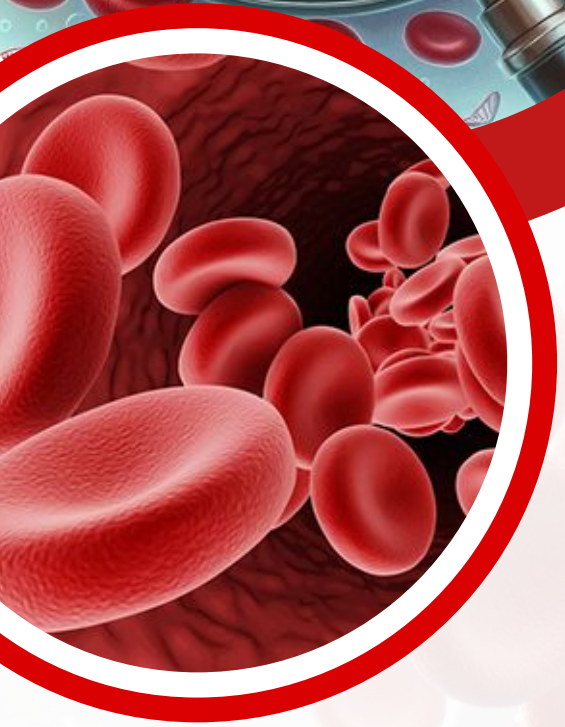
Beta Thalassemia



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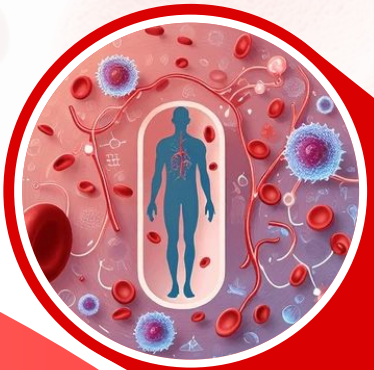
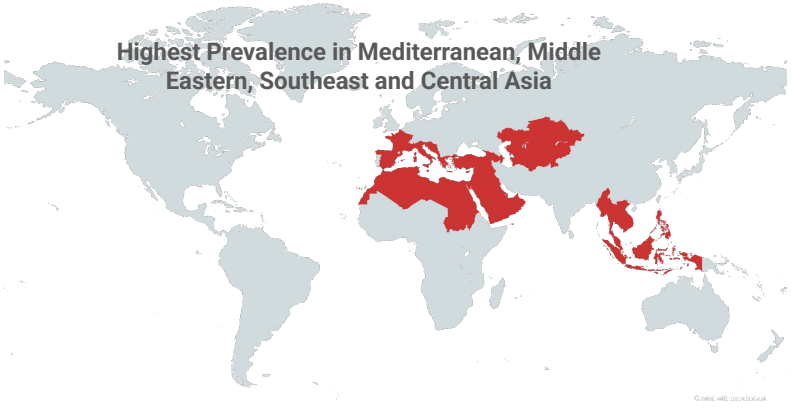


Beta thalassemia

Beta thalassemia is an autosomal recessive blood disorder caused by mutations in the HBB gene on chromosome 11, which results in the reduced or absent production of beta-globin chains. This quantitative deficiency creates an imbalance in alpha-globin chains, leading to the formation of unstable hemoglobin aggregates that damage and destroy red blood cells. The resulting ineffective erythropoiesis and chronic hemolytic anemia vary in clinical severity based on whether the individual inherits one (minor) or two (intermedia/major) mutated alleles.

