BURDEN IN THALASSEMIA:
CLINICAL MANAGEMENT

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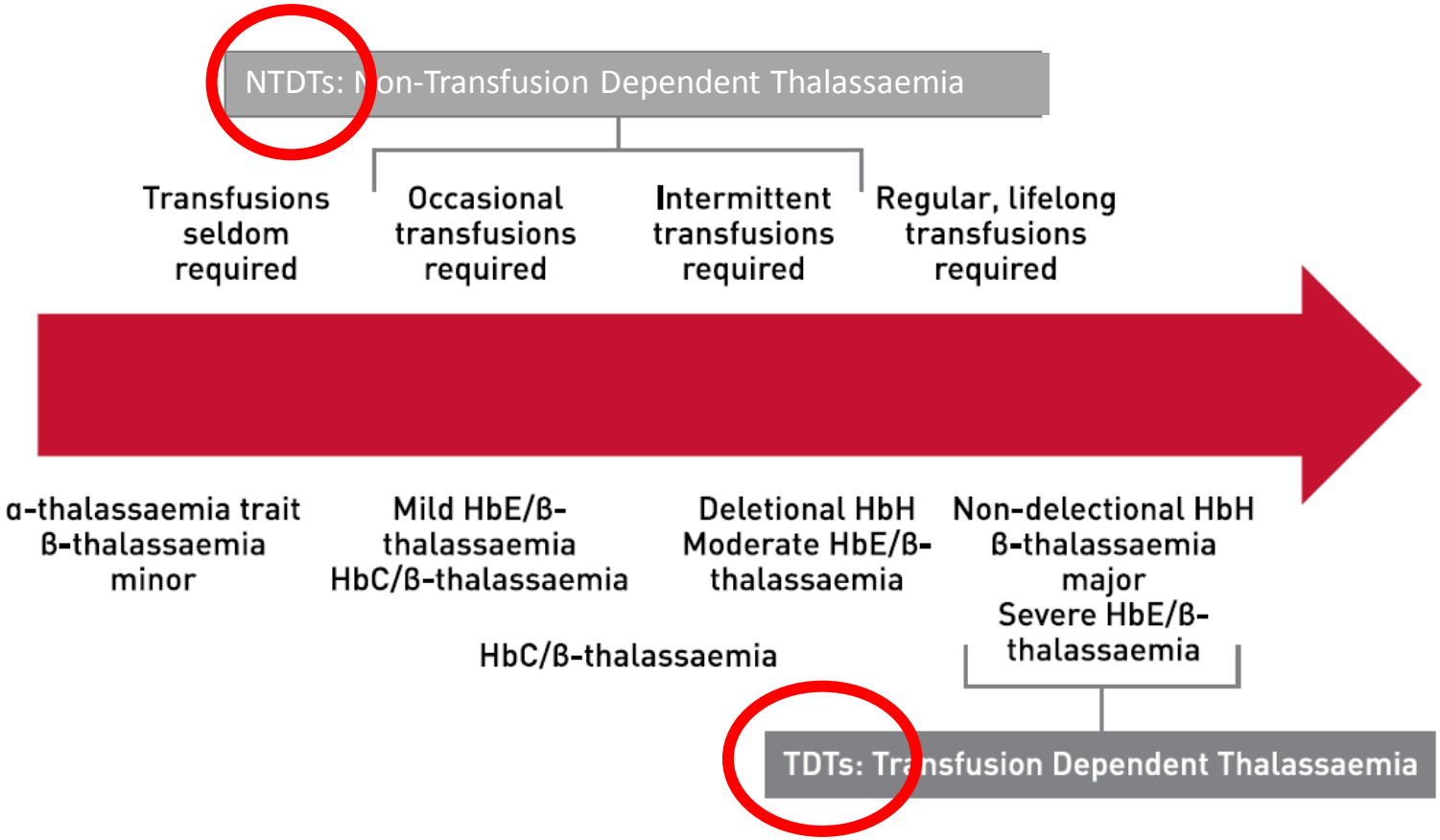
ประชุมสัมมนาวิชาการธาลัสซีเมียแห่งชาติ Action Plan for Thalassemia 2014

