CLINICAL PRACTICE GUIDELINES

November 2009 MOH/P/PAK/ 195.09 (GU)

Management of

TRANSFUSION DEPENDENT THALASSAEMIA

MINISTRY OF HEALTH MALAYSIA

MALAYSIAN SOCIETY OF PAEDIATRIC HAEMATOLOGY & ONCOLOGY

MALAYSIAN PAEDIATRIC ASSOICATION

ACADEMY OF MEDICINE MALAYSIA

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2009 and will be reviewed in 2013 or sooner if new evidence becomes available

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http://www.moh.gov.my
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GUIDELINES DEVELOPMENT

The development group for these guidelines consisted of paediatricians, paediatric haemato-oncologists, paediatric endocrinologists, haematologists, pathologists, public health physicians, a clinical geneticist, a family medicine specialist, a radiologist, a pharmacist and a nursing sister from the Ministry of Health and Ministry of Higher Education, Malaysia.

Literature search was carried out at the following electronic databases: International Health Technology Assessment website, PUBMED/ MEDLINE, Cochrane Database of Systemic Reviews (CDSR), Journal full text via OVID search engine, Database of Abstracts of Reviews of Effectiveness, Cochrane Controlled Trials Registered, Science Direct and CINAHL (**Refer to Appendix 1 for search terms**). In addition, the reference lists of studies selected for inclusion were scanned for relevant studies. Experts in this field were also contacted to identify further studies.

The clinical questions were divided into 14 major subgroups and members of the development group were assigned individual topics within these subgroups. All literature retrieved were appraised by at least two members using Critical Appraisal Skills Programme (CASP) checklists, presented in the form of evidence tables and discussed during group meetings. All statements and recommendations formulated were agreed by both the development group and the review committee. Where the evidence was insufficient, the recommendations were derived by consensus of the development group and review committee.

The articles were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendations in these guidelines was modified from the Scottish Intercollegiate Guidelines Network (SIGN).

The draft of these guidelines was posted on both the Ministry of Health Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. These guidelines had also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

OBJECTIVES

GENERAL OBJECTIVES

To provide evidence-based guidance in the management of transfusion dependent thalassaemia in paediatric and adult patients

SPECIFIC OBJECTIVES

- To provide guidance in diagnosing thalassaemia
- To provide guidance in counselling and cascade screening
- To provide guidance in blood transfusion for thalassaemia patients
- To provide guidance in iron chelation therapy
- To provide guidance in managing important complications in transfusion dependent thalassaemia

It is not the objective of these guidelines to cover:

- Management of thalassaemia patients who do not require regular blood transfusion
- Prenatal and intrauterine management
- Management of thalassaemia patients during pregnancy
- Population screening

TARGET POPULATION

Adult and paediatric transfusion dependent thalassaemia patients

INCLUSION AND EXCLUSION CRITERIA

a) Inclusion Criteria

Paediatric and adult transfusion dependent thalassaemia patients

Definition

- Transfusion dependent thalassaemia patients are those who require life-long regular blood transfusions

b) Exclusion Criteria

Thalassaemia patients who do not require regular blood transfusion

CLINICAL QUESTIONS

Refer to Appendix 2

TARGET GROUP/USER

All health care professionals/individuals who are involved in the management of transfusion dependent thalassaemia patients including:-

- Paediatrician
- Physician
- Haematologist
- Pathologist
- Radiologist
- Family Medicine Specialist
- Public Health Physician
- Medical Officer
- General Practitioner
- Pharmacist
- Dietitian/Nutritionist
- Nurse/Assistant Medical Officer
- Laboratory Personnel
- Medical Social Worker

Patients and their families/caregiver

HEALTH CARE SETTINGS

Outpatient, inpatient and community setting

PROPOSED CLINICAL INDICATORS FOR QUALITY MANAGEMENT

Primary Indicator

INDICATORS	FORMULA
Percentage of leucoreduced Packed Red Blood Cell (PRBC) units issued to transfusion dependent thalassaemia patients	$\frac{\text{Number of leucoreduced PRBC unit issued to transfusion dependent thalassaemia patients}}{\text{Total number of PRBC issued to transfusion dependent thalassaemia patients}} \times 100$
Percentage of transfusion dependent thalassaemia patients with serum ferritin above 1000 µg/L receiving iron chelation therapy	$\frac{\text{Number of transfusion dependent thalassaemia patients with serum ferritin level above 1000 µg/L receiving iron chelation therapy}}{\text{Total number of transfusion dependent thalassaemia patients with serum ferritin level above 1000 µg/L}} \times 100$
Percentage of transfusion dependent thalassaemia patients with mean annual serum ferritin below 2500 µg/L	$\frac{\text{Number of patients with mean annual serum ferritin below 2500 µg/L}}{\text{Total number of transfusion dependent thalassaemia patients}} \times 100$
Thalassaemia mortality rate per annum	$\frac{\text{Number of deaths of thalassaemia patients}}{\text{Total number of thalassaemia patients}} \times 100$

Secondary Indicator

Number of newly diagnosed thalassaemia major cases per annum

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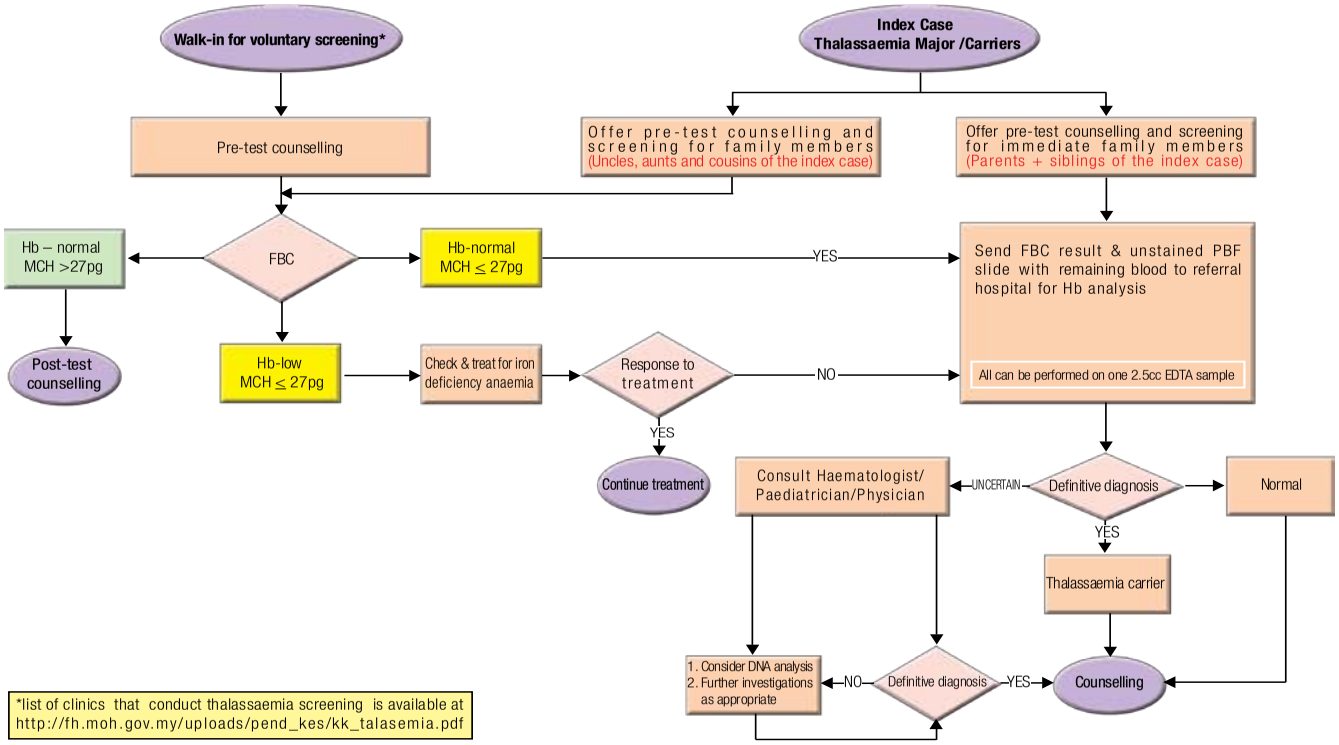
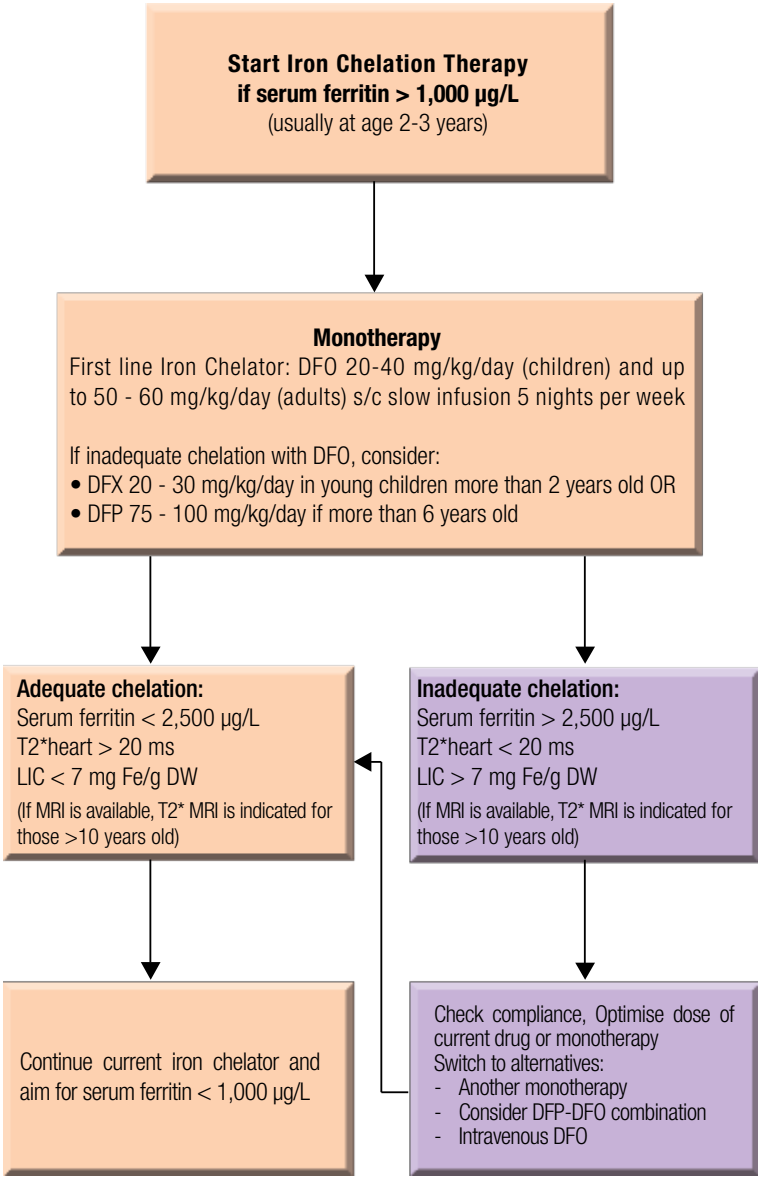
ALGORITHM FOR VOLUNTARY AND CASCADE SCREENING



ALGORITHM FOR IRON CHELATION IN TRANSFUSION DEPENDENT THALASSAEMIA



Abbreviations: DFO – Desferrioxamine DFP – Deferiprone DFX – Deferasirox LIC – Liver Iron Concentration

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1. INTRODUCTION

The thalassaemias are a heterogeneous group of genetic disorders with defective synthesis of one or more globin chains. In Malaysia, the most common types are the α and β thalassaemias. The β thalassaemias together with its heterozygous interaction with HbE disease constitute the bulk of the patients' load.

The most recent data from the Malaysian Thalassaemia Registry (2009, August) showed a total of 4,541 registered patients of which 3,310 consist of the transfusion dependent β thalassaemia major and HbE β thalassaemia patients. The thalassaemia intermedias accounted for 455 patients while HbH disease affected 410 individuals and the other subtypes made up the rest.[1]

The East Malaysian state of Sabah had the most number of registered patients standing at 1,272 with the Kadazan-Dusun ethnic group contributing almost half of these affected individuals. The neighbouring state of Sarawak however only registered 133 patients with incidentally no indigenous thalassaemic Ibans. The peninsular states showed a distribution pattern that followed the population density but with a distinct pattern of HbE β thalassaemia being more pronounced in the northern states bordering Thailand.[1]

The National Thalassaemia Prevention and Control Programme gained the Malaysian Cabinet approval in the late 2004. In early 2005, budget was made available to acquire infusion pumps and provide iron chelation therapy nationwide. This national programme comprises of four major activities namely:

- ★ provision of comprehensive management for thalassaemia patients
- ★ provision of a population screening and counselling at the primary care level
- ★ development and establishment of a National Thalassaemia Registry
- ★ building partnerships for health education and promotion in facilitating the people to take positive action in the control and prevention of thalassaemia

During the first inaugural National Steering Committee meeting chaired by the Health Minister on 4th October 2005, a decision was made to create a Clinical Management Committee to provide oversight for one of the major components of the programme which is the provision of a comprehensive management for thalassaemia patients in the country.

One of the desired outcomes from the meeting was developing a common thalassaemia CPG to be used across the country. With proper management, there should be a significant improvement in morbidity and mortality outcomes of patients with thalassaemia. All healthcare professionals managing thalassaemia patients are to be trained well with the best clinical practice and there should be serious initiatives to encourage thalassaemia-related clinical research activities.

These CPG will address not only clinical issues but also look at important public health aspects of screening and counselling at the primary care level. The burden of thalassaemia to Malaysian healthcare services will become more apparent in future with the improvement in patient care. This paradox is due to the changing landscape of patient demographics with more long term adult survivors requiring even more healthcare attention. These CPG will evolve and its contents will change to reflect the growing body of science to find solutions to this multi-dimensional public health problem.

2. DIAGNOSIS

2.1 CLINICAL DIAGNOSIS

Clinical diagnosis of thalassaemia is based on:

A. Presentation of β thalassaemia major at 4 - 6 months or a child younger than 2 years of age.[2-3 Level III]

Clinical features for β thalassaemia major are:
- a. Anaemia[2-6 Level III]
- b. Hepatosplenomegaly[2-5,6 Level III]
- c. Jaundice[4, 6 Level III]
- d. Thalassaemia facies[3-5, 7-8 Level III]
- e. Growth failure/retardation[4-7 Level III]

B. Presentation of β thalassaemia intermedia is at a later age[3,4,6 Level III]

Clinical features of β thalassaemia intermedia are:
- a. Milder anaemia[3, 6 Level III]
- b. Extensive thalassaemia facies[6 Level III]
- c. Hepatosplenomegaly[6 Level III]

2.2 LABORATORY DIAGNOSIS

2.2.1 Screening Tests

Full blood count (FBC) generated by an automated blood counter
Scrutiny of the red cell indices is the first step. Red cell indices are of particular importance in screening for α and β thalassaemia trait and in distinguishing between δβ thalassaemia and hereditary persistence of foetal haemoglobin.[9 Level III]

★ Mean corpuscular volume (MCV) & mean corpuscular haemoglobin (MCH)
Red cells are hypochromic (MCH < 27 pg) and microcytic (MCV < 80 fl) in thalassaemia as well as iron deficiency.[9-10 Level III] MCH is preferable because it is less susceptible to storage changes.

Haemoglobinopathies such as Hb Constant Spring will have a normal MCV and normal MCH and so will be missed if the above indices are used as a screening test.[11 Level III]

- ★ Red Cell Distribution Width (RDW - measure of the degree of variation in red cell size). Iron deficiency is characterised by an increase in RDW (CV > 14%).[12 Level III] The thalassaemia trait produces a uniform microcytic red cell population without a concomitant increase in RDW. RDW is increased in thalassaemia intermedia and thalassaemia major.[13-14 Level III] If iron deficiency is present, it is essential to correct this before proceeding to haemoglobinopathy workups.[10 Level III]

- ★ Refer to Algorithm for Voluntary and Cascade Screening.

