Thalassaemia (part 2): Management

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The management of thalassaemia with a severe phenotype includes blood transfusion, iron chelation, bone marrow transplantation, prenatal diagnosis and national programmes to co-ordinate these in countries with a high prevalence. If blood transfusion and iron chelation therapy are not administered regularly, as was the case historically and as is still the case in many poorer regions, progressive deterioration occurs, viz.: impaired growth and development, hepatosplenomegaly, bony abnormalities, cardiac failure, increased susceptibility to infections and premature mortality. Remarkable progress has been made in the past few decades, which has led to much-improved survival rates. Transfusion therapy has evolved to a hyper-transfusion regimen designed to maintain a physiological haemoglobin level and achieve a post-transfusion haemoglobin of 14 g/dL, which, as a matter of course, necessitated intensification of iron chelation. The development of effective oral iron chelators has led to improved compliance. Exploration of novel therapeutic approaches continues, with several agents under study. The prospect of gene therapy is particularly exciting as it has potential to provide cure on a large scale. Currently, regular blood transfusion and iron chelation therapy remain the cornerstone of management of thalassaemia major.

Classification, pathophysiology and diagnosis of thalassaemia are discussed in part 1 of this 2-part CME series. The current article (part 2) discusses management aspects relating to the three clinical phenotypes, viz.: (i) thalassaemia major (TM), also referred to as transfusion-dependent thalassaemia (TDT); (ii) thalassaemia intermedia (TI), which is generally transfusion independent; and (iii) thalassaemia minor, which is asymptomatic, with no significant clinical sequelae.

Thalassaemia major

The management of TDT major requires appropriate transfusion therapy, frequent monitoring to assess iron overload, and treatment with focused chelation therapy. With these in place, patients will survive longer, without the morbidity of complications due to inadequate chelation. Transfused blood contains iron (Fe), which the body is unable to excrete. Regularly transfused patients accumulate iron at a rate of 0.3 - 0.6 mg/kg of body weight per day.[2] Once iron is >12 - 24 g of total body iron, it accumulates in the heart, liver and endocrine system.

Blood transfusion

Once the diagnosis has been made, the infant needs to be monitored clinically with regular full blood counts (FBC).

The decision to commence regular transfusions[2] is based on the following criteria:
- A haemoglobin (Hb) level <7 g/dL on two occasions, >2 weeks apart (excluding all other contributory causes such as infections); or
- A steady state Hb <7 g/dL with any one of the following:
  - failure to thrive
  - bone expansion or deformity, especially facial bones
  - inappropriate fatigue
  - poor feeding
  - developmental delay or regression
  - cardiac failure
  - increasing splenomegaly
- In most cases, it may be reasonable to administer the first transfusion, then wait and re-assess the indications and trends before the second and subsequent transfusions.
- Patients with TI should not receive regular transfusion therapy unless indicated. The diagnosis of TI and TM is not always absolute or predictable, and a period of watching and waiting may be necessary.

Before starting blood transfusions, baseline tests need to be performed, which includes an FBC, red cell phenotype, liver function
tests (LFTs), serum iron studies, serum ferritin and baseline viral
determination for hepatitis B (HBV), hepatitis C (HCV), HIV,
cytomegalovirus (CMV) and parvovirus B19. Regular follow-up with
blood tests at selected intervals is important for early identification of
complications (Table 1).

**Transfusion programme**

Transfusion therapy aims to permit normal growth and activity
levels, and prevent skeletal changes due to marrow hypertrophy.
Transfusions should initially be given every 3 - 5 weeks.[3]

The pre-transfusion Hb determines the volume of blood to be
transfused, and the aim is to maintain the pre-transfusion Hb
between 9 g/dL and 10.5 g/dL.

In paediatric patients, transfusion volume (mL) = (target Hb
14 g/dL – actual Hb) × weight (kg) × 3.5. The post-transfusion Hb
should not exceed 14 g/dL. Blood should be transfused at a rate of
5 mL/kg/hour.

In patients with severe anaemia (Hb <5 g/dL) or those with
cardiac compromise, transfusions should be administered at
2 mL/kg/h to avoid fluid overload. Diuretics may need to be
administered.

If cardiac insufficiency is present, pre-transfusion Hb levels need to
be maintained at higher levels, i.e. between 11 g/dL and 12 g/dL, and
small volume transfusions may need to be administered weekly or
every 2 weeks.

