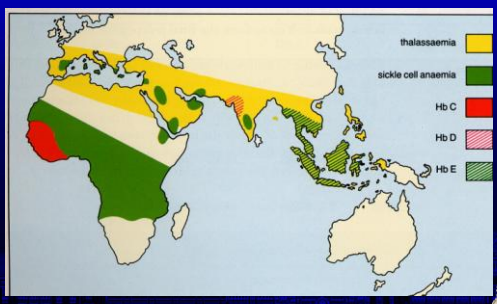
Thalassemia and hemoglobinopathy in Thailand

Chalinee Monsereenusorn, M.D.

Outline

- Incidence
- Pathophysiology
- Signs and symptoms
- Diagnosis
- Treatment and counseling
- Prenatal diagnosis
- National policy

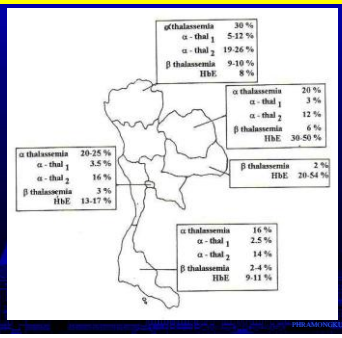
Incidence



Thalassemia

- Autosomal recessive inheritance
- Most common hematologic disease in Thailand

Incidence of thalassemia in Thailand



Incidence of thalassemia

Disease	Couple at risk (per year)	Birth (per year)	Living patients
Homozygous ß-thal	2,500	625	6,250[1]
ß-thal/Hb E	13,000	3,250	97,500[2]
Hb Bart's hydrops	5,000	1,250	0
Hb H disease	28,000	7,000	420,000[3]
Total	48,500	12,125	523,750

Estimated from 1 million birth per year
Estimated life expectancy for 1,2,3 are 10,30 and 60 years respectively

Cause

- Abnormal gene that control the genesis of globin chain

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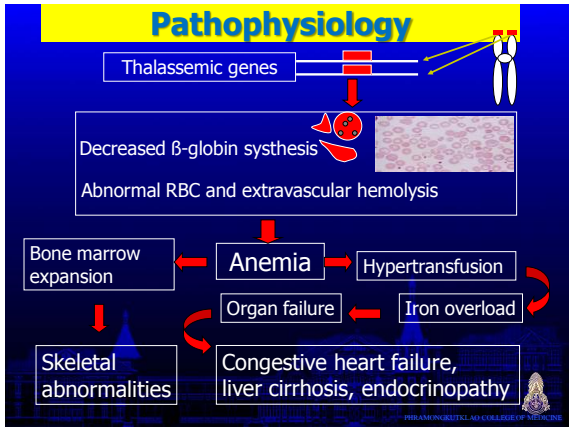
Pathophysiology



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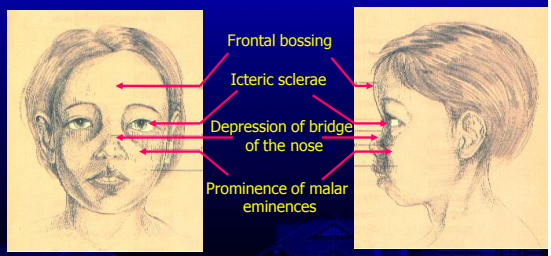
Clinical presentation



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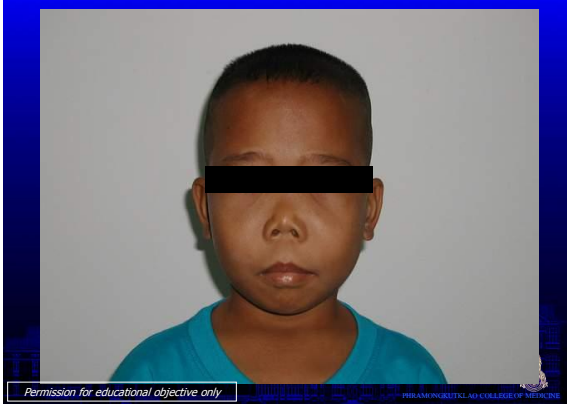