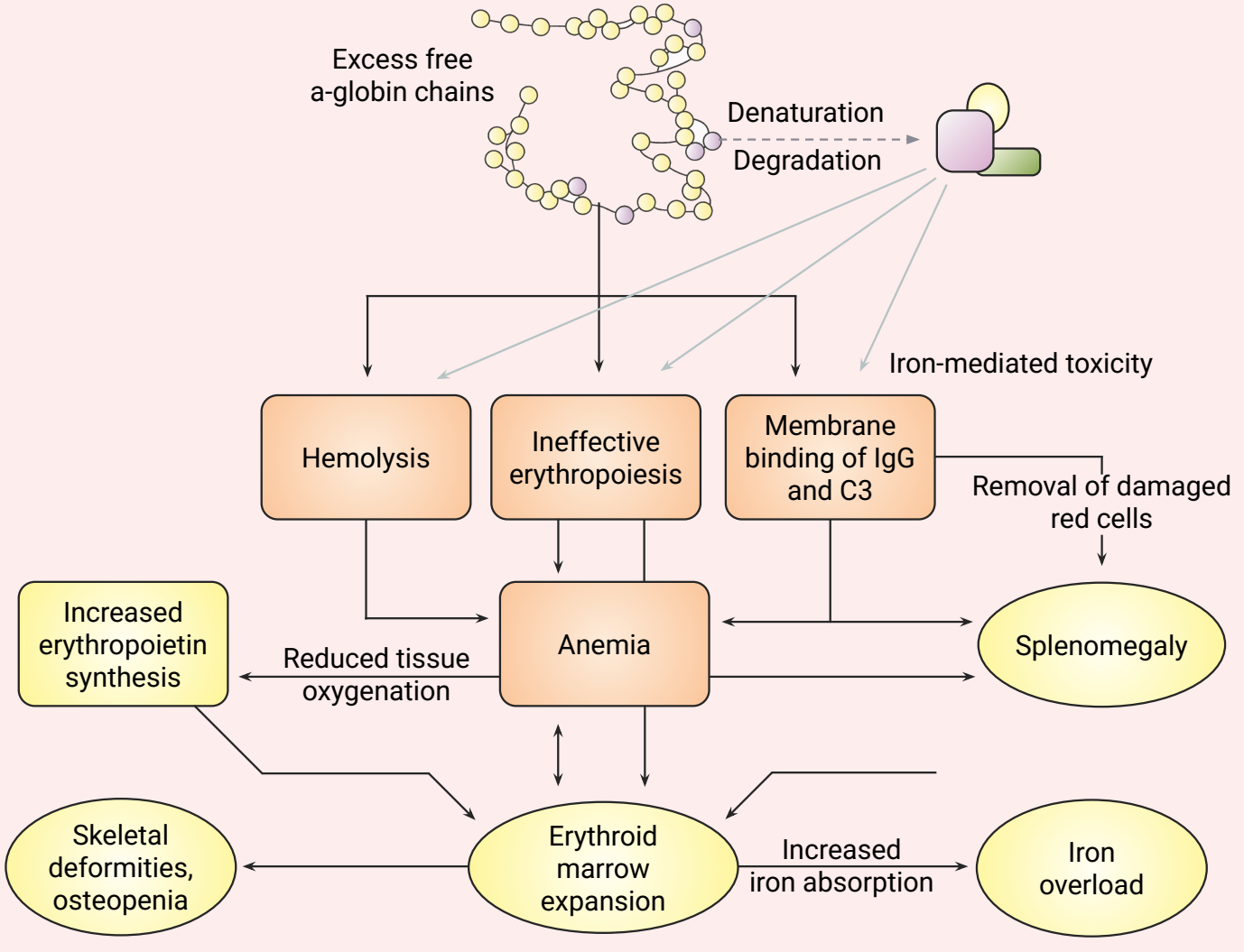
Epidemiology and prevalence of beta thalassemia



According to NCBI (2023)

- The worldwide prevalence of beta-thalassemia is ~ 80 to 90 million carriers, which represents about 1.5% of the global population.
- Approximately 68,000 children are born with beta-thalassemia globally each year
- The reported carrier prevalence in Greek and Turkish populations in Cyprus can be as high as 15%.

