Management of Thalassemia

Yingyong Chinthammitr, M.D.
Noppadol Siritanaratkul, M.D.
Division of Hematology
Department of Medicine
Thalassemia

- *Inherited* disorders of *globin synthesis* in which the production of globin chains is partially or completely *suppressed*

- *Autosomal recessive*
Pathophysiology

Excess α-chains → Precipitation → α-Inclusion bodies

α-Gene cluster
Chromosome 16
Heme

AHSP
Hb A

β-Gene cluster
Chromosome 11

Ineffective erythropoiesis
Extravascular hemolysis

Anemia

↑ Erythropoietin
Marrow expansion
Bone deformity
Osteopenia

↑ Iron absorption
Splenomegaly
Iron overload
## Common Phenotypes in Thailand

<table>
<thead>
<tr>
<th>Severity</th>
<th>Baseline Hb (g/dL)</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very severe</td>
<td>-</td>
<td>Hb Bart’s hydrops fetalis</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 7</td>
<td>Homozygous β-thal, Hb E/β-thal</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>7 – 9</td>
<td>Hb E/β-thal, Hb H disease, Homozygous β-thal</td>
</tr>
<tr>
<td>Mild</td>
<td>≥ 9</td>
<td>Hb H disease, Hb E/β-thal, Homozygous Hb CS</td>
</tr>
</tbody>
</table>
Prevalence of Thalassaemia and Hemoglobinopathies in Thailand

NORTHEAST
- \( \alpha \)-thalassemia: 20%
- \( \alpha \)-thal 1: 3%
- \( \alpha \)-thal 2: 12%
- \( \beta \)-thalassemia: 6%
- Hb E: 20-60%

NORTH
- \( \alpha \)-thalassemia: 30%
- \( \alpha \)-thal 1: 5-12%
- \( \alpha \)-thal 2: 19-26%
- \( \beta \)-thalassemia: 9-10%
- Hb E: 8%

CENTRAL
- \( \alpha \)-thalassemia: 20-25%
- \( \alpha \)-thal 1: 3.5%
- \( \alpha \)-thal 2: 16%
- \( \beta \)-thalassemia: 3%
- Hb E: 13-19%

SOUTH
- \( \alpha \)-thalassemia: 16%
- \( \alpha \)-thal 1: 2.5%
- \( \alpha \)-thal 2: 14%
- \( \beta \)-thalassemia: 2-4%
- Hb E: 9-11%
Diagnosis

- Clinical
- CBC, peripheral blood smear
- Inclusion body
- Hb typing

Inclusion body

Homozygous β-thal

Hb H disease
Management

- **Folic acid 5 mg/d**
- **Iron chelation**
  - Serum ferritin > 1,000 ng/mL
- **Acute hemolytic crisis**
  - Treatment of precipitating causes
  - Supportive care: oxygen, blood transfusion, antipyretics
  - Monitor complications: heart failure, hyperkalemia, renal failure
β-thalassemia

Supportive therapy
- Transfusion
- Iron overload
- Endocrinopathies
- Osteoporosis

Curative therapy
- Stem cell transplantation
- Experimental therapy
  - EPO
  - HbF modifiers
  - Antioxidants

Future therapy
- Gene therapy

Bone expansion (hair on end)
Hypopituitarism
Bronze skin
Hypothyroidism
Hypoparathyroidism
Pulmonary hypertension
Cardiomyopathy
Liver cirrhosis
Splenomegaly
Diabetes mellitus
Extramedullary hematopoiesis
Hypogonadism
Osteoporosis
Arthropathy
Short stature

Transfusion regimens

- Correction of anemia
- Suppression of erythropoiesis
- Inhibition of GI absorption of Fe
- Pretransfusion Hb
  - “supertransfusion regimen”  12
  - “hypertransfusion regimen”  10
  - “moderate transfusion regimen”  9.5
Homozygous β-thalassemia, HbE/β-thalassemia

● Management
  – Transfusion therapy:
    • Occasional transfusion
    • High transfusion: q 2-5 weeks, Hb 9-10.5 g/dL
  – Iron chelation
  – Endocrinopathies
  – Osteoporosis
High transfusion

- **Criteria**
  - Hb < 7 g/dl, > 2 weeks apart OR
  - with physical characteristics: facial changes, poor growth, fractures, and extramedullary hematopoiesis

- **Before first transfusion:**
  - Confirm laboratory diagnosis of thalassemia major
  - Check minor blood group (C, c, E, e, Mi\(^a\), Le\(^a\), Le\(^b\))
  - Check HBV vaccination

- **RBC:** fresh RBC, infectious screening test
  - Leukocyte-poor red cell (LPRC)
  - Leukocyte-depleted red cell (LD-RBC)

- Limit RBC ≤ 2 units/transfusion, diuretics, monitoring of BP & PR
Diagnostic Tests for Iron Overload

