



An overview of current treatment strategies for β -thalassemia

Maria Domenica Cappellini (Professor of Internal Medicine), Vip Viprakasit (Associate Professor in Hematology and Program Coordinator for Thalassemia Research) & Ali T Taher (Professor of Medicine at the Division of Hematology-Oncology)

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EXPERT OPINION

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An overview of current treatment strategies for β -thalassemia

Maria Domenica Cappellini[†], Vip Viprakasit & Ali T Taher

[†]University of Milan, Ca Granda Foundation IRCCS, Milan, Italy

Introduction: At least 40,000 people per year worldwide are born with β -thalassemia. Patients with β -thalassemia major are reliant on regular red blood cell transfusions for survival from a young age. For those with β -thalassemia intermedia or hemoglobin (Hb) E/ β -thalassemia, symptoms range from mild clinical presentation to a more severe phenotype and patients are not necessarily transfusion-dependent.

Areas covered: Here, β -thalassemia treatment strategies including transfusion, splenectomy, fetal hemoglobin induction, hematopoietic stem-cell transplantation, in addition to potential future treatment options, are reviewed. Approaches for the monitoring and management of complications are also described.

Expert opinion: The most important advances in the treatment of transfusion-dependent β -thalassemia major patients since the advent of iron chelation therapy are the introduction of oral iron chelators in addition to technologies for the direct measurement of iron in organs. For non-transfusion-dependent patients with β -thalassemia intermedia or HbE/ β -thalassemia, recent studies have highlighted the significance of iron overload-related complications and the increase in incidence with advancing age, prompting the development of much-needed clinical treatment guidelines. Future research should focus on improving the treatment of β -thalassemia major patients to further extend survival and quality of life, and continued identification of β -thalassemia intermedia or HbE/ β -thalassemia patients who may benefit from transfusion and iron chelation therapy.

Keywords: chelation, complications, hematopoietic stem-cell transplantation, hydroxyurea, iron, transfusion, β -thalassemia

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1. Introduction to β -thalassemia

Annually, over 40,000 people worldwide are born affected by β -thalassemia, though it has been suggested that this is likely to be an underestimate [1]. Incidence is highest in the Mediterranean, the Middle East, North America and South East Asia (particularly India, Thailand and Indonesia; this region accounts for ~ 50% of affected births) and incidence is increasing worldwide as a result of migration [2,3].

β -Thalassemias are characterized by a reduction or deficiency of β -globin chains and a subsequent imbalance in globin chains of the hemoglobin (Hb) molecule, which leads to impaired erythropoiesis. A wide variety of different mutations (> 200) have been documented that affect the β -globin gene, for which patients may be either homozygous or heterozygous. Phenotypic effects, therefore, range widely from slight impairment to the complete inhibition of β -globin chain synthesis [4].

β -Thalassemia therefore comprises a number of different conditions, including β -thalassemia major in addition to β -thalassemia intermedia and HbE/ β -thalassemia. Among these, β -thalassemia major and the most severe form of HbE/ β -thalassemia are frequently referred to as transfusion-dependent thalassemia (TDT). In contrast, β -thalassemia intermedia and the mild and moderate forms

Article highlights.

- Currently available treatment strategies for patients with β -thalassemia include red blood cell transfusion, splenectomy, fetal hemoglobin induction and hematopoietic stem-cell transplantation.
- Several potential future treatment options are also undergoing clinical trials, including gene therapy, Janus kinase 2 inhibitors and techniques for the correction of anemia without transfusions including angiotensin-converting enzyme-536, a modified activin type IIb receptor fusion protein.
- Iron overload occurs in patients with β -thalassemia, regardless of their transfusion status, and is associated with an increased likelihood of complications. Though access to cardiac MRI techniques has led to a reduction in mortality due to cardiac iron overload, liver damage is now coming to the forefront.
- A number of other complications may also occur, though they vary between patients with β -thalassemia major and those with β -thalassemia intermedia or hemoglobin E/ β -thalassemia. Cardiac and hepatic complications may occur in addition to endocrinopathies, pulmonary hypertension, extramedullary hematopoietic pseudotumors, osteoporosis, thromboembolic events and leg ulcers. Regular patient monitoring is essential to facilitate effective management.
- Tailored iron chelation regimens have led to improved survival in β -thalassemia major patients, as well as a substantial reduction in iron-related complications.
- Future research should focus on the continued improvement and refinement of treatment options for transfusion-dependent patients, in addition to the identification of patients who require prompt and effective clinical management in spite of a lack of dependence on regular blood transfusion.

This box summarizes key points contained in the article.

of HbE/ β -thalassemia are among several thalassemia types that are grouped as non-TDT (NTDT) (Figure 1).

Patients with β -thalassemia major have symptoms at the severe end of the clinical spectrum and are reliant on regular red blood cell transfusions for survival from a young age. Each year, ~ 23,000 people are born affected by β -thalassemia major [1,3]. In contrast, β -thalassemia intermedia occurs less frequently, although accurate global incidence has not yet been established [5]. In this case, the scale of severity varies significantly, ranging from mild clinical presentation with almost normal growth, to a more severe phenotype characterized by early onset anemia and symptoms including growth and development retardation and skeletal deformities. Some patients can also become transfusion-dependent during their lifetime [6]. Of note, though β -thalassemia major describes patients with a clinically severe form of the disease, whereas β -thalassemia intermedia describes patients with less severe symptoms, the underlying molecular and pathophysiological basis for the two diseases is not necessarily distinct [4].

