedly

Consider the patient’s wellbeing, particularly activity, growth, development and early appearance of skeletal changes or other disease complications

1. Taher A et al. Guidelines for the management of NTDT. 2013;TIF Publication No. 19;
In addition to treating the disease, complications should be managed appropriately.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Management options</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>• Sildenafil citrate, bosentan (favorable effects in small studies)</td>
</tr>
</tbody>
</table>
| Extramedullary hematopoietic pseudotumors | • Radiation  
• Surgery  
• Hydroxyurea                                      |
| Bone disease                          | • Ca\(^{2+}\), vitamin D, other preventive measures  
• Bisphosphonates (?)  
• Treat other endocrinopathies                     |
| Endocrinopathies                      | • Hormonal therapy as with β thalassemia major                                      |
| Thrombosis and cerebrovascular disease | • Antiplatelets, anticoagulants (no clinical trials)  
• Risk-assessment models                           |
| Leg ulcers                            | • Hypertransfusion  
• Topical growth factors                                                             |
| Hepatic complications                 | • Iron chelation  
• Antiviral therapy for hepatitis infection                                           |
| Gallstones                            | • Removal of gallbladder during splenectomy                                         |

PHT, pulmonary hypertension

Established management options: management of anemia

Transfusion
Indications for transfusion are based on relative or absolute requirements

- Growth failure or poor school performance
- Transient stressful conditions (pregnancy, infection, pre-operative)
- Symptomatic anemia
- Symptomatic splenic enlargement
- Congestive heart failure (± PHT)
- Leg ulcers
- Emergence of bone deformities
- Symptomatic EMH

Established management options: management of anemia

Modulators of Hb F
Elevations in Hb F ameliorate morbidity in NTDT

63 untransfused patients with β thalassemia intermedia

Hydroxyurea can increase Hb and decrease transfusion requirement via induction of Hb F

• Experience from Iran and India$^{1–3}$
  • Patients on transfusions reported to become transfusion-independent
  • Hb concentration increased in NTDT

• Experience from Europe$^4$
  • Constant increase of the erythrocyte volume and in Hb F, but only a modest effect on total Hb concentration
  • Italy → loss of response observed in 8/17 patients over long term$^4$
    - 17/24 responders
    - Mean Hb increase: 1.5 g/dL (up to 4 g/dL)

The majority of evidence for modulators of Hb F in NTDT is based on hydroxyurea

• Hydroxyurea is generally well tolerated; although myelosuppression can be observed at high doses

• NTDT patients show increases in Hb of 0.5 to 2.5 g/dL with hydroxyurea treatment; however, beneficial effects may be transient and attenuate in the long term

• Optimal dosing of hydroxyurea, duration of treatment and predictors of response in NTDT are still controversial

• Effects beyond Hb F induction have been noted (eg hypercoagulability)
  • Results from the OPTIMAL CARE study show that hydroxyurea may be protective for EMH, PHT, leg ulcers, hypothyroidism and osteoporosis

Other modulators of Hb F are available but still under clinical evaluation for NTDT

<table>
<thead>
<tr>
<th></th>
<th>Azacitidine</th>
<th>Decitabine</th>
<th>Short-chain fatty acids</th>
<th>Erythropoietic-stimulating agents</th>
<th>Thalidomide and derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological responses</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Well tolerated</td>
<td>–</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Favorable effects on red cell indices</td>
<td>–</td>
<td>✓</td>
<td>✓</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Favorable effects on clinical morbidities</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Established management options

Iron chelation therapy
At-risk NTDT patients who are not transfused and not treated have the greatest risk of complications


<table>
<thead>
<tr>
<th>Hydroxyurea</th>
<th>Transfusion</th>
<th>Iron chelation</th>
<th>Mean number of complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>0.83</td>
</tr>
<tr>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>1.31</td>
</tr>
<tr>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>1.30</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>2.00</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>0.85</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>N</td>
<td>2.02</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>N</td>
<td>1.54</td>
</tr>
</tbody>
</table>

n=584
Patients with NTDT should be assessed for iron overload and chelated when appropriate.