2.2.2 Diagnostic Tests

Special Haematological Tests

High performance liquid chromatography (HPLC)
HPLC provides precise quantification of HbA_2 and HbF, and presumptive identification and quantification of variant haemoglobins.[9 Level III]

Diagnosis of β thalassaemia trait requires accurate determination of increased HbA_2 percentage.[11 Level III] The proportion of HbA_2 is dependent on the precise mutation present. In most cases of heterozygosity for β^0 or severe β^+ thalassaemia, the HbA_2 is 4 - 9%. In mild β^+ thalassaemia it is usually 3.6 - 4.2%.[15 Level III]

A low serum ferritin indicates that there is iron deficiency but does not exclude a diagnosis of β thalassaemia trait.[16 Level III] If iron deficiency is excluded and the HbA_2 percentage is normal, the diagnosis of α thalassaemia should be considered.[9] The possibility should be borne in mind that thalassaemia indices with a normal HbA_2 may be due to coexisting β and δ thalassaemia.[10 Level III]

HbA_2 level can be falsely lowered by iron deficiency therefore this requires correction before repeating the HPLC to quantify Hb subtypes.[11 Level III] Further tests/alternative techniques are indicated when the nature of any variant haemoglobin detected by HPLC is of potential clinical relevance.[9 Level III]

Other useful haematological tests are:[10 Level III]
- ★ Peripheral blood film (PBF)
- ★ Haemoglobin electrophoresis
- ★ H-inclusion test
- ★ Kleihauer test
- ★ Sickle solubility test

2.2.3 Laboratory Findings

2.2.3.1 β Thalassaemia Major

In transfusion dependent β thalassaemia major, the patients are homozygous β^0 thalassaemia (β^0/β^0) or with minimal HbA synthesis (β^+/β^0).[11 Level III]

Features are:

- ★ Anaemia is severe (7 g/dL and below)
- ★ Haematocrit low
- ★ RBC low
- ★ MCV low (50 - 60 fl)
- ★ MCH low (12 - 18 pg)
- ★ MCHC reduced
- ★ PBF: Marked anisocytosis, poikilocytosis (including fragments and tear-drop poikilocytes), hypochromia and microcytosis. Basophilic stippling, Pappenheimer bodies and target cells. Circulating nucleated red cells showing defective haemoglobinisation and dyserythropoietic features are present. The total white cell count and the neutrophil count are increased. If hypersplenism develops, there is leucopaenia, neutropaenia and thrombocytopaenia.[12 Level III]

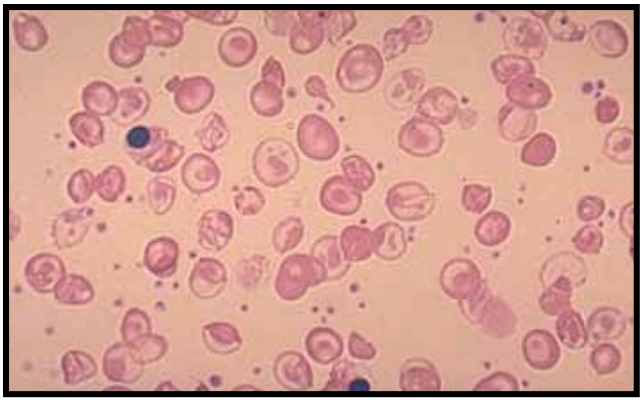

Figure 1. PBF of Thalassaemia Major

The predominant Hb subtype seen is HbF (> 90%). This will be significantly elevated in nearly every case of severe β thalassaemia unless a large blood transfusion has been administered immediately before the analysis. The complete absence of HbA indicates homozygous β^0 thalassaemia, while the diagnosis of β^+ thalassaemia is suggested by the finding of small amounts of HbA. It is important to carry out qualitative haemoglobin electrophoresis in order to rule out structural variants.[14 Level III]

2.2.3.2 Thalassaemia Intermedia

Features are:

- ★ Anaemia is moderate (8 - 10 g/dL)
- ★ PBF: a milder thalassaemia picture

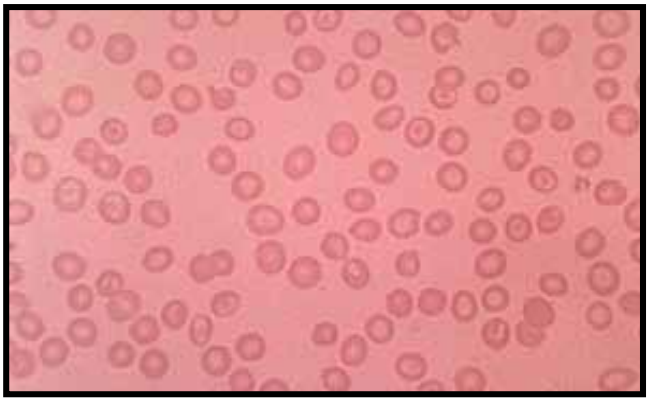

Figure 2. PBF of Thalassaemia Intermedia

In β thalassaemia intermedia, the Hb subtypes seen are HbF, HbA and HbA_2.[17 Level III] If the HbA_2 level is above 10%, this suggests the presence of HbE. If the predominant Hb consists of HbF and HbE, this corresponds to the diagnosis of HbE-β thalassaemia. In β^+ thalassaemia intermedia, there is raised HbF.

HbH disease presents as thalassaemia intermedia. It results from the interaction of α-thal 1 (α^0) with α^+-thalassaemia (deletional or non-deletional). The non deletional HbH disease ($--^{SEA}/\alpha\alpha^{CS}$) is clinically more severe than the deletional type ($--^{SEA}/-\alpha$).[18 Level III]

2.2.4 The Role of Molecular Diagnosis in Thalassaemia

DNA tests are required in:

1. Inability to confirm a haemoglobinopathy by haematological tests
2. Genetic counselling and prenatal diagnosis

DNA analysis is required to identify carriers of silent β thalassaemia or normal HbA_2 β thalassaemia, α^0 thalassaemia and some α^+ thalassaemia. These molecular methods are also required for identification of novel and rare haemoglobin variants.[19 Level III]

Majority of homozygous β thalassaemias can be diagnosed with simple investigations but in heavily transfused patients, DNA analysis will be able to identify the thalassaemia. The diagnosis is strengthened by findings of heterozygous β thalassaemia in both parents.[14 Level III]

2.2.5 Thalassaemia Mutations in Malaysia

α thalassaemias are most often due to gene deletions leading to α-thal 1 (α^0) and α-thal 2 (α^+) thalassaemia in the Malaysian population. α-thal 1 (α^0) results commonly from deletion of 17.5 to 20 kb of both duplicated α globin genes leaving the δ 1 globin gene intact (known as the Southeast Asian α^0 molecular defect).

Deletions of the globin gene complex that cause α-thal 2 (α^+)-thalassaemia remove one α globin gene. Two types of α-thal 2 deletional defects have been observed. One type involves a deletion of 4.2 kb of DNA (leftward type, $\alpha^{-4.2}$) and another removes 3.7 kb of DNA (rightward type, $\alpha^{-3.7}$). The latter is the most common α^+ thalassaemia defect in Malaysia and has been found both in Malays and Malaysian Chinese.[18 Level III]

β thalassaemias are heterogeneous at the molecular level with more than 200 different molecular defects identified.[17] Despite this heterogeneity, each at risk population has its own spectrum of common mutations, usually from 5 to 10, a finding that simplifies mutation analysis.[17 Level III]

In Malaysia, 14 β thalassaemia mutations contribute to the majority of β thalassaemia.[20 Level III] The interactions of these various mutations result in heterogeneity at phenotypic level. The predominant type of β thalassaemia among Malays has a β^+ phenotype [IVS 1-5 (G→C)].[21-24 Level III] In contrast, among Malaysian Chinese, this is found to be β^0 phenotype [FSC 41-42(-TCTT)].[18,25,26 Level III] β thalassaemia mutations in Malaysian Indians are heterogeneous. The common mutation seen in this group is IVS 1-5(G→C).[18 Level III] In Sabah, especially among the Kadazan-Dusuns, the predominant mutation is the 45kb deletion (Filipino deletion). Transfusion dependent β thalassaemia patients from Sabah accounted for 25% of the total patients in Malaysia.[27-28 Level III]

Table 1. β thalassaemia alleles in Malays and Malaysian Chinese[18]

Malays	Phenotype	%	Chinese	Phenotype	%
IVS 1-5(G to C)	β^+	50.0	Codon 41-42(-TCTT)	β^0	49.8
IVS 1-1(G to T)	β^0	19.4	IVS 2-654(C to T)	β^+	23.4
Codon 17(A to T)	β^0	13.9	-28(A to G)	β^+	13.3
Codon 35(-C)	β^0	8.3	Codon 17(A to T)	β^0	10.1
Codon 41-42(-TCTT)	β^0	5.6	FSC 71-72(+A)	β^0	2.1
IVS 2-654(C to T)	β^+	2.8	-29(A to G)	β^+	1.3

RECOMMENDATION

MCH level of ≤ 27 pg should be used as a threshold for identification of carriers in thalassaemia screening. **(GRADE C)**

Diagnosis of thalassaemia should include PBF, haemoglobin electrophoresis, H-inclusion test and HPLC. **(GRADE C)**

DNA tests should be done when there is inability to confirm a haemoglobinopathy by haematological tests. **(GRADE C)**

3. COUNSELLING AND SCREENING

3.1 GENETIC COUNSELLING

3.1.1 Introduction

★ Genetic counselling is the process in which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it, and of the ways in which this may be prevented/ avoided or ameliorated.[26] Level III

★ Genetic counselling is essential to protect the autonomy of an individual or couple and to fulfil their rights to maximum information about the disorder and to help them to understand and to choose among the options available.[30] Level III

★ Confidentiality of genetic information needs to be respected.[30] Level III

★ The success of genetic counselling depends crucially on its educational, voluntary and nonprescriptive/nondirective nature.[29] Level III

★ Psychological support and emphatic relationship between the counsellor and the counselee are important elements of genetic counselling.[30] Level III

3.1.2 Who should provide genetic counselling?

★ Genetic counselling should be provided by Clinical Geneticists, genetic counsellors or adequately trained medical/nursing staff who are confident at providing information regarding all aspects of thalassaemia.[30-34] Level II-3

★ Genetic counselling of at risk couples and families with affected individuals, and for people with unusual carrier states or particular problem/issue, should be provided by geneticists/ trained doctors.[29] Level III

★ Health workers involved in providing initial screening tests need to be able to provide simple and clear information about the reasons and objectives of the tests. **Lay counsellors should be avoided.**[29,34] Level III

3.1.3 When to provide the genetic counselling?

★ Counselling should be offered before carrier screening is conducted and after the result becomes available.[35] Level III

★ Genetic counselling should be offered once a diagnosis is made and further visits may have to be arranged.[35] Level III

3.1.4 Content of information

★ The topics of discussion should include; (1) information about thalassaemia, (2) treatment options, (3) the risk of having the condition and inheritance, (4) the purpose, nature and consequences of the genetic testing, (5) the risks involved in the procedure, (6) the limitations of testing, (7) alternatives the counselee should consider, (8) practical information on what will happen next, (9) the potential harm of testing, (10) the risks to family members, (11) the option of prenatal diagnosis and other choices, and (12) information on the available support groups.[30,34-37] Level III **[Refer to Appendix 3 and 4]**

★ Suitable information should be made available.[35] Level III This could be downloaded from MyHEALTH Portal *http://www.myhealth.gov.my,* and Thalassaemia Registry website *http://www.myTalasemia.net.my*

★ Contact of local support groups should be provided. **[Refer to Appendix 5]**

3.1.5 How should genetic counselling be conducted?

★ A counsellor should be trustworthy, proficient and knowledgeable, considerate and compassionate, maintain confidentiality, provide accurate and up to date facts, use plain and comprehensible language and allow the clients to decide for themselves.[33] Level III

★ An ideal genetic counselling process should comprise:[30]

- An appropriately trained professional who understands well genetics and its ethical implications;
- Relevant and objective information;
- Assurance of the counselee's understanding;
- Psychological support;
- Informed consent;
- Confidentiality of genetic information;
- Consideration of familial implications;
- Appropriate handling of potential discrimination as a result of testing; and
- Assurance of autonomous decision-making by the counselee

RECOMMENDATION

Genetic counselling should be provided by an appropriately trained professional. **(Grade C)**

Genetic counselling should be conducted in accordance to the following principles:

- ★ Provision of relevant and objective information;
- ★ Provision of psychosocial support;
- ★ Consideration of familial implications;
- ★ Obtaining informed consent for genetic testing;
- ★ Ensuring confidentiality of genetic information;
- ★ Appropriate handling of potential discrimination as a result of testing;
- ★ Assuring autonomous decision-making by the counselee **(Grade C)**

3.1.6 Should prenatal diagnosis be discussed?

- ★ In most cases, affected births stem from failure to inform parents of the possibility of risk and prevention adequately rather than their rejection of foetal testing.[29] Level III
- ★ Decisions for prenatal diagnosis are influenced by many factors, not religious or cultural factors alone.[38] Level II-3
- ★ Religion and faith are important factors in the decision making process but the perceived severity of the conditions will play a more important role.[36,38-41] Level III
- ★ Reproductive options for families affected with a transfusion-dependent β thalassaemia major patient should be decided by the families themselves after genetic counselling.[42-43] Level III

RECOMMENDATION

Prenatal diagnosis should be discussed regardless of religious and cultural background. **(Grade C)**

3.2 CASCADE SCREENING

3.2.1 Introduction

★ Genetic screening, defined by the European Society of Human Genetics (ESHG) as "any kind of test performed for the systematic early detection or exclusion of a genetic disease, the predisposition or resistance to such a disease, or to determine whether a person carries a gene variant which may produce disease in offspring. Cascade screening is a genetic-screening strategy that targets relatives of carriers/affected individuals of genetic disorders through the testing of their phenotypes or genotypes.[44] Level III

3.2.2 What is the role of cascade screening in the management of thalassaemia patients?

★ Preventing thalassaemia births is based on identifying individuals at risk, providing adequate information on risk and possibilities to reduce that risk.[29] Level III

★ Screening family members of an index case (thalassaemia major or carriers) should be performed.[45-46] Level II-3

★ Family members refer to siblings, parents, aunts, uncles and cousins.

Refer to Algorithm for Voluntary and Cascade Screening

RECOMMENDATION
Screening of family members of an index case should be offered. **(Grade C)**

4. BLOOD TRANSFUSION THERAPY

The aim of blood transfusion in thalassaemia is to suppress extramedullary haemopoiesis while minimising complications of under transfusion and maintaining normal well being.

The decision to start blood transfusion will require proper assessment of each individual thalassaemia patient. Transfusion should be started promptly when there is clinical evidence of severe anaemia with symptoms or signs of cardiac failure, failure to thrive, and/or thalassaemia bone deformity.

4.1 MANAGEMENT

4.1.1 Pre-Transfusion Investigations

- ★ Patient should be phenotyped for ABO, Rh, Kell,[47-49 Level II-3] Kidd, Duffy and MNSs[50 Level II] at diagnosis or before the first transfusion.
- ★ All anticipated multiply transfused thalassaemia patients should have their blood tested for viral markers at diagnosis or prior to first transfusion and at six monthly intervals: Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (Anti HCV) and HIV antibody (Anti HIV).[50 Level III]

4.1.2 Transfusion Regime for Thalassaemia Major

After presentation, patients should be monitored closely to ascertain ability to maintain Hb above 7 g/dL over a two-week period. Regular transfusion is started when a patient is confirmed to have thalassaemia major and is unable to maintain Hb > 7 g/dL or if there is poor growth.[51-52 Level III]

A pre-transfusion Hb of 9 - 10 g/dL would provide enough extramedullary suppression, allowing a reduction of blood consumption and reduce excessive iron absorption from the gut.[35,53,54 Level II- 3]

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.

