The American Journal of Medical Sciences and Pharmaceutical Research ISSN 2689-1026 Volume 08 - 2026

Thalassemia. Etiology, Pathogenesis, Clinical Picture, Diagnosis, Treatment

Norbibi Yadgarova
Tashkent State Medical University, Uzbekistan

Received: 31 Dec 2025 | Received Revised Version: 25 Jan 2026 | Accepted: 12 Feb 2026 | Published: 28 Feb 2026

Volume 08 Issue 02 2026 | Crossref DOI: 10.37547/tajmspr/Volume08Issue02-29

Abstract

Thalassemias are a group of inherited hemoglobinopathies caused by a quantitative deficiency in the synthesis of α- or β-globin chains of hemoglobin, leading to chronic hemolytic anemia of varying severity.

Keywords: Ineffective erythropoiesis; iron overload; hemoglobinopathies; HPLC; hemoglobin electrophoresis; gene therapy.

Cite This Article: Norbibi Yadgarova. (2026). Thalassemia. Etiology, Pathogenesis, Clinical Picture, Diagnosis, Treatment. The American Journal of Medical Sciences and Pharmaceutical Research, 8(2), 194–199. https://doi.org/10.37547/tajmspr/Volume08Issue02-29

1. Introduction

Thalassemia is a group of hereditary hemoglobinopathies, which are based on a quantitative deficiency in the synthesis of α- or β-globin chains, leading to an imbalance of the globin components of hemoglobin and chronic anemia with systemic consequences. The Global Burden of Disease Assessment shows that there were approximately 1,310,407 cases of thalassemia worldwide in 2021 and the age-standardized prevalence reached 18.28 per 100,000 population, while in the dynamics of 1990–2021. There were small changes in the rate, reflecting the heterogeneity of prevention and survival between countries. The geographic concentration of the disease in regions of historical endemicity for malaria is determined by population genetic mechanisms, however, modern migration and mixing of populations expand the range of detection of thalassemia in non-endemic countries and increase the requirements for laboratory vigilance.

The clinical significance of thalassemia is currently determined not only by the severity of the anemic syndrome, but also by multi-organ complications, primarily iron overload, cardiomyopathy, liver damage and endocrine dysfunction. Iron overload is formed both as a result of regular transfusions and as a result of reduced hepcidin expression and increased iron absorption with ineffective erythropoiesis, which is especially important for non-transfusion-dependent thalassemia phenotypes.

A methodologically correct description of the etiology, pathogenesis and clinical spectrum is necessary to prevent diagnostic errors, the most typical of which is the incorrect interpretation of microcytic anemia as iron deficiency and the subsequent unreasonable prescription of iron supplements. Clinical guidelines emphasize that control of complications can only be achieved through integration of the transfusion program, monitoring of iron overload, and individualized chelation therapy.

Finally, the advent of high-tech approaches, from gene therapy to new drugs targeting erythroid metabolism, is

changing standards of management and necessitating a re-evaluation of the effectiveness of lifelong maintenance strategies compared with potentially disease-modifying interventions.

The etiological basis of α-thalassemia is associated with mutations and/or deletions of the HBA1/HBA2 genes, while β-thalassemia is caused by a variety of mutations in the HBB gene, including point mutations changes, splice mutations and regulatory disorders leading to β^0- or β^+-phenotypes. The pathogenetic core of the disease is formed by an imbalance of globin chains: in β-thalassemia, excess α-chains aggregate in erythroid precursors, damage membranes and induce apoptosis, which is manifested by ineffective erythropoiesis and intramedullary cell death. In the periphery, hemolysis maintains chronic anemia and enhances compensatory mechanisms of hematopoiesis, including expansion of the bone marrow spaces and extramedullary hematopoiesis, which is clinically manifested by bone deformities and hepatosplenomegaly.

