Non-transfusion dependent thalassemia: translating evidence to guidelines

Afif R. Harb, Antoine N. Saliba, Ali T. Taher

Division of Hematology & Oncology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

Abstract

The thalassemias are a group of inherited disorders of hemoglobin synthesis characterized by various degrees of defective production of the α- or β-globin chains of adult hemoglobin A. Non-transfusion-dependent thalassemia (NTDT) includes a group of thalassemia patients who do not require regular RBC transfusions for survival, but may require occasional transfusions due to infection or pregnancy or may require more regular transfusions later in life due to splenomegaly or other complications. Due to the rising phenomenon of global migration, this previously well-localized entity is currently spreading more and more worldwide reaching Northern America and Northern Europe. The clinical picture of NTDT is governed by the severity of the ineffective erythropoiesis and the chronic hemolytic anemia, which, in turn, lead to iron overload, hypercoagulability, and an array of clinical complications involving almost every organ system. Patients with NTDT suffer from complications that are distinct from those encountered in patients with transfusion-dependent thalassemia (TDT) in addition to the complications shared by both TDT and NTDT. As a consequence, patients with NTDT deserve a care specifically tailored to their needs. In the care of patients with NTDT, aiming at a standardized yet personalized care is not an easy task especially that NTDT patients lie on a heterogeneous spectrum with a wide variability in their clinical presentation and response to therapy. Therefore, guidelines emerge as a necessity to answer the specific needs of NTDT patients and the clinicians caring for them. In this article, we summarize the complications most commonly associated with NTDT and the recommendations of the guidelines for the management of patients with NTDT, based on the best available evidence.

Introduction

Definition and diagnosis of NTDT

The thalassemias are a group of inherited disorders of hemoglobin synthesis characterized by various degrees of defective production of the α- or β-globin chains of adult hemoglobin A, leading to α- or β-thalassemia, respectively. Transfusion-dependence in these congenital anemias has been traditionally used as a tool to differentiate between the various thalassemia phenotypes and their respective severity. Non-transfusion-dependent thalassemia (NTDT) refers to a subset of thalassemia phenotypes that does not require lifelong regular transfusions for survival but may need transfusions in specific clinical settings and only for defined periods of time (pregnancy, infection, growth failure, splenomegaly-induced hemoglobin drop) (Figure 1).1-4 Out of the numerous NTDT genotypes, the three most studied are: β-thalassemia intermedia, hemoglobin E/β-thalassemia, and α-thalassemia intermedia (HbH disease) (Figure 2).5 The clinical picture of NTDT is governed by the severity of the ineffective erythropoiesis and the chronic hemolytic anemia, which, in turn, lead to iron overload, hypercoagulability, and an array of clinical complications involving almost every organ system. Diagnosing NTDT can be made by using simple lab tests (complete blood count (CBC) showing red cells with decreased cell size, reflected by a low mean corpuscular volume (MCV) and low hemoglobin content, reflected by a low MCH) or, more conclusively, using DNA molecular techniques. However, NTDT remains to be a clinical diagnosis par excellence because patients tend to present at an older age and show milder symptoms compared to TDT patients—mild to moderate anemia, splenomegaly, and variable need for transfusions. This is why both the physician’s clinical sense and the patient’s clinical picture are integral to reach a diagnosis.5

The global burden of the NTDT

Thalassemias are the most common disorders attributable to a single defective gene worldwide, with around 68,000 children born with either one of the various thalassemia phenotypes yearly.7,8 Estimates suggest that around 80 to 90 million people are carriers of a β-thalassemia mutation across the world (1.5% of population), with almost 50% of these carriers coming from South-East Asia.9 This high frequency of thalassemic disorders can be explained by the widespread tradition of consanguineous marriage as well as gene drift and founder effects. Moreover, epidemiological studies suggest that around 23,000 children are born with transfusion-dependent β-thalassemia each year, while a smaller number have the non-transfusion dependent phenotype (NTDT),7,8,10 distributed around parts of the
Eastern Mediterranean and Africa.\textsuperscript{10} Hemoglobin E/β-thalassemia currently affects around 1,000,000 people worldwide, with the highest prevalence being in India, Bangladesh, Thailand, Laos, and Cambodia.\textsuperscript{9,11-13} At least 19,000 children are born worldwide each year with hemoglobin E/β-thalassemia, with half of them falling into the category of NTDT.\textsuperscript{7,14} As for the α-thalassemia syndromes, the annual number of births for the NTDT form of α-thalassemia, α-thalassemia intermedia, or hemoglobin H disease, is about 10,000.\textsuperscript{7,14}