Volume of transfusion: between 15 - 20 ml/kg depending on the pre-transfusion Hb and haematocrit of packed cells provided by the blood bank (Refer to Table 2). Whenever possible, the whole bag of blood should be used to prevent wastage.[51,55 Level III]

Transfusion interval depends on pre- and post-transfusion Hb level and can be 2 - 4 weeks apart. To minimise the likelihood of alloimmunisation, antigen matched blood for ABO, Rh and Kidd and any other antigen negative blood for defined antibody should be given.[50 Level III]

Whenever possible, fresh blood of less than 14 days should be given. Leucoreduced blood should be given to all thalassemia patients.[50,56 Level II-3]

All transfusions should adhere to the Transfusion Practice Guidelines for Clinical and Laboratory Personnel [50 Level II]

4.1.3 Transfusion Regime for Thalassaemia Intermedia

Regular transfusion is indicated when there is growth failure, bone deformities or extramedullary masses such as paraspinal.

Once the decision to transfuse is made, the regime should be similar to the one adopted for thalassaemia major.[35,51,53 Level III]

Blood transfusion reduces native precoagulant RBC and the rate of thalassaemia-related hypercoagulopathy.[57 Level III]

Table 2. Expected haemoglobin rise with haematocrit levels

Target increase in Hb	Haematocrit of Donor Red Cells			
	50%	60%	75%	80%
1g/dL	4.2 ml/kg	3.5 ml/kg	2.8 ml/kg	**2.6 ml/kg**
2g/dL	8.4 ml/kg	7.0 ml/kg	5.6 ml/kg	**5.2 ml/kg**
3g/dL	12.6 ml/kg	10.5 ml/kg	8.4 ml/kg	**7.8 ml/kg**
4g/dL	**16.8 ml/kg**	**14.0 ml/kg**	**11.2 ml/kg**	**10.4 ml/kg**

Example: For patient weighing 20 kg, 360mls transfusion every 4 weeks; average Hct 60%

Annual blood requirement = 13 transfusion X 360 mls / 20 kg = 234 ml/kg/yr

Annual pure RBC requirement = 234 X 60% = 140.4 ml/kg/yr

Annual transfusional iron loading = 140.4 X 1.08 = 152 mg/kg iron.

★Usual Haematocrit level of Malaysian packed red cell ranges from 50 to 75%

4.2 MONITORING OF PATIENT DURING BLOOD TRANSFUSION

- ★ The patient should be reviewed prior to each transfusion, to determine pre-transfusion haemoglobin level and to ensure that the planned transfusion is appropriate.
- ★ Transfusion should be given in a proper clinical area with proper personnel supervising the transfusions.[50,56 Level II-3]
- ★ For suspected acute transfusion reaction, the blood transfusion must be **STOPPED** immediately and resuscitation measures taken and appropriate investigations carried out simultaneously to determine the cause.
- ★ For management of other transfusion reactions, reference should be made to the National Transfusion Practice Guidelines.[50 Level III]

RECOMMENDATION
All patients should have full red cell phenotyping at diagnosis or prior to first transfusion consisting of ABO, Rh, Kell, Kidd, Duffy and MNSs. **(GRADE C)**
All patients should also be tested for the following viral markers at diagnosis and every 6 months: a. HBsAg b. Anti HCV antibody c. Anti HIV antibody **(GRADE C)**
Pre-transfusion Hb should be kept between 9 - 10 g/dL. **(GRADE C)**
Transfusion should be initiated when the patient is confirmed to have thalassaemia major ★ and Hb < 7g/dL more than 2 weeks apart or ★ failure to thrive or bony deformities **(GRADE C)**
Volume of transfusion: 15 - 20 ml/kg; dependent on haematocrit of blood pack and preferably the whole pack of blood should be utilised. **(GRADE C)**
Interval of transfusion is usually 2 - 4 weeks apart. **(GRADE C)**

5. SPLENECTOMY

With the current practice of optimal transfusion, splenectomy can usually be avoided. However, some patients with hypersplenism might still require splenectomy to reduce transfusion requirements. Splenectomy can reduce blood consumption significantly, up to 30 - 50% and is long lasting.[58-63 Level II-3] But it is advisable to delay splenectomy until patients are more than five years of age because of the risk of overwhelming sepsis.[64-66 Level I]

In a thalassaemia patient, transfusion requirement is normally 180 ml/kg/yr of pure RBC.[67 Level II-2, 55 Level III]

Splenectomy should therefore be considered when there is:

- ★ Increased transfusion requirements which is 1.5 times than usual[51] or exceeding 200 - 250 ml/kg/yr of pure red blood cells[55,60-64 Level III]
- ★ Evidence of hypersplenism as documented by splenomegaly with persistent leucopaenia or thrombocytopaenia[68 Level III]
- ★ Massive splenomegaly causing discomfort and risk of infarct or rupture from trauma[51,52 Level III]

Medic alert should be given post-splenectomy.[69 Level III]

5.1 COMPLICATIONS OF SPLENECTOMY

5.1.1 Sepsis

Major long term risk after splenectomy is sepsis. Risk of sepsis post-splenectomy is more than that of normal population. Overwhelming post-splenectomy infection (OPSI) carries a mortality risk of 38 - 69%.[69 Level III, 70-71 Level II-3, 72 Level III]

Streptococcus pneumoniae accounts for 50 - 90% of infections in asplenic patients.[69 Level III] Other infective organisms include Haemophilus, Neisseria and other encapsulated gram negative organisms. Protozoan infections like babeosis and malaria are also reported to be more severe in asplenic patients.

Patients must be educated on the recognition and importance of seeking immediate medical attention if there are febrile episodes especially in the first 2 years post-splenectomy.[64-66 Level I]

Physicians should have high level of awareness of the infection and if bacteraemia is suspected, parenteral antibiotics against Pneumococcus and Haemophilus should be started.[64-66 Level I]

5.1.1.1 Overwhelming Post - Splenectomy Infection (OPSI)

Characteristics of OPSI include sudden onset of fever and chills, vomiting and headache. It can progress rapidly to hypotensive shock and DIVC. Therefore prevention and early intervention is important.

Risk factors are:

- ★ Age < 4 years old
- ★ First two years post-splenectomy - risk reduces with time[72 Level II-2]

Treatment of OPSI:

- ★ Empirical broad spectrum parenteral antibiotics should be immediately given such as third generation cephalosporins and aminoglycosides.

5.1.1.2 Prevention

Immunoprophylaxis and chemoprophylaxis are recommended:

1. Immunoprophylaxis: [64-66 Level I]
   - ★ Pneumococcal vaccination using 23-valent polysaccharide vaccine at least two weeks before surgery. Revaccination is required at five years post-splenectomy.
   - ★ HIB vaccination two weeks pre-surgery if not vaccinated previously.
   - ★ Meningococcal vaccination is recommended in endemic areas.

2. Chemoprophylaxis
   - ★ Use of penicillin has been shown to reduce risk of sepsis even without immunisation.[73 Level III]
   - ★ Oral Penicillin prophylaxis for life. Importance of compliance to prophylactic antibiotics should be repeatedly stressed to both patients and parents especially during the first two years post-splenectomy.[64-66 Level I, 74 Level II-3]

- ★ IM Benzathine penicillin 3 - 4 weekly can be used as an alternative.
- ★ For patients allergic to penicillin, alternatives include erythromycin, cotrimoxazole and moxifloxacin.[69] Level III

5.1.2 Thrombotic Risk

Thromboembolic phenomenon is more common in thalassaemia intermedia (4 - 10%) than thalassaemia major (0.9 - 4%). In splenectomised thalassaemia intermedia, the risk can increase up to 30%.[75-77] Level II-3 Use of short term anticoagulation may be indicated during periods of increased risk for example immobilisation and post-surgery.[78-82] Level II-3

5.1.3 Thrombocytosis

Post-splenectomy thrombocytosis is a known complication[83] and the use of low dose aspirin or dypyridamole if platelet count is more than 800 x 10^9/L may be considered.[59,84] Level II-3

RECOMMENDATION

Splenectomy may be considered when a patient of more than five years old presents with any of the following:

1. Increased transfusion requirements exceeding 200 - 250 ml/kg/year pure RBC
2. Evidence of hypersplenism
3. Massive splenomegaly **(Grade C)**

Immunoprophylaxis and chemoprophylaxis must be adhered to. Patients must also be educated on the risks so that they can seek early treatment. **(Grade A)**

Thromboembolic phenomenon is more common in patients with thalassaemia intermedia, therefore short term anti-thrombotic prophylaxis should be considered during risk periods. **(Grade C)**

Low dose aspirin can be considered for post-splenectomised patients with platelet count above 800 x 10^9/L. **(Grade C)**

6. ASSESSMENT OF IRON BURDEN

Monthly packed red blood cell (PRBC) transfusions will result in an iron intake of 0.3 - 0.5 mg/kg/day. After about 10 - 20 transfusions, most patients will have a serum ferritin (SF) level exceeding 1000 µg/L , an iron load considered high enough to warrant iron chelation therapy.[85-86 Level III]

Assessment of iron intake should include accurate documentation of the dates, frequency and volume of PRBC received. Information on the patient's weight and haematocrit of PRBC would enable calculation of the iron intake per day.

6.1 SERUM FERRITIN (SF)

There is correlation between the number of transfusions received and SF levels especially in those who are younger and have not received many units of blood.[87 Level II-3] In addition, measuring the mean SF level over a period of time and the trend of SF would give a good estimate on the risk of complications secondary to iron overload.[88 Level II-3] However, there are limitations on SF measurements and they may not accurately reflect total body iron stores. Patients may have low SF levels for years but also have severe myocardial siderosis measured by MRI.[89 Level II-3]

Currently, many patients may not readily have access to measurements of liver and cardiac iron stores by biopsy or radioimaging. Thus, SF levels may continue to be the main guide to management of iron chelation therapy and an increasing trend of SF levels would suggest inadequate chelation.

6.2 LIVER IRON CONCENTRATION (LIC)

There is evidence that total liver iron is a constant fraction of total body iron[90 Level II-3] and hence, LIC as measured by liver biopsy has been used in the past as the gold standard to reflect body iron load. Normal individuals have LIC < 1.8 mg Fe/g dry weight (DW). Values > 3 mg Fe/g DW would reflect overload and the need for iron chelation therapy. However liver biopsy is invasive and may be affected by sampling error particularly in cirrhotic livers or patients with hepatitis.[91 Level II-2]

6.3 MAGNETIC RESONANCE IMAGING (MRI)

MRI is a useful and non invasive tool for estimating tissue iron overload. Two basic approaches have been developed:

1. Indirect quantitative methods that use signal intensity ratio (SIR)
2. Direct quantitative methods that use T2, T2* or R2, R2* parameters

6.3.1 Cardiac and Liver T2

Cardiac and liver T2 can be measured directly. However, the techniques are limited due to its sensitivity to cardiac and respiratory motions.[92-93 Level II-3]

6.3.2 MRI T2*

MRI T2* is fast and easy to acquire, robust to motion, more sensitive to iron levels and reproducible over time in different centres with different scanners. However it requires a patient's cooperation and ability to do a breath-hold during the procedure. Studies have demonstrated the utility of this parameter in predicting early cardiac siderosis versus conventional echocardiography. Values of < 20 ms indicate cardiac iron overload.[94-95 Level II-3] The values are also comparable to liver iron concentration by biopsy.[72 Level II-3] Ongoing studies are being done to assess tissue iron in other organs by T2* measurements.

6.3.3 MRI R2

MRI R2 has been shown to correlate with LIC. Measurement of R2 by MRI has now been validated as a reliable and reproducible measurement of LIC.[96-97 Level II-2] However, analysis of MRI R2 is solely performed by a commercial entity and therefore expensive.

6.4 THE NEED TO DO BOTH LIVER AND CARDIAC IRON ASSESSMENTS

Studies have failed to show any significant correlation between liver and cardiac iron overload by MRI. Therefore, it is necessary to measure both liver and cardiac iron separately.[89,94,98 Level II-3]

RECOMMENDATION
Serum ferritin levels should be monitored every 3 - 6 months. **(Grade C)**
MRI T2* should be used to assess cardiac iron status in older children. **(Grade C)**
MRI R2 can be used to assess liver iron. **(Grade C)**

7. IRON CHELATION THERAPY

The treatment for iron overload in blood transfusion dependent thalassaemia patients is iron chelation. Experience with the earliest chelator desferrioxamine showed that good compliance and ability to keep the serum ferritin levels consistently < 2000 to 2500 µg/L was associated with improved survival.[99-102 Level II-2]

The aims of iron chelation therapy are to prevent or reduce iron overload and hence minimise tissue and organ damage. Accurate and reliable tools for measurement of iron overload are necessary for titration of iron chelation therapy. Serum ferritin level should be kept below 1000 µg/L as it is associated with less iron overload complications[51,52,101 Level III] while serum ferritin level maintained below 2,500 µg/L significantly improve cardiac disease free survival.[100,101 Level II-2]

Where liver and cardiac iron load are measurable, LIC should be kept between 3 - 7 mg Fe/g DW and cardiac T2* > 20 ms.

7.1 IRON CHELATORS

7.1.1 Desferrioxamine (DFO) Monotherapy

Indications

Desferrioxamine monotherapy has been used since 1960s in paediatric thalassaemia patients with iron overload.[99-101 Level II-2] Patients who are compliant and able to maintain serum ferritin levels consistently < 2500 µg/L have improved survival.[52 Level I] The current standard treatment is slow subcutaneous infusion over at least 8 hours per night for 5 nights per week in a dose of 20 - 40 mg/kg/day (children) and up to 50 - 60 mg/kg/day (adults).[51,103 Level III] The dose is adjusted based on the therapeutic index. To avoid excessive chelation, the therapeutic index is kept < 0.025 at all times.[51,104 Level III] DFO should be used with caution in children under 3 years of age in view of its potential toxicity to bone development and growth.

$$\text{Therapeutic Index} = \frac{\text{Mean daily dose (mg/kg)}}{\text{Serum ferritin (µg/L)}}$$

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

This tedious and unpleasant subcutaneous drug regime has resulted in poor compliance and hence compromises the effectiveness of DFO. In clinical practice, the compliance to DFO monotherapy was reported to range from 59 to 78%[105 Level III] leading to suboptimal DFO therapy and high body iron overload and cardiac iron toxicity.

DFO continuous intravenous infusion can be used as a rescue therapy in patients with acute cardiac problems and has been shown to reverse cardiomyopathy.[106 Level III]

There may be a role for subcutaneous DFO twice daily bolus treatment if infusion pump is not available.[107 Level III]

Monitoring
Refer to Table 3

Side effects
Refer to Table 4

7.1.2 Deferiprone (DFP) Monotherapy

Indications
Oral DFP given three times a day in a dose of 75 mg/kg/day is an effective iron chelator in children more than 6 years old and its efficacy is comparable to DFO.[51,75,108,109 Level I] Clinical studies consistently showed that DFP had a better cardio-protective effect than DFO.[110 Level II-1,111-114 Level II-2] The compliance to DFP monotherapy which ranged from 79 to 98% was better than that of DFO monotherapy.[105 Level II-2]

Monitoring
Refer to Table 3

Side effects
Refer to Table 4

The risk of agranulocytosis (ANC <500 x 10^3/L) is 0.2 to 0.6 per 100 patient years. The risk of neutropaenia (ANC <1500 x 10^3/L) is 2.8 to 5.4 per 100 patient years. The neutropaenia is reversible and more likely to occur in those with intact spleens.[108,115 Level II-2]

Any patient with documented neutropaenia (ANC<1000 x 10^3/L) should have DFP stopped and never to be rechallenged. Any patient who develops fever while on DFP should have DFP stopped temporarily, neutrophil count tested and reviewed.