- **NTDT ≥10 years (≥15 years in deletional Hb H disease)**
  - LIC every 1–2 years
  - SF every 3 months
  - LIC ≥ 5 mg Fe/g dw (SF ≥800 ng/mL)
    - Yes
    - Deferasirox 10 mg/kg/day
    - LIC ≤3 mg Fe/g dw (SF ≤300 ng/mL)
      - Discontinue deferasirox
    - LIC after 6 months >7 mg Fe/g dw (SF >1500–2000 ng/mL) and <15% decrease from baseline
      - Deferasirox 20 mg/kg/day
  - No

- **LIC every 6–12 months (SF every 3 months)**
  - LIC ≤3 mg Fe/g dw (SF ≤300 ng/mL)
    - Discontinue deferasirox
  - LIC after 6 months >7 mg Fe/g dw (SF >1500–2000 ng/mL) and <15% decrease from baseline
    - Deferasirox 20 mg/kg/day

**Taher A et al. Guidelines for the management of NTDT. 2013; TIF Publication No. 19.**

dw, dry weight; LIC, liver iron concentration; SF, serum ferritin
Established management options

Splenectomy
Splenectomy should not be the first management option if others are available

Splenectomy should be reserved for cases of:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening anemia leading to poor growth and development</td>
<td>When transfusion therapy is not possible or iron chelation therapy is unavailable</td>
</tr>
<tr>
<td>Hypersplenism</td>
<td>Leukopenia or thrombocytopenia causing clinical problems such as recurrent bacterial infection or bleeding</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Accompanied by symptoms such as left-upper-quadrant pain or early satiety. Massive splenomegaly (largest dimension &gt;20 cm) with concern about possible splenic rupture</td>
</tr>
</tbody>
</table>

1. Taher A et al. Guidelines for the management of NTDT. 2013;TIF Publication No. 19;
# Increased hypercoagulability and infection are significant adverse outcomes following splenectomy in NTDT

<table>
<thead>
<tr>
<th>Hypercoagulable state (abnormal platelets and RBCs)</th>
<th>Infection</th>
</tr>
</thead>
</table>
| • RBCs may be interacting with activated platelets, thus increasing the risk of thrombosis  
  - Venous thromboembolism  
  - PHT  
  - Leg ulcers  
  - Silent cerebral infarction | • May rapidly progress to hypotensive shock and disseminated intravascular coagulation with high mortality  
  • 10-year follow-up of 221 splenectomised patients, six died of sepsis ➔ No need to ‘wait and see’ in such patients with fever  
  • Particularly high risk in patients under 5 years of age ➔ not generally recommended  
  • More severe malaria |

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RBC, red blood cell

1. Taher A et al. Guidelines for the management of NTDT. 2013;TIF Publication No. 19;  
Splenectomy leads to increased thrombotic risk in NTDT

In patients already splenectomised, those at high risk of thrombosis may be identified early by their high nucleated RBC and platelet counts, evidence of PHT, and transfusion naïvety.

Adjusted odds ratio for thrombosis

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

Adjusted odds ratio: 0.97, 0.56, 0.28, 0.41, 1.86, 0.56, 0.97, 6.59

Splenectomy may also lead to increased risk of many disease-related complications in NTDT

OPTIMAL CARE study
spleenectomised patients: 325/584¹

<table>
<thead>
<tr>
<th>Complication</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMH</td>
<td>0.44</td>
<td>0.001</td>
</tr>
<tr>
<td>PHT</td>
<td>4.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>6.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>5.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>4.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>3.98</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6.04</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.88</td>
<td>0.051</td>
</tr>
</tbody>
</table>

Several other factors need consideration in NTDT patients who undergo splenectomy

**Recommended vaccinations**
- Pneumococcal 23-valent polysaccharide
- *Haemophilus influenzae*
- Meningococcal polysaccharide
- Influenza vaccine

