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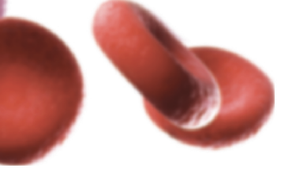
IT'S TIME TO

CHALLENGE OUR UNDERSTANDING

OF TRANSFUSION-DEPENDENT β-THALASSEMIA (TDT)

TDT is a severe, progressive, genetic disease that impacts patients for life[1,2]

Actor portrayals throughout. Not real patients.



β-THALASSEMIA OVERVIEW

TDT is a severe genetic disease that impacts patients for life, requiring them to have regular red blood cell transfusions for survival[1,3]

KEY POINTS[1,3,4]

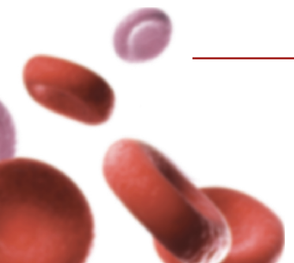
- TDT is the most severe form of β-thalassemia and is characterized by reduced or absent production of functional β-globin, which is essential for forming adult hemoglobin (HbA)
- In the absence of sufficient β-globin, excess unpaired α-globin impairs the development and survival of red blood cells (RBCs), leading to chronic anemia and other serious complications
- If left untreated, ineffective erythropoiesis and hemolysis resulting from β-globin deficiency can lead to anemia, potentially causing skeletal deformities, splenomegaly, a variety of growth and metabolic abnormalities, and an increased risk of early death

GLOBAL DISTRIBUTION OF β-THALASSEMIA IS CHANGING[4]

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 the exact prevalence of β-thalassemia in the US is unknown, migration is changing the global distribution of the disease.[1,4,5]

Due to immigration of people from affected regions, **the prevalence of all thalassemias (including β-thalassemia) has increased by approximately 7.5% in the US over the last 50 years.**[1,6]

Global studies of patients in both developed and developing countries have shown a progressive improvement in lifespan for patients with β-thalassemia.[1] But despite considerable improvement in life expectancy, serious complications over the long term, such as cardiac events, infections, and liver disease, remain a clinical concern for these patients.[1,3,7]



While migration is changing the global distribution, β-thalassemia major is **CONSIDERED A RARE DISEASE IN THE US**[4,8]

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RANGE OF SEVERITY

Historically, β-thalassemia has been classified into **3 groups: minor (trait), intermedia, and major**.[1,6] These terms may still be used by patients and some clinicians today. However, the *2021 Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT)*, published by the Thalassaemia International Federation (TIF), classify β-thalassemia phenotypically into 2 main groups based on clinical severity and transfusion requirement[1]:

NTDT

Non–transfusion-dependent β-thalassemia (NTDT):
a form of β-thalassemia in which patients need only occasional or intermittent blood transfusions.[1]

TDT

Transfusion-dependent β-thalassemia (TDT):
a form of β-thalassemia in which patients require lifelong regular blood transfusions to survive. Left untreated—that is, without a regular transfusion regimen—people with TDT cannot survive.[1]

THE THALASSAEMIA INTERNATIONAL FEDERATION (TIF)[1,9]

Founded in 1987 by a small group of patients and parents, TIF is a nonprofit, nongovernmental organization dedicated to promoting appropriate clinical management of thalassemia in every affected country.

Since 1996, TIF has had official relations with the World Health Organization (WHO). The outcome of this partnership is an extensive network of collaboration between scientific and medical professionals from more than 60 countries around the world. To further its mission, TIF has published important clinical documents for thalassemia, including guidelines for managing and caring for patients with both TDT and NTDT.

The above content was printed with the approval of TIF. bluebird bio does not endorse the nonprofit organization or any of its affiliates.

View more resources at ChallengeTDT.com

β-THALASSEMIA OVERVIEW

TDT affects a person's ability to produce HbA—the predominant form of hemoglobin in adults[3,10]

THE PATHOPHYSIOLOGY OF β-THALASSEMIA

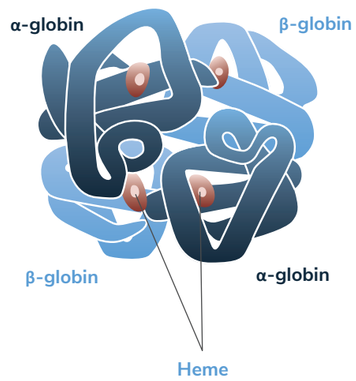
β-thalassemia is an autosomal recessive disease caused by a mutation in or near the *HBB* gene that results in **reduced or absent production of the β-globin protein**. Over 350 disease-causing genetic mutations have been identified, most of which are point mutations.[1,11,12]

In the absence of sufficient β-globin, adult hemoglobin (HbA) production is reduced and an excess of unpaired α-globin can impair the development and survival of red blood cells, leading to chronic anemia and other serious complications.[3]