Thalassemia

- Hereditary anemia
- Mutation of alpha or beta-globin genes causing production defect
- Ineffective erythropoiesis
- Anemia, jaundice, hepatosplenomegaly, bony changes

Spectrum of Thalassaemia Syndromes



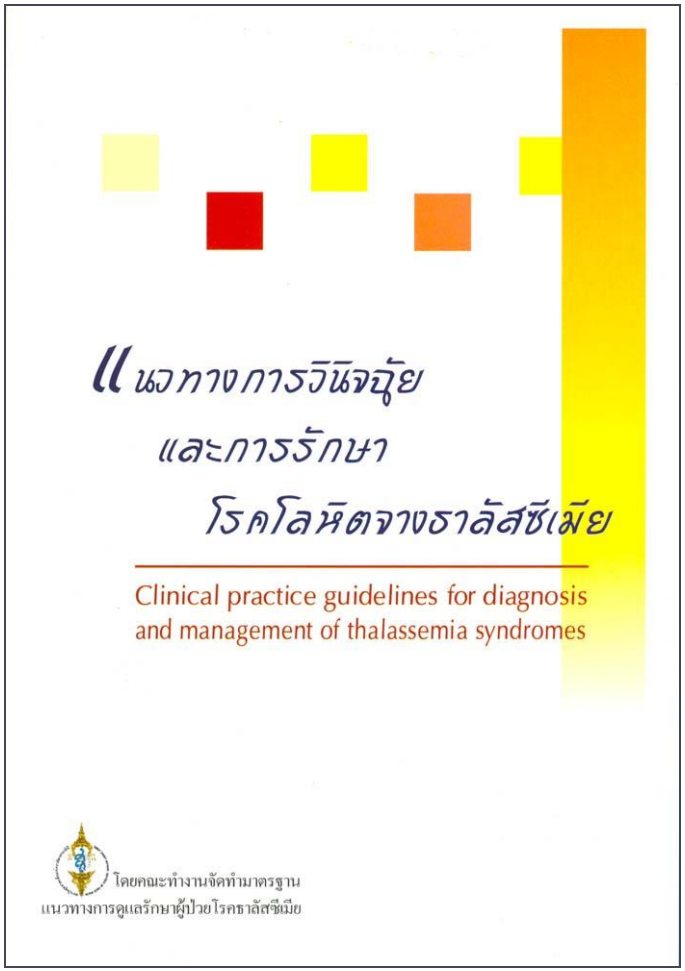
Thalassaemia International Federation.
Guidelines for clinical management of transfusion-dependent thalassaemia. 2014

Burden in thalassemia

- Clinical management
  - Red blood cell transfusion
  - Iron chelation
  - Splenectomy
  - Surveillance of complications:
    - DM, osteoporosis, growth failure, delayed puberty, pulmonary hypertension, EMH
  - Stem cell transplantation
  - Psychosocial aspects