These numbers might even be underestimates of the real burden of the disease because of the limited epidemiological studies of the thalassemia syndromes in regions where the disease is known to be most prevalent. Additionally, the increasingly growing rates of migration to Northern America and Northern Europe from areas of the world where thalassemias are endemic have been leading to an increasing prevalence of thalassemic disorders in the West.\textsuperscript{15,16}

**Medical complications in NTDT**

Patients with NTDT develop myriad complications that are shared with TDT patients as well as others that are unique to them. Of those many complications the most important to highlight in NTDT patients are: thrombotic disease, pulmonary hypertension, liver disease, endocrine and bone disease, leg ulcers, extramedullary hematopoiesis, and renal disease (Figure 3). A cross-sectional study evaluating 120 patients with NTDT who were naïve to any therapeutic modality showed that advancing age of the NTDT patient is a positive risk factor that correlates with an increased risk of all NTDT complications.\textsuperscript{3}

**Thrombotic disease**

Patients with NTDT have a hypercoagulable state that is mediated by several factors; however, abnormal functioning of platelets and red blood cells (RBCs) is thought to be the leading cause of clinical thrombosis in these patients.\textsuperscript{2,17-19} Patients with NTDT show chronically activated platelets with an enhanced platelet aggregation that is detected by increased expression of platelet activation markers.\textsuperscript{20-22} Moreover, RBCs in these patients have oxidized hemoglobin which, in turn, results in the formation of reactive oxygen species (ROS). ROS induce the oxidation of the RBC membrane and increase its phosphatidylserine content rendering the RBC negatively charged, rigid, and prone to aggregation.\textsuperscript{22}

In a study including nine Italian pediatric thalassemia centers, Borgna Pignatti et al. reported that 4% of 683 patients with TDT and 9.6% of 52 patients with NTDT had experienced a thrombotic event.\textsuperscript{22} 29% of a cohort including 83 splenectomized patients with NTDT experienced a venous thrombotic event over a 10-year follow-up period.\textsuperscript{23} Interestingly, these patients did not show any conventional risk factor for venous thrombosis, further highlighting the unique pathophysiology of hypercoagulability in NTDT patients. A large study that examined the data from 8,860 thalassemia patients in the Mediterranean area and Iran concluded that thrombotic events, mostly venous, occurred 4.38 times more frequently in NTDT patients than in TDT patients.\textsuperscript{24} Having evaluated 584 patients with NTDT at six comprehensive care centers (Lebanon, Italy, Iran, Egypt, United Arab Emirates, and Oman), the OPTIMAL CARE study established that thrombotic disease, mostly venous, affected 14% of the patient population and ranked as the fifth most common complication.\textsuperscript{25} The main independent risk factors for thrombotic events were splenectomy, age >35 year, serum ferritin level >1000 ng/mL, and a hemoglobin level <9 g/dL.\textsuperscript{23,25,26} A review of observational studies, assessing silent cerebral infarcts in β-thalassemia intermedia patients, estimated the prevalence to
be 27 – 60%, suggesting a role for closer follow-up of patients at risk.27 Moreover, a prospective observational study showed that WMLs and brain atrophy are a common finding in adult, splenectomized NTDT patients with the incidence and the number of lesions increasing with age and transfusion naïvety.28 Also, brain magnetic resonance angiography (MRA) and positron emission tomography-computed tomography (PET-CT) studies have been recently conducted in β-thalassemia intermedia. 27.6% of 29 asymptomatic, splenectomized adults had evidence of arterial stenosis on MRA. Two patients had more than one artery involved and the internal carotid artery was the most commonly involved artery. Among the 12 identified stenotic lesions, two were severe (>75% stenosis), one was moderate (51-75% stenosis), and the remaining nine were mild (≤50% stenosis).29 It is also worth mentioning that the risk of finding an abnormality on PET-CT increases with higher liver iron concentration values.30