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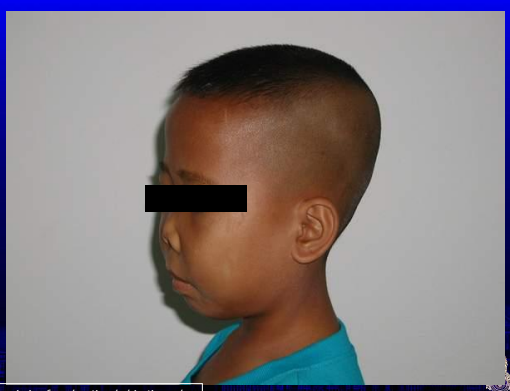

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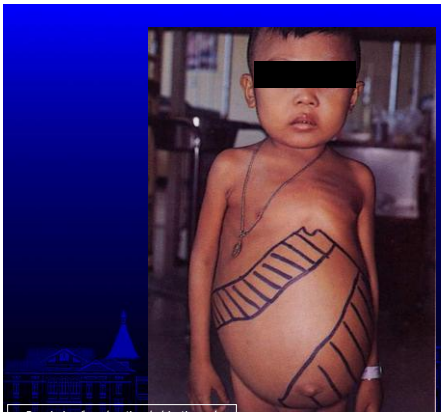

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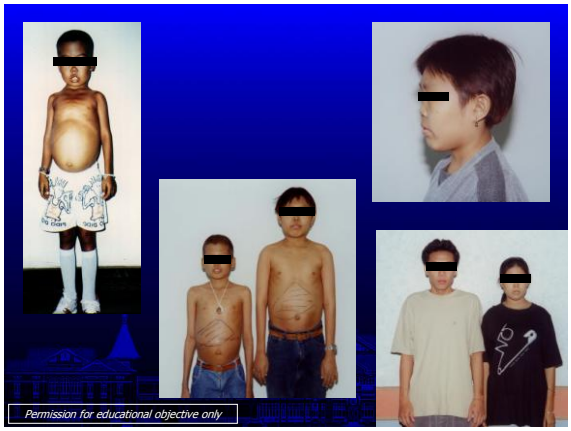


Thalassemia : types severity

- Hb Bart's hydrops fetalis (homozygous α-Thalassemia1 : α-thal1/α-thal1)
- Homozygous ß-Thalassemia (ß-Thalassemia major)
- ß-Thalassemia/HbE
- HbH disease (α-thal1/α-thal2)

Thalassemia : types severity

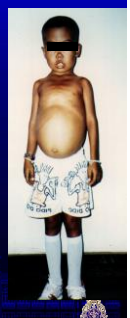
- Severe symptoms
  - Anemia in 1st to 2nd years of age
  - Marked hepatosplenomegaly
  - Hb ≤ 7 g/dl (Hct ≤ 20 %)
  - Homozygous ß-Thalassemia, ß-Thalassemia/HbE
- Moderate symptoms
  - ß-Thalassemia/HbE , HbH disease
- Mild symptoms
  - Mild or no splenomegaly
  - Hb ≥ 9 g/dl (Hct ≥ 27 %)
  - ß-Thalassemia/HbE , HbH disease

Thalassemia Major V.S. Intermedia(I)

	Thal. Major	Thal. Intermedia
Clinical		
•Presentation(yr.)	< 2	>2
•Hb level	< 7	7-8
•Liver/spleen enlargement	severe	moderate to severe
Hematologic		
•Hb F(%)	> 50	10-50
•Hb A2(%)	< 4	> 4

ß-Thalassemia

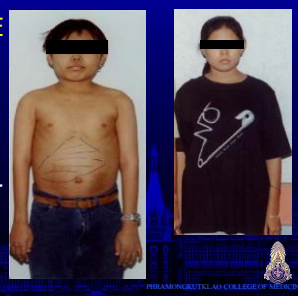
1. Homozygous ß-Thalassemia (ß-Thalassemia major)
- Severe anemia detected before 1st year of age
- Thalassemic facies
- Growth retardation
- Hepatosplenomegaly