CPG thalassemia

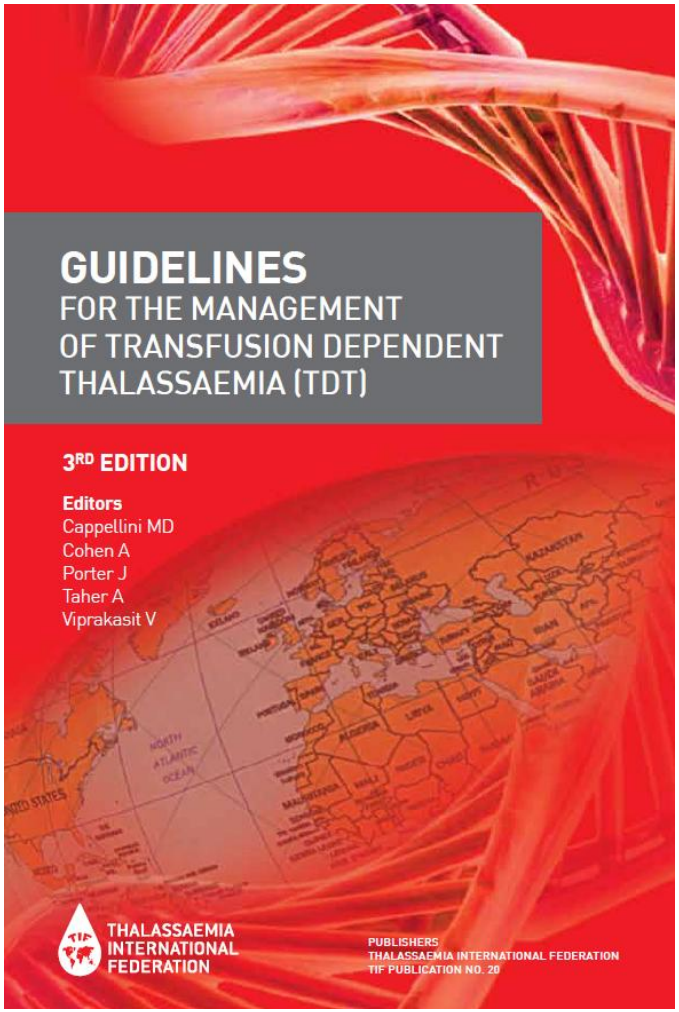
กรมการแพทย์ กระทรวงสาธารณสุข 2549



Guidelines

Thalassemia International Federation

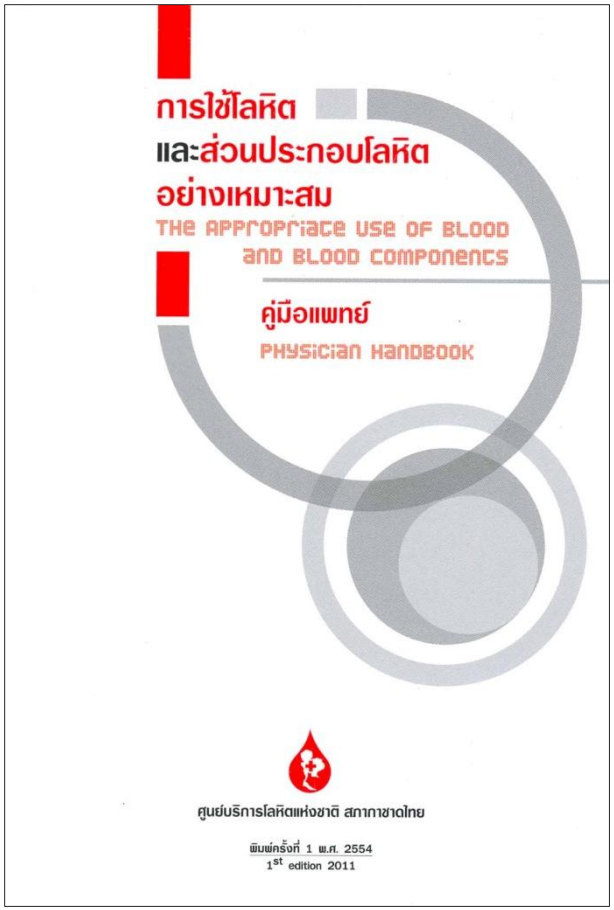
2014



คู่มือแพทย์

การใช้โลหิตและส่วนประกอบโลหิตอย่างเหมาะสม

ศูนย์บริการโลหิตแห่งชาติ สภากาชาดไทย 2554



Red blood cell transfusion

Goal of RBC transfusion

- To alleviate anemia
- To promote normal growth
- To prevent bony changes, enlarged liver and spleen

