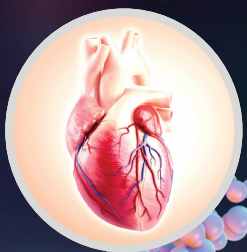
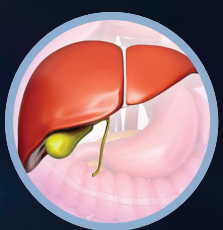
QUICK REFERENCE FOR HEALTHCARE PROVIDERS

MANAGEMENT OF THALASSAEMIA

(SECOND EDITION)





Ministry of Health Malaysia

Malaysian Society of Paediatric Haematology and Oncology

Malaysian Society of Haematology

Academy of Medicine Malaysia

KEY MESSAGES

1. Thalassaemia is a group of hereditary haemoglobin (Hb) disorders characterised by decreased or absent synthesis of normal globin chains & can be categorised into transfusion-dependent thalassaemia (TDT) & non-transfusion-dependent thalassaemia (NTDT).
2. Diagnosis of thalassaemia is made by screening with full blood count (FBC) & Hb typing, followed by confirmation with molecular/DNA analysis when indicated.
3. Targeted screening programmes & comprehensive genetic counselling are essential in increasing public awareness of thalassaemia. Pre-pregnancy counselling in at-risk couples is crucial to reduce the birth of thalassaemia babies.
4. All thalassaemia patients requiring blood transfusion should receive antigen- matched & leucodepleted blood.
5. Regular monitoring of iron burden in all thalassaemia patients is performed using serum ferritin (SF) & magnetic resonance imaging (MRI).
6. Iron overload results in deposition of iron in the organs commonly involving the heart, liver & endocrine organs. Excessive iron & transfusion can also predispose patients to infections. They should be regularly assessed & treated appropriately.
7. Optimisation of iron chelation therapy (i.e. dual oral iron chelators etc.) & ensuring adherence via patient counselling is important to minimise complications of iron overload in thalassaemia.
8. Pre-pregnancy counselling, optimisation of Hb level & intensive iron chelation in thalassaemia patients are essential to ensure safe & optimal pregnancy outcomes. Close monitoring of pregnant thalassaemia mothers under combined multidisciplinary care is important for the well-being of both mother & child.
9. Children of at-risk couples should have their thalassaemia status confirmed by 18 months to ensure early diagnosis & commencement of therapy for their disease.
10. In TDT, haematopoietic stem cell transplantation should be offered at an early age in those with matched sibling donor.

This Quick Reference provides key messages & summarises the main recommendations in the Clinical Practice Guidelines (CPG) Management of Thalassaemia (Second Edition).

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:
Ministry of Health Malaysia: **www.moh.gov.my**
Academy of Medicine Malaysia: **www.acadmed.org.my**

CLINICAL PRACTICE GUIDELINES SECRETARIAT
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Presint 1
Federal Government Administrative Centre 62590
Putrajaya, Malaysia
Tel: 603-88831229
E-mail: htamalaysia@moh.gov.my

DIAGNOSIS

- Thalassaemia phenotypes can be classified into TDT & NTDT based on transfusion requirement.
- Patients who require life-long regular transfusion for survival are considered as TDT.

- Common clinical presentation of thalassaemia is based on types of thalassaemia:
  a. TDT at 4 - 6 months up to 2 years of age
     - severe anaemia
     - hepatosplenomegaly
     - jaundice
     - thalassaemia facies
     - growth failure/retardation
  b. NTDT at a later age (>2 years of age)
     - mild - moderate anaemia
     - extensive thalassaemia facies
     - hepatosplenomegaly

- Hb analysis (capillary electrophoresis &/or high-performance liquid chromatography) should be used for presumptive diagnosis of beta-thalassaemia & other haemoglobinopathies.
- Molecular analysis should be done:
  - for all thalassaemia patients
  - to confirm α-thalassaemia, borderline Hb A2 thalassaemia, Hb variants & haemoglobinopathy other than classical β-thalassaemia trait & Hb E

SCREENING & PREVENTION

Strategies commonly practised in screening & prevention of thalassaemia are:
- public awareness & education
- population screening
- targeted population screening
- cascade screening
- pre-marital screening & genetic counselling
- pre-implantation genetic testing (PGT)
- pre-natal diagnosis followed by termination of affected foetuses

Current screening strategies in Malaysia include thalassaemia screening among Form 4 students, antenatal screening, cascade screening & voluntary screening with the aim to reduce the birth of thalassaemia babies.

GENETIC COUNSEIIING

Genetic counselling should be provided by trained professionals to thalassaemia & carriers. Individuals offered genetic testing should receive pre-test & post-test genetic counselling.

BLOOD TRANSFUSION THERAPY

TDT	NTDT
• Aim for pre-transfusion Hb at 9 - 10 g/dL • A higher Hb target of 11 - 12 g/dL for patients with heart disease & clinical evidence of extramedullary haematopoiesis	• Occasional blood transfusion in acute stressful conditions • Regular transfusion in the presence of ineffective erythropoiesis-related complications
○ All patients should have full red cell phenotyping consisting of ABO, Rh, Kell, Kidd, Duffy & MNSs prior to first transfusion. ○ All patients should receive antigen-matched & leucodepleted blood. ○ Fresh blood <14 days are advisable.	