**Pulmonary hypertension**

Pulmonary hypertension (PHT) in patients with NTDT is also a serious complication. Studies relying principally on echocardiographic measures reported prevalence rates ranging between 10% and 78.8% (averaging at ~30%). To note, a higher prevalence was generally observed in patients with NTDT (β-thalassemia intermedia and hemoglobin E/β-thalassemia) than in patients with TDT.31-40 Patients with NTDT, specifically β-thalassemia intermedia, had a 5-fold increased prevalence of pulmonary hypertension on right heart catheterization than TDT patients (4.8% versus 1.1%).41 The exact cause of PHT in NTDT patients is not fully understood, but many incriminating factors have been suggested including a hypercoagulable state, advancing age, splenectomy, thrombocytosis, and hemolysis.3,34,37,39

**Liver disease**

Liver disease is an important complication in NTDT patients with iron overload being the main culprit in this process. Results from patients with hereditary hemochromatosis along with other acquired liver diseases confirm the role of chronic iron deposition in hepatocytes in promoting liver fibrogenesis and cirrhosis.45,46 A longer duration of hepatic iron exposure is associated with a higher risk of significant fibrosis, while liver cirrhosis can develop within a decade in severely iron overloaded patients.45 The proliferative and mutagenic effects of excess iron result in an increased susceptibility to hepatocellular carcinoma (HCC), even in the absence of pre-existing liver cirrhosis.46-49 Iron overload promotes the production of oxygen free radicals, which, in turn, give rise to neoplastic clones through genetic or epigenetic alterations even in the absence of hepatitis infection. This is further corroborated by the results of a review of 36 case reports of HCC in thalassemia patients, out of whom 22 patients had the thalassemia intermedia phenotype and six (27%) patients were negative for Hepatitis B or C.50,51

**Endocrine and bone disease**

Growth retardation and skeletal deformity due to ineffective erythropoiesis, medullary expansion, and anemia may be seen in patients with NTDT. However, these are less frequently seen in patients with NTDT compared to patients with more severe forms of thalassemia.1,52,53 Although the prevalence of endocrine disease is relatively lower in patients with NTDT than TDT patients, reported prevalence rates of diabetes mellitus, hypothyroidism, hypoparathyroidism, hypogonadism, and adrenal insufficiency remain considerably high, especially as patients advance in age.1,13,25 These complications are mainly a result of the iron overload and its deposition in the various glands. Other factors such as splenectomy, severe ineffective erythropoiesis, and low fetal hemoglobin (HbF) levels have been also hypothesized to contribute to endocrinopathies in patients with NTDT.31,52,56

Osteoporosis is commonly found in NTDT, with additional risk factors including female gender, advanced age, iron overload, splenectomy, and low fetal hemoglobin levels.3,25,56-59

**Leg ulcers**

Leg ulcers are more common in patients with NTDT compared to those with TDT, and this risk increases with advancing age.1,3,52,53,55,56 It is hypothesized that the skin of the extremities of older NTDT patients can be thin due to decreased tissue oxygenation making the subcutaneous tissues fragile and vulnerable to ulceration with minimal trauma. Other factors including severe anemia, ineffective erythropoiesis, splenectomy, and the hypercoagulable state have been described as risk factors for the development of leg ulcers.1,3,55,56 In patients with NTDT, the hypercoagulable state, the deformability of red blood cells, and high venous pressure (secondary to right-sided heart failure and venous insufficiency) have been thought to increase the risk of developing leg ulcers as a result of ischemia to the skin.50,53 Data on the role of fetal hemoglobin levels is controversial. It has been theoretically suggested that the oxygen retaining capacity of hydroxyurea increases the risk of developing leg ulcers. Nonetheless, Musallam et al. showed a lower rate of leg ulcers in patients with high fetal hemoglobin levels.56 Results from observational studies have also showed higher rates of leg ulcers in NTDT patients with iron overload further advocating the important role of iron overload in the development of this particular complication as well.3,55,59 Results from an observational study on 11 patients with leg ulcers in a single center in Lebanon have shown that chelation therapy, hydroxyurea use, and blood transfusions are beneficial in the treatment of this condition, further supporting the role of iron overload, hypoxia, and abnormal RBC in this process.55