Pathophysiology of beta thalassemia



Classification of beta thalassemia

	Beta thalassemia minor (carrier/trait)	Beta thalassemia intermedia	Beta thalassemia major
Genotype	Heterozygous (one affected, one unaffected beta-globin gene)	Homozygous or compound heterozygous	Homozygous or compound heterozygous
Clinical severity	Usually asymptomatic with mild anemia (microcytosis)	Variable anemia, often presenting later in childhood or adulthood	Severe chronic anemia, typically presenting between 6 and 24 months of age
Transfusion dependence	Not transfusion dependent	Not regularly transfusion dependent	Requires routine blood transfusions
Hemoglobin analysis	Characteristically has increased HbA2 (4-8%) with variably normal-to-low elevations of HbF	The distinction between beta-thalassemia major and intermedia is a clinical one and does not have diagnostic laboratory findings	Typically shows markedly elevated HbF (30%-to-greater than 95%) with normal to mildly elevated HbA2

Risk factors

Genetic Inheritance	Beta thalassemia is an autosomal recessive inherited blood disorder caused by pathogenic variants in the HBB gene.
Parental Carrier Status	The risk is highest when both parents are carriers; each child has a 25% chance of inheriting the severe form.
Ancestry/ Geography	The condition is most prevalent among populations from the Mediterranean, the Middle East, South Asia, and of African descent

Symptoms

	Childhood (Onset 6–24 months)	Adulthood
Beta thalassemia major (TDT-Transfusion dependent)	Fatigue, Irritability, Stunted growth, Enlarged liver, Mild jaundice, Bone abnormalities	Arrhythmias, Liver fibrosis, Dilated cardiomyopathy, Heart failure, Diabetes mellitus, Osteoporosis
Beta thalassemia intermedia	Splenomegaly, Osteoporosis, Anemia, Slowed growth	Gallstones, Thrombosis, Iron Overload, Pulmonary hypertension

Diagnostic tests

Clinical Diagnosis

The Test: A physical medical examination assessing developmental milestones and physical markers like jaundice or organ enlargement.

The Diagnosis: Extreme pallor and enlarged liver/spleen (hepatosplenomegaly) or characteristic facial bone changes.

Hematological Diagnosis

The Test: A Complete Blood Count (CBC) and a Peripheral Blood Film (microscopic smear) to analyze red blood cell (RBC) physical properties.

The Diagnosis: Thalassemia is indicated by microcytic hypochromic anemia (very small, pale RBCs) and a smear showing nucleated red blood cells (erythroblasts) and varied cell shapes.

Qualitative and Quantitative Hemoglobin Analysis

The Test: Sophisticated separation techniques like HPLC or Capillary Electrophoresis that measure the different types of hemoglobin in the blood.