**Splenectomised patients should receive prophylactic antibiotic therapy for at least 2 years or until 5 years of age. May be life-long**

**Febrile episodes should be promptly evaluated and treated**

**Aspirin should be considered when platelet count ≥500x10⁹/L**

1. Taher A et al. Guidelines for the management of NTDT. 2013;TIF Publication No. 19;
Established management options

Vitamins and supplements
Antioxidants and vitamin supplements may improve NTDT patient outcomes

• Oxidative damage is one of the main contributors to cell injury in thalassemia patients

• Small studies reported promising roles of vitamin E, N-acetylcysteine and other compounds of plant origin

• Folic acid supplementation is also recommended

• Zinc levels have been found to be low in NTDT, but the benefit of supplementation has not been elucidated

Established management options: Summary

- **Transfusions**
  - Indicated for severe anemia, growth failure, skeletal deformity, exercise intolerance, decline in Hb due to progressive splenomegaly, infection, pregnancy and other disease-specific complications

- **Iron chelation therapy**
  - Recommended in patients with iron overload as assessed by LIC >5 mg Fe/g dw or serum ferritin >800 ng/mL

- **Hydroxyurea**
  - Can increase Hb and decrease transfusion requirement via induction of Hb F
  - Beneficial effects appear to be transient

- **Splenectomy**
  - Indicated for increased transfusion demand, hypersplenism and splenomegaly
  - Associated with increased risk of VTE, PHT and silent brain infarcts

Targeting ineffective erythropoiesis
Emerging management options: correction of anemia
Targeting ineffective erythropoiesis in thalassemia could correct anemia and improve other clinical sequelae

- Exploratory approaches in preclinical development
  - Hb F promoters
    - Decreased globin chain imbalance
  - Hepcidin agonists\(^1,^2\)
    - Decreased iron overload in liver and heart
    - Improved dyserythropoiesis and splenomegaly
    - Decreased iron absorption
  - Jak2 inhibitors\(^1\)
    - Decreased dyserythropoiesis
    - Decreasing spleen size

ONGOING CLINICAL TRIALS
- ACE-11, ACE-356 \(^3,^4\)

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Emerging management options: cure

Stem cell transplantation (SCT)
Stem-cell transplantation is a curative approach, and advances in understanding have improved patient survival

- Unrelated CBT for thalassemia: a single-institution experience of 35 patients
- SCT from mismatched-related donors for pediatric thalassemia patients

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CBT, cord blood transplantation  
SCT, stem cell transplantation

Advances in donor selection and conditioning regimens for stem-cell transplantation have improved patient outcomes

• Novel conditioning regimens
  • The introduction of novel drugs as well as the use of reduced-intensity conditioning in high-risk and adult patients have shaped the recent advancements in SCT

• Improved donor selection
  • MUD transplants (GITMO study)
    • Good results
    • Stringent HLA compatibility
    • No bone marrow donor registries in non-industrialized areas
  • Haploidentical
    • Limited experience
    • Experimental approach
  • Unrelated CBT
    • Interesting results
    • Need further experience

Emerging management options: cure

Gene therapy
Key points

• Management of NTDT is a continuous life-long process
• Patients should be observed with careful follow-up prior to the initiation of any treatment modality
• Transfusion therapy can ameliorate a variety of morbidities in NTDT patients; however, the risk of initiating too soon and of iron overload should be considered
• Although the benefits of hydroxyurea may only be transient, many patients can become transfusion independent or achieve increases in Hb levels
• Assessment of iron overload and chelation when appropriate is a key factor in managing NTDT patients
• Splenectomy is associated with a variety of adverse events, including infection and thrombosis, and should be performed only when indicated
• Emerging options such as curative SCT and gene therapy, and new molecules for the correction of anemia are being investigated with a promising outlook for the future
Do we need the NTDT disease severity scoring index?

