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REVIEW
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Abstract
Objective: The non-transfusion-dependent thalassemias (NTDT), including thalassemia intermedia (TI), hemoglobin E beta thalassemia, and hemoglobin H disease, have sometimes been regarded as less severe than their transfusion-dependent variants; however, these disorders carry a substantial disease burden (e.g., splenomegaly, iron overload, skeletal effects, and cardiopulmonary disease). The aim of this review is to increase clinician awareness of the growing global problem of NTDT and TI, and discuss the current management strategies for these conditions.

Methods: Recent peer-reviewed articles (publication years 2000 through 2015) addressing the epidemiology, complications, management, and monitoring of NTDT were identified in the PubMed database and reviewed.

Results: The changing epidemiology of thalassemia constitutes a growing health problem. Increased clinician awareness is necessary for the appropriate diagnosis and management of patients with NTDT.

Conclusions: Management of NTDT requires a comprehensive approach, beginning with screening and prenatal diagnosis, monitoring for iron overload and associated complications, and iron chelation therapy. Several novel strategies are in the early stages of investigation and may help increase treatment options in patients with NTDT. Importantly, ethnic or cultural barriers may exist within the affected populations and need to be considered in the management approach.
REVIEW

Non-transfusion-dependent thalassemia and thalassemia intermedia: epidemiology, complications, and management

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Key words: iron chelation therapy, iron overload, non-transfusion-dependent thalassemia, thalassemia intermedia

[Short title: Non-transfusion-dependent thalassemia/thalassemia intermedia]
**ABSTRACT**

**Objective:** The non-transfusion-dependent thalassemias (NTDT), including thalassemia intermedia (TI), hemoglobin E beta thalassemia, and hemoglobin H disease, have sometimes been regarded as less severe than their transfusion-dependent variants; however, these disorders carry a substantial disease burden (e.g., splenomegaly, iron overload, skeletal effects, and cardiopulmonary disease). The aim of this review is to increase clinician awareness of the growing global problem of NTDT and TI, and discuss the current management strategies for these conditions.

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INTRODUCTION

Hemoglobinopathies are a group of autosomal recessive disorders of hemoglobin (Hb), and mutations that cause these conditions can be divided into two main groups: Qualitative Hb variants (Hb S, Hb C, and Hb E), which change the amino acid structure of the globin, and quantitative mutations, which result in defective synthesis of the alpha or beta globin chains of adult Hb A\textsuperscript{1,2}. The alpha and beta thalassemias result from quantitative mutations, and are named after the affected globin chain.

Mutation of the alpha or beta chains can result in the complete absence of globin chain synthesis (α\textsuperscript{0} or β\textsuperscript{0}) or reduced globin chain synthesis (α\textsuperscript{+} or β\textsuperscript{+})\textsuperscript{2}. Both types of disorders are inherited in a recessive Mendelian manner\textsuperscript{1,3}.

In addition, multiple alleles of alpha and beta globin genes can be present in a given population. The interactions between these alleles can result in a wide spectrum of disease severity — even within the same class of disease. For example, Hb H alpha thalassemias that are caused by triple deletions in alpha globin genes produce a mild phenotype. However, patients with certain non-deletional mutant alpha globin alleles — such as Hb Constant Spring disease — can present with severe anemia\textsuperscript{4}. The interactions between alpha and beta globin genes also dictate disease severity. For patients with Hb E beta alleles, coinheritance with alpha mutations tends to produce mild phenotypes while coinheritance with mutant beta alleles has a wider range of disease phenotypes\textsuperscript{5}. Finally, these different forms of thalassemia may occur at varying frequencies within the same population\textsuperscript{1,6,7}.

The principle pathophysiology of thalassemia results from ineffective erythropoiesis and peripheral hemolysis, which results in anemia\textsuperscript{2}. Chronic anemia can induce compensatory changes in the hematopoietic system and subsequently cause complications such as splenomegaly or osteoporosis. In addition, transfusions that are used to treat patients with thalassemia can cause further complications as a result of iron overload. Therefore, it is essential to accurately determine disease status and phenotypic stability to ensure proper management.

Thalassemias are known to occur at higher frequencies in certain regions of the world, which may result from selective advantages such as resistance to severe forms of malaria, longer lifespan, and
greater number of offspring\textsuperscript{1,8}. In addition, the higher incidence of consanguineous marriages likely contributes to the prevalence of inherited recessive diseases within these regions. Altogether, these factors may lead to a patchy distribution of thalassemia genes due to selective pressures in certain geographic areas\textsuperscript{5}.

The problem of thalassemia is notably different today than it was in the past, and various ethnicities, phenotypes, and treatments now characterize this heterogeneous group of blood disorders. Additionally, because patients are surviving longer, there is a different pattern of complications than previously observed in this population\textsuperscript{9,10}. Moreover, the natural history is varied and poorly studied, with severity that can range from asymptomatic to transfusion dependency among patients with similar mutations\textsuperscript{9}. The non-transfusion-dependent thalassemias (NTDT) include beta thalassemia intermedia (TI), Hb E beta thalassemia, and alpha TI (Hb H disease)\textsuperscript{1,2}. NTDTs have sometimes been regarded as less severe than their transfusion-dependent variants, but these disorders still carry a substantial burden of morbidity and mortality\textsuperscript{11,12}. Indeed, recent studies indicate that patients with transfusion-independent thalassemia have much greater morbidity than previously thought, including a high rate of complications such as thrombosis, pulmonary hypertension, nonfocal brain infarction, iron overload, spinal cord compression, and decreasing quality of life with age\textsuperscript{11,13-23}. The current article highlights the growing public health problem of NTDT, and discusses the importance of appropriate monitoring and disease management.

