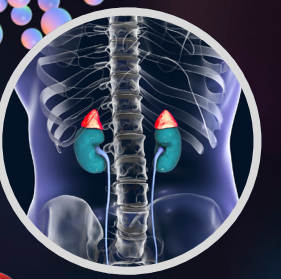
2024 MOH/P/PAK/557.24(GU)-e

CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF THALASSAEMIA

(SECOND EDITION)



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http://www.moh.gov.my
http://www.acadmed.org.my
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STATEMENT OF INTENT

This clinical practice guideline (CPG) is meant to be a guide for clinical practice, based on the best available evidence at the time of development. The guideline should not override the responsibility of the practitioners to make decisions appropriate to the circumstances of the individual. This should be done in consultation with the patients and their families or guardians, taking into account the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2024 and will be reviewed in a minimum period of four years (2028) or sooner if new evidence becomes available. When it is due for updating, the Chairperson of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed, and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which will be the definitive version at all time. This version can be found on the websites mentioned above.

TABLE OF CONTENTS

LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

Source: *U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG development group (DG).
- Recommendations are formulated based on **certainty of evidence** and the wording used denotes the **strength of recommendations**. This takes into account:
  - quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - relevancy and applicability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word **"should"** being considered. Otherwise, weak recommendations use the word **"may"** in proposing an action to be made.
- In the CPG, a yellow box highlights important message(s) in the management while a blue box contains evidence-based recommendation(s) for the particular condition.

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

Diagnosis

- MCH of ≤27 pg and/or MCV of <80 fL should be used as cut-off levels for a positive thalassaemia screening.
- Hb analysis (capillary electrophoresis and/or high-performance liquid chromatography) should be used for presumptive diagnosis of beta-thalassaemia and other haemoglobinopathies.
- Molecular analysis should be done:
  - for all thalassaemia patients
  - to confirm α-thalassaemia and borderline Hb A2 thalassaemia, Hb variants and haemoglobinopathy other than classical β-thalassaemia trait and Hb E
  - for prenatal diagnosis for at-risk couples and genetic counselling of prospective parents

Screening

- Screening programmes for thalassaemia should be done with proper planning, implementation and follow-up plan.

Genetic Counselling

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

Blood Transfusion

- Pre-storage filtration is the preferred choice for leucodepletion in thalassaemia.
- Pre-transfusion haemoglobin in transfusion dependent thalassaemia should be kept between 9 - 10 g/dL and a higher target of 11 - 12 g/dL should be aimed for patients with heart disease and clinical evidence of extramedullary haematopoiesis.
- All thalassaemia patients should have full red cell phenotyping at diagnosis or prior to first transfusion.
- Antigen matched blood and any other antigen negative blood for defined antibody should be given to all thalassaemia patients.
- In non-transfusion dependent thalassaemia patients:
  - occasional blood transfusion should be considered in acute stressful conditions
  - regular transfusion should be considered in the presence of ineffective erythropoiesis-related complications

Assessment of Iron Burden

- Serum ferritin level should be monitored every 3 - 6 months in all thalassaemia patients.
- Magnetic resonance imaging (MRI) T2* of the heart and liver should be done in all thalassaemia patients to assess iron overload at 10 years old or earlier if indicated.

Iron Chelation

- Optimisation of iron chelation therapy should be done to prevent and treat multiorgan complications of iron overload in thalassaemia patients.
- All transfusion dependent thalassaemia (TDT) patients with iron overload [serum ferritin (SF) >1000 ng/ml on two occasions at least two weeks apart] should receive iron chelation therapy.
  - The target of iron chelation should be SF <1000 ng/ml, liver iron concentration <7 mg Fe/g DW liver and cardiac T2* >20 ms.
- In patients with non-transfusion dependent thalassaemia:
  - iron chelators should be started at ≥10 years of age if liver iron concentration (LIC) ≥5 mg Fe/g dry weight or SF level ≥800 ng/ml
  - iron chelators should be temporarily discontinued when LIC ≤3 mg Fe/g dry weight or SF ≤300 ng/ml

Complications of Iron Overload

- In transfusion-dependent thalassaemia (TDT), magnetic resonance imaging (MRI) T2* should be done from age 10 years old:
  - to assess and monitor cardiac iron overload
  - to guide iron chelation therapy
- Continuous intravenous deferoxamine in combination with deferiprone should be considered in TDT with overt heart failure.
- To assess liver iron overload (LIO) in thalassaemia patients, the following should be done:
  - serum ferritin
  - magnetic resonance imaging (MRI) of the liver from 10 years of age
- Transient elastography may be used to assess LIO when MRI is not available.

- Growth of thalassaemia children and adolescents should be assessed every six months with accurate measurement.
- Transfusion-dependent thalassaemia (TDT) patients aged more than 10 years should be monitored for endocrine complications.
- Assessment of bone health in TDT patients should be commenced at the age of 10 years except for Dual Energy X-ray Absorptiometry scan which should be started later at the completion of puberty.

- All thalassaemia patients should be monitored for transfusion-related infections every 6-monthly.

Splenectomy

- Splenectomy may be considered in thalassaemia patients >5 years old with any the following:
  - increased pure red blood cell transfusion exceeding 200 - 250 ml/kg/year and severe iron overload not controlled by iron chelation
  - hypersplenism
  - massive splenomegaly
- Pre-splenectomy vaccination should be given 4 - 6 weeks prior or at least two weeks in advance.
- Post-splenectomy thalassaemia patients should be given the following:
  - low dose aspirin (75 - 150 mg daily) if the platelet counts >500,000/mm^3
  - oral penicillin life-long (in high-risk thalassaemia patients)

Pregnancy

- Invasive prenatal testing may be performed to diagnose thalassaemia in utero for at-risk couples of thalassaemia.
- Pre-transfusion haemoglobin level should be maintained at 10 g/dL in pregnant transfusion-dependent thalassaemia patients.
- Transfusion in pregnant thalassaemia patients should take into account worsening anaemia, cardiac decompensation and foetal growth restriction.
- Serial ultrasound scan 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 and guidelines.

HSCT

- In transfusion dependent thalassaemia, haematopoietic stem cell transplantation should be offered at an early age to those with matched sibling donor.

Lifestyle

- All thalassaemia patients should be given good nutritional support to minimise growth impairment.
- Psychological support has to be offered to all thalassaemia patients.
- A structured transition care should be arranged for all thalassaemia patients.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH), Ministry of Higher Education and private healthcare. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. PubMed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published on humans, publication from year "2012 to Current" and English language. In addition, the reference lists of all retrieved literature and guidelines were searched, and experts in the field contacted to identify relevant studies. All searches were conducted from 22 Oktober 2021 to 10 January 2022. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 December 2023 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other CPGs on Thalassaemia which are:

- Thalassaemia International Federation (TIF) - Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) 4th Edition (Version 2.0) (2021)
- Thalassaemia International Federation (TIF) - Guidelines for the Management of Non-Transfusion Dependent β-Thalassaemia 3rd Edition (2023)
- Thalassaemia International Federation (TIF) - Guidelines for the Management of Non-Transfusion Dependent α-Thalassaemia 3rd Edition (2023)

These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 27 clinical questions (CQ) were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 26 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the two groups. This CPG was developed largely based on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the U.S. Preventive Services Task Force Level of Evidence (2015), while the grading of recommendation was done using the principles of GRADE (refer to page i). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (Available at https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

The objective of the CPG is to provide evidence-based recommendations on the management of transfusion dependent thalassaemia (TDT) and non-transfusion dependent thalassaemia (NTDT) on the following aspects:

- diagnosis
- counselling and screening
- monitoring and follow-up
- treatment
- complications
- fertility and pregnancy

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria

- All patients with TDT and NTDT

Exclusion Criteria

- Any other chronic/congenital anaemia

TARGET GROUP/USERS

This document is intended to guide healthcare professionals and relevant stakeholders involved in the management of thalassaemia. This includes:

i. healthcare professionals (doctors, pharmacists, allied health professionals)
ii. professional organisations
iii. policy makers
iv. patients, caregivers and their advocates

HEALTHCARE SETTINGS

Primary, secondary and tertiary care settings

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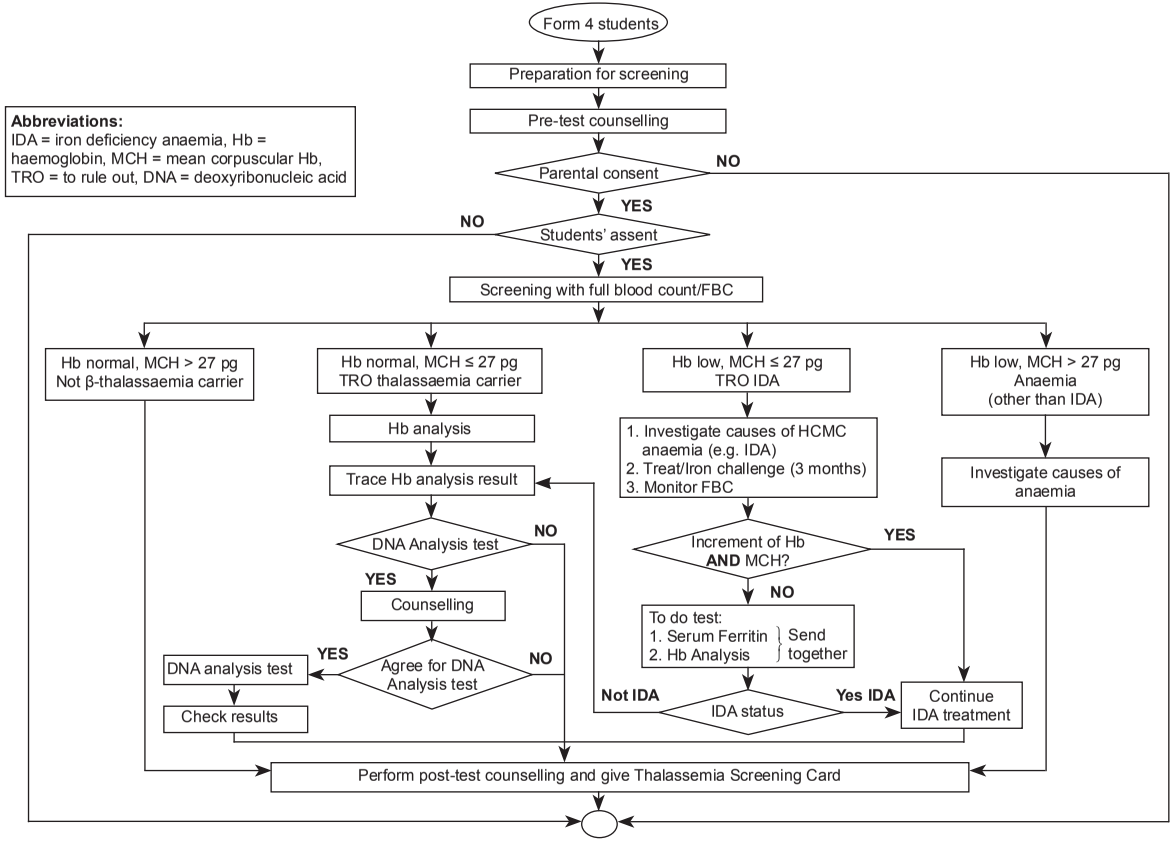
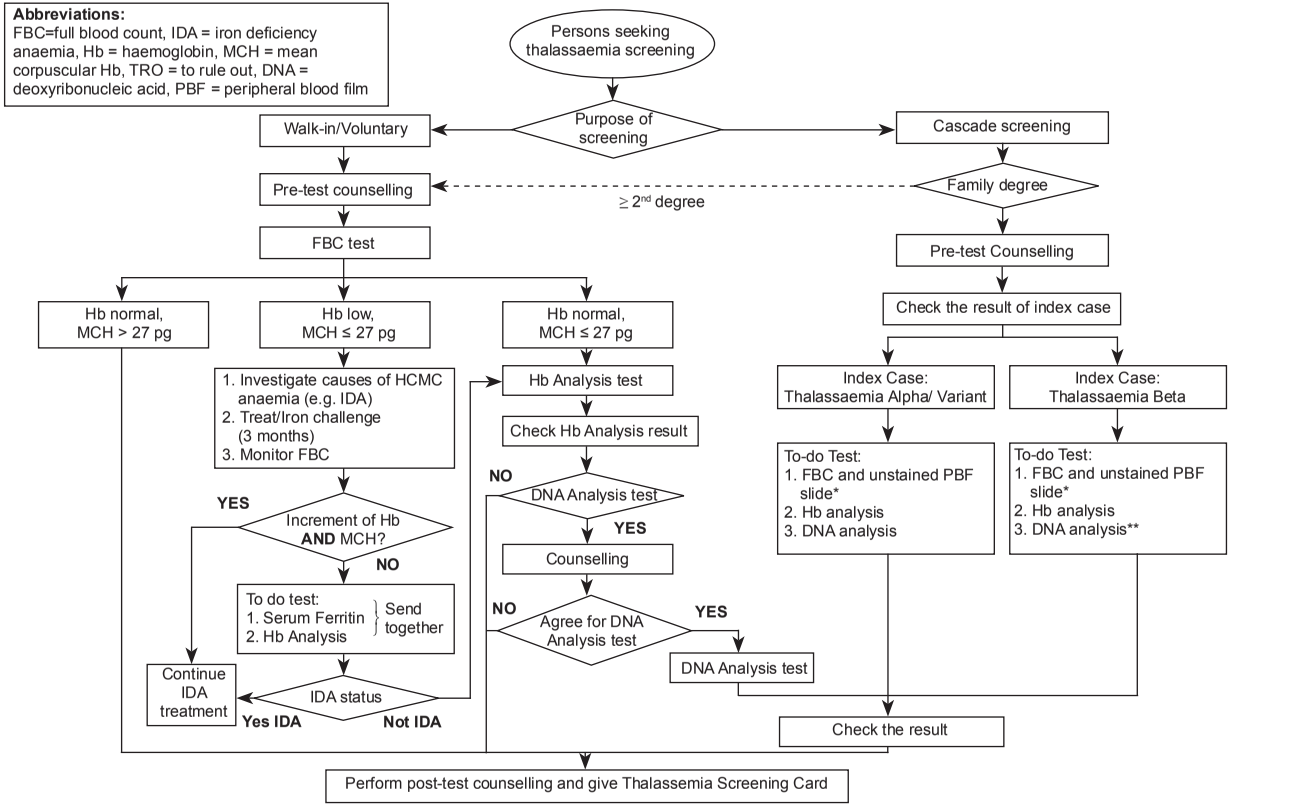
Algorithm 1: Form 4 Thalassaemia Screening Programme



Source: Family Health Development Division, Ministry of Health Malaysia. Garis Panduan Program Saringan Thalassemia Kebangsaan di Kesihatan Primer. 2024.[Unpublished]

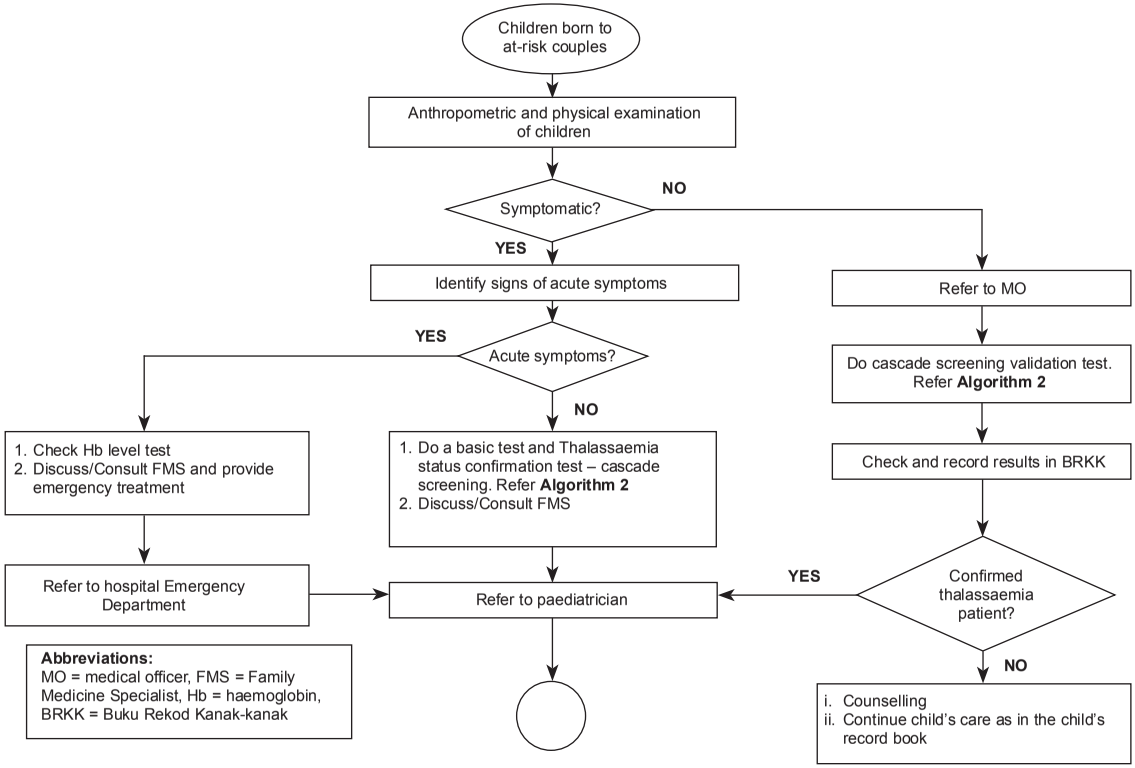
Algorithm 2: Thalassaemia Screening at Health Clinic - Walk-In/Voluntary/Cascade



Source: Family Health Development Division, Ministry of Health Malaysia. Garis Panduan Program Saringan Thalassemia Kebangsaan di Kesihatan Primer. 2024. [Unpublished]

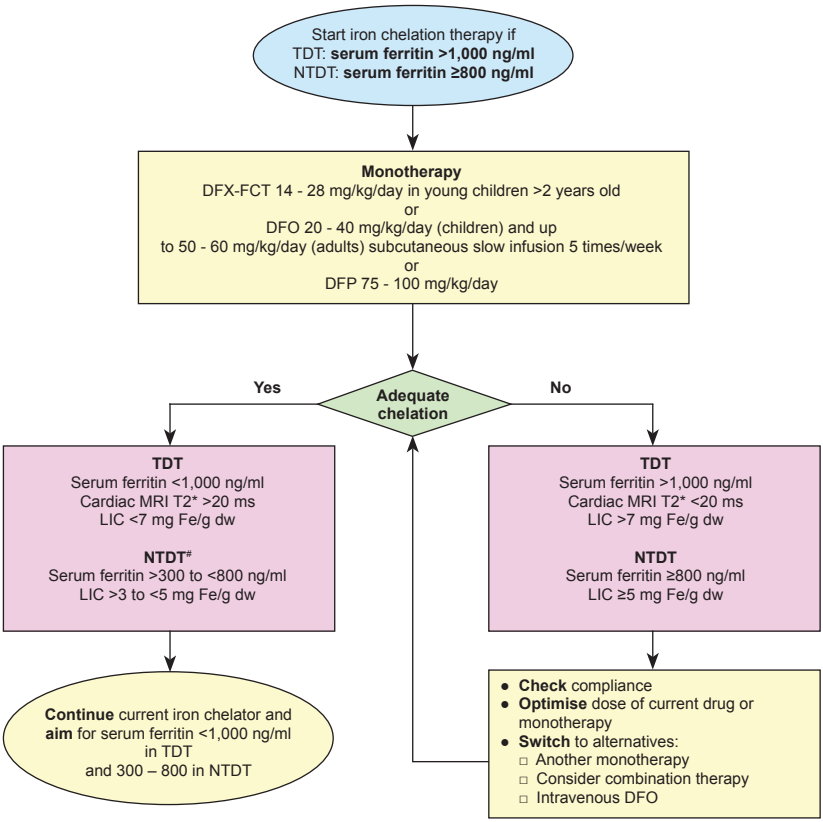
*Collection of FBC and unstained PBF slides based on local laboratory management
**DNA Analysis test will be carried out if necessary, depending on the result of Hb Analysis

Algorithm 3: Confirmation of Children's Thalassaemia Status to at-Risk Couples



Source: Family Health Development Division, Ministry of Health Malaysia. Garis Panduan Program Saringan Thalassemia Kebangsaan di Kesihatan Primer. 2024.[Unpublished]

Algorithm 4: 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

Adapted: Ministry of Health, Malaysia. Clinical Practice Guidelines on Management of Transfusion Dependent Thalassaemia. Putrajaya: MoH; 2009.

1. INTRODUCTION

Thalassaemia refers to a group of hereditary haemoglobin disorders characterised by decreased or absent synthesis of normal globin chains. Patients of this disorder can be categorised into two spectra; transfusion-dependent thalassaemia (TDT) and non-transfusion-dependent thalassaemia (NTDT).[1]

Thalassaemia is a major public health issue with an enormous cost burden for MoH.[2 - 3, level III] Effective control of the disease has led to increased survival, reduced morbidity and improved quality of life for thalassaemia patients. This guideline optimises the multi-discipline treatment and address adequate prevention of the disease.

TDT patients require regular, life-long blood transfusion to alleviate symptomatic anaemia, suppress ineffective erythropoiesis, enhance growth and development which will lead to improved survival rate. On the other hand, NTDT patients might require blood transfusion only when they have symptomatic anaemia, poor quality of life, compromising growth and development, or if there are features of extramedullary haematopoiesis. TDT and NTDT are fluid categories, based on clinical parameters, variations, and advances in the clinical management, as well as other modifiers of disease, which may shift a patient from one group to another during their lifetime.[4]

Patients with transfusional iron overload will require life-long, iron chelation therapy to help decrease the iron burden and prevent long-term complications associated with end-organ iron deposition including hepatic dysfunction and failure, endocrinopathies and cardiac dysfunction. Currently, haematopoietic stem cell transplant remains the only option for cure for TDT patients in Malaysia. Promising novel therapies e.g. gene therapy and molecules targeting ineffective erythropoiesis are emerging options for thalassaemia patients.

The National Thalassaemia Prevention and Control Programme was approved by Malaysian Cabinet in 2004. Numerous activities were carried out following that namely the establishment of Malaysian Thalassaemia Registry in 2007, formation of National Steering Committee, publication of Clinical Practice Guidelines for Management of Transfusion Dependent Thalassaemia and establishment of Thalassaemia Control and Prevention Programme in 2009. Thalassaemia Screening Programme was introduced with antenatal screening in 2009 which moved on to Form 4 School Screening Programme in 2016 and also includes voluntary and cascade screening.

The 2022 Annual Report of Family Health Development Division of MoH Malaysia stated that thalassaemia carrier rate was 579.3/10,000 school children screened. The highest number of carriers was detected in Kedah (79.27/10,000 school children screened). Kelantan recorded the highest Thalassaemia Hb E carrier (46.10/10,000 school children screened) while Sabah had the highest ß-thalassaemia carrier (45.23/10,000 school children screened). α-thalassaemia carrier, based on genotype, was highest in Kedah (33.43/10,000 school children screened).[5, level III]

The 2020 Malaysian Thalassaemia Registry reported 8,767 thalassaemia patients in Malaysia, an increase from 4,541 in 2009, of which 44.1% were TDT. Malays remain the ethnic group with the highest proportion of thalassaemia patients at 63.3%. The largest proportion of thalassaemia patients in Malaysia was diagnosed with haemoglobin (Hb) E-β thalassaemia (35.6%), followed by β-thalassaemia major (30.8%), Hb H disease (21.9%), β-thalassaemia intermedia (TI) (9.1%) and other forms of haemoglobinopathies (2.6%). The highest burden of disease was seen in the state of Sabah (22%) followed by Selangor and Kedah with 16% and 10% of the patients respectively.[6, level III]

The second edition of the CPG on Management of Thalassaemia intends to expand the scope of its previous edition by integrating the management of both TDT and NTDT into the CPG as well as address the management of thalassaemia patients during pregnancy and childbirth. It will also address fertility and prenatal diagnosis as well as screening and prevention of the disease. This CPG also aims to update recommendations based on new evidence that have emerged in the management of the disease to keep the CPG current and up to global standards.

2. DIAGNOSIS

2.1. Clinical Diagnosis

Thalassaemia phenotypes can be classified into TDT and NTDT based essentially on transfusion requirement. Patients who require life-long regular transfusion for survival is considered as TDT as compared with NTDT (refer to **Figure 1**).

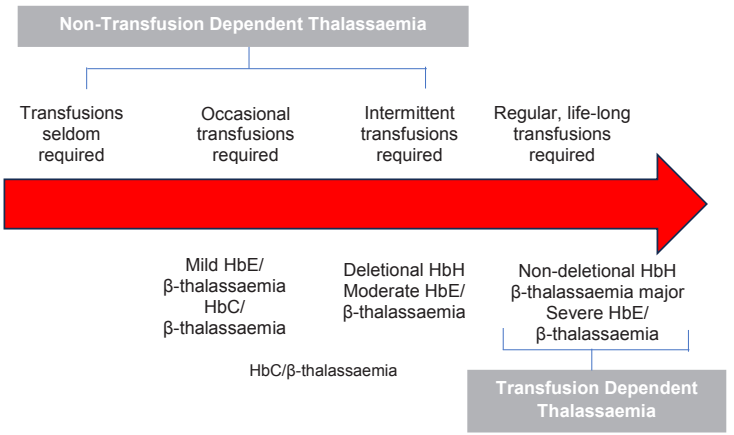


Figure 1: Transfusion requirement in various thalassaemia phenotypes

Adapted: Cappellini M, Farmakis D, Porter J, et al. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassaemia. Cyprus: Thalassaemia International Federation; 2021. E732 p.

It should be noted that the classification may change from one group to another. Thus, careful clinical evaluation using clinical and haematological parameters should be taken into consideration for the designation of TDT and NTDT based on patient's 'current' clinical course. This recent classification is used for standardisation of the terminology for research and clinical management. Therefore, it moves away from previous terminologies of β-thalassaemia major and intermedia that may give a false impression of disease severity.[1; 7, level III]

- 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
     - thalassaemia facies
     - hepatosplenomegaly
- Implementation of national screening programme helps to detect thalassaemia cases early before clinical manifestations appear.

2.2. Laboratory Diagnosis

Investigations of thalassaemia and haemoglobinopathies require step wise approach including screening and confirmatory diagnostic tests. A comprehensive evaluation from clinical history, physical examination and combination of laboratory results are important for precise diagnosis. Presumptive and confirmatory diagnosis of thalassaemia requires several tests including red blood cell (RBC) indices, Hb typing and deoxyribonucleic acid (DNA) analysis. The laboratory approach depends on mutation spectrum in the region, available resources and age of target population.

a. Screening tests

In the previous local CPG on thalassaemia, a few criteria for thalassaemia screening have been addressed as listed below.[8]

- Mean corpuscular haemoglobin (MCH) level of <27 pg should be used in thalassaemia screening.
- α^+-thalassaemia and haemoglobinopathies e.g. Hb Constant Spring and Hb E, may have a normal mean corpuscular volume (MCV) and MCH, thus may potentially be missed if MCH level of <27 pg is used as cut-off level for a screening test.
- Iron deficiency, characterised by an increase in red cell distribution width (RDW), should be treated before proceeding with haemoglobinopathy work-up.

Ideally, at-risk couples should be worked up for thalassaemia regardless of their iron status.

The above criteria should be maintained with the following additional updated information.

- MCH of ≤27 pg and/or MCV of <80 fL are currently being used as cut-off levels for a positive thalassaemia screening. MCH is preferred because it is less susceptible to storage changes. [8; 9]

Mentzer Index has been used in clinical practice to differentiate between iron deficiency anaemia (IDA) and β-thalassaemia trait. However, evidence showed contradictory results on its accuracy[10 - 12, level III] and thus the CPG DG does not recommend its use.

Refer to **Algorithm 2** on **Thalassaemia Screening at Health Clinic - Walk-In/ Voluntary/Cascade**.

b. Diagnostic tests

i. Hb analysis

High-performance liquid chromatography (HPLC) and capillary zone electrophoresis (CZE) are two recommended methods to provide presumptive identification and quantification of

normal and variant Hb. Both methods are complementary to each other for Hb variant identification.[9]

Hb analysis should be performed on pre-transfusion or three months post transfusion samples.

Two studies evaluated the utility of CZE against HPLC and found:

- Hb A and foetal haemoglobin (Hb F) level measurement correlated well between the two methods with r of 0.999[13, level III] and 0.994[14, level III] respectively. However, low level of Hb F may not be detected by CZE.[14, level III]
- Hb A2 measurement using CZE and HPLC with the presence of Hb variants (Hb C, Hb E and Hb S) resulted in unacceptable agreement (r=0.0356); however, the correlation improved without such variants (r=0.994).[13, level III]
- In Hb variants (Hb C, Hb E and Hb S):[13, level III]
  - Hb S was detected by both techniques with good agreement (r=0.996)
  - Hb C was detected by both techniques with good agreement (r=0.967)
  - Hb E was not detected in any of the patients using HPLC, but was detected in all of them using CZE
- Hb H was more difficult to measure by CZE than HPLC. The percentage of the Hb H was 8.1, 9.4 and 17.8 by HPLC in comparison with values of 0.5, 0.5 and 5.7 by CZE within acceptable sample stability time.[14, level III]

A hospital-based study on thalassaemia screening of newborns using CZE showed heterozygous α^0, homozygous α^+, compound heterozygous for α^+ with Hb Constant Spring, Hb H disease and Hb H-Constant Spring could be detected by the presence of Hb Bart's. It was also able to detect Hb E. However, heterozygous β-thalassaemia was not detectable by this method as switching of predominant Hb F to adult Hb (Hb A) in newborns only occurs after six months of age.[15, level III]

In pregnancy, Hb F can be physiologically raised. Therefore, Hb analysis done during antenatal period should be interpreted as below:[9]

- MCH <27 pg with isolated raised Hb F ≥5%: heterozygous δβ-thalassaemia should be suspected
- normal MCH with Hb F >10%: Hereditary Persistence Foetal Haemoglobin (HPFH) should be suspected

Diagnosis of β-thalassaemia trait requires accurate determination of increased Hb A2 percentage. The proportion of Hb A2 is dependent on the precise mutation present. In most cases of heterozygosity for β^0 or severe β^+ thalassaemia, the Hb A2 is 4 - 9%.[8]

For borderline Hb A2 thalassaemia, lower levels of Hb A2 had been shown to detect mild or β^+ mutations. A local cross-sectional study found a sensitivity of 94% in the detection of borderline Hb A2 thalassaemia at levels 3.3 - 3.9% by CZE method.[16, level III]

In iron deficiency anemia with Hb <8 g/dL, Hb A2 level can be reduced as much as 0.5% and thus it should be interpreted cautiously in this population.[9]

c. Other useful haematological tests

- Peripheral blood film
  - RBC morphology remains a useful feature to grade the morphological changes in thalassaemia.[8]
- H-inclusion test
  - Hb H bodies inclusion detected using H-inclusion test is useful to support the presumptive diagnosis of Hb H disease. Regardless of the result, the diagnosis needs to be confirmed by DNA analysis.[9]

- Sickle solubility test
  - The test can be used as a guide to differentiate between Hb S and Hb variant e.g. Hb G-Makassar.[9; 17, level III]
- Cellulose acetate electrophoresis
  - Cellulose acetate electrophoresis (CAE) at pH 8.4 - 8.9 is a simple, reliable and rapid method in Hb typing. It remains a valid method in resource-constrained settings and as secondary technique following a positive HPLC.[9]

Refer **Appendix 3** on **Peripheral Blood Film and Haemoglobin Profiles in β-Thalassaemia Syndrome and Hb H Disease**.

d. Molecular analysis (DNA analysis)

- Molecular analysis is not usually required to confirm the diagnosis of a β-thalassaemia carrier. However, it is mandatory to confirm the α-thalassaemia carrier status.[TIF, 2021]

In addition, molecular analysis is essential for genetic counselling, risk calculation and prenatal genetic diagnosis. Refer to **Table 1** for **Summary of molecular techniques for thalassaemia genotyping in Malaysia**.