• NTDT management cannot be standardized and patients should be evaluated individually
  • monitoring and early intervention are KEY to prevent complications

• The goal of the NTDT disease severity scoring index (DSSI) is to provide a simple and reliable method to
  • assess disease severity (i.e. patient status)
  • guide management decisions in clinical practice
    • therapy initiation
    • evaluation of disease progression and treatment response
    • comparison of outcomes among patients
Framework for the DSSI

• A working group of eight experts was established to reach a consensus regarding a disease severity score:
  • M.D. Cappellini, R. Galanello, A. Kattamis, K. Musallam, J. Porter, A. Taher, V. Viprakasit, and D. Weatherall

• Since disease severity can fluctuate, the score should be dynamic
  • allows assessment of disease severity at any stage

• The DSSI was structured to capture key variables that may change in response to disease progression or treatment intervention
Development of a new disease severity scoring system for patients with non-transfusion-dependent thalassemia

M. Domenica Cappellini 1,*, John B. Porter 2, Khaled M. Musallam 3, Antonis Kattamis 4, Vip Viprakasit 5, Renzo Galanello 6, Ali T. Taler 7

1 Università di Milano, Ceasar's Foundation (IRES), Milan, Italy
2 University College London, London, UK
3 American University of Beirut, Beirut, Lebanon
4 University of Stellenbosch, Stellenbosch, South Africa
5 Department of Pediatrics and Thalassemia Centre, Siriraj Hospital, Mahidol University, Bangkok, Thailand
6 Uppsala University, Uppsala, Sweden
7 Catholic University of Palermo, Department of Pediatrics, University of Palermo, Palermo, Italy

ABSTRACT

Patients with non-transfusion-dependent thalassemia (NTDT) present with a spectrum of disease severities. Since there are multiple pathophysiological parameters in each patient, tailoring treatment remains essential. Therefore, one simple, reliable tool would be beneficial to assist in disease severity and tailor therapy for internal medicine specialists who may treat a variety of NTDT patients with a multitude of complications. This would allow for standardization of assessments leading to better interventions and prevention of complications.

Introduction

Thalassemias are a group of inherited hemoglobin disorders characterized by impaired erythropoiesis, anemia and hypotension due to defective α- or β-globin chain synthesis [1-4]. There are a number of clinical phenotypes with marked differences in symptoms severity and treatment requirements observed—ranging from asymptomatic thalassemia trait to severe anemia and transfusion dependency in β-thalassemia major—as a result of varying degrees of dysfunction in globin chain production [1-4]. Differentiation between the phenotypes of thalassemia trait and β-thalassemia major, non-transfusion-dependent thalassemia (NTDT) patients do not require regular transfusions for survival, but may require transfusions during periods of stress such as infection, pregnancy or surgery [5-7]. The primary forms of NTDT include β-thalassemia intermedia (BTH), (β-thalassemia and α-thalassemia disease), which are prevalent in low- and middle-income regions, including parts of Asia (β-thalassemia intermedia, Southeast Asia (α-thalassemia and β-thalassemia), East India and Bangladesh (β-thalassemia major, β-thalassemia minor). However, as a result of population migration, an increasing prevalence of NTDT has been observed in more developed regions, such as the USA and Europe, and is therefore becoming a worldwide health problem [2,8].

Patients with NTDT present with a broad spectrum of severities, often influenced by environmental and genetic modifiers. From mild clinical presentation to severe symptoms such as retardation of growth and development, and skeletal deformities [2,9-10]. Considerable differences in the attitude of clinicians regarding whether it is best to treat or observe these patients also exist. Morbidity in NTDT is directly linked to the severity of ineffective erythropoiesis and peripheral
Proposed DSSI

Disease severity score index

- NTDT patients > 16 years old
  - 21 domains

- NTDT patients ≤ 16 years of age
  - + 6 extra domains (growth & development)