Diagnostically important is the distinction between thalassemia and iron deficiency, since both situations give microcytosis, but have fundamentally different consequences of iron administration and different trajectories of complications. From a clinical point of view, it is appropriate to operate in the categories of transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT), since intervention thresholds, frequency of monitoring and late outcome profiles differ significantly. The basic components of therapy remain regular red blood cell transfusions to prevent severe hypoxia and suppress ineffective erythropoiesis, as well as iron chelation therapy for the prevention of cardiac and hepatic complications. Clinical guidelines emphasize the role of MRI assessment of iron overload, including cardiac T2* imaging, as the most informative approach to the prevention of myocardial dysfunction during iron loading. New technologies have entered clinical practice in recent years, including single-dose autologous gene therapy for patients with transfusion-dependent β-thalassemia, approved by the FDA in 2022, setting a new framework for assessing clinical outcomes and long-term safety.

This work was carried out in the format of an analytical review with elements of a systematic synthesis of data, focused on the clinically significant links "etiology-pathogenesis-clinical-diagnosis-treatment" and on comparing management standards with the dynamics of the global burden of the disease. Data from a systematic analysis of the Global Burden of Disease 2021 study on the prevalence and time trends of thalassemia 1990–2021 were used as the baseline, providing population context and quantitative benchmarks for interpreting clinical strategies. To assess current clinical approaches, international guidelines from Thalassaemia International Federation (TIF) for the management of transfusion-dependent β-thalassemia, including provisions on monitoring iron overload and the use of MRI parameters (LIC and myocardial T2*) in chelation therapy correction algorithms. A separate block of sources consisted of FDA regulatory documents on the gene therapy betibeglogene autotemcel (Zynteglo), containing information about the study population and principles for assessing transfusion independence as a clinically relevant endpoint. Data from systematic reviews and meta-analyses of deferiprone and combination chelation regimens were used to summarize the effectiveness and safety of chelation regimens, as these approaches are often considered for poor response to monotherapy and cardiac iron loading.

Additionally, information about new pharmacological options for α- and β-thalassemia was taken into account, including reports of the expansion of the regulatory indications of mitapivat at the end of 2025, which was included in the analysis as an indicator of the expansion of the therapeutic field and a shift in emphasis from exclusively transfusion support to the correction of erythroid function. The selection of materials was carried out according to the principle of priority of primary and official sources (open access publications, guidelines, regulatory documents), and the interpretation of the data was carried out with an emphasis on comparability of definitions (TDT/NTDT), clinical endpoints (transfusion independence, iron load markers) and reproducibility of diagnostic algorithms. The final synthesis is performed as a cause-and-effect model, where each clinical decision (transfusions, chelation, high-tech interventions) is correlated with a specific pathogenetic mechanism and measured monitoring indicators.

At the population level, analysis of GBD 2021 data demonstrates that thalassemia remains a persistently significant inherited disease with a global number of cases of approximately 1.31 million in 2021 and an age-standardized prevalence of 18.28 per 100,000, with a change in trend from 1990–2021. were relatively moderate and reflected divergent processes of prevention and survival in different regions.

These numbers indicate that clinical improvements in individual countries have not translated into comparable

global burden reductions, consistent with uneven access to screening, transfusion support, and chelation agents. From a clinical and pathogenetic point of view, the key mechanism of severe outcomes is associated with iron overload, since it is a predictable consequence of transfusion therapy and at the same time a product of dysregulation of the hepcidin-ferroportin axis with ineffective erythropoiesis.

TIF guidelines state that MRI-guided assessment of iron load, including myocardial T2*, is the best available approach to preventing cardiac dysfunction, and more recent versions of the guidelines emphasize regular (usually annual) MRI assessment of the liver and heart, starting at approximately 8–10 years, with frequency varying depending on the level of iron load and adjustments in therapy. Thus, a qualitative transition in the management of thalassemia is determined not so much by the expansion of the list of laboratory tests, but by the introduction of standardized iron monitoring and algorithms for adapting chelation regimens.