Multiple searches were conducted in the PubMed database using various terms, including, but not limited to, “non-transfusion dependent thalassemia,” “thalassemia intermedia,” “hemoglobin E thalassemia,” “epidemiology,” “pathogenesis,” “iron overload,” “complications,” and “iron chelation therapy.” Peer-reviewed publications were given first priority and articles were limited to publication years 2000 through 2015; articles deemed not relevant to the current topic were not utilized.

**Epidemiology of thalassemias: an increasing health problem**

Inherited Hb disorders are observed in an estimated 300,000 births yearly and consist mostly of sickle cell disease and thalassemias\textsuperscript{1,8}. However, the actual burden of diseases such as thalassemia is difficult
to estimate for several reasons\textsuperscript{8}. Most data were collected before 1980, and information on clinical
course, mortality, and complications are scarce in poorer, developing countries where thalassemias are
most common; data are also limited in wealthier countries. As such, it has been suggested that the
current situation regarding management and control of Hb disorders is unsatisfactory\textsuperscript{8}. Most
epidemiologic data should be interpreted with caution as they are based on data from a limited
number of centers in each country. Moreover, micromapping studies, which take into account
multiple centers within the same country, indicate heterogeneity in the distribution of thalassemias,
even within the same region\textsuperscript{8}. Therefore, additional micromapping studies are needed within countries
that have a high prevalence of thalassemias.

Approximately 80\% of thalassemias are observed in the low- and middle-income countries of the
tropical belt, which extends from sub-Saharan Africa to the Mediterranean region, the Middle East,
and South and Southeast Asia\textsuperscript{1}. Many regions of the world where thalassemias are common are
undergoing an epidemiologic transition, whereby improved health and nutrition are allowing for
greater survival of affected children\textsuperscript{1,8}. Growth of the thalassemia population must also be considered
in those regions with a high prevalence of thalassemia and rapid population increases, such as Africa
and Southeast Asia\textsuperscript{8}. All of these factors will lead to an increasing incidence of Hb disorders\textsuperscript{8}. A study
of neonatal hemoglobinopathy screening programs in California, for example, reported the frequency
of alpha thalassemia as one in 9000 births and beta thalassemia as one in 55,000 births; screening
programs like these provide for the accurate diagnosis of hemoglobinopathies\textsuperscript{24}. Results of such
studies also demonstrate an increasing incidence of diverse mutations that will require new strategies
for screening, counseling, and management\textsuperscript{24}.

Thalassemias are a growing health problem worldwide, with increasing numbers of clinically
significant cases expected over the next 2 decades, and individuals with Hb E beta thalassemia
expected to account for much of this projected increase\textsuperscript{10}. The epidemiology of thalassemia is also
changing, due in part to changes in migration patterns to North America and improved treatments\textsuperscript{10,12}.
For example, the highly common Hb E variant affects approximately 1 million people around the
world and causes Hb E beta thalassemia, which has a variable phenotype ranging from asymptomatic
transfusion-dependent. Changes in the prevalence of Hb E beta thalassemia may be due to the migration to North America from regions with a high prevalence of Hb E mutations (e.g., Thailand, Laos, and Cambodia). A rise in immigration to North America from Southeast Asian countries over several decades has been paralleled by an increase in some thalassemia mutations. For example, the overall distribution of ethnicity in newborns in California with Hb H disease reveals a very high prevalence among Southeast Asian immigrants, including those of Laotian/Thai (26%), Filipino (15%), Vietnamese (9%), and Cambodian (5%) ethnicity (Figure 1).

Thalassemias can be considered an “emerging minority disease” in North America, as most cases of NTDT occur in immigrant populations from high-risk areas for NTDT. Recently, the Centers for Disease Control and Prevention’s report on thalassemia noted that 27% of US patients with thalassemia who are studied were born outside of the United States. Overall, 80% of individuals with NTDT were members of minority populations, particularly those from Southeast Asia, India, and the Middle East. These findings underscore the growing health problem of NTDT, and a shifting disease prevalence from predominantly underdeveloped nations, to major healthcare systems, including those of the United States and Europe. Thalassemias are common in coastal regions, and understanding specific target populations is an important consideration. A lack of cultural knowledge, interpretation services, or didactic methods of healthcare delivery may have adverse health consequences. Southeast Asian communities, encompassing diverse populations and minorities, are particularly hard hit, with a high incidence of Hb E and Hb E beta thalassemia demonstrated in this population. Addressing this problem requires counseling strategies that consider both cultural and psychological aspects of these diverse populations. Increased awareness of the challenges that may occur during interactions between patients and providers can help improve outcomes.

Pathogenesis and natural history of NTDT

The principle pathophysiology of TI involves ineffective erythropoiesis and hemolysis, which leads to the clinical signs and symptoms of anemia and eventual transfusion dependence (Figure 2). Compensatory homeostatic mechanisms to overcome chronic anemia in NTDT include increased
production of erythropoietin, reduced hepcidin levels, bone marrow expansion, and increased absorption of iron in the gut; these mechanisms result in clinical complications observed in patients with NTDT (e.g., osteoporosis, progressive splenomegaly) and other complications resulting from iron overload (e.g., endocrinopathies, liver disease). Pathophysiology in NTDT may also result from other molecular mechanisms, such as dysregulation of coagulation mechanisms, leading to a hypercoagulable state.

The natural history of TI is variable, ranging from mild (e.g., anemia, jaundice) to severe (e.g., severe anemia, iron overload, hypersplenism, bone abnormalities, leg ulcers) symptomatology and complications. Severity of disease depends on the balance of the alpha and non-alpha chains, and is also impacted by genetic and nongenetic determinants. The variation in clinical severity of the NTDT (Table 1) may complicate diagnosis and treatment; despite frequently presenting with anemia, patients with NTDT are by definition not dependent on regular transfusion for survival, a characteristic that distinguishes NTDT from conditions such as beta thalassemia major or transfusion-dependent thalassemia (TDT). Moreover, although the survival of patients with NTDT is not dependent on regular transfusion, transfusion requirements may change over time, and transfusions may be occasionally required due to events such as pregnancy, splenomegaly, or infections (see below).