Indications for molecular analysis in thalassaemia in the local setting includes:[18, level III]

- confirmation for haemoglobin variant/haemoglobinopathy other than classical heterozygous beta and Hb E
- genotyping for all cases registered under Malaysian Thalassaemia Registry (MTR)
- borderline Hb A2 thalassaemia
- α^0-thalassaemia genotype with MCH <25 fL
- cascade screening of confirmed α-thalassaemia
- prenatal diagnosis for at-risk couples and genetic counselling of prospective parents

Other indication is for α-gene triplication or amplification in heterozygous β-thalassaemia with α-thalassaemia intermedia phenotype.[1]

Various molecular techniques have been used for point mutation detection in β-thalassaemia and large deletion detection in α-thalassaemia. All of these techniques have some advantages and disadvantages. DNA or molecular analysis for definitive diagnosis are performed either by mutation-specific detection (targeted panel) or genome scanning by direct sequencing.[TIF, 2019]

i. Mutation specific detection

A diagnostic study found that single-tube multiplex polymerase chain reaction (PCR)–based reverse dot blot (RDB) assay for simultaneous detection of both common α- and β-thalassaemia reduced the time and the complexity of diagnosis compared with conventional methods (Gap-PCR, RDB and PCR-Sanger sequencing) with high concordance rate ($p<0.001$).[19, level III]

ii. Genomic scanning

Conventional methods for thalassaemia diagnosis require the use of several techniques which leads to long turnaround time. The single platform Next-Generation Sequencing (NGS) may replace all these methods. It reduces the time of laboratory workflow.

One local cross-sectional study on the application of targeted NGS for investigation of thalassaemia in a developing country showed that NGS:[20, level III]

- was able to determine additional mutations that were not identified by conventional methods

- may overcome misdiagnosis of complex thalassaemia cases due to gene interactions
- may increase the speed of establishing a correct diagnosis for genotyping

Three cross-sectional studies on the performance of NGS for application in clinical management of thalassaemia in a large-scale population showed:

- the technology was able to simultaneously analyse *HBB*, *HBA1* and *HBA2* genes and thus reduce the turnaround time[21 - 22, level III]
- high concordance rate for analysis of α- and β-globin gene (99.98% and 100% respectively) compared with conventional molecular method (RDB, Gap-PCR, MLPA and PCR-Sanger sequencing)[21, level III]
- additional variants and couples who are at risk of having child affected by thalassaemia were identified by NGS that were not identified by conventional methods[21, level III]
- increased detection of α- and β-thalassaemia and, co-inheritance α- and β-thalassaemia carrier rate that were missed by conventional methods[22 - 23, level III]

Table 1: Summary of molecular techniques for thalassaemia genotyping in Malaysia

Mutation-specific detection (Targeted panel)	Genome scanning (Unknown mutation/ deletion)	Modifier gene (Secondary modifier)
RDB	DNA sequencing (*HBB, HBA1, HBA2, HBD* gene)*	PCR for XMN-1 polymorphism*
ARMS-PCR	NGS	Multiplex-PCR for Anti-3.7 and anti-4.2*
Gap-PCR	MLPA	α-MLPA*
*Real time PCR with melting curve analysis	**WES/ Long read sequencing	NGS/WES for BCL11, KLF-1**

*Methods currently applied in clinical laboratories of Institute for Medical Research (IMR)
**Used for research purposes in IMR
Abbreviations: RDB=reverse dot blot; DNA=deoxyribonucleic acid; PCR=polymerase chain reaction; ARMS=amplification refractory mutation system; NGS=next-generation sequencing; MLPA=multiplex ligation-dependent probe amplification; WES=whole exome sequencing

e. Genetic modifier

Several genetic modifiers play an important role in contributing to phenotypic variability in thalassaemia patients. The genetic modifiers can be classified as the following:

- primary - *HBB* gene mutations in those with underlying β-thalassaemia
- secondary - involve in regulation of Hb F
- tertiary - not involved in globin synthesis but might modify the severity of the disease

A scoring system for classification of Hb E/β-thalassaemia disease severity into mild, moderate and severe has been developed based on clinical criteria (Hb at steady state level, age at receiving first blood transfusion, requirement of blood transfusion in a year, size of spleen, age of thalassaemia presentation and, growth and development).[24, level III]

A cross-sectional study using the above scoring system on predictive single nucleotide polymorphism (SNPs) for β^0-thalassaemia/Hb E disease severity in Thailand and Malaysia showed:[25, level III]

- the most common primary modifiers in severe disease were different between the two population -
  - Thai patients: HBB:c.126-129delCTTT (45.7%) and HBB:c.52A>T (26.3%)
  - Malaysian patients: HBB:c.92 + 5G>C (37.9%) and HBB:c.92 + 1G>A (22.4%)
- three predictive SNPs associated with secondary modifiers included rs766432 BCL11A, rs9399137 HBS1L-MYB and rs72872548 HBE1

In another cross-sectional study on α-triplication as secondary modifiers among β-thalassaemia patients with diverse phenotypes, the findings were:[26, level III]

- 69.4% heterozygous β-thalassaemia with α-triplication require blood transfusion
- symptomatic heterozygotes β-thalassaemia with α-triplication had significantly lower Hb level and higher Hb F levels compared with asymptomatic group of the same population.

- An α-gene triplication or quadruplication is important to be considered in heterozygous β-thalassaemia subjects with a TI phenotype.[1]

f. Thalassaemia mutations in Malaysia

The mutation spectrum of β- and α-thalassaemia among Malaysian population are presented in the table below. Genotype mapping and characterisation of various mutations according to ethnicity and location are important especially in the development of targeted panel based on ethnic distribution (refer to **Appendix 4 on Molecular Spectrum of β-thalassaemia** and **α-Thalassaemia Commonly Identified Among Malaysian Population Based on Ethnicity**). It also helps to facilitate the establishment of prenatal diagnostic and mutation definition in carrier and genetic counselling. An accurate, fine-scale epidemiology data are necessary to guide sustainable national and regional health policies for thalassaemia management.

g. Malaysia Thalassemia Diagnosis (MTD) Code for Hb Analysis and Molecular Analysis

The National Committee on Thalassaemia Screening and Diagnostic Test was established in 2013 to facilitate thalassaemia diagnostic laboratory processes. In 2016, the committee further improvised the mechanism for result tracing, standardisation of report between MoH laboratories, turn-around time for Hb analysis and molecular result by introducing the national thalassaemia coding system. This coding system was revised in 2023 as listed in **Appendix 5** on **Malaysia Thalassemia Diagnosis (MTD) Code for Hb Analysis and DNA Analysis**.

Recommendation 1

- MCH of ≤27 pg and/or MCV of <80 fL should be used as cut-off levels for a positive thalassaemia screening.
- Hb analysis (capillary electrophoresis and/or high-performance liquid chromatography) should be used for presumptive diagnosis of beta-thalassaemia and other haemoglobinopathies.
- Molecular analysis should be done:
  - for all thalassaemia patients
  - to confirm α-thalassaemia, borderline Hb A2 thalassaemia, Hb variants and haemoglobinopathy other than classical β-thalassaemia trait and Hb E
  - for prenatal diagnosis for at-risk couples and genetic counselling of prospective parents

3. SCREENING AND PREVENTION

Strategies commonly practised in screening and prevention of thalassaemia are:

- public awareness and education
- population screening
- targeted population screening
- cascade screening
- pre-marital screening and genetic counselling
- pre-implantation genetic testing (PGT)
- pre-natal diagnosis followed by termination of affected foetuses - refer to **Subchapter 12.3** on **Pre-pregnancy Care**

In Malaysia, thalassaemia screening started in 2009 through passive screening e.g. every patient with normal Hb and MCH ≤27 pg will be further investigated with Hb analysis to rule out thalassaemia. However, throughout the years, the screening evolved to focus more on younger generation for better prevention of the disease. Hence, thalassaemia screening in Form 4 students was introduced in 2016 as one of the strategies to reduce birth of thalassaemia babies up to 75% by 2030.[27, level III]

The Annual Report of Family Health Development Division 2022 on the Form 4 Thalassaemia Screening of 2017 - 2020 showed 924,487 students had been screened. Of these, 25.5% had undergone Hb analysis while 11.3% had DNA analysis done. Throughout the period, 53,559 students were confirmed as thalassaemia carrier (579.3/10,000) and 109 (1.18/10,000) were diagnosed with thalassaemia. The highest prevalence of carriers according to types of thalassaemia were α-thalassaemia in Kedah (33.43/10,000), β-thalassaemia in Sabah (45.23/10,000) and Hb E in Kelantan (46.10/10,000).[5, level III]

According to a local qualitative study on adolescents' experiences and views of the national school-based thalassaemia screening programme, respondents stated that age 16 - 17 years old was appropriate for screening. Among recommendations on the programme were to improve pre-test education for both students and parents as well as follow-up care and support for those identified as carriers.[28, level III]

Besides Form 4 thalassaemia screening locally, antenatal screening, cascade screening and voluntary screening are still ongoing. All individuals who underwent screening will be given a Thalassaemia Screening Card stating their thalassaemia status. Refer to **Appendix 6** on **Thalassaemia Screening Card.** Currently, there is no retrievable evidence on cost-effectiveness between different screening programmes for thalassaemia.

3.1. Population Screening

There is no recent evidence on the effectiveness of population screening in the prevention of thalassaemia. In Malaysia targeted population screening i.e. thalassaemia screening of Form 4 students has started in 2016 and its effectiveness is yet to be seen. Refer to **Algorithm 1** on **Form 4 Thalassaemia Screening Programme.**

A local study on economic burden in the management of TDT patients showed that TDT proved to be a costly disease. Implementation of an effective national screening programme may contribute to reduction in new thalassaemia cases.[29, level III]

3.2. Cascade Screening

Cascade screening is a genetic-screening strategy that targets family members (e.g. siblings, parents, aunts, uncles, etc.) of carriers/affected individuals of genetic disorders through the testing of their phenotypes or genotypes.[8]

Refer to **Algorithm 2** on **Thalassaemia Screening at Health Clinic - Walk-In/ Voluntary/Cascade.**

3.3. Pre-marital Screening

Evidence on pre-marital screening showed various findings on the outcomes. A study in Saudi Arabia on haemoglobinopathies trend following establishment of Mandatory Premarital Screening Programme in 2004 showed an increase in prevalence of haemoglobinopathies among subjects born after initiation of the programme. The prevalence of Hb S increased from 5.4% to 8.8% while that of β-thalassaemia increased from 1.1% to 2.1%.[30, level III]

On the other hand, another study in Saudi Arabia using secondary data where genetic counselling was added on premarital screening showed decreasing trend in the prevalence of β-thalassaemia trait from 24.2/1000 in 2011 to 12/1000 in 2015.[31, level III] A single centre cohort study in Iraq on feasibility and effectiveness of preventive programme for haemoglobinopathies which included education, pre-marital screening, counselling, prenatal diagnosis (PND) and selective termination of affected foetus revealed a 65% reduction in number of reported affected births over 5-years period.[32, level II-2]

In Malaysia, pre-marital screening is largely conducted as a voluntary screening.

3.4. Antenatal Screening

In Malaysia, screening among antenatal mothers started in 2009 targeting primigravidas. Currently, antenatal mothers with anaemia or abnormal MCV/MCH are further worked up for thalassaemia. Refer to Garis Panduan Program Saringan Thalassaemia Kebangsaan di Kesihatan Primer[33, level III] and Perinatal Care Manual 4th Edition.[34, level III]

3.5. Pre-implantation Genetic Testing

PGT is the genetic screening of embryos created in-vitro by assisted conception. Specifically, Pre-implantation Genetic Testing and Mapping (PGT-M) is a subset of PGT that allows the identification and exclusion of embryos carrying familial monogenic diseases. In cases of couple who are patient/carrier of thalassaemia, PGT-M for thalassaemia screening may be considered.

A cross-sectional study on 138 couples with thalassaemia who underwent PGT-M for diagnosis and HLA matching reported that:[35, level III]

- overall, there were 1180 blastocysts biopsied and suitable for clinical use
  - 58.6% of thalassaemia alone
  - 16.8% of thalassaemia-HLA embryos
- there were 15 live births, out of which 12 had been used for successful HSCT of disease-affected siblings

Another retrospective study on 171 thalassaemia couples who had undergone 327 preimplantation HLA typing cycles showed the following findings:[36, level III]

- 92% of blastomeres were biopsied and a full diagnosis was achieved; 17.6% were HLA-matched
- embryo transfer was performed with
  - 34.9% clinical pregnancy rate per transfer
  - 59 healthy and HLA-compatible babies were born
  - 21 affected children had been cured through HSCT

The clinical pregnancy rate based on 2016 - 2017 data from the European Society of Human Reproduction and Embryology was 35% per embryo transfer.[37, level III]

- Currently, PGT-M is widely accepted worldwide for prevention of thalassaemia offspring. Additionally, the use of combination HLA-matching with PGT-M may be useful for HLA-matching sibling donor saviour programme. In Malaysia, it is currently offered in some centres for these purposes and can be highlighted to thalassaemia couple.

Recommendation 2

- Screening programmes for thalassaemia should be done with proper planning, implementation and follow-up plan.

4. GENETIC COUNSELLING

- Thalassaemia is a single gene (monogenic) disorder. All thalassaemias are inherited in an autosomal recessive manner, and various compound heterozygosities with different abnormal alleles may occur, adding to the complexity and diversity of the disorder.
- Genetic counselling is therefore an essential and integral component in the comprehensive management of thalassaemia.

Genetic counselling:[38, level III]

- is a communication process of helping people understand and adapt to the medical, psychological and genetic contributions of a disease or condition so as to allow for informed decisions to be made with regard to the disease/condition or the risk of having a disease/condition. It includes -
  - interpretation of family and medical histories, and assessment of the likelihood of disease occurrence or recurrence
  - education about inheritance, testing, management and prevention of a disease/condition
  - provision of relevant support resources and research

Important ethical principles of genetic counselling emphasise on:

- the autonomy of the individual or couple
- the rights to complete, accurate information
- the respect for strict confidentiality of genetic information

4.1. Personnel Providing Genetic Counselling

Genetic counselling should be provided by qualified clinical geneticists or genetic counsellors. In view of the lack of these professionals, appropriately trained medical/nursing practitioners who are competent at providing information regarding all aspects of thalassaemia may also provide the counselling.[8; 39, level III]

Genetic counselling of the following groups of people is ideally done by a clinical geneticists or genetic counsellors:[8]

- at-risk couples seeking reproductive options (i.e. preconception and antenatal)
- individuals with unusual/complex carrier states

4.2. Persons Who Should Receive Genetic Counselling

All individuals offered genetic testing should receive a pre-test and post-test genetic counselling. Genetic counselling is directed towards adults and mature individuals, and should be offered to: [8; 39 - 40, level III]

- thalassaemia carriers detected via various screening opportunities -
  - population screening e.g. high school students in their teenage years
  - pre-marital screening
  - screening for married couples planning to start a family (pre-conception)
  - antenatal screening
  - opportunistic screening (e.g. individuals with abnormal FBC detected on routine test)
- affected thalassaemia individuals and/or parents/guardians at diagnosis (newly diagnosed)
- family members of an index case (thalassaemia patients or carriers) for cascade screening

- at-risk couples seeking counselling on reproductive options; both partners are carriers or have the disease, or one has the disease and the other is a carrier

The CPG DG opines that affected individuals (patients and carriers) diagnosed during childhood should receive genetic counselling when approaching adulthood and before starting their family. This should ideally be done again during transition of care.

4.3. Content of Genetic Counselling

The followings are important components to be discussed during genetic counselling of thalassaemia patients/carriers: [8; 41, level III]

- information about thalassaemia - nature of disease, symptoms, natural history and principles of treatment
- inheritance pattern, risk of having the condition and recurrence risk - refer to **Appendix 7** on **Risk of Inheritance Based on Carrier or Disease Status of Couples**
- genetic testing and description of the genetic test which includes -
  - purpose and nature of the test
  - implications of genetic testing
  - genetic testing process and procedure risks
  - effectiveness and limitations of the genetic test
  - potential outcomes of the genetic test and results interpretation
  - informed consent
- pedigree documentation, risk to family members and importance of cascade screening
- reproductive options to at-risk couples planning to start a family e.g. PND, Pre-implantation Genetic Testing and Mapping (PGT-M) and adoption
- other foreseeable consequences arising from genetic testing -
  - impact on insurability
  - employment
  - ethical and psychological concerns (e.g. stress, stigma, discrimination)
- psychosocial support and information on available resources and support groups

- The content of genetic counselling should be tailored to the needs of the person seeking counselling. Certain components of counselling may need to be emphasised based on the situation and where necessary, referral for further genetic counselling may be initiated.

4.4. Genetic Counselling on Reproductive Risk

Culturally-sensitive, non-directive genetic counselling is particularly important for at-risk couples so that they can make unbiased informed decisions relating to their reproductive choices. They should be counselled about the genetic risk and the options available for reducing it which include PND or pre-implantation genetic testing (PGT). Standard diagnostic methods for PND are via DNA analysis of the foetus obtained from chorionic villus sampling (CVS) or amniocentesis.

Four cohort studies involving centres with high β-thalassaemia carrier frequency reported successful reduction in affected newborns via preventive methods of PND or PGT as mentioned below.[42 - 45, level II-2]

- Formal genetic counselling and psychological support was provided to at-risk couples before testing to facilitate informed decision-making.
- Increasing number of PND performed over time was observed.

- Following informed parental choices, 96% - 98.4% of foetuses affected by β-thalassaemia major and 100% affected by Hb Bart's underwent termination of pregnancy (TOP).
- Increasing awareness and prevention strategies resulted in marked reduction in affected births.

Decisions for prenatal diagnosis and the selective abortion of an affected foetus is influenced by many factors besides the information a couple receive which include cultural, religious and social backgrounds and, personal beliefs and experiences.

In most cases, affected births stem from failure to adequately inform parents of the risk of thalassaemia and prevention rather than their rejection of foetal testing. Reproductive options for families affected with a transfusion-dependent thalassaemia major patient should be decided by the families themselves after genetic counselling.[8]

Genetic counselling supports decision-making at all stages.

Refer to **Subchapter 3.5** on **Pre-implantation Genetic Diagnosis** and **Subchapter 12.3(a)** on **prenatal diagnosis** for further information.

Recommendation 3
- Genetic counselling should be provided by trained professionals to thalassaemia patients and carriers*.
- Individuals offered genetic testing for thalassaemia should receive pre-test and post-test genetic counselling.

*refer to **Subchapter 4.2** on **Persons Who Should Receive Genetic Counselling**

5. BLOOD TRANSFUSION

Blood transfusion in thalassaemia generally aims to deliver a safe and effective transfusion regimen whilst minimising complications of transfusion therapy in order to maintain good quality of life.

The decision to start blood transfusion should be individualised. Particularly in NTDT, transfusion remains the ideal intervention only in specific clinical conditions.

Patients should be reviewed prior to each transfusion to determine pre-transfusion Hb levels and to ensure that the planned transfusion is appropriate.

Transfusion should be given in a proper clinical area and supervised by proper health personnel. Patients should be monitored closely during blood transfusion. For suspected acute transfusion reaction, the blood transfusion must be stopped immediately and resuscitation measures taken, and appropriate investigations must be carried out simultaneously to determine the cause of reaction.

For management of other transfusion reactions, refer to Transfusion Practice Guidelines for Clinical and Laboratory Personnel.

5.1. Leucodepletion

Regular blood transfusion remains the main conventional treatment modality for TDT. Frequent blood transfusion that contains leucocytes can contribute to some adverse reactions

e.g. febrile non-haemolytic transfusion reactions, Human Leucocyte Antigen (HLA) alloimmunisation of recipients and cytomegalovirus transmission. Reduction of leucocytes to ≤1x10^6/L per unit is considered the critical threshold in eliminating these reactions.[46, level III]

There are several methods for leucocytes filtration as discussed below.[1]

- Pre-storage filtration of whole blood provides high-efficient filtration, low residual leucocytes in processed red cells and high red cell recovery. Centrifugation of leucodepleted whole blood produces packed red blood cells (pRBC)
- Pre-transfusion laboratory filtration refers to the filtration of pRBC at the blood bank
- Bedside filtration refers to the pRBC unit that is filtered at the bedside during transfusion. This method may not allow optimal quality control because the techniques used for bedside filtration may be highly variable.

There is no retrievable evidence comparing pre-storage leucodepletion and bedside filtration method.

An RCT on pre-storage leucodepletion in β-thalassaemia major compared the techniques of red cell concentrate (RCC) which were:[47, level I]

- RCC-A - obtained by whole blood leucoreduction and subsequent plasma removal
- RCC-B - obtained by removing plasma and buffy coat first, followed by leucoreduction

The RCC-A was more effective in terms of:

- higher total Hb content by 9.4 g/unit (p<0.00001)
- higher average pre-transfusion Hb concentration (Cohen's d=0.792 g/dL, 95% CI 0.474 to 1.104)
- longer median transfusion interval (Cohen's d=0.800 days, 95% CI 0.481 to 1.112)
- lesser number of blood units transfused/year by 4.5 unit (Cohen's d= -1.609, 95% CI -2.023 to 1.188)

Thalassaemia International Federation (TIF) guidelines recommends the following.[1]

- Use leucodepleted packed red cells.
- Pre-storage filtration is strongly recommended but blood bank pre-transfusion filtration is acceptable.
- Bedside filtration is only acceptable if there is no capacity for pre-storage filtration or blood bank pre-transfusion filtration.

Recommendation 4

- Pre-storage filtration is the preferred choice for leucodepletion in thalassaemia.

5.2. Pre-transfusion Haemoglobin

There is no new evidence on pre-transfusion Hb target in TDT. Pre-transfusion Hb should be kept between 9 - 10 g/dL.[8] In those with heart disease, clinically significant extramedullary haematopoiesis or other medical conditions, higher target of 110 - 120 g/l (11 - 12 g/dL) is recommended.[1]

Volume of transfusion required is between 15 - 20 ml/kg which depend on the pre-transfusion Hb and haematocrit of pRBC provided by the blood bank (refer to **Table 2**). Whenever possible, the whole bag of blood should be used to prevent wastage and fresh blood of less than 14 days should be given.[8]

Table 2. Expected haemoglobin rise with haematocrit levels

Target increase in Hb	Haematocrit of donor red cells	
	60%	75%
1 g/dL	3.5 ml/kg	2.8 ml/kg
2 g/dL	7.0 ml/kg	5.6 ml/kg
3 g/dL	10.5 ml/kg	8.4 ml/kg
4 g/dL	14.0 ml/kg	11.2 ml/kg

Adapted: Ministry of Health, Malaysia. Management of Thalassaemia. Putrajaya: MoH; 2009.

Example: For a patient weighing 20 kg and has 360 ml transfusion every 4 weeks with average haematocrit 60% -

Annual blood requirement = 13 transfusion x 360 ml/20 kg = 234 ml/kg/year
Annual pure RBC requirement = 234 x 60% = 140.4 ml/kg/year
Annual transfusional iron loading = 140.4 x 1.08 = 152 mg/kg iron

Usual haematocrit level of Malaysian packed red cell ranges from 60 to 75%.

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

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

Post-transfusion Hb should be between 13.5 - 15.5 g/dL. It should be taken at least one-hour post-completion of the transfusion. Transfusion interval depends on pre- and post-transfusion Hb level and can be 2 - 4 weeks apart.[8]

Recommendation 5

- Pre-transfusion haemoglobin in transfusion dependent thalassaemia should be kept between 9 - 10 g/dL and a higher target of 11 - 12 g/dL should be aimed for patients with heart disease and clinical evidence of extramedullary haematopoiesis.

5.3. Auto- or Allo-antibodies and Blood Transfusion in Transfusion Dependent Thalassaemia and Non-Transfusion Dependent Thalassaemia

The development of RBC antibodies (both allo- and auto-antibodies) remains a major complication of RBC transfusion in thalassaemia patients. Studies showed the prevalence of allo-antibodies were between 5.64% and 42.5% while for auto-antibodies were between 5.0% and 28.2%.[48 - 50, level III]

Two local studies among thalassaemia patients showed the rate of allo-antibodies ranged from 10.15% to 11.4%.[51 - 52, level III]

Several factors influence the development of allo- and auto-antibodies.

- The significant risks of allo-antibodies development are age at first transfusion (risk higher in those who start transfusion later in life), splenectomy and transfusion of ≥20 units of blood.[48 - 50, level III]
- Risk of auto-antibodies development increases with higher numbers of blood transfusion (p=0.01).[50, level III]

Another group with high risk of alloimmunisation is pregnant women with NTDT who were never- or minimally-transfused.[4]

The most common antibodies observed in thalassaemia patients are those directed against antigen in the Rh and Kell blood group system.[48 - 50, level III]

In Malaysia, the most frequently detected allo-antibodies belong to Rh, Kidd and Duffy blood group system. The most common antibody found is anti-E. [51 - 52, level III]

In the local Transfusion Practice Guidelines for Clinical and Laboratory Personnel, baseline data for each potential multiply transfused patient shall be established before starting the transfusion programme. This involves:[53, level III]

- phenotyping of red cells, which should include Rh, Kell, Kidd, Duffy and MNSs
- screening for red cell antibodies

The use of extended antigen matched donor blood is effective in reducing the rate of allo-antibody development. The CPG DG opines that thalassaemia patients should receive antigen-matched blood for ABO, Rh, Kell, Kidd, Duffy and MNSs and any other antigen negative blood for defined antibody. RBC genotyping can be offered for investigation in TDT patients without baseline phenotyping or those with complex allo-antibodies. However, the results must be interpreted by taking into consideration the clinical and transfusion history, as well as the serological investigation results. Red cell auto-antibodies can cause haemolysis, crossmatching difficulties and increased transfusion rates. These patients need to be managed by a multidisciplinary team as they may require immunosuppressive drugs, splenectomy or alternative treatments.

Recommendation 6

- All thalassaemia patients should have full red cell phenotyping at diagnosis or prior to first transfusion consisting of ABO, Rh, Kell, Kidd, Duffy and MNSs
- Antigen matched blood for ABO, Rh, Kell, Kidd, Duffy and MNSs and any other antigen negative blood for defined antibody should be given to all thalassaemia patients.

5.4. Transfusion in Non-Transfusion Dependent Thalassaemia

Although transfusion independence is a characteristic of NTDT, ineffective erythropoiesis will lead to a multitude of subsequent pathophysiology including chronic anaemia.

TIF guidelines on NTDT recommend that initiation of transfusion therapy in NTDT should not be based on Hb level alone**.** Occasional blood transfusions should be considered in the following settings e.g. anticipated acute stress, Hb drop or blood loss in pregnancy, infection and surgery.[4; 54]

Apart from above, the guidelines also recommend considering more frequent transfusions in the following ineffective erythropoiesis-related complications, in a defined duration until a sustained clinical benefit is achieved:[4; 54]

- declining Hb level in line with profound splenomegaly (at a rate exceeding 3 cm/year)
- growth failure
- poor performance at school
- diminished exercise tolerance
- failure of secondary sexual characteristics development
- signs of bony changes
- frequent haemolytic crisis (Hb H disease)
- poor quality of life

Transfusions may be considered for the primary prevention (in high-risk populations) or secondary prevention of the following complications in NTDT:[55]

- thrombotic or cerebrovascular disease
- pulmonary arterial hypertension (PAH) with or without secondary heart failure
- extramedullary haematopoietic pseudotumour
- leg ulcers

A cross-sectional study showed that regularly transfused NTDT patients had fewer thalassaemia-related complications (mainly extramedullary haematopoiesis (EMH), PAH and thrombosis) while having a higher rate of iron overload-related endocrinopathy compared with occasionally transfused group.[56, level III]

NTDT patients are not reliant on transfusions for survival but transfusion has been shown to be protective against complications e.g. thrombosis, EMH, PAH, heart failure, cholelithiasis and leg ulcers in patients with NTDT.[57, level III]

In a small prospective cohort study, early regular blood transfusion therapy to maintain Hb 10 - 14 g/dL in moderately severe NTDT was shown to prevent diastolic dysfunction.[58, level II-2]

Recommendation 7
- In non-transfusion dependent thalassaemia patients:
  - occasional blood transfusion should be considered in acute stressful conditions
  - regular transfusion should be considered in the presence of ineffective erythropoiesis-related complications*

*Refer to the preceding texts.

6. ASSESSMENT OF IRON BURDEN

The rate of iron loading depends on volume of blood transfusion and gastrointestinal (GI) absorption of the iron. A unit of packed RBC from 420 ml of donor blood contains approximately 200 mg of iron or 0.47 mg/ml of whole donor blood. For packed RBC with variable haematocrits, the iron in mg/ml of blood can therefore be estimated from 1.16 x the haematocrit of the transfused blood product. Transfusion regimens which aim at keeping the pre-transfusion Hb above 90 g/L (95 - 105 g/L) or equivalent to 9.0 g/dL have been shown to prevent extramedullary haematopoiesis and reduce GI iron absorption.[1]

Iron burden can be assessed using serum ferritin, magnetic resonance imaging (MRI) and biopsy to determine iron content in a particular organ. Iron concentration needs to be monitored:[1]
- to assess the control of body iron
- to determine effective iron chelation regimes, tailored to individual specific needs

6.1. Serum Ferritin

Serial serum ferritin (SF) is the recommended method to assess iron burden in thalassaemia patients. It should be monitored 3 - 6 monthly in all patients.[8] A single SF level should be interpreted with caution as it may be influenced by many factors. The result should be considered with MRI liver and cardiac findings as there is no good correlation between these methods.