HbE/ β -thalassemia is the most common form of thalassemia in North Eastern/Eastern India, Bangladesh and South East Asia [2], and occurs as a result of co-inheritance of HbE (caused by substitution in the β -globin gene, leading to the production of structurally abnormal Hb) and a β -thalassemia allele. Clinically, HbE/ β -thalassemia is a highly heterogeneous disease. Typically, anemia with splenomegaly develops from 6 to 12 months of age, with impaired growth during the first decade of the patient's life [7]. Clinical symptoms among patients with mild and moderate forms of the disease vary widely; patients may be transfusion-dependent or require occasional or intermittent transfusion. In contrast, patients with the severe form are often transfusion-dependent and are generally managed in the same way as β -thalassemia major patients.

2. Treatment strategies

2.1 Transfusion

As mentioned, β -thalassemia major patients are dependent on transfusions for survival. For other patients, transfusion may occur rarely, occasionally or intermittently (Table 1). For example, occasional or intermittent transfusion therapy may be appropriate for β -thalassemia patients who are not transfusion-dependent as it provides healthy erythrocytes and reduces the occurrence of ineffective erythropoiesis [8,9]. Of note, such NTDT patients should also be closely monitored for triggers of regular transfusion, as delayed transfusion can lead to growth and pubertal delay, thalassemic facies and hypersplenism [6].

Clinicians should follow transfusion practices and policies recommended in relevant regional guidelines as these often vary depending on local considerations [6,10-15]. Particular attention should be given to hemovigilance practices [16] in order to minimize issues relating to appropriate blood screening, such as transmission of infectious diseases. A record should be kept of the patient's transfusion history as the rate of transfusional iron loading may be important for subsequent iron chelator dose selection.

Furthermore, a number of considerations should be taken into account when initiating and continuing transfusion in patients with β -thalassemia intermedia or mild/moderate HbE/ β -thalassemia. Caution should be exercised so that the patient is not subjected to frequent transfusions unnecessarily. Hb levels can fluctuate in non-transfusion-dependent patients, and therefore, upon diagnosis, patients should be followed carefully over several months before a treatment decision is made. Quality of life must also be taken into account as patients can survive and even thrive with an Hb level around 7 g/dl (particularly those with HbE/ β -thalassemia) [17-19]. Finally, it is important that patients are regularly reassessed, following initiation of transfusion, to determine whether continued transfusion is necessary.

A number of complications can occur as a result of transfusion. These include iron overload and related complications, such as cardiac, liver and endocrine problems. In addition,

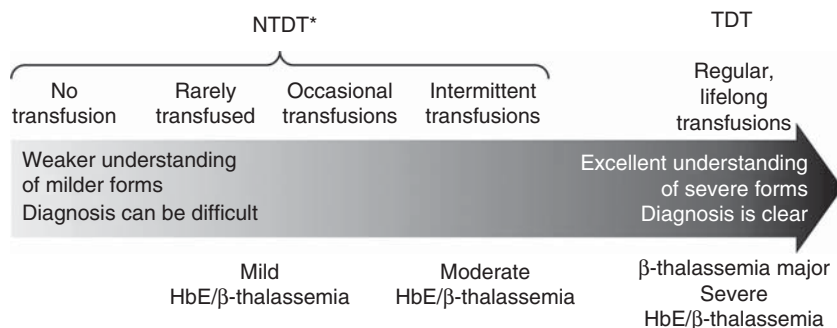


Figure 1. Transfusion dependence distinguishes β -thalassemias and their severity.

Adapted from [117]. Obtained from Haematologica/the Hematology Journal website <http://www.haematologica.org>.

*NTDT also includes α -thalassaemia and HbH disease.

Hb: Hemoglobin; NTDT: Non-transfusion-dependent thalassaemia; TDT: Transfusion-dependent thalassaemia.

Table 1. Clinical requirements for occasional, intermittent or chronic transfusions in patients with β -thalassaemia.

Transfusion frequency	Disease	Clinical requirement
Chronic	β -Thalassaemia major or severe HbE/ β -thalassaemia Severe β -thalassaemia intermedia	Patients require regular blood transfusions for survival [12] Frequent blood transfusion may become necessary when symptoms are severe [6,12,19,96]
Intermittent	Moderate β -thalassaemia intermedia or HbE/ β -thalassaemia	Patient requires transfusion as a result of specific clinical features and symptoms [6] Reduction in Hb with profound splenomegaly Growth failure Failure of secondary sexual development Poor quality of life Patient requires transfusion for the prevention/management of complications [6] Thrombotic or cerebrovascular disease Pulmonary hypertension Extramedullary hematopoietic pseudotumors Leg ulcers
Occasional	Mild β -thalassaemia intermedia or HbE/ β -thalassaemia	Patients may require a one-off blood transfusion on the occurrence of a specific event [19,96] Anticipated acute stress and/or blood loss (e.g., pregnancy, surgery, infection) Hb decrease

Hb: Hemoglobin.

alloimmunization may occur, whereby the recipient mounts an immune response to donor antigens, resulting in various clinical consequences. Of note, this is more likely in non-transfusion-dependent patients (as transfusion is often initiated later in life), and in pregnant women and splenectomized patients. Alloimmunization can be minimized with good blood matching procedures [20,21].

2.2 Splenectomy

Hypersplenism may occur as a result of large numbers of cells being pooled and destroyed in the spleen's reticulo-endothelial system and hemodilution because of an increased

plasma volume. Therefore, spleen size should be carefully monitored in all patients with β -thalassaemia.

Many patients with β -thalassaemia major require splenectomy. This should be performed in specific, defined clinical circumstances [12] including splenic enlargement accompanied by left upper quadrant pain or early satiety, or leucopenia or thrombocytopenia due to hypersplenism. However, good clinical management may delay or prevent hypersplenism, reducing the need for splenectomy [22].