The spectrum of disease in thalassemia is outlined in Figure 3. Among the three clinically distinct forms, the transfusion requirements in alpha and beta thalassemia major are greatest.

**Screening, diagnosis, and assessment**

Genetic testing is an important component in the management of thalassemias to ensure correct diagnosis and guide treatment strategies. Genotype analysis helps to define clinical severity and plan the therapeutic clinical course for the patient. Since TI often involves an interaction of both alpha and beta thalassemia mutations, adequate diagnosis requires evaluating both globin genes as well as genetic polymorphisms that alter the severity of the disease. There are three categories of genetic modifiers for thalassemia. The primary modifier is the specific mutation of the alpha or beta globin gene. Secondary modifiers are polymorphisms or mutations that minimize the globin chain imbalance.
For instance, coinheritance of alpha thalassemia decreases the severity of beta thalassemia. Tertiary modifiers are polymorphisms that alter the susceptibility to complications such as the common coinheritance of the UGT1A1 gene (Gilbert’s syndrome). In the United States, almost 20% of beta TI cases were initially identified as a beta thalassemia heterozygote. Alpha genotyping demonstrated that many of these cases coinherited alpha triplication. Genotyping illustrated that many of these patients coinherited alpha triplication or a dominant, severe beta thalassemia allele. A longitudinal analysis of children with Hb H Constant Spring disease demonstrated that they were highly susceptible to severe anemia during infection, had growth delays, required intermittent transfusion, and were subject to iron overload within their first decade of life. In comparison, children with deletional Hb H disease have a more benign clinical course as they rarely develop severe anemia during infection and generally do not require transfusion. Adequate diagnosis of Hb H Constant Spring disease usually requires DNA testing since it is an unstable Hb that is often missed by other methods such as routine electrophoresis. Early genetic testing in newborns is important to correctly distinguish between these distinct disorders to determine the best treatment approach. Novel diagnostic methods such as multiplex ligation-dependent probe amplification are now being used to identify both previously identified and novel deletions within the beta globin gene cluster. These simple and reliable methods may be useful to clarify the clinical relevance of these large deletions within the beta globin gene in affected individuals and carriers. In light of the changing epidemiology of Hb disorders, genetic screening is becoming increasingly important. Prenatal screening allows parents to be duly informed of the likelihood of producing a seriously affected child, and provides important information to regional government health agencies as well as world health authorities to help accurately estimate disease burden and incidence. It is also important that patients with thalassemias are accurately diagnosed in order to prevent a lifetime of potentially unnecessary transfusions. Indeed, thalassemias may appear as severe anemias early in life; therefore, it is important for these patients to be judiciously followed up in order to evaluate their steady-state Hb level. For certain NTDTs, the clinical characteristics can also change significantly during a child’s development. In Hb E beta thalassemias, the phenotype may be unstable in patients under 15 years of
age and, during this time, it is possible for the disease to progress from mild to severe\(^5\). Therefore, frequent follow-ups are also necessary in certain patient groups who present with mild disease.

The clinical characteristics of patients with thalassemia can be used to distinguish patients with TDT or thalassemia major from NTDT (Table 2). Once a diagnosis of NTDT is confirmed, the presence of severe anemia alone is not necessarily an indication for transfusion therapy; indeed the patient may have an infection or acute hemolytic syndrome that is exacerbating the anemia in the short term\(^3\). Rather, patients with NTDT should be monitored for several months following the initial diagnosis to assess the need for transfusion or other therapy based on factors such as disease activity, growth and development, and the presence of complications; clinicians should also be cognizant of conditions such as growth spurt or pregnancy, which could further decompensate a low Hb level\(^3\). While there are existing guidelines for the diagnosis and management of NTDT, these considerations also must be factored in\(^30,31\).

**Complications associated with NTDT**

Complications of NTDT include skeletal deformities, pregnancy complications, extramedullary hematopoiesis (pseudotumors), silent brain infarctions, pulmonary hypertension, leg ulcers, endocrine disorders (including growth failure), thromboembolic events, and iron overload (Figure 2)\(^3,6,33\).

Whereas some complications are common to both TDT and NTDT (e.g., extramedullary hematopoiesis, splenomegaly), others such as pulmonary hypertension and thrombosis are more commonly observed in NTDT\(^3\). Transfusion may prevent many complications associated with NTDT such as splenomegaly, growth retardation, skeletal abnormalities, and pulmonary hypertension\(^3\).

**Skeletal-related complications**

One study conducted across a large cohort of patients found a high prevalence of low bone mineral density, fractures, and bone pain in patients with alpha and beta thalassemias\(^34\). Patients with beta TI commonly develop osteoporosis, which increases with age and is associated with pain, skeletal deformities, and fractures. Osteoporosis and its consequences in patients with NTDT have not been well-studied, but these patients may experience bone pain, fractures, and skeletal and spinal
deformities; data on the benefit of preventive therapy such as bisphosphonates is limited in patients with NTDT. Recommendations for the prevention of osteoporosis in patients with NTDT include annual bone mineral density assessment, and imaging studies for events such as back pain; hormonal and nutritional deficiencies contributing to osteoporosis should be corrected where possible, in accordance with recommendations for transfusion-dependent patients with beta thalassemia major.

In the OPTIMAL CARE study, a benefit of iron chelation and hydroxyurea therapy was noted in patients with TI who had lower rates of osteoporosis compared with those who were not treated.

Overall, lower rates of osteoporosis have been noted in patients with beta TI receiving iron chelation.