Volume of blood to be transfused is calculated based on body weight as below.

Volume required (ml) = Body weight (kg) x Hb rise required (g/dL) x transfusion factor (3 - 4)

ASSESSMENT OF IRON BURDEN

Serial SF is the recommended method to assess iron burden in thalassaemia patients. It should be monitored 3 - 6 monthly in all patients. A single SF level should be interpreted with caution as it may be influenced by many factors. The result should be interpretated with MRI liver & cardiac findings as there is no good correlation between these methods.

MRI T2* of the heart & liver should be done in all thalassaemia patients from 10 years old or earlier if indicated to assess iron overload.

Cardiac MRI values & suggested schedule

Degree of cardiac iron load	Cardiac T2* Value (ms)	Timing for repeat MRI
Normal	>20	2-yearly
Mild overload	16 - 20	Annually[#]
Moderate overload	10 - 15	
Severe overload	<10	6-monthly[#]

[#]The CPG DG opines that this has to be done after intensification of chelation

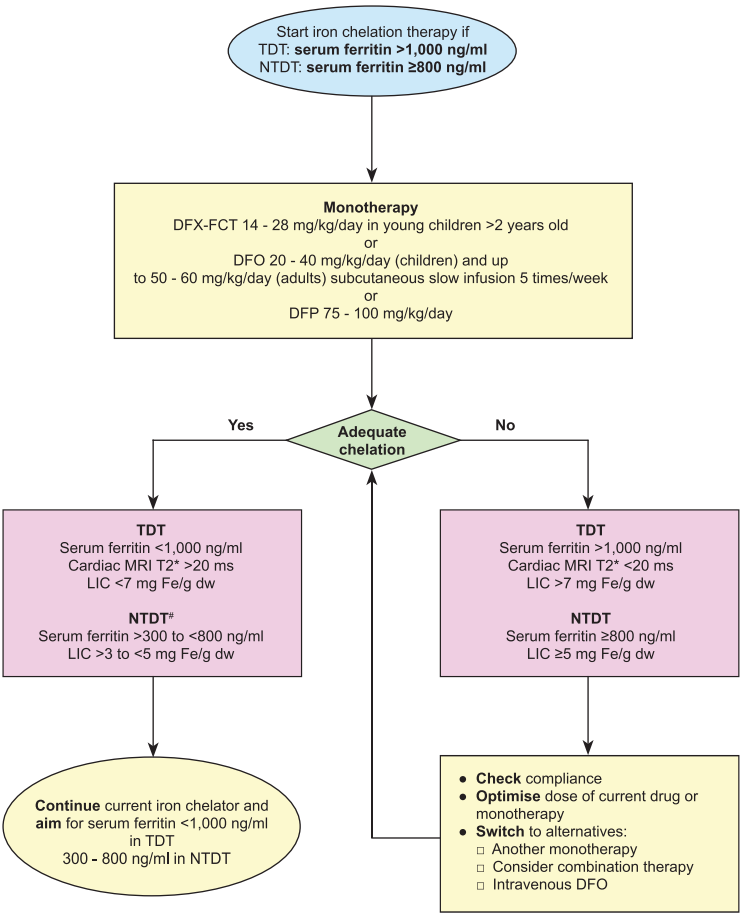
Liver MRI values of iron overload severity

Degree of liver iron load	Liver T2* Value (ms)	LIC (mg Fe/g dw)	Timing for repeat MRI
Normal	>11.4	< 2	2-yearly
Mild overload	3.8 - 11.4	2 - 7	
Moderate overload	1.8 - 3.8	7 - 15	Annually[#]
Severe overload	<1.8	>15	

[#]The CPG DG opines that this has to be done after intensification of chelation

All patients with NTDT ≥10 years of age should be frequently assessed for iron overload status.

IRON CHELATION IN THALASSAEMIA



Abbreviations: DFX-FCT=deferasirox film-coated tablet, DFO=deferoxamine, DFP=deferiprone, LIC=liver iron concentration

#iron chelators should be temporarily discontinued when LIC ≤3 mg Fe/g dw or SF ≤300 ng/ml

