Revisiting Beta Thalassemia Intermedia: Past, present, and future prospects

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I. Introduction

Thalassemia syndromes constitute the most common genetic diseases worldwide (1). Beta(β)-thalassemia comprises a heterogeneous group of hemoglobin (Hb) disorders characterized by a reduction or complete absence of β-globin gene expression. They are inherited in an autosomal recessive fashion(2) and are characterized by an extreme diversity in phenotype, making diagnosis a real challenge. The spectrum of β-thalassemias is wide ranging from thalassemia minor which consists of mild hypochromic microcytic anemia without obvious clinical manifestations, to β-TM which is characterized by severe anemia since the first years of life and are transfusion dependent(3). In the middle lies β-TI, a term developed to describe patients with manifestations too mild to be considered β-TM and too severe to be called thalassemia minor (Figure 1). TI belongs to the group of non-transfusion dependent thalassemias (NTDT), which also includes mild/moderate HbE/β thalassemia, and α-TI (HbH disease). The aim of this review is to describe the genetic features and major clinical complications in β-TI, and the therapeutic approaches available in the management of this disease.

II. Genetic Features

β-thalassemia is caused by an imbalance in globin chain synthesis. Disease severity depends on the extent of this imbalance. The β-thalassemias including TI, arise from a defective gene function leading to partial suppression of beta globin protein production(4). The phenotypic diversity of β-TI results from its underlying genetic diversity, which can be explained by primary, secondary or tertiary modifiers (5, 6). The primary modifier is the severity of the β-globin gene mutation itself. They are the numerous different alleles at the beta-chain locus that can cause either complete or marked reduction in beta-chain synthesis. Secondary modifiers include co-inheritance of α- thalassemia, and increased synthesis of the γ-chains and fetal Hb production after infancy (7, 8). Anything that modifies the magnitude of the
surfeit of α-chains should have an important impact on the phenotype (9). The co-inheritance of α thalassemia leads to a reduction in the excess of α-chain pool and inclusion-body formation in erythroid precursors (9). As the spectrum of molecular forms of α-thalassemia is broad, this interaction leads to a wide range of different β-thalassemia phenotypes. The alpha-hemoglobin stabilizing protein (AHSP) is another described modifier. It is an abundant, erythroid-specific protein that forms a stable complex with free α Hb. It specifically protects free α Hb from precipitation, reducing the deleterious effects of free α Hb precipitation and modulates pathological states of α Hb excess, in patients with β thalassemia (6, 9, 10). Similarly, the variation of fetal hemoglobin (HbF) production is one of these secondary modifiers. The degree of globin-chain imbalance can be reduced by the more effective synthesis of the gamma chains of HbF after birth. Different genes are involved in modifying the gamma chain response, some that are encoded in the beta globin gene cluster, others that are on different chromosomes. Tertiary modifiers include genetic and environmental factors that alter specific complication rates (8, 11, 12).

β-TI may also result from the increased production of α-globin chains by a triplicated or quadruplicated α-genotype associated with β- heterozygosity, or when a single β-globin locus is affected while the other is completely normal (dominant inclusion body β-thalassemia)(8, 13, 14).

III. Clinical features and complications

Three main factors are responsible for the clinical sequelae of β-TI: ineffective erythropoiesis, chronic anemia and iron overload (Figure 2)(4). Table 1 summarizes the clinical complications of β-TI, along with their management.

Extramedullary haematopoietic pseudotumors

Transfusion independence comes at the cost of an important hypertrophy of erythroid marrow at the medullary and extramedullary sites. It results in characteristic deformities of the skull and the face. Masses of erythropoietic tissue primarily affect the spleen, liver, lymph nodes, broad ligaments, kidneys, adrenal glands, pleura, retroperitoneal tissue, skin, peripheral and cranial nerves, and spinal canal (15-19). More frequently than in β-TM, extramedullary haematopoiesis occurs in 15-20% of β-TI cases by the age of 20 to 30 years old and in more than one third of cases after the age of 30 (4, 20). While usually causing mild compression
symptoms, some extramedullary hematopoietic lesions are present as pseudotumors that can cause various neurological symptoms due to spinal compression (4).