**Pregnancy complications**

Because patients are surviving longer with TI, pregnancy is becoming an increasingly important issue, and there is little information on the outcome of these patients. In general, fertility is preserved in most patients with TI, but these pregnancies should be considered high-risk and followed by multidisciplinary team care. Pregnancy is complicated by worsening maternal anemia, increased pulmonary hypertension, cardiac decompensation, and thromboembolism; prematurity and intrauterine growth retardation are relatively common. At the onset, discontinuation of iron chelators and hydroxyurea should be discussed; transfusion therapy is often used during pregnancy to improve fetal outcome and decrease maternal complications. Alloimmunization (from transfusion) is a particular risk in patients who initiate transfusions later in life; these patients would benefit from the use of extended red cell phenotypically-crossmatched units. In a recent study examining outcomes of 60 pregnancies in 34 women with TI over a 20-year period, full-term pregnancies were reported in 49 patients. Although some complications did occur, the study suggests that successful deliveries can be achieved with careful and frequent monitoring by a hematologist and obstetrician. General recommendations for patients with NTDT who become pregnant include a need for comprehensive counseling on the risk of having an affected child, and the introduction of blood transfusions according to factors such as Hb level, cardiac and overall status of the mother, and the status of fetal growth. Splenectomy, either prior to conception or postpartum, may be considered for pregnant
patients with NTDT with hypersplenism or splenomegaly\textsuperscript{31}. Fully phenotype-matched blood should be used for never- or minimally-transfused pregnant women with NTDT requiring transfusion, as they can be considered at high risk for alloimmunization\textsuperscript{31}. In order to decrease the high rate of thrombotic events, routine use of low molecular weight heparin in the peripartum period is recommended.

\textit{Extramedullary hematopoiesis}

Ineffective erythropoiesis in TI can also drive extramedullary hematopoiesis in all body sites. One of the most serious and common areas is the paraspinal space, which can result in sudden spinal cord compression and paraplegia\textsuperscript{40}. On routine screening, asymptomatic paraspinal masses are noted in approximately 15\% of patients with TI who are imaged. As these patients age, they develop more severe symptoms, including back pain, paresthesias, abnormal reflexes, and urinary and/or bowel incontinence\textsuperscript{42,43}. Magnetic resonance imaging (MRI) is the diagnostic procedure of choice; in most cases, acute transfusion or hydroxyurea treatment is therapeutic\textsuperscript{20}. In selected cases, low-dose radiotherapy and/or surgical decompression may be necessary\textsuperscript{42,43}.

\textit{Neurological complications}

The presence of asymptomatic white matter lesions detectable by MRI appears to be a common finding in adult patients with TI who have been treated with splenectomy; white matter lesions may be even more pronounced in patients of increasing age and those who are transfusion-naïve\textsuperscript{14}. In a cross-sectional brain MRI study of 30 splenectomized adults with TI without neurologic dysfunction, 18 (60\%) patients had ≥1 subcortical white matter infarction\textsuperscript{14}. Other studies have documented this finding and have also noted associated mild cerebral atrophy and possible cognitive dysfunction\textsuperscript{14,15,44}. Risk factors for central nervous system injury include low Hb levels, hypercoagulability, thrombocytosis, iron overload, and older age\textsuperscript{15}. Optimal chelation therapy, aspirin prophylaxis, and avoidance of splenectomy may be protective. All patients who present with nonfocal neurologic symptoms require neuroimaging, but the optimal therapy for patients with lesions is unclear\textsuperscript{15}. Based on data from patients with sickle cell disease, transfusion therapy is beneficial in both the primary and secondary prevention of central nervous system lesions and should be studied in TI\textsuperscript{14,45,46}. 

Pulmonary hypertension

Pulmonary hypertension, particularly in splenectomized patients, occurs in approximately 30% of patients with NTDT. Hemolysis, nitric oxide and arginine deficiency, and hypercoagulability are factors that may contribute to vasculopathy and development of microthrombi. Diagnosis is generally established by echocardiogram, which most likely overestimates prevalence. Therefore, right heart catheterization is indicated in patients with significant echocardiographic evidence of likely pulmonary hypertension (tricuspid regurgitant velocity >3.2 m/sec). Prospective therapeutic trials are lacking; however, transfusion therapy appears to be beneficial. Practical management of pulmonary hypertension in patients with NTDT includes annual echocardiographic assessment, particularly for selected subgroups such as patients with beta TI and Hb E beta thalassemia, splenectomized patients, and those with elevated platelet counts. Blood transfusion, hydroxyurea, control of iron overload, and anticoagulant therapy may be beneficial for patients with possible, likely, or confirmed pulmonary hypertension. In addition, although larger trials are needed, the results of small-scale studies of sildenafil citrate have been encouraging, with good tolerability and benefits observed in hemodynamic and functional status.

Leg ulcers

Leg ulcers are common in NTDT and occur in as many as one-third of patients, particularly in later adulthood. They tend to recur and cause increasing morbidity. The etiology is multifactorial, including local trauma, anemia, and hypercoagulability. Notably, a higher rate of leg ulcers has been found to occur in patients with iron overload. Presently, there is insufficient evidence to recommend treatments such as blood transfusion, iron chelation, or hydroxyurea therapy, although some benefit of these treatments has been observed, and blood transfusion could be considered as a primary treatment option; some simple lifestyle interventions (e.g., raising the feet 1–2 hours per day above the heart) may also be beneficial. Other general recommendations for leg ulcer management include regular skin examination of patients with NTDT on physical exam, and use of topical antibiotics and dressings as needed; topical sodium nitrite may also be considered. Platelet-derived
wound healing factors, anticoagulation therapy, vasodilators such as dilazep, skin grafting, and oxygen chamber may be useful for controlling leg ulcers, but insufficient evidence exists from clinical trials to recommend these therapies in patients with NTDT. 