7.1.3 Deferasirox (DFX) Monotherapy

Indications

The newest iron chelator DFX is an alternative to DFO in children from 2 years old.[116,117 Level I, 118,119 Level II-1] Oral DFX monotherapy taken once daily in a dose of 20 - 30 mg/kg/day is as efficacious as conventional DFO slow infusion therapy in reducing liver iron concentration and serum ferritin. DFX has been used in clinical practice for less than five years. The high cost of DFX therapy at present may be a hindrance to its wider usage. In a recent systematic review, DFX was more cost effective than DFO based on quality adjusted life years (QALY), and DFP was more cost-effective than DFX in older children.[120 Level I]

Monitoring

Refer to Table 3

Side effects

Refer to Table 4

DFX may cause a reversible, dose-related, non-progressive increase in serum creatinine within the upper limit of normal.[121 Level I]

7.1.4 Combination Therapy DFO and DFP

Indications

Combination of DFO and DFP therapy is indicated when monotherapy fails.[121,122 Level II-1, 123,124 Level II-2]

Monitoring

Refer to Table 3

Side effects

Refer to Table 4

The side effects of DFO-DFP combination are the same as the side effects of the individual chelators.[122 Level II-1, 123 Level II-2]

7.2 WHEN TO START IRON CHELATION THERAPY?

The optimal threshold to start iron chelation therapy is undetermined but based on good clinical practice, patients who have received > 10 units of blood and when serum ferritin is > 1000 µg/L on more than two occasions in at least two weeks apart [51 Level III] are recommended to start on iron chelation therapy.[51,125,126 Level III]

All iron chelators are listed as specialist item **(list A/A*)** in Ministry of Health Drug Formulary 2008.[127]

RECOMMENDATION
All patients with iron overload (SF > 1000 µg/L on two occasions in at least two weeks apart) should receive iron chelation therapy. **(Grade C)**
Iron chelation therapy should be started after discussion with a paediatrician/physician. **(Grade C)**

7.3 CHOICE OF CHELATORS

Patients who have received regular PRBC transfusions for only a few years are likely to have mild iron overload. For these patients, all three iron chelators (DFO, DFP and DFX) are efficacious in reducing serum ferritin levels and LIC. Comparison between subcutaneous DFO at 40 - 50 mg/kg/day and DFP at 75 mg/kg/day showed similar efficacy in patients whose SF levels were generally < 3000 µg/L,[110,116,121,128 Level I,129 Level II-1] Cappelini *et al.* showed that DFX at 20 - 30 mg/kg/day had similar efficacy compared with DFO at 30 - 50 mg/kg/day in reducing SF and LIC.[116 Level I] The choice of an iron chelator for patients with mild to moderate iron overload would depend on availability, cost, tolerability, patient preferences and quality of life issues.[130-134 Level II-3] DFO has the advantage of a long history of use in terms of safety and efficacy and currently should be offered as the first line agent when starting iron chelation therapy. Compliance issues with DFO need to be monitored, counselled and rectified wherever possible before a change of chelator is contemplated.

For patients with significant iron overload (SF 2000 - 8000 µg/L or LIC 5 - 15 mg Fe/g DW), Piga *et al.* showed that both DFX at 20 mg/kg/day and DFO at 40 mg/kg/day were able to reduce LIC.[119 Level II-1] Similarly, DFP at 75 mg/kg/day is comparable to DFO at 40 - 50 mg/kg/day.[135 Level II-1] There is evidence that combination therapy with DFO and DFP is better than monotherapy.[122 Level I] Patients who do not show adequate response while on optimised doses of monotherapy would be suitable candidates for combination therapy. Definition of combination therapy has varied but rests on DFP at 75 - 100 mg/kg/day with DFO at 40 - 50 mg/kg/day given two to five times per week.[121,128 Level I]

For the use of DFO, optimisation would include increasing the dose to 60 mg/kg/day, increasing the duration of infusion (even up to 24 hours per day) and the number of days of therapy (up to 7 days per week). For DFP a dose of 100 mg/kg/day[100,116 Level II-2,118 Level I] should be considered while for DFX, doses of 40 mg/kg/day have been used.[136 Level I]

Adequate response to iron chelation therapy is reflected by a reduction in serum ferritin levels over time such as SF reduced by 1000 µg/L over 12 months. Iron is removed from tissues at a slow rate and decisions to change chelators should not be made on a single serum ferritin level.

RECOMMENDATION

Desferrioxamine (DFO) therapy

- ❒ Subcutaneous slow DFO infusion over five days per week is the first line iron chelator in view of its efficacy in compliant patients and proven safety record. **(Grade A)**
- ❒ Patients on DFO therapy should be monitored for non-compliance or intolerance to the therapy. **(Grade B)**

Deferiprone (DFP) therapy

- ❒ DFP monotherapy is indicated in patients older than 6 years if DFO treatment is inadequate or intolerable. **(Grade B)**
- ❒ DFP is indicated in patients who are at risk of cardiac iron toxicity. **(Grade B)**
- ❒ Patients on DFP should have weekly FBC. **(Grade B)**
- ❒ DFP should be discontinued in the presence of neutropaenia. **(Grade B)**

Deferasirox (DFX) therapy

- ❒ DFX monotherapy once daily is indicated in patients from 2 years old where DFO is unacceptable, inadequate or intolerable. **(Grade B)**
- ❒ Patients who are on DFX should have their serum creatinine monitored monthly. **(Grade B)**

Combination of DFO & DFP

- ❒ DFO & DFP combination is indicated in patients with severe iron overload or inadequate chelation with monotherapy. **(Grade B)**

Tailoring chelation by iron load*

- ❒ Patients with mild iron overload (SF < 2500 µg/L or LIC < 7 mg Fe/g DW liver) may use DFO, DFP or DFX. **(Grade B)**
- ❒ Patients with moderate iron overload (SF 2500 - 5000 µg/L or LIC 7 - 15 mg Fe/g DW liver) should optimise their respective chelator monotherapy or consider combination therapy. **(Grade B)**
- ❒ Patients with severe iron overload (SF > 5000 µg/L or LIC >15 mg Fe/g DW liver) should consider combination therapy. **(Grade B)**

Treatment Target

- ❒ Aim to keep SF level near to 1000 µg/L, LIC < 7 mg Fe/g DW liver and cardiac T2* > 20 ms. **(Grade C)**

* The above categorisation of mild, moderate and severe iron overload is partly arbitrary and derived from accumulated literature.

Table 3. Summary of Iron Chelators[105 Level III]

Characteristics	Desferrioxamine (DFO) (500mg vial, add 5ml water)	Deferiprone (DFP) (500mg tablet)	Deferasirox (DFX) (125mg tablet; 500mg tablet)
Dose range (mg/kg/day)	20 - 60	50 - 100 (usually ≥ 75 mg/kg/day to achieve negative iron balance)	20 - 30
Half-life	20 min	2 - 3 hours	8 - 16 hours
Administration	Parenteral Standard treatment is slow s/c infusion over 8 - 12 hours for 5 nights per week	Oral, tds	Oral daily dose (tablet dispersed in water)
Iron excretion	Urine, stool	Urine	Stool
Monitoring	Auditory/eye assessment annually If high fever, DFO should be stopped temporarily	FBC & differentials weekly ALT every 3 months	Serum creatinine, ALT, proteinuria monthly Auditory and eye assessment annually
Advantages	Efficacious Used > 40 years May reverse cardiac disease May be combined with DFP	Enhanced removal of cardiac iron May be combined with DFO	Once daily oral administration
Disadvantages	Poor compliance Potential ear, eye, bone toxicity	Risk of agranulocytosis Need for weekly FBC	Need to monitor renal function Drug is expensive compared to other chelators Long term data not available

* Drug cost for different type of iron chelating agents (**Refer to Appendix 6**).

Table 4. Summary of Common Side Effects of Iron Chelators

Side Effects	Desferrioxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
Skin - local pain, infection at injection sites	6 - 85%[51,75,110,122]	Not Applicable	Not Applicable
Skin rashes	As above	Dry skin if associated with zinc deficiency	7%[116]
Haematological	NA	Agranulocytosis (ANC < 500 x 10^3/L) is 0.2 per 100 patient years and Neutropenia (ANC < 1500 x 10^3/L) is 2.8 per 100 patient years.[108,115] Thrombocytopaenia in 45% of children < 7 years old.[137]	NA
Gastro-intestinal symptoms - pain, nausea, vomiting	24%[122]	33%[115]	15.2%[116] 2% raised liver enzymes.[116]
Renal (increase in serum creatinine)	14%[111]	NA	38%[116] Reduce dose by 10 mg/kg if serum creatinine levels rise above the age-appropriate upper limit for paediatric patients and > 33% above baseline at two consecutive visits for adults measurements.
Joint pain and stiffness	18 - 19%[110,122]	28 - 37.5%.[110,75] If severe, consider temporary or permanent cessation of drug.	NA
Reduced visual acuity and impaired visual field	Present if dose is high.[51]	NA	< 1% lens opacities.
Sensorineural deafness	Present if dose is high.[51,104]	NA	< 1% high frequency hearing losses.

NA= Not Available

8. HAEMOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Bone marrow transplantation from human leucocyte antigen (HLA) identical family donors is an established curative treatment option for children with thalassaemia.[138 Level II-2]

Three patient classes have been identified on the basis of the following risk factors, which have been found to have a significant negative influence on post-transplant outcome:

- ★ Inadequate iron chelation therapy
- ★ Presence of liver fibrosis
- ★ Hepatomegaly

Patients in Class I have none of the above characteristics, patients in Class II have one or two, while patients in Class III exhibit all three characteristics.

Experience from the largest series of patients in Italy showed that in Class I patients, the probabilities of overall survival (OS) and disease-free survival (DFS) are 93% and 91% respectively, with a 2% risk of rejection and an 8% risk of transplant-related mortality. Class II patients have an 87% probability of OS and an 83% chance of DFS, with a 3% risk of rejection and a 15% risk of non-rejection mortality. Class III patients have a 79% probability of OS and a 58% chance of DFS, with a 28% risk of rejection and a 19% risk of non-rejection mortality. [138,139-140 Level III] **(Refer to Figure 3)**

Among adults aged >16 years old, the probability of surviving a bone marrow transplant procedure is 66% with a 62% probability of cure, a 35% chance of transplant-related mortality and a 5% chance of returning to the pre-transplant thalassaemia condition.[139-140 Level III]

Based on these outcomes,[139,140 Level II-2] bone marrow transplantation (BMT) in thalassaemia should be considered for patients at an early age or before complications due to iron overload have developed.

However, a final decision must be based on an assessment of the relative advantages and disadvantages of HSCT and conventional therapy which requires the physician, patient and family to weigh the outcomes and risks of each option.

8.1 HLA-MATCHED SIBLING DONORS

HLA matched sibling BMT is the most established mode of cure for thalassaemia major.[5] Level II-2, 139 Level III, 140-142 Level II-2

However, its applicability is limited by the availability of a HLA-matched sibling donor. There is a one-in-four chance that any sibling will be HLA identical, with the likelihood of a thalassaemia patient having an HLA identical sibling donor varying according to family size. However, there is also a one-in-four chance that a sibling of the index patient will have thalassaemia major too, thus reducing the chances of having a potential matched sibling donor. Siblings who are carriers can be potential donors.

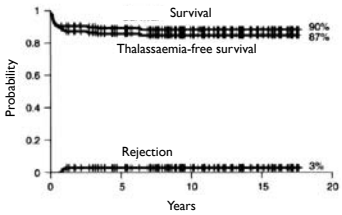

Figure 1. Kaplan-Meier probability of survival, thalassaemia free survival and cumulative incidence of rejection in class 1 patients

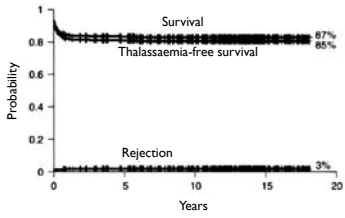

Figure 2. Kaplan-Meier probability of survival, thalassaemia free survival and cumulative incidence of rejection in class 2 patients

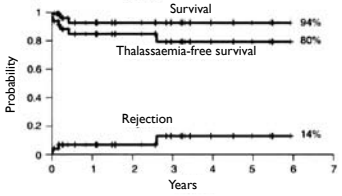

Figure3 Kaplan-Meier probability of survival, thalassaemia free survival and cumulative incidence of rejection in class 3 patients

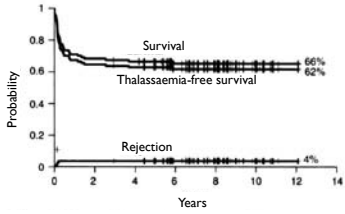

Figure 4. Kaplan-Meier probability of survival, thalassaemia free survival and cumulative incidence of rejection in adult patients

Figure 3.
Probability of survival and cumulative incidence of rejection for transplantation according to classes. (With permission from Javid Gaziev, Guido Lucarelli; Mediterranean Institute of Haematology, International Centre for Transplantation in Thalassemia and Sickle Cell Anemia, Azienda Ospedaliera San Camillo, Forlanini di Roma, Italy in Vol JO. No 1. 2005 111-115 Reproductive BioMedicine Online: www.rbmonline.com/Article/1525 on web 10 November 2004)

8.2 CORD BLOOD TRANSPLANTATION

Umbilical cord blood cells are a potential source of stem cells for transplantation. The results of using cord blood cells alone as a source of stem cells are variable, with slower engraftment and higher rejection risks, but there are increasing numbers of successful transplants reported.[143,144 Level II-2; 145-147 Level III]

There are several possible advantages to this approach namely:

- ★ Stem cells can be obtained easily at birth
- ★ Cord blood allows a lesser HLA match compared to marrow donors for use in transplantation
- ★ It has been suggested that graft versus host disease (GVHD) may be less severe when stem cells are obtained from cord blood compared to marrow cells

Evidence suggests that sibling cord blood transplantation can be used to treat some patients with thalassaemia.[143,144 Level II-3] Transplant outcome is good when it is performed on young recipients with early disease status and good HLA match.

Unrelated cord blood transplants have also proved feasible[145-147 Level III] but such grafts are still regarded as having higher risks and being appropriate only under research protocol or clinical trials.

8.3 MATCHED UNRELATED DONOR TRANSPLANTATION

As most patients with thalassaemia do not have a suitable sibling donor, there is considerable interest in using unrelated but otherwise matched donors.[148,149 Level II-2] Compared to matched sibling transplants, the complication rates of transplants using matched unrelated donors are high. It is hoped that with continued improvements in clinical care and HLA matching techniques, complication rates will be reduced.

This has been proven recently suggesting that if unrelated donors are from a closely related genetic background the outcome may be improved.[149 Level II-2] Experience so far is still limited and it carries higher morbidity and mortality. However it may be feasible in experienced centres and the treatment needs to be individualised.

RECOMMENDATION

Matched sibling donor transplantation should be offered at the earliest age possible. **(GRADE C)**

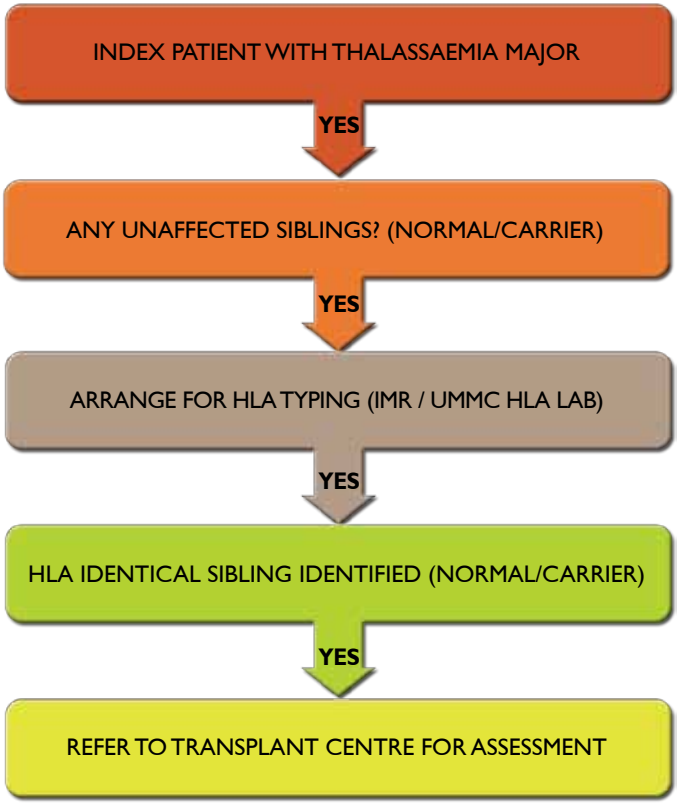

Figure 4.
Referral Algorithm for Consideration of Bone Marrow Transplant

9. COMPLICATIONS & THEIR MANAGEMENT

9.1 ENDOCRINE COMPLICATION

9.1.1 Short Stature and Growth Failure

Growth failure in thalassaemia have been attributed to hypothyroidism, delayed sexual maturation, diabetes mellitus, zinc deficiency, low haemoglobin levels, bone disorders, DFO toxicity, IGF-1 deficiency and growth hormone deficiency (GHD). Folate deficiency, undernutrition and hypersplenism are other causes of poor growth.[51 Level III; 150 Level II-3]

Growth failure is defined as:

- ★ Height less than 3rd percentile for age and gender
- ★ Significantly short for the family (10 cm or more below mid-parental height (MPH)) (**Refer to Appendix 7** for calculation of MPH)
- ★ Slow growth rate observed over a period of 6 months to 1 year

Average growth rate at different phases of life:

- ❒ 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)

- ★ Downward crossing of height percentiles on growth chart (such as from 50th percentile to 25th percentile after the age of 18 months)

Prevalence

- ★ Prevalence of short stature varies from 31 to 64%.[150-151 Level II-2]
- ★ Short stature is more prevalent in those above the age of 10 years.[152 Level II-3]

Investigations

Investigation of a child with thalassaemia who has stunted growth is generally similar to that of a child without it.[51 Level III] A reliable stadiometer (ideally Harpenden) should be made available to measure the height accurately.

