

When to consider transfusion therapy for patients with non-transfusion-dependent thalassaemia

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Vox Sanguinis

Non-transfusion-dependent thalassaemia (NTDT) refers to all thalassaemia disease phenotypes that do not require regular blood transfusions for survival. Thalassaemia disorders were traditionally concentrated along the tropical belt stretching from sub-Saharan Africa through the Mediterranean region and the Middle East to South and South-East Asia, but global migration has led to increased incidence in North America and Northern Europe. Transfusionists may be familiar with β -thalassaemia major because of the lifelong transfusions needed by these patients. Although patients with NTDT do not require regular transfusions for survival, they may require transfusions in some instances such as pregnancy, infection or growth failure. The complications associated with NTDT can be severe if not properly managed, and many are directly related to chronic anaemia. Awareness of NTDT is important, and this review will outline the factors that should be taken into consideration when deciding whether to initiate and properly plan for transfusion therapy in these patients in terms of transfusion interval and duration of treatment.

Key words: haemoglobin E/ β thalassaemia, haemoglobin H disease, iron chelation, non-transfusion-dependent thalassaemia, red cell transfusion, β -thalassaemia intermedia.

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Introduction

Thalassaemia describes all the inherited genetic abnormalities that affect the synthesis of α - or β -globin chains and, consequently, normal erythropoiesis and the oxygen-carrying capacity of blood by haemoglobin. This condition is inherited as an autosomal recessive disorder and can be classified into two main categories: α - and β -thalassaemia. Patients with thalassaemia disease commonly develop chronic haemolytic anaemia and ineffec-

tive erythropoiesis due to imbalanced globin synthesis. The severity of anaemia is linked to the number of genetic aberrations, the specific combination of affected genes, other genetic and environmental modifiers and physiological stressors [1–5]. For instance, patients with β -thalassaemia major are transfusion dependent, which is the extreme end of transfusion requirement in thalassaemia syndromes [6]. Approximately 23 000 children are born every year with the transfusion-dependent form of β -thalassaemia or β -thalassaemia major, while the number with non-transfusion-dependent β -thalassaemia is less well defined [7–9]. Due to a wide range of transfusion requirements between transfusion-dependent and asymptomatic thalassaemia carriers, the term non-transfusion-dependent thalassaemia (NTDT) was introduced to include β -thalassaemia intermedia (β -TI) and patients with β -thalassaemia and β -globin variants in particular HbE (Hb E/ β thalassaemia) that do not require regular blood transfusions for survival [10–14]. In addition, most patients with α -thalassaemia syndrome such as haemoglobin

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H (HbH) disease are asymptomatic and may only require transfusion therapy when they experience a sudden increase in red cell demand, such as during pregnancy or intercurrent infection [10].

Therefore the most common types of NTDT are β -TI, α -thalassaemia (mainly HbH disease) and HbE/ β -thalassaemia. There are also a number of less common NTDT thalassaemias that will not be dealt with here [15–19].

β -thalassaemia intermedia results from inheritance of a β -thalassaemia genotype that is milder than the transfusion-dependent disease β -thalassaemia major. β -thalassaemia is prevalent worldwide but is most common in South-East Asia and the Eastern Mediterranean.

HbE/ β -thalassaemia, which results from the co-inheritance of the haemoglobin structural variant known as HbE and many different β -thalassaemia alleles, is highly prevalent in Southeast Asia, the Indian subcontinent and the southern part of mainland China [20]. More than 19 000 children a year are born with HbE/ β -thalassaemia, around half with transfusion-dependent disease and half with NTDT [7, 8].

Haemoglobin H disease, which is caused by the inactivation of three α -globin genes, is highly prevalent in Southeast Asia and Africa. In some regions, such as the West Pacific Islands, incidence of carriers (having one α -globin gene deletion) may be as high as 80–90% [10].

The clinical severity of patients with NTDT ranges widely because a diversity of phenotypes is included in this classification and because patients with the same phenotype can have very different symptoms. The extent of chronic anaemia that NTDT patients experience, rather than their specific thalassaemia phenotypes, determines the severity of clinical complications [2, 11, 12, 21].

Non-transfusion-dependent thalassaemia patients can generally be described as having mild to moderately severe chronic anaemia. The state of anaemia in patients with NTDT can rapidly change when they experience a physiological stressor, such as infection, or it can become more severe over time for various reasons, including the development of splenomegaly. In addition, a low Hb level can hamper physiological processes such as growth and development, and chronic anaemia initiates a cascade of compensatory mechanisms that lead to diverse clinical complications [22–25].