Iron overload

Hemosiderosis and induced organ dysfunction are major issues in NTDT. Even moderate hemosiderosis in TI is a strong predictor of mortality and morbidity. For every 1-mg increase in liver iron per gram of dry weight, there is a significant increased risk of pulmonary hypertension, endocrinopathies, thrombosis, bone disease, and other target organ injuries. While cardiac iron accumulation does occur, it is significantly slower than in thalassemia major. Patients with NTDT are at particular risk for hepatic fibrosis and liver failure, which have recently been associated with hepatocellular carcinoma. Elevated liver iron significantly increases morbidity of all NTDT phenotypes regardless of severity, which is amplified as these patients age. The lack of early diagnosis and treatment of hemosiderosis in NTDT is common. Many patients are not monitored, despite recommendations that chelation be initiated at a significantly lower ferritin level than in transfusion-dependent patients. Ferritin best correlates with reticular endothelial liver iron and underestimates iron deposition in hepatocytes. In nontransfused patients, there is relatively more hepatocytic iron deposition than in thalassemia major, resulting in high total body iron with lower than expected serum ferritin levels. 

Hypercoagulable state in NTDT

Patients with NTDT have laboratory evidence of increased risk of thrombosis, and with increasing survival in patients with thalassemia, thrombotic complications are becoming an increasing concern, particularly for patients with TI. The risk varies among subtypes and clinical characteristics. In one study, a higher prevalence of thrombotic complications was observed among patients with TI compared with transfused patients with thalassemia major (29\% vs 2\%), and the risk was greatest in splenectomized patients. Consistent with these findings, plasma levels of markers of thrombin activity were higher in splenectomized patients with TI compared with nonsplenectomized patients.
and those with thalassemia major. Similar findings were observed in a larger study, which showed a significantly greater risk of thrombotic events in patients with TI compared with thalassemia major \((p<0.001)\), and risk was again greater in patients who had undergone splenectomy. Patients with NTDT commonly have thrombocytosis and evidence of endothelial injury and dysfunction, and iron overload may further exacerbate this risk. Understanding of the morbidity of this hypercoagulable state is increasing and suggests that the high rate of subclinical and overt strokes is in part due to this thrombophilia. Although the role of interventions such as blood transfusion has not been evaluated in sufficient trials, one of the general recommendations for addressing the hypercoagulable state in patients with NTDT is to consider them at higher risk for thrombotic complications; splenectomized patients with NTDT with elevated platelet counts should consider anticoagulant therapies such as aspirin. Although a beneficial impact of iron chelation or hydroxyurea therapy may be observed with different indications, neither intervention is currently recommended as primary or secondary intervention.

**Quality of life**

The impact of these potential complications on patients living with these disorders is important to consider. In a study comparing the impact of thalassemia on quality of life in patients with transfusion-dependent \((n=29)\) or transfusion-independent \((n=19)\) disease, patients were asked to rate various dimensions of health status. Results of the study showed that anxiety, depression, concern about overall health, and recent deterioration in health status were the most commonly impacted domains. Importantly, overall health was rated worse in non-transfusion-dependent patients. The results demonstrate that NTDT has a significant impact on quality of life in affected patients. The frequent assessment of health-related quality of life and mental health status, preferably with the use of standardized instruments, is now recommended for patients with NTDT.

**Disease management and monitoring in NTDT and TI**

NTDT requires a multidisciplinary approach that focuses on each patient’s clinical course. Prevention and early detection of complications previously discussed are necessary to prevent morbidity and poor
quality of life. Principle management strategies for NTDT include four therapeutic options: Splenectomy, transfusion therapy, iron chelation therapy, and fetal Hb induction. Increased understanding of the risks and benefits of these interventions over the last decade has dramatically changed the approach to TI.

**Splenectomy**

Increase in splenic volume is common in patients with NTDT regardless of transfusional requirements. Splenectomy may become necessary for patients with NTDT due to complications such as recurrent infection and/or bleeding (resulting from chronic leukopenia and/or thrombocytopenia), or complications associated with splenomegaly such as upper quadrant pain, early satiety, and to reduce the risk of splenic rupture. Nevertheless, the risk for complications with splenectomy, including thrombosis and infection, should be carefully considered for patients with NTDT. Recent data indicate that splenectomy in thalassemia may markedly increase the morbidity of babesiosis and malaria. In the OPTIMAL CARE study, splenectomized patients were found to have higher rates for nearly all complications than were nonsplenectomized patients, whereas the procedure was only protective for extramedullary hematopoiesis.

Interventions such as partial splenectomy and/or splenic embolization aim to maintain the benefit of splenectomy without the potential pathologic consequences, but their long-term efficacy and toxicity are poorly studied. The use of appropriate preventive measures such as antibiotic prophylaxis and immunization is recommended for patients with NTDT post-splenectomy. Additionally, many programs have initiated prophylactic aspirin or anticoagulant therapy before thrombotic events occur.

General indications for splenectomy in NTDT include progressive anemia resulting in growth retardation, hypersplenism resulting in recurrent infection or bleeding, severe splenomegaly with clinical symptoms or risk of splenic rupture, and in cases where interventions such as blood transfusion or iron chelation therapy may be unavailable; splenectomy should generally be avoided in patients less than 5 years of age.
**Transfusion therapy**

The use of blood transfusion and iron chelation therapy have improved the prognosis of patients with thalassemias over the last 3 decades. However, the decision to transfuse a patient with any thalassemia should be based not only on Hb level but other individual factors such as activity level, feeding, growth, and development. In addition, the need for transfusion must also be balanced with the risks of transfusion-associated infection, hemosiderosis, and alloimmunization. In patients who initiated transfusions later in life, alloimmunization rates are higher than in those transfused early in life. Use of extended red cell phenotyping is beneficial in decreasing this risk.