Transfusion volume should be recorded at each visit, and the
transfusion requirements reviewed 6 - 12-monthly. The usual transfusion
requirement is between 200 mL/kg/year and 250 mL/kg/year.

Ideally, the type of blood product to be used is leukodepleted
packed red cells, preferably <5 days old. Some blood banks can supply
highly packed red cells by a process of spinning and aspirating excess
plasma.

Blood transfusions should be given in a dedicated facility, and
administered with minimal disruption to the patient, to maintain
good quality of life. Good transfusion practice should be observed
with written policies (standard operating procedure).

**Iron overload and chelation therapy**

Regularly transfused patients accumulate iron at a rate of 0.3 -
0.6 mg/kg of body weight per day.[2] The human body does not have a
physiological mechanism to excrete iron. When total body iron exceeds
12 - 24 g, it accumulates in the heart, liver and endocrine system.

<table>
<thead>
<tr>
<th>Test</th>
<th>Age, years</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>FBC differential count and platelets</td>
<td>All</td>
<td>Monthly (or more frequently if indicated)</td>
</tr>
<tr>
<td>LFTs</td>
<td></td>
<td>Monthly if on DEP or DFX</td>
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<tr>
<td>U&amp;E, urine dipstix</td>
<td></td>
<td>Monthly if on DFX</td>
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<tr>
<td>Ferritin</td>
<td>All</td>
<td>Every 3 months</td>
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<tr>
<td>Hepatitis B and C, HIV</td>
<td>All</td>
<td>Annual</td>
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<tr>
<td>FSH, LH</td>
<td>≥10</td>
<td>Annual. If abnormal, GnRH stimulation test, where indicated</td>
</tr>
<tr>
<td>Testosterone, oestradiol/oestrogen</td>
<td>≥10</td>
<td>Annual</td>
</tr>
<tr>
<td>Calcium</td>
<td>≥10</td>
<td>Every 6 months</td>
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<tr>
<td>PTH, vitamin D</td>
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<td>Annual</td>
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<tr>
<td>TSH, T4</td>
<td>≥10</td>
<td>Annual</td>
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<tr>
<td>Fasting/random glucose</td>
<td>≥10</td>
<td>Every 6 months. OGGT if abnormal</td>
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<td>a FP/liver ultrasound</td>
<td>≥10</td>
<td>Annual</td>
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<tr>
<td>FerriScan (MRI R2)</td>
<td>≥10</td>
<td>Annual</td>
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<tr>
<td>Liver MRI T2 (if FerriScan not available)</td>
<td>≥10</td>
<td>Annual</td>
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<tr>
<td>TRV (echocardiogram)</td>
<td>≥10</td>
<td>Annual</td>
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<tr>
<td>Cardiac MRI T2*</td>
<td>≥10</td>
<td>&gt;20 ms: biennially</td>
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<td></td>
<td></td>
<td>10 - 20 ms: annually</td>
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<td></td>
<td></td>
<td>&lt;10 ms: 6 monthly</td>
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<tr>
<td>Bone mineral density scan/DEXA</td>
<td>≥10</td>
<td>Every 18 - 24 months</td>
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<tr>
<td>Tanner stage</td>
<td>10 - 20</td>
<td>Every 6 months</td>
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<tr>
<td>Anthropometrics (height, truncal height, weight, head circumference, growth velocity)</td>
<td>All</td>
<td>Annual, every 3 - 6 months, during puberty and chronic transfusion, as indicated</td>
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<tr>
<td>Menstrual history and reproductive health</td>
<td>≥10 or earlier</td>
<td>Annual</td>
</tr>
<tr>
<td>Transfusion history</td>
<td>All</td>
<td>Monthly or more frequently if indicated</td>
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<tr>
<td>Chelation history and toxicity monitoring</td>
<td>All</td>
<td>Annual</td>
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<tr>
<td>Reproductive health</td>
<td>≥12</td>
<td>Annual</td>
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<tr>
<td>Dental assessments</td>
<td>All</td>
<td>Annual</td>
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<tr>
<td>Ocular and auditory assessments</td>
<td>All</td>
<td>Annual, once chelation commenced</td>
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<tr>
<td>Genotype</td>
<td>All</td>
<td>Once</td>
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<tr>
<td>Transplant evaluation/HLA typing</td>
<td>All</td>
<td>Once</td>
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</tbody>
</table>