Transfusionists and haematologists may be very familiar with β -thalassaemia major because of the necessary lifelong transfusions in these patients. However, awareness of NTDT and the special considerations relevant to these patients is important. Although NTDT is less severe than transfusion-dependent thalassaemia (TDT), the associated complications can be severe, and quality of life may actually be more impaired in patients with NTDT [26]. Moreover, in the light of increasing evidence that

many NTDT complications are directly related to chronic anaemia, and with the availability of oral iron chelators, it may be time to revisit the guidelines for transfusion therapy in patients with NTDT.

This review will focus on the factors that should be taken into consideration when deciding whether to transfuse in patients with β -TI, α -thalassaemia and HbE/ β -thalassaemia.

Clinical characteristics of NTDT: recognition

Irrespective of the underlying genetic mutation(s), thalassaemia patients who require regular blood transfusions for life support are considered transfusion dependent and those who require occasional transfusions to overcome a period of severe/debilitating anaemia are considered non-transfusion dependent [22, 25, 27, 28]. Although the division between transfusion dependent and non-transfusion dependent is theoretically relatively simple, classifying a patient as either transfusion dependent or non-transfusion dependent in a clinical setting can be much more complex. Table 1 shows the clinical and haematological characteristics that can be used to differentiate between β -thalassaemia major (transfusion dependent) and β -TI (non-transfusion-dependent) [29]. This guideline can be applied to other types of thalassaemia including HbE/ β -thalassaemia or HbH disease. Patients with NTDT can present with severe anaemia for several reasons, including acute infection. In the absence of a diagnosis or a long medical history, it is not possible to predict what baseline Hb levels would be in the absence of infection or how well a patient manages with 'usual' baseline Hb levels. Studies have shown that some patients with NTDT function well even if they have very low Hb levels [30, 31].

The findings of several studies and trials have identified characteristics of both patients with TDT and patients with NTDT that can be used as a guide for clinical decisions regarding the transfusion need of a patient [22, 25,

Table 1 Differential characteristics of β -thalassaemia major (β -TM) and β -thalassaemia intermedia (β -TI) [29]

	β -TM more likely	β -TI more likely
Clinical		
Presentation (years)	<2	>2
Hb levels (g/dl)	6–7	8–10
Liver/spleen enlargement	Severe	Moderate to severe
Haematological		
Fetal Hb (HbF) (%)	>50	10–50 but may be up to 100
HbA ₂ (%)	<4	>4

Modified from Ref. [29].

27, 28]. Patients with TDT usually present in the first year of life with symptoms of severe anaemia (Hb <7 g/dl), pallor, lethargy, failure to thrive, bone and skeletal deformities, marked splenomegaly and hepatomegaly. Patients with NTDT, in contrast, usually present when they are older than 2 years of age and often have moderate to severe spleen/liver enlargement. Patients with moderately severe anaemia (Hb 8–9 g/dl), a state often associated with β -TI, often present between 2 and 6 years of age, but thalassaemia patients with milder anaemia (Hb >9 g/dl) can present much later, sometimes only in adulthood [6, 27].

Patients with NTDT are usually diagnosed because of chronic anaemia rather than the complications that may arise from chronic anaemia, although these complications can be severe if diagnosis and appropriate management are delayed [22, 25, 27, 28, 32].

Complications of NTDT and indications for transfusion therapy

On initial presentation and diagnosis of NTDT, it is not recommended to initiate transfusion therapy immediately. A patient may present with severe anaemia that is exacerbated by infection and acute haemolysis and therefore be placed on lifelong transfusion therapy unnecessarily. One study found that 37 out of 84 patients with HbE/ β -thalassaemia could be withdrawn from a previous regular blood transfusion regimen without any deleterious effects, suggesting that many of these HbE/ β -thalassaemias were in fact NTDT but had received inappropriate regular blood transfusion [33]. It is important to monitor the patient for several months after diagnosis of a NTDT thalassaemia. Assessment of transfusion requirement should be based