Chronic transfusion therapy is increasingly being considered in patients with moderately severe NTDT. Transfusions decrease erythroid activity and the side effects of ineffective erythropoiesis and hemolysis. Transfusion therapy in thalassemia major is likely responsible for the low rate of thrombosis, pulmonary hypertension, extramedullary pseudotumors, brain infarctions, skin ulcers, and growth failure compared with NTDT. Temporary transfusion programs are being used in patients with NTDT in order to prevent and treat specific complications.

**Assessing iron overload**

Patients with NTDT develop clinically significant iron overload irrespective of their transfusion exposure. Ineffective erythropoiesis leads to low hepcidin levels and marked increase in intestinal iron absorption. Iron overload is a major cause of morbidity for patients with NTDT and TI. Indeed, a rise in liver iron in NTDT has been proportionally associated with an increased risk of multiple complications, including thrombosis, cardiopulmonary disease, endocrinopathies, and osteoporosis. Figure 4 shows liver iron concentrations (LICs) in patients with and without beta TI–associated comorbidities; notably, LIC is significantly increased in patients with NTDT complications such as leg ulcers ($p=0.027$), thrombosis ($p=0.002$), pulmonary hypertension ($p<0.001$), and osteoporosis ($p<0.001$). The dynamic state of ongoing, ineffective erythropoiesis with increased iron absorption leads to preferential loading of hepatocyte iron compared with reticuloendothelial iron. Measuring serum ferritin levels is an easy and inexpensive assessment method, but underestimates the severity of
iron overload in NTDT. Serum ferritin primarily reflects reticuloendothelial iron and is lower in patients with NTDT compared with patients with thalassemia major with the same total body iron burden. In order to adequately use serum ferritin as an indicator of iron levels, it should be periodically correlated with LIC\textsuperscript{2,21}.

Serum ferritin level guidelines for initiating chelation therapy in NTDT are lower than for transfusion-dependent patients. Following thalassemia major guidelines will delay initiation and appropriate dose of iron chelation therapy in NTDT\textsuperscript{21}. Chelation therapy should be considered for all iron-overloaded patients with NTDT >10 years of age. Chelation is initiated when LIC reaches 5 mg Fe/g dry weight and interrupted when the level drops to 3 mg Fe/g dry weight. If quantitative liver iron assessments are unavailable, initiating iron chelation at >800 ng/mL and interrupting therapy at <300 ng/mL is recommended. A decision on when to use iron chelation therapy may also be guided by use of a decisional treatment algorithm. In an exploratory study, it has been proposed to initiate iron chelation therapy in patients who have been transfused with >1000 g of red blood cells or when transferrin saturation is >90% in patients with <1000 g transfused\textsuperscript{53}. This method will need to be validated in a larger prospective study based on repeated transferrin saturation assessments.

Recently, the use of MRI for the direct assessment of LIC has become the new standard of care for patients with NTDT when readily available, and assessment of LIC every 1 to 2 years has been recommended; the extent of iron overload and the rate of iron accumulation as assessed by this method is used to evaluate the need for iron chelation therapy\textsuperscript{3,30}. In the event that both MRI-assessed LIC and serum ferritin levels are available, LIC should be the measurement of choice to guide treatment decisions\textsuperscript{31}.

Management strategies: old and new

Managing iron overload

Several new therapeutic approaches to treat iron overload in TI, including new iron chelators and drugs that decrease gastrointestinal iron absorption, are in preclinical and early trials\textsuperscript{54-60}. Presently, there are three iron chelators—deferoxamine, deferiprone, and deferasirox—that are available and
have been studied in NTDT; each has specific benefits and limitations. Deferoxamine has been available for use in iron chelation therapy for more than 40 years, but has been associated with poor adherence due to the requirement of parenteral infusion for at least 8 hours daily. Studies in NTDT are limited but indicate improved iron balance. Deferiprone was the first available oral iron chelator and has been extensively used in transfusion-dependent patients with thalassemia major; it was recently approved in the United States for the treatment of iron overload in patients with TDT.

Deferiprone has a relatively short half-life and requires three times a day oral dosing. Due to the rare risk of agranulocytosis-associated fatal bacteremia, weekly monitoring of white blood cell count is required. Limited observations are available for deferiprone in NTDT, but suggest a reduction in iron stores. In a study that included seven patients with beta TI or Hb E beta thalassemia not requiring transfusions, treatment with deferiprone was associated with significant decreases in serum ferritin, hepatic iron, red cell membrane iron, and serum non-transferrin-bound iron, and serum erythropoietin increased; adverse events were mainly gastrointestinal events and arthralgia. In a study of 17 Chinese patients with non-transfusion-dependent Hb H disease and serum ferritin over 900 μg/L, treatment with deferiprone was associated with a significant reduction in serum ferritin at 6 months and 18 months, and levels remained decreased at 24 months (6 months after stopping treatment). No agranulocytosis or severe neutropenia was observed and the drug was well-tolerated by all but one patient.

Deferasirox has been extensively studied in hemosiderosis across multiple conditions, including thalassemia major, sickle cell disease, and myelodysplastic syndromes, and these studies have demonstrated stabilization and decrease in total body iron. Presently, deferasirox is the most well-studied iron chelator in NTDT, having undergone prospective randomized clinical trials. It is the only oral iron chelator that is approved by the US Food and Drug Administration for NTDT.