**Thrombosis and pulmonary hypertension**

Thromboembolic events in general are more common in \(\beta\)-TI than in \(\beta\)-TM (21). There are several factors that contribute to this hypercoagulable state in patients \(\beta\)-TI. These include: formation and precipitation of hemichromes, formation of reactive oxygen species, expression of negatively charged phospholipids, increased platelet aggregation, increased expression of activation markers, presence of platelet morphologic abnormalities, expression of endothelial adhesion molecules and tissue factor on endothelial cells, formation of microparticles, monocyte and granulocyte activation (22). These factors have been observed at a higher rate in splenectomized \(\beta\)-TI patients (23).

Pulmonary hypertension (PHTN) is another hematological complication in patients with \(\beta\)-TI. It is 5-times more prevalent in \(\beta\)-TI than in \(\beta\)-TM as revealed by right heart catheterization (24). Although the exact mechanism underlying the association between PHTN and thalassemia remains unknown (25, 26), it is believed to be due to vasculopathy resulting from excessive haemolysis combined with nitric oxide depletion and enhanced platelet activation. Transfusions have been shown to significantly reduce PHTN in patients with thalassemia (8, 27, 28). This, however, needs to be reproduced in clinical trials before any conclusions can be drawn.

**Silent brain infarcts**

Although strokes are uncommon in \(\beta\)-TI, silent brain infarctions have been detected on magnetic resonance imaging (MRI) in patients with \(\beta\)-TI (29, 30). Transfusion independence and age showed a significant correlation with the presence of either single or multiple white matter lesions (WM) in MRI, which remains a gold standard in the detection of ischemic lesions in the brain (30, 31). There currently exists no data in order to determine whether these silent abnormalities are really clinically asymptomatic. We believe that further studies are needed to evaluate the long term implications and eventual complications of silent brain infarcts in \(\beta\)-TI.

**Hepatocellular carcinoma**
The accumulation of the majority of iron in the liver leads to an increased risk of developing fibrosis, cirrhosis and hepatocellular carcinoma (HCC) mainly in non-chelated patients. The incidence of HCC in patients with thalassemia has been increasing with time (32). HCC seems to be more commonly seen in patients with β-TI than βTM (33-35). This is because β-TI patients usually have improved survival compared with those who have β-TM, which enables them to live long enough to develop HCC (33). The first well recognized risk factor for HCC in β-TI is iron overload (36, 37). Another risk factor for HCC in patients with β-TI is chronic viral infection, namely, with HCV or HBV, related to blood transfusion exposure. Current management options for HCC in patients with thalassemia include screening and prevention plans in addition to treatment strategies that target the abovementioned HCC risk factors.

**Leg ulcers**

TI patients are generally at a higher risk of developing leg ulcers when compared with regularly transfused β-TM patients (4, 38). The risk of developing these leg ulcers further increases with age (38, 39). Their pathogenesis has been attributed to reduced tissue oxygenation which is believed to be due to the combination anemia, hypercoagulability, and ineffective erythropoiesis (2, 40, 41). Once it develops, the management of leg ulcers is often painful and difficult. Chelation therapy, hydroxyurea, oxygen chambers, and blood transfusions could be beneficial without any sufficient evidence to be clearly recommended (8, 42, 43).

**Endocrine disease**

Although less frequent than in β-TM, endocrine complications are among the most common complications in β-TI. They are attributed to iron overload and to suboptimal iron chelation (44, 45). Delayed puberty and hypogonadism are the most common endocrine complications in β-TI and are attributed to iron-mediated damage leading to dysregulation of the hypothalamic-pituitary axis. Hypothyroidism can be observed late in life (45). It is a late consequence of iron deposition in the thyroid gland ultimately leading to parenchymal fibrosis (45). Splenectomy is a specific risk factor for hypothyroidism in β-TI. Hypoparathyroidism, which is seen in up to 6.7% of β-TM patients, is not well studied in β-TI (45).

**Diabetes Mellitus and Glucose Intolerance**
Diabetes mellitus (DM) and glucose intolerance are common complications in thalassemia patients. While glucose intolerance occurs at an earlier stage during adolescence in TI patients, DM frequently occurs at later stages and is usually secondary to iron overload and subsequent chronic liver disease. The prevalence of DM and glucose intolerance is 2% and 24% respectively in β-TI. The development of DM in thalassemia is attributed to impaired insulin excretory function secondary to chronic iron overload in the pancreas, selective immune system activation against pancreatic β-cells leading to cell damage, and/or pancreatic cell death due to fat transformation. Iron-mediated diabetes can be reversed if treated early.

