Indian Academy of Pediatrics (IAP)

STANDARD TREATMENT GUIDELINES 2022

Thalassemia

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Thalassemia

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Introduction

Thalassemia is an autosomal recessive disease. It is of two main types, i.e., alpha and beta.

Alpha-thalassemia	***Beta-thalassemia***
Mutation in the *HBA1* and *HBA2* genes, four such, two from each parent, severity of signs and symptoms directly proportional to the number of genes mutated.	Mutation in the *HBB* gene, two genes, one from each parent, involved in the synthesis of beta-globin.
With one mutated gene, one has no signs or symptoms but is a carrier of the disease and can pass it on to the children.	Children with one mutated gene will have mild signs and symptoms. Condition also called thalassemia minor or beta-thalassemia.
People with two mutated genes will have mild signs and symptoms, also called alpha-thalassemia trait.	Children with two mutated genes will have moderate-to-severe signs and symptoms. This condition is called thalassemia major. These babies are usually healthy at birth and develop signs and symptoms within the first 2 years of life.
People with three mutated genes have moderate-to-severe signs and symptoms from birth.	Some children with two mutated genes will manifest a milder form, called thalassemia intermedia.
Four mutated genes usually result in stillbirth or death shortly after birth or lifelong transfusion therapy.	

Symptoms and Signs

- ☑ Fatigue/weakness/shortness of breath
- ☑ Pale or yellowish skin/anemia
- ☑ Facial bone deformity
- ☑ Slow growth/failure to thrive
- ☑ Abdominal swelling
- ☑ Hepatosplenomegaly.

Complications

- ☑ Jaundice and pigment gallstones
- ☑ Hypersplenism
- ☑ Complications of extramedullary hematopoiesis
- ☑ Skeletal changes
- ☑ Iron overload
- ☑ Growth impairment
- ☑ Complications of iron overload
- ☑ Endocrine and metabolic abnormalities
- ☑ Heart failure and arrhythmias
- ☑ Pulmonary abnormalities and PH.

Laboratory Findings

Syndrome	*Typical findings on complete blood count (CBC)*	*Hemoglobin (Hb) analysis [high-performance liquid chromatography (HPLC) or electrophoresis]*
Hydrops fetalis with Hb Barts	Severe microcytic anemia with hydrops fetalis; usually fatal in utero	Hb Barts (γ globin tetramers); Hb Portland (embryonic hemoglobin); no Hb F, Hb A, or Hb A_2
Hb H disease	Moderate microcytic anemia	Hb H (up to 30%); Hb A_2 (up to 4%)
Minor	Mild microcytic anemia	Hb Barts (3–8%, only in the newborn period)
Silent carrier	Normal or mildly decreased hemoglobin, normal or mildly decreased mean corpuscular volume (MCV)	Normal
Transfusion-dependent (TDT, beta-thalassemia major)	Severe microcytic anemia with target cells (typical Hb 3–4 g/dL)	Hb A_2 (5% or more); Hb F (up to 95%); no Hb A
Non-transfusion-dependent (NTDT, beta-thalassemia intermedia)	Moderate microcytic anemia	Hb A_2 (4% or more); Hb F (up to 50%)
Minor (also called trait or carrier)	Mild microcytic anemia	Hb A_2 (4% or more); Hb F (up to 5%)

Diagnosis of thalassemia is best done by globin gene studies, especially for those who have been transfused.

Management

Optimal Transfusion

15–20 mL/kg of optimally screened (ideally NAT tested), leukodepleted packed red cells, to maintain a pretransfusion hemoglobin of 9.5–10.5 g/dL. Extended phenotype-matched packed red cells should be given to limit the chances of alloimmunization.

Target pretransfusion hemoglobin	9.5–10.5 g/dL
Blood product	Packed red cells with Hct > 60% not older than 2 weeks
Crossmatch	For ABO and Rh, (C, c, D, E, e, Kell where feasible)
Frequency	2–4 weeks
Volume	15–20 mL/kg
Rate	5 mL/kg/hour
Processing	Leukodepletion (prestorage/bedside)
Screening	Hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), human immunodeficiency virus (HIV), malaria [ideally nucleic acid testing (NAT)-tested)
Furosemide/chlorpheniramine/ hydrocortisone	Not indicated routinely

Chelation

Iron chelation must commence once serum ferritin exceeds 1,000 µg/L, which is usually reached after 10–20 transfusions.