In contrast, among patients with β -thalassaemia intermedia or mild/moderate HbE/ β -thalassaemia, splenectomy should not be the first management option if others are available as

it is associated with multiple adverse outcomes [6,23-25]. As abnormalities of platelets and red blood cells in these patients become more prominent following splenectomy, patients are at an increased risk of thrombotic and vascular events, with an associated increased mortality rate [26,27]. Splenectomy should be avoided in NTD patients younger than 5 years of age, and in general should be reserved for very specific patients, including those with worsening anemia leading to poor growth and development; where transfusion and iron chelation are not possible or available; and in cases of hypersplenism or splenomegaly/massive splenomegaly.

For all patients, should splenectomy be performed, laparoscopic splenectomy is preferable to open surgery, and preventative measures – such as vaccination, prophylactic antibiotics and coagulation prophylaxis – should be taken to minimize the risks [6,12,28].

2.3 HbF induction

Inducing agents such as hydroxyurea may be used in patients with β -thalassemia to increase the production of γ -globin (a β -globin-like molecule), which binds to α -chains to produce HbF, addressing the imbalance in globin chains. This, in turn, reduces the occurrence of ineffective erythropoiesis, decreases hemolysis and increases total Hb. There is, unfortunately, a lack of randomized clinical trials investigating the efficacy of hydroxyurea treatment. Though data are available from a large number of single-arm trials or retrospective analyses of hydroxyurea therapy, patient numbers are small and results have not been consistently reproduced (for a review of all of these studies, see reference [29]). However, the clinical outcomes for patients in these studies are summarized as they represent an indication of potential efficacy.

In patients with β -thalassemia major, the proportion of patients who are no longer dependent on transfusion after treatment varies greatly between studies from around 25 to 80%. Around 20 – 50% of patients exhibit a ‘partial response’ whereby transfusion requirements are reduced [29]. Improvements in transfusion requirements are also associated with a reduction in iron overload and hemolytic indices.

In β -thalassemia intermedia, responses vary greatly and study end points differ according to the severity of the disease before treatment. In a small study of β -thalassemia intermedia patients who were previously transfusion-dependent as a result of the severity of the disease, eight of nine patients showed a good response (> 70% reduction in transfusion requirements) [30]. In studies of non-transfusion-dependent β -thalassemia intermedia patients, Hb increases of > 10 g/dl were observed in around 60 – 70% of patients, though this was not always maintained during a follow-up of more than 12 months [31,32]. Hydroxyurea treatment is associated with a decreased incidence of many of the morbidities associated with this disease. In a study of 584 patients in the OPTIMAL CARE study, hydroxyurea treatment was associated with a reduction in pulmonary hypertension, leg ulcers, hypothyroidism, osteoporosis and

extramedullary hematopoietic tumors, although there was an increased risk of hypogonadism [33].

Fewer studies have been performed in patients with HbE/ β -thalassemia, and again end points tend to vary between studies. A positive response (such as elimination of transfusion requirement or a significant increase in Hb) has been observed in around 35 – 40% of patients [34,35], and improvement in anemia is generally associated with improvement in quality-of-life-related parameters [29].

Where there is no immediate need for transfusion or splenectomy, and no indication that Hb levels will drop suddenly, it is suggested that a modulator of HbF is trialed. If Hb levels do drop suddenly, then transfusion prior to splenectomy might be more appropriate.

2.4 Hematopoietic stem-cell transplantation

Hematopoietic stem-cell transplantation (HSCT) is the only treatment that can be considered a cure for β -thalassemia [36], and enhanced conditioning regimens and donor selection procedures have improved outcomes of this treatment in recent years [37]. In such a procedure, the donor is ideally a human leukocyte antigen (HLA)-identical sibling of the patient, though ~ 60% of patients lack such a suitable family donor. In these cases, transplant from matched unrelated donors may be possible [37].

In patients with β -thalassemia major, the outcomes of HSCT vary according to a variety of factors. Patients are classified as Class 1, 2 or 3 based on iron overload, liver fibrosis and hepatomegaly status, and the highest survival rates are observed among Class 1 and 2 patients. It is also preferable that HSCT is performed at a young age, during the patient’s childhood, as survival rates \geq 88% and thalassaemia-free survival \geq 83% are observed among these patients [12,38]. Of note, HSCT is not generally performed for patients with less severe disease (i.e., β -thalassemia intermedia or HbE/ β -thalassemia) as a result of a high risk of complications.

HSCT is a challenging procedure associated with several risks and complications. Graft-versus-host disease (GVHD) is the major cause of morbidity and mortality following allogeneic HSCT [39]. Risk factors include older age of the recipient, use of a female donor for a male recipient, alloimmunization of the donor and HLA mismatching [40]. In order to minimize the risk of GVHD, immunosuppressant conditioning should take place before and after HSCT [37].

Veno-occlusive disease (VOD) may also occur in the first month after treatment, caused by hepatocyte and sinusoidal endothelial vessel damage following HSCT [41]. Risk factors include patient age < 6.7 years, the type of VOD prophylaxis and the use of busulfan-containing conditioning regimens [41]. Symptoms include pain in the upper right abdomen, weight gain, jaundice and ascites. In severe cases, VOD may lead to liver failure, hepato-renal syndrome, portal hypertension and eventual death from multiorgan failure [41]. It is recommended that patients are monitored to allow prompt identification of VOD-induced inversion of portal flow as these

patients might benefit from treatment with heparin and recombinant tissue plasminogen activator [41].