**Bone Disease**

Osteoporosis is commonly seen in β-TI patients and can be related to increased bone resorption or decreased bone formation. Iron overload, in addition to nutritional imbalance and increased erythron (due to ineffective erythropoiesis), also explains the occurrence of osteoporosis, osteopenia, and other low bone mineral density states in β-TI patients.

**Pregnancy and fertility**

In most β-TI patients, fertility is not affected and most pregnancies can be achieved spontaneously. However, pregnancy is considered a high risk one, as it is associated with intra-uterine growth retardation, spontaneous abortions and thrombotic events. This is due to many factors including anemia, hypoxia, acute hypersplenism, splenomegaly, and hypercoagulability state. Increased risk of thromboembolism may necessitate short-term anticoagulation with low-molecular weight heparin (LMWH) and platelet anticoagulants followed by a long-term oral anticoagulant. Introduction of transfusion therapy should depend on Hb level, fetal growth status and maternal general and cardiac status. Such transfusions should be considered at high risk of alloimmunization. Splenectomy may be required before conception or in postpartum in cases of hypersplenism or splenomegaly. Folic acid deficiency is commonly seen and can cause neural tube defects so folic acid supplementation is recommended. Optimal management of pregnant women with β-TI requires a multidisciplinary approach with close maternal and fetal surveillance.

**IV. Conventional Management**
There are a number of options currently available for managing patients with β-TI including transfusion therapy, iron chelation therapy, splenectomy, and hemoglobin F inducers (Figure 3).

**Transfusion therapy**

Whether to initiate transfusion and when are challenging decisions in β-TI. Although β-TI patients are transfusion independent, they might require blood transfusions in certain clinical scenarios (Table 2). Transfusion therapy in patients with β-TI is guided by clinical necessity. The decision to transfuse a patient with any thalassemia should be based not only on Hb level but also on other individual factors such as activity level, feeding, growth, and development. Occasional blood transfusions in β-TI are indicated in pregnancy, surgical settings in anticipation of acute blood loss, or in cases of serious infections (8, 55). Frequent blood transfusions should be considered for children with growth failure and poor performance at school, and for adults being treated for specific complications (8, 55). Preventive transfusions should be initiated for patients at high risk of developing thrombotic disease, PHTN, extramedullary hematopoiesis or leg ulcers (8, 55).

**Iron chelation therapy**

Iron overload in β-TI develops from increased intestinal absorption. Results from the OPTIMAL CARE study, have suggested that β-TI is associated with high morbidity rates. Moreover, there exists an age-related increase in the severity of the TI-associated complications (27). Several modalities are currently available for the diagnosis and monitoring of iron overload in β-TI, each carrying their own advantages and disadvantages. Serum ferritin assay is widely available and remains to be heavily relied on in resource-poor countries where MRI technology is not available (58). Current available guidelines recommend measurement of serum ferritin every three months (8). In patients with β-TI, serum ferritin values of >800 μg/l and <300 μg/l are used to indicate the need for iron chelation initiation or interruption (8, 59). However, studies have showed that serum ferritin underestimates the iron burden in NTDT (60, 61).

Measurement of liver iron concentration (LIC) is another modality that is commonly used to diagnose iron overload in β-TI. Since LIC and total body iron stores are linearly related (62), LIC quantification with R2 or R2* MRI is currently the test of choice for estimation of total body iron in all thalassemia patients. In patients with β-TI, LIC values ≥5
mg have been associated with more complications and thus increased morbidity(63). As per the available guidelines, assessment of LIC should be performed every 6, 12 or 24 months. This will depend on the severity of the iron overload(8). Other available markers for iron overload that have been investigated in β-TI include non-transferrin bound iron (NTBI) and transferrin saturation(64).