Score

Domain
- 2 or more items
- Each item is scored from 0–4

Total score
- Sum of domains
- Adults (max. 50 points)
- Paediatric (50 + 10 = 60 points)
## Haematological and iron status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
</table>
| **Haemoglobin**<sup>1,2</sup>  
(within 3 months) |   |
| > 10 g/dL | 0 |
| > 7 and ≤ 10 g/dL | 1 |
| > 5 and ≤ 7 g/dL | 2 |
| ≤ 5 g/dL | 3 |
| **Platelets**  
(within 3 months) |   |
| Normal | 0 |
| < 150,000/mm<sup>3</sup> | 1 |
| > 400,000/mm<sup>3</sup> | 2 |
| **LIC**<sup>3</sup>  
(within 6 months) |   |
| ≤ 3 mg Fe/g dry wt | 0 |
| > 3 to ≤ 5 mg Fe/g dry wt | 1 |
| > 5 to ≤ 7 mg Fe/g dry wt | 2 |
| > 7 to ≤ 15 mg Fe/g dry wt | 3 |
| > 15 mg Fe/g dry wt | 4 (if not > 15, add 1 point for historical record > 15) |
| **SF**<sup>4</sup>  
(only if LIC is not available)  
(within 3 months) |   |
| ≤ 300 μg/L | 0 |
| > 300 to ≤ 800 μg/L | 1 |
| > 800 to ≤ 1,500 μg/L | 2 |
| > 1,500 to ≤ 2,500 μg/L | 3 |
| > 2,500 μg/L | 4 (if not > 2,500, add 1 point for historical record of > 2,500) |

## Liver status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT</strong> (within 3 months)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 3 x ULN</td>
<td>1</td>
</tr>
<tr>
<td><strong>Liver disease</strong> (any history)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Fibrosis or cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hepatitis B/C</strong> (within 6 months)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>Positive (ELISA)</td>
<td>1</td>
</tr>
<tr>
<td>Significant viral load</td>
<td>2</td>
</tr>
<tr>
<td><strong>Bilirubin (indirect)</strong> (within 3 months)</td>
<td></td>
</tr>
<tr>
<td>≤ 3 x ULN</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 3 to ≤ 6 x ULN</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 6 to ≤ 10 x ULN</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 10 x ULN</td>
<td>3</td>
</tr>
<tr>
<td><strong>Gallbladder</strong> (any history)</td>
<td></td>
</tr>
<tr>
<td>No disease</td>
<td>0</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>1</td>
</tr>
</tbody>
</table>
| Cholelithias                             | 1     | (except for cholecystectomy, add 1 point if active on current presentation)
## Cardiovascular status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEF (within 3 months)</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>LVEF &lt; 55%</td>
<td>1</td>
</tr>
<tr>
<td>*<em>Cardiac T2</em> (MRI) (within 3 months)**</td>
<td></td>
</tr>
<tr>
<td>&gt; 20 ms</td>
<td>0</td>
</tr>
<tr>
<td>10 to ≤ 20 ms</td>
<td>1</td>
</tr>
<tr>
<td>6 to &lt; 10 ms</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 6 ms</td>
<td>3</td>
</tr>
<tr>
<td><strong>Heart failure (within 6 months)</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>NYHA Class I</td>
<td>1</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>2</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>3</td>
</tr>
<tr>
<td>NYHA Class IV</td>
<td>4</td>
</tr>
<tr>
<td><strong>Arrhythmias (any history)</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
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</tr>
<tr>
<td><strong>Thrombosis (any history)</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>VTE</td>
<td>1 (add 1 point if active on current presentation)</td>
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</table>
## Other co-morbidities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenomegaly (within 3 months)</td>
<td></td>
</tr>
<tr>
<td>• No splenomegaly or N/A</td>
<td>0</td>
</tr>
<tr>
<td>• &gt; 2 to ≤ 10 cm below costal margin or</td>
<td></td>
</tr>
<tr>
<td>12–20 cm on ultrasound</td>
<td>1</td>
</tr>
<tr>
<td>• &gt; 10 cm below costal margin or &gt; 20 cm</td>
<td>2</td>
</tr>
<tr>
<td>on ultrasound</td>
<td></td>
</tr>
<tr>
<td>Renal(^1) (within 3 months for eGFR; any history for nephrolithiasis)</td>
<td></td>
</tr>
<tr>
<td>• Normal</td>
<td>0</td>
</tr>
<tr>
<td>• eGFR ≥ 15 to &lt; 60 mL/min/1.73 m(^2)</td>
<td>1</td>
</tr>
<tr>
<td>• eGFR &lt; 15 mL/min/1.73 m(^2) or dialysis</td>
<td>2</td>
</tr>
<tr>
<td>• Nephrolithiasis</td>
<td>1</td>
</tr>
<tr>
<td>PHT(^2) (any history)</td>
<td></td>
</tr>
<tr>
<td>• Normal</td>
<td>0</td>
</tr>
<tr>
<td>• TRV jet &gt; 2.5 m/s</td>
<td>1</td>
</tr>
<tr>
<td>• TRV jet &gt; 2.5 m/s AND symptomatic or other Echo criteria suggestive of PHT</td>
<td>2 (add 1 point if active on current presentation)</td>
</tr>
<tr>
<td>• TRV jet &gt; 3.2 m/s or cardiac catheterization-confirmed PHT</td>
<td></td>
</tr>
<tr>
<td>• TRV jet &gt; 3.2 m/s or cardiac catheterization-confirmed PHT</td>
<td>2 (add 1 point if active on current presentation)</td>
</tr>
<tr>
<td>Leg ulcers (any history)</td>
<td></td>
</tr>
<tr>
<td>• Absent</td>
<td>0</td>
</tr>
<tr>
<td>• Present</td>
<td>1     (add 1 point if active on current presentation)</td>
</tr>
</tbody>
</table>