- Serum ferritin
- Liver iron concentration (LIC)
- Cardiac T2*

Screening:
- Serum ferritin q 3-6 months
- Cardiac T2* annually; if serum ferritin >1,000 ng/mL

Porter Hematology education: the education programme for the annual congress of the European Hematology Association 2012; 6(1)
## Severity of Iron Overload

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Iron overloaded state</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Serum ferritin, ng/mL</td>
<td>&lt;300</td>
<td>1,000 - 2,500</td>
</tr>
<tr>
<td>LIC, mg Fe/g dw of liver</td>
<td>&lt;1.2</td>
<td>3-7</td>
</tr>
<tr>
<td>T2*, ms</td>
<td>&gt;20</td>
<td>14-20</td>
</tr>
</tbody>
</table>

- Increased risk of complications
- Increased risk of cardiac disease

*Porter Hematology education: the education programme for the annual congress of the European Hematology Association 2012; 6(1)*
Iron chelation

Indication
- Transfuse > 10-20 units of blood
- Regular transfusion > 1 years\(^3\)
- Serum ferritin > 1,000 ng/mL

Target values\(^2\)
- Serum ferritin < 2,500 ng/mL
- LIC < 7 mg/g dry weight of liver
- Cardiac T2* > 20 ms

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\(^1\) Thalassaemia International Federation. Guidelines for the clinical management of thalassemia, 2008
\(^2\) Porter Hematology education: the education programme for the annual congress of the European Hematology Association 2012; 6(1)
\(^3\) มูลนิธิโรคโลหิตจางธาลัสซีเมียแห่งประเทศไทย. แนวทางการวินิจฉัยและการรักษาโรคโลหิตจางธาลัสซีเมีย พ.ศ. 2549
Iron Chelators in Siriraj Hospital

Desferrioxamine

Deferiprone

Deferasirox
# Comparison of Iron Chelators

<table>
<thead>
<tr>
<th>Property</th>
<th>DFO</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dose (mg/kg/day)</td>
<td>30 - 50</td>
<td>50 - 75</td>
<td>20 - 30</td>
</tr>
<tr>
<td>Route</td>
<td>Sc, iv</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td>(8–12 hours, 5 days/week)</td>
<td>3 times daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 - 30 minutes</td>
<td>3 - 4 hours</td>
<td>8 - 16 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, fecal</td>
<td>Urinary</td>
<td>Fecal</td>
</tr>
</tbody>
</table>

Modified from Hershko C. Haematologica 2006;91:1307-12
Sites of DFO injection
Common Side Effects of Deferoxamine

- Local reactions
  - Erythema (localized redness)
  - Induration (localized swelling)
  - Pruritus (itchiness)
- Ophthalmologic
  - Reduced visual acuity
  - Impaired color vision
  - Night blindness
  - Increased by presence of diabetes
- Hearing loss
- Zinc deficiency
Deferiprone: side effects

- Arthropathy 15 - 40%
- Agranulocytosis 1 - 2%
- Neutropenia 2%
- GI symptoms 15%
- Zn deficiency
- Progression of hepatic fibrosis: 1 report
### Guideline for Iron Chelation in Siriraj Hospital

<table>
<thead>
<tr>
<th>Serum ferritin (ng/mL)</th>
<th>Treatment</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 – 2,500</td>
<td>Deferiprone OR DFO sc</td>
<td>3-6 d/wk</td>
</tr>
<tr>
<td>2,500 – 8,000</td>
<td>Deferiprone + DFO sc</td>
<td>3-6 d/wk</td>
</tr>
<tr>
<td>&gt; 8,000</td>
<td>Deferiprone + DFO sc</td>
<td>5-7 d/wk</td>
</tr>
<tr>
<td></td>
<td>DFO iv 24 hr</td>
<td></td>
</tr>
</tbody>
</table>

**F/U q 3 mo**

<table>
<thead>
<tr>
<th>Level</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1,000</td>
<td>Decrease dose</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>Off chelation</td>
</tr>
</tbody>
</table>

**Toxicity* or intolerance or poor compliance**

- Deferasirox

*ALT >2.5xULN, ophthalmologic or auditory adverse effects, agranulocytosis, neutropenia after rechallenge
## Monitoring Recommendations

<table>
<thead>
<tr>
<th>Test</th>
<th>DFO</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Monthly</td>
<td><em>Weekly in first 2 month then monthly</em></td>
<td>Monthly</td>
</tr>
<tr>
<td>UA</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Monthly</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>Liver function test</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>BUN/Cr</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Monthly</td>
</tr>
<tr>
<td>Zn (optional)</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>-</td>
</tr>
<tr>
<td>Audiogram and ophthalmic exam</td>
<td>Annually</td>
<td>Annually</td>
<td>Annually</td>
</tr>
</tbody>
</table>