Iron chelation therapy is currently the cornerstone of managing β-TI patients and minimizing disease-related complications. In β-TI, it is indicated in patients ≥10 years of age (or 15 years in hemoglobin H disease) if their LIC ≥5 mg Fe/g DW or when their serum ferritin level is ≥ 800 μg/l (when LIC is not available) (65). Iron-chelating drugs currently available for the treatment of iron overload in thalassemia patients include deferoxamine in subcutaneous or intravenous injection, oral deferiprone in tablet or solution form, and oral deferasirox in dispersible tablet (Table 3)(8, 66-68) Whereas these three agents are currently available in TDT, deferasirox remains to be the only chelator to have received Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval in NTDT based on results from the THALASSA trial(2, 69). In this study, one-year deferasirox treatment in β-TI patients older >10 years was found to decrease LIC by a mean of 2.33 ±0.70 and 4.18 ± 0.69 mg Fe/g dw at a daily dose of 5 mg/kg and 10 mg/kg, respectively, compared to placebo.(69) Doses were doubled after 6 months for patients with LIC >7 mg Fe/g dry weight and <15% reduction from baseline. Sub-analyses from the study showed that reduction in LIC with deferasirox 5 and 10 mg/kg/day starting dose groups is consistent irrespective of baseline LIC/serum ferritin, age, gender, race, splenectomy status, and underlying NTDT form. The analyses also showed that greater reductions in LIC were achieved in patients dose-escalated at 6 months from deferasirox 10 mg/kg/day starting dose to 20 mg/kg/day. The overall incidence of adverse effects was comparable between the deferasirox and placebo arms, and the main side effects were nausea, gastrointestinal discomfort, and headache. These side effects, which were mild to moderate in severity, resolved spontaneously without discontinuation of the drug.

The THETIS study, a phase IV, multicenter efficacy and safety study of deferasirox targeting a larger population of patients with NTDT, showed at 1-year analysis of the results that deferasirox is effective in reducing iron overload in NTDT at a starting dose of 10 mg/kg/day, with dose escalations starting at week 4 up to 30 mg/kg/day according to the LIC response (70). In addition, the THESIS study provided more evidence about the satisfactory
safety profile of the drug and reported on cases of pancreatitis and ocular toxicity possibly related to treatment with deferasirox (70).

Successful management of iron overload extends beyond chelator efficacy and safety. Ensuring adherence is essential, and applicable to most chelators irrespective of administration form. Currently, some of the barriers to optimal adherence to deferasirox dispersible tablets (DT) include palatability, preparation time, and requirements for a fasting state at the time of dosing. A new film-coated tablet (FCT) formulation has been developed. This formulation can be swallowed once-daily, whole or crushed, with or without a light meal. The open-label, phase II ECLIPSE study (71) evaluated the patient-reported outcomes (PRO) in TDT or lower-risk myelodysplastic syndromes patients randomized to receive deferasirox DT or FCT over a 24-week period. FCT recipients consistently reported better adherence, greater satisfaction, and fewer concerns, with a safety profile consistent with the known DT formulation (71). These findings suggest that there exists a preference in favor of the new formulation, with better patient satisfaction and adherence reported which translates into reduced iron overload-related complications (71). The utility of this new formulation in patients with NTDT remains to be investigated.

Splenectomy

Splenectomy is common practice in NTDT patients, and serves to increase total Hb level by 1-2 g/dl (2, 38). However, cumulative evidence confirms an association with a variety of adverse outcomes. The spleen functions to scavenge procoagulant platelets and RBCs, which together are the key factors underlying the hypercoagulable state observed in NTDT. Splenectomized NTDT patients are at increased risk for venous thromboembolism, PHTN, leg ulcers and silent cerebral infarction than their non-splenectomized counterparts (72). Nonetheless, splenectomy may be indicated in certain clinical settings such as: hypersplenism (resulting in worsening anemia, leucopenia or thrombocytopenia or their clinical manifestations), worsening anemia leading to poor growth (when transfusion therapy is not possible) or splenomegalgy (accompanied by left upper quadrant pain, early satiety or concern of splenic rupture) (Table 2)(8).