Iron overload should also be considered in patients undergoing HSCT as excess iron can accumulate before and after HSCT. Levels may remain high for several years, even among patients who become transfusion-independent. Iron overload can affect survival, increasing the risks of infection and GVHD, and acting as a negative prognostic factor. Therefore, patients should be assessed and treated as appropriate for iron overload both pre- and post-HSCT [42].

2.5 Future treatment options

Several new molecules and treatment strategies are currently in development, some of which show some promise for the treatment of β -thalassemia. Gene therapy has been trialed in several exploratory studies, with the aim of transferring β -globin in stem cells to reduce the α - β imbalance in erythroid cells, eventually leading to transfusion independence [43]. In one exploratory clinical trial, an adult patient with severe HbE/ β -thalassemia dependent on monthly transfusions since early childhood became transfusion-independent for 21 months following gene therapy [44]. In this patient, Hb levels of 9–10 g/dl have been maintained, of which one-third contain vector-encoded β -globin.

Janus kinase 2 (Jak2) inhibitors have also been investigated for the treatment of β -thalassemia as they may limit the overproduction of immature erythroid cells in thalassemia, potentially reversing extramedullary hematopoiesis [45]. Based on the available preclinical evidence, it is anticipated that Jak2 inhibitors might reduce the occurrence of splenomegaly, transfusion requirements and possibly iron overload in patients with β -thalassemia intermedia, though clinical data are not yet available [46].

Finally, techniques for the correction of anemia without transfusions have been explored, including sotatercept (angiotensin-converting enzyme [ACE]-011) and ACE-536, modified activin type IIa or IIb receptor fusion proteins that inhibit signaling induced by other members of the transforming growth factor β super family, promoting maturation of terminally differentiating erythroblasts [47,48]. In a murine model of β -thalassemia, the murine ortholog of ACE-536 (RAP-536) attenuated ineffective erythropoiesis, ameliorated anemia and improved associated comorbidities [47], and in healthy volunteers ACE-536 produced a dose-dependent increase in red blood cells and Hb levels [49]. Phase II trials of sotatercept are currently underway, though interim results are promising with a ≥ 2 g/dl increase in hemoglobin occurring in 33% of patients in the highest dose cohort, and generally good tolerability [48].

3. Management strategies (complications)

3.1 Iron overload and chelation

In patients with transfusion-dependent β -thalassemia major, iron overload occurs as a result of accumulation of iron

from transfusions and, to a lesser extent, increased intestinal absorption. Conversely, iron overload in patients with β -thalassemia intermedia or mild/moderate HbE/ β -thalassemia is due to increased intestinal absorption secondary to ineffective erythropoiesis and, to a much lesser extent, accumulation of iron from transfusions [50].

Iron overload is associated with an increased likelihood of complications. In β -thalassemia major patients, if left untreated, iron overload is fatal early in life, usually as a result of cardiac failure [51]. Of note, access to cardiac MRI techniques has led to a significant reduction in mortality as a result of cardiac iron overload in recent years [3,52]. However, as the management of cardiac disorders is improving, liver damage is coming to the forefront, and deaths from hepatic complications are increasing relative to other iron overload-related conditions [53]. Among patients with β -thalassemia intermedia or mild/moderate HbE/ β -thalassemia, there is generally an absence of cardiac siderosis irrespective of liver iron concentration (LIC), and the most common complications include osteoporosis, extramedullary hematopoiesis, hypogonadism and cholelithiasis [33].

Iron load should be regularly monitored in patients with β -thalassemia and iron load values used to guide treatment decisions, including initiation and cessation of chelation and dose escalation [54]. MRI is considered the gold standard; however, associated facilities and the required technical expertise are not always available. Serum ferritin assessment may be a practical and useful alternative for β -thalassemia major patients in particular [55-57]. However, caution is advised as serum ferritin may underestimate LIC in patients with β -thalassemia intermedia or mild/moderate HbE/ β -thalassemia compared with those with β -thalassemia major [58,59]. Furthermore, serum ferritin may also fluctuate in response to infection/inflammation. For NTDT patients, data from the THALASSA study show that serum ferritin thresholds of 800, 2000 and 300 ng/ml may be useful to guide treatment decisions in terms of initiating chelation therapy, escalating dose and interrupting therapy, respectively, in the absence of access to liver MRI techniques [6,60].

The introduction of regular transfusion and chelation regimens has led to improved survival in β -thalassemia major patients, as well as a substantial reduction in iron-related complications. In a study of 977 such patients treated with transfusion and deferoxamine (DFO), lower iron burden was associated with a lower probability of heart failure and hypogonadism and with prolonged survival [61]. Increased survival without cardiac disease was observed in transfused patients in whom iron overload had been reduced as a result of chelation [62].

It has also been acknowledged that optimal outcomes are achieved when chelation is tailored according to individual patient requirements, including transfusional iron loading [57], as well as patient factors that may influence adherence [63]. In regularly transfused patients, details of the rate of transfusional iron loading can guide chelation therapy decisions.

Where this information is unavailable, this is estimated based on the assumption that one donor unit contains 200 mg iron [12].

