Transfusion-Dependent β-Thalassemia (TDT) is a severe, progressive, genetic disease that impacts patients for life.1,2

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Historically, β-thalassemia has been classified into 3 groups: minor (trait), intermedia, and major. These terms are still used by patients and some clinicians today. However, current Thalassaemia International Federation (TIF) guidelines characterize the clinical severity of β-thalassemia as:

- **Range of Severity**

<table>
<thead>
<tr>
<th>TDT</th>
<th>NTDT</th>
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<tbody>
<tr>
<td>transfusion-dependent</td>
<td>non–transfusion-dependent</td>
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**β-Thalassemia Around the World Is Changing**

The incidence and prevalence of β-thalassemia vary around the world. Endemic populations are primarily found in South Asia, the Middle East, North Africa, and Southern Europe. While migration is changing the global distribution of the disease, β-thalassemia is a rare disease in most of Europe and the United States.

**Key Points**

- TDT is the most severe form of β-thalassemia, characterized by severe anemia resulting from ineffective erythropoiesis and hemolysis.
- β-thalassemia is primarily found in South Asia, the Middle East, North Africa, and Southern Europe, but global migration patterns are changing the global distribution of the disease.
- β-thalassemia is an autosomal recessive disease resulting in reduced or absent synthesis of β-globin chains.
- Ineffective erythropoiesis and hemolysis resulting from β-globin deficiency can lead to anemia, potentially causing skeletal deformities, splenomegaly, and a variety of growth and metabolic abnormalities.
Anemia, in turn, stimulates erythropoietin synthesis, resulting in intense proliferation of the bone marrow, skeletal deformities, and a variety of growth and metabolic abnormalities. Splenomegaly is typically seen in patients with β-thalassemia as a result of extramedullary hematopoiesis or as a response to extravascular hemolysis.

### The Pathophysiology of β-Thalassemia

β-thalassemia is inherited as an autosomal recessive disease (though dominant mutations have also been reported in rare cases), resulting in reduced or absent synthesis of the β-globin chains of the adult hemoglobin (HbA) tetramer, which is made up of 2 α-globin and 2 β-globin chains. When β-globin chains are absent, α-globin chains precipitate, causing ineffective erythropoiesis and hemolysis, which leads to anemia.

#### How It Happens:

**Ineffective Erythropoiesis and Hemolysis in β-Thalassemia**

- **Bone Marrow**
  - Erythroblast
  - Mutations and deletions, chromosome 11 (β-thalassemia)

- **Extramedullary**
  - Defective synthesis of β-globin subunit; Accumulation of toxic α-globin chain aggregates
  - Shortened RBC survival
  - RBC → Hemolysis

- **Intramedullary**
  - Excess α chains (β-thalassemia)
  - Inclusion bodies
  - Premature death of erythroid precursors
  - Apoptosis → Ineffective Erythropoiesis

Anemia, in turn, stimulates erythropoietin synthesis, resulting in intense proliferation of the bone marrow, skeletal deformities, and a variety of growth and metabolic abnormalities. Splenomegaly is typically seen in patients with β-thalassemia as a result of extramedullary hematopoiesis or as a response to extravascular hemolysis.
Transfusion Therapy

Patients with transfusion-dependent β-thalassemia (TDT) must undergo frequent RBC transfusions, which can lead to iron overload.1

#### Key Points

- Currently, chronic transfusions enable survival and are central to the treatment of TDT, but lead to iron overload, treatment-related complications, and reduced quality of life.1,8
- TIF guidelines recommend transfusions every 2 to 5 weeks to maintain a pretransfusion hemoglobin (Hb) level of 9–10.5 g/dL.1
- RBC transfusions can cause iron overload, which can subsequently lead to multi-organ damage.1

#### Lifelong Supportive Care With Regular Transfusions Is Necessary in TDT1,9,10

Patients with TDT require lifelong supportive care with regular RBC transfusions. Transfusion and iron chelation therapy have significantly improved the survival of TDT patients over the last few decades.1,9,10

**TIF Guidelines for Transfusion1:**

**Maintaining a Pretransfusion Level of 9–10.5 g/dL**

- Transfuses to ≤14.0–15.0 range
- Repeat transfusion at >9.0–10.5 range
- Transfusions are typically required every 2 to 5 weeks

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**Initiate transfusions if**

- Confirmed thalassemia diagnosis
- Hb levels <7.0 g/dL on 2 occasions >2 weeks apart, OR
- Other criteria are met

As Hb levels wane between transfusions, patients with TDT may experience various symptoms of anemia.11
RBC Transfusions Are the Main Driver for Iron Overload, Which Can Lead to Multi-Organ Damage\(^1\),\(^9\)

The advent of effective iron chelation therapy has dramatically improved survival and quality of life in patients with \(\beta\)-thalassemia.\(^{12,13}\) However, challenges remain.\(^{14}\)

Heart

**Left ventricular dysfunction, heart failure, arrhythmias\(^1\),\(^9\)**

Symptomatic cardiac arrhythmias associated with myocardial iron overload pose significant clinical risk in older patients.\(^{12}\)