Hemoglobin F inducers:

HbF inducers work by increasing γ-globin production, a β-like globin molecule which can bind excess α-chains, thus decreasing the α/β-chain imbalance inherent to thalassemia,
and improving effective erythropoiesis(73). Hydroxyurea (or hydroxycarbamide) has been the most studied HbF inducer in β-TI. Early case reports documented hematological improvements in β-thalassemia patients treated with hydroxyurea, and since then several studies have evaluated this drug in β-TI and have considered it to be clinically effective with a satisfactory long-term safety (73). However, the data is conflicting and mostly comes from single-arm trials or retrospective cohort studies. Although HbF inducers are a potentially promising aspect in NTDT treatment, large, randomized, controlled trials are needed before these agents or their derivatives are widely used in management.

V. New therapeutic approaches

Recently, the discovery of previously unknown mechanisms leading to anemia has enabled the development of novel therapies. The aim is to improve the treatment, and possibly to cure the disease. Newly emerging therapies include minihepcidins, TMPRSS6, JAK2 inhibitors, apo-transferin therapy, activin receptor fusion proteins, stem cell transplantation, and gene therapy and gene editing.

a) Minihepcidins

It is known that hepcidin plays a key role in the limitation of both iron absorption and utilization. Minihepcidins, or long acting hepcidin analogues, have been shown to restrict iron absorption and utilization in the setting of iron overload, with beneficial effects on ineffective erythropoiesis(74-76). They are known to increase the levels of hepcidin therefore decreasing iron absorption from the gastrointestinal tract, increasing the redistribution of iron to macrophages, and limiting end-organ toxicity (77). Studies on mice have also shown that minihepcidin therapy not only increases Hb concentrations but also decreases reticulocyte counts, and reduces spleen size(77, 78).

b) TMPRSS6

Transmembrane protease serine 6 (TMPRSS6), has been found to play a key role in hepcidin expression from the liver. Its inactivation leads to increased hepcidin levels and subsequent amelioration of iron overload and improved ineffective erythropoiesis(79, 80). Anti-sense oligonucleotides and small interfering RNA (siRNAs) targeting TMPRSS6 have been effectively used in β-TI murine models to stimulate hepcidin, leading to a reduction in
Iron burden (81-83). Genetic ablation of TMPRSS6 also improved ineffective erythropoiesis and decreased splenomegaly in β-TI, without a concomitant decrease in erythropoietin production (80). Normalization of RBC survival is a significant component of the effects of TMPRSS6 inhibition on both hemoglobin and spleen size. The abovementioned data on TMPRSS6 provide proof of principle that pharmacologic manipulation of hepcidin may be an effective treatment for human diseases of iron dysregulation.

c) Janus Kinase 2 inhibitors

Thalassemia patients tend to demonstrate an increased expression of phosphorylated Janus Kinase 2 (JAK2). This in turn leads to excessive proliferation and decreased differentiation of erythroid progenitors (84, 85). JAK2 inhibitors might therefore be effective in thalassemia (86). Ruxolitinib is a JAK2 kinase inhibitor that is already being used in the treatment of myeloproliferative diseases. Studies in thalassemic mice indicated that a short treatment with a JAK2 inhibitor can ameliorate ineffective erythropoiesis and decrease spleen size (84, 87, 88). For example, the TRUTH study, a phase IIa study, revealed up to a 26.8% decrease of spleen volume during the 30-week study period, in addition to slightly improved pre-transfusion Hb levels, with a benign safety profile overall (87). Although all subjects of the study had TM, the results of this clinical trial might be promising for TI patients with enlarged spleens.

d) Apo-transferrin therapy

Transferrin can circulate in the blood in three major forms: monoferric transferrin, dimeric transferrin, and apo-transferrin (89). Daily apo-transferrin injections on thalassemic mice increased Hb levels, decreased apoptosis of erythroid precursors and improved their maturation, and decreased the size of the spleen (89). These findings have promising clinical implications in TI patients.

e) Activin receptor fusion proteins

Sotatercept (ACE-011), an activin type IIA receptor (ActRIIA) fusion protein, acts mainly on late-stage erythropoiesis leading to increased hemoglobin production. Results from a study by Ruckle et al. have confirmed that sotatercept therapy increases RBC counts and Hb concentrations (90). In NTDT murine models, sotatercept therapy caused a decrease in ineffective erythropoiesis and bilirubin levels and markedly improved anemia (91). Another study by Porter et al. concluded that the subcutaneous administration of sotatercept every
three weeks might improve anemia in NTDT patients with a good safety profile (91). Other fusion proteins of the same family include luspatercept (ACE-536), which is currently undergoing extensive research, especially in TDT (92).