It is important to detect other causes of short stature in thalassaemia patients. Additional endocrine tests that can be done would include thyroid function tests, sex hormones, zinc, calcium, alkaline phosphatase and oral glucose tolerance test (OGTT). Other useful tests are IGF-1, IGFBP-3 and bone age assessment.[51 Level III]

For short children with suspected GHD, other tests that are normally done in the referral or tertiary centres are:

- ★ GH stimulation tests. GHD should be confirmed by conducting two GH stimulation tests using two different pharmacologic agents.[153 Level III]
- ★ Anterior pituitary function tests

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 (GHIS).[154 Level II-1]

Management

Management of growth failure should include addressing other causes of short stature in thalassaemia patients, such as malnutrition, suboptimal transfusion, hypothyroidism, delayed puberty, diabetes mellitus, zinc deficiency, bone disorders and DFO toxicity.

After confirmation of GHD and the correction of other factors for growth failure, consider GH therapy:

1. Treatment with recombinant human growth hormone (rh-GH) for 1 - 2 years at a dose of 0.5 - 1.0 IU/kg/week will result in an increase in growth velocity from 2 - 3 cm/year to 6 - 7 cm/year. However, there is limited evidence that the final height may improve.[155 Level II-1, 156 Level II-3]

2. In a study among older patients, favourable outcome was noted in the first year of rh-GH treatment which did not persist during the second and third years because of increase in bone age.[157 Level II-3]

3. Recombinant human GH is a safe mode of treatment in thalassaemia children.[155 Level II-1]

RECOMMENDATION
Thalassaemia patients with short stature should be assessed and screened for growth hormone deficiency after excluding other common causes of short stature. **(Grade C)**
Growth hormone deficiency should be confirmed by conducting two GH stimulation tests using two different pharmacologic agents. **(Grade C)**
Growth hormone therapy if required should be tried for one year and assessed for response. **(Grade C)**

9.1.2 Delayed Puberty and Hypogonadism

Failure to progress normally through puberty is associated with failure of adequate bone mineralisation and achievement of peak bone mass in thalassaemia patients. The management of these patients should therefore be pro-active to anticipate problems and facilitate normal sexual maturation.[158-159 Level II-2]

Definition

- ★ Delayed puberty is the complete lack of pubertal development in girls by the age of 13 years and in boys by the age of 14 years.[160-161 Level III]
- ★ Hypogonadism is defined in boys as the absence of testicular enlargement (< 4 mls), and in girls as the absence of breast development (thelarche) by the age of 16 years.[51 Level III]
- ★ Arrested puberty is characterised by a lack of pubertal progression over one year or more. The testicular size remains 6 - 8 mls and breast size at Tanner stage 3. In such cases, the annual growth velocity is either markedly reduced or completely absent.[51 Level III]

Prevalence

Hypogonadism (delayed puberty and prepubertal GnRH response) was noted in 59% of patients who reached pubertal age. High serum ferritin level during puberty is a risk factor for hypogonadism.[162 Level II-3]

Investigations

Tanner staging should be determined every six months from the age of 10 years onwards.

Orchidometer (Prader) should be made available for the assessment of testicular volume.

Patients with delayed puberty require screening with thyroid function tests, LH, FSH, oestradiol or testosterone and bone age. Pelvic ultrasound should be done to assess ovarian and uterine size. If results are abnormal, perform gonadotropin releasing hormone (GnRH) stimulation test.[51 Level III]

Management

For the induction of puberty in thalassaemia patients diagnosed with probable hypogonadism, ethinyl oestradiol had been used in girls and testosterone depot in boys without adversely affecting the final height. [163 Level II -3]

For girls with delayed puberty at 13 years of age:

- ★ It is important to induce puberty gradually over a duration of 2 - 3 years to allow adequate development of secondary sexual characteristics and feminisation before attainment of menarche.[160 Level II]
- ★ Therapy may begin with oral administration of ethinyl oestradiol (2.5 - 5.0 µg daily) or conjugated oestrogen preparation (0.3 mg every other day) for 6 months and stopped for reassessment (Tanner staging).
- ★ If spontaneous puberty does not occur within 6 months after stopping treatment, oral oestrogen is reintroduced in gradually increasing dosages (10, 15, 20 µg for ethinyl estradiol or 0.3 mg daily, 0.625 mg daily for conjugated oestrogen) to full replacement doses (20 µg for ethinyl oestradiol and 0.625 mg for conjugated oestrogen preparation) within two to three years.[160-161 Level III]
- ★ Cyclical progesterone or medroxyprogesterone acetate (5 - 10 mg daily) is added for 12 days every month after full oestrogen replacement to ensure cyclical endometrial shedding and decrease the risk of endometrial dysplasia.[160 Level III]

For boys with delayed puberty at 14 years of age:

- ★ Low dose IM depot testosterone esters (25 mg) are given monthly for six months, and stopped for reassessment (Tanner staging).
- ★ If spontaneous puberty does not occur within six months after stopping treatment, IM depot testosterone esters can be reintroduced at a dose of 50 mg. Dose is gradually increased every six months to a maximum of 200 mg. Full replacement dose in adults is 200 mg every 2 - 3 weeks.
- ★ In boys with pubertal arrest, the treatment consists of testosterone esters which are administered as for delayed puberty and hypogonadism.

Though human chorionic gonadotrophin (hCG) has been used in thalassaemia patients with hypogonadism, the response rate is low.[159 Level II-2]

Patients with severe iron overload have potentially irreversible hypogonadism and do not respond to pulsatile GnRH therapy. Therefore, testosterone therapy should be the mainstay of treatment in thalassaemia patients with hypogonadism.[164 Level II-2]

RECOMMENDATION
All thalassaemia patients with delayed puberty should be treated in an appropriate sequential manner. **(Grade C)**
For induction of puberty, ethinyl oestradiol or conjugated oestrogen preparation can be used in girls and testosterone injection in boys. **(Grade C)**

9.1.3 Hypothyroidism

The majority of patients have primary thyroid dysfunction. Secondary hypothyroidism caused by iron damage to the pituitary gland is rare.

Incidence of primary hypothyroidism varies from 6.2 - 51.7%[165-166 Level II-3] and increases with age (mean age 15.8 years).[167 Level II-2] There is a strong association between high iron overload and decreased thyroid function.[168 Level II-3]

Signs and Symptoms

There are no obvious clinical signs and symptoms of hypothyroidism despite abnormal thyroid function.[168-169 Level II -3]

Investigations

★ Free T4 and TSH

★ Bone age

Management

Full L-thyroxine replacement dose is 100 μg/m^2/day. Subsequent dosage should be titrated according to thyroid function.

RECOMMENDATION
The treatment for hypothyroidism is L- thyroxine. **(Grade A)**
Thalassaemia patients aged more than 10 years should be monitored annually for hypothyroidism. **(Grade C)**

9.1.4 Diabetes Mellitus

Diabetes mellitus (DM) is a chronic disease characterised by elevated blood glucose caused by abnormal insulin production or abnormal insulin action that leads to disordered carbohydrate, lipid and protein metabolism.[170 Level III]

Pathophysiology

★ It is believed to be due to damage of pancreatic β cells caused by iron overload. There is reduced insulin secretion in normoglycaemic β thalassaemia major patients.[171-172 Level II-3]

★ The appearance of DM in thalassaemia patients may be due to a combination of insulin resistance and insulin deficiency caused by either exhaustion of β cells, iron deposition in islet cells or a combination of these factors.[173 Level II-3]

★ Overt DM in thalassaemia major patients is preceded by a long period of insulin resistance[172 Level II-3] and hyperinsulinaemia.[173 Level II-3]

★ The main risk factors associated with DM are poor compliance with DFO treatment, delayed age at start of chelation therapy, liver cirrhosis or severe fibrosis,[174 Level II-3] and hepatitis C infection.[175-176 Level II-3]

★ The risk factors associated with impaired glucose tolerance (IGT) are male, poor compliance with DFO therapy and LIC four times above the normal value.[174 Level II-3]

★ Liver disorders and positive family history seem to be additional predisposing factors.[174,177 -178 Level II-3]

Prevalence

★ The prevalence of DM ranges from 10.4 - 19.5%.[172,175-176,179 Level II-3]

★ The mean age at diagnosis is between 17 and 18 years.[165, 174-175, Level II-2]

★ The prevalence of IGT is 8.5 - 14.6% and the mean age at diagnosis is 16.6 $\pm$ 4.9 years.[175-176 Level II-3]

★ 31.1% of patients with diabetes present with diabetic ketoacidosis.[175 Level II-3]

Investigations

★ The diagnosis of DM may be made using any one of the following criteria:[180 Level II]

- Symptoms and a random plasma glucose of more than 11.1 mmol/L. Symptoms include polyuria, polydipsia, and unexplained weight loss.
- Fasting plasma glucose of > 7.0 mmol/L
- 2 hour post-prandial plasma glucose of > 11.1 mmol/L on an OGTT. (An OGTT requires the equivalent of 1.75 gm/kg to a maximum of 75 gm of anhydrous glucose dissolved in water)

★ The diagnosis of IGT is made when the 2 hour post-prandial glucose is between 7.8 - 11.1 mmol/L on an OGTT.[180 Level III]

Management

★ The early and adequate use of iron chelation can prevent DM and major endocrinopathies.[175,181-182 Level II-2, 179 Level II-3]

★ Both DM and IGT improved in a third of patients after intensive combined chelation treatment.[183 Level II-3]

★ In thalassaemias with IGT, the condition may improve with a strict diabetic diet, weight reduction where applicable and intensive iron chelation.[51 Level III]

★ Use of insulin:

- In thalassaemia patients with DM, insulin treatment is normally required but metabolic control may be difficult to achieve.[51,184 Level III]
- Insulin requirement (0.15 - 1.72 U/kg) varies due to a wide variation in pancreatic β cell function as determined by C-peptide level.[184 Level III]

★ The use of oral anti-diabetic agents in DM remains undetermined.

RECOMMENDATION
A 2 hour OGTT should be performed annually on thalassaemia patients ≥ 10 years old. **(Grade C)**
Thalassaemia patients with IGT should be managed by a strict diabetic diet, weight reduction where applicable and intensive iron chelation. **(Grade C)**
Thalassaemia patients with DM should be treated with insulin. **(Grade C)**

9.1.5 Osteoporosis/Osteopaenia

Low bone mass is present in a significant proportion of children with transfusion dependent thalassaemia despite hypertransfusion and optimal chelation.

The Bone Mineral Density (BMD) of thalassaemia children cluster around the normal curve until the age of 10 - 12 years, when there is a deviation away from it.[158,185 Level II-2] The mean decline of BMD z score is -0.38 per year.[186 Level II-3]

β thalassaemia trait is not a contributing factor for low bone mass.[187 Level II-3]

Bone changes related to DFO toxicity should be suspected and investigated in children with bone or joint pain.[129 Level II-2]

Definition

To date, there are insufficient data to formally define osteopaenia/osteoporosis in children and adolescents.

Osteopaenia is defined as mild decrease in bone mineral content, 1.1 to 2.4 SD below the mean for age and sex.

Osteoporosis is defined as a decrease in bone mineral content, 2.5 SD or more below the mean for age and sex, and resulting in weak bones and pathological fractures.[188 Level III]

Prevalence

- ★ 16.1% of the β thalassaemia patients had normal bone mass (z score ≥ -1)
- ★ 22.6% had reduced bone mass (z score between -1 to -2)
- ★ 61.3% had low bone mass (z score ≤ -2)[189 Level II-3]
- ★ Vitamin D deficiency:
  - 25-OH vitamin D concentrations are significantly lower in patients with thalassaemia major and iron overload compared to normal controls.[190 Level II-3]
  - 30.9% of patients have 25-OH vitamin D3 levels below the normal range. These patients tend to have a lower BMD z-scores.[158 Level II-2]
- ★ Zinc deficiency:
  - Zinc deficiency is associated with osteoporosis and with BMD z scores below -2 in 68.7% and 17.6% of patients at the lumbar and femoral regions respectively.
  - 84.8% of patients aged 10 - 20 years have been reported to be zinc deficient while 44.7% have severely low levels.[191 Level II-2]

Investigations

- ★ Serum calcium, phosphate, ALP
- ★ 25-OH Vitamin D level
- ★ Parathyroid hormone
- ★ Serum zinc
- ★ 24 hour urinary calcium
- ★ Spinal radiograph (AP and lateral views)
- ★ MRI scan of the spine may be considered for patients with severe back pain[52 Level II-2]
- ★ Currently, Dual Energy X-ray Absorptiometry (DEXA) scan is the method of choice to assess BMD[192 Level II-3]
- ★ Quantitative computed tomography (QCT) could play a role in the future[192 Level II-3]
- ★ Quantitative ultrasound (QUS) of the heels is a non-invasive assessment of skeletal status. Though it may be used in monitoring effects of specific treatment, it cannot be used to substitute DEXA.[193 Level III]

Management

Adequate vitamin D and calcium intake according to recommended dietary allowances (RDA) should be ensured in all thalassaemia patients.[194-195 Level III]

Table 5. Recommended dietary intake of calcium and vitamin D

Age (years)	**Calcium** (mg/day)	**Vitamin D** (IU/day)
4 - 8	800	200
9 - 13	1300	200
14 - 18	1300	200
19 - 30	1000	200
31 - 50	1000	200
51 - 70	1200	400
>70	1200	600

(Adapted from Institute of Medicine, Food and Nutrition Board (1997)).[196 Level III]

- ★ Non-pharmacologic interventions which include regular weight-bearing exercises, avoidance of smoking and excessive alcohol consumption should be advised to all patients.[52 Level II-1]
- ★ In vitamin D deficiencies, oral vitamin D of 1000 - 1500 IU and calcium supplementation of 500 - 1000 mg should be given daily.[51 Level III]
- ★ Zinc supplementation should be offered to patients with zinc deficiency or suspected deficiency. Recommended daily allowance is 10 - 15 µg for children older than 10 years.[191 Level III]
- ★ In osteopaenic patients, non-pharmacologic interventions should be optimised.
- ★ In osteoporotic patients, besides optimising non-pharmacologic interventions, 500 mg/day of calcium and 400 IU/day of vitamin D supplementations are required.[197 Level III]
- ★ Bisphosphonates may be considered in older patients with osteoporosis and not responding to the above measures.
- ★ Other contributory causes of low bone mass such as hypogonadism and other endocrinopathies should be promptly and adequately managed.[52 Level II-1]

RECOMMENDATION
Adequate dietary intake of calcium and vitamin D should be ensured. (**Grade C**)
Regular weight-bearing exercises should be encouraged with avoidance of smoking and excessive alcohol consumption. (**Grade C**)
Vitamin D, calcium and zinc status of thalassaemia patients should be evaluated regularly and annually from 10 years old onwards. (**Grade C**)
Annual bone density studies should be considered in thalassaemia patients more than 10 years of age. (**Grade C**)

9.1.6 Hypoparathyroidism

Incidence of hypoparathyroidism varies from 4.5 - 20%.[198-201 Level II-3] The age of diagnosis range from 11 to 24 years (mean between 13 and 18 years).[198-201 Level II-3]

Signs and Symptoms

Majority of thalassaemia patients with hypoparathyroidism have no clinical symptoms of hypocalcaemia. Therefore annual screening is suggested from age of 10 years onwards.[198,200-201 Level II-3]

Hypoparathyroidism tends to be accompanied with other endocrinopathies.[198,199-201 Level II-3]

Investigations

Screening for hypoparathyroidism includes:

- serum calcium
- serum phosphate
- serum magnesium
- serum alkaline phosphatase

In patients with low serum calcium and high phosphate level, proceed with serum parathyroid level.[199 Level II-3]

Management

1. Calcitriol 0.25 - 1.0 µg once to twice daily.
2. In patients with persistent high phosphate levels, phosphate binders (such as calcium carbonate) may be considered.
3. Calcium supplements may be offered to patients with poor dietary intake.