on factors such as activity, growth and development, skeletal changes and disease complications, rather than on Hb levels alone [22]. Several studies in HbE/ β -thalassaemia found that there was only 1.8–2.6 g/dl difference in Hb levels between the mildest and most severe groups, highlighting the limitations of Hb level as a decision criterion for initiating transfusion therapy [33, 34]. In addition, some children with HbE/ β -thalassaemia are able to adapt to lower Hb levels and function well without transfusions [30, 31]. A low baseline Hb might be well compensated in most conditions, but become de-compensated in several clinical circumstances or even normal situations such as pregnancy or growth spurt. Therefore, the patient should be regularly monitored for any signs and symptoms of disease complications. It is important to note that all complications seen in NTDT are also characteristic of TDT, however with adequate blood transfusion, many of these complications have become less common in patients with TDT. The profiles of complications seen most often in NTDT vs. TDT are shown in Fig. 1. If the decision is taken to initiate transfusion therapy, the patient should be monitored closely and the regimen adjusted according to the patient's needs. Therapeutic goals may be reached with temporary transfusion therapy, thus avoiding the need for lifelong regular transfusions [35]. Earlier initiation of occasional transfusions may be beneficial in preventing the development of disease complications and alloimmunization [36].

Table 2 outlines the current indications for transfusion in each NTDT subtype, although the phenotypic variation of NTDT should be taken into account and decisions made on a case-by-case basis. It is important to note that the clinical phenotype of HbE/ β -thalassaemia can be divided into mild, moderate and severe. At the mild end

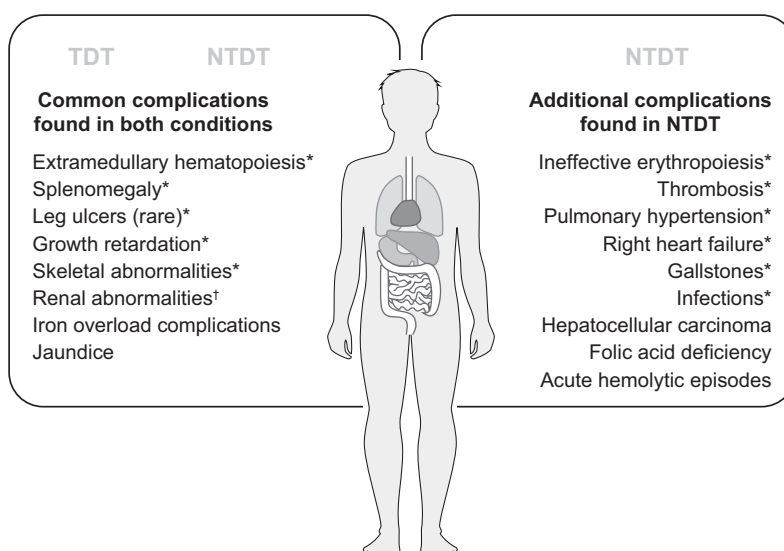


Fig. 1 Common complications of TDT and NTDT. *Preventable by blood transfusion; †Probably preventable by blood transfusion. NTDT, Non-transfusion-dependent thalassaemia.

Table 2 Current indications for transfusion therapy in NTDT subtypes

NTDT subtype	Indications for transfusion
HbH disease [11, 94, 95]	Infections exacerbating anaemia Growth retardation
HbE/ β -thalassaemia [6]	
Mild	Generally none
Moderate	As per β -TI (see below)
Severe	Transfusions required for survival, as per β -thalassaemia major
β -TI [6, 22]	Hb <5 g/dl Failure to thrive secondary to anaemia Emergence of bone deformities Tendency to thrombosis Presence of leg ulcers Development of pulmonary hypertension Poor growth and development Splenic enlargement Pregnancy Infection Cardiovascular disease

HbH, haemoglobin H; NTDT, Non-transfusion-dependent thalassaemia; β -TI, β -thalassaemia intermedia.

of the spectrum, patients generally require no transfusional intervention, and at the severe end, patients should be managed as TDT. Moderate HbE/ β -thalassaemia is clinically more similar to β -TI and therefore falls into the category of NTDT.

Ineffective erythropoiesis

The body's response to chronic anaemia is increased erythropoietin (EPO) production, but because of the ineffective erythropoiesis characteristic of NTDT, the erythroid marrow is unable to respond properly to the EPO signal, resulting in proliferation of erythroid precursors which fail to differentiate and die prematurely [37]. This causes erythroid marrow expansion, which is associated with osteoporosis and bone deformities, as well as hepatosplenomegaly due to build-up of erythroid precursors in the spleen and liver [38]. Ineffective erythropoiesis also leads to the formation of extramedullary haemopoietic pseudotumours, which are essentially masses of haemopoietic tissue. These can occur almost anywhere in the body, but the most concerning are those with parasplenic involvement (around 11% of cases), which can have debilitating consequences due to neuronal compression [39].

