KEY MESSAGES

- Thalassaemia is an inherited blood disorder affecting all major ethnicities in Malaysia.

- All patients with MCH < 27 pg should be screened for thalassaemia.

- Cascade screening and appropriate genetic counselling should be provided to the immediate and extended family members of an index patient.

- All thalassaemia major patients should receive safe and optimal blood transfusions.

- Monitoring and treatment of iron overload must be optimised to improve survival.

- Monitoring and treatment of cardiac, infective and endocrine complications will ensure better quality of life and survival.

- Effective patient management requires good collaboration between transfusion medicine, laboratory and clinical services.

- Bone marrow transplantation from a matched sibling donor is an established curative treatment option.

This Quick Reference provides key messages and a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Transfusion Dependent Thalassaemia (November 2009).

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:

Ministry of Health Malaysia : http://www.moh.gov.my
Academy of Medicine Malaysia : http://www.acadmed.org.my
ALGORITHM FOR VOLUNTARY AND CASCADE SCREENING

Walk-in for voluntary screening*

Pre-test counselling

FBC

Hb – normal MCH >27pg

Post-test counselling

Hb-normal MCH <27pg

Response to treatment

YES

Consult Haematologist/ Paediatrician/Physician

Definitive diagnosis

Normal

Thalassaemia carrier

YES

Definitive diagnosis

NO

Counselling

1. Consider DNA analysis
2. Further investigations as appropriate

UNCERTAIN

YES

Definitive diagnosis

NO

Definitive diagnosis

Offer pre-test counselling and screening for family members (Uncles, aunts and cousins of the index case)

Offer pre-test counselling and screening for immediate family members (Parents + siblings of the index case)

Send FBC result & unstained PBF slide with remaining blood to referral hospital for Hb analysis

Hb-low MCH < 27pg

Check & treat for iron deficiency anaemia

NO

YES

Continue treatment

Index Case

Thalassaemia Major /Carriers

FBCHb – normal

MCH >27pg

Hb-low

MCH < 27pg

Response to treatment

YES

Consult Haematologist/ Paediatrician/Physician

Definitive diagnosis

Normal

Thalassaemia carrier

YES

Definitive diagnosis

NO

Counselling

1. Consider DNA analysis
2. Further investigations as appropriate

UNCERTAIN

YES

Definitive diagnosis

NO

Definitive diagnosis

Post-test counselling

Hb-normal MCH <27pg

Response to treatment

YES

Consult Haematologist/ Paediatrician/Physician

Definitive diagnosis

Normal

Thalassaemia carrier

YES

Definitive diagnosis

NO

Counselling

1. Consider DNA analysis
2. Further investigations as appropriate

UNCERTAIN

YES

Definitive diagnosis

NO

Definitive diagnosis

Offer pre-test counselling and screening for family members (Uncles, aunts and cousins of the index case)

Offer pre-test counselling and screening for immediate family members (Parents + siblings of the index case)

Send FBC result & unstained PBF slide with remaining blood to referral hospital for Hb analysis

Hb-low MCH < 27pg

Check & treat for iron deficiency anaemia

NO

YES

YES

YES

YES

YES

# DIAGNOSTIC CRITERIA

<table>
<thead>
<tr>
<th></th>
<th>CLINICAL FEATURES</th>
<th>LABORATORY FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassaemia Major</td>
<td>Anaemia</td>
<td>Hb  :  &lt; 7 g/dL</td>
</tr>
<tr>
<td>(presentation usually at 4-6 months or child younger than 2 years old)</td>
<td>Hepatosplenomegaly</td>
<td>HbF :  &gt; 90%</td>
</tr>
<tr>
<td></td>
<td>Growth failure / retardation</td>
<td>HbA2 : normal or high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA : usually absent</td>
</tr>
<tr>
<td>Thalassaemia Intermedia</td>
<td>Milder anaemia</td>
<td>Hb  : 8-10 g/dL</td>
</tr>
<tr>
<td>(presentation at later age)</td>
<td>Thalassaemia facies</td>
<td>HbF : &gt; 10%</td>
</tr>
<tr>
<td></td>
<td>Hepatosplenomegaly</td>
<td>HbA2 : 4-9%, if &gt; 10% - suggests HbE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA : 5-90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbH disease : presence of H band</td>
</tr>
<tr>
<td>β Thalassaemia Trait</td>
<td>Normal to mild anaemia</td>
<td>Hb  :  &gt; 10 g/dL</td>
</tr>
<tr>
<td></td>
<td>No organomegaly</td>
<td>MCH :  &lt; 27 pg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hbf : 2.5 - 5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA2 : 4-9%, if &gt; 20% suggests HbE trait</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA :  &gt; 90%</td>
</tr>
<tr>
<td>α Thalassaemia Trait</td>
<td>Normal to mild anaemia</td>
<td>Hb  :  &gt; 10 g/dL</td>
</tr>
<tr>
<td></td>
<td>No organomegaly</td>
<td>MCH :  &lt; 27 pg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hbf analysis : normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H inclusion may be present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DNA studies may be necessary</td>
</tr>
</tbody>
</table>

- For more difficult cases, molecular studies may be employed.