The summary of advantages and disadvantages of SF in the assessment of iron burden and treatment monitoring is shown below.[1]

Advantages	Disadvantages
Easy to repeat	Indirect estimate of iron burden
Inexpensive	Influenced by inflammation (increased)
Trend identification is possible with repeat samples	Non-linear response to iron load at high level
Long-term control linked to clinical outcome	Absence of changes does not exclude response to chelation
Useful for dose adjustment of chelation based on change in SF levels	Relationship to iron load varies with chelator
	Relationship to liver iron concentration differs in different diseases (e.g. hepatitis)

6.2. Magnetic Resonance Imaging

MRI is a useful, non-invasive tool for iron overload quantification in both TDT and NTDT. MRI T2* is a fast and easy technique to acquire, more sensitive to iron levels and reproducible over time with different scanners.

The strength of magnetic field applied by these scanners is measured in Tesla (T) unit. MRI machines with 1.5T are widely used for T2* technique with reliable accuracy based on standardised validation procedures. Measurement of liver and heart T2* using 3T MRI machine has good correlations with 1.5T values ($p<0.001$) in iron overload. However, 3T has greater susceptibility to artifacts and lower reproducibility trends causing difficulty in quantifying low T2* values with severe iron overload.[59, level III]

- It is necessary to measure both liver and cardiac iron separately using MRI T2* because studies have failed to show significant correlation between liver and cardiac iron overload by MRI.[8]

i. Cardiac iron assessment

The utility of cardiac T2* MRI was originally identified on the basis of shortened T2* values. Cardiac MRI (CMR) T2* should be done in patients with TDT from age 10 years onwards and T2* values of <20 ms indicate cardiac siderosis.[8] This test can be done at earlier age if patient is cooperative.

The severity of cardiac iron overload based on the cardiac T2* values and timing for repeat MRI are presented in the following table.[8]

Table 3: Cardiac MRI values and 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

Diagnostic studies had shown that black-blood T2* sequence had superior reproducibility and lower imaging artifacts than conventional white blood T2* technique.[60 - 61, level III]

The risk of developing heart failure and cardiac arrhythmia in thalassaemia increases significantly with the severity of cardiac iron overload based on cardiac T2* MRI.[62, level III]

In the presence of known cardiovascular (CV) abnormalities, symptoms suggestive of cardiac disease or abnormal findings during basic cardiac assessment, additional CMR sequences e.g. ventricular function analysis and myocardial tissue characterisation may be added.[1]

The use of cardiac T2* MRI in NTDT patients cannot be widely recommended. It may be considered in older patients with severe iron overload or as clinically indicated.[4]

ii. Liver iron assessment

In the past, liver biopsy was used as the gold standard for liver iron concentration (LIC) measurement to reflect body iron load. Normal individuals have LIC <1.8 mg/gm dry weight. However, liver biopsy is an invasive procedure and its result may be affected by sampling error e.g. in hepatitis or cirrhotic liver. An LIC >3 mg/mg dry weight may indicate iron overload and the need for chelation therapy.[8]

MRI T2* is a non-invasive method that replaces liver biopsy to quantify LIC, guide treatment and plan for follow-up. The severity of liver iron load based on the liver T2* values is shown in the following table:[63, level III]

Table 4: Liver MRI values of iron overload severity

Degree of liver iron load	Liver T2* Value (ms)	LIC (mg Fe/g dw)
Normal	>11.4	< 2
Mild overload	3.8 - 11.4	2 - 7
Moderate overload	1.8 - 3.8	7 - 15
Severe overload	<1.8	>15

The CPG DG opines that moderate to severe LIC should have repeat MRI T2* done annually after intensification of chelation.

Liver disease remains one of the leading causes of death in NTDT population. LIC levels ≥5 mg Fe/g dw are associated with a considerable risk of morbidity and mortality in both patients with β-thalassaemia intermedia and Hb E/β-thalassaemia.[4]

Recommendations by TIF guidelines on NTDT are:[4; 54]

- All patients with NTDT ≥10 years of age should be frequently assessed for iron overload status.
- Assessment of iron overload status in NTDT patients should be done through LIC or serum ferritin measurement as shown below.

Group of NTDT patients	LIC by MRI T2*	Serum Ferritin
All NTDT patients	Baseline at 10 years old	Baseline at 10 years old
Patients not receiving chelation therapy	Repeat 1 - 2-yearly	Repeat 3 - 12-monthly
Patients receiving chelation therapy	Repeat 6 - 12-monthly	Repeat 3-monthly

iii. Endocrine organs assessment

Diabetes mellitus, hypothyroidism, hypoparathyroidism and hypogonadotropic hypogonadism are complications of iron overload in the endocrine organs in thalassaemia. Research is being done to look at the usefulness of MRI in predicting endocrine complications or to identify the affected patients before irreversible damage.

Pancreatic iron is a predictor for alterations of glucose metabolism and cardiac iron in regularly transfused β-thalassaemia intermedia. A diagnostic study showed that the global pancreas

T2* <17.9 ms was able to predict an abnormal oral glucose tolerance test (OGTT) in TI with AUC of 0.61 (95% CI 0.53 to 0.69).[64, level III]

Growth and delayed puberty are sequalae of pituitary iron overload in thalassaemia. Diagnostic study showed that higher pituitary R2 values and smaller anterior pituitary volumes were found in young TDT patients (8 - 18 years old) with hypogonadism or short stature compared with those without the features. The pituitary R2 value of 22.85 Hz had an AUC of 0.864 in detecting iron overload in TDT patients.[65, level III]

Recommendation 8
- Serum ferritin level should be monitored every 3 - 6 months in all thalassaemia patients.
- Magnetic resonance imaging (MRI) T2* of the heart and liver should be done in all thalassaemia patients to assess iron overload.
  - MRI T2* using 1.5T scanner is the preferred choice.
  - It should be done at 10 years old or earlier if indicated.
  - Repeat MRI should be done accordingly and after intensification of iron chelation[#]

[#]refer to the relevant preceding texts

7. IRON CHELATION

Iron chelation aims to balance the rate of iron accumulation from blood transfusion by increasing iron excretion in urine and/or faeces with chelators. The effectiveness of chelation is closely related to the morbidity and mortality of thalassaemia population. Eliminating excessive amount of stored iron is crucial in preventing and reversing iron-mediated organ damage. Deferoxamine [also known as desferrioxamine (DFO)], deferiprone (DFP) and deferasirox (DFX) are currently the commercially available chelators in the market which can be used alone or in combination. However, the harms of chelation therapy must be weighed against their benefits, which are typically more prevalent when dosages are high compared with the degree of iron excess.

7.1. Iron Chelation in TDT

Optimisation of iron chelation therapy should be done to prevent and treat multiorgan complications of iron overload in thalassaemia patients e.g. cardiac, liver, endocrine organs and others.

a. Commencement on iron chelation therapy

- Generally, iron chelation therapy in thalassaemia patients starts after the first 10 - 20 blood transfusions, and/or when the SF level rises above 1000 ng/ml on >2 occasions at least two weeks apart.[1; 8]
- The target of iron chelation is to keep SF <1000 ng/ml, LIC <7 mg Fe/g dw liver and cardiac T2* >20 ms.[8]

Optimal threshold to start iron chelation therapy is yet to be determined. Therefore, it should be started after discussion with a paediatrician/physician. Careful monitoring of growth and bone development is advised. Commencement at a reduced dosage of chelators should be done if iron chelation therapy is started below three years of age. Adequate response to iron chelation therapy is reflected by a reduction in SF levels over time e.g. SF reduced by 1000 ng/ml over 12 months. Iron is removed from tissues at a slow rate and therefore decisions to change chelators should not be made on a single SF level.[1; 8]

A number of pharmacogenetic studies found various responses towards oral iron chelators (DFX and DFP) based on the inter-individual genetic differences which includes the effectivenss, toxicity and metabolism rate of the chelators.[66 - 68, level III]

b. Deferoxamine

DFO was the first developed iron chelator used in paediatric patients with iron overload since the 1960s. Currently, the treatment is given as slow subcutaneous infusion. Keeping the therapeutic index at <0.025 at all times avoids over chelation by DFO in compliant patients. Children under three years of age should refrain from using this chelator as it may retard bone growth and development.

$$\text{Therapeutic index} = \frac{\text{Mean daily dose (mg/kg)}}{\text{Serum ferritin (ng/ml)}}$$

$$\text{Mean daily dose} = \frac{\text{(Actual dose in each daily infusion x doses per week)} \div 7 \text{ days}}{\text{Body weight (kg)}}$$

In general, DFO monotherapy reduces serum ferritin (SF), liver iron concentration (LIC) and myocardial iron concentration (by MRI T2*) which in turn improves cardiac function caused by iron overload as discussed below.

Two meta-analyses on TDT showed that DFO was generally more effective in reducing SF and LIC by biopsy or SQUID (superconducting quantum interference device) compared with DFX. However, there were no significant differences in AEs between the two chelators except for raised serum creatinine, ALT and incidence of rash with DFX.[69 - 70, level I]

c. Deferiprone

DFP is one of the orally available iron chelators. The dose starts at 75 mg/kg/day divided into three doses and can be escalated up to 100 mg/kg/day according to response.

Previously, DFP was not recommended for children <6 years of age. A recent multicentre, open-label, non-inferiority RCT compared DFP to DFX in TDT patients aged one month to 18 years old with 59 subjects were aged <6 years old out of a total of 393. It showed that DFP was non-inferior to DFX in terms of effectiveness and safety. In a subgroup analysis of those <6 years old, there was NS difference in effectiveness between DFP and DFX. This suggested that DFP may be a possible option for TDT paediatric population.[71, level I]

Two large meta-analyses involving children and adults with TDT showed that monotherapy DFP had significantly better cardio-protective effect than monotherapy DFO in terms of:

- reduction in myocardial iron concentration by MRI T2* (MD= -0.35, 95% CI -0.63 to -0.08)[72, level I]
- significant improvement of LVEF[72 - 73, level I]

There was NS difference in AE between DFP and DFO monotherapies.[72, level I] However, the primary papers used in both meta-analyses were of low to moderate quality.

Severe but rare AEs e.g. agranulocytosis (ANC <500 x 10^3/L) and neutropenia (ANC <1500 x 10^3/L) were found in patients taking DFP. In the event of neutropenia, rechallenge is not recommended. While in the event of agranulocytosis, rechallenge is contraindicated.[74]

Compliance to DFP monotherapy was better than DFO monotherapy (ranging from 79 - 98%).[8]

The United States Food and Drug Administration recently approved a twice-a-day modified-release formulation of DFP for TDT patients. However, there is currently no RCT

demonstrating direct treatment benefits e.g. improvement in disease-related symptoms, functioning or increased survival.[74, level III]

d. Deferasirox

DFX currently comes in the form of film-coated tablets (FCT) with a dose between 14 - 28 mg/kg/day once daily. It is not recommended for children below the age of 2 years old.[8; 75, level III]

A meta-analysis of six RCTs comparing DFX dispersible tablets with DFO or placebo in TDT patients with iron overload found that DFX at 30 mg/kg/day was more effective than DFO in reducing LIC (MD= -2.50, 95% CI -4.55 to -0.45) and SF (MD= -377.57, 95% CI -488.65 to -266.50). However, DFO was more effective than DFX at other doses. On safety profile, DFX had higher serum creatinine (RR=2.69, 95% CI 1.98 to 3.67) and ALT (RR=5.67, 95% CI 1.01 to 31.79) with NS difference in rash and serious AEs between them.[69, level I] The meta-analysis used primary papers of mixed quality.

The higher cost of DFX compared with other iron chelators at present may be a hindrance to starting it as a first-line treatment.

Divided twice daily dosage of DFX may be beneficial in some patients. A small retrospective cohort study of TDT patients unresponsive or intolerant to once daily DFX and were changed to twice daily DFX of the same total daily dose showed a significant median decreased in SF after six months compared with baseline. No serious AEs were observed.[76, level II-2]

e. Combination/sequential therapy

Combination or sequential dosing of DFO with DFP is indicated when monotherapy fails. Three meta-analyses showed that combination or sequential dosing of DFO with DFP was more effective than monotherapy in improving ejection fraction, reducing LIC and reducing SF as discussed below. In the combination therapy, the DFP dose was at 75 - 100 mg/kg/day given daily and DFO at 40 - 50 mg/kg/day given 2 - 5 times per week. For sequential therapy, DFO was administrated alternately with DFP on different days of the week.[72 -73, level I; 77, level I]

The first meta-analysis involving children and adults with TDT on either combination DFP and DFO or monotherapy of DFP or DFO showed that combination therapy was better in terms of:[73, level I]

- improvement of LVEF (MD=5.67%, 95% CI 1.32 to 10.02)
- reduction in SF (MD= -0.36 mg/L, 95% CI -0.66 to -0.07)

Another two large meta-analyses compared combination or sequential DFP+DFO with monotherapy DFO, DFP or DFX in TDT patients of all ages and showed:

- greater SF reduction in sequential DFP+DFO than DFP monotherapy (MD=279.73, 95% CI 48.3 to 511.16)[72, level I]
- greater LVEF improvement in -
  - combination DFP+DFO compared with DFO monotherapy (SMD= -0.70, 95% CI -1.16 to -0.23)[72, level I]
  - combination DFO+DFP compared with DFP or DFO monotherapy (MD=3.37%, 95% CI 0.79 to 5.95)[77, level I]
  - sequential DFP+DFO compared with DFO monotherapy (MD=9.02%, 95% CI 6.40 to 11.64)[77, level I]
- mixed results in reduction of LIC -
  - combination DFO+DFP was more effective than DFP or DFO monotherapy (SMD= -1.06, 95% CI -1.54 to -0.58)[77, level I]
  - NS difference between combination DFP+DFO and DFO monotherapy[72, level I]

- NS difference in reduction of myocardial iron concentration between[72, level I]
  - combination DFO+DFP and other chelators as monotherapy
  - sequential DFP+DFO and DFO monotherapy
- DFO monotherapy had lesser AE compared with combination DFP+DFO (RR=1.46, 95% CI 1.04 to 2.04)[72, level I]

A double-blind RCT demonstrated that combination DFX+DFO significantly reduced myocardial iron by MRI T2* and SF compared with DFX monotherapy but not LIC. However, adversely this combination showed significantly higher total bilirubin.[78, level I]

A Cochrane systematic review showed that combination DFP+DFX was significantly more favoured than combination DFP+DFO in terms of adherence (RR=0.84, 95% CI 0.72 to 0.99). However, there was NS difference in safety profile between the two combination.[79, level I]

There is no retrievable evidence to support the use of combination of three iron chelators in thalassaemia.

Refer to **Algorithm 4** on **Iron Chelation in Thalassaemia** and **Appendix 8** on **Summary of Iron Chelators** and **Summary of Common Adverse Effects of Iron Chelators.**

Recommendation 9
- Optimisation of iron chelation therapy should be done to prevent and treat multiorgan complications of iron overload in thalassaemia patients.
- All transfusion-dependent thalassaemia patients with iron overload [serum ferritin (SF) >1000 ng/ml on two occasions at least two weeks apart] should receive iron chelation therapy.
  - It should be started after discussion with a paediatrician/physician.
- The target of iron chelation in thalassaemia should be SF <1000 ng/ml, liver iron concentration <7 mg Fe/g dw liver and cardiac T2* >20 ms.
- Combination iron chelation therapy in thalassaemia should be considered to optimise the therapy in cases of monotherapy failure.

For iron-chelation in pregnancy and fertility, refer to **Chapter 12**

7.2. Iron Chelation in NTDT

Ineffective erythropoiesis in NTDT patients leads to suppression of hepcidin levels which causes increased in both intestinal iron absorption and release of recycled iron from the reticuloendothelial system. These, with occasional or more frequent transfusions, result in iron overload in the patients.[80 - 81, level III]

A cross-sectional study showed that TI patients on iron chelation had lower risk of pulmonary hypertension (p=0.032), cholelithiasis (p<0.001), osteoporosis (p=0.001) and hypogonadism (p=0.001) compared with those not on iron chelation.[56, level III]

In an RCT comparing the effectiveness and safety of DFX (5 and 10 mg/kg/d) and placebo in NTDT patients ≥10 years of age with iron overload (LIC ≥5 mg Fe/g DW and SF ≥300 ng/ml), the former was significantly more effective in reducing LIC and SF at 52 weeks. The frequency of AE in patients receiving DFX was similar to placebo. The most common drug-related AE were nausea, rash and diarrhoea; most of which were of mild to moderate severity and resolved without discontinuing treatment.[82, level I]

A one-year extension of the above study showed further reduction in LIC and SF over two years. Safety profile of DFX was consistent with that seen in the core study.[83, level I]

A pre-post study on NTDT patients with iron overload showed that DFX at starting dose of 10 mg/kg/day, with dose escalations from week 4 (maximum 20 mg/kg/day) up to 30 mg/kg/day at week 24, significantly reduced LIC at week 52 compared with baseline. AEs were reported in 31.3% patients and were predominantly GI.[84, level II-3]

In a 5-year open-label trial between DFP vs DFO in NTDT, both treatments had a significant linear reduction in mean SF, but there was no significant difference between the groups. There was higher number of agranulocytosis and neutropenia in DFP group. Compliance rates were 85% and 76% in DFP and DFO groups respectively.[85, level I]

Recommendations from TIF guidelines for iron chelation in NTDT are:[4]

- DFX should be started in patients ≥10 years of age if:
  - LIC ≥5 mg Fe/g DW
  - SF level ≥800 ng/ml
  - SF level 300 - 800 ng/ml and other clinical or laboratory measures indicative of iron overload when LIC measurement is not possible
- starting dose of DFX film-coated tablets at 7 mg/kg/day
- dose escalations after one month are as below

Baseline LIC (mg Fe/g dw)	Baseline SF (ng/ml)	Dose escalation
5 - 7	800 - 1500	No escalation
>7 - 15	>1500 - 3000	Escalate to 11.5 mg/kg/day
>15	>3000	Escalate to 14 mg/kg/day

- dose escalations after six months are as below

LIC at six months (mgFe/g dw)	SF at six months (ng/ml)	Dose
3 - 7	300 - 1500	Same dose with maximum dose of 7 mg/kg/day
>7 - 15	>1500 - 3000	Escalate by 3.5 mg/kg/day (maximum 14 mg/kg/day)
>15	>3000	Escalate by 3.5 - 7 mg /kg/day (maximum 21* mg/kg/day)

*the dose is based on clinical expert opinion

- DFX should be discontinued when LIC ≤3 mg Fe/g DW or SF ≤300 ng/ml and patients should continue to be monitored for iron overload as indicated
- monitor AE as per local product prescribing information
- monitor closely compliance to iron chelation
- use of other iron chelators cannot be recommended yet
- encourage tea consumption as it may have some benefit in decreasing iron absorption from the gut
- NTDT patients who require regular blood transfusions should be managed as per guidelines for patients with TDT

Recommendation 10
- In patients with non-transfusion dependent thalassaemia:
  - iron chelators should be started at ≥10 years of age if liver iron concentration (LIC) ≥5 mg Fe/g dw or serum ferritin (SF) level ≥800 ng/ml
  - iron chelators should be temporarily discontinued when LIC ≤3 mg Fe/g dw or SF ≤300 ng/ml

Refer to **Algorithm 4** on **Iron Chelation in Thalassaemia** and **Appendix 8** on **Summary of Iron Chelators** and **Summary of Common Adverse Effects of Iron Chelators.**

8. COMPLICATIONS OF IRON OVERLOAD

8.1. Cardiovascular System

In thalassaemia patients, iron overload cardiomyopathy is caused by accumulation of iron in the myocardium.

- Cardiovascular (CV) complication is the leading cause of mortality in thalassaemia in Malaysia where the rate was 33.9% in 2020 as reported by the Malaysian Thalassaemia Registry.[6]

In populations with limited access to modern therapy, the burden of CV disease in thalassaemia remains high.[86, level III]

In a large meta-analysis of 142 studies on β-thalassaemia major, the overall prevalence of cardiac complications was 42%. The specific cardiac complications are listed in **Table 5** below.[86, level III]

Table 5: Cardiac complications in β-thalassaemia major

Cardiac complications	Prevalence
Iron overload (cardiac siderosis) (T2*<20 ms) • Mild-moderate (T2*=10 – 20 ms) • Severe (T2*<10 ms)	25% 26% 17%
Heart failure	9%
Arrythmias	10%
Diastolic dysfunction	34%
Systolic dysfunction	9%
Pulmonary hypertension	13%

The risk of developing cardiac complications and mortality is higher in patients with SF >2,500 µg/L. However, SF is not a sensitive predictor of CIO as cardiomyopathy and cardiac mortality have been reported with low ferritin levels.[8]

The onset of CIO can be as early as 8 - 10 years old although the risk is usually higher in the late teens and twenties.[1; 8]

a. Signs and symptoms

A high degree of clinical suspicion is necessary to identify thalassaemia patients with iron overload. Diagnosis can be very challenging in the early stages of the disease as patients may be asymptomatic, while severely overloaded patients can have terminal irreversible heart failure symptoms.

The common presentations of cardiac complications in thalassaemia are:[1]

- dyspnoea
- chest discomfort
- palpitation
- syncope or fainting
- lower limb oedema
- exercise intolerance

The presence of these symptoms warrants further CV evaluation.

b. Investigations

i. Electrocardiogram

Rhythm disorders which include conduction abnormalities and ventricular arrhythmias are associated with severe CIO. Studies on electrocardiogram (ECG) in thalassaemia patients showed that repolarisation abnormalities, heart rate variability and arrhythmias e.g. premature atrial ectopic, premature ventricular ectopic, atrial fibrillation and ventricular tachycardia were common findings.[87- 90, level III]

ECG and/or 24-hour ambulatory ECG are done in all thalassaemia patients, especially in those >10 years old.[8]

ii. Echocardiography

Echocardiography is the easiest way to evaluate diastolic left ventricular (LV) function/dysfunction in thalassaemia patients. It is the preferred alternative after CMR, and 3-dimensional is preferable to 2-dimensional because of improved longitudinal reproducibility.[91, level III]

A cohort study on conventional Doppler echocardiography and tissue Doppler imaging in TM patients compared with anaemic patients and healthy controls demonstrated that TM patients had more diastolic dysfunction as shown by significantly higher values of the following parameters:[92, level II-2]

- left atrium volume/BSA index
- mitral septal E/Em ratio
- duration of reverse pulmonary vein flow
- mitral E/A ratio

Left ventricular ejection fraction (LVEF) values are significantly higher in thalassaemia patients compared with healthy controls and LV function is usually preserved until an advanced stage. LVEF <56% indicates impaired myocardial function and, should prompt further evaluation of CIO by MRI T2* and intensification of chelation therapy.[8]

A cohort study on echocardiography in TM adult patients showed:[93, level II-2]

- reduction in LVEF ≥7% increased the risk of cardiac mortality (OR=4.93, 95% CI 1.61 to 15.11)
- reduction of LVEF ≥7% had AUC of 0.70 in detection patients at risk of mortality due to cardiac disease
- NS negative correlation between change in LVEF and SF levels (r= -0.11; p=0.22)

Myocardial deformation imaging by tissue Doppler and speckle tracking echocardiography is able to unmask subtle LV dysfunction in TM.[94 - 95, level III]

A meta-analysis looked at the use of global longitudinal strain (GLS) for the detection of CIO in thalassaemia patients. It showed:[94, level III]

- GLS was lower in patients with CIO compared with those without (WMD=1.6%, 95% CI 0.76 to 2.4) and normal population (WMD=2.2%, 95% CI 0.91 to 3.5)

- GLS < -19.5% had AUC=0.659 (95% CI 0.6 to 0.7) in predicting CIO
- GLS < -6% had 100% PPV for detection of CIO and GLS ≥ -24.5% had 100% NPV for detection of CIO

iii. MRI T2*

CMR T2* is currently the best available method for early detection of CIO and guide treatment. Refer to **Table 3** on **Cardiac MRI values and suggested schedule**.

A cross-sectional study of CMR in TM patients showed that 83% of patients who developed arrhythmia had cardiac T2* <20 ms and 98% of those who developed heart failure had cardiac T2* <10 ms.[62, level III]

MRI T2* should be done from the age of 10 onwards where possible and should be repeated 2-yearly if normal, yearly if the value is between 10 - 20 ms and 6-monthly if it is <10 ms.[8] Refer to **Table 3** on **Cardiac MRI values and suggested schedule**.

A retrospective cohort study on serial CMR in β-thalassaemia adults on iron chelation therapy showed that a 1% absolute increase in EF from baseline was significantly associated with a reduction in the risk of future development of heart failure for both the lower EF stratum (EF 56 - 62% with RR of 0.818) and the higher EF stratum (EF 63 - 70% with RR of 0.893).[96, level II-2]

c. Treatment

Treatment of CIO mainly aims to decrease body iron to the safest level by balancing iron uptake from blood transfusion with iron chelation therapy. Chelation therapy removes myocardial storage iron gradually (over months or years) and compliance is very crucial to ensure effective treatment.[1]

The previous MoH CPG on Thalassaemia recommends:[8]

- iron chelation monotherapy should be intensified or switched to combination therapy for asymptomatic thalassaemia patients with mild to moderate CIO and normal cardiac function
- continuous intravenous (IV) DFO is the best treatment option for thalassaemia patients with severe CIO or symptomatic cardiac disease; alternatively, combination therapy can be considered

MRI T2*-guided chelation therapy represents the best available approach to prevent cardiac dysfunction related to iron overload.[1]

A meta-analysis on amlodipine as adjuvant therapy to chelating agents in TM patients showed NS difference in cardiac T2* value between amlodipine and control.[97, level I] This is supported by a recent Cochrane systematic review on six RCTs, amlodipine plus standard iron chelation compared with standard iron chelation (alone or with placebo) have no effect on cardiac T2* and LVEF values at 12 months. The evidence was of low certainty.[98, level I]

i. Emergency therapy

Emergency therapy is required if a patient develops heart failure symptoms that need urgent modification of treatment which includes intensifying the chelation therapy.

A 24-hours continuous IV infusion of DFO is recommended in high-risk thalassaemia patients with decreased LVEF in overt heart failure as it can reverse iron-mediated cardiac dysfunction rapidly within weeks. DFO and DFP combination therapy is the best intensive chelation choice for TM patients with CIO with or without overt cardiac dysfunction or heart failure.[1]

Echocardiography assessment and cardiac T2* should be done as soon as possible to confirm the diagnosis of heart failure and screen for other causes of worsening cardiac function e.g. pulmonary embolism, myocarditis etc.[91, level III]

The summarised management of acute decompensated heart failure in TM is as follows.[91, level III]

- Commence continuous IV iron chelation treatment with DFO 50 mg/kg/day immediately.
- Introduce DFP as soon as possible at a dose of 75 mg/kg/day (the total dose given in three divided doses).
- Use supportive hemodynamic therapy with caution with the aim of maintaining cerebral and renal perfusion as blood pressure is typically low in TM patients.
- Use minimum diuretics because of the importance of maintaining cardiac preload.
- Introduce β-blockers as anti-failure treatment as they reduce the propensity to arrhythmia and may take priority over angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers as the latter are often compromised by causing a low blood pressure.

ii. Management of pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is more common in NTDT than TDT and is a cause of heart failure.

Annual echocardiographic screening for PAH during regular CV assessment is recommended. Tricuspid regurgitation velocity (TRV) >3 m/s warrants a diagnostic cardiac catheterisation for confirmation of PAH.[1]

PAH in β-thalassaemia was evaluated using confirmatory right heart catheterisation in a cross-sectional study which found:[99, level III]

- prevalence of PAH of 2.5% was 5-fold higher in TI compared with TM
- independent risk factors for confirmed PAH were age (OR=1.102 per 1-year increase, 95% CI 1.06 to 1.15) and splenectomy (OR=9.31, 95% CI 2.57 to 33.7)

Another cross-sectional study on NTDT revealed that:[100, level III]

- 9.2% of patients had PAH
- previous splenectomy, higher cumulative RBC transfusions (≥10 RBC transfusions), higher nucleated red blood cells (NRBCs) and a high non-transferrin-bound iron (NTBI) level were significantly associated with PAH
- NS correlation between LIC or SF and PAH

In an RCT, patients on regular blood transfusion had a greater reduction in pulmonary artery systolic pressure than those on occasional blood transfusion at 12 months (MD= -16.83, 95% CI -26.35 to -7.32). The 6-minute walk distance was also greater in those on regular transfusion (MD=46.55, 95% CI 18.08 to 75.02).[101, level I]

Another RCT on β-thalassaemia intermedia patients with PAH showed that, when compared with placebo, tadalafil significantly improved:[102, level I]

- TRV
- pulmonary artery systolic pressure
- parameters related to the systolic function of the right ventricle [tricuspid annular plane systolic excursion (TAPSE) and S]

A pre-post study on thalassaemia patients with PAH found that sildenafil:[103, level II-3]

- significantly decreased TRV by 13.3% and, improved LV end-systolic volume and diastolic volume
- had NS change in 6-minute-walk test distance
- was well tolerated, although minor expected AEs were commonly reported

d. Monitoring

Annual monitoring of CV system in thalassaemia patients from the age of 10 onwards include ECG, echocardiography and where possible MRI T2*.[8]

Apart from that, the following have been recommended:[1]

- CV assessment and management should ideally be performed by or in consultation with physicians with experience in CV disease in haemoglobinopathies and in close collaboration with the attending thalassaemia physician
- healthy lifestyle to ensure good CV health

e. Prevention

The main factors to prevent the complications of CIO are optimising the management of TDT including aiming for a pre-transfusional Hb of 10 g/dL, optimising iron chelation agents and targeting cardiac T2* value >20 ms. A healthy lifestyle is also crucial for the prevention of CV disease.[1]

Recommendation 11

- In transfusion-dependent thalassaemia (TDT), magnetic resonance imaging (MRI) T2* should be done from the age of 10 years old:
  - to assess and monitor* cardiac iron overload
  - to guide iron chelation therapy
- Continuous intravenous deferoxamine in combination with deferiprone should be considered in TDT with overt heart failure.