ß-Thalassemia

Severe symptoms Mild symptoms

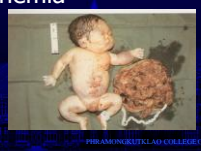
2. ß-Thalassemia/ HbE
- Variety of clinical presentation
- Same clinical symptoms as ß-Thalassemia major



α-Thalassemia

1. Hb Bart's hydrops fetalis (Homozygous α-Thalassemia 1)

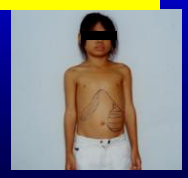
- Not compatible with life
- Intrauterine or neonatal death
- Anarsarca and severe anemia
- Toxemia of pregnancy

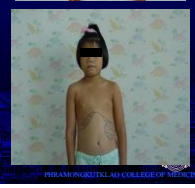


α-Thalassemia

2. Hb H disease

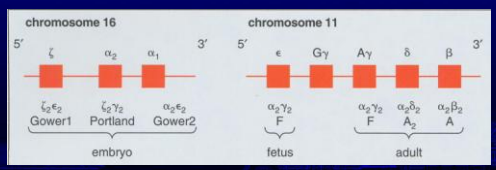
- Variety of symptoms
- Mild anemia
- Mild jaundice
- Intravascular hemolysis while infection or fever



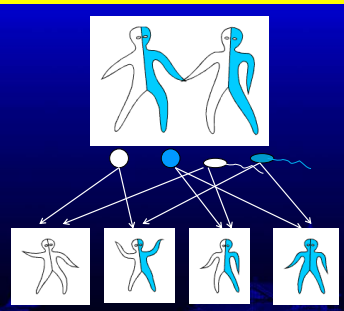


Thalassemia : genetic

- α-thalassemia gene : chromosome 16
- ß-thalassemia gene : chromosome 11



Genetic transmission



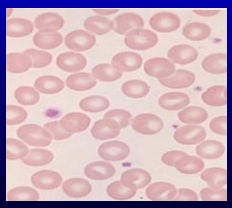
Diagnosis

- CBC
- Peripheral blood smear
- Reticulocyte count : reticulocytosis
- Hb typing

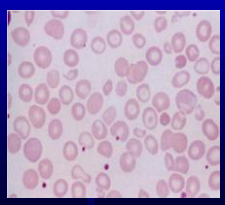
Laboratory diagnosis

- CBC : anemia
- Red cell indicies
  - MCV <80, MCH < 27, RDW > 16%
- Red cell morphology
  - anisocytosis, poikilocytosis, target cell
- Reticulocytosis
- Inclusion bodies
  - Hb H disease
- Hb analysis (electrophoresis)

Peripheral blood smear



Normal



Thalassemic patient

Thalassemia disease: Genotype (disease) and Phenotype

Alpha-thalassemia

Disease	Genotype
• Hb Bart's hydrops fetalis	□ α-thal 1/α -thal 1
• Hb H disease	□ α-thal 1/α -thal 2
• Hb H disease with Hb CS	□ α-thal 1 / Hb CS
• Hb AE Bart's disease	□ α-thal 1 / α -thal 2 / Hb E

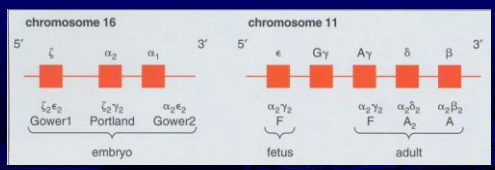
Beta-thalassemia

Disease	Genotype
■ Homozygous β-thalassemia	■ β-thal/β-thal
■ β-thalassemia/Hb E	■ β-thal/Hb E

Basic knowledge for Hb type interpretation

Thalassemia : genetic

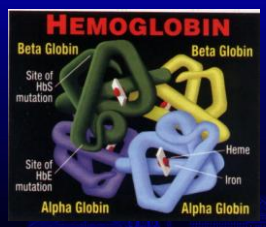
- α-thalassemia gene : chromosome 16
- ß-thalassemia gene : chromosome 11