f) Hematopoietic Stem cell transplantation

Hematopoietic stem cell transplantation (HSCT), which involves the replacement of mutant hematopoietic cells, is the only existing curative therapy that is available for both β-TI and β-TM patients(93). It is now an established approach to correct the defective erythropoiesis, particularly when matched sibling donors are available. It is now widely applied with a disease free survival exceeding 80% with HLA-matched sibling donor transplants(94-97). For example, a retrospective study by Baronciani et al. on the natural history of thalassemia patients who received HSCT showed a 2-year overall survival rate of 88±1% and a 2-year event-free survival incidence of 81±1% (93). Patients who received a transplant from an HLA-identical sibling had the best results, with 2-year overall and event-free survival rates of 91±1% and 83±1%, respectively.

g) Gene therapy and genome editing

Gene therapy is another promising treatment modality in the management of thalassemia. Some recent studies have described the long-term correction of murine models of human β-thalassemia and sickle cell anemia by lentivirus-mediated gene transfer (98, 99). Furthermore, evidence of high gene transfer and expression in transduced hematopoietic cells in humans has also been noted.

The emergence of gene editing technology, whether by direct correction of genetic mutations in the endogenous DNA of the cell or by disruption of specific DNA sequences in the genome, offers a new approach for treating β-thalassemias. This is facilitated by site specific double strand breaks (DSB) which can be induced with zinc finger nucleases, transcription activator-like effector nucleases (TALENS), meganucleases and more recently with Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 system(100). Other alternatives that could allow more efficient and immediate treatment of β-thalassemiawith genome editing include the disruption of factors that silence the γ-globin genes, such as BCL11A, or γ-globin repressive elements within the β-globin gene locus(79, 101).

VI.Conclusion
B-TI is a subset of thalassemia patients that do not require regular transfusion therapy for survival. It encompasses several genotypes and is mainly a clinical diagnosis. The interplay of three hallmark pathophysiologic factors (ineffective erythropoiesis, chronic anemia, and iron overload) leads to the clinical presentations seen in β-TI. Therapy involves a tailored combination of transfusions, HbF inducers, splenectomy, and iron chelation. New treatment modalities are currently being investigated to broaden options available for β-TI management, with ultimate goals of prolonging longevity, promoting greater compliance and better adherence and improving quality of life. Cappellini et al have recently developed a new scoring system for NTDT patients in order to assess disease severity and thus tailor therapy(102). Though promising, this scoring system has yet to be validated.
<table>
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<tr>
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<th>Management</th>
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<td>Extramedullary Haematopoietic Pseudotumors</td>
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<td>- Hydroxyurea</td>
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<td>Thromboembolic events and Silent Brain Infarcts</td>
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<td>- Anticoagulants or antiaggregants</td>
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<td>- Control of iron overload</td>
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<td>Hepatocellular Carcinoma</td>
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<td>- Chemoembolization</td>
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<td>- Simultaneous percutaneous radiofrequency thermoablation</td>
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<td>- Ethanol injection</td>
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<td>Lég ulcers</td>
<td>- Transfusion as first treatment option</td>
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<td>- If persistent: Hydroxyurea, Dialzep (vasodilators), Oxygen chamber,</td>
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<td>Skin grafts, Platelet derived wound healing factors and granulocyte</td>
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<td>macrophage, Anticoagulation, Topical antibiotics, Sodium nitrite cream</td>
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<td>Endocrinopathies</td>
<td>- Iron chelation therapy</td>
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| Bone Disease                      | - Hormonal therapy  
|                                 | - Hypertransfusion  
|                                 | - Iron chelation therapy  
|                                 | - Nutritional supplementation, and Bisphosphonates  
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|                                 | - Transfusion therapy (depending on Hb level, fetal growth status and maternal general and cardiac status)  