***Refer to **Table 3** on **Cardiac MRI Values and Suggested Schedule**.

8.2. Liver Disease

The improved survival in thalassaemia patients has brought to the attention of associated long-term complications e.g. liver cirrhosis and hepatocellular carcinoma (HCC). Liver cirrhosis in thalassaemia is contributed by a few main factors e.g. iron overload or infection. Despite improved screening of blood products for hepatitis viruses, improved hepatitis B vaccination, hepatitis virus eradication and accessibility of iron chelation, the cumulative effect of iron overload increases the thalassaemia patients' risk of HCC.[104, level III]

This subchapter will cover liver iron overload and liver cancer. The liver infection is covered in **Subchapter 9.1** on **Transfusion-related Infection**.

a. Iron overload/hepatic siderosis

The liver plays a central role in iron homeostasis. About one-third of iron in the body is found in the liver and approximately 98% of liver iron is found in hepatocytes. Iron, in excess of the requirements of the organs and various metabolic processes, is stored in the hepatocytes, heart and endocrine tissues.[105, level III]

Progressive accumulation of storage iron is associated with cellular toxicity, although the specific pathophysiologic mechanisms for hepatocyte injury and liver fibrosis are not entirely understood.[106, level III]

b. Assessment and monitoring

Quantification of hepatic iron load can be a reliable index for the total body iron pool.[107, level III] There are various methods in assessing liver iron load including liver biopsy, SF, MRI scan and transient elastography (TE).

i. Liver biopsy

Liver iron quantification by needle biopsy sample was regarded as the gold standard. However, the invasive nature of biopsy procedure, sampling error and variation in tissue processing make it less favourable now.[108, level III]

ii. Serum ferritin

SF generally correlates with total body iron stores. A diagnostic study to determine cut-off point in diagnostic test values of SF test on liver haemosiderosis showed:[109, level III]

- a cut-off point of 1090 ng/ml in SF gave a sensitivity of 66.7% (95% CI 60.1 to 72.8), specificity of 68% (95% CI 57.8 to 77.1), PPV of 82.9% (95% CI 76.6 to 88.1), NPV of 46.8% (95% CI 38.4 to 55.4) and AUC of 0.68 (95% CI 0.63 to 0.73) for liver haemosiderosis
- SF levels >1090 ng/ml was associated with increased risk of liver haemosiderosis (OR=3.93, 95% CI 2.02 to 7.64)

Serial SF is the method of choice to assess iron burden in thalassaemia patients and it should be monitored 3 - 6 monthly in all patients.[8] Refer to **Subchapter 6.1**. on **Serum Ferritin**

iii. MRI

MRI is now widely used for liver iron evaluation and can be considered the standard of care where available. MRI T2* is a non-invasive method that replaces liver biopsy to quantify LIC, guide treatment and follow-up.[1] Refer to **Subchapter 6.2.(ii)** on **Liver Iron Assessment**. The CPG DG opines that MRI of the liver in TDT patients should be done together with cardiac MRI from the age of 10 years old.

iv. Transient elastography

TE of the liver is an established tool to measure liver stiffness, mainly in the assessment of hepatic fibrosis. Its role in estimation of iron overload in thalassaemia patient has been studied in several studies.

A diagnostic study comparing liver stiffness measurement (LSM) by TE with MRI T2* and SF in detecting liver iron overload (LIO) in thalassaemia major showed:[110, level III]

- strong positive linear correlation between LSM and MRI R2* ($r=0.85$, $p<0.001$)
- poor correlation between LSM and SF ($r=0.19$, $p=0.11$)
- LSM>13.5, 7.8 and 5.5 kPa predicted severe, moderate and mild LIO with AUC of 94.8% (95% CI 0.91 to 0.98), 84.5% (95% CI 0.78 to 0.90) and 84.7% (95% CI 0.77 to 0.91) respectively

A retrospective cohort study of all transfusion-independent adults with β-thalassaemia intermedia evaluated the effect of longitudinal changes in SF levels on measures of hepatic fibrosis through TE and found:[111, level II-2]

- median TE value increased in non-chelated patients (4.4 to 5.7 kPa, $p<0.001$) while it decreased in those receiving chelation therapy (7.0 to 4.7 kPa, $p=0.005$) over two years
- strong correlation between rate of change in SF and TE value ($R^2=0.836$, $p<0.001$); noted in both non-chelated ($R^2=0.806$, $p<0.001$) and chelated patients ($R^2=0.758$, $p<0.001$)

Apart from iron overload, an elevated liver stiffness measurement may be observed in other conditions e.g. viral hepatitis, liver congestion or liver tumour. Hence, an abnormal LSM should prompt further investigations for the underlying cause.

TIF guidelines on TDT recommends the following with regards to monitoring of liver iron overload.[1]

- SF should be regularly monitored and is most useful in identifying trends.
- SF level should be maintained at <1000µg/L.
- MRI R2 or R2* is the method of choice to assess LIC and monitor the effectiveness of chelation therapy.

c. Prevention/Treatment

TIF guidelines on TDT states that DFO, DFP and DFX are effective in decreasing total body iron burden as well as LIC.[1]

Recommendation 12

- To assess liver iron overload (LIO) in thalassaemia patients, the following should be done:
  - serum ferritin
  - magnetic resonance imaging (MRI) of the liver from 10 years of age
- Transient elastography may be used to assess LIO when MRI is not available.

d. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) has been increasingly recognised as one of the liver complications in thalassaemia patients. A multicentre study in Italy has recorded a cumulative incidence of 1.02% among thalassaemia patients.[112, level III] The median age at HCC onset in thalassaemia patients is younger at <50 years compared with 70 years in the general population. Few studies have recorded more frequent occurrence of HCC among TI than in TM. [112 - 114, level III]

Iron overload and viral hepatitis with or without cirrhosis are established risk factors for the development of HCC in these populations of patients.

i. Screening and surveillance

Screening for HCC offers early detection of the disease which can improve survival. Ultrasonography (USG) of the liver and serum alpha-fetoprotein (AFP) are used in screening of HCC. However, there is no direct evidence on screening/surveillance of HCC in thalassaemia patients.

A meta-analysis of 15 studies on patients with liver cirrhosis for the detection of early-stage HCC as defined by Milan criteria showed USG with AFP vs without AFP detected early-stage HCC with 63% sensitivity (95% CI 48% to 75%) and 45% sensitivity (95% CI 30% to 62%) respectively.[115, level III]

A cohort study of HCC patients from Taiwan on the role of AFP in HCC surveillance showed that 10.9% patients with elevated AFP levels >20 ng/ml had undetectable early HCC on USG.[116, level II-2]

Thalassaemia patients should have HCC screening as follows: [1, 4; 54]

- biannual USG abdomen with AFP in cirrhotic patients
- biannual USG abdomen with AFP in TDT patients with high risk factors e.g. HCV and/or HBV infection, LIC ≥7 mg Fe/g DW or SF ≥1000ng/ml
- annual USG abdomen with AFP in NTDT patients with high risk factors e.g. HCV and/or HBV infection, LIC ≥5 mg Fe/g DW or SF level ≥800 ng/mL

Any abnormal screening results warrant further evaluation by a gastroenterologist.

ii. Treatment

Because of limited data, the treatment of HCC in patients with thalassaemia is primarily based on experience in non-thalassaemia patients.

Treatment strategies according to stage of HCC and severity of liver disease used for the treatment of HCC in the general population (i.e. surgical resection, transarterial chemoembolisation, percutaneous radiofrequency ablation and ethanol injection) have been used with success.

8.3. Endocrinopathies and Osteoporosis

Over the years, advances in the knowledge of pathophysiology and medical therapies in TDT have resulted in a considerable increase in patients' survival. However, endocrine dysfunction e.g. disturbances in growth and pubertal development, impaired gonadal, thyroid, parathyroid and adrenal functions and, abnormal glucose homeostasis and bone metabolism remain commonly encountered complications. It is principally attributed to excessive iron overload and suboptimal chelation.[117, level III] The prevalence varies because of the different levels of treatment followed by centres across the world, particularly severity of defective genetic background, Hb concentration and degree of iron overload in various patient groups.[1]

Thus, early detection and institution of appropriate transfusion regimen and chelation therapy as well as treatment of complications are the keys to managing these patients including regular follow-up. This subchapter covers common endocrine complications encountered in thalassaemia.

a. Short stature and growth failure

Prevalence of short stature varies from 30 to 60%.[118, level II-2; 119, level III] Short stature is more prevalent in those above the age of 10 years.[1; 120, level III]

The pathogenesis of growth failure in thalassaemia is multifactorial. It has been attributed to chronic anaemia and hypoxia, transfusion-related iron overload, chronic liver disease, nutritional deficiencies, intensive use of chelating agents, emotional factors and endocrinopathies [hypogonadism, delayed puberty, hypothyroidism, disturbed calcium homeostasis, bone disease and impaired growth hormone (GH) - insulin-like growth factor 1 (IGF-1) axis].[1; 120, level III]

Assessment of a child with thalassaemia who has growth failure is generally similar to that of a child without it.

Growth failure is defined as:[121, level III]

- height less than third percentile for age and gender
- significantly short for the family [≥10 cm below mid-parental height (MPH)] - refer to **Appendix 9A** on **Mid-Parental Height Calculation** for calculation of MPH
- slow growth rate observed over a period of six months to one year
- downward crossing of height percentiles on growth chart (after the age of 18 months)

Average height velocity at different phases is as below:[121, level III]

- prenatal: 1.2 - 1.5 cm/week
- infancy: 23 - 28 cm/year
- childhood: 5 - 6.5 cm/year
- puberty: 8.3 cm/year (girls), 9.5 cm/year (boys)

Serial measurement of growth parameters is suggested every 4 - 6 months including assessment of standing and sitting height (alternatively upper and lower segment ratio

measurement). A reliable stadiometer (ideally Harpenden) is the gold standard tool for accurate height measurement. Pubertal assessment can be done using Tanner staging.[8; 121 - 122, level III]

It is important to detect other causes of short stature (as mentioned above) in thalassaemia patients. Additional endocrine tests that will be done include thyroid function tests, serum calcium, phosphate, magnesium and zinc, alkaline phosphatase and OGTT. For patients within pubertal age, gonadotropins and sex steroids should be measured. Other useful tests are IGF-1 (with IGF binding protein-3 if available) and bone age assessment.[8; 123, level III] The CPG DG opines that pubertal age refers to age >10 years. In subjects with disproportionate short stature, radiographs of the hand, wrist, tibia and spine are done to exclude the presence of platylospondylosis or metaphyseal cartilaginous dysplasia changes.[1]

For short children with suspected growth hormone deficiency (GHD), other tests that are normally done in the referral or tertiary centres include two GH stimulation tests (using two different pharmacological agents) and anterior pituitary function tests.[124; 125]

Children with β- thalassaemia major frequently have growth retardation in the presence of low serum IGF-1 and a normal GH response to pharmacological stimulation suggesting that they have GH insensitivity.[1; 8; 117, level III]

Management of growth failure should include addressing the multifactorial causes of short stature in thalassaemia patients as mentioned above.[1; 8; 117, level III] After confirmation of GHD and correction of other factors for growth failure, GH therapy may be considered. Recombinant human GH is a safe mode of treatment in thalassaemia children. However, there is limited evidence that the final height may improve.[126, level I]

b. Delayed puberty and hypogonadism

Delayed puberty and hypogonadism in β-thalassaemia major patients are caused by iron deposition mainly in the pituitary gland [hypogonadotropic hypogonadism (HH)] followed by gonads or both. The prevalence of pubertal disorders and hypogonadism in patients with thalassaemia is up to 40% and 80% respectively in various studies.[127; 128, level II-2]

Pubertal disorder in thalassaemia patients may present in three ways. In delayed puberty, there is a complete lack of pubertal development by 13 years of age in girls and 14 years in boys. On the other hand, hypogonadism is defined as the absence of testicular enlargement (<4 ml) in boys and breast development (thelarche) by the age of 16 years in girls. In the third condition, arrested puberty is characterised by a lack of pubertal progression over one year or more. The testicular size remains 6 - 8 ml and breast size at Tanner stage 3. In such cases, the annual growth velocity is either markedly reduced or completely absent.[1]

- It is recommended that all thalassaemia patients with pubertal disorder be referred to a paediatric endocrinologist for diagnostic work-up and therapeutic management.[129; 127; 1] Thus, healthcare providers are discouraged from starting oral combined hormone therapy at presentation.

Screening of pubertal disorder may be done using:

- Tanner staging – should be determined 6-monthly from the age of 10 years[8]
- Orchidometer – should be used for the assessment of testicular volume

Refer to **Appendix 9B** on **Tanner Staging and Orchidometer.**

Patients with pubertal disorder require the following investigations: [1; 127; 129]

- Thyroid function tests [thyroid stimulating hormone (TSH) and free thyroxine (FT4)]

- Luteinising hormone (LH)/Follicle stimulating hormone (FSH) and oestradiol in girls or testosterone in boys
  - Low basal FSH and LH for age suggest HH
  - Elevated FSH and LH suggest primary hypogonadism (very rare)
- X-ray of left hand and wrist [anteroposterior (AP) view] to determine bone age
- Pelvic USG for assessing ovarian and uterine maturation

Treatment for girls with delayed puberty at 13 years of age is as follows. [1; 8; 127; 129; 130]

- It is important to induce puberty gradually over 2 - 3 years to allow adequate development of secondary sexual characteristics and feminisation before attainment of menarche.
- Low dose oestrogen in the following preparations may be used for pubertal induction:
  - 17-β oestradiol (transdermal or oral)
  - oestradiol valerate
  - ethinyl oestradiol
  - conjugated oestrogen
- Pubertal induction should be continued for 3 - 6 months and stopped for reassessment (Tanner staging) after that to differentiate between constitutional delay of growth and puberty (CDGP) and HH.
- If spontaneous puberty does not occur within six months after stopping treatment, oestrogen is reintroduced gradually in increasing dosages until full replacement doses within 2 - 3 years.
- Cyclical oral progesterone (e.g. medroxyprogesterone acetate, micronised progesterone, dydrogesterone or norethisterone) is added for 12 days every month after full oestrogen replacement to ensure cyclical endometrial shedding and decrease the risk of endometrial dysplasia.
- Monitor response to oestrogen therapy through the evaluation of pubertal stage, height growth, changes in dimensions of uterus and ovaries, and bone age.
- Change pubertal induction treatment regimen to full adult replacement therapy at the end of pubertal induction.

Treatment for boys with delayed puberty at 14 years of age is as follows.[1; 8; 127; 129; 130]

- It is important to induce puberty gradually over 2 - 3 years to allow adequate development of secondary sexual characteristics.
- Low dose IM depot testosterone esters (25 mg) is given monthly for 3 - 6 months and stopped for reassessment (testicular volume) after that to differentiate between CDGP and HH.
- If spontaneous puberty does not occur within six months after stopping treatment, IM depot testosterone esters may be reintroduced at a dose of 50 mg and gradually increased every 6 - 12 months until full replacement dose of 200 mg over 2 - 3 years. Adult dosing is 200 - 250 mg every 2 - 4 weeks.
- Other hormonal preparations that may be used is transdermal testosterone gel
- Monitor response to testosterone therapy through evaluation of pubertal stage, height growth and bone age.

Men with thalassaemia who have low or falling BMD should be evaluated for hypogonadism.[130] Male adult patients should have annual screening for hypogonadism by assessment of serum testosterone and gonadotrophins (FSH and LH) levels.[127]

c. Diabetes mellitus

Impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and insulin-dependent diabetes mellitus (IDDM) are relatively common abnormalities of glucose homeostasis in TM patients who have been inadequately iron chelated.[131, level III]

Abnormality of glucose homeostasis begins with iron-mediated insulin resistance rather than defective insulin production. Subsequently, pancreatic β-cell damage and insulin deficiency will develop as a result of direct toxic damage from iron deposition.[1]

The risk factors associated with IGT are male, poor compliance with DFO therapy and LIC four times above the normal value. Liver disorders and a positive family history of diabetes mellitus (DM) are additional predisposing factors.[131 - 132, level III]

In addition to the above risk factors, other factors associated with DM are delayed age at the start of chelation therapy, liver cirrhosis or severe fibrosis and hepatitis C infection.[131 - 132, level III]

A large meta-analysis found the rate of DM at 6.54% (95% CI 5.30 to 7.78), IFG 17.21% (95% CI 8.43 to 26.00) and IGT12.46% (95% CI 5.98 to 18.94) in TM.[128, level II-2] In a local study, 13.8% of TDT patients had glucose abnormalities on OGTT at a median age of 16.8 (range 11.4 to 20.1) years.[133, level III]

The onset of DM is often associated with the presentation of cardiac dysfunction and high risk for additional complications e.g. thyroid dysfunction or hypogonadism.[131 - 132, level III; 134, level III]

Early detection of glucose abnormalities is important as prediabetes and clinical diabetes can potentially be prevented or reversed with optimum chelation treatment. [8; 132, level III] OGTT remains the gold standard test for assessing glucose homeostasis and TIF guidelines recommends it should be done in every patient with thalassaemia after the age of 10 years or earlier if needed.[1] However, a systematic review found that most of the international guidelines recommend a fasting glucose every 6-monthly. If it is ≥5.6 mmol/L, OGTT can be considered. The diagnosis of DM is made based on the same established criteria for the general population with the exception of HbA1C in transfused patients.[135 - 136, level III]

Treatment of IGT and DM in TDT patients include the following:[1; 131, level III]

- intensive iron-chelation therapy
- individualised management of DM
- healthy diet
- regular physical activity
- oral antidiabetic agents (limited evidence on effectiveness and safety)
- when overt IDDM develops, patients require daily subcutaneous injections of insulin
- prevention and treatment of chronic hepatitis C infection
- regular specialised multidisciplinary team review with expertise in both DM and TM which includes endocrinologist and dietician

d. Hypothyroidism

Hypothyroidism in thalassaemia is mainly attributed to iron overload and is uncommon in optimally treated patients.[128, level III] Majority of patients have primary thyroid dysfunction. Central hypothyroidism is uncommon.[137, level II-2] The prevalence of hypothyroidism in TM patients ranges from 4% to 29%.[138, level III] Subclinical hypothyroidism is more prevalent than overt primary hypothyroidism. [117, level III; 119; level III]

The median age at diagnosis of overt hypothyroidism in TDT patients is 14.5 years, while that of subclinical hypothyroidism is 15.7 years.[133, level III] Central hypothyroidism occurs in 4.8% of adults and only 0.5% of children and adolescents.[139, level III]

Symptoms and signs of hypothyroidism are usually non-specific. The patients may be asymptomatic despite abnormal thyroid function. Hence, regular screening of thyroid function is needed for early detection of this condition.

Screening of thyroid function (includes measurement of serum TSH and free T4) should be performed annually, beginning at the age of 9 - 12 years or earlier if symptomatic.[1; 9; 140, level III]

Guidelines recommend that overt and central hypothyroidisms to be treated with levothyroxine (L-thyroxine). In subclinical hypothyroidism with elevated serum TSH level but <8 mU/L, chelation should be intensified and the patient carefully monitored. The decision to start treatment in subclinical hypothyroidism should be individualised, considering various factors e.g. age, TSH levels and clinical presentation. Treatment with L-thyroxine should be started when TSH >10 mU/ml.[1; 123; 141, level III]

e. Hypoparathyroidism

Hypoparathyroidism is a late complication of iron overload, typically manifesting in the second decade of life in TDT patients. Its prevalence varies from 1.2% to 32 %.[119, level III; 142 - 143, level III] A majority of patients have mild form of disease. They may be asymptomatic at diagnosis or present with paraesthesia and/or muscle cramps. More severe cases may present with tetany, seizures, ECG changes or cardiac failure.[142, level III; 144, level III]

Annual screening is suggested from the age of 10 years onwards.[8; 127; 144, level III;] Screening for hypoparathyroidism includes measurement of serum (corrected) calcium, serum phosphate, serum magnesium and serum alkaline phosphatase. In patients with low serum calcium and high phosphate levels, serum parathyroid hormone (PTH) level should be measured. The diagnosis is based on low serum calcium, high phosphate and low or inappropriately normal PTH levels.[8; 144, level III]

The aim of treatment is to place the corrected calcium at the lower limit of the normal range to avoid complications of hypercalciuria and subsequent nephrocalcinosis.[1]

- Calcitriol is usually needed to normalise plasma calcium and phosphate levels. This is accompanied by regular monitoring of serum and urine calcium levels.
- In patients with persistent high phosphate levels, phosphate binders (e.g. calcium carbonate) may be considered.
- Calcium supplements may be offered to patients with poor dietary intake.

f. Adrenal insufficiency

Iron overload may result in adrenal dysfunction by affecting the hypothalamic-pituitary adrenal axis at the hypothalamic or pituitary and/or adrenal level. Several studies reported a significant prevalence of 'biochemical' adrenal insufficiency in patients with thalassaemia up to 45%. However, they are usually asymptomatic. 'Clinical' adrenal insufficiency, i.e. adrenal crisis, on the other hand is extremely rare.[123, level III; 145, level III]

Screening for adrenal insufficiency should be performed annually, starting after the age of 10 years, especially those with other endocrinopathies.[1; 146, level III]

Morning baseline cortisol level (8 - 9 a.m.) can be used to detect subtle adrenal insufficiency. In view of constant stress experienced by TM patients, a higher cut-off point should be used. Adrenal insufficiency can be excluded if morning baseline cortisol is >400 nmol/L.[127; 130] Due to the lack of conclusive scientific evidence, the CPG DG suggests to use cortisol cut-off <200 nmol/L as an indication for adrenocorticotropic hormone stimulation test.

Subclinical adrenal insufficiency in patients with TM may develop into acute adrenal crises during stressful events and should be promptly given a stress dose of hydrocortisone as a life-saving treatment.[1]

Recommendation 13

- Growth of thalassaemia children and adolescents should be assessed every six months with accurate measurement.
  - Those with short stature should be further assessed and screened for growth hormone deficiency after excluding other common causes of short stature.
- Transfusion-dependent thalassaemia (TDT) patients aged more than 10 years should be monitored every 6-monthly for:
  - pubertal disorder by Tanner staging; those with pubertal disorder should be referred to a paediatric endocrinologist.
  - fasting blood sugar; if the value is ≥5.6 mmol/L, oral glucose tolerance test is indicated.
- TDT patients aged more than 10 years should be monitored annually for:
  - hypothyroidism
  - hypoparathyroidism
  - hypoadrenalism especially those with other endocrinopathies

g. Bone disease

Bone abnormalities are common in thalassaemia and may present as:[128, level III; 147, level III]

- growth retardation
- spontaneous fractures
- skeletal deformities
- decreased bone mineral density (BMD)
- arthropathies
- disc degeneration
- spinal deformities with compression of the vertebrae and nerves (often causing severe back pain)

Low BMD is seen in a high proportion of adults with TM despite regular transfusions and iron chelation therapy.[148, level III] It often develops as early as the second decade of life and its prevalence increases with age. A study revealed that the prevalence of low bone mass (Z-score ≤ -2) in patients with TM was low at 8.8% for those aged 6 - 10 years, 43.6% in patients aged 11 - 19 years and 60.5% for those ≥20 years.[149. level III]

In a narrative review on TM patients with a mean age of 16.0 - 30.8 years, the prevalence of fractures ranged from 16% to 49%.[150, level III] Another study on thalassaemia syndromes found that the prevalence of fracture was highly dependent on age i.e. 2.5% in patients of 0 - 10 years old, 7.4% in those 11 - 19 years old and 23.2% in patients >20 years old. These data indicated that fractures remained a frequent complication among older thalassaemia patients.[151, level III]

There are multiple predisposing factors to low BMD which include inadequate transfusion, AE of chelation, genetic predisposition, chronic liver disease, vitamin D deficiency, zinc deficiency and endocrine disorders.[148, level III; 152 - 153, level III] The prevalence of vitamin D deficiency and insufficiency is reported to be high at 30 - 90% in thalassaemia.[154, level III] Zinc deficiency has been reported in 84.8% of thalassaemia patients aged 10 - 20 years while 44.7% have severely low levels.[8]

Dual Energy X-ray Absorptiometry (DXA) is the gold standard for the measurement of BMD.[1; 155] BMD is reported as a T-score or Z-score using units of standard deviation (SD). T-score is used for post-menopausal women and men >50 years old while Z-score should be used for premenopausal women, men <50 years old and children. T score of -1 and above is normal bone density while Z score of > -2 is within the expected range for age. Refer to the Malaysian CPG Management of Osteoporosis 2022 for further information.[155]

- The diagnosis of osteoporosis in children should not be made on the basis of densitometric criteria alone.
- The presence of at least one vertebral compression fracture is indicative of osteoporosis, in the absence of local disease or high-energy trauma. In the absence of the fracture, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture* history and a BMD Z-score ≤ -2.0 (adjusted for height, age and sex as appropriate to avoid overdiagnosis)
- BMD/BMC Z-score > -2.0 does not preclude the possibility of skeletal fragility and increased fracture risk.[156, level III]

*In a child with a known risk factor for bone fragility, a low trauma long bone fracture is considered a clinically significant fracture. In chronic illness, low trauma is defined as falling from a standing height or less at no more than walking speed.[157 - 158, level III]

Assessment of bone health in TM patients should commence at the age of 10 years and based on the following investigations:[1; 153, level III]

- serum calcium, phosphate, alkaline phosphatase (ALP)
- 25-OH Vitamin D
- parathyroid hormone
- serum zinc
- 24-hour urinary calcium; CPG DG suggests initial screening with early morning urine calcium:creatinine ratio if 24-hour urine collection is not feasible
- spinal radiograph (AP and lateral views)
- MRI scan of the spine - may be considered for patients with severe back pain
- bone turnover markers (includes at least 1 bone formation and 1 bone resorption markers) if available

Performing DXA scans on children with thalassaemia is challenging. Besides, there is a lack of evidence to support the treatment of low bone mass in children. Taking these factors into consideration, screening of bone health using BMD measurement by DXA scan should start at completion of puberty and repeated every 2 - 3 years.[130]

Peak bone mass is only achieved when an individual is in their late 20s and thus emphasis on maximising the opportunities to achieve this peak is advocated.[130]

Prevention and treatment of early bone loss in thalassaemia include the following:[1; 130; 148, level III]

- periodic checking of BMD starting in adolescence
- all patients should be advised on lifestyle changes -
  - adequate vitamin D and calcium intake
  - avoidance of smoking and excessive alcohol consumption
  - weight bearing exercise

Most of the time, thalassaemia patients do not meet the daily requirement intake for vitamin D and calcium. Therefore, low dose supplementation of vitamin D and calcium is recommended. Refer to **Appendix 10** on **Micronutrients Supplementation and Assessment Strategy Recommendations for Thalassaemia Patients.**

Supplements are advised in the following insufficiency:

- Vitamin D
  - Oral vitamin D supplement if serum vitamin 25-OH D is <20 ng/ml (50 nmol/L) to target a vitamin D level of 75 - 80 nmol/l; serum 25-OH D level is monitored every three to six months in patients on high-dose supplementation[148, level III; 154, level III]

- Calcium
  - low dose calcium supplement is preferred and if higher doses are needed, this is divided into 2 - 3 individual doses over a 24-hour period[148, level III]
- Zinc
  - supplementation when serum plasma zinc ≤70 µg/dL[153, level III]

Other interventions to prevent and treat early bone loss include:[1; 130]

- optimisation of thalassaemia treatment which includes adequate iron chelation and blood transfusion; the recommended DFO dose in childhood should not be exceeded to minimise the risk of bone toxicity or reduce height velocity
- prompt diagnosis and appropriate treatment with hormonal therapy of hypogonadism, diabetes mellitus and other endocrinopathies

A Cochrane systematic review showed that bisphosphonates significantly increased BMD at the femoral neck and lumbar spine compared with placebo over two years' therapy in adult thalassaemia patients with low BMD. Back pain was significantly better in the neridronate group compared with placebo at 3 - 12 months. Denosumab had NS difference in BMD but showed a reduction in bone pain at 12 months compared with placebo [VAS (MD= -2.40 cm, 95% CI -3.80 to -1.00]. There was uncertainty on the effect of strontium on BMD and back pain.[159, level I]

- Thalassaemia patients with the following features should be assessed by paediatric endocrinologists and adult specialists for consideration of biphosphonates:[130]
  - osteoporosis or with a low BMD for age (z-score < -2.0 if pre-menopausal or under 50 years, t-score < -2.5 if post-menopausal or over 50 years)
  - presence of fragility fractures
  - falling BMD despite adequate vitamin D levels and hormone supplementation in hypogonadism

Recommendation 14

- Assessment of bone health in transfusion-dependent thalassaemia (TDT) patients should be commenced at the age of 10 years except for Dual Energy X-ray Absorptiometry scan which should be started later at the completion of puberty.
- Prevention and treatment of early bone loss in TDT patients should include:
  - lifestyle changes:
    - adequate vitamin D and calcium intake (including supplementation)
    - avoidance of smoking and excessive alcohol consumption
    - weight-bearing exercise
  - optimisation of thalassaemia treatment which includes adequate iron chelation and blood transfusion
  - prompt diagnosis and appropriate treatment with hormonal therapy of hypogonadism, diabetes mellitus and other endocrinopathies
- Refer to paediatric endocrinologists/adult specialists for consideration of bisphosphonates in thalassaemia when indicated*

*Refer to yellow box above.

9. INFECTIVE COMPLICATIONS

Infection is the second leading cause of death in thalassaemia patients with a cumulative rate of 40.63%.[6]

9.1. Transfusion-Related Infection

Patients with TDT face risks of transfusion-transmitted infections. The most common infectious agents via packed RBC (pRBC) transfusions include hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV). It is recommended that TDT patients undergo screening for HIV, Hepatitis B and Hepatitis C every six months.[8]

a. Hepatitis B

The global prevalence of HbsAg positivity in thalassaemia patients receiving multiple transfusions ranges from <1% to >20%.[160 - 161, level III] In Malaysia, the reported incidence rate of hepatitis B is approximately 12.64 in 100,000 population[162, level III] while the prevalence is 4%.[163, level III] Hepatitis B is a significant cause of chronic liver disease and HCC in thalassaemia patients, particularly in developing countries.

i. Investigations

For patients identified to be HBsAg positive, the following tests should be performed: LFT, HBeAg and anti-HBe, HBV-DNA PCR. The blood bank should be informed for donor tracing in cases of transfusion-related infections.

ii. Treatment

The primary goal of treatment for chronic hepatitis B is long-term suppression of HBV-DNA viral load to low or preferably undetectable levels, and HBeAg seroconversion in HBeAg positive subjects. This is intended to reduce the progression to cirrhosis, liver failure and HCC.

Patients with viral replication but persistently normal or minimally elevated ALT levels typically do not require treatment but should undergo close follow-up and HCC surveillance every 3 - 6 months.[164, level III] Liver fibrosis assessment is recommended for viraemic patients with high normal or minimally elevated ALT levels and patients older than 40 years, except for patients with clinical evidence of cirrhosis.