RECOMMENDATION

Thalassaemia patients older than 10 years of age, especially those who have other endocrinopathies need to be monitored annually for hypoparathyroidism. **(Grade C)**

Treatment of hypoparathyroidism consists of calcitriol with or without calcium carbonate/lactate. **(Grade C)**

9.1.7 Hypoadrenalism

Hypoadrenalism may be under-diagnosed and can potentially cause mortality during acute illnesses. Prevalence of hypoadrenalism varies widely from 0 - 45% due to different patient characteristics and different diagnostic tests used. The mean age of patients detected to have impaired adrenal function is 13.5 ± 3.9 years.[202 Level II-2] Thus there is a need to have an annual estimation of basal cortisol level in patients who are more than 10 years old especially those with wasting.[203 Level II-2]

Signs and Symptoms

Patients are usually asymptomatic.[203 Level II-2]

Investigations

★ Baseline cortisol
- Morning baseline cortisol level (8 - 9 AM) can be used to detect subtle adrenal insufficiency.
- In view of constant stress experienced by patients with thalassaemia major, a higher cut off point (> 400 nmol/L) should be used.

★ ACTH stimulation test should be done in patients with abnormal baseline cortisol level. A peak cortisol level of < 500 nmol/L with stimulation is abnormal.[203 Level II-2]

Management

During stressful conditions, patients with adrenal insufficiency should be promptly given stress dose of hydrocortisone as a life saving treatment. [204-205 Level III]

RECOMMENDATION

Thalassaemia patients more than 10 years of age, especially those with wasting and other endocrinopathies should be monitored annually for hypoadrenalism. **(Grade C)**

9.2 CARDIAC COMPLICATION

Cardiac complication due to iron overload is a major cause of mortality (71%) and morbidity in patients with transfusion dependent thalassaemia.[101,206,207 Level II-2]

Patients with serum ferritin > 2,500 µg/L have a higher risk of developing cardiac complications and death.[100,208] However, SF is not a sensitive predictor of cardiac iron overload and cardiomyopathy, and cardiac deaths have been reported with low ferritin levels.[89,209 Level II-3]

The onset of cardiac iron overload can be as early as 10 years old although the risk is usually higher in the late teens and twenties.[210 Level II-3]

Standard dose s/c desferrioxamine infusion may not be sufficient to prevent cardiac iron overload in a significant proportion of thalassaemia major cases (6.9 - 65%), even amongst some compliant patients.[111,209,211 Level II-3]

Signs and Symptoms

★ Usually asymptomatic until late stage

★ Can present as heart failure, arrhythmias, and sudden death

★ Unlike other cardiomyopathies, cardiac failure due to iron overload is potentially reversible with intensification of chelation therapy

Investigations

★ 12 lead ECG and Holter monitoring

- Useful to investigate specific symptoms such as palpitations, shortness of breath and syncope but not useful for screening of those at risk
- Non-specific ECG changes such as depolarization of T waves are common but the clinical significance is uncertain

★ Echocardiogram

- Left ventricular ejection fraction (LVEF) values are significantly higher in thalassaemia patients[212] and LV function is usually preserved until advanced stage. LVEF < 56% indicates impaired myocardial function and should prompt for further evaluation of cardiac iron overload by MRI T2* where possible and intensification of chelation therapy.[98] Level II-3
- Tissue Doppler echo may detect wall motion abnormalities as an early sign of cardiac disease.[213] Level II-3

★ MRI T2*

- Currently the best available method for early detection of cardiac siderosis.
- T2 * level < 20 ms indicates presence of cardiac iron overload.
- T2* level < 10 ms indicates severe cardiac iron overload. Of patients with heart failure, 89% have T2* < 10 ms.[209]
- MRI T2* should be done from age 10 onwards where possible and should be repeated every 2 years if normal, yearly if the value is between 10 - 20 ms and 6 monthly if it is <10 ms.[98] Level II-3

Management

1. Thalassaemia patients with myocardial siderosis may be asymptomatic. Patients with cardiac failure or arrhythmia should be co-managed with the cardiologist. Other contributing factors such as hypothyroidism, acute infections and pulmonary hypertension should also be managed appropriately.

2. Asymptomatic cardiac siderosis
   a. Maximise current monotherapy
      - Desferrioxamine 40 - 60 mg/kg/day to increase frequency from five to seven days and duration from 8 to 24 hours[214] Level II-3
      - Deferiprone at higher doses of 90 - 100 mg/kg/day[110] Level I

   b. Combination therapy with s/c desferrioxamine 40 - 50 mg/kg/day at least five times a week and oral deferiprone (75 mg/kg/day).[122] Level I

      Preliminary data on deferasirox suggests that a higher dose of 40 mg/kg/day may be required to reduce cardiac iron.

3. Symptomatic cardiac siderosis

- Continuous i/v desferrioxamine 50 - 60 mg/kg/day.[106,215,216 Level II-3]
- Combination therapy with deferiprone 75 mg/kg/day and s/c desferrioxamine 40 - 50 mg/kg/day at least five times per week.[217 Level II-2, 218 Level III]
- There is no data on the ability of deferiprone monotherapy to reverse heart failure.

Monitoring

★ Full clinical examination of the cardiovascular system at least six monthly

★ Echocardiogram annually from age of 10 years

RECOMMENDATION
Annual monitoring of cardiovascular system for thalassaemia patients from age 10 onwards would include ECG, echocardiogram and where possible MRI T2*. **(Grade C)**
For asymptomatic thalassaemia patients with mild to moderate cardiac siderosis (T2* 10 -20 ms) and normal cardiac function, iron chelation monotherapy should be intensified or switched to combination therapy. **(Grade B)**
If MRI T2* assessment is not possible, then thalassaemia patients with poor chelation history and high risk of cardiac iron overload such as serum ferritin > 2,500 µg/L or poor compliance should have intensive chelation monotherapy or switched to combination therapy. **(Grade C)**
For thalassaemia patients with severe cardiac iron overload or symptomatic cardiac disease, continuous i/v DFO is the best treatment option. Alternatively, combination therapy can be considered. **(Grade C)**

9.3 INFECTION

9.3.1 Hepatitis B

The prevalence of HBsAg positivity in multiply transfused thalassaemia patients varies worldwide (< 1% to >20%).[51 Level III] In Malaysia, the reported figure was low (2.4%) but not negligible.[219 Level III]Hepatitis B infection remains a significant cause of chronic liver disease and hepatocellular carcinoma in patients with thalassaemia especially in the developing countries. Routine screening of hepatitis B is recommended and should also include anti-HBs level if resources permit. Full hepatitis B vaccination needs to be given to unvaccinated patients and those unsure of vaccination status. In patients who had completed prior vaccination with anti-HBs level < 10 mIU/ml, a booster dose needs to be given. If anti-HBs level one month post - booster vaccination is still low, consider 3-dose re-vaccination.[220 Level III]

Investigations
In patients found to be HBsAg positive, the following tests should be done: LFT, HBeAg, anti-HBe and HBV-DNA.

All thalassaemia patients requiring hepatitis B treatment should be co-managed by gastroenterologist. Furthermore, the blood bank needs to be informed for donor tracing in transfusion mediated infections.

Diagnostic and treatment criteria for chronic hepatitis B infection are as follows:

1. HBsAg positivity > 6 months
   AND
2. Serum HBV DNA > 20,000 IU/ml (10^5 copies / ml) in HBeAg positive cases, serum HBV DNA > 2,000 IU / ml (10^4 copies/ml) in HBeAg negative cases
   AND
3. Persistent or intermittent elevation in ALT/AST levels, typically more than twice of Upper Limit Normal or significant liver disease on liver biopsy

Management

The primary goal of treatment for chronic hepatitis B are long-term suppression of HBV-DNA viral load to low and preferably undetectable level and HBeAg seroconversion in HBeAg positive subjects with the aim to reduce progression to cirrhosis, liver failure and hepatocellular carcinoma.

Treatment should be started as early as possible in cases of impending or overt hepatic decompensation (i.e. raised bilirubin unrelated to thalassaemia, prolonged PT or presence of ascites). Otherwise, 3 - 6 months observation is recommended.[221 Level III]

Patients can be treated with:

1. Interferon α (IFN α) or Pegylated IFN α
   For conventional IFN α, the recommended duration of treatment is 4 - 6 months for HBeAg positive patients and at least a year for HBeAg negative patients. For Peg-IFN, the recommended duration is at least six months for HBeAg positive patients and 12 months for HBeAg negative patients.[220 Level III] or

2. Lamivudine
   Lamivudine 100 mg daily is especially recommended if there is a concern regarding hepatic decompensation.[220 Level III]

   Anti-viral drug resistance can occur and may be recognised by viral breakthrough which is defined as 1 log increase from nadir, ALT flares and liver decompensation. When this occurs, addition of a second anti-viral agent (adefovir/tenofovir) which does not have cross resistance should be initiated.[221 Level III]

   In HBeAg positive patients, treatment can be stopped when HBeAg seroconversion with undetectable HBV-DNA has been documented on two separate occasions at least six months apart unless there is evidence of decompensated liver disease/liver cirrhosis. In HBeAg negative patients, treatment discontinuation depends on individual cases and should be decided by the gastroenterologist.[221 Level III]

Monitoring
During therapy,

- ★ HBeAg and HBV-DNA should be monitored every three months
- ★ Monitor renal function if adefovir is used[221] Level III

At the end of therapy,

- ★ Monitor ALT and HBV-DNA monthly for the first three months to detect early relapse, then every three months (for cirrhotic patients and those who remain HBeAg/HBV-DNA positive) to six months (for responders)[220] Level III

For non-responders, further monitoring of HBV markers is required to recognise delayed response and plan retreatment when indicated.[221] Level III

In chronic hepatitis B and hepatitis C patients, hepatocellular carcinoma surveillance and checking for and vaccination against Hepatitis A virus should be done.[221] Level III

RECOMMENDATION

Monitoring for hepatitis B infection using HBsAg needs to be done six monthly. **(Grade C)**

Treatment should be considered for cases:

- with HBsAg positivity > six months and serum HBV DNA > 20,000 IU/ml (10^5 copies/ml) in HBeAg positive cases
- with HBsAg positivity > six months and serum HBV DNA > 2,000 IU/ml (10^4 copies/ml) in HBeAg negative cases **(Grade C)**

9.3.2 Hepatitis C

The seroprevalence of hepatitis C in transfusion dependent thalassaemia patients in Malaysia ranges from 13.9% to 22.4%.[222,223] Level III

Both HCV infection and iron overload are independent risk factors for development of liver fibrosis and cirrhosis and may act synergistically to increase the risks of cirrhosis and hepatocellular carcinoma (HCC).[224,225] Level III

Treatment of hepatitis C in thalassaemia is aimed at achieving sustained viral clearance, preventing liver damage and reducing the risk of liver cirrhosis and HCC. It should be managed in close collaboration with the gastroenterologist.

Investigations

★ Anti-HCV antibody (ELISA)

- This is indicative of exposure to the virus but does not differentiate whether the infection is acute, chronic or resolved

★ HCV-RNA (PCR)

- Confirmation of viraemia
- Monitoring response to antiviral therapy
- Viral load is a prognostic indicator of treatment outcome

★ HCV genotype

- Determines the duration of antiviral therapy and the likelihood of response. In general, genotype non-1 has a better response rate compared to genotype 1

★ Liver biopsy

- In thalassaemia patients with liver siderosis, it is useful in assessing severity of liver damage, provides information on prognosis and adds information on response to treatment

Diagnostic and treatment criteria for chronic hepatitis C infection are as follows:

1. Persistent anti-HCV positivity > six months
   AND
2. Serum HCV RNA positivity (regardless of viral titre)
   AND
3. Significant liver disease on liver biopsy

Management

1. Both conventional interferon (IFN) and peg-IFN with or without ribavirin can be used to treat patients with chronic hepatitis C infection for 24 - 48 weeks depending on HCV genotype (Genotype 1 generally needs a longer duration of treatment). However, sustained viral response (SVR) might be considerably reduced without the addition of ribavirin in genotype 1, cirrhosis or high viral load.[226-228 Level III, 229 Level I]

2. There is an increase in transfusion requirement by 30 - 40% with the combined antiviral therapy due to ribavirin-induced haemolysis.

3. Patients with compensated cirrhosis should also be considered for treatment. The reversibility of early cirrhosis in patients with thalassaemia has been reported following the treatment of iron overload and viral hepatitis.[230 Level II-3]

4. Patients on deferiprone and interferon therapy should be closely monitored as both agents can cause neutropaenia. Apart from FBC, LFT and thyroid function should also be monitored while on interferon therapy. Mood changes such as depression can occur.

RECOMMENDATION
Monitoring of hepatitis C infection should be done six monthly. **(Grade C)**
The preferred treatment option for hepatitis C in thalassaemia is combination therapy (either conventional or PEG-IFN) with ribavirin. **(Grade C)**

9.3.3 HIV Infection

Transfusion acquired HIV infection, though very rare, remains a potential risk in multiply transfused thalassaemia patients. HIV serology therefore should be carried out six monthly in these patients. Liaison with microbiologist for urgent confirmation of preliminary positive 'anti-HIV Antibody' test is required. Confirmed HIV positive cases should be referred urgently to Infectious Disease Physician for counselling and management. Blood bank needs to be contacted for donor tracing.

9.3.4 Bacterial Infections in Transfusion Dependent Thalassaemia

Apart from heart failure, infection is the main cause of death in transfusion dependent thalassaemia patients. All transfusion dependent thalassaemia patients need to be educated to seek early medical treatment when fever develops. Risk factors for severe infection include post-splenectomy, diabetes[231 Level II-3], previous history of melioidosis[232] and iron overload (especially if SF ≥ 5000 µg/L).[233 Level II-3]

Management

- ★ Patients who appear ill or toxic with hypotension, tachycardia, tachypnoea or hypoxia (O_2 saturation < 96% on air) need to be admitted urgently.
- ★ Patients with fever > 38°C and chills, vomiting, abdominal or localised pain or swelling to suggest abscess also need to be admitted for prompt treatment and investigations.
- ★ Blood cultures need to be done and empirical antibiotics started immediately.
- ★ For ill patients, especially if post-splenectomy; first line antibiotics regime should include broad spectrum anti-Klebsiella and anti-Pseudomonal agents such as third generation cephalosporins[51 Level II-2] with or without aminoglycosides.[52 Level III]
- ★ Antibiotic choice depends on local pathogens susceptibility and endemicity such as area where melioidosis is endemic in Sabah, ceftazidime (150 mg/kg in three divided doses for patients < 40 kg body weight and 2 g TDS for patients ≥ 40 kg body weight) should be the first line pending blood culture results.[232 Level II-2]
- ★ Ultrasound or CT scan should be carried out promptly in cases suspected to have abscess formation. Drainage of abscesses should be carried out early.
- ★ Febrile patients on DFO should stop its use until the cause of the fever has been determined and treated.
- ★ Febrile patients on DFP should stop its use and have neutropaenia excluded urgently.