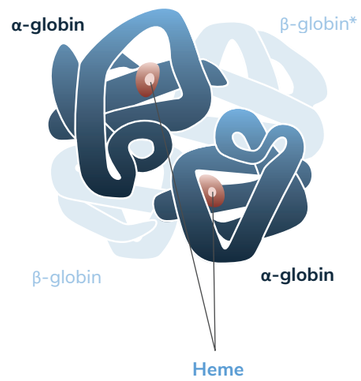
DEFICIENT β-GLOBIN SYNTHESIS IMPAIRS HbA PRODUCTION[3]

HbA is a tetramer that is made up of 2 α-globin subunits and 2 β-globin subunits. The number of β-globins must precisely match that of α-globins. If not, the α/β-globin imbalance impairs the body's ability to produce functional HbA.[1,3,10]

NORMAL HEMOGLOBIN[1]



HEMOGLOBIN IN TDT (β-THALASSEMIA MAJOR)[1]



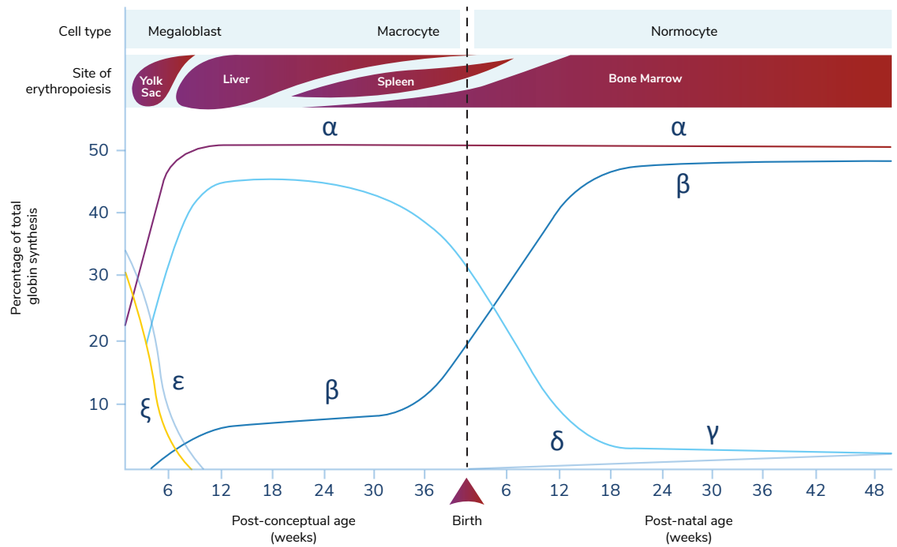
*Faded blue indicates reduced or absent β-globin

Deficient β-globin synthesis
IS A DEFINING CHARACTERISTIC OF β-THALASSEMIA

HbA BECOMES THE PRIMARY FORM OF HEMOGLOBIN AFTER 6 MONTHS OF AGE, ACCOUNTING FOR ≥90% OF TOTAL Hb[1,13]

Under normal conditions, HbA becomes the predominant form of hemoglobin in the body by about 18 to 36 weeks of age. Prior to HbA production, the predominant form of hemoglobin is fetal hemoglobin (HbF), which is composed of **2 α-globin subunits** and **2 γ-globin subunits**.[10]

THE SWITCH FROM HbF TO HbA IN INFANTS IS CRITICAL FOR THE NORMAL FUNCTIONING OF THE HUMAN BODY AS IT GROWS[1]



HbF is important for oxygen transport during fetal gestation because it has a high affinity for oxygen and a decreased affinity for 2,3-diphosphoglyceric acid (2,3-DPG) relative to HbA. This allows HbF to easily bind oxygen found in the maternal bloodstream. However, **post birth, HbA is more optimal because it has a higher affinity for 2,3-DPG, which enables oxygen release; this is essential for RBCs to be able to deliver oxygen to the organs and tissues of the body.** The switch from HbF to HbA at the appropriate time in an infant's life is critical for the normal functioning of the body as it grows.[14]

Adults who express variants of Hb with high oxygen affinity (including HbF) have been shown to deliver less oxygen than normal to tissues, leading to mild tissue hypoxia and, over time, to polycythemia and other thrombotic events.[15]

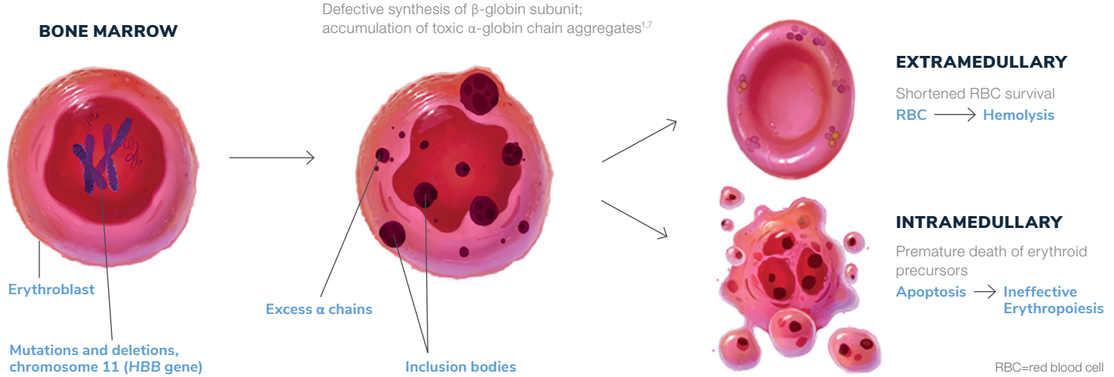
β-THALASSEMIA OVERVIEW

TDT can lead to anemia and, if untreated, growth and metabolic abnormalities

WITHOUT SUFFICIENT β-GLOBIN, EXCESS α-GLOBIN PROTEIN CAN LEAD TO INEFFECTIVE ERYTHROPOIESIS AND HEMOLYSIS[1,3]