As part of the synthesis of evidence on the effectiveness of chelation, systematic reviews in recent years have focused on the clinically significant effects of deferiprone, including reduction in iron load and improvement in cardiac parameters in patients at risk for cardiac complications, which supports the practice of individualizing the choice of chelator depending on the target organ. At the same time, reviews of combination regimens (eg, deferasirox + deferiprone) indicate that combinations are considered a rational strategy when response to monotherapy is limited, although increased monitoring of safety and adherence is required.

On the therapeutic side, the most pronounced paradigm shift is associated with the advent of disease-modifying technologies, where the end point is not "optimization of transfusions", but the achievement of transfusion independence or a clinically significant increase in hemoglobin without regular transfusions. FDA Regulatory Materials indicate that the approval of the gene therapy betibeglogene autotemcel (Zynteglo) for transfusion-dependent β-thalassemia in 2022 relied on clinical trials that assessed transfusion independence as a key outcome measure, institutionalizing a new standard of evidence for innovative interventions.

The practical implication is that clinical algorithms should include stratification of patients according to potential suitability for advanced treatment (age, comorbidity, iron load profile, site accessibility), and weighing long-term risks and benefits compared with lifelong chelation. At the level pharmacotherapy, the end of 2025 is characterized by increased interest in drugs affecting erythroid metabolism and anemia in α- and β-thalassemia, which is reflected in reports of regulatory expansion of mitapivat indications and the formation of a new niche of "oral therapy for anemia" for some patients with transfusion and non-transfusion dependence. As a result, the therapeutic field for thalassemia becomes multicomponent: the basis of transfusions and chelation retains a leading role, but is complemented by selection programs for transplantation and gene-cell interventions, as well as new drug strategies to reduce the need for transfusions.

The most consistent conclusion at the clinical and organizational level is that the reduction in late mortality and disability in thalassemia is determined not by a single drug, but by a management system: early diagnosis, regulated monitoring of iron load (including MRI indicators) and timely correction of therapy. At the same time, a critical gap remains in the availability of such systemic solutions between countries and regions, which is in good agreement with the moderate dynamics of global indicators in 1990–2021. and emphasizes the need to scale up prevention programs and specialized care centers.

The modern understanding of thalassemia is increasingly shifting from the interpretation of the disease as "chronic anemia of hereditary origin" to a model of multifactorial systemic pathology, where the clinical outcome is determined by the controllability of several parallel risk circuits. At the population level, GBD 2021 data show a continued significant burden: about 1.31 million cases of thalassemia were estimated in 2021, with an age-standardized prevalence of about 18.28 per 100,000 population, and the dynamics of 1990–2021. demonstrated a redistribution of burden between regions rather than a universal reduction.

This epidemiological profile indirectly indicates that clinical progress in some countries does not compensate for the inadequacy of preventive programs and the limited availability of specialized care in others, which is especially critical for hereditary diseases with a high carriage rate.

In clinical practice, this means that outcomes depend not only on the "correct diagnosis", but also on the patient's integration into a long-term monitoring system, including monitoring of iron load, organ complications and adherence to therapy. Distinguishing between TDT and NTDT phenotypes is of particular importance, since the same laboratory signs of microcytosis can lead to fundamentally

different trajectories of complications and different thresholds for intervention. The risk-based strategy is supported by clinical guidelines, which emphasizes the need for standardized monitoring and adjustment of therapy based on objective parameters, and not just clinical impression. In this logic, thalassemia becomes a model example of a chronic disease, where the "manufacturability" of management is measured by the regularity and accuracy of control of key pathogenetic variables. Finally, the discussion inevitably goes beyond pharmacotherapy, touching on issues of organizational availability of MRI monitoring, the work of multidisciplinary teams and the implementation of screening programs, without which the incidence of severe forms remains stable.