Consideration for treatment in chronic HBV-infected patients should be based on several criteria:[164, level III; 165]

- ALT ≥2 times the upper limit of normal
- HBV DNA ≥2.0 x 10^4 IU/ml if HBeAg positive or ≥2.0 x 10^3 IU/ml if HBeAg-negative
- presence of advanced fibrosis or cirrhosis irrespective of ALT level

Treatment should be initiated as early as possible in cases of impending or overt hepatic decompensation [i.e. raised bilirubin unrelated to thalassaemia, prolonged prothrombin time (PT) or presence of ascites]. The treatment options for chronic hepatitis B infection may include pegylated interferons and oral nucleoside/nucleotide analogues.[166, level III] A gastroenterologist should be consulted for the decision for treatment.

iii. Prevention

All patients who are unvaccinated or unsure of their vaccination should receive full hepatitis B vaccination. Locally, anti-HBs are monitored 6-monthly. For patients who have completed the vaccination but have anti-HBs levels <10 mIU/ml, a booster dose is required. If the anti-HBs levels remain low one month after the booster vaccination, a 3-dose revaccination should be considered.[8] Hepatits B vaccinations are given at 0, 1 and 6 months intervals.

b. Hepatitis C

The global prevalence of hepatitis C among thalassaemia patients is estimated to be between 19 - 36%.[167 - 168, level III] In Malaysia, the seroprevalence rate of hepatitis C in general population was 0.3% between year 2006 and 2012.[163, level III] and the incidence rate in 2020 was 10.13 per 100,000 population.[162, level III] Meanwhile the prevalence in TDT patients range from 13.9% to 22.4%.[169 - 170, level III] HCV infection is recognised as a risk factor for development of liver cirrhosis and HCC.[171, level III]

i. Investigation

The diagnosis of chronic HCV infection should be based on the detection of antibodies to HCV (anti-HCV) or hepatitis C core antigen (HCVAg).[172] For all patients positive for anti-HCV, active viraemia should be confirmed by nucleic acid testing (HCV RNA PCR).[173, level III]

HCV genotyping testing and USG-based TE can be performed based on consultation with the gastroenterologist. Liver biopsies are not always recommended for making decisions for the treatment of hepatitis C.[173, level III]

ii. Treatment

The treatment of HCV has evolved dramatically with the availability of direct-acting anti-viral agents (DAAs), which yield >95% rates of sustained virological response (SVR), equivalent to a complete cure.[1] DAAs have a safe profile and pan-genotypic regimens provide high SVR rates across genotypes, further simplifying therapy.

All patients with chronic HCV infection and detectable HCV viraemia are candidates for antiviral treatment to prevent progression of liver damage to cirrhosis or HCC.[174, level III] A gastroenterologist should be consulted for the decision for treatment. The treatment duration varies between 8 and 12 weeks.

c. Human Immunodeficiency Virus

Tranfusion-acquired human immunodeficiency virus (HIV) infection, although very rare, remains a potential risk in thalassaemia patients who receive multiple transfusions. Therefore, regular HIV screening using HIV Ag/Ab ELISA should be performed every six months for these patients.[8]

i. Investigations

For children above 18 months old and adults, if the initial HIV Ag/Ab ELISA screening test is reactive, the microbiology laboratory will perform a supplementary test [e.g. particle agglutination or HIV-1/2 differentiation assay] using the same specimen. If the supplementary test is also positive, a second sample will be requested for verification before the patient is considered HIV positive. If the supplementary test is negative or indeterminate, a new sample should be requested for repeat HIV ELISA and HIV-1 RNA PCR testing.[175, level III]

For infants below 18 months old, a negative HIV Ag/Ab ELISA test is adequate to rule out HIV. However, a positive HIV Ag/Ab ELISA test should be confirmed using HIV-1 RNA PCR.[175, level III]

ii. Treatment

Confirmed HIV positive cases should be urgently referred to an infectious disease specialist for management including counselling. Additionally, the blood bank needs to be contacted for donor tracing.

Recommendations 15

- All thalassaemia patients should be monitored every 6-monthly for:
  - hepatitis B using HBsAg
  - hepatitis C using anti-HCV
  - HIV using HIV Ag/Ab ELISA
- Treatment for hepatitis B and hepatitis C should be initiated by the gastroenterologist if a patient fulfils the criteria.
- All thalassaemia patients receiving blood transfusion should be vaccinated for hepatitis B and booster vaccination should be considered if anti-HBs levels <10 mIU/ml
- Confirmed HIV cases should be referred to the infectious disease specialist.

9.2. Splenectomy-Related Infection

One of the risk factors for severe infection is splenectomy. A cohort study of splenectomised patients where the majority were thalassaemia patients revealed:[176, level II-2]

- an incidence of serious bacterial infections of 35% and mortality rate of 11%
- the most frequent pathogens were *Escherichia coli* and *Streptococcus pneumoniae*
- NS difference in mortality rate between patients with *Streptococcus pneumoniae* infection (40%) vs infections caused by other pathogens (24%)

Overwhelming post-splenectomy infection is a medical emergency which is defined as fulminant sepsis, meningitis or pneumonia. It can progress rapidly to multiorgan failure and death. According to the local thalassaemia registry report in 2020, 25% of infection-related deaths were among splenectomised patients.[6]

Guidelines recommend the following.[1; 8]

- Patients should be educated to seek early care when fever develops.
- Patients with fever >38^0 C and chills, vomiting, abdominal or localised pain/swelling suggesting abscess need to be admitted for prompt investigations and treatment.
- Blood cultures need to be done and empirical broad-spectrum antibiotic regimens need to be started promptly.
- The antibiotics used should have anti-Klebsiella and anti-Pseudomonal properties e.g. third-generation cephalosporin (cefotaxime or ceftriaxone) combined with gentamicin, ciprofloxacin or vancomycin, and tailored according to local pathogens susceptibility and endemicity.

Recommendation 16

- Splenectomised thalassaemia patients who are suspected to have infection should be investigated and treated promptly with broad spectrum antibiotics.

9.3. Iron Chelation Therapy-Related Infection

Certain pathogens, including *Yersinia enterocolitica, Vibrio vulnificus* and *Mucorales*, can utilise DFO as a siderophore to increase their pathogenicity. Guidelines recommend:[1; 8]

- discontinuation of DFO during a febrile illness until it is established that the febrile episode is not caused by a pathogen that can use DFO as a siderophore
- discontinuation of DFP in febrile patients until neutropaenia have been excluded
- DFX can be continued during febrile episodes

- Thalassaemia patients on DFO and DFP who developed infection should discontinue their chelators until relevant investigations exclude their contraindication of use.

9.4. Covid-19-Related Infection

Evidence regarding COVID-19 infection in patients with thalassaemia is still lacking. A systematic review on β-thalassaemia with COVID-19 found the following:[177, level III]

- patients with chronic conditions, e.g complications of chronic transfusions, heart failure, PAH and DM, were more susceptible to the infection
- mortality rate was 26.5% which was higher than general population

In a recent small cross-sectional study on β-thalassaemia patients with COVID-19, the rate of hospitalisation was 37.5%. Half of the hospitalised patients developed pneumonia and none developed thrombosis.[178, level III]

Management of thalassaemia with COVID-19 patients should be based on national guidelines.[179, level III] Patients with thalassaemia are considered a vulnerable group and should be prioritised to receive COVID-19 vaccination.[179, level III; 180]

10. COMPLICATIONS OF NON-TRANSFUSION DEPENDENT THALASSAEMIA

Though most of the complications seen with TDT and NTDT are similar when attributed to iron overload, NTDT patients also suffer from a unique set of complications not commonly seen in TDT patients.

One prospective cohort study on NTDT showed that disease-related complications occurred in 43% of the patients (splenectomy done in 24.6% of them) with the commonest being PHT, thromboses and leg ulcers (unique to NTDT). Two main significant clinical risk factors of complication were female and splenectomy.[181, level II-2] Two cross-sectional studies on TI patients demonstrated that common complications were thrombosis, PHT, EMH, leg ulcers and cholelithiasis. Splenectomy was a significant risk factor to develop the complications.[182 - 183, level III]

a. Hypercoagulability and clinical thrombosis

A hypercoagulable state is present in NTDT patients since childhood and contributed by ineffective erythropoiesis and chronic haemolysis. This gives rise to pathological RBC, chronically activated platelets and increased procoagulant microparticles leading to a more thrombogenic state.

NTDT patients is at higher risk of thrombosis or cerebrovascular disease than normal individuals, especially the following subgroups:[4; 54]

- splenectomy
- minimal- or never-transfused
- haemoglobin level ≤10 g/dL
- platelet counts ≥500 x 109/L
- NRBC counts ≥300 x 106/L
- iron overload (LIC ≥5 mg Fe/g dw or SF level ≥800 ng/ml)
- history of PAH
- pregnancy
- personal or family history of thrombosis

Within medical or surgical risk-assessment setting, the above patients should receive prophylactic intervention with anticoagulant or antiplatelet therapy according to local practice.

b. Pulmonary arterial hypertension

Prevalence of PAH in NTDT is high. A cohort study of NTDT patients showed that the most common disease-related complications was PAH at 7.6%.[181, level II-2] Long-term post-splenectomy complication (>5 years) was PAH (OR=2.6, 95% CI 1.1 to 6.9).[184, level III] In a cross-sectional study, TI patients on iron chelation had lower risk of PAH compared with those not on chelation (p=0.032).[56, level III]

For monitoring and management of PAH, refer to **Subchapter 8.1.c(ii)** on **Management of pulmonary arterial hypertension.**

c. Leg ulcers

Leg ulcers are often painful but benign lesions commonly seen in NTDT. The risks of developing this complication are iron overload, skin thinning at the extremities (age-related), high venous pressure due to right heart failure and venous insufficiency.[4]

d. Extramedullary haematopoiesis

Ineffective erythropoiesis in NTDT patients forces expansion of haematopoietic tissue in areas other than liver and spleen, mostly in the form of masses commonly termed EMH pseudotumours. The prevalence of these pseudotumours is considerably higher in NTDT than TDT patients. Its prevalence is higher in older patients, those with more severe ineffective erythropoiesis, Hb levels ≤10 g/dL and low foetal Hb levels. It can occur anywhere in the body with paraspinal lesions being the most common location. Hence, diagnosis is made via imaging, usually an MRI.

Apart from transfusion and hydroxyurea, monotherapy with low-dose radiation yields excellent results in up to 50% of patients with neurological improvement as soon as 3 - 7 days after initiation of treatment. However, there is a high risk of recurrence that is often amenable to further doses.[4]

Summary of recommendations from TIF in the management of NTDT complications are:[4]

- blood transfusions for prevention (pre-transfusion Hb target >10 g/dL)
- hydroxyurea to treat complications
- referral or co-management with specific subspecialty i.e. refer cardiologist for PAH, refer dermatologist for leg ulcer and refer for oncologist/surgeon for EMH pseudotumour

11. SPLENECTOMY

In thalassaemia, splenomegaly is due to excessive destruction of RBCs and EMH. On the other hand, EMH could be significantly reduced by optimal blood transfusion and iron chelation.[185, level III]

- Splenectomy is not performed routinely in thalassaemia patients as a standard of care especially in a child <5 years old due to risk of sepsis and thromboembolism. With the current practice of optimal blood transfusion and chelation, splenectomy can be avoided.[1; 8]

a. Indication for splenectomy

Splenectomy is indicated in the following conditions:[1; 8]

- pRBC transfusion requirement exceeds 200 - 250 ml/kg/year and severe iron overload could not be adequately controlled with iron chelation. The average blood transfusion requirement in TDT patient is 180 ml/kg/year.[8]
- evidence of hypersplenism (persisting anaemia, leucopenia and thrombocytopenia)
- massive splenomegaly that crosses the umbilicus causing discomfort and risk of infarct or rupture from trauma

b. Peri-operative management

Pre-splenectomy screening for gallstones by USG has been advocated. If gallstones are present, concomitant cholecystectomy may be performed in symptomatic patients.[1; 186, level III]

Splenectomised patients are at risk of overwhelming sepsis from encapsulated organisms e.g. *Streptococcus pneumoniae, Haemophilus influenza type b* (Hib) and *Neisseria meningitidis*. Therefore, all patients are given polyvalent Pneumococcal, Hib and Meningococcal vaccine prior to splenectomy.[185, level III] These vaccinations are given 4 - 6 weeks pre-splenectomy or at least two weeks in advance.[1; 8]

The current recommended pre-splenectomy vaccination regimen is shown in the following table:[1]

Table 6: Pre-splenectomy vaccination schedule

Vaccination	Dose	Schedule
Pneumococcal • **pneumococcal conjugate vaccine (PCV13)** • **polysaccharide vaccine (PPSV23)***	0.5 ml IM 0.5 ml IM	Given first i.e. two months before PPSV23 4 – 6 weeks pre-splenectomy***
Haemophilus influenza type b	0.5 ml IM	4 – 6 weeks pre-splenectomy***
Meningococcal conjugate vaccine (MenACWY)**	0.5 ml IM	4 – 6 weeks pre-splenectomy***

*Revaccination with PPSV23 0.5 ml IM is recommended after five years post-splenectomy
**Repeat MenACWY two months after the first dose and 5-yearly thereafter only in endemic areas
***Patients undergoing emergency splenectomy can still benefit from vaccination two weeks post-splenectomy

c. Post-splenectomy

Evidence have shown that blood transfusion requirement was reduced post-splenectomy i.e.:

- significant reduction of transfusion requirement by 100 ml pRBC/kg/year[186, level III]
- significant reduction of annual blood transfusion requirement in first year (mean=138.41±90.38 ml/kg/year) and five years (mean=116±41.44 ml/kg/year) from pre-splenectomy (mean=294.85±226 ml/kg/year)[185, level III]

d. Complications of splenectomy

Immediate complications of splenectomy via laparascopic or open method in TM or TI included atelectasis and bleeding. However, there were no significant differences between the two methods.[187, level I]

Long-term post-splenectomy complications (>5 years) were pulmonary hypertension, heart failure and hypogonadism as shown in table below.[184, level III]

Splenectomy	Pulmonary hypertension	Heart failure	Hypogonadism
NTDT	OR=2.6, 95% CI 1.1 to 6.9	OR=7.6, 95% CI 1.1 to 53.3	OR=9.5, 95% CI 1.4 to 64.2
TDT	OR=10.4, 95% CI 2.2 to 49.9	NS	OR=4.5, 95% CI 1.2 to 18.2

Independent risk factors for confirmed PAH are age (OR=1.102 per 1-year increase, 95% CI 1.06 to 1.15) and splenectomy (OR=9.31, 95% CI 2.57 to 33.7).[99, level III]

Splenectomised TI patients who develop thromboembolic events may be identified early by high NRBC (≥300 x 10^6/L) and platelet counts (≥500 x 10^9/L), evidence of pulmonary hypertension and transfusion naivety.[183, level III]

Splenectomised thalassaemia patients are at risk of thrombosis and thromboembolism:

- post-operative thrombocytosis is common with significant rise in platelet counts within 24 hours[185, level III]
- microparticles post-splenectomy induces platelet activation[188, level III]
- significant reduction in natural coagulation inhibitors (protein C and protein S) and thrombin activatable fibrinolysis inhibitor[189, level III]

Low dose aspirin 75 - 150 mg daily is recommended in all post-splenectomy patients when the platelet count is >500,000/mm^3 and no contraindication to the medication.[1]

The spleen is an important host defence organ that filters blood by removing cellular waste and, old and damaged RBCs. It also synthesises opsonising antibodies to fight infection.[1; 8]

The recommended penicillin dose and duration for post-splenectomy patients are:[190]

- patients < 5 years: tablet oral penicillin 125 mg BD
- patients > 5 years: tablet oral penicillin 250 mg BD
- duration: minimum 1 - 3 years post-splenectomy; life-long prophylaxis for those with other causes of asplenia, previous episode of sepsis and remains immunocompromised

Chemoprophylaxis with oral penicillin depends on the age of the individual and the preference of the treating physician. Life-long prophylactic antibiotics should be offered to patients considered at continued high risk of pneumococcal infection using oral penicillins or macrolides.[1]

Recommendation 17

- Splenectomy may be considered in thalassaemia patients >5 years old with any the following:
  - increased pure red blood cell transfusion exceeding 200 - 250 ml/kg/year and severe iron overload not controlled by iron chelation
  - hypersplenism
  - massive splenomegaly
- Pre-splenectomy vaccination should be given 4 - 6 weeks prior or at least two weeks in advance.*
- Post-splenectomy thalassaemia patients should be given the following:
  - low dose aspirin (75 - 150 mg daily) if the platelet counts >500,000/mm^3
  - oral penicillin life-long (in high-risk thalassaemia patients)

*Refer to **Table 5** on **Pre-splenectomy vaccination schedule**.

12. FERTILITY AND PREGNANCY

12.1 Fertility

Thalassaemia patients are at risk of subfertility depending on severity of disease and, modality and duration of treatment. Therefore, special needs are required to reduce the risk and preserve fertility in the future.

a. Puberty, menstruation and fertility

For puberty and primary amenorrhoea, refer to **Subchapter 8.3 (a)** on **Short Stature** and **8.3 (b)** on **Delayed Puberty and Hypogonadism.**

Most TDT adolescents with iron overload are at risk of primary gonadal failure i.e. testicular or ovarian failure which may manifest as the following:[191, level III]

- hypergonadotropic hypogonadism
- low sperm concentration and high sperm DNA fragmentation
- delayed puberty due to hypergonadotropic hypogonadism
- low anti-mullerian hormone (AMH) secretion
- impaired fertility due to ovarian tissue iron overload

TDT patients on oral chelators (DFX or DFP) should be advised to switch to DFO prior to induction of ovulation/spermatogenesis due to concerns of its teratogenicity.[1]

b. Fertility treatment option in paediatric population

As there is possible risk of permanent gonadal failure due to risk of iron overload in thalassaemia, the fertility preservation (FP) option should be recommended as discussed below.[191, level III]

In thalassaemia boys:[191, level III]

- sperm cryopreservation (as young as 13 years old) via ejaculation or testicular sperm extraction (TESE) procedures can be offered
- biopsy and cryopreservation of prepubertal germ cells (testicular tissue) in males is currently experimental

In thalassaemia girls:

- oocyte cryopreservation by vitrification can be offered and is applicable only to post-pubertal patients[191, level III]
- Ovarian Tissue Cryopreservation (OTC) is the only strategy available to pre-pubertal patients; although it was previously regarded as experimental, there is now sufficient evidence to justify its implementation in selected cases[191 - 192, level III]
- Egg donation from a family member or friend followed by in-vitro fertilisation is an option for girls with reasonable uterine status but this is not permissible in Malaysia[191, level III]

In a small cross-sectional study on OTC and Ovarian Tissue Transplantation (OTT), the findings were:[192, level III.]

- significant negative linear association between follicle density and age at OTC in the β-thalassaemia group compared with the reference group
- OTT using OTC done before puberty gave rise to livebirth in two patients with β-thalassaemia

c. Subfertility

i. Assessment

Majority of thalassaemia patients with good compliance to transfusion and iron chelation are able to have spontaneous conception. In cases of subfertility, the assessment is similar to non-thalassaemia patients as discussed below.

The subfertility assessments include:[193, level III]

- baseline thalassaemia status
  - baseline Hb
  - SF level
  - baseline organ-related iron deposition status
- analysis of gonadal function through medical history and hormone assays
  - FSH/LH, oestradiol, serum AMH level (female)
  - semen analysis (male)
- standard pelvic examination in female
  - pelvic USG
  - tubal patency test using hysterosalpingography (HSG)

- partner
  - screening for thalassaemia status
  - blood and infective disease status

d. Fertility preservation

ii. Fertility preservation in male

Impairment of spermatogenesis occurs due to gonadal failure secondary to iron overload. The risk decreases with iron chelation. However, the usage of HU among thalassaemia males poses a risk of abnormal spermatogenesis leading to subfertility. To date, the data on recommendation for FP in male thalassaemia patients is inconclusive.

There is no study on male thalassaemia on HU. In one small multi-centre retrospective study on sickle-cell disease (SCD) men, HU worsened all sperm parameters including one case of azoospermia.[194, level III]

In a cohort study on SCD, assessment on gonadal reserve for males with post-transplant cyclophosphamide-containing regimen revealed high risk of azoospermia (OR=4.35, 95% CI 1.02 to 18.45).[195, level III]

iii. Fertility preservation in female

Similarly, ovarian function alteration can be due to iron overload as well as post-HSCT. In the same cohort study on gonadal reserve with post-transplant cyclophosphamide-containing regimen in females, the findings were:[195, level III]

- increased risk of secondary amenorrhea (OR=9.30, 95% CI 4.94 to 17.50) and ovarian insufficiency (OR=37.8, 95% CI 2.03 to 700.94)
- secondary ovarian insufficiency developed in all women post-transplant

- Despite lack of direct evidence on thalassaemia, inference on HU treatment and HSCT in SCD warrants an intervention of FP. Therefore, the CPG DG encourages the following groups of patients to be referred to obstetrics and gynaecology specialists:
  - all post-pubertal male thalassaemia patients prior to HU and HSCT initiation
  - all pre- and post-pubertal female thalassaemia patients prior to HSCT initiation

12.2 Pre-pregnancy Care

Patient with thalassaemia who is planning to conceive should be referred for pre-pregnancy clinic for assessment of her functional status in determining safety of the pregnancy. Hb level and iron chelation should be optimised prior to pregnancy.

MoH Perinatal Care Manual 4th Edition states that if either partner or the couple is a thalassaemia carrier, a referral should be made to a family medicine specialist (FMS) or obstetrics & gynaecology (O&G) specialist for detailed counselling which includes information regarding prenatal diagnosis. An untested partner should be screened for thalassaemia and the patient should be advised for early booking before 12 weeks of gestation.

At-risk couples require adequate genetic consultation from trained health professionals to determine their risk in having thalassaemia offspring. A referral to the fertility specialist should be considered as preimplantation genetic testing with IVF can be offered to ensure only healthy embryos are implanted. Refer to **Chapter 4** of **Genetic Counselling** and **Chapter 12.1** on **Fertility**.

12.3 Pregnancy

The main concerns for pregnancy in patients with thalassaemia are:
i. maternal and foetal complications
ii. risk of offspring inheriting major thalassaemia in at-risk couples

a. Prenatal diagnosis

Various screening and diagnostic tests may be offered to at-risk couples to determine the offspring's thalassaemia status, depending on the gestational age. PND of thalassaemia is important because termination of pregnancy (TOP) may be offered to at-risk couples, as well as to facilitate management of foetal anaemia during the antenatal period. Prenatal testing can be performed by either invasive (diagnostic) or non-invasive (screening) methods. However, analysis of both cell-free foetal DNA (cffDNA) in non-invasive test and DNA analysis of sample obtained from invasive CVS, amniocentesis or cordocentesis are performed in private laboratories.

i. Non-invasive test

The non-invasive test for prenatal diagnosis involves extraction of foetal DNA from maternal plasma. It is also known as non-invasive chromosomal check (NICC) or non-invasive prenatal test (NIPT).

In a meta-analysis of nine studies, cell-free foetal DNA (cffDNA) in maternal plasma had high sensitivity (0.99, 95% CI 0.69 to 1.00) and specificity (0.99, 95% CI 0.89 to 1.00) in detecting paternally inherited mutation of β-thalassaemia.[196, level III] However, there was no mention on quality assessment of primary studies. Detection of the paternal allele in maternal plasma is possible in couples with different mutations. If the paternal allele is present in maternal plasma, the probability of the foetus having thalassaemia major is 50% and thus the necessity to proceed with invasive procedure to confirm the diagnosis. This may reduce the need for performing invasive prenatal diagnosis test by 50%.

Another study also demonstrated cffDNA had high sensitivity and specificity (ranging from 98.81 to 100% and 94.72 to 99.31% respectively) in the detection of HbBarts.[197, level III]

Currently, this test is widely accepted as a screening test but not for diagnostic purpose.

ii. Invasive test

There are three invasive tests that can be used to diagnose thalassaemia prenatally which are CVS, amniocentesis and cordocentesis. The procedure chosen depends on gestational age, expertise of maternal-foetal medicine specialist as well as availability of molecular analysis test. Refer to **Subchapter 2.2(d)** on **Molecular analysis (DNA Analysis)**.

In a cross-sectional study to detect HbBarts using invasive prenatal diagnosis testing:[198, level III]

- there was no DNA analysis failure and false negative
- in terms of safety profile, in comparison with amniocentesis, transcervical CVS had:
  - higher success rate of first-time sampling (92.96% vs 90.48%)
  - lower haemorrhage (3.29% vs 12.50%)
  - higher foetal loss rate (2.35% vs 0%) but this was still lower than average spontaneous abortion rate (15%)

A Cochrane systematic review of 16 RCTs comparing the safety and accuracy of all types of amniocentesis (early i.e. before 15 weeks' gestation and late i.e. after 15 weeks' gestation) and CVS (e.g. transabdominal, transcervical) for prenatal diagnosis concluded that:[199, level I]

- CVS (any route) was associated with higher overall pregnancy losses and miscarriages, as well as more technical difficulties -

  - overall pregnancy loss (RR=1.43, 95% CI 1.22 to 1.67)
  - spontaneous miscarriage after test (RR=3.46, 95% CI 2.21 to 5.42)
  - sampling failure (RR=3.09, 95% CI 1.98 to 4.82)
  - multiple insertions (RR=4.85, 95% CI 3.92 to 6.01)
  - need for second test (RR=2.83, 95% CI 1.94 to 4.13)
- When performed in early pregnancy, in comparison with transabdominal CVS, early amniocentesis had more spontaneous miscarriages after the procedure (RR=1.71, 95% CI 1.12 to 2.61). Nevertheless, there were no significant difference in pregnancy losses or in foetal anomalies.
- Second trimester amniocentesis compared with no amniocentesis increased the risk of amniotic fluid leakage (RR=3.90, 95% CI 1.95 to 7.80). However, no difference between the two in terms of pregnancy loss, vaginal bleeding or number of congenital anomalies.
- first trimester amniocentesis resulted in more risk compared with second trimester amniocentesis as illustrated by -
  - increased pregnancy loss and congenital anomalies
    - total pregnancy losses (RR=1.29, 95% CI 1.03 to 1.61)
    - congenital anomalies including talipes (RR=1.73, 95% CI 1.26 to 2.38)
  - higher procedure-related complications
    - amniotic fluid leakage (RR=2.05, 95% CI 1.43 to 2.94)
    - multiple needle insertions (RR=2.79, 95% CI 1.92 to 4.04)
    - laboratory failures (RR=9.76, 95% CI 3.49 to 27.26)

Another meta-analysis of 21 studies (14 on amniocentesis and seven on CVS) showed that procedure-related risks of miscarriage for amniocentesis and CVS were 0.11% and 0.22% respectively.[200, level II-2]

Recommendation 18
- Invasive prenatal testing may be performed to diagnose thalassaemia in utero for at-risk couples of thalassaemia major offspring.

b. Termination of pregnancy

The decision of TOP is bounded by medical indications and legal considerations, as well as religious and cultural beliefs. A local survey on thalassaemia parents revealed that the acceptance rates for abortion vary markedly depending on ethnicity and religious background Despite an overall 71.6% acceptance rate in performing prenatal diagnosis, only 28.4% agreed to proceed with TOP of thalassaemia major foetuses. Religious restriction was the main reason in 77.6% of parents who declined abortions whereby 73.4% were Muslims, 25% Christians and 13.3% Buddhists.[201, level III]

Guideline on Termination of Pregnancy for Hospitals in the Ministry of Health Malaysia states that pre-requisite for TOP are two doctors, one of whom is a specialist, should concur that TOP is necessary and that continuation of pregnancy would involve risk to the life of the pregnant woman, or injury to her mental or physical health, greater than if the pregnancy is terminated e.g. Hb Barts Hydrops Foetalis. For mental health reasons, an opinion from a psychologist/psychiatrist is not needed unless it is deemed necessary by the attending doctor e.g. because of severe depression or suicidal risk.[202, level III] The decision on the most suitable method i.e surgical or medical termination would depend on the period of gestation and the condition of the cervix.

A cross-sectional study on the use of misoprostol for termination of 741 pregnancies between 14 - 32 weeks of gestation, where foetal thalassaemia was the most common indication, showed the following findings:[203, level III]

- use of misoprostol alone gave 96.4% success rate of TOP

- overall TOP was achieved within 48 hours in 85.9% cases with a mean of 25.35 hours
- commonest side effects were chills (43.7%) and fever (34.3%)
- commonest complications were incomplete miscarriage requiring uterine curettage (14.8%) and post-partum haemorrhage (1.9%) with no uterine rupture reported

As for Muslims, 52nd Muzakarah Jawatankuasa Fatwa Majlis Kebangsaan on 1 July 2002 decided that TOP for foetus with thalassaemia or thalassaemia carrier was:[204, level III]

- not encouraged (*makruh*) for embryo between 1 - 40 days, if it does not endanger the mother's life and agreed by both husband and wife
- permissible (*harus*) for embryo <120 days, if it has congenital malformation and a disease that can endanger the mother's life
- forbidden (*haram*) for embryo >120 days unless it is performed in order to save the mother's life as a result of severe congenital malformation

c. Antenatal care

Pregnant thalassaemia patients should be managed by a multidisciplinary team which include obstetrician and physician/haematologist, as well as cardiologist, endocrinologist and neonatologist if required. This is to ensure optimal management throughout the perinatal period.

i. Maternal complications

Pregnant thalassaemia patients are at risk of various maternal complications due to frequent transfusion and increase in iron burden. These include cardiac failure, alloimmunization, viral infection, venous thromboembolism (VTE), osteoporosis, as well as endocrinopathies (primarily diabetes mellitus, hypothyroidism and hypoparathyroidism).

Hydrops foetalis due to Hb Bart's may also predispose the mother to maternal Mirror Syndrome and its associated complications such as severe preeclampsia and primary postpartum haemorrhage.