Several iron chelation agents are available. DFO was the first available chelator and has been in regular use since the 1980s [64]. In transfusion-dependent patients with β -thalassemia major, DFO is effective in reducing liver iron overload. Among patients with baseline LIC between 7 and 14 mg Fe/g dry weight (dw), LIC was reduced by 1.9 ± 2.93 mg Fe/g dw, and among those with LIC > 14 mg Fe/g dw, the value was reduced by 6.4 ± 6.93 mg Fe/g dw [55]. Furthermore, myocardial iron is improved; treatment with doses equivalent to 35 mg/kg/day for 7 days per week over ~ 1 year led to changes in myocardial T2* from 13.3 to 15.0 ms [65], and over 2 years from 11.6 to 14.2 ms [66]. In β -thalassemia major patients with acute decompensated heart failure, continuous 24 h per day intravenous chelation with DFO is recommended, supplemented with deferiprone [67]. Among 14 patients with β -thalassemia intermedia treated with DFO, a significant increase in urinary iron excretion was observed [68]. However, growth retardation and bone changes (e.g., metaphyseal dysplasia) are common with doses > 60 mg/kg/day, especially those who begin chelation in the first 3 years of life [69]. The risk of such complications may be reduced at doses ≤ 40 mg/kg, and pediatric patients should be monitored for body weight and growth every 3 months [64].

Treatment with DFO requires frequent and prolonged subcutaneous administration, which can lead to concerns with patient compliance and quality of life. The introduction of oral chelators, together with routine MRI assessments of liver and cardiac R2 iron load, has substantially improved clinical outcomes for patients [70].

Deferiprone is a bidentate oral iron chelator introduced in 1999 [71]. Deferiprone improves LIC and cardiac iron load in β -thalassemia major patients and allows for combination chelation strategies with DFO [65,72]. A very small number of patients with β -thalassemia intermedia have been treated with deferiprone in clinical trials, though iron overload was reduced [73,74]. In 30 non-transfusion-dependent HbE/ β -thalassemia patients with iron overload, serum ferritin, non-transferrin-bound iron and malondialdehyde decreased significantly ($p < 0.05$) after 1 year [75]. Agranulocytosis and neutropenia are the most serious adverse events associated with deferiprone [76-78]; patient absolute neutrophil count should be determined before starting treatment and monitored on a weekly basis, and therapy stopped if neutropenia develops (absolute neutrophil count $< 1.5 \times 10^9/l$) [71].

Deferasirox is the first once-daily oral iron chelator. Among β -thalassemia major patients, treatment with deferasirox 40 mg/kg/day resulted in LIC decreases from 30.6 ± 18.0 mg Fe/g dw at baseline to 14.4 ± 16.6 mg Fe/g dw after 2 years [66,79]. Combination therapy of deferasirox and DFO has also been assessed, with serum ferritin decreases of 2174 from 5551 ng/ml at baseline and cardiac T2* increases

from 7.03 to 8.24 ms after 1 year [80]. Furthermore, as the only iron chelator to have gained approval for the treatment of iron burden in non-transfusion-dependent patients, deferasirox is indicated for the treatment of chronic iron overload in patients ≥ 10 years of age with β -thalassemia intermedia and HbE/ β -thalassemia [81]. In the THALASSA study, significant decreases in LIC and serum ferritin were observed over 12 months with deferasirox (least squares mean \pm SD LIC decreased by 1.95 ± 0.50 mg Fe/g dw [from baseline 13.11 ± 7.29 mg Fe/g dw] with deferasirox 5 mg/kg/day, and by 3.80 ± 0.48 mg Fe/g dw [from baseline 14.56 ± 7.92 mg Fe/g dw] with deferasirox 10 mg/kg/day) and reductions continued over 2 years of treatment with similar safety profile [82]. Furthermore, chelation with deferasirox can continue until iron reaches near-normal levels [83,84]. Patients undergoing treatment with deferasirox do require regular, close monitoring as rare cases of acute renal failure, hepatic injury or gastrointestinal hemorrhages have been reported, mostly in elderly patients with multiple comorbidities and those with advanced hematologic malignancies [81,85,86].

3.2 Other complications

A number of other complications occur in patients with β -thalassemia, involving several different organ systems (Table 2, Figure 2). Historically, in patients with β -thalassemia major, the most common complications have been cardiac-related. However, as mentioned above, with increased use of cardiac MRI techniques and effective chelation, liver complications are becoming more prominent. Infections (bacterial, viral or fungal) are also a significant cause of mortality and morbidity, particularly in patients with immune abnormalities, severe anemia, splenectomy or iron overload [24,53,61,87], and chelation therapy with DFO has been associated with opportunistic infections by microorganisms that utilize the iron bound by the chelator [88]. In addition, transmission of viruses such as hepatitis viruses or human immunodeficiency virus may occur where transfusion screening practices are not optimal [89,90].

Patients with β -thalassemia intermedia or HbE/ β -thalassemia exhibit a different profile of disease- and treatment-related complications (Figure 2). The OPTIMAL CARE study was a retrospective review of 584 patients with β -thalassemia intermedia at six comprehensive care centers (Lebanon, Italy, Iran, Egypt, UAE and Oman), performed to assess the rate of complications in relation to currently practiced treatment options [33]. This demonstrated that the most common disease-related complications were osteoporosis (23%), extramedullary hematopoiesis (21%), hypogonadism (17%) and cholelithiasis (17%), followed by thrombosis (14%), pulmonary hypertension (11%), abnormal liver function (10%) and leg ulcers (8%), whereas hypothyroidism, heart failure and diabetes mellitus were less frequently observed (all $< 6\%$). The highest rates of complications were seen in patients who did not receive any treatment (Figure 3), and among those who received transfusion, the incidence of

Table 2. Management options for specific β -thalassemia complications.