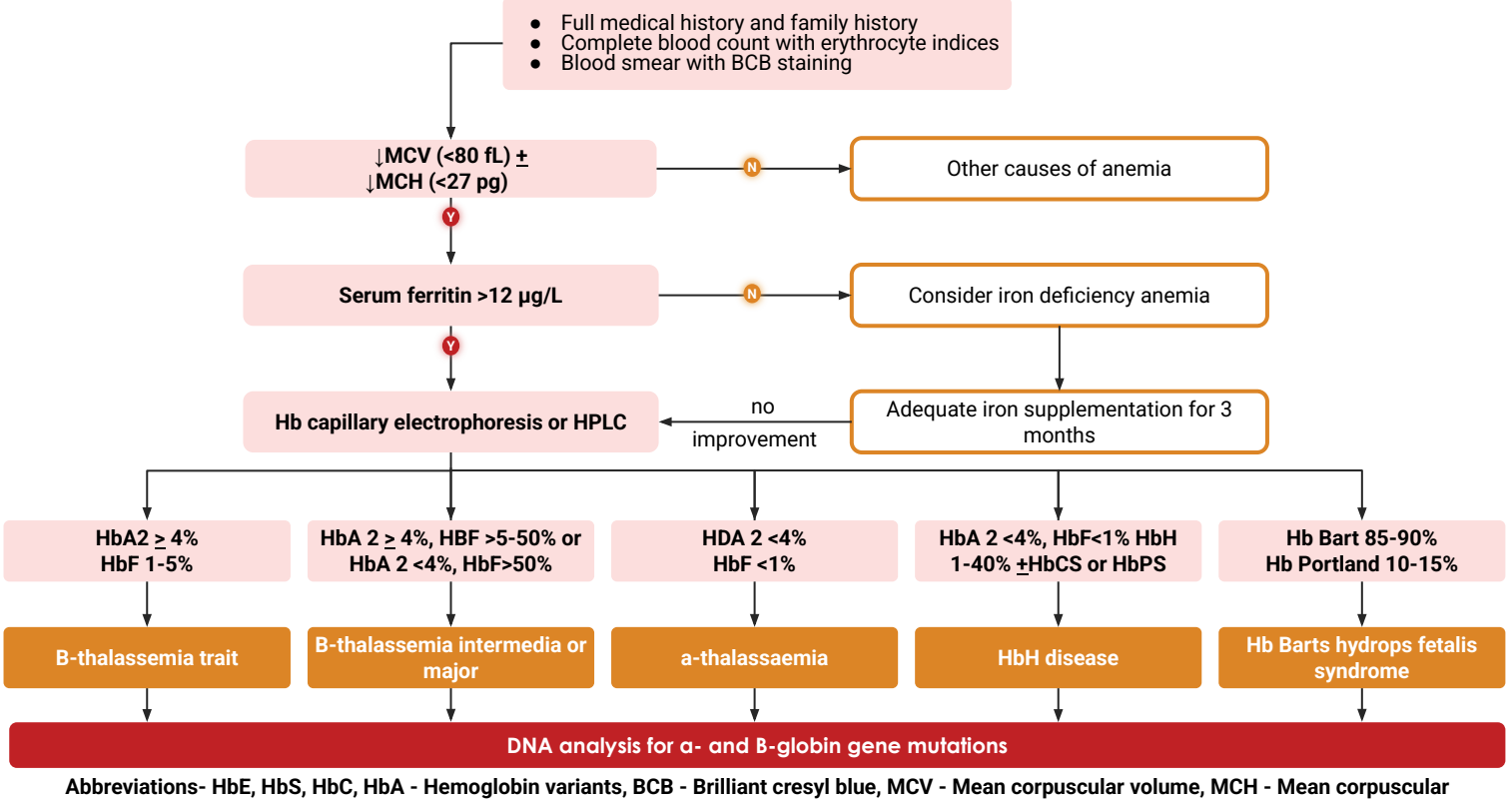
The Diagnosis: Carriers are identified by elevated HbA2 levels, while major forms are confirmed by a total absence or severe reduction of HbA and a high percentage of fetal hemoglobin HbF.

Molecular Analysis

The Test: DNA-based procedures, including PCR, Sanger Sequencing, or Next-Generation Sequencing (NGS), to examine the β-globin gene.

The Diagnosis: This provides definitive confirmation by detecting the specific genetic mutation or deletion in the DNA that is causing the defective hemoglobin production.

Algorithm for the diagnosis of thalassemia



Abbreviations- HbE, HbS, HbC, HbA - Hemoglobin variants, BCB - Brilliant cresyl blue, MCV - Mean corpuscular volume, MCH - Mean corpuscular hemoglobin, N-No, Y-Yes, HPLC- High performance liquid chromatography, fL-femtoliters, pg-picograms

Note: This report is generated based on publicly available data

Treatment Overview

Managing beta thalassemia

Regular blood transfusions

To correct severe anemia, suppress ineffective red blood cell production (erythropoiesis), and prevent associated complications like bone abnormalities and growth problems. Typically, every 2 to 4 weeks for beta thalassemia major to maintain a pre-transfusion hemoglobin (Hb) level target (often 9-10.5g/dL).

Iron chelation therapy

To remove excess iron that accumulates from regular blood transfusions and prevent iron overload (hemochromatosis), which can damage organs like the heart, liver, and endocrine glands. Iron overload is the leading cause of death in regularly transfused patients
Three main chelating agents used are Desferrioxamine, Deferiprone and Deferasirox.

Monitoring and management

Iron Monitoring: Regular assessment of iron levels in the body, including Serum Ferritin (SF), and crucial evaluations of Liver Iron Concentration (LIC) and Myocardial T2 MRI to check for iron damage in the heart.
Management of Complications: Screening and treatment for common complications like endocrine issues,
bone health, heart issues, gallstones.