FBC = full blood count; LFT = liver function test; DEP = deferiprone; DFX = deferasirox; U&E = urea and electrolytes; FSH = follicle-stimulating hormone; LH = luteinising hormone; GnRH = gonadotrophin releasing hormone; PTH = parathyroid hormone; TSH = thyroid stimulating hormone; T4 = thyroxine; OGGT = oral glucose tolerance test; a FP = alpha fetoprotein; MRI = magnetic resonance imaging; TRV = tricuspid valve regurgitant velocity; DEXA = dual energy X-ray absorptiometry; HLA = human leukocyte antigen.

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If cardiac insufficiency is present, pre-transfusion Hb levels need to be maintained at higher levels, i.e. between 11 g/dL and 12 g/dL, and small volume transfusions may need to be administered weekly or every 2 weeks.

Transfusion volume should be recorded at each visit, and the transfusion requirements reviewed 6 - 12-monthly. The usual transfusion requirement is between 200 mL/kg/year and 250 mL/kg/year.

Ideally, the type of blood product to be used is leukodepleted packed red cells, preferably <5 days old. Some blood banks can supply highly packed red cells by a process of spinning and aspirating excess plasma.

Blood transfusions should be given in a dedicated facility, and administered with minimal disruption to the patient, to maintain good quality of life. Good transfusion practice should be observed with written policies (standard operating procedure).

**Iron overload and chelation therapy**

Regularly transfused patients accumulate iron at a rate of 0.3 - 0.6 mg/kg of body weight per day.[2] The human body does not have a physiological mechanism to excrete iron. When total body iron exceeds 12 - 24 g, it accumulates in the heart, liver and endocrine system.
Iron is extremely toxic to many tissues. Excess iron that exists as non-transferrin bound iron (NTBI) in the plasma and unbound iron in the intra-cellular compartment results in free radical damage to cells. It takes 3 - 10 years of chronic exposure to high iron levels before any measurable organ dysfunction occurs. Each organ has a different rate of iron deposition and reduction.\(^2\)\(^\text{[9]}\)

The most effective strategy to prevent significant iron overload and tissue damage is early institution of chelation therapy, i.e. as soon as the patient is iron-overloaded.

Chelation therapy has two goals: (i) binding of toxic NTBI in the plasma; and (ii) removal of iron from the body.

Since removal of iron from normal tissues can be detrimental, chelation should not be started without evidence of iron overload. In infants, chelation therapy should be delayed until after the first year of life due to the toxicity of the chelators. It is generally commenced after 10 - 12 transfusions, or when the ferritin is persistently >1 000 µg/L. First-line therapy is usually oral deferasirox (DFX), which can be commenced in an infant >1 year of age. Subcutaneous administration of desferrioxamine (DFO) is an alternative but more traumatic for both patients and parents/caregivers, given the parenteral route of administration and longer duration of administration.

The aims of iron chelation therapy are:\(^2\)\(^\text{[8]}\)\(^\text{[9]}\)

\(i\) to prevent iron overload and maintain a safe level of body iron by balancing iron intake from transfusion with iron excretion through chelation.

\(ii\) rescue therapy: once excess iron accumulates in organs, damage starts to occur. Removal of iron is slow and inefficient, therefore prevention is superior to rescue therapy.

\(iii\) emergency therapy: if heart failure develops, this requires urgent modification of chelation therapy with intensive treatment (see below).

There are currently three chelators available in South Africa (SA), viz. DFO mesylate (DFX) (Desferal), deferasirox (Exjade) and deferiprone (DFP)(Ferriprox). DFP availability is limited, and it currently requires a section 21 application via the SA Health Products Regulatory Authority. Characteristics of each iron chelator are detailed in Table 2.

All chelation regimens aim to attain and maintain an annual average serum ferritin of 500 µg/L - 1 000 µg/L, a liver iron between 3 mg/g and 7 mg/g dry weight (dw) and cardiac T2* >20 ms.