Complication	Incidence and diagnosis	Management options
Cardiac complications	Common complication among patients with β -thalassemia major, less prevalent with β -thalassemia intermedia or HbE/ β -thalassemia Cardiac iron should be measured by MRI annually, starting after the first decade of life	Cardiac iron increased but cardiac function normal: take measures to improve chelation Cardiac impairment: improve chelation, consider slow blood transfusion with diuretics and cardiac medications (e.g., ACE inhibitors, β -blockers, digitalis) [12] Follow guidelines for effective iron chelation
Hepatic complications	Liver complications, including damage such as fibrosis and cirrhosis, are increasing among β -thalassemia major patients [53,97] HCC frequently complicates hepatic cirrhosis secondary to iron overload. Therefore, both transfusion-dependent and non-transfusion-dependent patients with β -thalassemia are at risk of developing HCC [98] Monitoring the risk of HCC: assessment of α/β protein (with echography) may not be reliable in thalassemia Liver iron assessed annually using MRI	
Infections	Second most frequent cause of mortality in patients with β -thalassemia major, particularly among patients with immune abnormalities, splenectomy, iron overload or severe anemia [12,24,53,61,87]. Major complication in patients with HbE/ β -thalassemia [99] Risk of contracting viral agents during transfusion Regular monitoring not required. However, clinicians should be aware of high likelihood of infection and treatment should be prompt	In addition to standard vaccines administered to healthy population, vaccinate high-risk patients – such as those undergoing splenectomy – against organisms including pneumococcus (pre-splenectomy and with boosters every 5 – 10 years, as dictated by antibody titers), hemophilus influenzae type B, meningococcus serogroup C and hepatitis B virus [12] Bacterial and fungal infections treated with appropriate broad spectrum/specific antibiotic; consider treating immediately, prior to confirmed cultures [12,24] Transfusion practices should minimize or eliminate risk of transmission of blood-borne viruses. On infection, antiviral therapy should be administered to achieve sustained virologic response. Studies have shown efficacy of pegylated interferon plus ribavirin in patients with thalassemia. However, standard of care is under constant review with the approval of several new agents, particularly for HCV genotype 1 [100,101] Chelation with deferoxamine suspended on diagnosis of some specific bacterial infections [12,24]
Thrombosis/ thromboembolic events	β -Thalassemia intermedia and HbE/ β -thalassemia patients at increased risk for thromboembolic events as a result of hypercoagulable state; incidence up to fourfold higher than in patients with transfusion-dependent thalassemia [27,33,102,103] Among β -thalassemia intermedia patients, silent brain lesions are observed in the great majority and overt strokes occur in 5 – 9% with history of thrombosis; incidence correlates with increasing age, splenectomy and transfusion naivety [27,103,104] Patients should be assessed individually and high-risk patients identified based on intrinsic (thalassemia type, number of circulating red blood cells) and extrinsic (splenectomy, transfusion status) factors. Patients can then be referred for further testing [105]	Transfusion reduces rates of thromboembolic events; consider more regular transfusions to increase Hb and avoid/delay splenectomy [6] Consider aspirin therapy for splenectomized patients with elevated platelet counts [27] Hydroxyurea therapy may also provide benefit. However, data to support this approach are limited

ACE: Angiotensin-converting enzyme; FT4: Free total thyroxine; Hb: Hemoglobin; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HRT: Hormone replacement therapy; TRH: Thyrotropin-releasing hormone; TSH: Thyroid stimulating hormone.

Table 2. Management options for specific β -thalassemia complications (continued).

Complication	Incidence and diagnosis	Management options
Pulmonary hypertension	Most common in β -thalassemia intermedia and HbE/ β -thalassemia, although it can occur in β -thalassemia major [106] Annual echocardiographic assessment, particularly in high-risk groups Diagnosis via right heart catheterization and ventilation/perfusion lung scan for patients considered likely to have pulmonary hypertension	Confirmed cases should be referred to a cardiologist Transfusion, hydroxyurea, sildenafil citrate, iron chelation, bosentan and anticoagulant therapy may be of some benefit [6]
Extramedullary hematopoietic pseudotumors	Occurrence ~20% in β -thalassemia intermedia and HbE/ β -thalassemia patients [33], but infrequent with β -thalassemia major [107] Many sites can be affected. However, paraspinal involvement has a particularly negative impact on patient quality of life [108,109] No regular monitoring recommended. MRI of the spine to confirm diagnosis if suspected based on clinical features	Mild-to-moderate neurological deterioration: transfusion, radiotherapy, steroids and/or hydroxyurea Severe neurological deterioration: preoperative transfusion followed by laminectomy, radiotherapy and/or hydroxyurea [110]
Osteoporosis	Affects high proportion of β -thalassemia major patients and also many β -thalassemia patients [111] Diagnosis by bone density scan	Preventative measures include diet and exercise changes, as well as calcium, vitamin D and hormonal supplementation, antiresorption agents (bisphosphonate) or combination therapy (bisphosphonate + HRT) [12,107]
Endocrinopathies	Common in β -thalassemia major, β -thalassemia intermedia and HbE/ β -thalassemia patients, as a result of iron overload Assessment of thyroid function using FT4, TSH and TRH [107] For diabetes, HbA _{1c} assessment may be unreliable in patients with hemoglobinopathies and those receiving regular transfusion. Glucose tolerance test or monitoring of fructosamine levels more appropriate [112,113]	Hypogonadism: early HRT with treatment individualized to each patient [107] Hypothyroidism: replacement treatment and chelation depending on severity of condition Diabetes: acarbose and possibly insulin therapy and chelation therapy [107,114,115]
Leg ulcers	More common in β -thalassemia intermedia and HbE/ β -thalassemia patients [106] Diagnosed by physical examination	Raise legs and feet above heart level for 1 – 2 h during day and while sleeping; topical antibiotics and occlusive dressing; consider transfusion [6] Where ulcers are persistent, options include transfusion, hydroxyurea with/without erythropoietin, oxygen chamber, zinc supplementation, pentoxifylline and skin grafts

ACE: Angiotensin-converting enzyme; FT4: Free total thyroxine; Hb: Hemoglobin; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HRT: Hormone replacement therapy; TRH: Thyrotropin-releasing hormone; TSH: Thyroid stimulating hormone.

complications was lower in those who also received chelation, compared with those who did not. However, older age and splenectomy were also independently associated with an increased risk of most complications.