RECOMMENDATION

In transfusion dependent thalassaemia with sepsis, especially post-splenectomised, first-line antibiotic regimes should include broad spectrum anti-Klebsiella and anti-Pseudomonal agents. **(Grade C)**

10. NUTRITION & SUPPLEMENTS

Generally, patients with thalassaemia do not have specific dietary requirements.[51 Level III] However there is evidence showing that thalassaemia children have compromised nutritional status.[234 Level II-2] The children were significantly shorter ($p < 0.05$) and had smaller mid-arm circumference (MAC) and triceps skin fold thickness (SFT) as compared to the control group. Children with thalassaemia major who are on regular transfusion and chelation therapy have significantly lower serum zinc, selenium, copper, retinol and α-tocopherol levels.[235 Level II-2]

Growth stunting in thalassaemia children can be minimised with good nutritional support from an early age (1 - 3 years old). High-calorie diets significantly increase IGF-1 production and lead to growth improvement. The BMI, MAC and triceps SFT also increase significantly.[234 Level II-2]

Vitamin E

Thalassaemia children are in a state of enhanced oxidative stress and anti-oxidant deficiency even without iron overload. They have significantly lower superoxide dismutase (SOD) enzymes which are the first line of defence against oxidant stress. Low levels of SOD activity with high free oxygen radicals lead to reduced levels of vitamin E.[236 Level II-2]

Vitamin E supplementation helps to reduce platelet hyperactivity, and reduce oxidative stress.[237 Level II-1] Vitamin E protects erythrocytes in β thalassaemia patients from early lysis due to oxidative stress and significantly improves their Hb level.[238 Level II-2] Vitamin E therapy (10 mg/kg) for four weeks, significantly improves Hb levels and plasma ascorbate, and restores enzymatic antioxidants of erythrocytes to near normal values.[238 Level II-2]

Vitamin C

Vitamin C helps to mobilise iron from the intracellular stores and effectively increase the efficacy of chelation with desferrioxamine.[52 Level III] It is recommended to be given (not more than 2 - 3 mg/kg /day) as supplements during the time of desferrioxamine infusion to increase iron excretion.[51 Level III]

Folic Acid

Thalassaemia patients may have folate deficiency[239] Level I, in particular those not on blood transfusion or on low transfusion regime.[51] Level III Daily folic acid supplementation is recommended especially for those planning for pregnancy.[52] Level III

Iron Rich Food

Patients with transfusion dependent thalassaemia should take less foods rich in iron.

Table 6. Selected food items with iron content per 100 gm edible portion

Food item	Iron contents (mg)/100 gm edible portion
Liver	9.0
Chicken	2.8
Beef	2.7
Pork	1.7
Lamb	2.3
Egg yolk	7.9 (0.9 mg per egg yolk)
Oysters	6.1
Clams	6.7
Tuna	1.6
Shrimp	1.5
Soy beans	1.8 (tempeh) 0.2 (soya bean milk, packet of 250 ml)
Tofu	2.2
Kale	2.0
Mustard leaves	1.0
Spinach	5.0
Broccoli	0.7
Asparagus	0.6

(Source: Nutrient Composition of Malaysian Food, 1997)

RECOMMENDATION
All thalassaemia patients should be given good nutritional support at an early age to minimise growth impairment. **(Grade B)**
Vitamin E is useful for thalassaemia patients. **(Grade B)**
Vitamin C supplementation to be given to thalassaemia patients during desferrioxamine therapy. **(Grade C)**
Folic acid supplementation is useful for thalassaemia patients on low transfusion regime and those planning for pregnancy. **(Grade C)**

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APPENDIX I

SEARCH STRATEGY

The following free text terms or MeSH terms were used either singly or in combination:

Thalassemia[MeSH] OR Thalassaemia OR haemoglobinopathies OR Thalassaemia major; Physical examinations OR "clinical features" OR diagnoses OR diagnosis; "laboratory diagnosis" OR "laboratory investigations"; Thalassaemia intermedia AND "laboratory investigations"; Thalassaemia AND serum ferritin measurement; iron overload OR total body iron AND Thalassemia; Thalassaemia AND T2*; Thalassemia AND T2*; Thalassemia AND T2* AND "iron overload"; R2* AND thalassemia; MRI AND iron overload; Thalassemia AND MRI; Thalassaemia AND "hepatic iron"; Thalassemia AND "chelation therapy"; Thalassemia AND survival AND "chelation therapy"; Thalassemia AND "iron chelation" AND cost-effective; Thalassemia AND "iron chelation" AND compliance; Thalassemia AND "chelation therapy" AND "quality of life"; Thalassaemia AND "Vit C"; Thalassaemia AND Supplements; Thalssaemia AND Calcium; Thalassaemia AND Nutrition; Thalassaemia AND Vitamins; Thalassaemia AND supplements; Thalassaemia AND Screen*; Thalassaemia AND Cascade; Thalassaemia AND extended famil*; Thalassaemia AND Counsel*; Genetic counselling AND ideal; Thalassaemia AND "blood transfusion"; Thalassaemia AND hypertransfusion; Thalassemia AND transfusion; "Thalassaemia" [Mesh] AND "deferoxamine" [Mesh] OR 'deferiprone" [Substance Name] OR "deferasirox" [Substance Name" AND ("last 10 years" [Pdat] AND (Humans[Mesh])); "Thalassaemia" [Mesh] AND "deferoxamine" [Mesh] OR 'deferiprone" [Substance Name] OR "deferasirox" [Substance Name"; Thalassemia[Mesh] AND "blood transfusion"; Thalassaemia AND hypertransfusion; Thalassemia AND transfusion; Transfusion dependent thalassemia AND pre-transfusion testing; Multiply transfused AND pre-transfusion screening; Transfusion dependent thalassemia OR red cell phenotyping OR alloimmunization;

Pre-storage leucodepletion OR transfusion reaction; Transfusion dependent thalassemia OR leucodepleted blood OR reduced transfusion reaction; Multiply transfused AND fresh blood AND increased oxygen capacity; Thalassaemia AND splenectomy; Hypersplenism AND definition; Thromboembolic event AND thalassaemia; Post-splenectomy AND platelet count; Thrombocytosis AND aspirin; Aspirin AND splenectomy; Thalass* AND coagulopathy; Post-splenectomy AND OPSI; Post-splenectomy AND vaccines; Desferrioxamine AND cardiac; Reversal of heart failure AND desferal AND thalassaemia; Deferiprone and cardiac; Combined therapy with deferrioxamine and deferiprone; Reversal of heart failure AND combined therapy AND thalassaemia; Deferasirox and cardiac; Hepatitis C treatment and thalassaemia; Thalassaemia AND DEXA AND osteoporosis; "Osteopenia OR Osteoporosis" AND Thalassaemia; B Thalassaemia AND Growth hormone; Thal intermediate AND Growth hormone; Thalassaemia AND Short stature; Thalassaemia AND hypothyroidsm and treatment; Thalassaemia AND hypotparathyriodism treatment; Thalassaemia AND hypoadrenalismAND treatment; Thalassaemia AND puberty; Treatment AND puberty AND Thalassaemia Intermediate; Thalassaemia AND puberty AND sex steroid; Thalassaemia AND puberty AND testosterone; Thalassaemia AND puberty AND estrogen; Thalassaemia AND Combine therapy AND diabetes mellitus; Thalassaemia AND desferrioxamine AND diabetes mellitus; Thalassaemia AND deferiprone AND diabetes mellitus; Thalassaemia AND insulin AND DM; Thalassaemia AND Oral hosphatisec AND DM; Thalassaemia AND metformin AND DM; Thalass* AND Transplant*; thalassemia AND transplant*; infection and thalassaemia; Postsplenectomy Infection AND Thalassaemia; Treatment of Post-splenectomy Infection; Hepatitis B AND booster AND Thalassemia; Hepatitis B treatment AND Thalassemia.

APPENDIX 2

CLINICAL QUESTIONS

1. What is the epidemiological data for thalassaemia in Malaysia?

2. How is thalassaemia diagnosed? (β thalassaemia & thalassaemia intermedia)
   - ❑ Clinical diagnosis
   - ❑ Laboratory diagnosis
     - How is thalassaemia diagnosed in the laboratory?
     - How is β thalassaemia major diagnosed in the laboratory?
     - How is β thalassaemia intermedia diagnosed in the laboratory?

3. How should affected individuals, parents of affected individuals and extended family members be counselled?

4. What is the role of cascade screening in thalassaemia management?

5. Blood transfusion therapy
   - ❑ What are the indications for blood transfusion therapy?
   - ❑ What are the pre-transfusion evaluations?
   - ❑ Does RBC genotyping reduce the risk of alloimmunisation?
   - ❑ Is the use of leucocyte reduced packed cells effective in reducing transfusion reactions?
   - ❑ Is the use of pre-storage filtration better than bedside filters?
   - ❑ What is the transfusion regimen that is effective in reducing extramedullary haematopoiesis and iron load?
   - ❑ During blood transfusion, what are the common adverse reactions and their management?
   - ❑ How should a thalassaemia patient be monitored during transfusion?

6. Splenectomy
   - ❑ What are the indications for splenectomy in thalassaemia patients?
   - ❑ In post-splenectomy patients, will the use of vaccines pre-splenectomy and antibiotics post-splenectomy reduce the risk of OPSI?
   - ❑ In post-splenectomy patients, does aspirin reduce the risk of thrombosis?

7. Iron burden
   - ❑ Is serum ferritin a reliable measurement of iron overload?
   - ❑ What is the best measurement/indicator of total body iron?
   - ❑ What is the best measurement/indicator of cardiac iron overload?
   - ❑ What is the best measurement/indicator of liver iron overload?

8. Iron chelation therapy
   - ❑ Does iron chelation therapy affect survival or mortality in thalassaemia major?
   - ❑ What are the indications for use and the side effects for current iron chelators?
   - ❑ When should iron chelation therapy be started?
   - ❑ In liver iron overload, what is the best method of iron chelation?
   - ❑ Does the choice of iron chelators affect the quality of life/ compliance in patients with thalassaemia major?

9. What is the role of nutrition and supplements in thalassaemia patients?

10. What is the role of matched sibling haematopoietic stem cell transplantation?

11. What is the role of alternative donors and stem cell sources of stem cell transplantation?

12. How should infections be managed?
    - ❑ How to manage thalassaemia patients presenting with acute febrile illness?
    - ❑ How to manage hepatitis B and C infections in thalassaemia patients?

13. Evaluation and management of cardiac complications
    - ❑ What are the major cardiac complications?
    - ❑ What are the risk factors for developing cardiac complications?
    - ❑ What are the modalities for monitoring cardiac complications and recommendations on frequency of monitoring?
    - ❑ Comparison of various iron chelators either as monotherapy or combination therapy
    - ❑ What is the efficacy of parenteral desferrioxamine in reducing myocardial iron and improving cardiac function?
    - ❑ Is deferiprone better than desferrioxamine in reducing myocardial iron and improving cardiac function?
    - ❑ Is combination therapy better than desferrioxamine alone in reducing myocardial iron and improving cardiac function?
    - ❑ Is combination therapy better than deferiprone alone in reducing myocardial iron and improving cardiac function?
    - ❑ What is the efficacy of deferasirox in reducing myocardial iron and improving cardiac function?

14. How should endocrine complications diagnosed and managed in thalassaemia patients with regards to
    - ❑ Short stature
    - ❑ Delayed puberty
    - ❑ Diabetes mellitus
    - ❑ Hypothyroidism
    - ❑ Hypoparathyroidism
    - ❑ Hypoadrenalism
    - ❑ Osteoporosis/osteopaenia

APPENDIX 3

GENETICS RISKS IN THALASSAEMIA

A. β THALASSAEMIA RECURRENCE RISK

1. Patients with β thalassaemia major:

His/her spouse should check their carrier status.

- If the spouse is not a carrier, all of their offsprings will be asymptomatic carriers.
- If the spouse is also a carrier, half of their offsprings will have thalassaemia major, half will be carriers.
- If the spouse is also affected with thalassaemia major, all of their offsprings will have thalassaemia major.

2. Parents of a patient with β thalassaemia major:

As both parents are likely to be carriers themselves, the recurrence risk for another affected child in each of their future pregnancies will be one in four or 25%.

3. Carrier of β thalassaemia:

His/her spouse should check their carrier status.

- If the spouse is not a carrier, none of their offspring will have thalassaemia major but half of their offsprings will be asymptomatic carriers.
- If the spouse is also a carrier, there is one in four chance of having an affected (thalassaemia major) child in each pregnancy. Clinically unaffected children have 2/3 chance of being carriers.
- If the spouse is affected with thalassaemia major, half of their offspring will have thalassaemia major and half will be carriers.

B. α THALASSAEMIA RECURRENCE RISK

Parents ♂ / ♀	Hb H disease	α^0 trait	α^+ trait	non α carrier
Hb H disease	• 50% Hb H disease • 25% α thal. major • 25% α^+ homozygote	• 25% α thal. major • 25% Hb H disease • 25% α^0 trait • 25% α^+ trait	• 25% Hb H disease • 25% α^0 trait • 25% α^+ trait • 25% α^+ homozygote	• 50% α^0 trait • 50% α^+ trait
α^0 trait	• 25% α thal. major • 25% Hb H disease • 25% α^0 trait • 25% α^+ trait	• 50% α^0 trait • 25% α thal. major • 25% normal	• 25% α thal. major • 25% Hb H disease • 25% α^0 trait • 25% α^+ trait	• 25% α^0 trait • 25% normal
α^+ trait	• 25% Hb H disease • 25% α^0 trait •25% α^+ trait • 25% α^+ homozygote	• 25% α thal. major • 25% Hb H disease • 25% α^0 trait • 25% α^+ trait	• 50% α^+ trait • 25% α^+ homozygote • 25% normal	• 50% α^+ trait • 50% normal
non α carrier	• 50% α^0 trait • 50% α^+ trait	• 50% α^0 trait • 50% normal	• 50% α^+ trait • 50% normal	•100% normal

Legend: thal. = thalassaemia; α^+ = α plus; α^0 = α zero

Clinical significance of:

1. α thalassaemia major: : Hydrops foetalis
2. Hb H disease: moderate anaemia and usually not transfusion dependent
3. α^0 trait: asymptomatic
4. α^+ trait: asymptomatic
5. α^+ homozygote: asymptomatic

C. REPRODUCTIVE RISK OF Hb E, α & β THALASSAEMIA CARRIERS

Parents ♂ / ♀	Hb E trait	α^0 trait	α^+ trait	β trait
Hb E trait	• 50% Hb E trait • 25% Hb E homozygote • 25% normal	•25% Hb E trait/α^0 trait • 25% α^0 trait • 25% Hb E trait • 25% normal	• 25% Hb E trait/α^+ trait • 25% α^+ trait • 25% Hb E trait • 25% normal	• 25% Hb E trait/β thal. • 25% Hb E trait • 25% β trait • 25% normal
α^0 trait	•25% Hb E trait/α^0 trait • 25% α^0 trait • 25% Hb E trait • 25% normal	• 50% α^0 trait • 25% α thal. major • 25% normal	• 25% normal • 25% Hb H disease • 25% α^0 trait • 25% α^+ trait ERRATUM 2013	• 25% α^0 trait/β trait • 25% α^0 trait • 25% β trait • 25% normal
α^+ trait	• 25% Hb E trait/α^+trait • 25% α^+ trait • 25% Hb E trait • 25% normal	• 25% normal • 25% Hb H disease • 25% α^0 trait • 25% α^+ trait ERRATUM 2013	• 50% α^+ trait • 25% α^+ homozygote • 25% normal	• 25% α^+ trait/β trait • 25% α^+ trait • 25% β trait • 25% normal
β trait	• 25% Hb E trait/β thal. • 25% Hb E trait • 25% β trait • 25% normal	• 25% α^0 trait/β trait • 25% α^0 trait • 25% β trait • 25% normal	• 25% α^+ trait/β trait • 25% α^+ trait • 25% β trait • 25% normal	• Refer to Appendix 3A

Clinical significance of:

1. Hb E trait: asymptomatic
2. Hb E homozygote: asymptomatic
3. Hb E trait/α^0 trait: asymptomatic
4. α^0 trait: asymptomatic
5. Hb E trait/α^+ trait: asymptomatic
6. α^+ trait: asymptomatic
7. Hb E trait/β thalassaemia: moderate to severe anaemia
8. β trait: asymptomatic
9. α thalassaemia major: Hydrops foetalis
10. Hb H disease: moderate anaemia and usually not transfusion dependent
11. α^+ homozygote: asymptomatic
12. α^0 trait/β trait: asymptomatic
13. α+ trait/β trait: asymptomatic

APPENDIX 4

PRENATAL DIAGNOSIS

The standard diagnostic method is chorionic villi sampling and DNA analysis around 10 - 12 weeks of pregnancy. Amniocentesis is performed around 16 weeks of gestation and the results may not be available early enough to allow for broader termination of pregnancy options.