The selection of drugs and doses will require adjustments depending on the iron burden and drug toxicities (Fig. 1).
Iron overload needs to be monitored regularly. Direct measurement of liver iron concentration via liver biopsy is invasive. The following are methods of indirect measurement of tissue iron stores:

- **serum ferritin**
- **magnetic resonance imaging (MRI) T2\* for cardiac iron assessment**
- **MRI R2 (FerriScan) for liver iron assessment.**

Serum ferritin is simple to perform, inexpensive and widely available. It is most useful in identifying trends. Levels should be monitored 3-monthly after the first 10 transfusions. Decisions to modify dosages should be based on serial measurements of ferritin as opposed to a single reading. Persistently high levels (>2500 µg/L) are associated with increased risk of cardiac disease and death. Ferritin levels correlate well with liver iron levels in a linear fashion, but do not always correlate well with myocardial iron deposition, as patients with low ferritin levels may have severe cardiac iron loading and left ventricular (LV) impairment.

Liver iron: The R2 technique (FerriScan) can be performed on a standard MRI machine, but the analysis requires specific software. The advantage of the T2\* technique is that liver and cardiac iron can be measured at the same time. The target should be 3-7 mg/g dry weight equivalent measured by the FerriScan technique. Liver iron >7 mg/g dw is associated with increased complications, including a higher risk of cardiac disease and early death.

Cardiac iron: The best available method for the measurement of cardiac iron is the cardiac MRI T2\*. There is a relationship between low T2\* and impaired LV function. LV impairment becomes increasingly likely when T2\* falls below 20 ms, and is therefore used as a cut-off for the early detection of iron overload.

Cardiac MRI T2\* and the FerriScan are recommended for routine monitoring in children from age ≥10 years. The intervals of the scans depend on whether the results are abnormal or normal (Fig. 1).

Chelation therapy needs to be modified when there is evidence of severe iron overload and/or organ dysfunction. This may be achieved with the following strategies:

(i) **Combination therapy:** combination treatment with DFO and DFP has been shown to be more effective than DFO monotherapy in: a) reducing serum ferritin; b) reducing liver iron; c) improving cardiac function; d) reversing cardiac failure; and e) reversing impaired glucose tolerance.

(ii) **Optimising dosing or switching of preparations.**

(iii) **Intensive intravenous chelation with continuous high-dose DFO:** this is used when aggressive chelation is required with severe iron overload and cardiac or liver dysfunction. This can be given twice a month for a minimum of 72 hours at a maximum dose of 6 g/kg/day, and is given in addition to the regular chelation therapy.

Chelation therapy also needs to be modified if body iron falls or reaches low levels, and doses need to be adjusted to prevent toxicity. Doses should be gradually decreased when the serum ferritin falls below 1000 µg/L. Although the current recommendation is to stop the drug when the ferritin is <500 µg/L, one must be cautious, as this may result in rebound labile iron. This can be avoided by gradual dose reductions coupled with more intensive monitoring (monthly ferritin levels) to maintain the ferritin between 500 µg/L and 1000 µg/L.

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**Fig. 1. Algorithm for optimal monitoring of iron accumulation and chelation.** (Hb = haemoglobin; DFX = deferisirox; DFO = desferrioxamine; SC = subcutaneous; MRI = magnetic resonance imaging; LIC = liver iron concentration; Fe = iron; DFP = deferiprone; IV = intravenous.)

*if available.

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3 - 4-weekly transfusions
- Maintain pre-transfusion
  - Hb at 9 - 10.5 g/dL.

Commence transfusion

Measure serum ferritin after 10 - 12 transfusions

Commence chelation if ferritin persistently >1000 µg/L

**Age >1 year: DFX (Exjade) 20 - 30 mg/kg orally as first line**
- OR
  - DFO (Desferal) 20 - 40 mg/kg, SC over 8 - 10 hours, 5 days per week

Monitor iron overload
- • serum ferritin every 3 months
  - • FerriScan annually from age 10 years*
  - • MRI T2\* annually from age 10 years

Ferritin 1000 - 2500 µg/L,
  - LIC 7 - 15 mg Fe/g dry weight, or
  - cardiac T2\* 10 - 20 ms

Assess cardiac function
  - If normal cardiac function, optimise chelation
    - • increase DFX to 40 mg/kg/d, or
    - • increased DFP to 100 mg/kg/d
      - Review in 6 months

Ferritin >2500 µg/L,
  - LIC >15 mg Fe/g dry weight,
  - cardiac T2\* <10 ms, or
  - abnormal cardiac function

Intensive therapy with
  - • DFO IV 50 mg/kg/24 h, or
  - • change to DFP*, or
  - • consider combination therapy with DFO and DFP*