Regular patient monitoring is important in order for the clinician to identify and appropriately manage all complications, thus achieving the optimal outcome for the patient, though the financial resources, expertise and facilities required for assessments should also be taken into consideration. Table 2 provides a comprehensive summary of β -thalassemia complications and appropriate management strategies. Table 3 details the recommended frequency and relative expense of observation strategies for monitoring potential complications. In addition, monitoring may alter throughout the patient's life, for example, growth and sexual development should be

monitored most frequently in pediatric patients and monitoring in relation to iron overload may become more important in later life (from 8 to 10 years of age), as iron load increases with time.

4. Expert opinion

Since the introduction of transfusion and iron chelation therapy with DFO in the 1970s and 1980s, the lives of patients with β -thalassemia major have been transformed, demonstrating that prolonged life is possible with effective iron removal. In recent years, the most important advances in the treatment of patients with β -thalassemia major have been the introduction of oral iron chelators and the availability of technologies that allow the direct measurement of iron

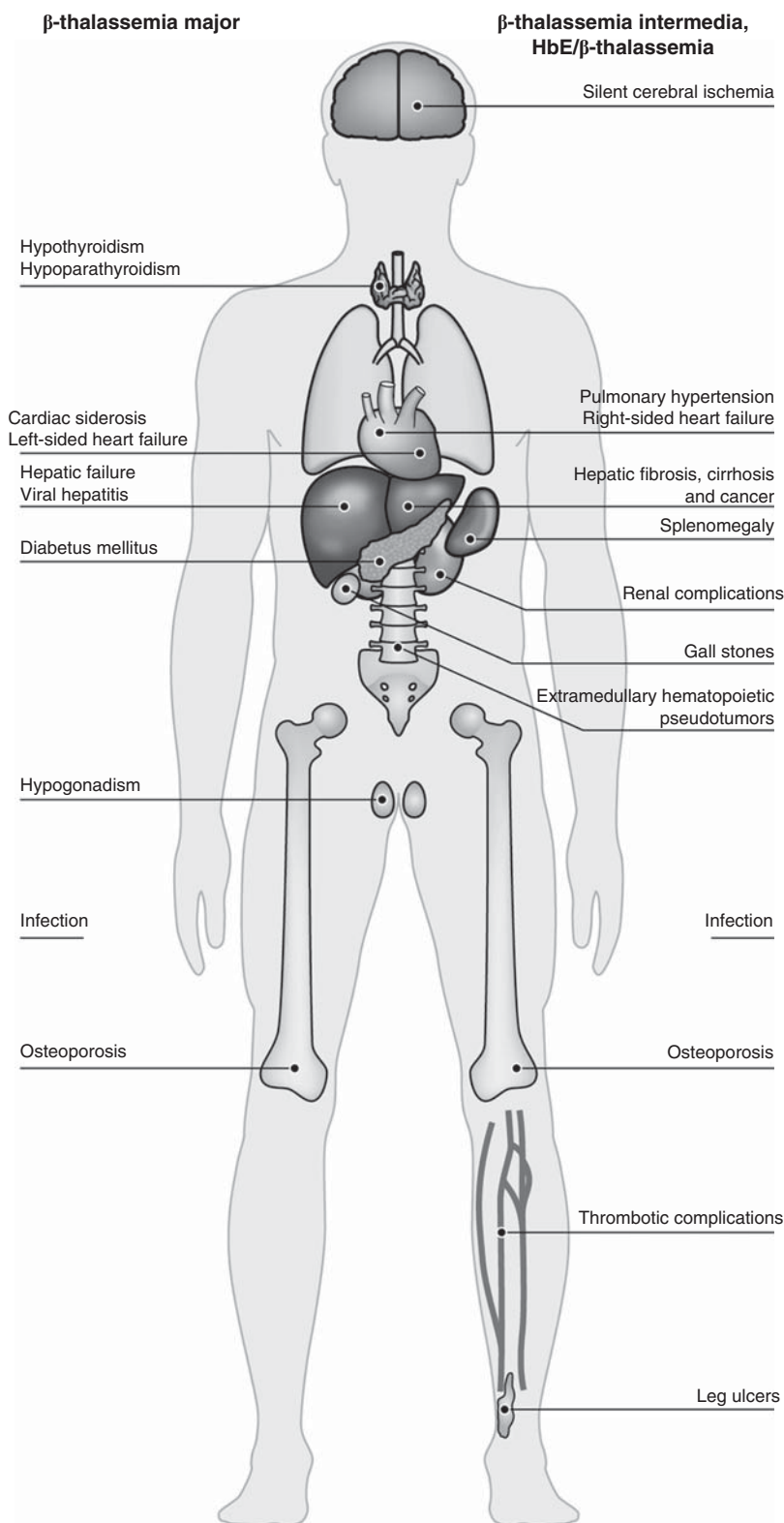


Figure 2. Major complications observed in patients with either transfusion-dependent or non-transfusion-dependent β -thalassemia. Patients with β -thalassemia intermedia or HbE/ β -thalassemia exhibit a unique profile of complications compared with those with β -thalassemia major, although several complications including osteoporosis, endocrinopathies and hepatic complications, are observed across all patient types.

Adapted from [117]. Obtained from Haematologica/the Hematology Journal website <http://www.haematologica.org>.

Hb: Hemoglobin.