When β-globin is absent, α-globin and its degradation products precipitate, causing ineffective erythropoiesis and hemolysis, which lead to anemia.[1,3]

INEFFECTIVE ERYTHROPOIESIS AND HEMOLYSIS IN β-THALASSEMIA



Anemia 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.[1,4]

RBC transfusions, which are central to the treatment of severe disease, enable survival by helping to correct the anemia characteristic of β-thalassemia and limit bone marrow expansion. However, many complications still remain and, ultimately, **transfusions only address the symptoms of TDT.**[1,3]

PATIENT PERSPECTIVES

How do you explain the genetic nature of TDT to your patients? Visit the resource section on *ChallengeTDT.com* to download a patient-friendly brochure.

TRANSFUSION THERAPY

For patients with TDT, treatment means lifelong symptom management with regular RBC transfusions[1,3]

KEY POINTS

- Thalassaemia International Federation (TIF) guidelines for TDT recommend lifelong regular transfusions every **2 to 5 weeks to maintain a pretransfusion Hb level of 9.5–10.5 g/dL**[1]
  - Adhering to the recommended guidelines can promote standard growth, enable normal physical activities, adequately suppress bone marrow activity, improve anemia, and minimize transfusion accumulation and ineffective erythropoiesis in patients with TDT[1,4]
  - In children, lifelong regular transfusions at the recommended hemoglobin level of 9.5–10.5 g/dL can help avoid skeletal abnormalities, organomegaly, and growth retardation associated with β-thalassemia[1,6]
- **Lifelong regular transfusions enable survival** but lead to unavoidable iron overload and treatment-related complications, and can significantly impact the quality of life of patients and their caregivers[3,16]
  - Excess iron accumulates in the vital organs of patients with TDT, increasing the risk of liver, cardiac, and endocrine disease, which may lead to premature death[3,6]
  - Even current or modern-day iron chelation treatment cannot entirely prevent iron overload in patients[3]

Hemoglobin level is measured as the amount of hemoglobin in grams (g) per deciliter (dL) of whole blood, with a deciliter being 100 milliliters (mL). **The mean hemoglobin levels are as follows[17,18]:**

MALE			FEMALE		
2–9 years	10–17 years	≥18 years	2–9 years	10–17 years	≥18 years
11.5–14.5 g/dL	12.5–16.1 g/dL	13.5–18 g/dL	11.5–14.5 g/dL	12–15 g/dL	12.5–16 g/dL

Although transfusion therapy addresses hemoglobin levels temporarily,
THIS ADDRESSES ONLY THE SYMPTOMS OF TDT[1]

TRANSFUSION THERAPY

For patients with TDT, treatment means lifelong symptom management with regular RBC transfusions[3]

LIFELONG SUPPORTIVE CARE WITH REGULAR TRANSFUSIONS IS NECESSARY IN TDT[3]

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. However, many challenges, such as **organ damage due to underlying disease and iron overload**, still exist.[1,3]

TIF GUIDELINES FOR TRANSFUSION:

The *2021 Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT)*, published by the TIF, recommend regular lifelong transfusions. These typically occur every 2 to 5 weeks in patients who meet the following criteria[1]:

- **Confirmed diagnosis of β-thalassemia**
- **Laboratory criteria:**
  - Hemoglobin level <7 g/dL on 2 occasions, >2 weeks apart (excluding all other contributory causes, such as infections) *AND/OR*
- **Clinical criteria irrespective of hemoglobin level:**
  - Hemoglobin >7 g/dL with any of the following:
    - Significant symptoms of anemia
    - Poor growth/failure to thrive
    - Complications from excessive intramedullary hematopoiesis, such as pathological fractures and facial changes
    - Clinically significant extramedullary hematopoiesis

TIF guidelines for TDT recommend regular lifelong transfusions, typically **EVERY 2 TO 5 WEEKS[1]**