The degree of ineffective erythropoiesis in NTDT can vary from one patient to another and is directly associated with morbidity, as it is the underlying dysfunction causing many of the severe clinical complications. Even

though patients with NTDT are not reliant on transfusions for survival, transfusion therapy supplies normal erythrocytes and reduces the bone marrow expansion caused by ineffective erythropoiesis [40–42]. Transfusion therapy can therefore be beneficial in reducing the risk of complications that are associated with ineffective erythropoiesis. Table 3 shows the suppressive effects of transfusion therapy on erythroid activity in patients with β -thalassaemia major with differing pretransfusion Hb levels. In addition, it should be noted that the prevalence of extramedullary pseudotumours is <4% in transfusion-dependent patients, compared with around 20% in patients with NTDT, and transfusion has been shown to be protective against the development of these masses [23]. Transfusion therapy has also been successfully used to treat extramedullary pseudotumours, even in the most severe cases with parasplenic involvement [39].

Splenectomy may be considered as an alternative to transfusion therapy to alleviate splenomegaly and increase Hb levels. However, splenectomized patients with NTDT are at higher risk of venous thromboembolism, pulmonary hypertension (PHT), leg ulcers, silent cerebral infarcts and serious infections such as meningitis and sepsis than non-splenectomized patients [23, 43–45]. Splenectomized patients with NTDT have higher rates of organ iron loading than non-splenectomized patients [46–49]. For these reasons, splenectomy is only recommended in circumstances in which transfusion and iron chelation are not available, where hypersplenism results in severe anaemia, leucopenia or thrombocytopenia with recurrent infection and bleeding, or if the spleen exceeds 20 cm (largest dimension) and is at risk of rupture [22, 32, 35].

Increased intestinal iron absorption

Ineffective erythropoiesis, accompanied by anaemia and hypoxia, results in suppression of hepcidin production, increased intestinal iron absorption and release of iron from the reticuloendothelial system in patients with NTDT [50]. This leads to iron accumulation, particularly in the liver, and as a result, patients with NTDT commonly experience liver disease such as fibrosis and cirrhosis and may be at risk of hepatocellular carcinoma (HCC)

Table 3 Suppression of erythroid activity by transfusion therapy [42]

Pretransfusion Hb level (g/dl)	Erythroid activity after transfusion
8–6–9	2–6 times normal
9–10	1–4 times normal
10–11	1–2 times normal

[49, 51, 52]. This is in contrast with the situation in regularly transfused patients with β -thalassaemia major, who do not have low hepcidin levels. In 211 TI patients with risk factors for HCC, 2.8% developed HCC over 9 years of follow up [52]. In patients with NTDT, intestinal absorption of iron can be as much as 3–4 mg/day or 1000 mg/year [35]. Transfusion therapy may help to reduce intestinal iron absorption and thus reduce the risk of liver disease and other complications. However, patients with NTDT who receive blood transfusion also require appropriate and adequate iron chelation therapy; otherwise, the effect of transfusional iron overload would outweigh the benefit of reducing intestinal iron absorption.

Vascular complications

Thalassaemia is associated with a hypercoagulable state caused by aggregation of platelets and red-blood-cells (RBCs), increased thrombin production and vasoconstriction [53]. As a result, patients are at higher risk of thromboembolic events, and this risk may be up to fourfold higher in patients with β -TI compared with regularly transfused patients with β -thalassaemia major [44]. In 584 patients with β -TI enrolled in the OPTIMAL CARE study, splenectomy, older age (over 35 years) and high serum ferritin (≥ 1000 $\mu\text{g/l}$) were significantly associated with increased risk of thrombosis, whereas transfusion therapy significantly decreased the risk by more than 70% [23]. Patients with β -TI are also at increased risk of silent brain infarcts, with one study finding that 18 out of 30 splenectomized patients had evidence of asymptomatic white matter lesions by magnetic resonance imaging (MRI) [54]. Older patients and those not previously transfused had the highest incidence and number of lesions. One possible mechanism by which transfusion therapy may protect against thrombotic and vascular events is the reduced proportion of circulating RBCs with membrane damage that contribute to the hypercoagulable state [55].