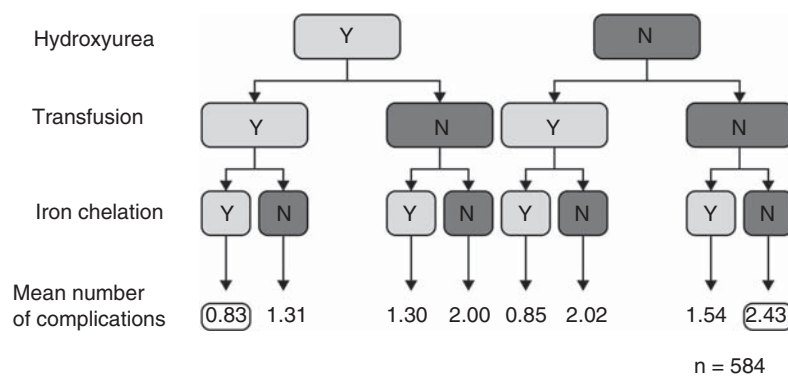


Figure 3. Flow chart depicting the mean number of complications that occurred in patients with β -thalassemia intermedia undergoing different management schemes. Numbers reported are mean incidences for the 584 patients included in the retrospective OPTIMAL CARE study, according to the management strategy applied that may have involved hydroxyurea, red blood cell transfusion and iron chelation.

Republished with permission of American Society of Hematology, from [33].
N: No; Y: Yes.

Table 3. Frequency and relative expense of observation strategies for monitoring iron overload and other complications in β -thalassemias.

Observation	Frequency	Expense
Iron intake	Each transfusion	
Chelation dose and frequency	Every 3 months	
Growth and sexual development	Every 6 months in pediatric patients	
Occurrence of endocrinopathies	Every 6 months from age 10 years	
Bone mineral density	Yearly	
Liver function	Every 3 months	
Sequential serum ferritin	Every 3 months	
Glucose tolerance test, thyroid, calcium metabolism	Yearly in adult patients	
Liver iron	Yearly from age 8 to 10 years	
Cardiac function	Yearly from age 8 to 10 years	
Cardiac iron (T2*)	Yearly from age 8 to 10 years (some suggestion that this could be from 7 years) [116]	

in various organs, such as the heart and the liver. Therefore, physicians are now able to monitor and adjust iron chelation therapy more effectively based on more than just serum ferritin levels alone (e.g., see data from patients in the UK [91]). As a result, further improvements in patient survival and quality of life are anticipated. In addition, the development of effective antibiotics and vaccinations along with recommendations for optimal screening practices prior to transfusion have had a positive impact on patients with thalassemia, though the prevention and treatment of infection does remain a challenge.

For patients with β -thalassemia intermedia, the OPTIMAL CARE study outlined various associated clinical complications related to iron overload (such as liver disease and liver cancer), and demonstrated how incidence increases with age. These observations highlighted the need for iron chelation therapy in these patients and prompted the development of guidelines for the clinical management of patients with non-transfusion-

dependent β -thalassemia [6]. The guidelines, along with data from randomized clinical trials in this patient group, can help inform treatment decision making. Data from the first randomized, placebo-controlled study evaluating iron chelation therapy in patients with β -thalassemia intermedia, HbE/ β -thalassemia and other NTD conditions (the THALASSA study) not only demonstrated the efficacy and safety of deferasirox in this patient population [82,83], but also confirmed significant iron burden requiring chelation.

Further research is needed into the treatment and management of all β -thalassemia patients. There is still room for improvement in the conventional treatment of patients with β -thalassemia major to further extend survival and quality of life. For patients with β -thalassemia intermedia and HbE/ β -thalassemia, efforts should be focused on the identification and recognition of patients who may benefit from transfusion therapy complemented by iron chelation therapy. As studies

have highlighted the impact of iron accumulation in the absence of regular transfusion, and the increased rate of complications with advancing age, the importance of effective monitoring and early treatment intervention have become very clear. Clinicians would benefit from increased availability of educational resources and tools for the identification of such patients, as well as to guide their treatment.

Currently, gene therapy is proving to be an interesting approach in the treatment and possible cure of β -thalassemias. Few patients have received gene therapy to date; one trial in France is ongoing with results for one patient published [44] and the remainder still under evaluation; and two Phase I/II trials are currently recruiting patients in the US and France, with the first patient transplanted in France in December 2013 [92-95]. Another interesting and promising approach is the induction of erythropoiesis by molecules such as ACE-536 and sotatercept; the final results of ongoing Phase II trials are awaited.

In conclusion, it is suggested that the most important developments in the treatment of thalassaemia patients have been an increased appreciation of the clinical significance of iron overload – in both transfusion-dependent and non-transfusion-dependent patients with β -thalassaemia – along with the introduction of techniques for the direct measurement of iron load and oral iron chelators. It is proposed that future research should focus on the continued improvement and

refinement of treatment options for transfusion-dependent patients and the identification of patients who require prompt and effective clinical management in spite of a lack of dependence on regular blood transfusion.

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Affiliation

Maria Domenica Cappellini^{†1} MD,
Vip Viprakasit² MD & Ali T Taher³ MD
[†]Author for correspondence
¹Professor of Internal Medicine,
University of Milan, Ca Granda Foundation
IRCCS, Milan, Italy
Tel: +0039 02 55033358;
E-mail: maria.cappellini@unimi.it
²Associate Professor in Hematology and Program
Coordinator for Thalassemia Research,
Mahidol University, Siriraj Hospital, Bangkok,
Thailand
³Professor of Medicine at the Division of
Hematology-Oncology,
American University of Beirut, Beirut, Lebanon