แนวทางการใช้ยาขับเหล็กในโรงพยาบาลศิริราช 2553
Splenectomy

- Delayed until at least 5 years of age
- Indications
  - RBC transfusion > 200 - 220 mL of RBC/kg/yr
  - Splenic enlargement with symptoms: LUQ pain/ early satiety
  - Hypersplenism: leucopenia/ thrombocytopenia
- Complication: sepsis, thromboembolism, pulmonary hypertension
- Management
  - Counseling: risk of sepsis
  - Pneumococcal vaccine at least 2 weeks before splenectomy
  - Influenza vaccine annually
  - Low dose aspirin if platelet count > 800 x 10⁹/L
  - Penicillin (250 mg) 1 tab bid for 2 years after splenectomy

Thalassaemia International Federation guidelines for the clinical management of thalassemia 2007
Endocrinopathies

- **Hormone deficiency**
  - Hypogonadism
  - Short stature
  - Diabetes mellitus
  - Primary hypothyroidism
  - GH deficiency
  - Hypoparathyroidism

- **Mechanisms:**
  - Iron deposition, irreversible damage

- **Intensive iron chelation may be the key to normal growth and sexual development**

- **Treatment**
  - Hormone replacement
  - Insulin in DM
    - $\text{HbA}_1\text{C} :$ false low
    - Iron chelation: not improve glycaemic control

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1. NEJM 1990 Sep 13;323(11):713-9
Infection

- **Infection in Thalassemia**
  - Upper respiratory tract infection, diarrhea, pneumonia, gram negative septicemia, Melioidosis and death
  - Post-splenectomy sepsis
  - Treatment: antibiotics

- **Pythium insidiosum infection**
  - Arterial occlusion, gangrene, and death
  - Treatment: amputation, vaccine, antifungal therapy
Extramedullary Erythropoiesis

- Increased erythropoiesis
  - Paravertebral mass with spinal cord compression: paraplegia
  - Intracranial mass: seizure

- Treatment
  - Transfusion
  - Local radiation
  - Hydroxyurea
Healthy lifestyles

- Well-balanced & sanitary diet
- Avoidance of iron-rich diet, iron supplementation
- Folic acid supplement
- Physical exercise as tolerate
- Avoidance of contact sport: fracture, splenic rupture
- Vaccination: HBV, influenza, pneumococcal vaccine
- Cautions of fever
- No smoking, no excess alcohol consumption
Screening test

- Red cell indices
  - MCV < 80 fL, MCH < 27 pg
- Osmotic fragility (OF) test
  - 0.36% NaCl → hemolysis of normal RBC
  - Test for
    - α-thal 1 trait
    - β-thal trait
      (Sensitivity 95%)
  - False positive: normal 5%, iron deficiency anemia

- Dichlorophenol Indophenol precipitation (DCIP) test
  - Dye: oxidize unstable Hb
  - Test for
    - HbE (Sensitivity 100%)
    - HbH
Detection of carriers

- **MCV > 80 fL**
  - DCIP negative
  - Normal, cannot be exclude α-thal 2 trait

- **MCV < 80 fL**
  - DCIP positive

- **DCIP positive**
  - exclude iron deficiency*

- **Hb typing**
  - Abnormal Hb typing
    - HbE trait
    - Homozygous HbE
    - HbCS trait
    - Homozygous HbCS
    - Hb H disease
    - β-thal/Hb E, ect.
    - At risk couple
  - A₂A, A₂ > 3.5%
    - β-thal trait
  - A₂A, A₂ < 3.5%
    - PCR for α-thal
    - α-thal 1 trait

*Serum ferritin < 15 ng/mL, Therapeutic trial, Hb < 10 g/dL
Genetic counseling

- Reassure
- Risk of severe thalassemia
- Choice
  - Prenatal diagnosis and termination of pregnancy in high-risk couple (Bart’s hydrop fetalis, homozygous $\beta$-thal, $\beta$-thal/HbE)
  - Take risk
    - Contraception
    - Artificial insemination/ donor ovum
    - Adopted child
    - Pre-implantation genetic diagnosis
Prenatal diagnosis

**GA 10^{th} - 12^{th} wk**
- CVS

**GA 12^{th} - 18^{th} wk**
- Ultrasound: Hb Bart’s hydrop fetalis
- Amniocentesis

**GA 18^{th} - 24^{th} wk**
- Cordocentesis
- PCR-based DNA analysis
- Hb analysis
Summary

- The thalassemias are a heterogeneous group of genetic disorders that affect millions of people around the world.
- Regular or intermittent blood transfusions are indicated for many patients with certain types of thalassemia syndromes:
  - β-thalassemia major: life-long, regular blood transfusions.
- Iron overload is a significant complication in the thalassemia syndromes due to:
  - Transfusion therapy
  - Increased intestinal iron absorption
- Iron chelation therapy is a key component of treatment for certain types of thalassemia.
- Effective chelation therapy has demonstrated significant morbidity and survival benefits in patients with β-thalassemia major and intermedia.