**Extramedullary hematopoiesis**

Ineffective erythropoiesis in patients with NTDT results in the expansion of hematopoietic tissue in the liver, spleen, and other organs, a process known as extramedullary hematopoiesis (EMH). In these organs, EMH appears mostly in the form of masses termed extramedullary hematopoietic pseudotumors. The prevalence of extramedullary hematopoietic pseudotumors is significantly higher in patients with NTDT than in those with TDT (20% versus <1% respectively)1,3,51 The incidence of EMH is higher in patients with older age, worse ineffective erythropoiesis, and lower fetal hemoglobin levels.5,25,56 Almost all body sites may be involved in EMH; this can be explained by the fact that these sites are believed to be normally engaged in active hematopoiesis in the fetus during gestation, a process that normally stops at birth. Yet, these sites retain the ability to produce red cells under situations of prolonged ineffective erythropoiesis which is the case in almost all NTDT patients.64 Among the various body regions reported, paraspinal involvement received special attention due to the debilitating clinical consequences secondary to neural element compression.64 Paraspinal EMH is reported to occur in 11 to 15% of cases with extramedullary hematopoietic pseudotumors, resulting in a variety of neurological symptoms due to spinal compression.5,65 However, it is believed that more than 80% of cases may remain asymptomatic and are only discovered incidentally by radiologic studies performed for other reasons.

**Renal disease**

Little attention has been paid to the possible involvement of the kidney in patients with β-thalassemia. However, recent studies outlined the presence of tubular and glomerular dysfunction in children with thalassemia, even before clinical signs or symptoms develop.57,60 These abnormalities are generally attributable to a state of persistent hypoxia, anemia and severe iron overload. A cross-sectional study assessing...
kidney function in 50 patients with thalassemia intermedia showed that a total of 24 (48%) patients showed markers of glomerular hyperfiltration and a total of 7 (14%) had proteinuria.\textsuperscript{65} Renal disease in thalassemia patients can progress to reach end stage renal disease (ESRD), as evident by an observational study that followed up 127 thalassemia intermedia patients over 10 years with 6 (4.7%) developing ESRD requiring regular hemodialysis.\textsuperscript{66} Early proximal tubular markers such as NAG, ß2-microglobulin, phosphaturia and uricosuria should be evaluated in these patients to detect early tubular abnormalities and to try to decrease the burden on the kidney.\textsuperscript{68}

The importance of guidelines in NTDT

Over the years, optimal medical care has gradually shifted to the concept of cost-effective, standardized, yet personalized care that is tailored to a specific patient with one or more specific conditions in a specific clinical setting. As a consequence, the patients with NTDT deserve a care specifically tailored to their needs. Moreover, in the care of patients with NTDT, aiming at a standardized yet personalized care is not an easy task especially that NTDT patients lie on a heterogeneous spectrum with a wide variability in their clinical presentation and response to therapy. Therefore, guidelines emerge as a necessity to answer the specific needs of NTDT patients and the clinicians caring for them.

Guidelines should always be adapted not only to the specific patient but also to the specific clinical setting where the care is provided. Therefore, recommendations emanating from guidelines should take into consideration the characteristics of the clinical setting where they are applied. For instance, guidelines should acknowledge the fact that costs of clinical care, whether therapeutic or diagnostic, vary among countries and among different healthcare systems. A clear example of this to NTDT is the attempt to optimize the use of serum ferritin as a surrogate to other more accurate markers to assess the burden of iron overload in countries where the use of MRI to calculate LIC is not an option whether because of financial or technical difficulties.

There remains an essential need to bridge the gap between the developing and developed countries in order to make sure that every patient in any region in the world has an equal chance to receive the best available medical care.

The mosaic pattern in the care of NTDT necessitates using Clinical Practice Guidelines (CPGs) (1) to provide a framework for the standardized care, which individual clinicians can sculpt into personalized care, and (2) to make sure every NTDT patient on the globe can benefit from the best evidence available and the richest fund of knowledge reached towards better clinical care and quality of life. Based on the aforementioned concepts, CPGs have become a necessity with the continuous spread of NTDT all over the globe. In addition, pooling the experience of experts in the field around the world and carefully examining the evidence available to come up with guidelines will help guide the management of patients with a disease that is prevalent enough to warrant collective attention but rare enough to require collaborative knowledge and expertise.