Deferasirox has a long half-life, allowing for once-daily dosing, which most likely improves patient satisfaction. The most common adverse events are gastrointestinal disturbances and a nonprogressive increase in serum creatinine. Due to the rare risk of severe renal toxicity, monthly monitoring of renal function is required. The THALASSA study was the first large, randomized,
placebo-controlled trial of iron chelation therapy in NTDT. A significant reduction in LIC was observed in the 166 patients with NTDT treated with deferasirox, while an increase in iron levels was seen in the control group\textsuperscript{67,68}. Over the 2-year extension study, a progressive reduction in iron overload was observed in patients with NTDT treated with deferasirox (Figure 5). Nausea, rash, and diarrhea were the most common drug-related adverse events\textsuperscript{67,68}.

**Hydroxyurea and fetal Hb therapy**

Drug therapy that increases production of the fetal beta globin like molecule (gamma globin) may help to improve the alpha/beta globin chain imbalance in NTDT by binding the excess alpha chains, increasing fetal Hb levels, and improving erythropoiesis\textsuperscript{2,31,71}. Several small and nonrandomized clinical trials with fetal Hb–modulating drugs have been performed in patients with thalassemia, and studied agents that affect different pathways in fetal Hb regulation. These drugs include hydroxyurea (a ribonucleotide reductase inhibitor), sodium phenylbutyrate, arginine butyrate (histone deacetylase inhibitors), decitabine and azacytidine (demethylating agents), and erythropoietin and darbepoetin (erythropoiesis stimulating agents)\textsuperscript{71}. The best-studied agent for inducing fetal Hb production in patients with NTDT is hydroxyurea, a cytotoxic, antimetabolic, antineoplastic agent, which has been used extensively in treating sickle cell disease\textsuperscript{31,71}. Only hydroxyurea has sufficient long-term safety data in thalassemia to be considered clinically indicated.

The overall response rate to hydroxyurea is quite variable, and studies are often not comparable. However, approximately 40% of patients with NTDT will experience a 1-g/dL rise in Hb with hydroxyurea treatment\textsuperscript{31,71}. In addition, there are reports from the OPTIMAL CARE study suggesting that hydroxyurea treatment improves complications such as extramedullary hematopoietic tumors, leg ulcers, and quality of life\textsuperscript{35}. Although the use of hydroxyurea cannot be recommended in an evidence-based manner based on controlled clinical trials in patients with NTDT, its use can be considered for those patients with selected comorbid conditions, including pulmonary hypertension, extramedullary hematopoiesis, and pseudotumors, and in patients with leg ulcers, based on results of observational cohort studies and small clinical trials\textsuperscript{31}. The efficacy of hydroxyurea is influenced by the primary
mutation and associated polymorphisms in genes that regulate fetal Hb; patients with thalassemia are more sensitive to hydroxyurea than patients with sickle cell disease, and starting and maximum doses are lower. Most investigators initiate therapy with 10 mg/kg/day, gradually increasing to a maximum of 20 mg/kg/day, with concomitant folic acid supplementation recommended. 

Several novel management strategies for stimulating erythropoiesis and modulating iron levels are currently in the early stages of investigation; these therapies may have value as short- or long-term management strategies for improving clinical symptoms in NTDT. A fusion protein comprised of modified activin receptor type IIIB (ActRIIB; a member of the transforming growth factor beta [TGF-β] superfamily) and human IgG1 Fc acts as a ligand trap for TGF-β superfamily ligands (e.g., activins and/or growth and differentiation factors) and inhibits Smad2/3 signaling. This innovative therapy promotes late-stage red blood cell precursor cell differentiation via a mechanism distinct from that of erythropoietin. Additionally, clinical trials of a recombinant fusion protein containing ActRIIB and IgG1 Fc have been developed for the treatment of anemias due to ineffective erythropoiesis. Results of pilot studies in TI have been very encouraging. In healthy volunteers, the drug was well-tolerated and increased Hb levels. In phase 2, open-label studies in TI, patients demonstrated increased Hb and reduced erythropoiesis without adverse side effects. Results of dose-escalation trials and long-term efficacy studies are ongoing.

The Janus kinase 2 (JAK2) pathway is essential for signaling by erythropoietin and its receptor and plays an essential role in modulating erythrocyte proliferation, differentiation, and survival. In beta thalassemias, overactivation of JAK2 leads to increased erythrocyte proliferation and reduced differentiation, resulting in ineffective erythropoiesis. Inhibitors of the JAK2 pathway are therefore being investigated for their potential to reduce symptoms, such as splenomegaly, resulting from ineffective erythropoiesis in NTDT and TI. Also under investigation are modulators of the hepcidin pathway, which serves to regulate iron homeostasis. Increased hepcidin production limits intestinal absorption of iron and increases the sequestration of iron by macrophages, which are involved in recycling iron from senescent erythrocytes; there is also evidence that erythropoiesis serves to regulate hepcidin expression. Agonists of hepcidin (i.e., hepcidin mimetics) may therefore
have clinical utility in conditions such as beta TI. However, these agents have only been investigated in mouse models. Finally, the use of apotransferrin therapy is also under investigation as a possible means of managing iron overload and improving anemia as the transferrin pathway serves to transport iron between the major sites of uptake, storage, and utilization.

CONCLUSIONS

Although patients with NTDT in the past have been regarded to have less severe disease, it is now known that these patients have a substantial disease burden that negatively impacts quality of life. Indeed, over time, patients with NTDT and TI can accumulate similar levels of iron in the liver as patients with TDT. The increasing incidence of these disorders in developed healthcare systems such as those in North America and Europe calls for new strategies to increase access to appropriate treatment. While there has been more prenatal diagnosis and neonatal screening to confront this growing problem, a comprehensive approach is needed to further optimize care, with an emphasis on increased understanding of the at-risk populations. Care of affected patients may be improved by increasing physician awareness and addressing cultural and economic barriers to therapy. Frequent screening of patients with thalassemia using relatively simple assessments such as complete blood count and serum ferritin can also contribute toward identifying the functional impairments that have the greatest impact on quality of life. Management strategies such as iron chelation therapy can reduce iron burden and have been well tolerated in patients with NTDT. A number of other novel management strategies, such as JAK2 inhibitors and hepcidin mimetics, are currently under investigation for these disorders. Management of NTDT should entail comprehensive education and patient management strategies. It will also be important to continue to develop screening, counseling, and prenatal diagnosis programs in the most affected developing countries around the globe.
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FIGURE LEGENDS

Figure 1. Ethnicity of hemoglobin H disease in California.