If abnormal cardiac function

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*if available.
Management of complications

Iron overload is the major cause of morbidity and mortality in TM/TI, and occurs rapidly in patients on a chronic transfusion programme. Most deaths occur due to iron-related cardiomyopathy. Cardiac iron loading takes 8 - 10 years to develop, and the heart is initially devoid of iron for years. Once iron loading in the heart starts, the rate of deposition is rapid. Iron overload also affects the liver, resulting in cirrhosis and liver failure. Iron deposition in the liver occurs in a linear fashion, and significant iron loading ensues after 6 months of regular transfusions. Pancreatic, thyroid, parathyroid, hypothalamic and pituitary damage may result in endocrinopathies.

Hepatic complications

Liver disease in thalassaemia is common, and frequently multifactorial. The liver is a primary site of iron overload, and is one of the leading causes of mortality in TDT. Chronic liver iron deposition stimulates fibrogenesis and cirrhosis.

Patients may present with acute or chronic hepatitis (viral or drug-induced), obstructive jaundice, cholangitis, portal hypertension, liver insufficiency or hepatocellular carcinoma. Chronic active HCV infection should be actively managed. The current recommended treatment for HCV is with a combination of pegylated interferon alpha and ribavirin. Ribavirin may result in endocrinopathies. Hormone replacement therapy is advised for adolescents with hypogonadism.

Endocrine complications

Iron is commonly deposited in endocrine organs, and damage that occurs is usually irreversible. This may result in diabetes mellitus (DM), growth failure, hypothyroidism, hypoparathyroidism, delayed puberty, hypogonadism, gonadal failure and sterility, as well as osteopenia and osteoporosis. The pituitary gland is particularly sensitive to even modest iron overload, with short stature in poorly chelated patients presenting around age 10 years. Regular monitoring of endocrine function is important (Table 1). Growth retardation and skeletal changes may also ensue from DFO toxicity. Patients with a fall-off on growth curves, decreased height velocity or delayed bone age should be referred to an endocrinologist for assessment and management. Hormone replacement therapy is advised for adolescents with hypogonadism.

Infections

Patients with iron overload are susceptible to infection with bacteria such as Yersinia enterocolitica and Vibrio vulnificus. Yersinia is a Gram-negative bacillus that causes severe infection and disseminated tissue sepsis. V. vulnificus is a Gram-negative bacillus that can cause severe endotoxaemia, and is associated with high mortality.

Other bacteria such as Escherichia coli and Klebsiella pneumoniae also occur with increased frequency in the presence of iron overload.

Despite significant improvements in blood safety, there remains a risk of transfusion-transmitted infections (TTI). The four major TTIs are caused by HIV, HBV, HCV and syphilis. Routine paediatric vaccinations should be kept up to date, including the annual influenza vaccine.

Bone complications

Bone disease in thalassaemia results from bone marrow expansion, iron overload, iron chelation, endocrine dysfunction and vitamin D, C and K and zinc deficiencies.
The clinical presentation includes growth impairment, rickets-like bony lesions, back pain, spinal deformities, signs of nerve compression, severe osteoporosis and fragility fractures. Long bones, especially the humeri, may be short, with loss of the concave profile, and signs of growth arrest.

Timeous and adequate transfusion therapy will prevent irreversible bony abnormalities that occur due to bone marrow expansion, viz. dental abnormalities, malocclusion, recurrent sinusitis and increased susceptibility to fractures. Paediatric patients on DFO may develop rickets-like bony lesions and sclerotic lesions, severe epiphyseal dysplasia resulting in genu valgum or genu varum, short stature, truncal shortening and vertebral dysplasia.[18] These skeletal abnormalities are associated with early initiation of DFO or high doses of DFO in the presence of reduced iron stores. In the latter scenario, skeletal changes are preventable by using lower doses of DFO (20 - 30 mg/kg/d). Bony changes have not been associated with the oral iron chelators, such as DFP and DFX. However, DFP may result in arthropathy and is associated with bone mineralisation defects, hypercalciuria and nephrocalcinosis.

There is a high prevalence of vitamin D deficiency, and this may contribute to osteopenia. Vitamin D supplementation should be commenced when levels are suboptimal. Established osteoporosis in adults should be treated with bisphosphonates and managed by an endocrinologist. Zinc supplementation should be instituted in those with low zinc levels.