The formulation and the publication of the Guidelines for the management of NTDT

The Guidelines for the management of NTDT, released by the “Thalassaemia International Federation” in 2013, aim at providing guiding principles to clinicians caring for patients with NTDT all over the world.\textsuperscript{71} The guidelines were formulated by a group of highly trained and extensively experienced experts, in the field of thalassemia in general and NTDT in particular, who joined forces to scan the literature for the best evidence available on the topic of NTDT and share clinical experiences to publish the handbook on the guidelines for the management of NTDT based on the principles of evidence-based medicine.\textsuperscript{71} In order to help keep the guidelines user-friendly and centered on the NTDT patient, the authors of the guidelines have used a problem-based approach, using cases to introduce each topic to allow physicians to have a better grasp of the clinical situation presented and the proposed therapeutic and diagnostic recommendations.\textsuperscript{71}

Highlights from the Guidelines for the management of NTDT

The management of patients with NTDT revolves around four main therapeutic pillars: (i) transfusion therapy, (ii) HbF inducers, (iii) splenectomy, and (iv) iron chelation (Figure 4).

Transfusion therapy

As previously mentioned, transfusion therapy is not a therapeutic mainstay in NTDT patients, as opposed to TDT patients. Nevertheless, the selective use of transfusion therapy should be resorted to in specific situations and over a short period of time, only when needed to provide healthy erythrocytes and decrease ineffective erythropoiesis.\textsuperscript{15,72} Patients newly diagnosed with NTDT should be closely watched over the first few following the establishing of the diagnosis; clinicians should avoid starting regular transfusion therapy too hastily. Observational studies have shown that when used appropriately, transfusion therapy will help reduce the risk of many complications of NTDT, including leg ulcers, thrombotic events, pulmonary hypertension, silent brain infarcts, and extramedullary hematopoietic pseudotumors.\textsuperscript{4,24,25,27,28,64,73} However, in the absence of clear guidelines to govern the amount and duration of transfusion therapy required, this therapy should be individually tailored to each patient depending on the clinical picture. The Guidelines advise the clinician to consider...
occasional blood transfusions in patients with NTDT during periods of acute stress, severe hemoglobin drops, and infection. The Guidelines also recommend initiating more frequent blood transfusion therapy when patients with NTDT show growth failure, declining hemoglobin levels coupled with significant splenectomy, skeletal changes, exercise intolerance, poor performance at school, or frequent hemolytic crises, especially in HbF disease. Special attention must be given to detect and prevent alloimmunization. The risk of alloimmunization increases in transfusion naïve or minimally transfused patients, splenectomized patients, and pregnant patients. This risk can be reduced by extensive genotyping and phenotype screening along with the use of fully phenotype-matched blood.

Fetal hemoglobin (HbF) inducers

The mode of action of HbF inducers in NTDT is mainly increasing globin production which subsequently results in a decrease in the chain imbalance. This ultimately improves the processes of ineffective erythropoiesis and hemolysis by prolonging the RBC lifespan and thus increasing hemoglobin levels. Among the various HbF inducers, hydroxyurea is by far the most studied HbF inducer. Hydroxyurea is a potent HbF inducer in patients with hemoglobinopathies, especially in sickle cell disease. In -thalassemia, hydroxyurea therapy substantially increases mRNA expression with a good correlation between in vitro mRNA expression and in vivo increase in HbF. Hydroxyurea may also play a potential role in minimizing the hypercoagulable state, especially in splenectomized patients with NTDT. It is worth mentioning that HbF inducers have not been extensively studied in NTDT. Therefore, there is a great need for more randomized placebo-controlled trials that assess the effect of HbF inducers on a homogenous group of thalassemia patients, while using maximally tolerated doses in order to better explore the net effect of these agents and possible adverse events in this population. The Guidelines recommend considering treatment with hydroxyurea in patients with thalassemia intermedia homozygous for the XmnI polymorphism, patients with Lepore or -thalassemia, patients who cannot be transfused because of alloimmunization, and patients with PHT, extramedullary pseudotumors, and leg ulcers.