Figure 2. Pathophysiology of NTDT. GI, gastrointestinal; NTDT, non-transfusion-dependent thalassemia; RBC, red blood cell.

Figure 3. Spectrum of transfusion requirements in thalassemias. Hb, hemoglobin.

Figure 4. LICs in patients with beta thalassemia intermedia–associated morbidities. Squares represent means and whiskers represent standard deviations, except for heart failure and diabetes mellitus, for which corresponding markers represent medians and 25th and 75th percentiles, respectively. p-values were calculated using independent samples t-test, except for heart failure and diabetes mellitus, for which Mann-Whitney U test was used. ALF, abnormal liver function; dw, dry weight; EMH, extramedullary hematopoiesis; LIC, liver iron concentration; PHT, pulmonary hypertension. Reprinted from Musallam KM et al. Elevated liver iron concentration is a marker of increased morbidity in patients with β thalassemia intermedia. Haematologica. 2011;96(11):1605-1612. Obtained from the Haematologica Journal website http://www.haematologica.org.

Figure 5. THALASSA: Absolute change in (A) LIC and (B) serum ferritin. p-value adjusted with the Dunnett method. dw, dry weight; LIC, liver iron concentration; LSM, least squares mean; SEM, standard error of the mean.
<table>
<thead>
<tr>
<th>Thalassemia Subtype and Etiology</th>
<th>Disease Characteristics</th>
<th>Primary Geographic Regions</th>
<th>Common Complications</th>
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<tbody>
<tr>
<td>Alpha thalassemia (Hb H disease)</td>
<td>Most cases characterized by mild to moderate anemia, marked microcytosis, and hypochromia; phenotype is rarely similar to alpha thalassemia major</td>
<td>Prevalent in Southeast Asia and Africa</td>
<td>Bone/skeletal abnormalities, acute hemolytic episodes, cholelithiasis, splenomegaly</td>
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<tr>
<td>• Caused by inactivation of three alpha globin genes</td>
<td></td>
<td></td>
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<tr>
<td>Beta thalassemia intermedia</td>
<td>Clinical severity is variable, ranging from mild to moderate NTDT</td>
<td>Worldwide prevalence, but most common in Southeast Asia and the Eastern Mediterranean region</td>
<td>Splenomegaly, pulmonary hypertension, cholelithiasis, leg ulcers, extramedullary hematopoiesis, thrombotic events</td>
</tr>
<tr>
<td>• Results from inheritance of a milder beta thalassemia phenotype</td>
<td></td>
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<tr>
<td>Hb E beta thalassemia</td>
<td>Clinical severity is variable, ranges from non-transfusion-dependent to transfusion-dependent</td>
<td>Prevalent in Southeast Asia, Indian subcontinent, and south mainland China</td>
<td>Splenomegaly, bone/skeletal abnormalities, growth retardation, acute hemolytic episodes</td>
</tr>
<tr>
<td>• Caused by coinheritance of Hb E structural Hb variant and other beta thalassemia alleles</td>
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</tbody>
</table>
Hb, hemoglobin; NTDT, non-transfusion-dependent thalassemia.
Table 2. Differentiating transfusion-dependent or major thalassemia and non-transfusion-dependent or intermediate thalassemia. Clinical characteristics based on data from Cappellini MD et al. *Guidelines for the Clinical Management of Thalassaemia* [Internet]. 2nd Revised edition. Nicosia (CY): Thalassaemia International Federation; 2008.

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<tr>
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<th>TDT/TM</th>
<th>NTDT/TI</th>
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</thead>
<tbody>
<tr>
<td>Age of clinical presentation</td>
<td>0–2 years</td>
<td>2–6 years</td>
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<tr>
<td>Hb concentration</td>
<td>6–7 g/dL</td>
<td>8–10 g/dL</td>
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<tr>
<td>HbA2 composition</td>
<td>&lt;4%</td>
<td>&gt;4%</td>
</tr>
<tr>
<td>Anemia severity</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>Spleen and liver enlargement</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

NTDT, non-transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia; TI, thalassemia intermedia; TM, thalassemia major.
Figure 1.
Figure 2.

- Ineffective erythropoiesis
- Hemolysis, RBC loss
- Chronic anemia

- Increased erythropoietin
- Bone marrow expansion
- Reduced hepcidin
- Increased GI iron absorption

- Extramedullary hematopoiesis
- Osteoporosis
- Leg ulcers
- Pulmonary hypertension

- Iron overload complications
  - Liver disease
  - Endocrinopathies
Figure 4.
Figure 5A.

Absolute change from baseline in LIC. LSM ± SEM (mg Fe/g dw).

- Deferasirox 5 mg/kg/d (n=55)
- Deferasirox 10 mg/kg/d (n=55)
- Placebo (n=50)

Time (weeks):
- 24
- 52

Statistical significances:
- p=0.009
- p<0.001
- p=0.001
Figure 5B.

Absolute change from baseline in serum ferritin, LSM ± SEM (ng/mL)

Deferasirox 5 mg/kg/d (n=55)
Deferasirox 10 mg/kg/d (n=55)
Placebo (n=56)

Time (weeks)
24 52

$p=0.088$  $p<0.001$

$p=0.001$