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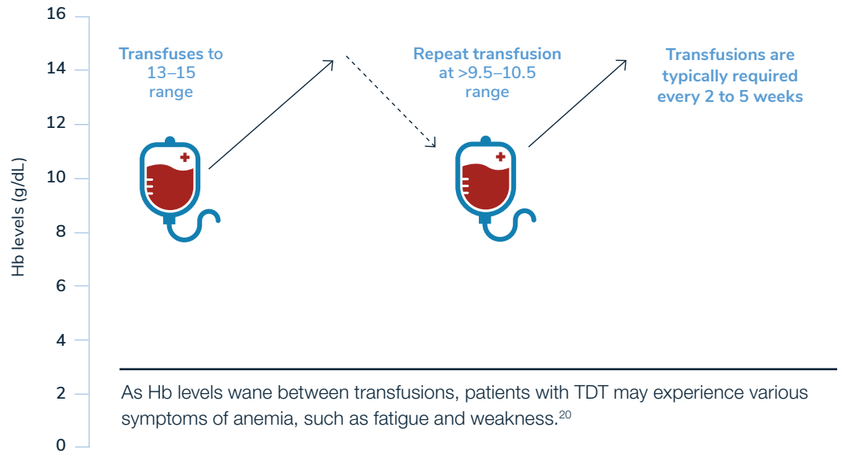
IT IS ESSENTIAL TO MAINTAIN HEMOGLOBIN LEVELS IN PATIENTS WITH TDT[1,19]

The recommended treatment for TDT involves lifelong regular blood transfusions, usually administered **every 2 to 5 weeks**, to maintain pretransfusion **hemoglobin levels above 9.5–10.5 g/dL[1]**. This is lower than normal hemoglobin levels, but is considered to be sufficient for normal growth and physical activity and can adequately suppress ineffective erythropoiesis in most patients while preventing excessive iron loading.

Since hemoglobin levels are higher post transfusion, which increases the risk of stroke, post-transfusion **hemoglobin target should be 13–15 g/dL[1]**. Hemoglobin levels should be measured intermittently after transfusion to determine how quickly hemoglobin levels drop. This decrease may be valuable for evaluating the effects of changes in the transfusion regimen.[19]

TIF GUIDELINES FOR TRANSFUSION[1]: MAINTAINING A PRETRANSFUSION LEVEL OF 9.5–10.5 g/dL



As Hb levels wane between transfusions, patients with TDT may experience various symptoms of anemia, such as fatigue and weakness.[20]

As the understanding of β-thalassemia and its pathophysiology continues to improve, so does disease management. Today, adult patients with β-thalassemia receiving regular transfusions may have the option of adding an erythroid maturation agent to their chronic transfusion schedule to help moderate their transfusions.[1]

Understanding your patient's symptoms between transfusions can help you **OPTIMIZE THEIR TREATMENT SCHEDULE**

EFFECTS OF **IRON OVERLOAD**

RBC transfusions lead to unavoidable iron overload, which can lead to multi-organ damage[1,3]

The introduction of effective iron chelation therapy has significantly improved survival and quality of life for people living with TDT. However, even present-day chelators cannot completely prevent iron overload. Thus, **rigorous and continuous monitoring of iron burden is essential**.[1,4]

In a 2018–2019 real-world, observational study of 165 patients with TDT conducted in the UK, a subset of patients exhibited significant iron overload while being managed and monitored in a specialist center. Despite receiving this level of care and utilizing iron chelation therapy, these patients experienced iron overload.[21]

Heart

Left ventricular dysfunction, heart failure, arrhythmias[22,23]
Symptomatic cardiac arrhythmias associated with myocardial iron overload pose significant clinical risk in older patients.

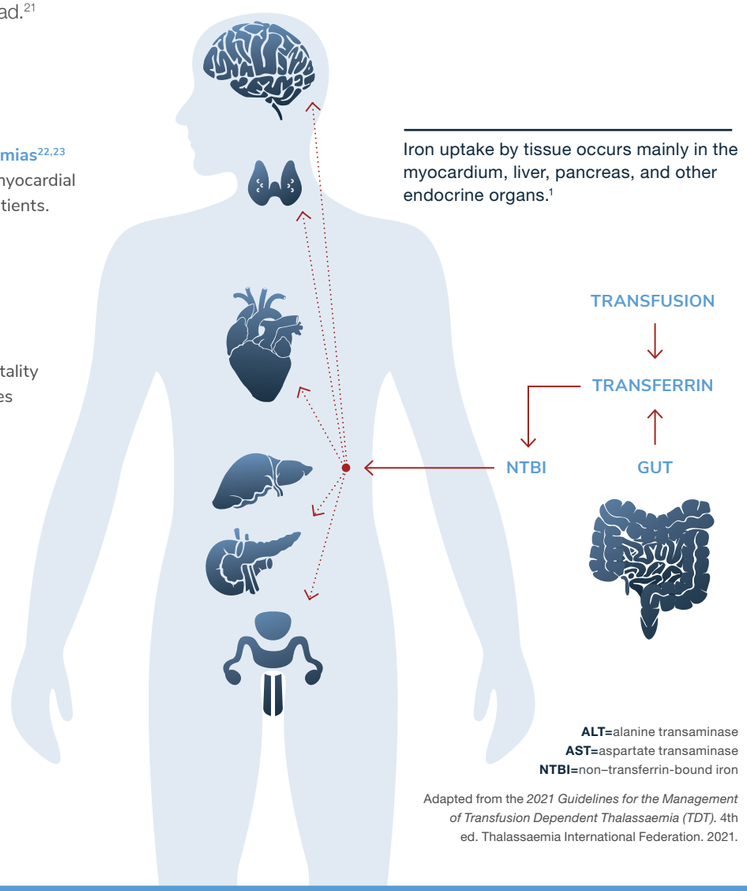
Liver

Increased ALT, AST, fibrosis, cirrhosis[23]
Hepatic disease is becoming a leading cause of mortality as cardiac-related mortality declines due to advances in monitoring and chelation treatment.