# BLOOD TRANSFUSION THERAPY

Transfusion should be initiated when the patient is confirmed to have thalassaemia major and Hb < 7 g/dL more than 2 weeks apart.

In thalassaemia intermedia, consider transfusion when patient has failure to thrive or bony deformities or extramedullary masses.

All patients should have full red cell phenotyping consisting of ABO, Rh, Kell, Kidd, Duffy and MNSs prior to first transfusion.

Pre-transfusion Hb should be kept between 9 – 10 g/dL.

Post transfusion Hb should be between 13.5 - 15.5 g/dL.

Fresh blood < 14 days and leucodepleted blood are advisable.

Volume of transfusion: 15 – 20 ml/kg, 2 – 4 weeks apart.

In the presence of hypersplenism, consider splenectomy.
**DEGREE OF IRON OVERLOAD**

<table>
<thead>
<tr>
<th></th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>&lt; 2500</td>
<td>2500 - 5000</td>
<td>&gt; 5000</td>
</tr>
<tr>
<td>LIC (mg Fe/g DW)</td>
<td>&lt; 7</td>
<td>7 - 15</td>
<td>&gt; 15</td>
</tr>
<tr>
<td>Cardiac T2* MRI (ms)</td>
<td>&gt; 20</td>
<td>10 - 20</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>

**ALGORITHM FOR IRON CHELATION THERAPY**

**Start Iron Chelation Therapy if serum ferritin > 1,000 µg/L**  
(usually at age 2-3 years)

**Monotherapy**
First line Iron Chelator: DFO 20-40 mg/kg/day (children) and up to 50 - 60 mg/kg/day (adults) s/c slow infusion 5 nights per week

If inadequate chelation with DFO, consider:
- DFX 20 - 30 mg/kg/day in young children more than 2 years old OR
- DFP 75 - 100 mg/kg/day if more than 6 years old

**Mild iron overload:**
- Serum ferritin < 2,500 µg/L
- T2*heart > 20 ms
- LIC < 7 mg Fe/g DW
(if MRI is available, T2* MRI is indicated for those >10 years old)

**Moderate to severe iron overload:**
- Serum ferritin > 2,500 µg/L
- T2*heart < 20 ms
- LIC > 7 mg Fe/g DW
(if MRI is available, T2* MRI is indicated for those >10 years old)

Continue current iron chelator and aim for serum ferritin < 1,000 µg/L

Check compliance, optimise dose of current drug or monotherapy
Switch to alternatives:
- Another monotherapy
- Consider DFP-DFO combination
- Intravenous DFO

**Abbreviations:**  
DFO – Desferrioxamine  
DFP – Deferiprone  
DFX – Deferasirox  
LIC – Liver Iron Concentration
# MONITORING OF PATIENT