Pulmonary hypertension is a severe and common clinical complication in β -TI and HbE/ β -thalassaemia [56–58], with an incidence of more than 50% [59–61]. However, this complication is rarely reported in HbH disease [62, 63]. Factors thought to be involved in the development of PHT in patients with NTDT include chronic anaemia, iron overload, splenectomy and hypercoagulability [32, 64–67]. Importantly, PHT is a leading cause of right-sided heart failure in patients with NTDT [59, 68]. Response to symptomatic and supportive treatment is poor, and in patients with PHT class III–IV, survival is usually only 2–3 years [69]. Transfusion therapy has been shown to ameliorate PHT in cases of sickle cell disease [70] and in splenectomized patients with HbE/ β -thalassaemia [70, 71], suggesting that transfusion therapy can be

considered as a potentially life-saving management strategy for severe PHT in patients with NTDT. However, at present, there is no clear guideline on when to start blood transfusion to prevent potential, long-term development of PHT. It is recommended that particular NTDT types with aforementioned risk factors be regularly evaluated by echocardiography to early detect signs of PHT such as increased tricuspid regurgitation velocity (TR jet), and such patients should be candidates for regular blood transfusion therapy [35].

Patients with NTDT are at risk of developing leg ulcers, particularly as they get older [23, 70, 72], but transfusion therapy may protect against this complication. Risk factors for the development of leg ulcers include splenectomy and iron overload, which may contribute to lesions becoming chronic [23, 51, 70, 73].

Impaired growth and development

One of the potential consequences of chronic anaemia in children with NTDT is growth retardation and pubertal delay [2, 23, 74, 75]. At the severe end of the spectrum, children with Hb levels of 5–6 g/dl develop skeletal deformities [26]. A study of the effects of different transfusion regimens on growth in 12 patients with β -thalassaemia major and 36 patients with HbE/ β -thalassaemia found that children of both sexes who received regular transfusions during the first 10 years grew normally. In patients who were transfused infrequently, both males and females became increasingly retarded in their linear growth [76]. Hence, transfusion therapy, along with adequate iron chelation and hormone therapy, may be beneficial in helping to ensure normal development in some paediatric patients with NTDT.

Endocrine complications

Endocrine problems are well characterized in patients with TDT as a consequence of transfusion-related iron overload. However, the prevalence of adrenal insufficiency in children with HbE/ β -thalassaemia was recently found to be 50% for transfusion-dependent patients and 53.5% for non-transfusion-dependent patients [77]. It was also recently shown that vitamin D deficiency was significantly more common in children with non-transfusion-dependent HbE/ β -thalassaemia than those with transfusion dependency (33.3% vs. 12.2%, $P = 0.01$) [78]. A total of 23% of the OPTIMAL CARE study cohort had osteoporosis, a common complication in β -TI, secondary to bone marrow expansion and vitamin D deficiency [23, 79]. Transfusion therapy, along with appropriate iron chelation, may be beneficial in paediatric patients to minimize endocrine problems and the

development of osteoporosis later in life. However, in a study of 50 paediatric patients (aged 8–13 years) with HbE/ β -thalassaemia, osteopenia was common (>50% of patients) even in those receiving adequate transfusion and iron chelation therapy, suggesting that there are other factors influencing the development of this complication apart from anaemia and bone marrow expansion [80].

Transfusion considerations

Transfusion therapy has been shown to be protective against complications such as thrombosis, extramedullary haematopoiesis, PHT, heart failure, cholelithiasis and leg ulcers, but the accompanying increased risk of endocrinopathy secondary to iron overload should be taken into account when making the decision to transfuse a patient with NTD [23]. In addition, the risks of alloimmunization should be considered.

Blood selection and alloimmunization

Alloimmunization is more frequent in patients with thalassaemia than the general population, with reported rates of 4–37% (compared with 1–4% in the general population) [81–87]. Alloimmunization rates in patients with thalassaemia appear to vary according to the homogeneity of donor and recipient populations. For example, alloimmunization rates are relatively lower in patients with thalassaemia in Greece and Italy [81, 82], whereas a study in the US of Asian patients with thalassaemia, where only 5% of local blood donors were Asian, reported an alloimmunization rate of 20.8% [83]. The risk of alloimmunization is 1–1.6% per unit of blood and is highest in older, transfusion-naïve and splenectomized patients, although it is not known why this is the case [81, 84, 85]. It may be that RBC membranes are altered and antigenic exposure increased in splenectomized patients, causing increased immunomodulation and increased risk of alloimmunization [84]. The risk of alloimmunization is also increased during pregnancy [35]. Reports from Western countries suggest that, in patients with thalassaemia, alloimmunization usually involves C, E and Kell antibodies [81, 82, 84, 86, 87]. Though some thalassaemia treatment centres routinely perform extended antigen matching, it is not yet clear whether this significantly reduces alloimmunization rates [81, 83, 87]. A recent study examined clinical and transfusion records for 10 years of follow up in 37 patients with thalassaemia intermedia [88]. In 2009, the institution had implemented full Rh (C,c,E,e), Kell (K, Kpa, Kpb), Kidd (Jka, Jkb), Duffy (Fya, Fyb), S and s antigen matching for this group of patients. Of the whole cohort, seven patients were alloimmunized, with these antibodies developing