- To suppress ineffective erythropoiesis

High transfusion

- Confirmed laboratory diagnosis of thalassemia major
- Laboratory criteria:
  - Hb < 7 g/dL on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections) OR
- Clinical criteria irrespective of Hb level:
  - Hb > 7g/dL with any of the following:
    - Facial changes
    - Poor growth
    - Fractures
    - Clinically significant extramedullary hematopoiesis

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Occasional transfusion

- RBC 10-15 mL/kg
- For mild clinical severity
  - Hb H disease
  - Some beta-thalassemia/Hb E disease
- Anemic symptoms/Hb <7g/dL or Hct <20%
- Acute hemolysis

Transfusion program

- For thalassemia major
  - Lifelong regular transfusion
  - Usually administered every two to five weeks
  - To maintain the pre-transfusion Hb level > 9-10.5 g/dL
  - Promote normal growth, adequately suppresses bone marrow activity
  - Higher pre-transfusional Hb level (11-12 g/dL) may be appropriate for patients with heart complications, significant extramedullary hematopoiesis
  - Keep post-transfusion Hb not higher than 14-15 g/dL

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Transfusion program

- Before each transfusion, full cross-match and screen for new antibodies
- Use PRC stored in CPD-A, as fresh as possible (less than 7 days old)
- Before first transfusion, extended RBC antigen typing of patients at least for C, c, E, e, and Kell
- (Thai guideline: E, c, Mi^a, Le^a, Le^b)
- Use leukocyte-depleted RBC, pre-storage filtration is strongly recommended.

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Red blood cell transfusion

- Red blood cells (RBC), Packed red cell (PRC)
- Leukocyte-poor red blood cells (LRBC)
  - Prevent febrile non-hemolytic transfusion reaction
- Leukocyte-depleted red blood cells (LDRBC)
  - Prevent febrile non-hemolytic transfusion reaction
  - Prevent HLA antibody formation
  - Decreased CMV transmission
- Two-unit red cells, single donor red cells (SDR)
  - Decreased donor exposure, risk of RBC antibody, risk of viral transmission
  - Prevent FNHTR, HLA antibody (leukocyte-depleted)

Iron overload and iron chelation

Iron overload in thalassemia

- Red cell transfusion
  - A 420 mL donor blood contains approximately 200 mg of iron (0.47 mg/mL of whole blood)
  - Pure red cells 100-200 mL/kg/year gives 0.32-0.64 mg/kg/day of iron
- Increased GI absorption
  - Healthy individuals 1-1.5 mg/day
  - Thalassemia intermedia: up to 5-10 times increase
  - Thalassemia major, hypertransfusion: 1-4 mg/day
  - Thalassemia major, poorly transfused: 3-4 mg/day or more
  - Equals to 1-2 g/year or up to 3 months of chelation

Porter JB. Br J Haematol 2001;115:239–52.

Indications for treatment

- Optimal chelation
  - Prevents heart failure, DM, hypogonadotropic hypogonadism, poor growth, hypothyroidism, hypoparathyroidism
- Indications
  - To start when ferritin value reaches 1000 mcg/L or 10-20 transfusions have been given
  - LIC > 7 mg/g liver
  - In thalassemia intermedia: LIC measurement is advisable

Porter JB. Br J Haematol 2001;115:239–52.

	Deferoxamine	Deferiprone	Deferasirox
Molecular weight (Da)	657	139	373
Chelating properties	Hexadentate	Bidentate	Tridentate
Recommended dose (mg/kg/day)	25-60 SC or IV in 8-12 hours, 5 d/wk	75 orally, three times daily	20-30 orally once daily
Half-life	20-30 min	3-4 hr	8-16 hr
Excretion	Urinary and fecal route	Urinary route	Fecal route
Main adverse effects	Local reactions, ophthalmology, auditory, growth retardation, allergic reactions	GI disturbances, agranulocytosis, neutropenia, arthralgia, elevated liver enzymes	GI disturbances, rash, mild nonprogressive Cr increase, elevated liver enzymes, ophthalmological and auditory

Hershko C. Haematologica 2006;91:1307-12.