In the absence of primary/secondary studies on management of thalassaemia patients in pregnancy, the following recommendations are based on existing guidelines.[1; 4; 8; 54; 205]

At booking, the recommendations are:

- to determine infective status (HIV, hepatitis B and hepatitis C), ABO blood group, full blood group genotype and RBC antibody titres
- to perform dating scan between 7 - 9 weeks of gestation
- to review patient's medication -
  - discontinue:
    - iron chelators (DFO may be used if needed in second and third trimesters)
    - hormone replacement therapy
    - HU
    - bisphosphonates
    - interferon/ribavirin
    - ACE inhibitors
  - change warfarin to heparin and oral hypoglycaemic agent (other than metformin) to insulin

For management throughout pregnancy, the followings are recommended:

- maternal anaemia
  - in TDT, maintain pre-transfusion Hb above 10 g/dL
  - in NTDT α-thalassaemia, maintain pre-transfusion Hb above 8 g/dL; when required, transfusion of RBC should be performed every 3 - 4 weeks with the aim of maintaining pre- and post- transfusion Hb levels at 9 and 12 g/dL respectively

  - in NTDT β-thalassaemia, maintain pre-transfusion Hb above 10 g/dL
  - regular transfusion is to be considered if there is worsening maternal anaemia or cardiac status, and foetal growth restriction
  - fully-phenotyped matched blood should be transfused in NTDT due to high risk of alloimmunisation
- iron burden
  - serial serum ferritin level (monthly in TDT β-thalassaemia)
  - hepatic
    - liver function should be checked once in each trimester
    - iron chelators (low-dose DFO) should be considered in severe hepatic iron overload from 20 weeks of gestation
  - cardiac
    - cardiac function by echocardiography should be checked once each trimester
    - in patient at highest risk of cardiac decompensation, iron chelators (low-dose DFO) should be commenced from 20 weeks of gestation
    - if cardiac function deteriorates, DFX may be used cautiously after first trimester
- diabetes mellitus
  - in pre-existing diabetes patients, diabetic control is monitored via serum fructosamine level
  - GDM screening is performed at 16 weeks and repeated at 24 - 28 weeks of gestation
- hypothyroidism
  - thyroid function should be checked once in each trimester
- VTE
  - aspirin 75 mg/day should be commenced to those with platelet >600x10^9/L
  - thromboprophylaxis with low molecular weight heparin (LMWH) is recommended from mid-trimester

The MoH Guidelines on Prevention and Treatment of Thromboembolism in Pregnancy and Puerperium suggests initiation of thromboprophylaxis from 28 weeks of gestation until three weeks post-delivery for thalassaemia major patients and splenectomised TI patients in the absence of other additional VTE risks.[206, level III]

ii. Iron chelation

Two small studies on TDT patients who unintentionally used DFO or DFX during early pregnancy (6 to 14 weeks gestation) showed that all pregnancies resulted in live births of healthy babies.[207 - 208, level III]

TIF guidelines recommends the following regarding the use of iron chelators in thalassaemia and pregnancy.[1]

- oral iron chelating agents (DFP, DFX) should be discontinued three months before conception
- DFO is not required during pregnancy in patients who are not iron overloaded and have adequate cardiac function prior to pregnancy
- if cardiac function deteriorates during pregnancy, DFO may be used with caution after the first trimester
- in patients with a history of previous myocardial iron deposition or borderline myocardial cardiac function, DFO may be considered in the final trimester or in the peri-delivery period, as a prolonged labour with acidosis may increase the risk of cardiac decompensation
- after delivery, DFO can be recommenced because its concentration is very low in breast milk and it is also not absorbed by the oral route

The CPG DG opines that all iron chelators should be discontinued once pregnancy is confirmed in thalassaemia patients. These patients should be referred immediately to the haematologist for further management.

Recommendation 19
- All pregnant thalassaemia patients:
  - should be managed by a multidisciplinary team
  - should have cardiac and liver function monitored closely
- In pregnancy, pre-transfusion haemoglobin level should be maintained at:
  - 10 g/dL in transfusion-dependent thalassaemia
  - 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 of worsening anaemia, cardiac decompensation and foetal growth restriction.
- Phenotype-specific blood should be used if transfusion is required.

iii. Foetal complications

Foetal complications associated with thalassaemia include miscarriage and foetal losses, foetal growth restriction (FGR), foetal anaemia and preterm birth, in at-risk couples. Adequate surveillance for FGR and foetal anaemia is required to enable timely intervention and prevent stillbirth.

- **Foetal growth restriction**

Chronic hypoxia due to maternal anaemia results in placenta insufficiency and FGR. Various evidence from cohort studies looking at pregnancy outcomes between TDT and NTDT patients and normal control showed that the former had higher FGR.[209, level II-2] Apart from that, other complications in pregnant thalassaemia patients include:
- higher risk of low-birth-weight babies[209 - 211, level II-2]
- lower Hb level[209 - 210, level II-2;]
- higher miscarriage rate[210, level II-2]
- higher preterm birth rate[209 - 211, level II-2]

Existing guidelines suggest that serial ultrasound scans should be performed in pregnant thalassaemia patients from 24 - 26 weeks and repeated every 4 weeks.[1; 4; 205]

Recommendation 20
- Serial ultrasound scans should be performed in pregnant thalassaemia patients to detect foetal growth restriction.

- **Foetal anaemia**

Surveillance for foetal anaemia and hydrops foetalis should be performed by maternal-foetal medicine specialists during pregnancy in at-risk couples who have not undergone prenatal diagnostic procedure, as well as in pregnancy with homozygous alpha thalassaemia foetus that is not terminated. Failure to detect and treat severe foetal anaemia can result in hydrops foetalis and intrauterine foetal demise. Foetal anaemia can also lead to maternal Mirror Syndrome and severe pre-eclampsia. Options of either intrauterine transfusion (IUT) or delivery can be considered depending on gestational age as well as the available neonatal support at the time of diagnosis of foetal anaemia of hydrops foetalis.

Foetal doppler study via middle cerebral artery peak systolic velocity (MCA-PSV) has been used as a primary technique to detect foetal anaemia.[212] A meta-analysis showed that MCA-PSV cut-off of ≥1.5 multiples of the median (MoM) was a predictor in detecting moderate to

severe anaemia in untransfused foetuses with AUC of 87%. Nonetheless, the sensitivity of MCA-PSV significantly declined with increasing number of previous intrauterine transfusion [78% (95% CI 63 to 88) for one transfusion, 74% (95% CI 48 to 90) for two transfusions and 60% (95% CI 34 to 82) for ≥3 transfusions].[213, level III]

The Society of Maternal-Foetal Medicine guideline recommends the following.[212]

- Foetal blood sampling should be performed if a foetus has MCA-PSV>1.5 MoM or hydropic, with preparation for an IUT, unless the pregnancy is at a gestational age when the risks associated with delivery are considered to be less than those associated with the procedure.
- MCA-PSV can also be used to determine the timing of a second transfusion in anaemic foetus. Alternatively, a predicted decline in foetal Hb is used to predict the timing.

Hydrops foetalis features can be detected in the second or third trimester. These can be reflected by ultrasound findings of:[54]

- increased cardiothoracic ratio (≥0.5)
- enlarged placenta (>18 mm before 15 weeks and >30 mm after 18 weeks)
- fluid collection in any one compartment - pericardial effusion, pleural effusion, ascites, or skin oedema

d. Intrapartum care

Available guidelines recommend that for thalassaemia patients in labour:[1; 4; 205, level I]

- blood should be cross-matched in the presence of red cell antibodies or if Hb <10 g/dL
- no consensus on the timing of delivery; uncomplicated pregnancy can wait for spontaneous labour
- caesarean section is not required in the absence of an obstetrics indication
- epidural analgesia is advisable for caesarean section to avoid risk of difficult intubation and general anaesthesia-associated trauma because of severe maxillofacial deformity
- continuous intrapartum electronic foetal monitoring should be instituted as there is increased risk of operative delivery due to possible foetal hypoxia
- in TDT patients especially those with cardiac disease, low dose IV DFO (e.g. 2 g over 24 hours) may be used as they are at high risk of cardiac dysrhythmias in prolonged labour
- active management of the third stage of labour to minimise blood loss

e. Postnatal care

i. Maternal care

- **Venous thromboembolism prophylaxis**

Both pregnancy and thalassaemia predispose patients to a hypercoagulable state, thus putting them at risk of developing VTE.

For thalassaemia patients, recommendations on LMWH for VTE prophylaxis based on international guidelines are as follows:[1; 205, level I]

- throughout hospital admission
- upon discharge with duration of treatment for the following conditions:
  - miscarriage or TOP: at least seven days
  - vaginal delivery: seven days
  - caesarean section: six weeks

However, MoH Guidelines on Prevention and Treatment of Thromboembolism in Pregnancy and Puerperium, based on VTE risk scoring, suggests extension of thromboprophylaxis until three weeks post-delivery for TM and splenectomised TI patients.[206, level III] The duration may be extended in the presence of additional VTE risk.

- **Breastfeeding**

Breastfeeding should be encouraged unless the patient is HIV positive.[1; 205, level I]

- **Medication**

Chelation therapy

For DFO: [1; 4; 205, level III]

- it can be recommenced after delivery as its concentration is very low in breast milk and not orally absorbed
- in patients who receive intrapartum IV or SC DFO infusion and:
  - breastfeeding, oral DFO can be restarted as soon as the initial 24-hour infusion of IV DFO finishes after delivery
  - not breastfeeding, IV or SC infusion is continued until discharge or resumption of her previous iron chelation regimen under haematology supervision, whichever is sooner

Other iron chelators should be restarted post-breastfeeding cessation as they have minimal safety data.

Other medications

Vitamin D and calcium supplement can be resumed during breastfeeding. Bisphosphonates should be resumed after cessation of breastfeeding.[1; 4]

Contraception

WHO Medical Eligibility Criteria for Contraceptive Use advocates the following for thalassaemia patients:[214, level III]

- no restriction for all hormonal contraception
- for intrauterine device (IUD), there is concern on initiation of usage due to theoretical increase in menstrual blood loss; however, patients who do not experience menorrhagia with IUD in-situ may continue to use it
- female surgical sterilisation should be performed with caution as it is associated with operative blood loss and risk of decrease wound healing

Nevertheless, TIF recommendations for TDT patients are:[1]

- avoid IUD (risk of infection) and oestrogen-containing preparations (risk of VTE)
- choose either progesterone-only or barrier method

The CPG DG opines that progesterone-only preparations should be the method of choice over other contraceptions.

ii. Newborn care and follow-up

Children born to at-risk couples should be followed-up in primary care. Symptomatic children should be investigated promptly. Asymptomatic children should have their thalassaemia status confirmed by 18 months. Refer to **Algorithm 3** on **Confirmation of Children's Thalassaemia Status to at-risk Couples**.

Recommendation 21

- Low molecular weight heparin for venous thromboembolism prophylaxis should be commenced in thalassaemia patients according to VTE risk assessment and guidelines.
- Progesterone-only preparations is the preferred method of contraception in thalassaemia patients.

13. HAEMATOPOIETIC STEM CELL TRANSPLANTATION

13.1. Matched Siblings Transplantation

HLA-matched sibling haemopoietic stem cell transplantation (HSCT) has long been a modality of curative option for thalassaemia and this still holds true till today.

Patients are stratified using Pesaro Classification based on the following risk factors which have adverse effects on transplant outcomes:[8]

- inadequate iron chelation therapy
- presence of liver fibrosis
- hepatomegaly

The classifications are as follows:

- Class I - Patient has none of the above characteristics
- Class II - Patient has one or two of the above characteristics
- Class III - Patient has all three characteristics

Based on a landmark study on thalassaemia transplant patients in Italy, the overall survival (OS) of Class I, Class II and Class III patients were 93%, 87% and 79% respectively. On the other hand, the disease free survival (DFS) for Class I, Class II and Class III patients were 91%, 83% and 58%.[8]

In view of the above evidence, matched sibling bone marrow transplantation (BMT) in thalassaemia should be offered to patients at an early age before iron overload-related complications set in to ensure the best outcome possible.

13.2. Alternative Donor Transplantation

While matched sibling HSCT offers the best curative outcome, only about 25 - 30% of patients will have a matched sibling donor. There is growing evidence that alternative donors can be safely used in transplants for thalassaemia.

A cohort study on young β-TM patients who received transplants with grafts from HLA-matched related, HLA-mismatched related (haploidentical), HLA-matched unrelated or HLA-mismatched unrelated donors showed:[215, level II-2]

- 5-year probabilities of OS for patients aged ≤6 years, 7 to 15 years and 16 to 25 years were 90%, 84% and 63% respectively ($p<0.001$). The corresponding probabilities for event-free survival were 86%, 80% and 63% ($p<0.001$).
- 5-year OS of HLA-matched related and HLA-matched unrelated donor transplantation was 89% and 87% respectively (HR=1.13, 95% CI 0.64 to 2.02)
- 5-year event-free survival of HLA-matched related and HLA-matched unrelated donor transplantation was 86% and 82% respectively (HR=1.25, 95% CI 0.75 to 2.07)

Another cohort study on severe thalassaemia patients who did not have an HLA-compatible-related or HLA-compatible-unrelated donor and underwent mismatched related (haploidentical) donor stem cell transplant showed:[216, level II-2]

- 2-year OS was 95% (95% CI 69.5 to 99.3)
- 2-year event-free survival was 94% (95% CI 76.6 to 98.4)

Thus, HSCT with HLA matched-unrelated and mismatched-related (haploidentical) donor stem cell transplant are feasible options for curative treatment of thalassaemia.

13.3. Cord Blood Transplantation

Umbilical cord blood cells are a potential source of stem cells for paediatric stem cell transplantation in thalasseamia. Although usage of cord blood cells alone as a source can result in slower engraftment and higher rejection risks, transplant outcome is good when performed very early on young recipients with early disease status and good HLA match.[8]

Recommendation 22
- In transfusion dependent thalassaemia, haematopoietic stem cell transplantation should be offered at an early age to those with matched sibling donor.

In local setting, a TDT patient with normal/carrier sibling is a candidate for HSCT. Alternatively, if parents keen for transplant when there is no matched donor available, treating clinicians may discuss with transplant centres for possible options. Refer to **Figure 2** below.

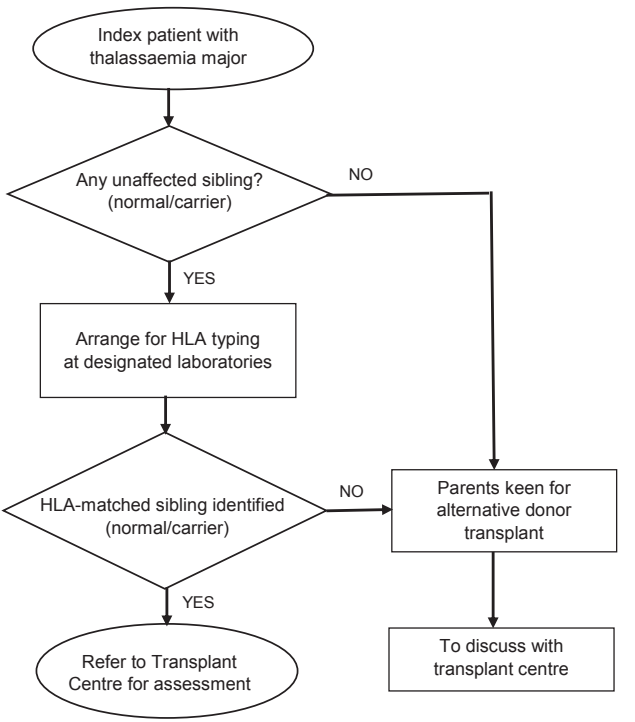


Figure 2: Referral for consideration of bone marrow transplant

14. LIFESTYLE AND QUALITY OF LIFE/SUPPORTIVE CARE

14.1. Nutrition and supplements

Generally, patients with thalassaemia do not have specific nutritional requirements. However, thalassaemia children have been shown to have growth stunting and poor bone mineralisation.[8]

Growth stunting in children with thalassaemia can be minimised with high-calorie diets which increase IGF-1 production. Supplementation of important micro-nutrients e.g. vitamin E and C helps to reduce oxidative stress and increase iron excretion during DFO therapy respectively. Folic acid supplementation is important for those planning for pregnancy.[8]

Apart from that, Vitamin D, calcium and zinc supplementation have also been shown to improve bone health and overall growth in these children.

a. Vitamin D and calcium supplementation

Vitamin D deficiency is associated with poor bone mineralisation, thus contributing to thalassaemic bone disease; deficiency is defined as serum 25-OH vitamin D <20 ng/ml (50 nmol/L) and insufficiency as serum 25-OH vitamin D of 20 - 30 ng/ml (50 - 75 nmol/L).[1]

Calcium homeostasis is intimately related to vitamin D. Low calcium intake in thalassaemia patients contributes to disturbances in calcium homeostasis.[1]

Vitamin D and calcium supplementation significantly improve bone mineral content (BMC), BMD and serum 25-OH vitamin D level without any AE in thalassaemia children.[217, level II-3]

Monitoring serum 25-OH vitamin D levels has been recommended every six months for thalassaemia patients. Vitamin D supplementation should be prescribed if indicated.[1]Refer to **Appendix 10** for **Micronutrients Supplementation and Assessment Strategy Recommendations for Thalassaemia Patients**

High calcium diet e.g. milk, cheese and oily fish is recommended for thalassaemia patients. However, calcium supplementation is also recommended if the patient needs vitamin D supplementation.[1] Refer to **Appendix 10** for **Micronutrients Supplementation and Assessment Strategy Recommendations for Thalassaemia Patients**

b. Zinc supplementation

Zinc deficiency has been demonstrated in thalassaemia and has shown to affect growth and bone health.[1]

In two Cochrane systematic reviews, zinc supplementation was more effective than placebo in thalassaemia patients.

- An RCT showed increase in bone mass at 18 months follow-up:[218, level I]
  - whole body BMC increased by 5.7% (95% CI 2.8 to 8.6)
  - whole body aerial BMD increased by 2.9% (95% CI 1.3 to 4.4)
- Another RCT showed increase in height velocity at one year (MD=3.37 cm/year, 95% CI 2.36 to 4.38).[219, level I]

Zinc supplements are available in various formulations with different contents of elemental zinc. The recommended dose is 15 mg up to a maximum of 40 mg per day of elemental zinc according to individual patient's need.[1]

On the other hand, patients with thalassaemia should restrict iron rich food intake.[1; 8] These are listed in **Appendix 11** on **Iron Content in Selected Food Items**.

Recommendation 23
- All thalassaemia patients should be given good nutritional support which include high-calorie diets and certain micro-nutrients supplementation* to minimise growth impairment.
- All thalassaemia patients should restrict iron-rich foods intake.

*Refer **Appendix 10** on **Micronutrients Supplementation and Assessment Strategy Recommendations for Thalassaemia Patients**.

14.2. Psychosocial support

Psychosocial support plays an important role in the management of chronic disease e.g. thalassaemia. Refer to **Appendix 12** on **Malaysian Thalassaemia Associations/Support Groups.**

a. Non-adherence to chelation

Good adherence to iron chelation therapy is crucial in management of thalassaemia.

Psychosocial factors (e.g. family dynamics and level of education) have negative impacts on adherence to treatment for thalassaemia.[220, level II-2] Unfortunately, two Cochrane systematic reviews showed lack of evidence on psychosocial support intervention[79, level I] and strategies using computer and mobile technology[221, level I] in promoting medication adherence in thalassaemia.

Expert psychological support (e.g. by family/child psychologists or social workers) has to be provided at all centres specialising in thalassaemia care and this should be tailored to the patient's age.[1]

b. Transition to adult care

As the thalassaemia children get older, there is a need for transition from paediatric to adult health care. This transition process requires a lot of psychological support from their parents and the medical providers.

There is no retrievable evidence directly on transition to adult care of thalassaemia patients. Nevertheless, three systematic reviews showed effectiveness of transition programme in other chronic diseases as below:
- patients with SCD with transition programme had significantly more successful transfer to adult clinic compared with non-participants[222, level I]
- patient education and specific transition clinics (either jointly staffed by paediatric and adult physicians or dedicated young adult clinics within adult services) were successful in some chronic diseases (e.g. diabetes mellitus)[223, level I]
- a structured transition programme incorporating detailed intervention descriptions about transition planning, transfer and integration into adult care often resulted in positive outcomes[224, level I]

To avoid the negative consequences of abrupt shifts in responsibility, the transition should occur gradually over time, starting when the children are young (e.g. preparing treatment) and increasing their involvement as they mature (e.g. getting medications, making medical appointments).[1]

Recommendation 24
- Psychological support has to be offered to all thalassaemia patients.
- A structured transition care should be arranged for all thalassaemia patients.

c. Education and employment

In a cross-sectional study on thalassaemia in North America, about 75% of adult patients had completed tertiary education. Furthermore, 82% percent of school-age children were at expected grade level.[225, level III] In another cross-sectional study in the Middle-East, about 60% of adult thalassaemia patients had completed tertiary education.[226. level III]

Higher education level was achieved in:
- patients on regular transfusion and those on regular chelation therapy within this group (OR=2.06, 95% CI 1.03 to 4.10 and OR=3.87, 95% CI 1.36 to 11.0 respectively).[225, level III]
- patients with no complications e.g. heart disease and joint disease.[226, level III]

Higher employment was observed in:
- patients on regular chelation therapy (OR= 6.67, 95% CI 1.96 to 25.0).[225, level III]
- patients with lower average of SF level <1500 ng/ml.[226, level III]

Neither type nor treatment of thalassaemia seemed to influence education and employment in both studies.

d. Marriage

Getting married and having a family have been reported in thalassaemia patients. A study in Lebanon showed that around one-third (30.3%) of the sample population was married compared with 75% of the general Lebanese population who were married. Out of 72 married patients, 21 of them did not have children. Among those who had children, average number of children was 1.47 and average time elapsed to first child was 0.85 years. The odds of being married were 2.5 times higher for those not being transfused compared with those transfused (OR=2.45, 95% CI 1.07 to 5.63).[226, level III]

Recommendation 25
- All thalassaemia patients should be given education and offered employment as the general population.

15. OTHER THERAPIES

a. Hydroxyurea

The molecular mechanisms involving the persistence of Hb F in the first year of life are not completely understood. HU promotes the production of Hb F by reactivating gamma-genes. Inducing the production of Hb F in patients with thalassaemia may alter the transfusion requirement in the patients.

In an open-label RCT on β-thalassaemia intermedia patients of ≤18 years old, combined HU and recombinant human erythropoietin was significantly more effective than HU alone in terms of:[227, level I]
- decreased transfusion frequency and index
- higher haemoglobin level
- higher HRQoL score

No serious AEs necessitating discontinuation or interruption of therapy in both groups were observed. Combined therapy was well tolerated with mild AEs (bone pain and headache) in a few patients.

In a cross-sectional study on NTDT, long-term use of HU (mean duration of 18.2 ± 4.0 years) at the dose of 8 - 15 mg/kg led to:[228, level III]

- 82.3% patients having sustained transfusion independence response
- average Hb levels increased from the baseline values as much as 1.3 ± 1.0 g/dL ($p<0.001$)

None of the patients had serious haematological AEs e.g. leukaemia or any signs of bone marrow suppression. All AEs were mild and transient which did not require drug interruption.

TIF recommends that HU may be considered in NTDT patients.[4]

Recommendation 26

- Hydroxyurea may be offered in non-transfusion dependent thalassaemia.

b. Novel therapy

Better understanding of β-thalassaemia pathophysiology has paved the way for development of novel therapies. These can be classified into the following categories based on the underlying pathophysiology that they address:

- correction of the α/β globin chain imbalance
- targeting ineffective erythropoiesis
- targeting iron dysregulation: hepcidin or ferroportin pathways

i. Correction of the α/β globin chain imbalance

The pathophysiology in thalassaemia is contributed by imbalance of the α and β chains leading to premature destruction of RBCs and anaemia. Gene therapy aspires to provide cure for thalassaemia through manipulation of the genome of haematopoetic stem cell (HSC), thus compensating for the inadequate or faulty function of mutated genes. This can be achieved by:

- gene addition via a semi-random insertion of a healthy copy of therapeutic gene into the cells using viral vectors
- gene editing via a precisely directed mutation that repairs gene in-situ or induces a disease-modifying effect (i.e. reactivation of Hb F synthesis) using site-specific nucleases

The modified cells then need to be introduced into the thalassaemia patients via two methods described below:

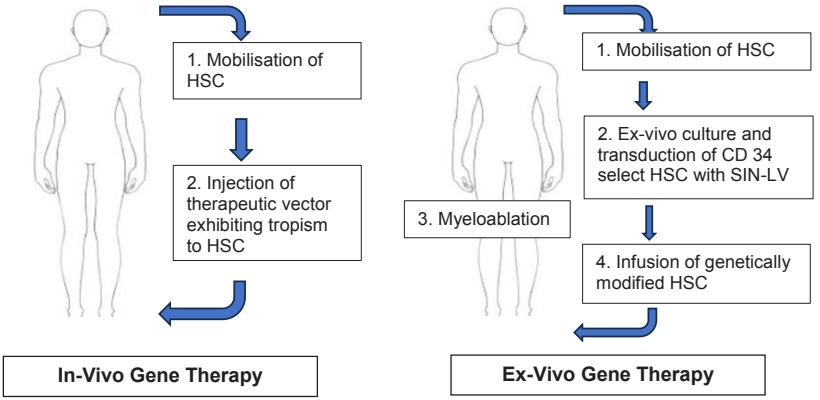
- **Ex-vivo gene therapy**

This is a HSC transplantation-based procedure. The autologous (patient-derived) HSCs are mobilised with granulocyte colony-stimulating factor (G-CSF) plus plerixafor, harvested by apheresis; separated by immunomagnetic separation and then the CD34+ cells are genetically modified ex-vivo. The patient then undergoes myeloablative conditioning followed by infusion of the gene-modified cells.

- **In-vivo gene therapy**

This has also been preclinically pursued, aiming to overcome the limitations of ex-vivo gene therapy. However, there are no commercially available therapy via this method at the time of writing these guidelines.

Refer to **Figure 3** on **Concepts of Gene Therapy.**



HSC: Haematopoietic Stem Cells
SIN – LV: self-inactivating lentiviral vectors

Figure 3: Concepts of Gene Therapy

ii. Targeting ineffective erythropoiesis and iron dysregulation

- **Erythroid maturating agent - luspatercept**

Luspatercept (ACE-536) is a recombinant fusion protein comprising of a modified extracellular domain of human activin receptor type IIB fused to the Fc domain of human IgG1. The domains bind selectively to transforming growth factor (TGF) β superfamily ligands, block SMAD2/3 signalling and enhance erythroid maturation. Murine studies showed enhanced erythroid, reduced α-globin chain aggregation and haemolysis, increased erythrocyte life span and improved iron overload.

Luspatercept is the most recently approved therapy for the management of TDT[229 - 230, level III] and NTDT.[229, level III] The approval was based on the results of the phase 2 BEYOND trial for NTDT and phase 3 BELIEVE trial for TDT which showed that subcutaneous administration of luspatercept led to a reduction in transfusion burden as discussed below.

In the BELIEVE trial, there was at least 33% transfusion reduction in 71% of patients along with a reduction of at least 2 red-cell units in 21% of patients over a 12-week interval with clinically meaningful and maintained reduction of serum ferritin levels.[231, level I]

On the other hand, BEYOND trial showed that 77.1% of patients in luspatercept arm vs none in placebo group achieved a mean Hb increase of ≥1.0 g/dL from baseline during weeks 13 – 24 in the absence of transfusions (RD=77.1, 95% CI 68.7 to 85.5).[232, level I]

AEs commonly seen with luspatercept were bone pain, arthralgia, dizziness, hypertension and hyperuricaemia.[231 - 232, level I] Data on the long-term luspatercept use, its real-life application and use in the paediatric population are lacking.

The indications for luspatercept use based on the TIF guidelines are: [1; 4]

- age ≥18 years
- TDT: patients who require regular RBC transfusions
- NTDT: Hb is <10 g/dl with symptoms of anaemia or ineffective erythropoiesis

Patients should be referred to haematologist for management if luspatercept is indicated.

- **Mitapivat**

Mitapivat (AG-348) is a first-in-class oral, small-molecule, allosteric activator of the RBC specific form of pyruvate kinase (PK) and approved for treatment of anaemia in adult patients with PK deficiency.

A small pre-post study on mitapivat in adults with NTDT showed 80% of the patients achieved a Hb increase by ≥1.0 g/dL compared with baseline ($p<0.0001$). Favourable changes in markers of erythropoiesis and haemolysis were also noted. The most common treatment-emergent AEs were initial insomnia (50%), dizziness (30%) and headache (25%).[233, level II-3] Phase 3 trials are currently ongoing for both TDT and NTDT patients.

- **Janus Kinase (JAK) inhibitor**

A pre-post study on TDT patients with spleen enlargement revealed that ruxolitinib (JAK 2 inhibitor) was well tolerated but had a limited effect in improving pre-transfusion Hb and reducing transfusion needs. There was a NS mean decrease of 5.9% in transfusion requirement of haematocrit-adjusted volume of RBC compared with baseline but this did not achieve a pre-determined >10% threshold.[234, level II-3]

Other agents targeting iron dysregulation e.g. hepcidin or ferroportin pathways are still under clinical trials.

16. IMPLEMENTING THE GUIDELINES

The management of thalassaemia should be guided by an evidence-based approach, in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

16.1. Facilitating and Limiting Factors

Existing facilitating factors for application of the recommendations in the CPG include:
- wide dissemination of the CPG to healthcare providers
- regular thalassaemia updates nationally according to zones
- National Thalassaemia Steering Committee that oversees the development and implementation of thalassaemia services in Malaysia
- established National Thalassaemia Screening Programme
- Malaysia Thalassaemia Registry that captures all thalassaemia patients in Malaysia

Existing barriers for application of the recommendations of the CPG are:
- lack of knowledge on thalassaemia and its management among healthcare providers in general
- inadequate coverage of thalassaemia training at all levels of healthcare
- inadequate coverage of national thalassaemia screening programme
- lack of resources for comprehensive management of thalassaemia especially in remote or high thalassaemia burden areas
- lack of awareness, knowledge and understanding on thalassaemia among patients, carriers and caregivers

16.2. Potential Resource Implications

The recommendations in this CPG require additional resources in terms of funds, healthcare infrastructures and human resources/expertise for their successful implementation as discussed below. The two main equally important aspects in thalassaemia management are

preventive measures (including screening) and treatment. Evidence have shown that good screening and prevention programmes effectively reduced the disease burden in the long run.

Diagnosis of thalassaemia need to be confirmed with molecular test. This is important especially for genetic counselling and genotype-phenotype correlation. In Malaysia, only limited centres offer this test e.g. Institute of Medical Research, Hospital Kuala Lumpur, Hospital Sultanah Bahiyah and a few university hospitals. These centralised laboratories should be expanded to other zones in Malaysia to improve the diagnostic services.

Despite the existence of dedicated thalassaemia screening programme among Form 4 students, there is lack of resources in terms of budget and manpower to implement the programme effectively. Currently, the programme is unable to achieve full coverage of Form 4 students in the country. There is also inability to retain information on the carrier status due to lack of proper centralised database. Thus, issues of newborn thalassaemia due to unknown parental thalassaemia carrier status continues despite the existence of the screening programme.