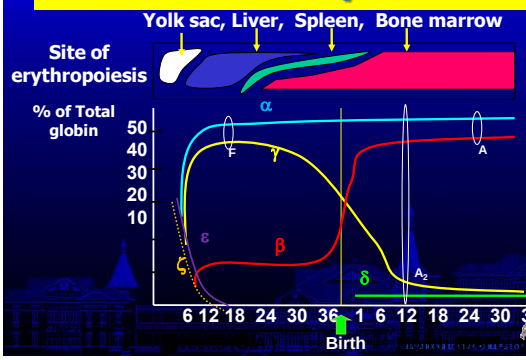
Structure of hemoglobin

(Hemoglobin (Hb) = Heme + Globin)

- Heme
  - **Porphyrin**
  - **Iron**
- Globin
  - **Alpha globin**
  - **Beta globin**
- Normal adult Hb
  - **Hb A ($\alpha_2\beta_2$) = 97.5%**
  - **Hb A_2 ($\alpha_2\delta_2$) = 2.5%**



Globin chain synthesis



Hemoglobin and globin structure

Normal adult

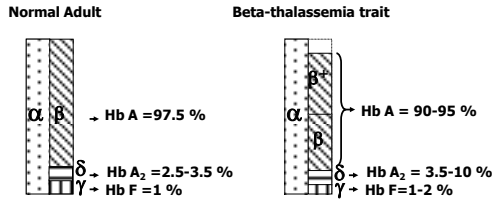
- Hb A $\alpha_2\beta_2$
- Hb A_2 $\alpha_2\delta_2$
- Hb F $\alpha_2\gamma_2$

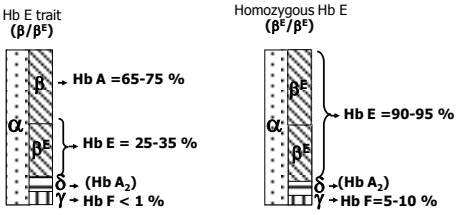
Embryo

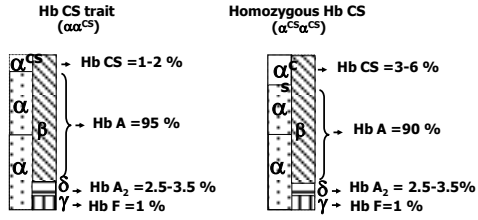
- Hb Gower1 $\zeta_2\varepsilon_2$
- Hb Gower2 $\alpha_2\varepsilon_2$
- Hb Portland $\zeta_2\gamma_2$

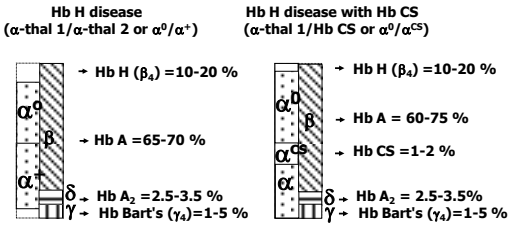
Disease/abnormal Hb

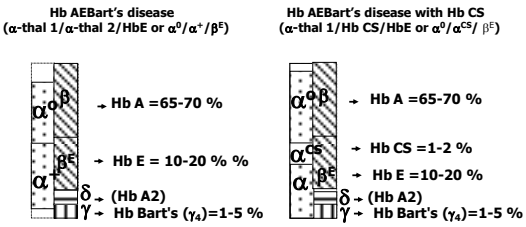
- Hb Bart's γ_4
- Hb H β_4
- Hb E $\alpha_2\beta^E_2$