Liver

**Increased ALT, AST, fibrosis, cirrhosis\(^1\),\(^9\)**

Hepatic disease is becoming a leading cause of mortality as cardiac-related mortality declines due to advances in monitoring and chelation treatment.\(^{12}\)

Endocrine glands

**Hypogonadism, hypothyroidism, hypoparathyroidism, diabetes\(^1\),\(^9\)**

Endocrine glands can be affected, resulting in conditions such as hypogonadotropic hypogonadism. Growth hormone deficiency can occur despite effective chelation therapy, due to iron deposition in the pituitary gland.\(^{13}\)

PATIENT PERSPECTIVES

How do you explain and characterize the risks of iron overload to your patients?
Allogeneic Hematopoietic Stem Cell Transplant (HSCT)

A potentially curative option for a limited number of patients with transfusion-dependent β-thalassemia (TDT)\(^{1,2,15}\)

**Key Points**

- Allogeneic HSCT is a treatment option with the potential to correct the genetic deficiency in TDT\(^1,16\)
- HSCT is generally performed in younger patients with human leukocyte antigen (HLA)–matched donors\(^2,15,16\)
- Many patients with TDT do not receive allogeneic HSCT due to increased risk of mortality stemming from the lack of a suitable matched donor, presence of existing complications, and/or age\(^1,2,15-18\)
- A retrospective, non-interventional study of 1493 patients with thalassemia major who underwent allogeneic HSCT estimated 2-year overall survival (OS) and thalassemia-free survival (TFS) to be 88% and 81%, respectively\(^2\)
  - Mortality risk increased with age, with optimal outcomes seen in patients ≤14 years of age with an HLA-matched sibling donor (MSD)\(^2\)

**The Best Outcomes Are Seen in Patients With an MSD\(^1,2,15\)**

Although potentially curative, HSCT carries risks and has primarily been used in younger patients with HLA-matched donors. The best outcomes of the procedure are observed in pediatric patients with an MSD\(^1,2,15\)

- OS and TFS rates were estimated to be 91% and 83%, respectively, in patients with an MSD\(^2\)
- On average, only 25% to 30% of patients have an available MSD\(^15\)
- Acute graft-versus-host disease (GVHD) is responsible for almost 50% of transplant-related mortality\(^19\)
  - Applying highly stringent criteria for HLA typing for donor selection is the best strategy for GVHD prevention\(^19\)

Many patients with TDT do not receive allogeneic HSCT due to increased risk of mortality stemming from:

- Lack of a suitable matched donor\(^{16,17}\)
- Presence of existing complications\(^1,2,18\)
- Age\(^2,15,16\)
Mortality Risk Increases With Age

In patients who received an HSCT from HLA identical sibling donors, OS and TFS decreased with age. The threshold age for optimal transplant outcomes was around 14 years.

### Survival rates by age group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>OS (range)</th>
<th>TFS (range)</th>
</tr>
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<tbody>
<tr>
<td>All ages</td>
<td>91% (90%–92%)</td>
<td>83% (82%–84%)</td>
</tr>
<tr>
<td>&lt;14 years</td>
<td>≥90% (90%–96%)</td>
<td>≥83% (83%–93%)</td>
</tr>
<tr>
<td>≥14 years</td>
<td>≥80% (80%–82%)</td>
<td>≥74% (74%–76%)</td>
</tr>
</tbody>
</table>

**Optimal outcome group**

- **All patient ages**
  - 91% (range 90%–92%)
  - 83% (range 82%–84%)
- **Patients <14 years**
  - ≥90% (range 90%–96%)
  - ≥83% (range 83%–93%)
- **Patients ≥14 years**
  - ≥80% (range 80%–82%)
  - ≥74% (range 74%–76%)

**2-year OS (P<0.001)**

**2-year TFS (P<0.001)**

**PATIENT PERSPECTIVES**

Which TDT patients would you consider eligible for HSCT?
How do you discuss HSCT and eligibility with your patients?
Quality of Life

Transfusion-dependent β-thalassemia (TDT) can significantly impact patients and caregivers\(^8,20\)

### Key Points

- Lifelong transfusion and chelation therapy significantly impact quality of life for both patients with TDT and their caregivers\(^8,20\).
- Patients with thalassemia reported significantly lower health-related quality of life (HRQOL) scores in multiple SF-36 measures compared with the general population in the US\(^8\).