Splenectomy

Splenectomy

- Increased blood requirement that prevents adequate control with iron chelation therapy
  - Requirement of more than 200-220 mL of PRC/kg/year
  - Alloimmunization, concurrent infections, suboptimal therapy should be ruled out
- Hypersplenism: cytopenias
- Symptomatic splenomegaly: early satiety, concern about possible splenic rupture

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Immunizations

- Should be administered at least 2 weeks before splenectomy and then in 3-5 years
  - Pneumococcal vaccine
  - Hemophilus influenza B vaccine
  - Meningococcal vaccine
- Annual influenza vaccine
- *Oral penicillin prophylaxis post splenectomy

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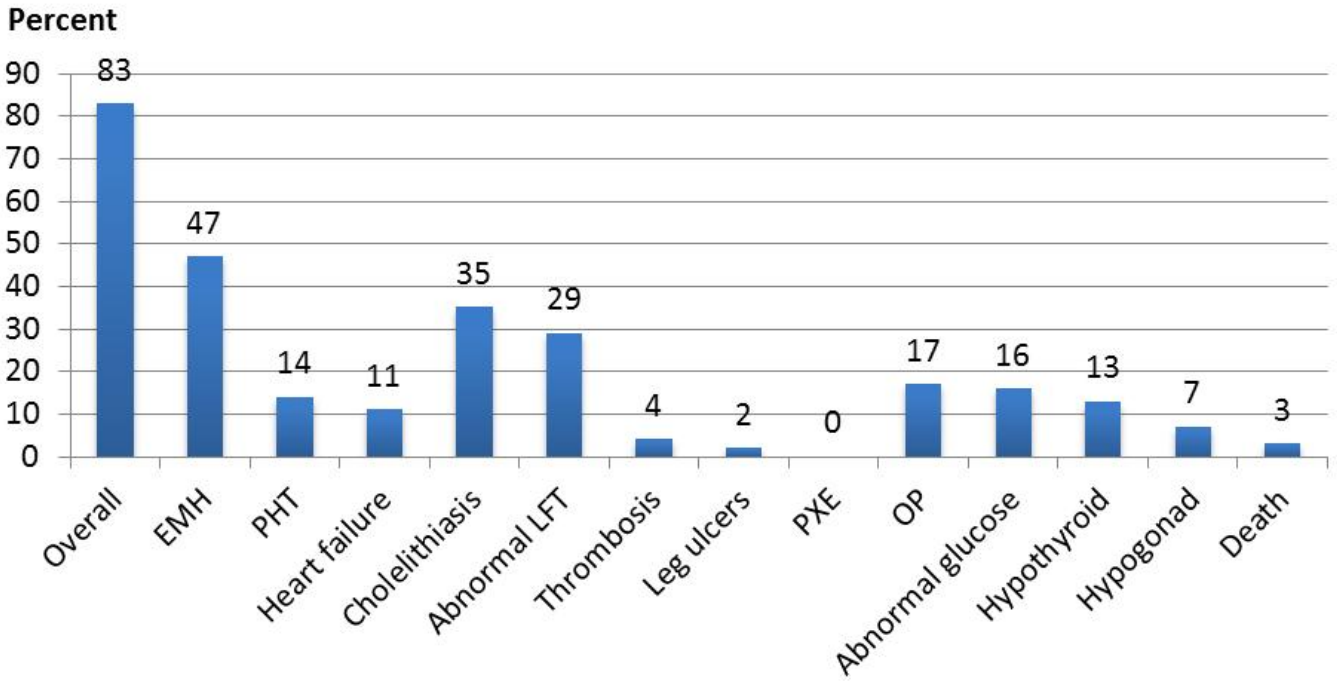
Complications