- Excess iron is primarily stored in the liver and can reach clinically critical levels

Endocrine glands

Hypogonadism, hypothyroidism, hypoparathyroidism, diabetes[23,24]
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.



Iron uptake by tissue occurs mainly in the myocardium, liver, pancreas, and other endocrine organs.[1]

ALT=alanine transaminase
AST=aspartate transaminase
NTBI=non–transferrin-bound iron

Adapted from the *2021 Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT)*. 4th ed. Thalassaemia International Federation. 2021.

PATIENT PERSPECTIVES

How do you explain and characterize the potential risks of iron overload to your patient?

ALLO-**HSCT**

Allogeneic hematopoietic stem cell transplant (allo-HSCT) is a potentially curative option, but is associated with a risk of transplant-related mortality (TRM) and graft failure, as well as with severe immunological complications like GVHD[1,25]

KEY POINTS[1,2,25,26]

- Allo-HSCT is a treatment option with the potential to correct the genetic deficiency in TDT by replacing the patient's hematopoietic stem cells (which carry the mutated *HBB* gene) with cells from a donor that contain a functional copy of the *HBB* gene; it may alleviate the need for regular transfusions and chelation
- Best outcomes with allo-HSCT are achieved in pediatric patients (<14 years of age) who have well controlled iron levels, lack iron-related morbidities, and have a human leukocyte antigen (HLA) matched sibling donor (MSD)
- Many patients do not receive transplant due to lack of a suitable matched donor, presence of existing complications, and age.
  - On average, only 25% to 30% of patients have an MSD
  - The use of donor cells in allo-HSCT introduces the risk of potentially life-threatening graft versus host disease (GVHD) and graft rejection

THE BEST OUTCOMES ARE SEEN IN PEDIATRIC PATIENTS WITH AN HLA MSD, BUT THERE ARE RISKS, INCLUDING TRANSPLANT-RELATED MORTALITY[2,25]

Overall survival and thalassemia-free survival rates are highest in patients with an MSD.

A retrospective, non-interventional study, extracting data from the European Society for Blood and Marrow Transplantation (EBMT) hemoglobinopathy prospective registry database of 1493 patients (91% <18 years old; n=1359) with thalassemia major who underwent allo-HSCT (between 2000 and 2010) estimated 2-year overall survival (OS) and thalassemia-free survival (TFS) to be 88% and 81%, respectively.[2] In recipients of MSD transplants, the results were markedly different than those from other donor groups, with OS and TFS of 91 ± 1% and 83 ± 1%, respectively.[2,25]

Donor Type	Overall Survival Rate* (2 years post-HSCT)	Thalassemia-Free Survival Rate* (2 years post-HSCT)
Matched Sibling Donor (n=1061)	0.91 ± 0.01	0.83 ± 0.01
Matched Related Donor (n=127)	0.88 ± 0.04	0.78 ± 0.05
Mismatched (n=57)	0.68 ± 0.11	0.68 ± 0.11
Unrelated Donor (n=210)	0.77 ± 0.03	0.77 ± 0.03

*P<0.001

In a separate analysis (focused on transplantations outcomes for β-thalassemia outside Europe) demonstrated similar findings. These findings confirmed that patients (especially those 15 years and older) with mismatched-related or mismatched-unrelated donors are less desirable. Careful evaluation between the best available treatment and transplantation is always recommended when evaluating survivability.[26]

ALLO-HSCT

Allo-HSCT is a potentially curative option, but is associated with a risk of TRM and graft failure, as well as with severe immunological complications like GVHD[1,25]

SURVIVAL OUTCOMES IN PEDIATRIC PATIENTS WITH AN HLA-MATCHED DONOR DECREASED WITH AGE

In patients who received allo-HSCT from HLA-identical sibling donors, OS and TFS decreased with age. Survival rates for children <14 years old (2-year OS of 90%–96% and TFS of 83%–93%) were higher than those for adolescents (2-year OS of 82% and TFS of 74%) and adults (2-year OS of 80% and TFS of 76%).[2]

THRESHOLD AGE FOR OPTIMAL TRANSPLANT OUTCOMES WAS ~14 YEARS[2]

		Overall Survival		Thalassemia-Free Survival	
Age	Number of Patients	Events	2-year OS	Events	2-year TFS
<2	66	3	0.95 ± 0.03	4	0.93 ± 0.03
2 to <5 years	266	13	0.94 ± 0.02	32	0.86 ± 0.03
5 to <10 years	352	33	0.90 ± 0.02	52	0.83 ± 0.02
10 to <14 years	197	8	0.96 ± 0.02	24	0.86 ± 0.03
14 to <18 years	97	14	0.82 ± 0.04	20	0.74 ± 0.05
≥18 years	82	16	0.80 ± 0.05	18	0.76 ± 0.05
P value (for trend)		<0.001		<0.001	