As an initial step, the patient's DNA will be analysed to look for mutations that caused the disease in the family. If both mutations (homozygotes or compound heterozygotes) can be detected, such mutations can be confirmed in the parents and among other potential carrier family members. Prenatal diagnosis can be offered to the couples whose mutations are known.

Linkage analysis instead of mutation analysis can be employed in families where only one or no mutation is detected.

a. Chorionic villi sampling (CVS):

CVS can be performed through the cervix (transcervical) or through the abdomen (transabdominal), depending on where the placenta is located. In both procedures, a small amount of placenta tissue is biopsied.

The transcervical procedure is performed by inserting a thin plastic tube through the vagina and cervix to reach the placenta under ultrasound guidance.

The transabdominal procedure is performed by inserting a needle through the abdomen and uterus and into the placenta under ultrasound guidance.

There is a small risk of miscarriage after the procedure (0.5 - 1%). In addition there is a small risk of infection or bleeding.

b. Amniocentesis

Amniocentesis is performed by inserting a needle through the abdominal wall into the uterus under ultrasound guidance and withdrawing a small amount of fluid from the sac surrounding the foetus.

There is a small risk of miscarriage after the procedure (0.5%). In addition there is a small risk of infection or leaking of amniotic fluid.

APPENDIX 5

MALAYSIAN THALASSAEMIA ASSOCIATIONS

Thalassaemia Association of Malaysia
3rd Floor, National Cancer Society Building,
66, Jalan Raja Muda Abdul Aziz,
50300 KUALA LUMPUR.
Tel: 03 - 26941141
Email: malaysiathalassaemia@yahoo.com

Penang Thalassaemia Society
CO38-UP, Penang Caring Society Complex,
Jalan Utama,
10450 PULAU PINANG.
Tel: 04 - 2272133
Email: penthal@streamyx.com
http://www.penthal.org

Sarawak Thalassaemia Society
c/o B. Teo's Clinic,
Jalan Tun Ahmad Zaidi Adruce,
93150 Kuching, SARAWAK.
Tel: 082 - 420008
Email: bibianateo@hotmail.com
http://www.thalassaemia.cdc.net.my

Sabah Thalassaemia Society
Persatuan Thalassaemia Sabah,
P.O Box 22748,
88787 Luyang,
Kota Kinabalu, SABAH.
Tel: 088 - 218766
http://www.sabah.org.my/scss/thala/default.htm

Malacca Association of Thalassaemia
777B Jalan Kesidang 3/11,
Taman Kesidang, Bacang,
75200 MELAKA.

Perak Thalassaemia Society
190 Persiaran Bercham Selatan 26,
Taman Sri Kurau, Bercham,
31400 Ipoh, PERAK.
Tel: 05 - 5468476

Kelab Thalassaemia Kedah
No.93, Kampong Langgar,
06500 Alor Star, KEDAH.
Tel: 013-5993577

Johore Thalassaemia Society
Lot 5395 Jalan Kurniawati,
Kampung Kurnia,
80250 Johor Bahru, JOHOR.
Tel: 07 - 3320369

Kuantan Thalassaemia Society
c/o Mr. Wong Cheng Wah
48, 2nd Floor, Jalan Gambut,
25000 Kuantan, PAHANG.
Tel: 010 - 9877131

Thalassemia Society of University Hospital
Department of Paediatrics,
University Hospital, Lembah Pantai,
59100 KUALA LUMPUR.
Tel: 03 - 79502270
http://www.thasuh.org

Kelantan Thalassaemia Society
c/o Zulkifli & Co
Lot 1251 Tingkat 1, Bangunan Zul Isma,
Jalan Sultan Yahya Petra
Kubang Kerian
15200 Kota Bharu, KELANTAN.
Tel: 09-7646206

Thalassaemia Association of Malaysia (Terengganu Branch)
c/o Pusat Rawatan Harian Kanak-Kanak
Hospital Sultanah Nur Zahirah
20400 Kuala Terengganu, TERENGGANU.
Tel: 09-6212064

APPENDIX 6

COST OF CHELATING AGENTS

Chelating agent	Unit Price	Drug cost for a 30 kg patient / month
Deferasirox Exjade®	125 mg = RM 22.79 500 mg = RM 91.21	20 mg/kg/day x 30 kg ~ 500 mg/day For 28 days = RM 91.21 x 28 tab/500 mg One month = RM 2553.88
Deferiprone (L1) Ferriprox®	500 mg = RM 3.32	75 mg/kg/day x 30 kg ~ 2.5 gm/day 1 week = 35 tablets 4 weeks = 140 tablet x RM 3.32 = RM 464.80
Deferiprone (L1) Kelfer®	500 mg = RM 4.18	75 mg/kg/day x 30 kg ~ 2.5 gm/day 1 week = 35 tablets 4 weeks = 140 tablet x RM 4.18 = RM 585.20
Desferrioxamine Desferal®	500 mg = RM 10.60	40 mg/kg/day x 30 kg ~ 1.5 gm/day 1 week = 18 vials 4 weeks = 72 vials x RM 10.60 = RM 763.20

Note: The actual cost of using any particular drug would be higher since it may include the use of consumables, infusion pump and laboratory investigations for toxicity monitoring purposes

APPENDIX 7

MID-PARENTAL HEIGHT MEASUREMENT

Family Measurements:

Measure height of parents for mid-parental height (MPH) and determine target height range

MPH for Boys = $\frac{\text{Father's height + (Mother's height +13) cm}}{2}$

MPH for Girls = $\frac{\text{Mother's height + (Father's height -13) cm}}{2}$

Target height range = MPH ± 2SD cm = MPH ± 8 cm

Example of calculation of MPH and target height range:

a) Patient is a girl. Mother's height: 154 cm Father's height: 172 cm.

MPH = $\frac{\text{Mother's height + (Father's height - 13)}}{2}$

MPH = $\frac{154 + (172 - 13)}{2} = 156.5$ cm

Target height range = MPH ± 2SD = 156.5 cm ± 8 cm
= 148.5 to 164.5cm

b) Patient is a boy. Mother's height: 154 cm. Father's height: 172 cm.

MPH = $\frac{\text{Father's height + (Mother's height + 13) cm}}{2}$

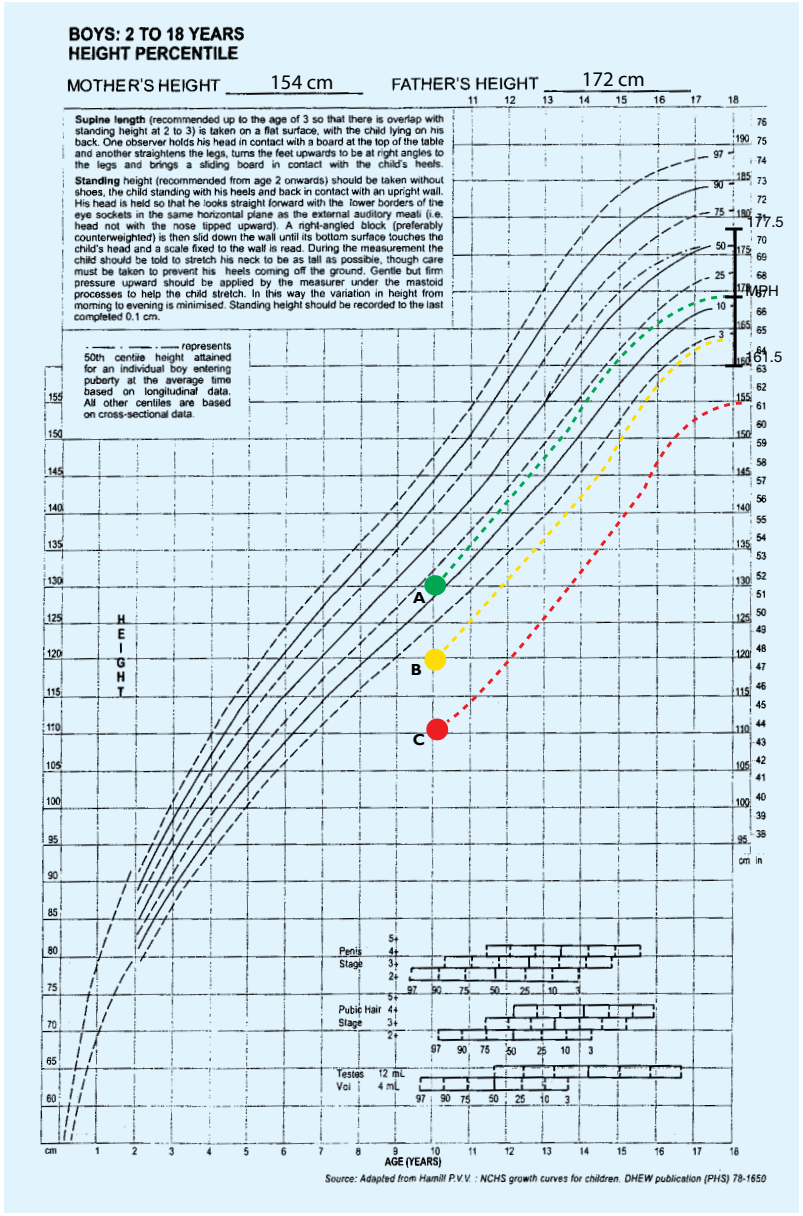
MPH = $\frac{172 + (154 + 13)}{2} = 169.5$ cm

Target height range = MPH ± 2SD = 169.5 cm ± 8 cm
= 161.5 to 177.5 cm

Plot the target height range on the growth chart at 18 years old point. Plot the patient's current height on the growth chart and extrapolate the growth curve until 18 years old.

Please refer to attached growth chart:

- ★ If the boy's height is 130 cm (point A), and extrapolated until 18 years old, his final height will be within the target height range. This is normal.
- ★ If the boy's height is 122 cm (point B), and extrapolated until 18 years old, his final height will be at the lower limit of target height range. This is still normal but monitoring of subsequent growth is crucial.
- ★ If the boy's height is 115 cm (point C), and extrapolated until 18 years old, his final height will be below target height range, this indicates short stature and further management is needed.


BOYS: 2 TO 18 YEARS
HEIGHT PERCENTILE
MOTHER'S HEIGHT 154 cm
FATHER'S HEIGHT 172 cm
Supine length (recommended up to the age of 3 so that there is overlap with standing height at 2 to 3) is taken on a flat surface, with the child lying on his back. One observer holds his head in contact with a board at the top of the table and another straightens the legs, turns the feet upwards to be at right angles to the legs and brings a sliding board in contact with the child's heels.
Standing height (recommended from age 2 onwards) should be taken without shoes, the child standing with his heels and back in contact with an upright wall. His head is held so that he looks straight forward with the lower borders of the eye sockets in the same horizontal plane as the external auditory meati (i.e. head not with the nose tipped upward). A right-angled block (preferably counterweighted) is then slid down the wall until its bottom surface touches the child's head and a scale fixed to the wall is read. During the measurement the child should be told to stretch his neck to be as tall as possible, though care must be taken to prevent his heels coming off the ground. Gentle but firm pressure upward should be applied by the measurer under the mastoid processes to help the child stretch. In this way the variation in height from morning to evening is minimised. Standing height should be recorded to the last completed 0.1 cm.
represents 50th centile height attained for an individual boy entering puberty at the average time based on longitudinal data. All other centiles are based on cross-sectional data.
97
90
75
50
25
10
3
177.5
MPH
161.5
A
B
C
HEIGHT
cm
in
Penis Stage
Pubic Hair Stage
Testes Vol
12 mL
4 mL
AGE (YEARS)
Source: Adapted from Hamill P.V.V. : NCHS growth curves for children. DHEW publication (PHS) 78-1650

APPENDIX 8

SCHEDULE OF INVESTIGATIONS FOR ENDOCRINE COMPLICATIONS IN TRANSFUSION DEPENDENT THALASSAEMIA

In general, the recommended age for screening for endocrine complications is 10 years old. However, the age for screening is individualized, i.e. depends on thalassaemia control and whether the patient has already developed an endocrine complication.

Endocrine Complications	Investigations
Short Stature and Growth Failure	Detect other causes of short stature, including bone disorders and DFO toxicity. Endocrine tests that can be done: • Thyroid function tests • Sex hormones • OGTT Other possibly useful tests: IGF-1, IGFBP-3 and bone age assessment. GH stimulation tests may be required.
Delayed Puberty and Hypogonadism	Tanner staging should be determined every six months from the age of 10 years. Investigations in delayed puberty include: • Thyroid function tests • LH, FSH, oestradiol or testosterone • Bone age Pelvic ultrasound to assess ovarian and uterine size. If results are abnormal, perform gonadotropin releasing hormone (GnRH) stimulation test.
Hypothyroidism	• Free T4 and TSH • Bone age
Diabetes Mellitus	Fasting plasma glucose or OGTT
Osteoporosis/Osteopaenia	• Serum calcium, phosphate, ALP • 25-OH Vitamin D • Serum zinc • 24-hour urinary calcium • Spinal radiograph (AP and lateral views) • DEXA scan • MRI scan of the spine may be considered for patients with severe back pain.
Hypoparathyroidism	• Serum calcium • Serum phosphate • Serum magnesium • Serum alkaline phosphatase • Parathyroid hormone
Hypoadrenalism	• Baseline cortisol • ACTH stimulation test

APPENDIX 9

LIST OF ABBREVIATIONS

ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AP	Anteroposterior
AST	Aspartate Aminotransferase
BMD	Bone Mineral Density
BMI	Body Mass Index
BMT	Bone Marrow Transplantation
BUSEC	Blood Urea Serum Electrolyte Creatinine
CT	Computed Tomography
DEXA	Dual-energy X-ray Absorptiometry
DFO	Desferrioxamine
DFP	Deferiprone
DFS	Disease Free Survival
DFX	Deferasirox
DIVC	Disseminated Intravascular Coagulation
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
DW	Dry Weight
ESHG	European Society of Human Genetics
FBC	Full Blood Count
GHD	Growth Hormone Deficiency
GHIS	Growth Hormone Insensitivity
GVHD	Graft Versus Host Disease
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
hCG	Human Chorionic Gonadotrophin
HCT	Haemotocrit
HCV	Hepatitis C Virus
HIB	Haemophilus Influenza B
HLA	Human Leucocyte Antigen
HPLC	High Performance Liquid Chromatography

HSCT	Haemopoietic Stem Cell Transplantation
IFN	Interferon
IGT	Impaired Glucose Tolerance
IM	Intramuscular
I/v	Intravenous
LFT	Liver Function Test
LIC	Liver Iron Concentration
LVEF	Left Ventricular Ejection Fraction
MAC	Mid-arm Circumference
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MPH	Mid-parental Height
MRI	Magnetic Resonance Imaging
OGTT	Oral Glucose Tolerance Test
OPSI	Overwhelming Post-splenectomy Infection
OS	Overall survival
PBF	Peripheral Blood Film
PRBC	Packed Red Blood Cell
PT	Prothrombin
QALY	Quality Adjusted Life Year
QCT	Quantitative Computed Tomography
QUS	Quantitative Ultrasound
RBC	Red Blood Cell
RDA	Recommended Dietary Allowances
RDW	Red Cell Distribution Width
Rh-GH	Recombinant Human Growth Hormone
S/c	Subcutaneous
SD	Standard Deviation
SF	Serum Ferritin
SFT	Skin Fold Thickness
SOD	Superoxide Dismutase
SVR	Sustained Viral Response
TSH	Thyroid Stimulating Hormone
Wt	Weight

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LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)