Complications of thalassemia

- Disease-related
  - Anemia
  - Hypercoagulability
  - Pulmonary artery hypertension
  - Stroke
  - Extramedullary hematopoiesis
- Treatment-related
  - Infection
  - RBC alloimmunization
  - Iron overload
  - Endocrinologic complications

Prevalence of complications in NTDT



- One hundred NTDT patients, median age 38 years (19-78). 54% Alpha thalassemia. Mean ferritin level: 1,563.46 ng/ml. 76% with ferritin >800 ng/ ml, 44% with ferritin >2,500 ng/mL.

Tantiworawit A, et al. Abstract no. 1360
Presented at 56th ASH Meeting and Exposition, December 6-9, 2014

Stem cell transplantation

Stem cell transplantation

Report	No.	Subjects	Source	Outcome
Suvatte, et al 1998	35	Thalassemia	BM, peripheral blood, cord blood	23/35 (79.4%) cured, 3 (10.3%) alive with disease, 3 (10.3%) died

Suvatte V, et al. Int J Hematol 1998;68:411-9.

Stem cell transplantation

Report	No.	Subjects	Source	Outcome
Hongeng, et al 2004	11	Severe thalassemia	T-cell nondepleted bone marrow, unrelated matched donor	All alive without disease at a median follow-up time of 397 day. 6/11 had grade 2-4 acute GVHD, 1 had grade 3-4. 3/11 had chronic GVHD (limited stage).
Pakakasama, et al 2004	9	BTM and BE	Peripheral blood stem cell, 6/6 or 5/6 HLA-matched sibling donors	All alive without disease at a median follow-up time of 23 months. 4/9 had grade 2-4 acute GVHD), 3 had chronic GVHD (2 limited, 1 extensive stage).

Hongeng S, et al. Bone Marrow Transplant 2004;33:377-9.
Pakakasama S, et al. J Pediatr Hematol Oncol 2004;26:248-52.

Stem cell transplantation

Report	No.	Subjects	Source	Outcome
Hongeng, et al 2006	49	Severe thalassemia	Related matched donor or unrelated matched donor	The 2-year thalassemia-free survival for recipients of related-donor stem cells was 82% compared with 71% in the unrelated-donor stem cell group.
Hongeng, et al 2007	8	Class 3 Lucarelli patients	7/8 received T cell non-depleted PBSCs from matched siblings, 1received purified CD34(+) cells from two HLA Ag mismatched maternal PBSCs.	6/8 had stable full donor engraftment. There were no deaths or Grade 3-4 acute GvHD.

Hongeng S, et al. Biol Blood Marrow Transplant 2006;12:683-7.
Hongeng S, et al. Am J Hematol 2007;82:1095-8.

Stem cell transplantation

Report	No.	Subjects	Source	Outcome
Anurathapan U, et al 2013	18	Thalassemia age ≥7 years and hepatomegaly	7/8 received T cell non-depleted PBSCs from matched siblings, 1received purified CD34(+) cells from two HLA Ag mismatched maternal PBSCs.	The 5-year overall survival and thalassemia-free survival were 89%. Two patients (11%) had acute grade III-IV graft-versus-host disease, and 5 patients had limited chronic graft-versus-host disease.

Anurathapan U, et al. Biol Blood Marrow Transplant 2013;19:1259-62.

Psychosocial aspect

Psychosocial problems

- Semi-structured interview and the Pediatric Symptom Checklist (PSC) to evaluate psychosocial problems in 82 thalassemia patients, 20 siblings, and 50 controls
- Psychosocial problems
  - Children with thalassemia 28.05% vs 4% in controls (p=0.001)
  - Siblings 5% vs 4% in controls (p=0.64)

Louthrenoo O, et al. J Med Assoc Thai 2002;85:881-5.

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Thank you for your attention