SEPARATE ANALYSIS SHOWED OPTIMAL OUTCOMES WITH HLA-MATCHED DONOR[26]

Age	Donor Type	5-Year Event-Free Survival Rate (95% CI)
≤6 years	HLA-matched relative	88% (84%-91%)
≤6 years	HLA-mismatched relative	73% (59%-86%)
≤6 years	HLA-matched unrelated	89% (83%-93%)
≤6 years	HLA-mismatched unrelated	83% (73%-91%)
7-15 years	HLA-matched relative	80% (75%-85%)
7-15 years	HLA-mismatched relative	83% (39%-73%)
7-15 years	HLA-matched unrelated	83% (82%-95%)
7-15 years	HLA-mismatched unrelated	71% (54%-85%)

Patients aged 16-25 years: N=24 patients who received HLA-matched related donor transplantation with event-free survival of 58% (14 of 24) and overall survival of 63% (15 of 24). N=4 patients received HLA-mismatched related donor transplantation and only 2 patients are alive. N=4 patients received HLA-matched unrelated donor transplantation and all patients are alive. N=1 patient received HLA-mismatched unrelated donor transplantation and is death.

A separate retrospective analysis of 1100 patients (97% <16 years old) with β-thalassemia who underwent allo-HSCT between 2000 and 2016 in China, India, and the US also demonstrated optimal outcomes in pediatric patients with an HLA-matched donor.

Event-free survival defined as death from any cause or graft failure.

On average, **ONLY 25% TO 30% OF PATIENTS HAVE AN MSD[26]**

THE USE OF DONOR CELLS IN ALLO-HSCT INTRODUCES THE RISK OF POTENTIALLY LIFE-THREATENING GVHD AND GRAFT REJECTION[1,25,27]

- Incidence of **severe acute GVHD (Grade III–IV) can range from 9% to 17%, and approximately 5% to 9% of patients develop extensive chronic GVHD[2,27,28]**
- **TRM is an inherent risk for patients with TDT undergoing allo-HSCT**, with a recent single-center study reporting an 11.6% rate of TRM[29]
- **Graft failure occurs in about 20% of patients** with TDT who undergo allo-HSCT[28-30]

Comprehensive and long-term follow-up after allo-HSCT for TDT is recommended to screen for disease-related outcomes and late effects of allo-HSCT. Patients should be managed and monitored for mixed chimerism, iron overload, chronic GVHD, immune reconstitution and susceptibility to infections, and screened for malignancies following exposure to transplant conditioning regimens and immunosuppression.[30]

There is limited experience of allo-HSCT in adult patients, as very few centers perform allo-HSCT in patients over the age of 18 years and TRM has persistently remained around 25%.[31]

MANY PATIENTS WITH TDT DO NOT RECEIVE ALLO-HSCT DUE TO INCREASED RISK OF MORTALITY STEMMING FROM[26,30,34]:

Lack of a suitable matched donor[25,32]

Presence of existing complications[2,25]

Age[2,25]

Although allo-HSCT may be a **POTENTIALLY CURATIVE TREATMENT OPTION** for your patients with TDT, there are risks involved[25]

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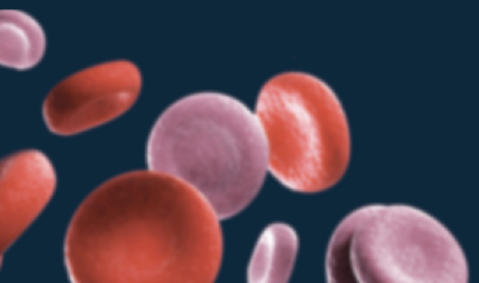
QUALITY OF LIFE

TDT can significantly impact the quality of life of patients and their caregivers[30,32]

KEY POINTS

- Lifelong complications and demanding therapeutic protocols affect the emotional condition, daily activities, family experiences, and occupational capabilities of patients and their caregivers[34]
- Patients with thalassemia reported significantly lower health-related quality of life (HRQoL) scores in multiple SF-36 measures compared with the general US population[33]
  - Caregivers of children with β-thalassemia are also reported to have decreased HRQoL and to have experienced impaired physical and psychological health[16]
- In the 2019 MyThalLog*, a bluebird bio–sponsored study (N=85), patients and caregivers reported the burden of TDT as being high and influenced by disease-management time, fatigue, pain, and quality-of-life impairment[16]
  - Mean scores at enrollment were 5.0 (n=82; 0-10 scale, 10=worst symptoms) for the Brief Fatigue Inventory and 51 (n=73; 0-100 scale, 100=best quality of life) for the transfusion-dependent quality of life (TranQoL)
  - When compared with other chronic diseases, the BFI levels of patients with TDT were similar to Crohn's disease (4.2), ulcerative colitis (4.1), and rheumatoid arthritis (7.3)
- In a 2012 study of patients with thalassemia receiving care in the US and Canada (N=252), 64% reported experiencing pain in the last 4 weeks, 22% of whom reported pain on a daily basis[35]
  - Approximately two-thirds of patients experiencing pain reported moderate to severe interference (rating of ≥4 out of 10) across all life activity dimensions (general activity, mood, walking ability, work, relationships with people, sleep and enjoyment of life)

*A bluebird bio–sponsored, prospective, observational, real-world study of adults with TDT and caregivers of adolescents with TDT in Italy, the UK, and the US. Over 90 days, participants used a smartphone app to respond to daily surveys about their or their dependent's TDT, including bespoke background and disease-management surveys, the BFI, the TranQoL, and the Brief Pain Inventory Short Form.