Curative therapies

Hematopoietic Stem Cell Transplantation (HSCT)
The process of replacing a patient's diseased and ineffective bone marrow with healthy hematopoietic stem cells from an allogeneic (genetically different) donor. For over four decades, it has been the primary "Gold Standard" for curing Beta Thalassemia.

Eradication

Patients undergo myeloablation, which destroys their defective bone marrow cells and creates space for new ones.

Replacement

Healthy stem cells from a donor (usually a matched sibling or matched unrelated donor) are infused into the patient's bloodstream.

Engraftment

New cells migrate to bone marrow and begin producing normal, mature RBCs that contain functional β-globin chains.

Result

Successful engraftment eliminates "ineffective erythropoiesis", effectively curing the anemia and ending the need for lifelong transfusions.

Gene Manipulation (Gene Therapy & Editing)
Refers to a group of advanced biotechnological techniques used to modify a patient's own (autologous) stem cells to correct the genetic defect of thalassemia. Unlike HSCT, this process uses the patient's own cells, eliminating the risk of Graft-versus-Host Disease (GvHD).

There are two primary mechanisms recognized in the 2025 guidelines

Gene Addition (Lentiviral Vector)

- **The Process:** A modified, harmless virus (lentivirus) is used as a "delivery truck" to carry a functional copy of the β-globin gene into the patient's stem cells.
- **The Result:** The newly inserted gene allows the red blood cells to produce enough functional adult hemoglobin (HbA) to maintain safe oxygen levels without transfusions.

Gene Editing (CRISPR/Cas9)

- **The Process**: Molecular "scissors" (CRISPR) are used to "knock out" or silence a specific gene called BCL11A.
- **The Result:** In humans, BCL11A normally acts as a "switch" that turns off fetal hemoglobin HbF after birth. By silencing this switch, the body is forced to start producing high levels of HbF again. HbF is excellent at carrying oxygen and can fully compensate for the lack of adult β-globin.

Approved drugs for beta thalassemia

casgevy (exagamglogene autotemcel) suspension for IV infusion	VERTEX	BCL11A knockout	CASGEVY is a one-time therapy used to treat people aged 12 yrs and above with transfusion-dependent beta-thalassemia.
zynteglo (betibeglogene autotemcel) suspension for IV infusion	bluebirdbio	Stem cell-based gene therapy (β globin gene)	ZYNTEGLO is a one-time gene therapy that addresses beta-thalassemia at the genetic level by using patients' blood stem cells.
Reblozyl (luspatercept-aamt) for injection 25mg • 75mg	Bristol Myers Squibb MERCK	Activin receptor type IIB (ActRIIB)	REBLOZYL is an EMA (Erythroid maturation agent) that helps immature RBCs (called erythroid cells) develop and become mature, working RBCs, resulting in healthier RBCs and improved anemia.
Aqvesme (mitapivat) tablets 100mg	agios	Pyruvate kinase Enzyme	AQVESME (mitapivat) works for beta thalassemia by activating the pyruvate kinase (PK) enzyme in red blood cells, improving cellular energy balance, leading to an increase in the number of healthy, circulating RBCs

Emerging therapies

INN/Code name	Company	Current phase	ROA	Molecule type
REGN7999	REGENERON	Phase 2		
Etavopivat	novo nordisk	Phase 2		
SP-420 (Petadeferitrin)	PHARMACOSMOS	Phase 2		
BD211	本导基因 BDGENE	Phase 1		
9MW3011	Mabwell 迈威生物	Phase 1		
CS-101	Correctseq 正序生物	Phase 1		

Monoclonal Antibody | Small Molecule | Stem cell therapy | Subcutaneous | Oral | Intravenous

Conclusion

Therapeutic Revolution: Clinical focus has shifted from lifelong transfusion dependence toward functional cures and disease modification through gene therapy and targeted agents like luspatercept and mitapivat.

Future Focus: The priority is bridging the gap between high-cost innovation and global accessibility for all patients.

Note: This report is generated based on publicly available data