### Other co-morbidities (cont.)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrinopathies</strong> (any history)</td>
<td>• Absent</td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>• Hypoparathyroidism</td>
</tr>
<tr>
<td></td>
<td>• Hypogonadism (≥ 16 years)</td>
</tr>
<tr>
<td></td>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>• Adrenal insufficiency</td>
</tr>
<tr>
<td></td>
<td>• Growth hormone deficiency</td>
</tr>
<tr>
<td><strong>Skeletal</strong> (any history)</td>
<td>• Absent</td>
</tr>
<tr>
<td></td>
<td>• Final height &lt; 3rd percentile on standardized charts</td>
</tr>
<tr>
<td></td>
<td>• Osteopenia (not osteoporosis)</td>
</tr>
<tr>
<td></td>
<td>• Osteoporosis</td>
</tr>
<tr>
<td></td>
<td>• Skeletal deformity</td>
</tr>
<tr>
<td></td>
<td>• Bone pain</td>
</tr>
<tr>
<td></td>
<td>• Pathological fractures</td>
</tr>
<tr>
<td></td>
<td>• Dental malocclusion</td>
</tr>
<tr>
<td></td>
<td>• Otitis media</td>
</tr>
<tr>
<td></td>
<td>• Chronic sinusitis</td>
</tr>
<tr>
<td><strong>Extramedullary haemopoiesis</strong> (any history)</td>
<td>• Absent</td>
</tr>
<tr>
<td></td>
<td>• Present (radiologic confirmation)</td>
</tr>
<tr>
<td></td>
<td>• Compressed other structures</td>
</tr>
</tbody>
</table>
DSSI: components of paediatric score

- Height (0–2)
- Activity (0–2)
- Weight (0–2)
- Bone age (0–1)
- School performance (0–1)
- Puberty (0–2)

Paediatric scale (0–10)
Instead of a summary...

• Feasibility of the score is important
  • how many of the domains are routinely evaluated in NTDT patients nowadays and how many novel tests are required?

• Validation of the DSSI is needed to determine utility in clinical practice
  • it will involve application of the score to a large study population

• The validation should establish
  • how does the DSSI correlate with other standard measure of disease status, intervention, patient-reported outcome (QoL)?
  • can the DSSI predict future adverse outcomes and morbidities by risk stratification?
  • can the DSSI be used to evaluate treatment response in clinical practice and trials?