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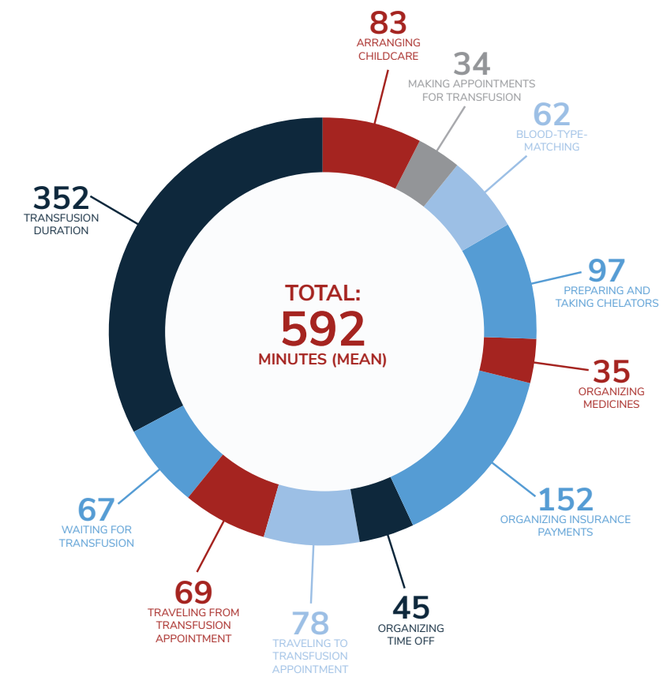
ONGOING MANAGEMENT OF TDT AND ITS COMPLICATIONS CAN BE DEMANDING ON PATIENTS AND CAREGIVERS[33,34]

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[5,16]

- Patients and caregivers in the MyThalLog study reported mean transfusion frequency as every **3.2 weeks**, with the mean time spent on TDT management being **9 hours and 52 minutes** on transfusion days and **91 minutes on non-transfusion days** (11 hours per week=528 hours per year)[16]

MEAN DAILY TIME SPENT (IN MINUTES) ON TDT MANAGEMENT ACTIVITIES ON TRANSFUSION DAYS[16]



PATIENT PERSPECTIVES

Have you discussed changing your patient's treatment plan to align with their personal goals?

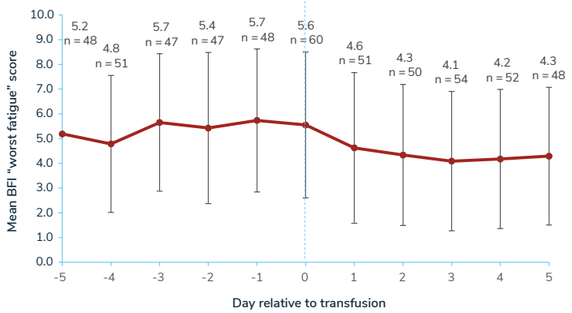
QUALITY OF LIFE

TDT can significantly impact the quality of life for patients and caregivers[33,34]

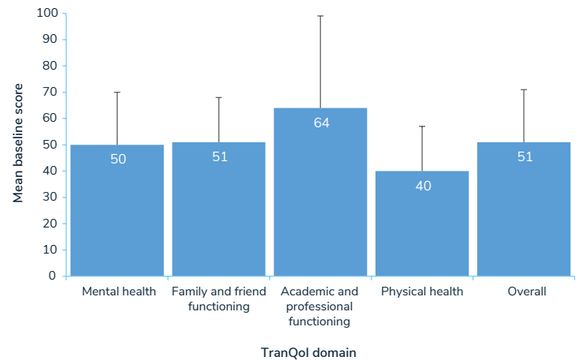
BRIEF FATIGUE INVENTORY (BFI) AND TranQoL SCORES SHOW INCREASED BURDEN FOR PATIENTS WITH TDT VS HEALTHY CONTROLS

The 2019 MyThalLog was a longitudinal, real-world, 90-day study that captured patient-reported outcomes of adults ≥18 years with TDT and caregivers of patients aged 12 to 17 years with TDT (N=85) living in the UK, USA, Italy, and Germany. Patients with TDT and caregivers reported that the burden of TDT is high, along with high fatigue and impairment to quality of life, when compared with healthy controls.[16]

Mean Brief Fatigue Inventory (BFI) "Worst Fatigue" Score Relative to Transfusion Day
(0–10 scale; 10=worst fatigue)[16]



Mean TranQoL Domain and Overall Scores
(0–100 scale; 100=best HRQoL)[16]



Adapted from Paramore C, Levine L, Bagshaw E, et al. Patient- and caregiver-reported burden of transfusion-dependent β-thalassemia measured using a digital application. *Patient*. Published online October 30, 2020. doi: 10.1007/s40271-020-00473-0.