Splenectomy

Splenectomy, which was historically performed routinely in order to help increase patients’ hemoglobin level, is no longer recommended as an initial therapeutic option. Evidence from multiple studies has shown that splenectomy is independently associated with an increased risk of most NTDT-related complications including venous thromboembolism (5-fold increased risk) with the median duration for the first thrombotic event being 8 years post splenectomy, PHT (4-fold increased risk), leg ulcers (4-fold increased risk), and silent cerebral infarcts. Factors possibly implicated include high nucleated red blood cell counts (≥300 x10^9/L) and platelet counts (≥500 x10^9/L) after the removal of the spleen in these patients. Moreover, splenectomy increases the risk of severe infection in these patients with the risk of post-splenectomy sepsis increasing more than 30 folds in comparison with the normal population, which makes it extremely important to follow up these patients closely and make sure they are up-to-date on their vaccines, especially against encapsulated bacteria. The Guidelines recommend reserving splenectomy for cases of hypersplenism leading to worsening anemia – especially if the latter affects growth, leukopenia, or thrombocytopenia. Splenectomy should be also considered in the case of splenomegaly with concern about possible rupture or with significant symptoms such as left upper quadrant pain or early satiety.

Iron chelation

Given the ineffective erythropoiesis in NTDT, hepcidin levels are inappropriately low, leading to increased intestinal iron absorption (92, 93, 92, 95). As the storage capacity of the hepatocytes and the macrophages gets saturated, circulating iron exceeds the binding capacity of transferrin. Therefore, non-transferrin bound iron (NTBI) starts circulating in the plasma and is deposited in cardiac myocytes, hepatocytes, pituitary cells, and pancreatic cells. Reactive oxygen species produced by the metabolism of NTBI play a central role in inducing cellular dysfunction, apoptosis, and necrosis. A study which included 168 patients with -thalassemia intermedia showed that elevated Liver Iron Concentration (LIC) was associated with increased risk of vascular, endocrine, and bone morbidity. Further analysis of the data in the study showed that patients with LIC > 5mg/g dry weight (dw) showed a much higher risk of vascular and endocrine morbidities compared to those with LIC<5 mg/g dw. Within the range of LIC between 3 and 15 mg/g dw, the 5mg/g dw cutoff showed the highest absolute risk for developing morbidity in TI patients. The ORIENT study suggested the use of the 800 ng/mL or over threshold to initiate iron chelation therapy in -thalassemia intermedia patients and the 300 ng/mL or under threshold to interrupt it as a possible surrogate for LIC measurement, especially in resource-poor countries.

The aforementioned evidence led to the fact that iron chelation therapy is currently the cornerstone of managing patients with NTDT and reducing disease-related complications. Three chelators are available to treat iron overload: deferoxamine, deferasirox, and deferiprone. Deferoxamine was first used in the 1970s and is administered either subcutaneously or intravenously, resulting in limitations on patient compliance. Deferiprone, the first orally administered chelator, has not been studied extensively in NTDT except in very few trials with relatively small sample sizes. On the other hand, deferasirox, also an oral chelator, has been extensively studied. The THALASSA study remains the largest and first randomized clinical trial of an iron chelator in NTDT patients including 166 study subjects. Results from this study showed that deferasirox, given orally once daily, resulted in significant reduction of LIC compared with placebo, following 12 months of therapy in patients ≥ 10 years of age with LIC ≥5 mg Fe/g dw. This decrease in LIC is directly proportional to the deferasirox dose used (5 versus 10 versus 20 mg/kg/day). This study also established the safety of deferasirox in this population with the most common drug-related adverse events being: nausea (6.6%), rash (4.8%), and diarrhea (3.6%). The promising results from the THALASSA study helped deferasirox receive the US Food and Drug Administration (FDA) approval as first-line therapy for the management of iron overload in NTDT patients, who are ten years and older (on January 23, 2013). Deferasirox also received the European Medicines Agency (EMA) approval for the treatment of chronic iron overload (on November 16, 2012). The Guidelines recommend initiating therapy in NTDT patients older than 10 years of age and with an LIC > 5 mg/g dw, to prevent complications of iron overload. It is also recommended to interrupt therapy once LIC < 3 mg/g dw is reached, to prevent over chelation (Figure 5).