prior to 2009, or prior to referral [88]. Since 2009, a total of 335 units were transfused in this group of patients, with only one antibody developing after necessary transfusion with non-phenotyped blood. No autoantibodies were found in this study [88]. Strategies to reduce the risk of alloimmunization should be employed where possible. Initiation of transfusion at an early age is thought to reduce the risk of alloimmunization, and fully ABO, Rh (D, C, c, E, e) and Kell matched blood should be used [35, 81]. The risk of autoimmunization should also be considered. In a recent study in 407 patients with thalassaemia, autoantibodies occurred in 6.5% [86]. Older age and splenectomy were associated with higher risk of autoimmunization, and 84% of patients with autoantibodies were also alloimmunized [86]. Further studies to identify predictive markers for susceptibility to alloimmunization and autoimmunization would be of value to reduce this risk in patients with NTD. Other complications of blood transfusion including exposure to pathogens and transfusion reactions pose a challenge in the management of patients with thalassaemia. Around half of transfused patients with thalassaemia experience transfusion reactions, and although most are mild or moderate, anaphylaxis can occur in rare cases [86].

Iron overload

Iron overload may occur in patients with NTD because of both increased intestinal iron absorption and subsequent transfusion therapy; therefore, there is a need to monitor iron burden, irrespective of transfusion. Iron overload associated with transfusion therapy develops more quickly than that caused by the underlying disease, but both can be managed with appropriate chelation therapy. It has been observed that serum ferritin levels can underestimate iron load in patients with β -TI, compared with patients with thalassaemia major. Therefore, relying on this measurement may expose patients with NTD to high iron levels and delay necessary chelation therapy [89–92]. Similar findings were reported in the THALASSA trial of deferasirox in patients with NTD including HbE/ β -thalassaemia and α -thalassaemia [93].

Instead, measurement of liver iron concentration (LIC) by MRI is the recommended method where possible, and chelation therapy should be initiated if LIC reaches ≥ 5 mg Fe/g dry weight [35, 50]. If LIC measurement is not possible, a serum ferritin level of ≥ 800 mg Fe/g dry weight can be used as an indicator for chelation [35]. The benefits of transfusion with iron chelation in patients with NTD was highlighted in the OPTIMAL CARE study, which found that treatment with both transfusion and iron chelation therapy was associated with fewer complications (including endocrinopathy) than either

treatment alone [23]. Iron overload in patients with NTDT undergoing frequent blood transfusions for any length of time can be managed similarly to patients with transfusion-dependent β -thalassaemia major [35].

Conclusion

Management of NTDT can be complex because of the diverse phenotypes and clinical spectrum of disease. These patients are not reliant on transfusions for survival, but transfusion therapy may convey substantial clinical benefits for some patients if administered properly. Transfusion therapy has been shown to be protective against complications such as thrombosis, extramedullary haematopoiesis, PHT, heart failure, cholelithiasis and leg ulcers in patients with NTDT. In addition, transfusion therapy may help to reduce intestinal iron absorption and thus reduce the risk of serious liver disease. Transfusion strategy should be tailored to the individual patient, and careful monitoring of clinical parameters is essential. Risk of infection and alloimmunization should be considered, and fully ABO, Rh (D, C, c, E, e) and Kell matched blood should be used. Transfusion therapy should be accompanied by the use of an appropriate iron chelator, and iron load should be carefully monitored. Some patients may

require frequent transfusions, but it is important to taper or withdraw transfusions when clinical goals have been met to avoid enforcing a lifelong transfusion regimen unnecessarily. Until recently, there have been no formal guidelines on the management of NTDT, but following the position paper in 2012, the Thalassaemia International Federation (TIF) NTDT guidelines are now available on the TIF website [35].

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Conflict of interests

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