Pathogenetic analysis suggests that the central mechanism linking the genetic defect and clinical outcome is ineffective erythropoiesis followed by a cascade of iron dysregulation and multiorgan damage. In β-thalassemia, an excess of α-chains in erythroid cells leads to membrane damage and premature death of precursors, which forms persistent anemia and compensatory hyperplasia of the bone marrow, and at the body level - hypoxic stress and remodeling of target organs. The clinically important consequence is the suppression of hepcidin and increased intestinal absorption of iron, causing iron overload becomes a problem even in some patients with limited transfusion load, especially in the NTDT group. That is why modern recommendations consider iron overload as a key modifiable factor in late complications, and its control as an equal goal along with the correction of anemia. In this context, a common clinical error - the mechanical interpretation of microcytosis as iron deficiency - acquires systemic significance, since it not only delays diagnosis, but can aggravate the iron load with unjustified ferrotherapy.

The diagnostic discussion, therefore, should include not only the "test battery" (Hb fractions and genetics), but also an algorithm for excluding iron deficiency and inflammation, which influence the interpretation of HbA2/HbF and the choice of tactics. The practical conclusion is that a rational diagnosis of thalassemia is a sequence of mutually validating steps (erythrocyte indices → iron profile → Hb fractions → molecular verification), and not a one-time study. An additional argument in favor of algorithmization is the reproducibility of morphological signs of a peripheral blood smear as an early "trigger" for referring a patient for an in-depth examination.

The therapeutic discussion in the 2020s is acquiring a fundamentally new dimension: along with the classic "transfusion + chelation" combination, a layer of interventions appears that claim to modify the disease, and therefore to change the very need for transfusions. TIF guidelines state that the success of basic therapy is determined not only by achieving the target hemoglobin level, but also by strict control of iron load, with the most critical control of myocardial iron, for which the T2* MRI parameter is considered a key tool for the prevention of cardiac dysfunction.

Importantly, the TDT phenotype provides a high "predictability" of iron accumulation due to transfusions, whereas in NTDT the clinician requires active vigilance because iron overload can progress with relatively mild anemia and infrequent transfusions. This difference explains why transferring TDT protocols to NTDT without adaptation leads to two opposing pitfalls: either late initiation of chelation or overtreatment with the risk of toxicity when overload is insufficiently demonstrated.

When discussing chelation therapy, the "target organ and dynamics" approach becomes decisive rather than the choice of drug "out of habit", since hepatic and cardiac iron load may require different intensities and treatment regimens. From a practical point of view, it is the implementation of measurable metrics (ferritin + MRI-LIC/T2*) that moves the management of thalassemia from an empirical field to a manageable and reproducible clinical system.

A separate issue remains the availability of MRI assessment, which is limited in many regions, forcing the development of stepwise algorithms, but even in such conditions the concept of risk stratification remains valuable. Therefore, the therapeutic discussion must include not only "what to prescribe," but also "how to ensure monitoring and adherence," since without this, the effect of any regimen will be lower than in clinical trials.

Finally, no discussion is possible without assessing the impact of innovation on the design of clinical goals and performance criteria. FDA approval of the gene therapy betibeglogene autotemcel (Zynteglo) in 2022 for patients with transfusion-dependent β-thalassemia has institutionalized the clinical goal of transfusion independence as a measurable endpoint, changing the framework of long-term treatment planning for a subset of patients. In parallel, in 2026, the FDA announced the approval of mitapivat(Aqvesme) as the first oral therapy for anemia in α- and β-thalassemia in adults, expanding the therapeutic continuum between "symptomatic support" and

"potential cure" and opening a new niche for patients who are not candidates for transplantation or gene therapy. However, it is precisely at the stage of innovation implementation that strict selection criteria, assessment of long-term safety and comparison of risks with expected benefits are especially important in real clinical practice, where comorbidity and variability in access to observation is higher than in research centers. A rational clinical model therefore suggests a three-tier architecture: basic standard management (transfusion/chelation/monitoring), targeted pharmacological management of anemia in appropriate patients, and advanced interventions for a carefully selected group. At the level of healthcare systems, this means the need for registers, centralization of some services and standardization of quality indicators (frequency of MRI control, proportion of patients with target iron load parameters, frequency of complications).