Other novel management options in the horizon

New therapeutic agents are currently being evaluated for safety and efficacy for use in NTDT patients. These new modalities can be divided into two categories: one that targets ineffective erythropoiesis and another that targets iron overload in NTDT patients.

Among the modalities that aim to ameliorate ineffective erythro-
The application of the Guidelines to special situations

In managing patients with NTDT, standardized guidelines aim to provide physicians with a helping hand by highlighting the best methods to deal with the growing population of heterogeneous NTDT patients. Out of the many scenarios where standardized guidelines have helped physicians manage their patients, this assistance becomes even more important in special situations such as pregnancy and sudden hemolytic crises.

Pregnancy in NTDT

Even though delayed puberty in NTDT patients may be very common due to the impact of the disease on the endocrine and reproductive systems, fertility is generally preserved making pregnancy a genuine possibility. Observational studies have shown that most pregnancies in NTDT patients are spontaneous. Common complications are a worsening in the anemia and an increased risk of thrombotic events, both of which greatly affect the fetal development and the general well-being of the pregnant NTDT patient. The guidelines suggest that pregnant NTDT patients should be transfused based on their hemoglobin level, general and cardiac conditions, and the fetal growth status. These patients should be followed up extensively in a multidisciplinary manner (hematologists, obstetricians, and cardiologists) and should be placed on prophylactic anticoagulation to prevent peripartum thrombotic events.

Hemolytic crises in NTDT

Another special scenario where the presence of standardized guidelines can prove to be extremely helpful is hemolytic crises in the patient with NTDT. In many instances, NTDT patients may develop sudden rapid hemolytic crisis ending up with a hemoglobin level plummeting as low as 3 g/dL overnight. These crises occur more readily in HbH disease patients and are generally induced by multiple factors, mainly infection (caused by Gram-negative bacteria more commonly than Gram-positive bacteria), oxidative challenge, hypersplenism, or pregnancy. Guidelines recommend a prompt attention to these patients with an aggressive approach focusing on rapid restoration of hemoglobin level to 8-9 g/dL, continuous monitoring of tissue perfusion and oxygenation, adequate assessment of total body fluid and cardiovascular status, and rapid detection of the causative agent with immediate administration of broad spectrum antibiotics.

Conclusions

It is extremely important to state that Clinical Practice Guidelines do not and should not replace individual clinical expertise. They cannot be used in the absence of information specific to the individual patient being treated. Factors such as comorbidities and individual preferences need to be factored into the equation of the clinical care. In applying CPGs, it is also important to take into account the characteristics of the system in which one practices and the resources available at both the individual and systemic levels. It is also extremely important to realize that not every clinical action that is not completely in line with CPGs is essentially wrong. The care provided to patients with NTDT should be standardized, but it is the role of the astute, highly trained, experienced, and up-to-date physician to provide the final piece of the puzzle that shapes the management, striking the right balance between standardized and individualized patient care. The physicians caring for patients with NTDT should keep in mind that standardized guidelines are based on the best evidence present at a certain period of time and, hence, are vulnerable to being refuted, edited, or improved with time as new evidence from ongoing studies emerges. Therefore, physicians will always need to be up-to-date, open to the fact that new evidence may always emerge, and malleable enough to mold their practice to the best evidence available.

The physician caring for the patient with NTDT should know the recommendations of the CPGs, think about the relevant ones during every patient encounter, and use them as a basis for clinical decision-making, seasoned with a personalized clinical assessment. The clinician should never forget to put into the care of every patient the sum of the clinical experiences (collective and personal), to exercise personalized clinical judgment, and to focus on the individual while keeping in perspective the larger framework that guidelines offer.

Finally, even if our latest problem-based guidelines seem to be inclusive of all the important and recent publications on NTDT, regulatory
bodies and expert groups should keep a keen eye on evolving research in the area. The Guidelines need to be frequently updated to incorporate the best evidence and to cover new emerging topics in the care of the patient with NTDT.

References


88. Crary SE, Buchanan GR. Vascular complications after splenectomy.