There is unequal availability of safe and high-quality blood products in certain states. For example, phenotyping and leucodepletion cannot be done at certain areas due to lack of resources. Lack of blood is a problem unique to Sabah which has the highest burden of thalassaemia. Improved networking and co-ordination of blood collection centres in other states in Malaysia is crucial to maintain sustainability of blood supply in Sabah.

Effective iron chelators e.g. DFX is not available to all patients and inability to continue its prescription beyond certain periods due to budget constraints is an important problem. Furthermore, monitoring of iron overload and its complications by MRI T2*, DXA scan and transient elastography may not be available in all hospitals. Due to these resource limitations, patients develop complications which require additional treatment and may lead to more costs.

Prenatal testing is costly. Although diagnostic procedures can be performed in public hospitals, the molecular tests are done in private laboratories for shorter turn-around-time and the cost is borne by the family.

Important issues that receive lack of attention among thalassaemia patients are education and employment. School absenteeism among thalassaemia patients is high due to regular hospital visits and admissions. Psychological support is important for patients with this chronic disease but this maybe lacking due to limitations of the related service.

Several key performance indexes on thalassaemia management being monitored by MOH is in line with the CPG recommendations. Thus, the following are proposed as clinical audit indicators for the CPG:

1. Percentage of thalassaemia (TDT) patients who have diagnostic molecular tests (Target 90%)

$$= \frac{\text{Number of TDT patients who have diagnostic molecular tests in a period}}{\text{Total number of TDT patients in the same period}} \times 100\%$$

2. Percentage of TDT patients who achieve serum ferritin <1,000 ng/mL after commencement of chelation (Target 40%)

$$= \frac{\text{Number of TDT patients on chelation who achieve serum ferritin <1,000 ng/mL in a period}}{\text{Total number of TDT patients who are on chelation in the same period}} \times 100\%$$

3. Percentage of thalassaemia patients >10 years old who undergo MRI for cardiac/liver over two years period (Target 80%)	=	Number of thalassaemia patients >10 years old who undergo MRI for cardiac/liver over two years period in a defined period / Total number of thalassaemia patients >10 years old in the same period	x 100%
4. Percentage of TDT patients* who have pre-transfusion Hb >9 g/dl (Target 75%)	=	Number of transfusion dependent thalassaemia patients who have a pre-transfusion Hb >9 g/dl in a period / Total number of transfusion dependent thalassaemia patients who receive blood transfusion in the same period	x 100%

*excluding hypersplenism, allo- and auto -antibodies, rare phenotype, defaulters, haemolysis

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the effectiveness and safety of the following chelators in TDT and NTDT?
a. deferoxamine b. deferiprone c. deferasirox d. combination therapy

Database: Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions® <1946 to January 03, 2022>

1. transfusion dependent thalass?emia*.tw.
2. transfusion-dependent thalass?emia*.tw.
3. non-transfusion dependent thalass?emia*.tw.
4. non transfusion dependent thalass?emia*.tw.
5. THALASSEMIA/
6. thalass?emia*.tw.)
7. BETA-THALASSEMIA/
8. (thalass?emia adj1 intermedia*).tw.
9. (thalass?emia* adj1 (minor or major or beta)).tw.
10. beta-thalass?emia.tw.
11. (beta type adj2 thalassemia*).tw.
12. ALPHA-THALASSEMIA/
13. a-thalass?emia.tw.
14. (alpha adj1 thalass?emia*).tw.
15. thalass?emia-alpha.tw.
16. alpha-thalass?emia*.tw.
17. (h?emoglobin h adj2 disease*).tw.
18. DELTA-THALASSEMIA/
19. delta thalass?emia*.tw.
20. delta-thalass?emia*.tw.
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. DEFEROXAMINE/
23. deferoxamine.tw.
24. (deferoxamine adj1 (b or mes#late or methanesulfonate)).tw.
25. deferrioxamine b.tw.
26. desferrioxamine b.tw.
27. desferioximine.tw.
28. desferrioxamine.tw.
29. desferroxamine.tw.
30. desferal.tw.
31. (desferrioxamine b adj2 mesylate).tw.
32. DEFERIPRONE/
33. 1,2 dimethyl 3 hydroxy 4 pyridinone.tw.
34. 1,2 dimethyl 3 hydroxypyrid* 4 one.tw.
35. 1,2-dimethyl-3-hydroxy-4-pyridinone.tw.
36. 1,2-dimethyl-3-hydroxypyrid*-4-one.tw.
37. 3 hydroxy 1,2 dimethyl 4 pyridinone.tw.
38. 3-hydroxy-1,2-dimethyl-4-pyridinone.tw.
39. deferiprone.tw.
40. ferriprox.tw.
41. DEFERASIROX/
42. Deferasirox.tw.
43. Exjade.tw.
44. IRON CHELATING AGENTS/
45. (iron adj2 (chelat* or chelating agent*)).tw.
46. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 21 and 46
48. limit 47 to (75nglish language and humans and yr=”2009 -Current”)

Appendix 2

CLINICAL QUESTIONS

For TDT

1. What is the accuracy of the following tests in the diagnosis of thalassaemia?
   a. Hb analysis
   b. Molecular tests – diagnosis and modifiers, phenotype corelations
   c. Sequencing
2. What are the most cost-effective screening programmes for thalassaemia?
   a. population screening
   b. cascade screening
   c. antenatal screening
   d. pre-marital screening
3. Genetic counselling
   3.1. Who should be targeted for genetic counselling in TDT and NTDT?
   3.2. What information should be discussed during genetic counselling in TDT and NTDT?
4. Blood transfusion
   4.1. What is the target pre-transfusion Hb in TDT and NTDT?
   4.2. What are the correlation between auto- or allo-antibodies and transfusion in TDT and NTDT?
   4.3. Is pre-storage leucodepletion more effective and safer than bedside filtration in TDT and NTDT?
5. Assessment of iron burden
   5.1. What is the accuracy and safety of MRI for iron overload quantification in TDT and NTDT? – liver and cardiac
   5.2. What is the role of MRI for assessment of iron overload in endocrine organs in TDT and NTDT?
6. What are the effectiveness and safety of the following chelators in TDT and NTDT: reducing iron burden, organ damage and mortality?
   a. deferoxamine
   b. deferiprone
   c. deferasirox
   d. combination therapy
7. What is the effective and safe assessment, monitoring, preventive measure and treatment for the following iron overload complications in thalassaemia?
   a. cardiovascular system
   b. liver disease
   c. endocrine and osteoporosis
8. What is the effective and safe assessment, monitoring, preventive measure and treatment for the following infective complications in thalassaemia?
   a. transfusion-related
   b. splenectomy-related
   c. iron chelation therapy-related
   d. Covid-19 related
9. What are the indications and complications of splenectomy in TDT and NTDT?
10. Fertility and pregnancy
    10.1. What is the effect of TDT and NTDT on puberty, menstruation and fertility? How should they be assessed?
    10.2. What is the safe and effective treatment for TDT- and NTDT-related problem of puberty, menstruation and fertility?
    10.3. What is the appropriate assessment for male, female or both couple with TDT and NTDT who are unable to conceive spontaneously?

10.4. What is the accuracy and safety of different methods of prenatal diagnosis for thalassaemia?
   a. chorionic villi sampling
   b. amniocentesis
   c. non-invasive prenatal testing
10.5. Regarding termination of pregnancy in TDT and NTDT, what are the:
   a. indication?
   b. effective and safe method?
   c. effective and safe timing?
10.6. What are the effective and safe foetal assessment, monitoring, preventive measure and treatment for the following complications of thalassaemia in pregnancy?
   a. foetal anaemia (including in-utero foetal transfusion)
   b. small for gestational age/intrauterine growth restriction
10.7. What are the effective and safe intrapartum managements for patients with thalassaemia?
10.8. What are the effective and safe post-partum managements of thalassaemia patients?
   a. venous thromboembolism prophylaxis
   b. contraception
   c. breastfeeding
11. What is the effectiveness and safety of the following in treatment of TDT?
   a. matched siblings haematopoietic stem cell transplant
   b. alternative donors and stem cell sources of stem cell transplant
12. Are the following treatments effective and safe in improving quality of life in TDT and NTDT?
   a. nutrition and supplements
   b. psychological support – non-adherence to chelation, transition to adult
   c. education/employment/marriage
13. What is the role of novel/other therapies (including gene therapy) in reducing transfusion requirement?
   a. hydroxyurea
   b. luspatercept and other erythrocyte stimulating agents
   c. gene therapy

For NTDT

14. What are the indications for blood transfusion in NTDT?
15. What is the effective and safe assessment, monitoring, preventive measure and treatment for the following complications in NTDT? (other than iron overload complications)
   a. thrombotic disease
   b. leg ulcers
   c. haemolytic crisis
   d. gallstones
   e. extramedullary haematopoiesis

Appendix 3

A. Peripheral Blood Film and Haemoglobin Profiles in Beta Thalassaemia Syndrome

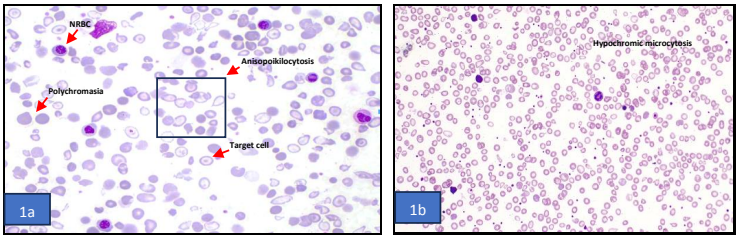


Figure 1a and 1b: Peripheral blood film from a patient with compound heterozygous Hb E/ β-thalassaemia ($\beta^{CD26}/\beta IVS^{1\text{-}5(G>C)}$) and homozygous β zero FIL deletion ($\beta^{0FIL}/\beta^{0FIL}$) shows severe anaemia with marked hypochromic microcytosis with anisopoikilocytosis, target cells, polychromasia and nucleated RBC (red arrows and box)

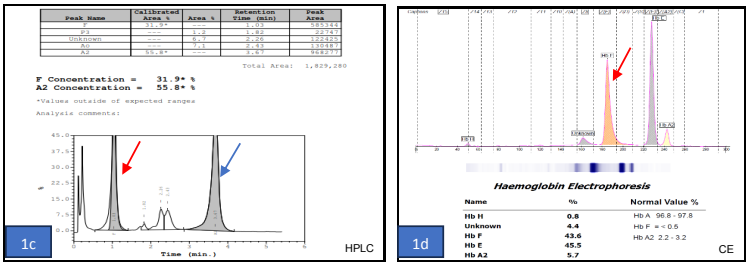


Figure 1c and 1d: HPLC and CE from a patient with patient Hb E/$\beta^{1\text{-}5(G>C)}$ thalassaemia. It shows that 31.9% and 43.6% of the haemoglobin present is haemoglobin F (red arrow) and zone 7 in HPLC and CE respectively. Apart from that, 55.8% is in the A2 (represent a combination of Hb E and Hb A2) window (blue arrow) and 45.5% in zone 4 (represent Hb E).

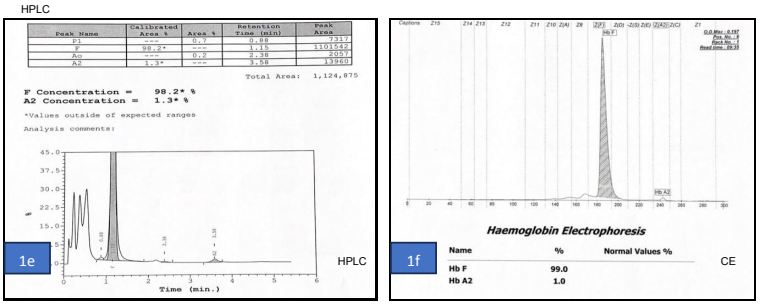
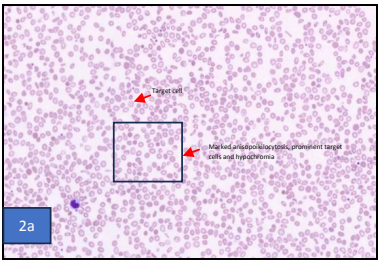


Figure 1e and 1f: HPLC and CE from a patient with β-thalassaemia major ($\beta^{0FIL}/\beta^{0FIL}$). There is no normal Hb A. Almost all Hb is Hb F. The Hb A2 fraction is increased.

B. Peripheral Blood Film and Haemoglobin Profiles in Hb H Disease



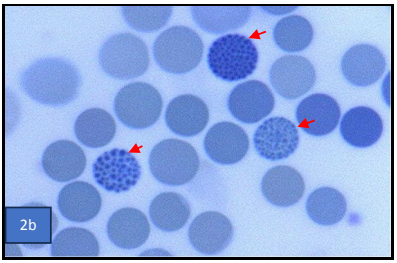
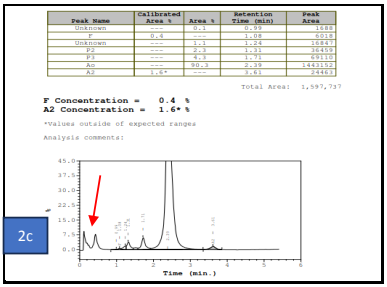


Figure 2a: Peripheral blood film from a patient with Hb H disease shows marked anisopoikilocytosis with prominent target cells and hypochromia (red arrows). **(2b)** Positive H inclusion test in α-thalassaemia shows golf ball appearance (precipitated Hb H in RBCs) in New Methylene Blue stain (red arrows).



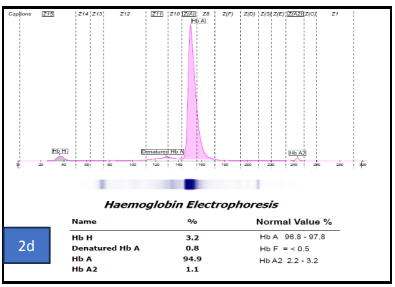


Figure 2c and 2d: Hb profiles using HPLC and CE show a variant Hb (Hb H by red arrow) in pre-calibration peak in patient with deletional Hb H disease ($--^{SEA}/-\alpha^{3.7}$).

Appendix 4

MOLECULAR SPECTRUM OF β-THALASSAEMIA AND α-THALASSAEMIA COMMONLY IDENTIFIED AMONG MALAYSIAN POPULATION BASED ON ETHNICITY

A. Molecular spectrum of β-thalassaemia identified among Malaysian population based on ethnicity

Ethnicity	β- gene mutation	HGVS Nomenclature	Severity	Source
Malay	codon 19 (A>G) Hb Malay IVS 1-5 (G>C) IVS 1-1 (G>T) PolyA(AATAAA>AATAGA) codon 26 (G>A)	NG_000007.3:g.70653A>G NG_000007.3:g.70691G>C NG_000007.3:g.70687G>T NG_000007.3:g.72130A>G NG_000007.3: g.70673G>A	β^{+} β^{0}/β^{+}(severe) β^{0} β^{+} $\beta^{+/variant}$	*2, level III*
Chinese	codons 41/42 (–TTCT) IVS 2-654 (C>T) codon 17 (A>T) -28 (A>G)	NG_000007.3:g.70848_70851 del NG_000007.3:g.71693C>T NG_000007.3:g.70646A>T NG_000007.3:g.70517A>G	β^{0} β^{+} (severe) β^{0} β^{+}	
Indian	codon 43 (G>T)	NG_000007.3:g.70854G>T	β^{0}	
Sabahan	--FIL (Filipino β^{0}-thal)	NG_000007.3: g.66259_184734del118477	β^{0}	
Sarawakian	--FIL (Filipino β^{0}-thal)	NG_000007.3: g.66259_184734del118477	β^{0}	
Malay	codon 26 (G>A) Hb E IVS 1-5 (G>C) IVS 1-1 (G>T) codon 19 (A>G) Hb Malay codons 41/42 (–TTCT) β^{0} Codon 17 (A>T) β^{0}	NG_000007.3: g.70673G>A NG_000007.3:g.70691G>C NG_000007.3:g.70687G>T NG_000007.3:g.70653A>G NG_000007.3:g.70848_70851 del NG_000007.3:g.70646A>T	$\beta^{+/variant}$ β^{0}/β^{+}(severe) β^{0} β^{+} β^{0} β^{0}	*4, level III*
Sabahan	--FIL (Filipino β^{0}-thal)	NG_000007.3: g.66259_184734del118477	β^{0}	*7, level III*
Malay	codon 26 (G>A) Hb E IVS 1-5 (G>C) IVS 1-1 (G>T) CD 41/42 (-TTCT) codon 19 (A>G) Hb Malay PolyA (AATAAA>AATAGA) Cap + 1 5'UTR (A>C)	NG_000007.3: g.70673G>A NG_000007.3:g.70691G>C NG_000007.3:g.70687G>T NG_000007.3:g.70848_70851 del NG_000007.3:g.70653A>G NG_000007.3:g.72130A>G	$\beta^{+/variant}$ β^{0}/β^{+} β^{0} β^{0} β^{+} β^{+} β^{+}	*5, level III*
Chinese	CD 41/42 (-TTCT) IVS 2-654 (C>T) -28 (A>G) IVS 1-5 (G>C)	NG_000007.3:g.70848_70851 del NG_000007.3:g.71693C>T NG_000007.3:g.70517A>G NG_000007.3:g.70691G>C	β^{0} β^{+} (severe) β^{+} β^{0}/β^{+} (severe)	
Indian	codon 43 (G>T) β^{0} Codon 15 (G>A) (β^{0})	NG_000007.3:g.70854G>T NG_000007.3:g.70641G>A	β^{0} β^{0}	
Orang Asli	codon 26 (G>A) Hb E	NG_000007.3: g.70673G>A	$\beta^{+/variant}$	*6, level III*

B. Molecular spectrum of α-thalassaemia identified among Malaysian population based on ethnicity

Ethnicity	α- gene mutation	HGVS Nomenclature	Severity	Source
Malay	αα/-$\alpha^{3.7}$	NG_000006.1:g.34164_37967del	α^{+}	*1, level III*
	αα/-^{SEA}	NG_000006.1:g.26264_45564del	α^{0}	
	$\alpha^{CS}\alpha$	NG_000006.1:g.34461T>C	α^{T}	
	$\alpha^{CD59}\alpha$	NG_000006.1:g.34071G>A	α^{T}	
Chinese	αα/-^{SEA}	NG_000006.1:g.26264_45564del	α^{0}	
	αα/-$\alpha^{3.7}$	NG_000006.1:g.34164_37967del	α^{+}	
	αα/-$\alpha^{4.2}$	NG_000006.1:g.30682_34939de	α^{+}	
	$\alpha^{CS}\alpha$	NG_000006.1:g.34461T>C	α^{T}	
Indian	αα/-$\alpha^{3.7}$	NG_000006.1:g.34164_37967del	α^{+}	
	αα/-^{SEA}	NG_000006.1:g.26264_45564del	α^{0}	
Sabahan	αα/-$\alpha^{3.7}$	NG_000006.1:g.34164_37967del	α^{+}	
	αα/-^{SEA}	NG_000006.1:g.26264_45564del	α^{0}	
Sarawakian	αα/-$\alpha^{3.7}$	NG_000006.1:g.34164_37967del	α^{+}	
	αα/-α^{FIL}	NG_000006.1:g.12483_43158de	α^{0}	
Orang asli	αα/-$\alpha^{3.7}$	NG_000006.1:g.34164_37967del	α^{+}	*1, level III; 6, level III*
	$\alpha^{CS}\alpha$	NG_000006.1:g.34461T>C	α^{0}	
Malay	αα/-$\alpha^{3.7}$	NG_000006.1:g.34164_37967del	α^{+}	*3, level III*
	αα/-^{SEA}	NG_000006.1:g.26264_45564del	α^{0}	
Chinese	αα/-^{SEA}	NG_000006.1:g.26264_45564del	α^{+}	
	αα/-$\alpha^{3.7}$	NG_000006.1:g.34164_37967del	α^{0}	
Indian	αα/-$\alpha^{3.7}$	NG_000006.1:g.34164_37967del	α^{+}	

Source:
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7. Tan JA, Lee PC, Wee YC, et al. High prevalence of alpha- and beta-thalassemia in the Kadazandusuns in east Malaysia: challenges in providing effective health care for an indigenous group. J Biomed Biotechnol. 2010;2010:706872.

Appendix 5

MALAYSIA THALASSAEMIA DIAGNOSIS (MTD) CODE FOR HB ANALYSIS AND DNA ANALYSIS

A. HB Analysis Code

Diagnosis	Code
No abnormality detected	N
α-thalassaemia	
Hb H disease	A1
Hb Constant Spring	A2
Hb H disease: Hb H-Hb Constant Spring (non-deletional)	A3
Hb H disease: Hb H-Hb Q	A4
Hb Barts Hydrops Foetalis	A5
Hb H disease with other Hb variant	A6
Hb Constant Spring Homozygous (new*)	A7
β-thalassaemia	
β-thalassaemia trait	B1
β-thalassaemia trait with iron deficiency (if iron status known)	B2
β-thalassaemia intermedia	B3
β-thalassaemia major	B4
β-thalassaemia trait with Hb variant	B5
β-thalassaemia trait with suspected alpha thalassaemia/iron deficiency	B6
β-thalassaemia trait with suspected triplication alpha (new*)	B7
Hemoglobinopathies/Thal Hemoglobinopathies	
Hb E Heterozygous/Hb E trait	C1
Hb E Homozygous	C2
Hb E β-thalassaemia	C3
Hb E with iron deficiency (if iron status known)	C4
Hb E with suspected α-thalassaemia/iron deficiency	C5
Hb E with co-inheritance Hb variant (e.g. Hb Malay, D, J, C, S etc.)	C6
Hb S trait	C7
Hb S with iron deficiency (if iron status known)	C8
Hb S with suspected α-thalassaemia/iron deficiency	C9
Hb S Homozygous	C10
Hb S β-interaction	C11
Hb Q Thailand	C12
Hb E-Beta with suspected α-thalassaemia/iron deficiency	C13
Hb Variant (Pending Molecular Confirmation)	
Hb C	D1
Hb D	D2
Hb J	D4
Hb Lepore	D7
Hb O Indonesia	D10
HPFH or Delta Beta Thalassemia (Hb F level ≥5 %)	D12
α-thalassaemia (Double gene deletion). DNA analysis for α gene required (MCH <25)	D13

Borderline Hb A2 β-thalassaemia trait (CE: A2≥ 3.3 HPLC: ≥3.4). DNA analysis for β gene required	D14
Other Hb variants	D15
α-thalassaemia cannot be excluded (MCH 25 - 26.9) MCV <80 pg, Hb N	D16
Others	
Iron deficiency anaemia (if iron status known)	E1
Suspected iron deficiency anaemia	E2
High F due to acquired/physiology (e.g. pregnancy, age, sepsis)	E3
Inconclusive (e.g. recent transfusion severe anaemia storage changes)	E4
Miscellaneous (e.g. post-transplant, JMML)	E5

NOTES:
*NEW CODE: A7, B7
DELETED CODE: D3,D5,D6,D8,D9,D11

Date of 8th revision: 4 September 2023

B. DNA Analysis (Alpha) Code

Code	Result
Heterozygous Alpha Plus (Single Gene Deletion)	
AP1	Heterozygous for the alpha plus thalassaemia 3.7 deletion
AP2	Heterozygous for the alpha plus thalassaemia 4.2 deletion
AP3	Heterozygous for the alpha plus thalassaemia 3.5^{MAL} deletion
APHE	Others
Homozygous Alpha Plus (Single Gene Deletion)	
AP11	Homozygous for the alpha plus thalassaemia 3.7 deletion
AP22	Homozygous for the alpha plus thalassaemia 4.2 deletion
AP33	Homozygous for the alpha plus thalassaemia 3.5^{MAL} deletion
APHO	Others
Compound Heterozygous Alpha Thalassaemia (Single Gene Deletion with Others)	
CH12	Compound heterozygous for the alpha thalassaemia 4.2 and 3.7 deletion
CH1CS	Compound heterozygous for the alpha thalassaemia 3.7 deletion and Termination codon (TAA → CAA) mutation (Hb Constant Spring)
CH2CS	Compound heterozygous for the alpha thalassaemia 4.2deletion and Termination codon (TAA → CAA) mutation (Hb Constant Spring)
CH1AD	Compound heterozygous for the alpha thalassaemia 3.7 deletion and Codon 59 (GGC → GAC) mutation (Hb Adana)
CH2AD	Compound heterozygous for the alpha thalassaemia 4.2 deletion and Codon 59 (GGC → GAC) mutation (Hb Adana)
CH1QS	Compound heterozygous for the alpha thalassaemia 3.7 deletion and Codon 125 (CTG → CCG) mutation (Hb Quang Sze)
CH2QS	Compound heterozygous for the alpha thalassaemia 4.2 deletion and Codon 125 (CTG → CCG) mutation (Hb Quang Sze)
CH1IC	Compound heterozygous for the alpha thalassaemia 3.7 deletion and Initiation codon
CH2IC	Compound heterozygous for the alpha thalassaemia 4.2 deletion and Initiation codon
CH	others
Alpha Zero (Heterozygous Two Genes Deletion)	
AZSE	Heterozygous for the alpha zero thalassaemia South East Asian deletion
AZFI	Heterozygous for the alpha zero thalassaemia Filipino deletion

AZTH	Heterozygous for the alpha zero thalassaemia Thailand deletion
AZME	Heterozygous for the alpha zero thalassaemia Mediterranean deletion
AZ20	Heterozygous for the alpha zero thalassaemia 20.5 kb deletion
AZ	Others
Hb Variant	
HVCS	Termination codon (TAA → CAA) mutation (Hb Constant Spring)
HVAD	Codon 59 (GGC → GAC) mutation (Hb Adana)
HVQS	Codon 125 (CTG → CCG) mutation (Hb Quang Sze)
HVPA	Termination codon (TAA → TAT) mutation (Hb Pakse)
HVEV	Codon 35 (TCC → CCC) mutation (Hb È vora)
HV30	Codon 30 (∆GAG) mutation
HVIC	Initiation codon (ATG → A-G) mutation identified.
HVQT	α1 Codon 74 (GAC>CAC) Hb Q-Thailand
HVOI	α1 Codon 116 (GAG>AAG) Hb O-Indonesia
HVJM	α1 Codon 120 (GCG>GAG) Hb J-Meerut
HV	Others
Heterozygous Hb Variant	
HTCS	Heterozygous Termination codon (TAA → CAA) mutation (Hb Constant Spring)
HTAD	Heterozygous Codon 59 (GGC → GAC) mutation (Hb Adana)
HTQS	Heterozygous Codon 125 (CTG → CCG) mutation (Hb Quang Sze)
HTPA	Heterozygous Termination codon (TAA → TAT) mutation (Hb Pakse)
HTEV	Heterozygous Codon 35 (TCC → CCC) mutation (Hb È vora)
HT30	Heterozygous Codon 30 (∆GAG) mutation
HTIC	Heterozygous Initiation codon (ATG → A-G) mutation identified.
HTQT	Heterozygous α1 Codon 74 (GAC>CAC) Hb Q-Thailand
HTOI	Heterozygous α1 Codon 116 (GAG>AAG) Hb O-Indonesia
HTJM	Heterozygous α1 Codon 120 (GCG>GAG) Hb J-Meerut
HTV	Others
Homozygous Hb Variant	
HVCSCS	Homozygous Termination codon (TAA → CAA) mutation (Hb Constant Spring)
HVADAD	Homozygous Codon 59 (GGC → GAC) mutation (Hb Adana)
HVQSQS	Homozygous Codon 125 (CTG → CCG) mutation (Hb Quang Sze)
HVHV	Others
Co-Inheritance 2 Types of Hb Variant	
HVCSAD	Termination codon (TAA → CAA) (Hb Constant Spring) and Codon 59 (GGC → GAC) (Hb Adana)
HVCSQS	Termination codon (TAA → CAA) mutation (Hb Constant Spring) and Codon 125 (CTG → CCG) mutation (Hb Quang Sze)
HVCSIC	Termination codon (TAA → CAA) (Hb Constant Spring) mutations and Initiation codon (ATG → A-G)
HVCSEV	Termination codon (TAA → CAA) (Hb Constant Spring) mutations and Codon 35 (TCC → CCC) mutation (Hb È vora)
HVHO	Others
Hb H Disease - Deletional	
HD1SE	Compound heterozygous alpha plus thalassaemia 3.7 and alpha zero thalassaemia South East Asian deletions

HD1FI	Compound heterozygous alpha plus thalassaemia 3.7 and alpha zero thalassaemia Filipino deletions
HD1TH	Compound heterozygous alpha plus thalassaemia 3.7 and alpha zero thalassaemia Thailand deletions
HD2SE	Compound heterozygous alpha plus thalassaemia 4.2 and alpha zero thalassaemia South East Asian deletions
HD2FI	Compound heterozygous alpha plus thalassaemia 4.2 and alpha zero thalassaemia Filipino deletions
HD2TH	Compound heterozygous alpha plus thalassaemia 4.2 and alpha zero thalassaemia Thailand deletions
HD	Others
Hb H Disease - Non-Deletional	
HNDSECS	Alpha zero thalassaemia South East Asian deletion and Termination Codon (TAA → CAA) mutation (Hb Constant Spring)
HNDSEAD	Alpha zero thalassaemia South East Asian deletion and Codon 59 (GGC → GAC) mutation (Hb Adana)
HNDSEQS	Alpha zero thalassaemia South East Asian deletion and Codon 125 (CTG → CCG) mutation (Hb Quang Sze)
HNDFICS	Alpha zero thalassaemia Filipino deletion and Termination Codon (TAA → CAA) mutation (Hb Constant Spring)
HNDFIAD	Alpha zero thalassaemia Filipino deletion and Codon 59 (GGC → GAC) mutation (Hb Adana)
HNDFIQS	Alpha zero thalassaemia Filipino deletion and Codon 125 (CTG → CCG) mutation (Hb Quang Sze) identified
HNDTHCS	Alpha zero thalassaemia Thailand deletion and Termination Codon (TAA → CAA) mutation (Hb Constant Spring)
HNDTHAD	Alpha zero thalassaemia Thailand and Codon 59 (GGC → GAC) mutation (Hb Adana)
HNDTHQS	Alpha zero thalassaemia Thailand deletion and Codon 125 (CTG → CCG) mutation (Hb Quang Sze)
HND	Others
Alpha Globin Gene Amplification / Insertion	
MCAT1	Triplication Alpha Anti 3.7
MCAT2	Triplication alpha anti 4.2
MSIN279	279nt insertion
MCATMC	Other rare duplication
RM	**Others - rare mutations detected by sequencing**
Hydrop Foetalis	
HFSESE	Homozygous for the alpha zero thalassaemia South East Asian deletion identified.
HFFIFI	Homozygous for the alpha zero thalassaemia Filipino deletion identified.
HFTHTH	Homozygous for the alpha zero thalassaemia Thailand deletion
HFSETH	Compound heterozygous for the alpha zero thalassaemia South East Asian and alpha zero Thailand deletions
HFSEFI	Compound heterozygous for the alpha zero thalassaemia South East Asian and alpha zero Filipino deletions
HFFITH	Compound heterozygous for the alpha zero thalassaemia Filipino and alpha zero Thailand deletion
HF	Others
Variant of Undetermined Clinical Significance (Alpha)	
AMC	Unknown Clinical Significance for alpha globin gene variant (heterozygous)
HAMC	Unknown Clinical Significance for alpha globin gene variant (homozygous)
CAMC	Unknown Clinical Significance for alpha globin gene variant (compound)