Renal disease
Renal disease in thalassaemia is a less well-recognised complication, caused by the disease itself, as well as iron chelators. Manifestations include tubular dysfunction, glomerular dysfunction and resultant proteinuria, haematuria, nephrolithiasis and renal failure.[18] Up to 60% of TDT patients develop tubular dysfunction, which is related to iron overload, chronic anaemia and DFO toxicity. A renal biopsy is invasive and risky; therefore, MRI is essential for non-invasive assessment of iron overload. There is also a significant correlation between serum ferritin and renal iron deposition. Splenectomy is an independent risk factor for tubular abnormalities.

DFX is very lipophilic and thus enters the tubular cells to form a highly charged complex with iron, causing a proximal tubulopathy and Fanconi syndrome.[19]

Thromboembolic disease
TM may be considered a hypercoaguable state, resulting from abnormalities in platelets and pathological red cells, endothelial dysfunction, coagulation system abnormalities and the presence of microparticles. Splenectomy in patients >35 years of age, anaemia (Hb <9 g/dL) and iron overload all contribute to the hypercoaguable
state. Patients should be treated according to standard local thrombosis management guidelines.

Splenectomy in TM

Thalassaemia in pregnancy

Supportive care[25]

Psychological support
Thalassaemia patients and their parents require strong social circles and regular psychological support through various stages of the disease, including diagnosis, initiation of transfusion and iron chelation, and transition to self-care.

Psychosocial factors strongly influence adherence to treatment and can also predispose to illnesses such as depression. Ongoing support and encouragement by a multidisciplinary team including a psychologist and social worker are essential to ensure continued adherence to treatment and to address any psychosocial issues.

Dental care
Patients with thalassaemia are vulnerable to many dental complications, including malocclusion, an increased risk of dental caries and periodontal disease. Regular dental follow-up is necessary.

Lifestyle and quality-of-life issues
With increasing life expectancy of thalassaemia patients, healthcare providers should try their best to ensure that the disease and its treatment cause the least amount of disruption as possible to patients’ daily lives. Clinic appointments and transfusion regimens should be arranged in such a way that they have minimal impact on school or work activities.

Physical activity and sport should be encouraged, bearing in mind limitations due to anaemia and cardiopulmonary complications of the disease.

Attention to adequate nutrition includes monitoring for zinc and vitamin D deficiency and encouraging a diet rich in calcium and vitamin E. L-carnitine supplements may have beneficial antioxidant and cardioprotective effects.

Education, prevention and counselling
Patients need to be provided with age-appropriate information and educational tools regarding their disease, its complications and treatment.

Genetic counselling
This should be available for couples who wish to have a child, and options for prenatal diagnosis must also be discussed.

Transition to adult care
Transition to self-care and adult clinics coincides with adolescence. This is a period when patients will challenge boundaries, and adherence is compromised. The transition must be gradual, and only when the patient is emotionally ready. Holding joint paediatric and adult outpatient clinics allows for a smoother transition to adult care, and is less intimidating to the patient.

Novel therapeutic approaches
New therapeutic strategies aimed at improving the quality of life and improving outcomes are evolving as a result of improved understanding of the pathophysiology of β-thalassaemia. These include the following:

Addressing ineffective erythropoiesis
Growth differentiation factor 11 (GDF-11): this is overexpressed in immature erythroblasts in β-thalassaemia and induces expansion of erythroid progenitors with consequent ineffective erythropoiesis.[24] Novel strategies to bind/trap GDF11 include sotatercept and luspatercept.

In the BELIEVE trial studying the use of luspatercept, 21% of adults showed a 33% reduction in transfusion requirements, compared with 4.5% on placebo.[20,21]

Janus kinase 2 (JAK2) inhibitors: preclinical studies of JAK2 inhibition in mouse models showed improvement in ineffective erythropoiesis and a decrease in splenomegaly, suggesting that the use of ruxolitinib (a JAK1/JAK2 inhibitor) could benefit β-thalassaemia patients.[22,23] The TRUTH Study in TDT showed a decrease in spleen size but no clinically significant improvements in pre-transfusion Hb, hence did not proceed into a phase III study.[24]

Improving iron overload
Minihemepcids: hepcidin is known to prevent iron utilisation and absorption. Preclinical studies propose that minihemepcids could restrict iron absorption and may be useful in addressing iron overload and improve ineffective erythropoiesis, anaemia and splenomegaly.[22,24]

Transmembrane protease serine 6 (TMPRSS6) inhibitors: TMPRSS6, a transmembrane serine protease produced by hepatocytes, negatively regulates hepcidin expression (by cleaving haemojuvelin) and is thus an important modulator of hepcidin expression.