<table>
<thead>
<tr>
<th>NO.</th>
<th>MONITORING</th>
<th>ASSESSMENT AND INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Blood transfusion</td>
<td>HBsAg, Anti HCV and Anti HIV 6 monthly</td>
</tr>
<tr>
<td>2.</td>
<td>Growth</td>
<td>Weight, height and physical examination 3 - 6 monthly</td>
</tr>
<tr>
<td>3.</td>
<td>Iron overload</td>
<td>Serum ferritin 3 monthly</td>
</tr>
<tr>
<td></td>
<td>Patient &gt; 10 years old</td>
<td>ECG and cardiac echocardiography annually</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LIC by MRI 1 – 2 yearly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac MRI T2* 1 – 2 yearly</td>
</tr>
<tr>
<td>4.</td>
<td>Drug toxicity</td>
<td>Auditory/ophthalmology annually</td>
</tr>
<tr>
<td></td>
<td>Desferrioxamine</td>
<td>Full blood count weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALT 3 monthly</td>
</tr>
<tr>
<td></td>
<td>Deferiprone</td>
<td>Renal profile and urine protein monthly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALT monthly</td>
</tr>
<tr>
<td></td>
<td>Deferasirox</td>
<td>Auditory/ophthalmology annually</td>
</tr>
<tr>
<td>5.</td>
<td>Complications*</td>
<td>Especially in older patients &gt; 10 years old</td>
</tr>
<tr>
<td>5.1</td>
<td>Growth failure</td>
<td>Test for diabetes mellitus, hypothyroidism, delayed puberty, zinc deficiency, bone disorders, DFO toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone age assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GH stimulation tests (in referral centre)</td>
</tr>
<tr>
<td>5.2</td>
<td>Delayed puberty and hypogonadism</td>
<td>Tanner staging 6 monthly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LH, FSH, oestradiol or testosterone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelvic ultrasound for girls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gonadotropin releasing hormone (GnRH) stimulation test if necessary</td>
</tr>
<tr>
<td>5.3</td>
<td>Hypothyroidism</td>
<td>Free T4 and TSH</td>
</tr>
<tr>
<td>5.4</td>
<td>Diabetes mellitus</td>
<td>Fasting plasma glucose or OGTT</td>
</tr>
<tr>
<td>5.5</td>
<td>Osteoporosis/Osteopaenia</td>
<td>Serum calcium, phosphate, alkaline phosphatase 25-OH Vitamin D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum zinc</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spinal radiograph (AP and lateral views)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DEXA scan</td>
</tr>
<tr>
<td>5.6</td>
<td>Hypoparathyroidism</td>
<td>Serum calcium, phosphate, alkaline phosphatase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum magnesium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>5.7</td>
<td>Hypoadrenalism</td>
<td>Baseline cortisol at 8.00 – 9.00 am</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACTH stimulation test</td>
</tr>
</tbody>
</table>

*Monitor annually and refer to appropriate specialist for management*
## MANAGEMENT OF COMPLICATIONS

### HEPATITIS B

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, > 2 X upper limit of normal or significant liver disease on liver biopsy

<table>
<thead>
<tr>
<th>TREATMENT CRITERIA</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon α (IFN α) for 4-6 months for HBeAg positive patients and at least a year for HBeAg negative patients or Peg-IFN for at least six months for HBeAg positive patients and 12 months for HBeAg negative patients or Lamivudine</td>
<td></td>
</tr>
</tbody>
</table>

### HEPATITIS C

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

<table>
<thead>
<tr>
<th>TREATMENT CRITERIA</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy (either conventional or PEG-IFN) with ribavirin</td>
<td></td>
</tr>
</tbody>
</table>

### BACTERIAL INFECTIONS

- Significant fever especially post-splenectomy
- Broad spectrum anti-Klebsiella and anti-Pseudomonal agents (3rd generation cephalosporin ± aminoglycoside)

### CARDIAC SIDEROSIS

- Asymptomatic, mild to moderate cardiac siderosis (T2* 10 -20 ms) and normal cardiac function
- Symptomatic or severe cardiac iron overload

<table>
<thead>
<tr>
<th>TREATMENT CRITERIA</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensify iron chelation monotherapy or switch to combination therapy</td>
<td></td>
</tr>
</tbody>
</table>

### DELAYED PUBERTY

- Absence of pubertal changes at 13 years old (girls) and 14 years old (boys)
- Girls : Oral ethinyl oestradiol or conjugated oestrogen preparation
- Boys : Depot testosterone

### SHORT STATURE

- Treat other causes of short stature
- Growth hormone injection may be considered if confirmed growth hormone deficiency

### DIABETES MELLITUS

- Subcutaneous insulin injection

### HYPOTHYROIDISM (primary or central)

- Oral L-thyroxine

### OSTEOPOROSIS/OSTEOPAENIA

- Oral calcium and Vitamin D supplements
- Bisphosphonates may be considered in osteoporosis

### HYPOPARATHYROIDISM

- Oral calcitriol and calcium

### HYPOADRENALISM

- Oral hydrocortisone
ALGORITHM FOR MANAGEMENT OF TRANSFUSION DEPENDENT THALASSAEMIA

Genetic counseling

Family cascade screening

Dietary advice

Index Case: Diagnosis Confirmed

Has unaffected siblings

Consider stem cell transplantation

Regular Transfusion Therapy
- Use leucodepleted PRBC < 14 days old
- Pre transfusion Hb - 9.0 - 10.0 g/dL
- Post transfusion Hb - 13.5 - 15.5 g/dL

Monitor for transfusion related complications
- Hepatitis B
- Hepatitis C
- HIV

Monitor for iron overload
- Serum ferritin
- Liver iron concentration
- Cardiac T2*

Iron chelation therapy
- Desferrioxamine
- Deferiprone
- Deferasirox
- Combination Therapy
Monitor for side effects of chelators

Monitor for complications
- Cardiac
- Infections
- Endocrine
- Hypersplenism

CLINICAL PRACTICE GUIDELINES SECRETARIAT
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