MONITORING OF PATIENTS

Monitoring	Assessment & Investigations
Growth	• Weight, height & physical examination 3 - 6-monthly • Tanner staging 6-monthly
Blood transfusion	• HBsAg, anti-HCV & anti-HIV 6-monthly
Iron overload	• SF 3 - 6-monthly • LIC by MRI T2* 1 - 2-yearly • Cardiac MRI T2* 1 - 2-yearly
Cardiac	• ECG & echocardiography annually
Liver (screening for HCC)	• Biannual ultrasonography (USG) in all TDT patients • Annual USG in NTDT >10 years old with LIC ≥5 mg Fe/g DW or SF level ≥800 ng/mL • Annual AFP in cirrhotic NTDT patients & those aged >40 years
Endocrinopathy	Refer endocrinologist for the following work-up:
• Growth failure	• Bone age assessment • GH stimulation tests
• Delayed puberty & hypogonadism	• LH, FSH, oestradiol or testosterone • Pelvic USG for girls • Gonadotropin-releasing hormone (GnRH) stimulation test
• Hypothyroidism	• Free T4 & TSH
• Diabetes mellitus	• Fasting plasma glucose followed by OGTT if needed
• Osteoporosis/osteopenia	• Serum calcium, phosphate, alkaline phosphatase, 25-OH Vitamin D, zinc • Spinal radiograph (AP & lateral views) • DEXA scan
• Hypoparathyroidism	• Serum calcium, phosphate, alkaline phosphatase, magnesium • Parathyroid hormone
• Hypoadrenalism	• Baseline cortisol at 8.00 - 9.00 am • ACTH stimulation test
Drug toxicity	
• Desferrioxamine	• Auditory/ophthalmology annually
• Deferiprone	• Full blood count • ALT 3 - 6-monthly
• Deferasirox	• Renal profile & urine protein monthly • ALT monthly • Auditory/ophthalmology annually

COMPLICATIONS OF IRON OVERLOAD

Complication	Management
Cardiovascular System	
Asymptomatic, mild to moderate cardiac siderosis (T2* 10 - 20 ms) & normal cardiac function	Intensify iron chelation monotherapy or switch to combination therapy
Symptomatic or severe cardiac iron overload	Appropriate cardiac therapy & continuous intravenous deferoxamine in combination with deferiprone
Pulmonary hypertension	Regular transfusion Phosphodiesterase-5 inhibitors
Thrombosis	Prophylactic anticoagulant & antiplatelet if indicated
Liver Disease	
Liver siderosis	Intensify iron chelation monotherapy or switch to combination therapy
Hepatitis B	Consider antiviral treatment in chronic HBV-infected patients should be based on several criteria: • ALT ≥2 times upper limit of normal • HBV DNA ≥2.0 x 10⁴ IU/ml if HBeAg positive; or ≥2.0 x 10³ IU/ml if HBeAg-negative • presence of advanced fibrosis or cirrhosis irrespective of ALT level
Hepatitis C	Consider direct-acting anti-viral agents (DAAs) in all patients with chronic HCV infection & detectable HCV viremia.
Bacterial Infection	
Significant fever especially post-splenectomy	Stop iron chelation therapy Antibiotics use should have anti-Klebsiella & anti-Pneumococcal properties e.g. third-generation cephalosporin (cefotaxime or ceftriaxone) combined with gentamicin, ciprofloxacin or vancomycin.
Endocrinopathies	
Delayed puberty Absence of pubertal changes at 13 years old (girls) & 14 years old (boys)	Girls: Low dose oestrogen may be used for pubertal induction followed by combined hormonal therapy. Boys: Testosterone
Short stature	Treat other causes of short stature. Growth hormone injection may be considered
Diabetes mellitus	Subcutaneous insulin injection
Hypothyroidism	Oral L-thyroxine
Osteoporosis/osteopenia	Oral calcium & vitamin D supplements Bisphosphonates may be considered
Hypoparathyroidism	Oral calcitriol & calcium
Hypogonadism	Oral hydrocortisone
Others	
Leg ulcers & extramedullary haematopoiesis	Regular transfusion Hydroxyurea

FERTILITY & PREGNANCY

- **Fertility**
  - Fertility preservation options may be offered to:
    - all post-pubertal male thalassaemia patients prior to hydroxyurea & haematopoietic stem cell transplantation (HSCT) initiation
    - all pre- & post-pubertal female thalassaemia patients prior to HSCT initiation

- **Pre-pregnancy**
  - Identify at-risk couple.
  - Offer options e.g. pre-marital counselling & Pre-implantation Genetic Testing.
  - Optimise Hb levels, SF & iron overload complications before embarking on pregnancy.

- **Antenatal care**
  - Combined multidisciplinary care throughout pregnancy.
  - Invasive prenatal testing may be performed to diagnose thalassaemia in-utero for at-risk couples.
  - Pre-transfusion Hb level should be maintained at:
    - 10 g/dL in TDT
    - 8 g/dL in non-transfusion dependant α-thalassaemia
    - 10 g/dL in non-transfusion dependant ß-thalassaemia
  - Transfusion in pregnant thalassaemia patients should take into account worsening anaemia, cardiac decompensation & foetal growth restriction.
  - Serial ultrasonography should be performed in pregnant thalassaemia patients to detect foetal growth restriction.
  - Low molecular weight heparin for venous thromboembolism prophylaxis should be commenced in thalassaemia patients according to VTE risk assessment & guidelines.

- **Post-natal care**
  - Progesterone-only preparations are the preferred method of contraception in thalassaemia patients.
  - DFO can be recommenced after delivery whereas other iron chelators should be restarted post-breastfeeding cessation

HAEMATOPOIETIC STEM CELL TRANSPLANTATION

- In TDT, HSCT should be offered at an early age.
- Source of donors for HSCT are:
  - HLA-matched unaffected sibling
  - HLA-matched unrelated stem cell donor
  - Haplo-identical stem cell donor