Manipulation of ferroportin inhibitors and HIF2a: ferroportin plays a crucial role in iron homeostasis by exporting iron from enterocytes to the circulation. Intestinal HIF2a (hypoxya-inducible factor-2α) regulates ferroportin expression in response to changes in systemic iron requirements.[25]

Hemoglobin F (fetal haemoglobin) inducers
Hemoglobin F inducers include: (i) DNA methylation inhibitors, such as 5-azacytidine and decitabine; (ii) hydroxyurea; and (iii) short-chain fatty acids.

Bone marrow transplantation

Gene therapy

Thalassaemia intermedia
TI or non-transfusion dependent thalassaemia (NTDT) refers to the clinical phenotype of thalassaemia where patients do not require regular lifelong blood transfusions for survival.[20] This group includes α-thalassaemia intermedia (HbH disease), β-thalassaemia intermedia and mild to moderate forms of HbE/β-thalassaemia.[26]

Patients with TI present with anaemia with varying degrees of severity. Ineffective erythropoiesis, chronic anaemia and iron overload can lead to more severe clinical complications in TI than in a routinely transfused, well-chelated patient with β-thalassaemia major[27] (see Table 3, part 1, CME[1] for clinical complications of thalassaemia).

Patients with TI should be on routine folic acid supplementation. The specific management of patients with TI includes conventional modalities, novel agents and stem cell transplantation.

Transfusion therapy
Patients with TI are generally transfusion independent. They may require blood transfusions during certain clinical situations, such
as pregnancy, surgery or infection. Selected patients may also be instituted on a more regular transfusion regimen for the primary or secondary prevention of specific clinical complications, such as pulmonary hypertension, thromboembolic events, leg ulcers and extramedullary haematopoiesis.

Iron chelation
Iron overload in TI results from increased intestinal iron absorption as a result of chronic hypoxia. Serum ferritin levels underestimate the degree of iron overload in NTDT, but are nonetheless still a useful test to guide chelation therapy in resource-constrained settings where MRI may not be available. Ferritin levels should be monitored 3-monthly, starting at the age of 10 years, and chelation therapy instituted or interrupted at levels of >800 μg/L and <300 μg/L, respectively. Based on available evidence, DFX is currently the only approved iron chelator for use in NTDT.

Modulation of HbF
Hydroxyurea has been shown to be safe and effective in reducing transfusion requirements in patients with TI. While HbF inducers in general appear promising, larger randomised and controlled trials are needed before their use in TI is widely advocated.

Stem cell transplantation
Stem cell transplantation is rarely performed in TI, and is reserved for those patients who develop transfusion dependency.

Novel therapies
Many targeted therapies (discussed above) show promise in the future management of TI, and may be considered for use where it is cost-effective.

Thalassaemia minor
TM is usually asymptomatic and characterised by a borderline or mild anaemia and thalassaemic red cell indices (microcytosis, hypochromia, elevated red cell count and Mcentzer index (MCV/RCC ratio) <13. It must be differentiated from iron deficiency anaemia (IDA).

β-thalassaemia minor
The HbA2 level is typically raised, but may be masked by co-existing IDA (as IDA decreases the HbA2 level). In such individuals, the IDA should be treated prior to HB electrocophoresis.

Premarital and prenatal counselling are important in β-thalassaemia minor. If the partner also has β-thalassaemia minor, there is a 25% risk of affecting the child. In the case of β-thalassaemia major, there is a 50% risk of the child being affected.

No specific treatment is required for those patients with isolated β-thalassaemia minor.

Alpha thalassaemia minor
Alpha thalassaemia minor (deletion or inactivation of 1 or 2 α globin genes) is usually asymptomatic. In contrast to β-thalassaemia minor, the HbA2 level is normal or borderline low, and the diagnosis is suspected upon exclusion of other causes of a miccrocytic anaemia. DNA analysis may be employed in instances where confirmation is necessary, such as in prenatal testing. No specific treatment is required for individuals with isolated α-thalassaemia minor.

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