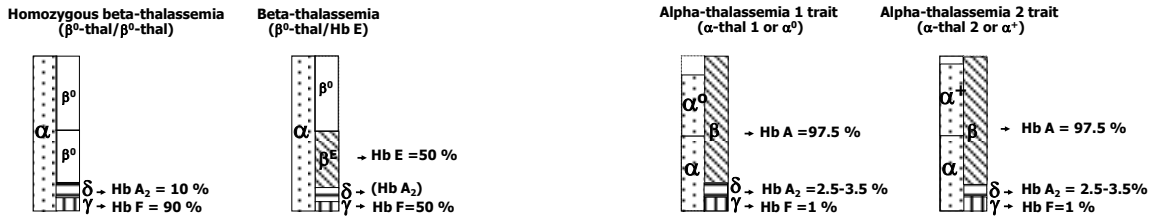












Hb type: Criteria for diagnosis

Conditions	Hb type
• Normal	A_2 A (A_2 2.5-3.5%)
□ α-thal 1 trait	A_2 A (A_2 2.5-3.5%)*
□ α-thal 2 trait	A_2 A (A_2 2.5-3.5%)*
□ β-thal trait	A_2 A (A_2 > 4%)
• Hb E trait	EA (E= 25- 35 %)
• Hb E homozygous	EE (E >85%)
• Hb CS trait	CS A_2 A (CS 1-2 %)
• Hb CS homozygous	CS A_2 A (CS 3-6%)

Can not diagnose by Hb type

**Diagnose by PCR for α-thal 1 trait and α-thal 2 trait respectively*

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Hb type: Criteria for diagnosis

Diseases	Hb type
■ Hb Barts' hydrops	Portland, Barts'
■ Hb H disease	A_2 A H Barts'
■ Hb H with Hb CS	CS A_2 A H Barts'
■ Hb AEBarts' disease	A E Barts'
■ Homozygous β-thal	A_2 F
■ β-thal / Hb E	EF

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Treatment and prevention

1. Treatment
   - Improved quality of life
   - Prevent complications
   - Curative treatment
2. Prevention
   - Prenatal diagnosis
   - Genetic counseling

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General treatment

- Folic acid
- Vaccination
- Exercise
- Dental hygiene

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Blood transfusion

- Low transfusion
  - When symptomatic : Hb ‹ 7 g/dl (Hct ‹ 20 %)
- High transfusion
  - Suppression of erythropoiesis
  - Improved quality of life and increased life expectancy
  - Every 2-4 weeks : LPRC 12-15 ml/kg
  - Keep Hb > 10 gm/dl

Blood transfusion

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Prevent complication

- Iron chelation

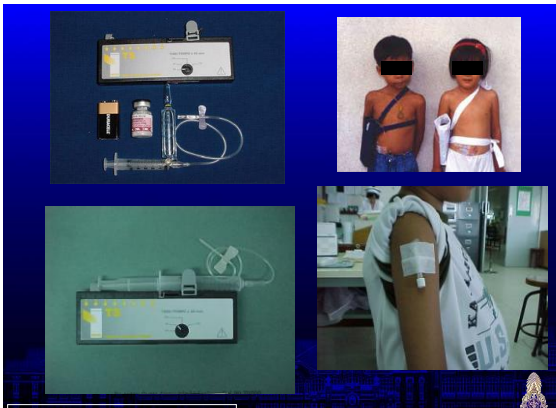
Indication

- Blood transfusion > 15-20 units
- Regular transfusion > 1 year
- Serum ferritin > 1,000 ng/ml

Iron chelation

Desferioxamine (Desferal®)

- Subcutaneous infusion :
  - ❑ 20 - 40 mg/kg/day SC infusion in 8-12 hrs x 5 –7 days/week
- Continuous intravenous infusion :
  - ❑ Indication :cardiac problems from iron overload
  - ❑ 50 - 70 mg/kg/day IV infusion in 12-24 hrs x 5-6 days/week



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Iron chelation

Oral iron chelation :
Deferiprone (L1, Kelfer®)

Second line monotherapy
75 mg/kg/day, t.i.d

Iron chelation

Oral iron chelation :
Deferasirox : ICL670
(Exjade®)

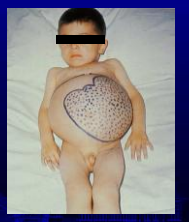
Second line monotherapy
10-30 mg/kg/day, O.D.

	Desferoxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
Chelating properties	Hexadentate	Bidentate	Tridentate
Drug : Iron binding ratio	1:1	3:1	2:1
Dose (MKD)	30-60	75-100	20-40
Delivery	SC or IV 8-12 hrs 5-7 days/week	Oral 3 times daily	Oral O.D.
Half life	8-10 min	1.5-4 hrs	12-18 hrs
Excretion	40-60% fecal	90% urinary	90% fecal
AE	Ocular, auditory, toxicity, growth retardation, local reaction,allergy	GI upset Arthralgia, neutropenia, agranulocytosis	GI upset ,rash, ocular auditory toxicity, reversible increased in creatinine

Splenectomy

Indications

- Splenomegaly > 6 cm below LCM with pressure symptoms
- Hypertransfusion
  > 250 ml/kg/year
- Hypersplenism
- Age ≥ 5 years of age

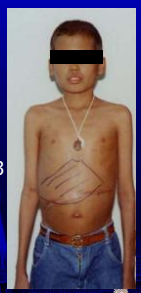


Preparation for splenectomy

- Pneumococcal, HIB vaccines 4-6 weeks before splenectomy
- Parental counseling

Post-operative splenectomy

- Penicillin V 250 mg b.i.d.
- Aspirin 2-4 mg/kg/day if platelets > 80,000 cell/cumm^3



Stem cell transplantation

- Bone marrow, cord blood or peripheral blood stem cell
- 1st choice : Allogenic matched sibling donor
- Curative treatment :
  success rate 75-80 %

Pesaro Risk Classification

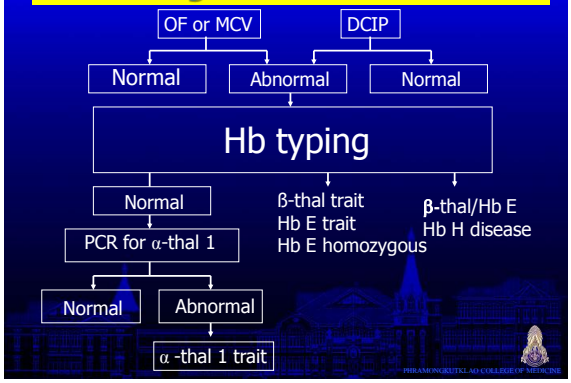
- Chelation
- Hepatosplenomegaly
- Liver fibrosis

Low risk	: No risk factor
Intermediate risk	: 1-2 risk factors
High risk	: 3 risk factors

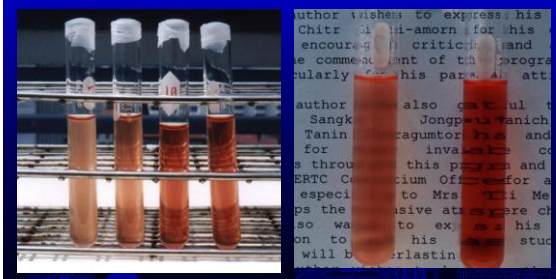
NEJM 1998;322:417-21, 1993;329:840-4

Stem cell transplantation in thalassemia 1988-1999 (49 cases)

Screening for thalassemia trait



Osmotic fragility test

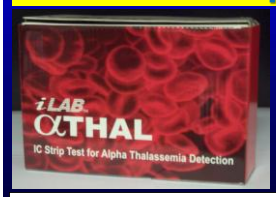


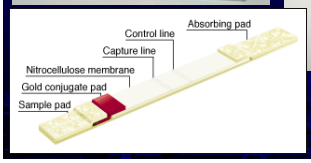
KKU-DCIP

Lab system

LAB	OF, CBC, DCIP	Electro phoresis	HPLC	PND	QC
Community hospital	✓				
City hospital	✓	✓			
Province hospital	✓	✓	✓		
Department of Health	✓	✓	✓	✓	
Department of medical science	✓	✓	✓	✓	

Immunochromatographic strip test





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