When to start	Serum ferritin >1,000 µg/L (usually after 10–20 transfusions)
Target ferritin	<1,000 µg/L
Monitoring	Serum ferritin 3–6 monthly, T2* MRI annually above 8–10 years of age. Liver function test (LFT) and serum creatinine to be monitored monthly for 3 months than 3 monthly
When to stop	Not recommended. Can continue at very low doses if ferritin < 500 µg/L

Currently, the chelator of choice is deferasirox which is available in dispersible tablet (to be dissolved in water/orange juice or apple juice) or in film-coated table which has better bioavailability hence dose is lower.

Chelator	***Deferasirox***	***Deferoxamine***	***Deferiprone***
Route	Oral (dispersible tablet/ film-coated tablet)	Subcutaneous/IV if intensive chelation warranted	Oral
Dose	DT: 20–40 mg/kg/d FCT: 14–28 mg/kg/d	30–40 mg/kg/d, 5–7 days/ week	75–100 mg/kg/d
Frequency	Once daily	12-hour infusions	Three divided doses
Side effects	Gastrointestinal (GI) disturbances, transaminitis, azotemia, microalbuminuria	Local reactions, ototoxicity, and retinopathy	Agranulocytosis and arthralgias
Monitoring	LFT/serum creatinine, urine monthly to begin with then 3 monthly	Annual ophthalmic and auditory review	CBC every 2 weeks

If despite optimal doses and good compliance, if the iron overload is not adequately controlled, two chelators can be combined but need close monitoring. Most robust data is available for deferasirox and deferoxamine, but the two oral chelators can also be combined.

Supportive Treatment

Growth and development	*To be routinely monitored*
Folic acid	Supplement in small doses
Vitamin C	Only in patients on deferoxamine infusion not exceeding 2 mg/kg/d
Other vitamins	Ensure optimal levels of vitamin D3
Dietary restrictions	None in optimally managed patients
Dietary supplements	Not routinely recommended
Immunization	As per schedule including hepatitis B. Hepatitis A vaccine also recommended in view of increased severity in patients with iron overload in liver. Ensure adequate titers of anti-HBs or give booster doses every 5 years
Monitoring	Annual monitoring for endocrinopathy and bone health after 10 years of age

Bone Marrow Transplant

This is the only curative treatment available currently.

Optimal age	*2–10 years*
Optimal patient status	Optimally chelated, no organomegaly, and no organ dysfunction
Ideal donor	Fully human leukocyte antigen (HLA)-matched sibling donor
Optional donors	Matched unrelated donor and haploidentical donor from family
Source of stem cells	Bone marrow (BM) preferred to peripheral blood stem cells

Newer Modalities

Modality	*Mechanism of action*	*Route of administration*	*Current status*
Luspatercept	Anti-apoptotic, prolongs red cell lifespan	Subcutaneous injection 3-weekly	Approved for patients > 12 years Not available in India
Thalidomide	HbF induction, immunomodulation	Oral	Currently being evaluated in this setting
Ruxolitinib	JAK-2 inhibition	Oral	May help in reduction of splenomegaly
Gene therapy		-	Not available in India

Management

Management of Non-transfusion-dependent Thalassemia

Patients who do not require regular transfusion and receive their first transfusion beyond 2 years of age are labeled as having NTDT. This condition represents a large spectrum and treatment should be individualized. They should receive hydroxyurea, which improves the Hb along with other benefits in a significant proportion with NTDT. The need for a regular transfusion program depends on growth, organomegaly, dysmorphism, and most importantly the quality of life.

Parameters	***Patients***
Monitoring of growth, Hb, organomegaly, iron overload, and dysmorphism	Indicated in all patients
Folic acid	Recommended for all patients
Hydroxyurea	Therapeutic trial in all patients at 10–20 mg/kg/d
Intermittent transfusion	Indicated in acute drop in Hb secondary to infection
Regular transfusion	To be decided by the hematologist taking into account—Hb, growth, organomegaly, facial disfigurement, and quality of life

Further Reading

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