Several limitations of our study design must be considered when interpreting the results. First, given the app-based approach, the population was restricted to confident smartphone users. This may have excluded some potential participants who were older, lacked access to a smartphone, or had difficulties with vision or dexterity. The remote app-based approach meant that participant eligibility and accuracy of data could not be directly verified by a clinician. Our study was also limited by the fact that each survey was analyzed independently, with participants included in the analysis if they responded to that particular survey, rather than if they responded to all surveys or, at a minimum, the background demographic survey. Another limitation was the short data-collection period, which meant that our results may not be representative of the long-term burden of TDT. Another factor limiting the quality of our study results was the use of a novel disease-management survey. One final area of the study design that may have had undesired effects was the financial reward system used to encourage participant engagement.

Although the app-based approach taken in this study introduced several potential limitations, it did provide some advantages over in-person methods, which should be noted. The ease with which participants could learn about the study, enroll, and contribute data promoted a large, diverse, and complete dataset, while digital data management and analysis reduced administrative burden and opportunities for human error.

PATIENT PERSPECTIVES

How has the treatment of TDT impacted your patients' social functioning, mental health, and other areas of their quality of life?

PATIENT PERSPECTIVES

It's time to rethink conversations with patients of all ages who have TDT

Over time, thalassemia care has evolved and the advances have been life changing. As a result, survival rates for patients with TDT have improved, but managing TDT and associated complications continues to be a concern for patients of all ages and for their caregivers.[3,5]

Frequent, ongoing conversations with patients and caregivers that address the patient's treatment goals can help you create and adjust your medical treatment plan. Starting these conversations early on in your relationship with patients and caregivers will enable you to forecast key points in the patient's life that may warrant conversation about treatment goals.

Some of the life events that your patients may be considering include:

- Starting elementary or high school
- Attending/going away to college or other higher education
- Playing sports
- Starting a new job
- Getting married
- Planning a family

At points like these, your treatment conversations may lead to deeper discussions. As you probe for insights, consider asking them not only about the impact of the disease itself, but also about their individual challenges, aspirations, and life goals.

Since TDT is a lifelong condition, it's important to ask some of the same life questions often, as the needs and goals of patients can change over time. We hope the patient perspectives and questions presented in this brochure will be helpful in guiding your conversations with patients and their caregivers.[36]

UNDERSTANDING YOUR PATIENT'S GOALS AND ASPIRATIONS
may help you make decisions about treatment and disease management

PATIENT PERSPECTIVES

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

Lifestyle:

- 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?
- Does TDT get in the way of the things they like to do? How so?

Day to day:

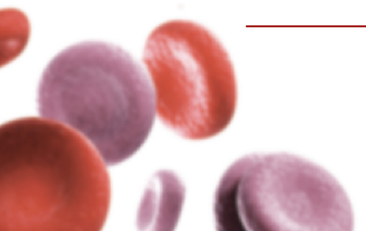
- Have they experienced any problems completing day-to-day tasks or activities as a result of their TDT?
- Have they described to you a good day and a bad day related to TDT?

Disease:

- 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 see TDT as an obstacle to overcome?
- Do they try to downplay the impact of TDT on their lives?

Goals:

- What are your patients' future plans and goals (personal, career, or educational), and how does TDT and its treatment impact those plans and goals?
- What goals would they like to achieve with their treatment?
- Have they felt themselves shy away from a promotion or a new job, or leave a job because of their TDT?
- Have their symptoms ever caused them to accomplish less than they would have liked?



Ongoing conversations with your patients can help you **OPTIMIZE THEIR CARE**

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NOTES

Having ongoing conversations in which patients and caregivers can openly and honestly communicate their concerns may help you make a plan that addresses their needs and goals.

START THE CONVERSATION.
HELP THEM MAKE A PLAN.

TRANSFUSION-DEPENDENT β-THALASSEMIA (TDT)

is a severe, progressive, genetic disease that impacts patients for life[1,2]

- **TDT is the most severe form of β-thalassemia**, characterized by reduced or absent production of functional β-globin, which is necessary to form adult hemoglobin[3,11]
- **Regular transfusions enable survival, but only temporarily address the symptoms of disease[1,3]**
  - TIF guidelines for TDT recommend lifelong transfusions every 2 to 5 weeks
  - Lifelong blood transfusions can lead to iron overload in the body, which requires management with chelation therapy
- **By correcting the genetic deficiency, allogeneic HSCT is an option** that can give patients with TDT the potential to become thalassemia-free[1,2,25,26]
  - Many patients do not receive transplant due to lack of a suitable matched donor, presence of existing complications, and age

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