### Ongoing Management of TDT and Its Complications Can Be a Burden on Patients and Caregivers

- A lifetime of transfusions compounded by treatment-related complications can be physically and psychologically demanding for TDT patients and their caregivers, significantly impacting HRQOL for both\(^8,20\).
- As Hb levels wane between transfusions, patients with TDT may experience symptoms of anemia\(^11\).
- The process of receiving a transfusion can take up a patient’s entire day when travel, blood tests and results, blood transport to the transfusion center, and the transfusion itself are considered\(^21\).
HRQOL Scores (SF-36*) in the Thalassemia Longitudinal Cohort vs US Norms

According to a longitudinal cohort study of 264 patients over the age of 14 (85.6% had regularly transfused β-thalassemia) conducted in North America (n=229) and the United Kingdom (n=35), patients reported having a lower HRQOL than the general population.8

HRQOL Scores (SF-36*) in the Thalassemia Longitudinal Cohort vs US Norms8

*These health domains are evaluated as part of the Medical Outcomes Study Short Form 36-Item (SF-36). They are defined as follows: Physical functioning covers limitations in daily life due to health problems. The role-physical scale measures role limitations due to physical health problems. The bodily pain scale assesses the frequency of pain and interference of pain with usual roles. The general health scale measures individual perceptions of general health. The vitality scale assesses energy levels and fatigue. The social functioning scale measures the extent to which ill health interferes with social activities. The role-emotional scale assesses role limitations due to emotional problems. From: Busija L, Pausenberger E, Haines T, Haymes S, Buchbinder R, Osborne RH. Adult measures of general health and health-related quality of life: Medical Outcomes Study Short Form 36-Item (SF-36) and Short Form 12-Item (SF-12) Health Surveys, Nottingham Health Profile (NHP), Sickness Impact Profile (SIP), Medical Outcomes Study Short Form 6D (SF-6D), Health Utilities Index Mark 3 (HUI3), Quality of-Well Being Scale (QWB), and Assessment of Quality of Life (AQOL). Arthritis Care Res (Hoboken). 2011;63(Suppl 11):S383-S412.

†One sample T test shows a significant difference between population and US norm (P<0.05).

PATIENT PERSPECTIVES

How does the treatment of TDT impact your patients' social functioning, mental health, and other areas of their quality of life?
Thalassemia care has constantly evolved over the years, and change is frequent and impactful. Whether it’s the impact of treatment schedules on daily routines, the advent of HSCT, or the potential for future scientific innovation, almost every aspect of the TDT experience is in constant flux—and each patient experiences the disease in different ways.

**AS THE TDT TREATMENT LANDSCAPE AND PATIENT EXPERIENCE EVOLVE, SO SHOULD THE WAY WE TALK ABOUT IT**

**Here Are Questions to Contemplate as You Think About the Impact of TDT on Your Patients’ Lives**

- How do your patients with TDT view their disease and how it affects their lives (eg, mental health, social functioning, and physical functioning)?
- Do they identify themselves through their disease?
- Do they see TDT as an obstacle to overcome?
- What do your patients with TDT and their caregivers say when they express their thoughts and concerns about their disease?
  - How do you address their concerns about the impacts of TDT on their relationships, personal goals, and education or career?
- Do they try to downplay the impact on their lives?
- In what ways do RBC transfusions and iron chelation therapy affect your patients’ and caregivers’ lifestyles—daily activities, schedule flexibility, and their relationship and career prospects?
- What are your patients’ future plans and goals (personal, career, or educational), and how does TDT and its treatment impact those plans and goals?
- How engaged are your patients in planning treatment and treatment goals?
  - In what ways do you take their personal goals into consideration when planning treatment and treatment goals?
- How does all of the information above affect treatment planning and treatment goals?
Questions to Ask Your Patients

This brochure includes questions that are meant to elicit thought surrounding the patient’s point of view, but here are a few more questions to help you dig deeper:

1. Can you describe any changes made to your life because of your symptoms or treatment? Are there instances where TDT and its treatment affected your relationships with family or friends? Your ability to perform at school or work?

2. I understand that managing symptoms and treatments for TDT can impact your life—school, work, and other areas of your routine and personal goals. Can you share some examples of these challenges?

3. If you could change a few things about how your treatment affects you, such as in your relationships or personal goals, what would they be? Can you tell me an instance of how treatment has impacted your life?

4. Can you share some of your personal goals with me? What would you like to accomplish in your life today? How about tomorrow and in the future?

Remember, the goal is not to have solutions to all of their problems. It is to create an ongoing conversation in which patients can communicate about their concerns openly and honestly, and to make a plan that helps to address their needs and goals.
TRANSFUSION-DEPENDENT β-THALASSEANIA (TDT)

IS A SEVERE GENETIC DISEASE THAT IMPACTS PATIENTS FOR LIFE

• TTD is the most severe form of β-thalassemia, characterized by severe anemia resulting from ineffective erythropoiesis and hemolysis.

• The available treatment options for TTD are lifelong chronic RBC transfusions with iron chelation or allogeneic HSCT.

• Chronic transfusions enable survival but lead to iron overload and treatment-related complications, which significantly affect quality of life for both patients with TTD and their caregivers.

• Allogeneic HSCT gives patients with TTD the opportunity to become thalassemia-free, but many patients do not receive this treatment due to increased risk of mortality stemming from:
  - Lack of a suitable matched donor.
  - Presence of existing complications.
  - Age.

• A longitudinal cohort study of 264 patients (in which 85.6% of patients had TTD) showed significantly lower HRQOL scores for patients with thalassemia compared with the general population.

For a deeper look into TDT, including videos, downloadable resources, and more

Explore Challenge TDT.com

References: