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SCOTTISH PAEDIATRIC AND ADULT HAEMOGLOBINOPATHIES NETWORK

Scottish Paediatric & Adult Haemoglobinopathy Network

Diagnosis and Management of Non-Transfusion-Dependent Thalassaemia (NTDT) phenotypes

Based on the Thalassaemia International Federation – TIF – Guidelines for the Management of Non-Transfusion Dependent Thalassaemia (NTDT), 2nd Edition, 2017

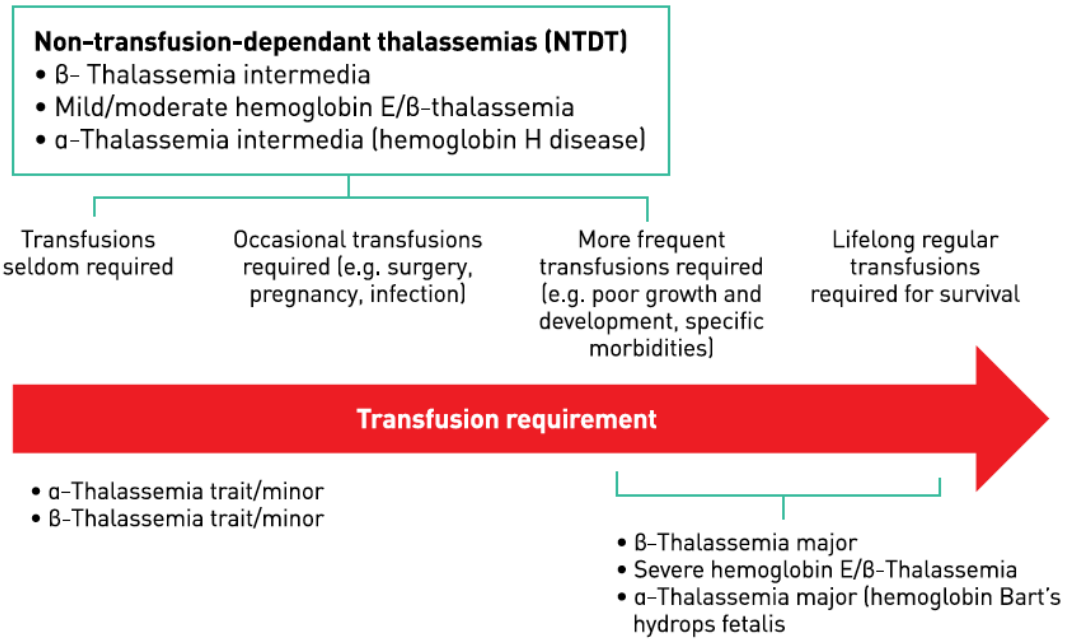
NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Introduction and Definitions

Patients with 'non-transfusion dependent thalassaemia (NTDT)' syndromes typically do not require regular lifelong transfusions from early age though tend to be more symptomatic than carrier states. These include:

1. All forms of β thalassaemia intermedia,
2. Mild/moderate forms of haemoglobin E/β thalassaemia and
3. Haemoglobin H disease (α Thalassaemia intermedia).

Even within this group, sub-phenotypes of more/less severity can be seen, ranging from patients who will rarely need any treatment to others who will require occasional or even more frequent transfusions depending on the clinical scenario (ie: pre-surgery, with sepsis episodes, if growth delay). The table below summarizes the spectrum of thalassaemia phenotypes, with carriers on one end, transfusion dependent thalassaemias (TDT) on another and NTDT in between (Musallam K.M. 2013).



-According to the Mahidol score, the clinical phenotype of haemoglobin E/β-Thalassaemia can be classified as mild (sum of all scores = 0 - 3.5), moderate (4 - 7) or severe (7.5 - 10) (Sripichai O. 2008). NTDT patients tend to be found within mild and moderate phenotypes.

Criteria	**Points scored**			
	0	**0.5**	**1**	**2**
Steady-state haemoglobin (g/L)	>75 g/L		60 – 75 g/L	<60 g/L
Age at presentation, years	>10	3-10	<3	
Age at 1st blood transfusion, years	>10		5-10	<5
Requirement for red cell transfusions	None/rare		Occasional	Regular
Size of spleen, cm below LCM	<3		3-10	>10 or splenectomy
Growth and development	>25th centile	3rd-25th centiles	<3rd centile	

The diagnosis and classification of severity of the above thalassaemia syndromes rely on a combination of laboratory haemoglobin characterisation techniques, interpretation of red cell indices and blood film morphology, confirmatory α and β-chain gene analysis and the clinical phenotype.

The current guidelines follow principles of management presented by the Thalassaemia International Federation in its latest 2nd Edition publication, 2017.

1. Transfusions

Although occasional transfusions can be useful in suppressing complications from ineffective erythropoiesis and improving symptoms in patients with NTDT, they are not without risks. Acute and delayed transfusion reactions, transfusion-transmitted infections (now rare in the UK), iron overload and the risk of alloimmunization (particularly in never or previously minimally transfused patients, the ones who underwent splenectomy and in pregnancy) should be thoroughly considered when making a decision to transfuse.

Transfusion in a NTDT patient is likely to be required in the following scenarios:

1. Significantly low Hb (ie.: < 50g/L) or if Hb higher and patient clinically symptomatic
2. Baseline low Hb and anticipated acute stress, Hb drop or blood loss (ie.: sepsis, surgery, pregnancy)
3. Consider a defined period of regular transfusions in:
    a. Dropping Hb with enlarging spleen (>3cm/year) in periods of growth spurt
    b. Growth failure (based on height)
    c. Poor performance at school
    d. Decreased exercise tolerance
    e. Delayed puberty
    f. Signs of bone changes
    g. Frequent haemolytic episodes (Hb H)
    h. Poor quality of life
4. Consider regular transfusions for the primary prevention (in high risk populations), management or secondary prevention of:
    a. Thrombotic or cerebrovascular disease
    b. Pulmonary hypertension with or without secondary heart failure
    c. Extramedullary haematopoietic pseudotumours
    d. Leg ulcers

Red cell product specifications should follow UK Transfusion Haemoglobinopathy guidelines and administration should follow published national guidelines (Harris A.M. 2009). All patients with NTDT should therefore also have an extended red cell phenotype done at baseline, prior to any transfusion.

2. Assessment of iron overload and Iron Chelation

In NTDT ineffective erythropoiesis leads to non transfusional iron overload.

Assessment of liver iron overload with magnetic resonance should be offered once yearly (to every 2 years) to patients with NTDT from the age of 10 years (or from 15 years if deletional Hb H disease, where morbidity related to iron overload tends to start later in life). Although 3-6 monthly serum ferritin levels can also be used for monitoring these patients the MRI is the preferred technique for initial assessment and follow up. Ferritin levels in NTDT patients tend to underestimate the extent of the liver iron deposition.

T2* MRI for assessment of cardiac siderosis in patients with NTDT is not universally recommended as it appears that in this population, iron deposition in the heart is not a common finding, even if liver iron accumulation is significant.

Iron chelation should be started with Deferasirox in older children with NTDT (>2y) if LIC ≥ 5 mg Fe/g dry weight or if serum ferritin ≥800 ng/ml. The use of other iron chelators in this setting (ie: Desferioxamine, Deferriprone) is not yet recommended by International Guidelines, until larger, randomised trial results are available. They have however been used in clinical practice and could be considered on an individual basis and following discussions in local and national MDTs.

If iron chelation is started, refer to Chelation Guideline available on the SPAH Paediatric Guideline website page.

3. Splenectomy

Splenectomy in patients with NTDT increases their risk of developing venous thromboembolism (5-fold), pulmonary hypertension (4-fold), leg ulcers (4-fold) and silent brain infarcts and infection (30-fold).

Therefore, splenectomy is no longer offered as standard of care in patients with NTDT and should be avoided in particular in NTDT patients younger than 5 years. However, it can be considered in clinical scenarios such as:

1. Worsening anaemia with poor growth and development
2. If red cell transfusions indicated but not possible or if iron chelation treatment not available
3. In established hypersplenism not improved by a period of regular transfusions
4. Massive splenomegaly with worsening anaemia or other cytopenias (complicated by recurrent infections or bleeding), debilitating pain or concerns of risk of splenic rupture.

If splenectomy indicated laparoscopic technique is preferred.

1. Partial splenectomy has been advocated by some centres but cannot be recommended at the moment due to lack of long-term data on efficacy.
2. Consider concurrent cholecystectomy if evidence of cholelithiasis, especially if symptomatic. Gallstones are more common in patients with NTDT (as compared with TDT ones) due to the chronic haemolysis status and unrelated genetic factors.
3. Immunizations (preferably pre-procedure) and post-splenectomy prophylactic antibiotic therapy should follow the most up to date national guideline recommendations.
4. Post-splenectomy thromboprophylaxis should follow indications described below.
5. The above risks of possible complications post splenectomy in this setting should be fully discussed with the family and consent to proceed documented in the patient's notes.

4. Hydroxycarbamide

Induction of foetal haemoglobin production by hydroxycarbamide can ameliorate the clinical phenotype in a variety of patients with NTDT. Although no randomized controlled trials exist, observational studies suggest that it can be tried in the following clinical scenarios:

1. β-Thalassaemia intermedia homozygous for the Xmnl polymorphism
2. Patients with Lepore or δβ-Thalassaemia
3. If transfusions indicated but not possible due to alloimmunisation
4. As adjunctive treatment in the management of
    a. pulmonary hypertension
    b. extramedullary haematopoietic pseudotumours
    c. leg ulcers

5. In other patients consider a trial with careful assessment of response.

If a trial of hydroxycarbamide is indicated, starting doses, escalation of treatment and monitoring of toxicity should follow published SPAH guidelines recommendations available on the SPAH Paediatric Guideline website page.

Evaluate for overall response after 3 and 6 months (target response: increase in Hb level of > 10g/L at 6 months)

1. If target response not reached (or if any significant toxicity), discontinue the drug.
2. If target response reached, continue to re-evaluate at 12, 18 and 24 months to ensure maintenance of response; complement evaluation with:
    a. assessment of growth, functional status, exercise tolerance, quality of life
    b. objective evidence of improvement in clinical morbidities (ie.: pulmonary hypertension, extramedullary haematopoietic tumours, leg ulcers)

5. Prevention and treatment of thromboembolism

A combination of factors leads to a hypercoagulable state in patients with NTDT, in particular, post splenectomy.

Patients with NTDT should be considered at high risk for thrombosis when assessed for the need of pharmacological thromboprophylaxis (ie: when additional risk factors are present, such as admissions to the hospital for medical or surgical reasons).

If following assessment the patient is deemed to be at high risk in the particular clinical scenario, prophylaxis with heparin (ie: LMWH) should be considered, following local guidelines. Long-term aspirin treatment should be considered in patients with NTDT who underwent splenectomy and have persistently elevated platelet counts (≥ 500 x10^9/L).

It has been suggested that patients with NTDT may have a higher incidence of silent brain infarcts but routine assessment with TCD or brain MRI/MRA is not currently recommended but can be done in an individual basis, depending on the clinical scenario.

Patients who develop thromboembolic events should be treated per local protocols.

6. Endocrine assessment and bone disease

If not transfused regularly, patients with Thalassaemia major phenotypes will invariably experience growth retardation and skeletal deformity/bone pathology (as a direct effect of the ineffective erythropoiesis, medullary expansion and severe anaemia) and also develop a variety of endocrinopathies which are usually linked to the progressive iron overload status characteristic of the disease. The risk increases with age and again, complications tend to be seen only into late adulthood.

Although the rates of endocrine dysfunction and bone pathology appear to be lower in patients with NTDT when compared with those seen in patients with TDT, they are non-negligible and the need for early diagnosis and treatment becomes clinically sound.

Therefore, children with NTDT over the age of 10 years should managed jointly with the endocrine team. See Endocrine Guidelines available on the SPAH Paediatric Guideline website page.

7. Infection prevention and treatment

With the advent of better iron chelation and reduction in deaths from cardiac toxicity, infection has become the primary cause of mortality amongst patients with Thalassaemia in many parts of the world and this is also true even in the non-splenectomised patient.

Both Transfusion Dependent (TDT) and Non-Transfusion Dependent (NTDT) Thalassaemia patients may be at a higher risk of developing severe episodes of sepsis due to a variety of different underlying factors, which include:

1. therapy related: allogeneic blood transfusions (transfusion transmitted infections, transfusion related immune modulation, iron overload), splenectomy status, possible toxicity of iron chelation (ie: Deferiprone-induced neutropenia), the presence of central lines and further immunesuppression when they undergo haematopoietic stem cell transplantation (HSCT), and
2. disease related: effects of chronic anaemia itself and a relative hyposplenic status and reticuloendothelial system dysfunction induced by ineffective erythropoiesis and haemolysis.