Uncharacterised Single Alpha Gene Deletion (Alpha Plus)	
AUP	Uncharacterised single alpha globin gene deletion (heterozygous)
HAUP	Uncharacterised single alpha globin gene deletion (homozygous)
CAUP	Uncharacterised single alpha globin gene deletion with other uncharacterised single alpha globin gene deletion (compound)
Uncharacterised Two Alpha Gene Deletion (Alpha Zero)	
AUZ	Uncharacterised two alpha globin gene deletion (heterozygous)
HAUZ	Uncharacterised two alpha globin gene deletion (homozygous)
CAUZ	Uncharacterised two alpha globin gene deletion with other uncharacterised two alpha globin gene deletion (compound)

C. DNA Analysis (Beta)

CODES	RESULTS
Beta Thalassaemia and Variant	
BP	Heterozygous Beta Plus
BZ	Heterozygous Beta Zero
BE	Heterozygous Hb E
BV	Heterozygous Beta Variants
HBPBP	Homozygous Beta plus
HBZBZ	Homozygous Beta zero
HBEBE	Homozygous Hb E
HBVBV	Homozygous Beta variant
BPBP	Compound Heterozygous Beta plus & Beta plus
BPBZ	Compound Heterozygous Beta plus & Beta zero
BPBE	Compound Heterozygous Beta plus & Hb E
BPBV	Compound Heterozygous Beta plus & Beta variant
BZBZ	Compound Heterozygous Beta zero & Beta zero
BZBE	Compound Heterozygous Beta zero & Hb E
BZBV	Compound Heterozygous Beta zero & Beta variant
BEBV	Compound Heterozygous Hb E & Beta variant
BVBV	Compound Heterozygous Beta variant & Beta variant
Variant of Undetermined Clinical Significance (Beta)	
BMC	Unknown Clinical Significance for beta globin gene variant (heterozygous)
HBMC	Unknown Clinical Significance for beta globin gene variant (homozygous)
CBMC	Unknown Clinical Significance for beta globin gene variant (compound)
Uncharacterised Beta Gene Deletion	
BU	Uncharacterised beta globin gene deletion (heterozygous)
HBU	Uncharacterised beta globin gene deletion (homozygous)
CBU	Uncharacterised beta globin gene deletion (compound)
Gamma Gene Polymorphism	
GMC	Gamma Plymorphism
Gamma Gene Duplication	
MCGD	Gamma gene duplication
Gamma Delta Beta Thalassaemia	
GDBZ	Heterozygous Gamma Delta Beta Zero
HGDBZ	Homozygous Gamma Delta Beta Zero

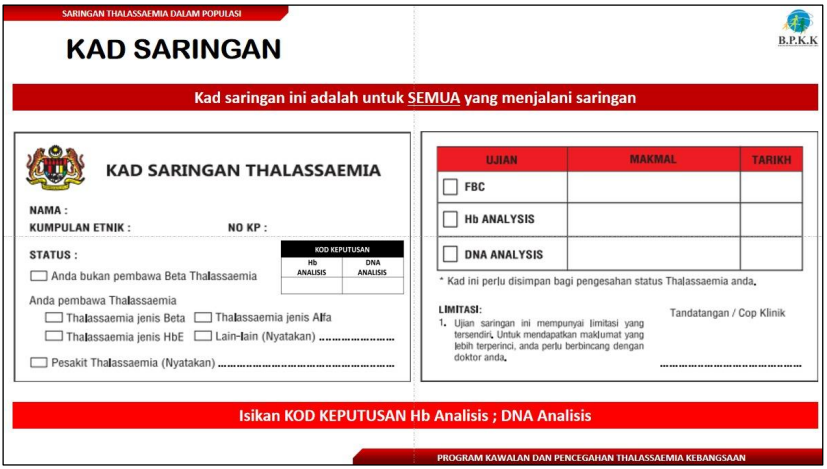
Gamma Delta Beta Thalassaemia and Beta Thalassaemia / Variant	
GDBZBZ	Compound gamma delta beta zero & beta zero
GDBZBP	Compound gamma delta beta zero & beta plus
GDBZBE	Compound gamma delta beta zero & Hb E
GDBZBV	Compound gamma delta beta zero & beta variant
Gamma Delta Beta Thalassaemia and Delta Plus/ Zero/ Variant	
GDBZDP	Compound gamma delta beta zero & delta plus
GDBZDZ	Compound gamma delta beta zero & delta zero
GDBZDV	Compound gamma delta beta zero & delta variant
Delta Plus Thalassaemia	
DP	Heterozygous delta plus
HDP	Homozygous delta plus
DPDP	Compound Heterozygous delta plus & delta plus
Delta Zero Thalassaemia	
DZ	Heterozygous delta zero
HDZ	Homozygous delta zero
DZDZ	Compound Heterozygous delta zero & delta zero
Delta Variant	
DV	Heterozygous delta variant
HDV	Homozygous delta variant
DVDV	Compound Heterozygous delta variant & delta variant
Delta Plus Thalassaemia and Beta Thalassaemia / Variant	
DPBP	Compound Heterozygous delta plus & beta plus
DPBZ	Compound Heterozygous delta plus & beta zero
DPBE	Compound Heterozygous delta plus & Hb E
DPBV	Compound Heterozygous delta plus & beta variant
Delta Zero Thalassaemia and Beta Thalassaemia / Variant	
DZBP	Compound Heterozygous delta zero & beta plus
DZBZ	Compound Heterozygous delta zero & beta zero
DZBE	Compound Heterozygous delta zero & Hb E
DZBV	Compound Heterozygous delta zero & beta variant
Delta Variant and Beta Thalassaemia / Variant	
DVBP	Compound Heterozygous delta variant & beta plus
DVBZ	Compound Heterozygous delta variant & beta zero
DVBE	Compound Heterozygous delta variant & Hb E
DVBV	Compound Heterozygous delta variant & beta variant
Delta Beta Zero Thalassaemia	
DBZ	Heterozygous delta beta zero
HDBZ	Homozygous delta beta zero
DBZDBZ	Compound Heterozygous delta beta zero & delta beta zero
Delta Beta Variant	
DBV	Heterozygous delta beta variant
HDBV	Homozygous delta beta variant
DBVDBV	Compound heterozygous delta beta variant & delta beta variant
Delta Beta Zero Thalassaemia and Delta Beta Variant	
DBZDBV	Compound heterozygous delta beta zero & delta beta variant

Delta Beta Zero Thalassaemia and Beta Thalassaemia / Variant	
DBZBP	Compound heterozygous delta beta zero & beta plus
DBZBZ	Compound heterozygous delta beta zero & beta zero
DBZBE	Compound heterozygous delta beta zero & Hb E
DBZBV	Compound heterozygous delta beta zero & beta variant
Delta Beta Variant Thalassaemia and Beta Thalassaemia / Variant	
DBVBP	Compound heterozygous delta beta variant & beta plus
DBVBZ	Compound heterozygous delta beta variant & beta zero
DBVBE	Compound heterozygous delta beta variant & Hb E
DBVBV	Compound heterozygous delta beta variant & beta variant
Delta Beta Zero/ Variant Thalassaemia and Gamma Delta Beta Thalassaemia	
DBZGDBZ	Compound heterozygous delta beta zero & gamma delta beta zero
DBVGDBZ	Compound heterozygous delta beta variant & gamma delta beta zero
Delta Beta Zero Thalassaemia and Delta Plus/ Zero/ Variant	
DBZDP	Compound heterozygous delta beta zero & delta plus
DBZDZ	Compound heterozygous delta beta zero & delta zero
DBZDV	Compound heterozygous delta beta zero & delta variant
Delta Beta Variant and Delta Delta Plus/ Zero/ Variant	
DBVDP	Compound heterozygous delta beta variant & delta plus
DBVDZ	Compound heterozygous delta beta variant & delta zero
DBVDV	Compound heterozygous delta beta variant & delta variant

Source: Ministry of Health. Malaysia. Laporan Tahunan 2024 Bahagian Perkembangan Kesihatan Keluarga. (Unpublished document)

Appendix 6

THALASSAEMIA SCREENING CARD



SARINGAN THALASSAEMIA DALAM POPULASI

B.P.K.K

KAD SARINGAN

Kad saringan ini adalah untuk SEMUA yang menjalani saringan

KAD SARINGAN THALASSAEMIA

NAMA :

KUMPULAN ETNIK : **NO KP :**

STATUS :

KOD KEPUTUSAN	
Hb ANALISIS	DNA ANALISIS

☐ Anda bukan pembawa Beta Thalassaemia

Anda pembawa Thalassaemia

☐ Thalassaemia jenis Beta ☐ Thalassaemia jenis Alfa

☐ Thalassaemia jenis HbE ☐ Lain-lain (Nyatakan) .....

☐ Pesakit Thalassaemia (Nyatakan) .....

UJIAN	MAKMAL	TARIKH
☐ FBC		
☐ Hb ANALYSIS		
☐ DNA ANALYSIS		

* Kad ini perlu disimpan bagi pengesahan status Thalassaemia anda.

LIMITASI:

1. Ujian saringan ini mempunyai limitasi yang tersendiri. Untuk mendapatkan maklumat yang lebih terperinci, anda perlu berbincang dengan doktor anda.

Tandatangan / Cop Klinik

.....

Isikan KOD KEPUTUSAN Hb Analisis ; DNA Analisis

PROGRAM KAWALAN DAN PENCEGAHAN THALASSAEMIA KEBANGSAAN

Appendix 7

RISK OF INHERITANCE BASED ON CARRIER OR DISEASE STATUS OF COUPLES

	α^o trait	α^+ trait	α^T trait	Not a carrier	Hb E trait	β trait
α^o trait	50% α^o trait 25% hydrop foetalis 25% not a carrier	25% Hb H disease 25% α^o trait 25% α^+ trait 25% not a carrier	25% Hb H disease 25% α^o trait 25% α^T trait 25% not a carrier	50% α^o trait 50% not a carrier	25% Hb E trait/α^o trait 25% α^o trait 25% Hb E trait 25% not a carrier	25% β trait/a^o trait 25% α^o trait 25% β trait 25% not a carrier
α^+ trait		25% α^+ homozygous 50% α^+ trait 25% not a carrier	25% α^T trait 25% α^+ trait 25% α^+/α^T compound heterozygous 25% not a carrier	50% α^+ trait 50% not a carrier	25% Hb E trait/α^+ trait 25% α^+ trait 25% Hb E trait 25% not a carrier	25% β trait/a^+ trait 25% α^+ trait 25% β trait 25% not a carrier
α^T trait			50% α^T trait 25% α^T homozygous 25% not a carrier	50% α^T trait 50% not a carrier	25% Hb E trait/α^T trait 25% α^T trait 25% Hb E trait 25% not a carrier	25% β trait/a^T trait 25% α^T trait 25% β trait 25% not a carrier
Not a carrier				100% not a carrier	50% Hb E trait 50% not a carrier	50% β trait 50% not a carrier
Hb E trait					50% Hb E trait 25% Hb E homozygous 25% not a carrier	25% Hb E β thal 25% Hb E trait 25% β trait 25% not a carrier
β trait						50% β trait 25% β thal major 25% not a carrier

	High-risk of severe phenotype
	Low-risk
	No risk
	Father's thalassaemia carrier status
	Mother's thalassaemia carrier status

thal: thalassaemia
trait: carrier
α^+: alpha plus – 1 gene deletion
α^o: alpha zero – 2 genes deletion
α^T: non-deletional

Genotype results and corresponding phenotypes:

Gene/genes affected	Phenotype	Patient/ Carrier	Symptoms
3 α genes affected	Hb H disease	Patient	Moderate anaemia and usually not transfusion dependent
2 α genes affected at both allele	Hb H phenotype	Patient	Moderate anaemia and usually not transfusion dependent
2 α genes affected	α^{o} trait (heterozygous)	Carrier	Asymptomatic (FBC parameters are more severe)
2 α genes affected at both allele	α^{o} homozygous	α thal major	Hydrop foetalis
1 α gene affected	α^{+} trait (heterozygous)	Carrier	Asymptomatic
1 α gene affected at both allele	α^{+} homozygous	Carrier	Asymptomatic
1 α gene affected	α^{T} trait	Carrier	Asymptomatic
2 α genes affected	α^{T} homozygous/ compound heterozygous	Patient	Variable phenotype depending on the variants
1 β gene affected	Hb E trait	Carrier	Asymptomatic
β genes affected at both allele	Hb E homozygous	Carrier	Asymptomatic
1 β gene with concomitant 2 α genes affected	Hb E trait with α^{o} trait	Carrier	Asymptomatic
1 β gene with concomitant 1 α gene affected	Hb E trait with α^{+} trait	Carrier	Asymptomatic
2 β genes affected	Hb E β thalassaemia	Patient	Moderate to severe anaemia
1 β gene affected	β trait	Carrier	Asymptomatic
2 α genes with concomitant 1 β gene affected	α^{o} trait with β trait	Carrier	Asymptomatic
1 α gene with concomitant 1 β gene affected	α^{+} trait with β trait	Carrier	Asymptomatic

Appendix 8

A. Summary of Iron Chelators

Drug / Characteristics	Deferoxamine (DFO) (500 mg vial; to be reconstituted with 5 ml of water for injection)	Deferiprone (DFP) (500 mg tablet; oral solution 100 mg/ml)	Deferasirox (DFX) (90 mg, 180 mg and 360 mg film-coated tablet)
Dose range (mg/kg/day)	• Children: 20 - 40 • Adults: 50 - 60	• 50 - 100 • Not recommended <3 years of age	• 14 - 28 • Not recommended <2 years of age
Half-life	• 20 mins	• 2 - 3 hours	• 8 - 16 hours
Route of administration	• SC: infused over 8 - 24 hours using a small portable pump for 5 - 7 days/week • IV: infused over 8 - 24 hours using a small portable pump for 5 - 7 days/week (infusion rate <15 mg/kg/hr) • IM: 0.5 - 1 g QID (max: 1 g QID)	• Oral: three times daily	• Oral: once daily • Can be crushed and sprinkled on to soft food e.g. yoghurt or apple puree
Iron excretion	• Urine and stool	• Urine	• Stool
Monitoring	• Vision and hearing assessment annually • Withhold if high fever develops	• Full blood count (ANC in particular) monthly • Liver function test (ALT in particular) 3 - 6 monthly	• Vision and hearing assessment annually • Renal function test and proteinuria monthly at initiation then 3 - 6 monthly • Liver function test (ALT in particular) monthly
Advantages	• Has highest iron binding affinity • May reverse cardiac disease • May be combined with DFP or DFX	• Enhanced removal of cardiac iron • May be combined with DFO or DFX • May improve adherence	• Once daily oral administration • Doesn't require to be dissolved in water (compared with previous effervescent tablet form)
Disadvantages	• Poor compliance • Requires to purchase infusion pump and injection kits • Potential ear, eye and bone toxicity	• Risk of thrombocytopaenia and agranulocytosis; thus, initial weekly FBC required when starting	• Risk of renal impairment; thus, requires close monitoring • Costly

Source:

1. European Medicines Agency. Ferriprox: EPAR - Product Information (Available at: https://www.ema.europa.eu/en/documents/product-information/ferriprox-epar-product-information_en.pdf).
2. Ministry of Health, Malaysia. Clinical Practice Guidelines on Management of Thalassaemia. Putrajaya: MoH; 2009.
3. Novartis Pharma AG. Understanding EXJADE® (Deferasirox) Film-Coated Tablets - A physician guide to dosing and administration. Basel: Novartis; 2017.

B. Summary of Common Adverse Effects of Iron Chelators

Drugs / Adverse effects	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
Skin – local pain, infection at injection sites	6 - 85%	N/A	N/A
Skin rashes	6 - 85%	Dry skin if associated with zinc deficiency	7%
Haematological	N/A	Agranulocytosis (ANC <500 x 10^3/L): 0.2/100 patient-years Neutropenia (ANC <1500 x 10^3/L): 2.8/100 patient-years Thrombocytopaenia: 45% of children <7 years old	N/A
Gastro-intestinal symptoms e.g. pain, nausea and vomiting	24%	33%	15.2% 2% raised liver enzymes
Renal – increase in serum creatinine	14%	N/A	38% Reduce dose by 7 mg/kg if serum creatinine levels rise above age-appropriate upper limit for paediatric patients' and >33% above baseline at two consecutive visits for adult patients' measurements. If eGFR <40 ml/min: discontinue treatment
Joint pain and stiffness	18 - 19%	28 - 37.5% If severe, consider temporary or permanent cessation of drug	N/A
Reduced visual acuity and impaired visual field	Present if dose is high	N/A	<1% lens opacities
Sensorineural deafness	Present if dose is high	N/A	<1% high frequency hearing losses

N/A= Not Available

Source:

1. European Medicines Agency. Ferriprox: EPAR - Product Information (Available at: https://www.ema.europa.eu/en/documents/product-information/ferriprox-epar-product-information_en.pdf).
2. Ministry of Health, Malaysia. Management of Thalassaemia. Putrajaya: MoH; 2009.
3. Novartis Pharma AG. Understanding EXJADE® (Deferasirox) Film-Coated Tablets - A physician guide to dosing and administration. Basel: Novartis; 2017.

Appendix 9

A. Mid-Parental Height Calculations

For boys, MPH (cm)	=	(Mother's height + 13 + Father's height) ÷ 2
For girls, MPH (cm)	=	(Father's height - 13 + Mother's height) ÷ 2
For boys and girls, MPH target height (cm)	=	MPH ± 10 cm, which represents the 3rd to 97th centiles

Source: Mavinkurve M, Azriyanti AZ, Jalaludin MY. The short child: Importance of early detection and timely referrai. Malays Fam Physician. 2021;16(3):6-15.

B. Tanner Staging and Orchidometer

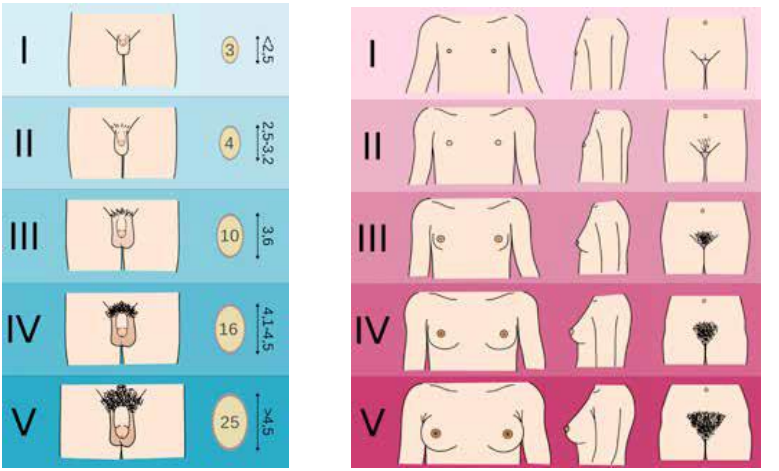


Figure I: Pubertal assessment in males and females according to Tanner. For the male figure, the average size of testis in cm and the capacity in ml is indicated.

Source: Cappellini M, Farmakis D, Porter J, et al. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. Cyprus: Thalassaemia International Federation; 2021. E732 p.

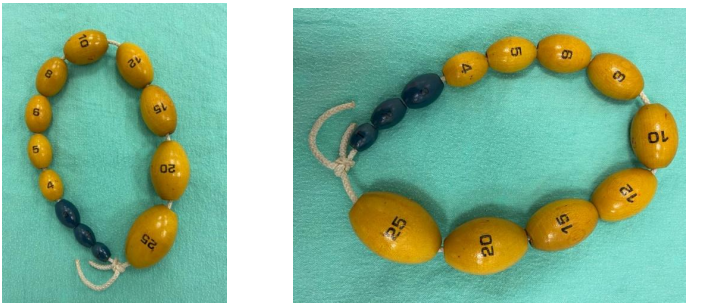


Figure II: Photos of orchidometer

Appendix 10

MICRONUTRIENTS SUPPLEMENTATION AND ASSESSMENT STRATEGY RECOMMENDATIONS FOR THALASSAEMIA PATIENTS

Nutrient	Recommended dietary allowance, (RDA)* (upper limit)	Recommended dose	Possible adverse effect
Folate	200 - 400 µg (400 - 1000µg)	1000 µg daily	None reported
Vitamin C	25 - 90 mg (650 - 2000mg)	100 mg daily	None reported
Vitamin D	600 IU (3000 - 4000 IU)	1000 IU daily 2000 IU daily if serum 25-OHD <20 ng/mL at baseline	None reported
Vitamin E	7 - 15 mg (300 - 1000mg)	200 mg daily	None reported
Zinc	5 - 11 mg (12 - 40 mg)	20 - 25 mg daily	Nausea
Calcium	250 - 1300 mg	500 mg daily (together with Vitamin D supplementation)	None reported

*RDA is the average daily level of dietary intake sufficient to meet the nutrient requirements of nearly 98% of healthy individuals

Source: Goldberg et al. Nutrition in Thalassemia: A Systematic Review of Deficiency, Relations to Morbidity, and Supplementation Recommendations. J Pediatr Hematol Oncol. 2022; 44(1): 1-11.

Appendix 11

IRON CONTENT IN SELECTED FOOD ITEMS

Food	Iron content (mg)/100 gm edible portion
Meat/Egg	
• Beef	2.7
• Lamb	2.3
• Pork	1.7
• Chicken	2.8
• Liver	9.0
• Egg yolk	7.9
Fish and seafoods	
• Dried anchovies (whole)	5.3
• Spanish mackerel	1.1
• Tuna	7.9
• Oysters	6.1
• Clams	6.7
• Shrimp	1.5
Vegetables	
• Spinach	5.0
• Fern shoots (pucuk paku)	5.2
• Bitter gourd	4.8
• Mustard leaves	6.1
• Kale	1.0
• Broccoli	2.0
• Asparagus	0.7
	0.6
Legumes and legume products	
• Chickpea	6.9
• Tofu	2.2
• Tempeh	1.8
• Soya bean milk (250 ml)	0.2
Fruits	
• Kedondong	3.4
• Jackfruit (nangka)	1.1
• Rambutan	2.5
Cereals and cereal products	
• Biscuits, wholemeal crackers	4.3
• Bread, wholemeal	3.2
• Kuih-teow	3.4

Source: Tee ES, Noor MI, Azudin MN et al. Nutrition Composition of Malaysian Foods. Malaysian Food Composition Database Programme Fourth Edition. Kuala Lumpur: Institute for Medical Research; 1997.

Appendix 12

MALAYSIAN THALASSAEMIA ASSOCIATIONS/SUPPORT GROUPS

No.	PERSATUAN	CONTACT
1.	**KELAB THALASSAEMIA KEDAH** No. 93, Kampung Langgar 06500, Alor Setar Kedah	**Email:** kelabthalassaemiakedah@yahoo.com ktkpresidents@gmail.com **Phone:** Pn. NoorHafiza: 0135993577 En. Azmi: 0125790230
2.	**MyTHAL Club (Kelab Talasemia Pusat Perubatan UKM)** Daycare Thalasemia, Tkt 2, Hospital Tuanku Ampuan Besar Tuanku Aishah Rohani, Hospital Pakar Kanak-Kanak UKM, Jalan Yaacob Latiff, Bandar Tun Razak, 5600, Cheras, Wilayah Persekutuan Kuala Lumpur	**Email:** mythalseminar@gmail.com **Phone:** Pn. Norhidayah: 019217319 Cik Mazian: 0126212517
3.	**KELAB TALASEMIA HOSPITAL AMPANG (KTHA)** Daycare Thalassaemia Hospital Ampang, Jalan Pandan Mewah Utara, Pandan Mewah, 68000, Ampang, Selangor	**Email:** kelabthalashospitalampang@gmail.com **Phone:** Pn. Soffiah: 01112405776 Pn. Noranaliza: 0192003675
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5.	**PERSATUAN ANAK-ANAK TALASEMIA PERLIS** Lorong Abi 6, Jalan Abi Kampung Tengah, 01000, Kangar, Perlis	**Email:** m.hilmiazhari@gmail.com **Phone:** En. Hilmi:0134143160
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12.	**THASUH (Thalassaemia Society of University Hospital)** No 17, Jalan BK5/6B. Bandar Kinrara 47180, Puchong, Selangor	**Email:** thasuhppum.society@gmail.com ireneng18@hotmail.com **Phone:** Pn. Hayati: 0192330568 Pn. Irene: 0123767800
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14	**GENETIC COUNSELLING SOCIETY OF MALAYSIA** c/o Cancer Research Malaysia 2nd Floor, Outpatient Centre, Subang Jaya Medical Centre, No 1, Jalan SS12/1A, 47500 Subang Jaya, Selangor	**Email:** admin@gcsocietymalaysia.org.my **Phone:** 0123747426

LIST OF ABBREVIATIONS

Ab	antibody
Ag	antigen
AE	adverse event/effect
AFP	alpha-fetoprotein
AGREE II	Appraisal of Guidelines, Research and Evaluation II
ALP	alkaline phosphatase
ALT	alanine transferase
AMH	anti-mullerian hormone
ANC	absolute neutrophil count
anti-HBe	hepatitis B e-antibody
Anti-HCV	antibodies to HCV
AUC	area under the curve
BD	twice daily
BMC	bone mineral content
BMD	bone mineral density
BMT	bone marrow transplantation
BSA	body surface area
CAE	cellulose acetate electrophoresis
CDGP	constitutional delay of growth and puberty
CZE	capillary zone electrophoresis
cffDNA	cell-free foetal DNA
CI	confidence interval
CIO	cardiac iron overload
cm	centimeter
CMR	cardiac MRI
CPG	clinical practice guidelines
CQ(s)	clinical question(s)
CV	cardiovascular
CVS	chorionic villus sampling
DAAs	direct acting anti-viral agents
DFO	deferoxamine or desferrioxamine
DFP	deferiprone
DFS	disease free survival
DFX	deferasirox
DG	Development Group
dL	decilitre
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DXA	Dual Energy X-ray Absorptiometry
ECG	electrocardiogram
EF	ejection fraction
e.g.	example
ELISA	enzyme-linked immunosorbent assay
EMH	extramedullary haematopoiesis
FCT	film-coated tablet
FGR	foetal growth restriction
fL	femtoliter
FMS	Family Medicine Specialist
FP	fertility preservation
FSH	follicle stimulating hormone
FT4	free thyroxine

g	gram
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GH	growth hormone
GHD	growth hormone deficiency
GLS	global longitudinal strain
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
Hb	haemoglobin
HBsAg	hepatitis B surface antigen
HBeAg	Hepatitis B e-antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCVAg	hepatitis C core antigen
HIV	human immunodeficiency virus
HH	hypogonadotropic hypogonadism
HLA	human leucocyte antigen
HPFH	hereditary persistence foetal haemoglobin
HPLC	high-performance liquid chromatography
HRQoL	health-related quality of life
HSC	haematopoietic stem cell
HSCT	haematopoietic stem cell transplantation
HSG	hysterosalpingography
HU	hydroxyurea
IDA	iron deficiency anaemia
IDDM	insulin dependent diabetes mellitus
IFG	impaired fasting glucose
IGF-1	insulin-like growth factor 1
IGT	impaired glucose tolerance
IM	intramuscular
IMR	Institute for Medical Reasearch
IU	international unit
IUD	intrauterine device
IUT	intrauterine transfusion
IV	intravenous
kg	kilogramme
L	litre
LFT	liver function test
LH	luteinising hormone
LIC	liver iron concentration
LIO	liver iron overload
LMWH	low molecular weight heparin
LSM	liver stiffness measurement
LV	left ventricular
LVEF	left ventricular ejection fraction
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular volume
MCA-PSV	middle cerebral artery peak systolic velocity
MD	mean difference
mg	milligram
mg Fe/g dw	milligram iron/gram dry weight
mg/kg	milligram per kilogram

MLPA	multiplex ligation-dependent probe amplification
ml	millilitre
µL	microlitre
mmol/L	millimol per litre
MPH	mid-parental height
ms	millisecond
m/s	meter per second
MoH	Ministry of Health
MoM	multiples of the median
MRI	magnetic resonance imaging
MTR	Malaysian Thalassaemia Registry
NICC	non-invasive chromosomal check
NIPT	non-invasive perinatal test
ng	nanogram
NGS	Next-Generation Sequencing
nmol	nano mol
NPV	negative predictive value
NRBC	nucleated red blood cell
NS	non-significant
NTDT	non-transfusion dependent thalassaemia
O&G	obstetrics & gynaecology
OGTT	oral glucose tolerance test
OR	odds ratio
OS	overall survival
OTC	ovarian tissue cryopreservation
OTT	ovarian tissue transplantation
p	p-value
PAH	pulmonary arterial hypertension
PCR	polymerase chain reaction
pg	picogram
PGD	pre-implantation genetic diagnosis
PGT-M	Pre-implantation Genetic Testing and Mapping
PK	pyruvate kinase
PND	prenatal diagnosis
PPV	positive predictive value
pRBC	packed red blood cell
PT	prothrombin time
PTH	parathyroid hormone
RBC	red blood cell
RCC	red cell concentrates
RDB	reverse dot blot
RDW	red cell distribution width
RC	Review Committee
RCT	randomised controlled trial
RNA	ribonucleic acid
RR	relative risk
SC	subcutaneous
SCD	sickle cell disease
SD	standard deviation
SF	serum ferritin
SMD	standardised mean difference
SNP	single nucleotide polymorphism
SVR	sustained virological response

T	tesla
TE	transient elastography
TESE	testicular sperm extraction
TI	thalassaemia intermedia
TIF	Thalassaemia International Federation
TDT	transfusion dependent thalassaemia
TM	thalassaemia major
TOP	termination of pregnancy
TRV	tricuspid regurgitation velocity
TSH	thyroid-stimulating hormone
USG	ultrasonography
WHO	World Health Organization
WMD	weighted mean difference
VTE	venous thromboembolism

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- All those who have contributed directly or indirectly to the development of the CPG

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MANAGEMENT OF THALASSAEMIA

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