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<thead>
<tr>
<th>Indications for Transfusion</th>
<th>Indications for Splenectomy</th>
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<tr>
<td>• Occasional Blood Transfusions</td>
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<td>- Surgery</td>
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<td>- Severe Infections</td>
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<td>- Pregnancy</td>
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<td>• Frequent Blood Transfusions</td>
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<td>a) Children:</td>
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<td>b) Adults:</td>
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<td>- failure of secondary sexual development</td>
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<td>- declining hemoglobin level</td>
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<td>- huge enlargement of spleen (&gt; 3cm/year)</td>
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<td>• Preventive transfusions</td>
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<td>- Patients at high risk of:</td>
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<td>a) thrombotic disease</td>
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<td>b) pulmonary hypertension</td>
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<td>c) extramedullary hematopoiesis</td>
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<td>d) leg ulcers</td>
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<td>• Worsening anemia leading to poor growth and development</td>
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<td>• Hypersplenism</td>
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<td>- Leukopenia or thrombocytopenia causing clinical problems such as recurrent bacterial infection or bleeding, respectively</td>
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<td>• Splenomegaly</td>
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<td>- Accompanied by symptoms such as left upper quadrant pain or early satiety</td>
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<td>- Massive splenomegaly (largest dimension &gt;20 cm) with concern about possible splenic rupture</td>
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<tr>
<td>Structure</td>
<td>Deferoxamine (DFO)</td>
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<tr>
<td><img src="image1" alt="Structure Diagram" /></td>
<td><img src="image2" alt="Structure Diagram" /></td>
</tr>
<tr>
<td>Administration route</td>
<td>Subcutaneous or Intravenous</td>
</tr>
<tr>
<td>Administration time</td>
<td>Every 8-12 hours 5-7 days/week</td>
</tr>
<tr>
<td>Half-life</td>
<td>20-30 minutes</td>
</tr>
<tr>
<td>Recommended dose</td>
<td>30-60 mg/kg/day</td>
</tr>
<tr>
<td>Route of iron excretion</td>
<td>Urinary and fecal</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Delay in bone growth, auditory and ocular complications, local reactions and allergies</td>
</tr>
</tbody>
</table>

TDT: Transfusion-dependent thalassemia; NTDT: non-transfusion-dependent thalassemia
Figure legends:

**Figure 1**: Spectrum of β-thalassemias according to disease severity and transfusion requirement

**Figure 2**: Mechanism of iron overload development due to ineffective erythropoiesis in β-TI

Tables:

**Table 1**: Complications of β-TI, and their management options

**Table 2**: Indications for transfusion and splenectomy in β-TI

**Table 3**: Characteristics of the currently available iron chelators in thalassemia management(8, 67)
Abstract

**Background:** The spectrum of thalassemias is wide ranging, from thalassemia minor which consists of mild hypochromic microcytic anemia without obvious clinical manifestations, to thalassemia major (TM) which is characterized by severe anemia since the first years of life and are transfusion dependent. Thalassemia intermedia (TI) describes those patients with mild or moderate anemia.

**Objective:** To describe the genetic features and major clinical complications of TI, and the therapeutic approaches available in the management of this disease.

**Methods:** Publications from potentially relevant journals were searched on Medline.

**Results and discussion:** Over the past decade, the understanding of TI has increased with regards to pathophysiology and molecular studies. It is now clear that clinical presentation and specific complications make TI different from TM. It is associated with greater morbidity, a wider spectrum of organ dysfunction and more complications than previously thought.

**Conclusion:** TI is not a mild disease. The interplay of three hallmark pathophysiologic factors (ineffective erythropoiesis, chronic anemia, and iron overload) leads to the clinical presentations seen in TI. New treatment modalities are currently being investigated to broaden the options available for TI management.

**Key words:** Thalassemia intermedia, iron chelation, iron overload, complications, management

**Conflicts of interest:** The authors declare that they have no conflict of interest.

**Funding:** None


Figure 1: Spectrum of β-thalassemias according to disease severity and transfusion requirement

*β-thalassemia intermedia (β-TI)
Blood transfusions not necessary for survival; reserved for certain indications only

β-thalassemia major (β-TM)
Regular, lifelong transfusions and chelation required for survival

β-thalassemia minor
Transfusions not required

Transfusion Requirement

Mild Moderate Severe

Severity of disease

*: Refer to Table 2 for indications for Transfusion in β-TI
Figure 2: Mechanism of iron overload development due to ineffective erythropoiesis in β-TT.