Therefore, all patients with Thalassaemia should be considered immunocompromised for the purposes of initial management of possible sepsis, whether neutropenic or not.

A variety of microorganisms have been implicated in infectious episodes seen in patients with Thalassaemia and include gram negative and gram positive bacteria. Broad spectrum antibiotic therapy should be considered with targeted treatment for the most likely source.

The approach to manage patients with NTDT (and TDT) who present with suspicion of infection should be individualised to the patient and presenting features. In view of their increased risk of infection there should be a low threshold for use of broad spectrum antibiotics if there are clinical concerns. Patients with central lines should usually be managed with intravenous broad spectrum antibiotics pending blood culture results.

8. Haemolytic and aplastic episodes

Haemolytic episodes can occur in both deletional (more frequently seen) and non-deletional forms of Haemoglobin H disease, with significant drops in Hb levels. Infections, oxidative challenges, hypersplenism and pregnancy are commonly described as potential triggers.
G6PD deficiency may commonly co-exist

Children with NTDT (particularly HbH disease) who present with a drop in the Hb (with or without suspicion of associated sepsis) should therefore have a full haemolytic screening sent (including FBC, blood film, reticulocytes, LDH, bilirubin) and red cell transfusions given if clinically indicated.

If the reticulocytes are low, a differential diagnosis of an aplastic episode should be made and blood serologies (IgM and IgG) and PCR for Parvovirus B19 should be sent.

9. Pulmonary hypertension (PHT)

Patients with NTDT are at risk of developing pulmonary hypertension and the risk increases with age.

There are no agreed guidelines on when to start screening children with NTDT with a cardiology referral and echocardiogram for assessment of peak TRV and overall cardiac function. A pragmatic approach is to start this screening in these patients from the age of 10 years when they will also have an MRI for assessing liver iron content, with annual routine echocardiograms after that. Screening in children with other potential associated risk factors, as above, can be started earlier depending on the clinical scenario. If abnormal TRVs are found, close liaison with the Cardiologists will be paramount to decide whether invasive measurements of pulmonary pressures are advised.

10. Extramedullary haematopoiesis (EMH)

Patients with NTDT are at a higher risk of developing sites of extramedullary haematopoiesis when compared with their regularly transfused TDT peers. It is mainly reported in patients with β thalassaemia intermedia and haemoglobin E/β thalassaemia and the overall prevalence is thought to be around 20%, particularly in older patients. Sites commonly involved include the lymph nodes, the thymus, heart, breasts, prostate, broad ligaments, kidneys, the adrenal glands, pleura, the retroperitoneum tissue, the skin, peripheral and cranial nerves, the brain and the spinal canal. Special consideration needs to be taken for the management of paraspinal EMH with cord compression (pseudotumours) which occurs in 11 to 15% of the cases, most frequently during the third and fourth decades of life (but which can also present in childhood), as early intervention may reduce the incidence of irreversible neurologic damage. The presentation normally mimics that of cord compression with back/lower limb pain, paresthesia, abnormal proprioception, exaggerated or briskdeep tendon reflexes, positive Babisnky and Lasegue, paraparesis, paraplegia, ankle clonus, spastic gait, urgency of urination and bowel incontinence.

Children with NTDT presenting with signs of spinal cord compression should be promptly assessed by the Neurology team and urgent imaging done. Ideally, MRI of the spine is preferable though a CT may need to be done if the MRI is not immediately available.

If a paraspinal site of EMH is found but there is none or mild evidence of neurological involvement, treatment options may involve a short course of regular red cell transfusions coupled with hydroxycarbamide. In moderate cases, consideration of urgent low-dose radiotherapy and steroids (+/- hydroxycarbamide) should be taken. In severe cases, input from the Neurosurgeons is advised as urgent laminectomy (with pre-operative transfusion and post-operative radiotherapy) may be indicated. Surgical approaches to resect pseudotumours should be avoided due to the high morbidity associated with the procedure (i.e.: risk of bleeding and worsened neurological damage) although cases should be discussed in and individual basis, with the multidisciplinary team.

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