Thus, discussions of thalassemia in the 2020s inevitably include not only the biology of the disease, but also the controllability of the patient's journey, as it is the "organization" that becomes the hidden modifier of outcome. In other words, the current evidence base supports the thesis that the outcome of thalassemia is determined by how early the diagnosis is made, how measurably key risks (especially iron loading) are controlled, and how timely the patient has access to disease-modifying technologies.

The analysis of modern ideas about the etiology, pathogenesis, clinical picture, diagnosis and treatment of thalassemia confirms that this disease is a complex multisystem pathology with pronounced genetic determination and a multi-level mechanism of clinical implementation. Despite the fact that the primary link is a quantitative defect in the synthesis of globin chains, the clinical outcome is determined not only by the severity of anemia, but also by the degree of ineffective erythropoiesis, the level of chronic hypoxia and the accumulation of iron in vital organs.

Global epidemiological data for 1990–2021 demonstrate a continued significant burden of disease, indicating the need for further improvements in screening and prevention programs. Modern diagnostics require an integrated approach, including morphological analysis of peripheral blood, study of hemoglobin fractions by HPLC or electrophoresis, assessment of iron metabolism and molecular genetic verification of mutations.

The distinction between thalassemia and iron deficiency anemia remains fundamentally important, since a diagnostic error can lead to adverse clinical consequences.

A key factor in long-term prognosis is the control of iron overload, which develops both as a result of transfusion therapy and as a result of dysregulation of the hepcidin mechanism. The introduction of MRI-based assessment of hepatic and myocardial iron load significantly increased the accuracy of risk stratification and reduced the incidence of cardiac complications.

Basic therapy based on regular red blood cell transfusions and adequate chelation support remains the cornerstone of the management of patients with severe forms of the disease. At the same time, in recent years, a new therapeutic paradigm has emerged, including cell-gene technologies and drugs aimed at improving erythroid function, which expands the possibilities of achieving transfusion independence in some patients.

Thus, the modern model of thalassemia management is a systemic, multidisciplinary and technology-oriented process, where the outcome is determined by early diagnosis, continuous monitoring and personalized choice of therapy. Further research should focus on optimizing patient stratification algorithms, assessing the long-term effectiveness of innovative treatments, and increasing the availability of specialized care in regions with high disease prevalence.

References

1. Cappellini M.D., Porter J.B., Taher A.T., Viprakasit V. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 4th ed. Nicosia: Thalassaemia International Federation; 2021.
2. Vos T., Lim S.S., Abbafati C., et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;401(10380):121–159.
3. Taher A.T., Musallam K.M., Cappellini M.D. β-Thalassemias. N Engl J Med. 2021;384(8):727–743.
4. Porter J.B., Garbowski M.W. Consequences and management of iron overload in β-thalassemia. Hematology Am Soc Hematol Educ Program. 2019;2019(1):337–345.
5. Pennell D.J., Udelson J.E., Arai A.E., et al. Cardiovascular function and treatment in β-thalassemia major: A consensus statement. Circulation. 2013;128(3):281–308.
6. FDA. Zynteglo (betibeglogene autotemcel) – Biologics License Application Approval Letter. U.S. Food and Drug Administration; 2022.
7. FDA. Mitapivat (Aqvesme) – Approval for treatment

of anemia in thalassemia. U.S. Food and Drug Administration; 2026.
8. Galanello R., Origa R. Beta-thalassemia. Orphanet J Rare Dis. 2010;5:11.
9. Weatherall D.J., Clegg J.B. The Thalassaemia Syndromes. 4th ed. Oxford: Blackwell Science; 2001.
10. Taher A.T., Saliba A.N. Iron overload in thalassemia: different organs at different rates. Hematology. 2017;2017(1):265–271.