

Thalassemia: An Extensive Analysis of Epidemiology, Diagnosis, and Treatment Approaches

Karande Samiksha*, Khot Seema, Kumbhar Sae, Dr. S. C. Burli

Ashokrao Mane College of Pharmacy, Peth Vadgaon Maharashtra, India

ABSTRACT

Thalassemia comprises a spectrum of genetic hemoglobin disorders due to impaired or complete loss of the synthesis of one or more globin chains, thus leading to chronic hemolytic anemia with different degrees of clinical severity. Here, thalassemia is reviewed fully from its inception in history up to the modern world's overall epidemiology of thalassemia specifically within areas such as the Middle East, the Mediterranean, and South Asia. The molecular pathogenesis and genetic basis of alpha and beta thalassemia are reviewed, with particular attention to the effect of individual mutations on presentation. Classification systems, such as the separation between thalassemia trait, intermedia, and major, are discussed in relation to both laboratory and symptomatology. The book also describes the key complications of thalassemia, including iron overload, organ dysfunction, and growth retardation, and reviews new diagnostic techniques, including hemoglobin electrophoresis and genetic analysis. Options for management from chronic transfusions and chelation with iron to cure by bone marrow transplantation and current gene therapies under investigation are assessed. Lastly, prevention via genetic counseling, premarital testing, and prenatal diagnosis is highlighted as important, especially in high-risk groups. This report is intended to be a reference for healthcare providers, researchers, and public health planners who are engaged in the prevention and care of thalassemia.

Keywords: Thalassemia, Stem Cell Transplantation, Alpha and Beta Thalassemia

INTRODUCTION

The thalassaemias are a class of recessive autosomal hereditary illnesses. [1] It is characterized by a reduction in red cell hemoglobin due to the absence or reduced production of one of the two polypeptide chains (beta/alpha) that comprise the typical adult human hemoglobin molecule (haemoglobin A, alpha₂/beta₂). [2] The term "thalassaemia," which comes from the Greek words "thalassa" (sea) and "haima" (blood), refers to the various thalassaemia syndromes that are named after the abnormal hemoglobin. β thalassaemia can be caused by defects in the β globin gene, whereas α thalassaemia can be caused by abnormalities in the α globin gene. [3]

There are more than Two hundred deletions or point mutations that affect the transcription, processing, or translation of α - or β -globin mRNA. [4] The clinical characteristics range from lack of symptoms to severe life-threatening anemias in womb or in early childhood if left untreated.[5] By the early 1900s, physicians in Europe had identified a splenomegaly-associated anemia condition in infants.[6] How this

nomenclature came to be is unclear, though it is stated that the initial patients were typically of Mediterranean descent.[7]The first clinical report of thalassemia in American literature is credited to the pediatricians Thomas B. Cooley and Pearl Lee of Detroit. George Whipple is the one who originally named the disease thalassemia. [8] As suggested in the 1960s, where they were associated with the unbalanced globin chain synthesis. The platform was laid for further advances. [9] An easier methodology was worked out by which ordinary laboratories could measure amount of hemoglobin A₂ and establish the diagnosis of thalassemia [10]. Additional noticeable changes about hemoglobin patterns in thalassemia patients resulted in the identification of HbH (β_4) and Hb Barts (γ_4), that is subsequently proved to be specific markers of alpha-thalassemia. [11] Reticulocytes from thalassaemic individuals treated in vitro with radiological amino acids, David Weatherall and associates at Johns Hopkins University demonstrated that alpha or beta chain synthesis was impaired in both alpha and beta thalassaemic patients as a result of an imbalance in globin chain synthesis.

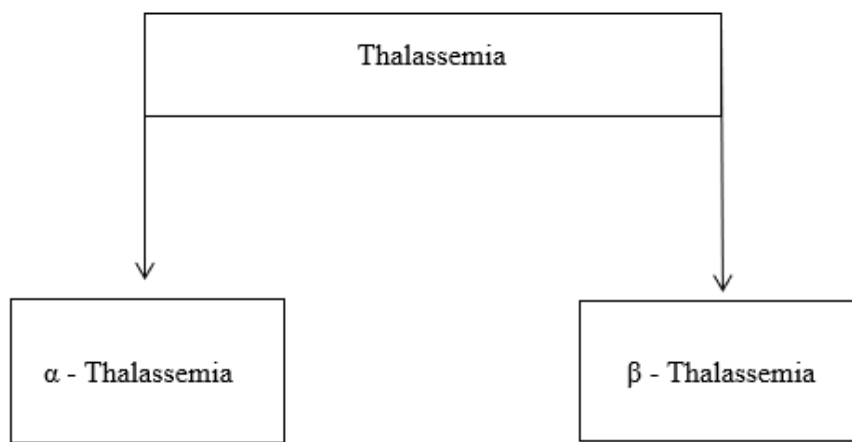
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[12] [13] Determining if protein formation was aberrant at the structural gene or globin chain synthesis level was now necessary. [14] The majority of thalassemia syndromes were found to have a shortage of specific messenger RNA, as well as problems in messenger RNA translation to protein, according to a series of investigations. [15] Ribosomal units that can start, lengthen, and stop the globin chain are involved in this later step. [16] Thus, a better understanding of genetic control of human hemoglobins had become apparent. It was now understood that several loci of structural genes, i.e., alpha, beta, gamma, and delta, regulated synthesis of their respective globin chains. [17] People from the

Mediterranean, Middle East, Transcaucasus, Central Asia, Indian subcontinent, and Far East have thalassemia, one of the most prevalent autosomal recessive illnesses in the world. However, populations in Africa also have a substantial amount of them. [18] Thalassemias are currently common in Australia, North Central and South America, and Northern Europe as a result of population migration [19]. 56,000 pregnancies worldwide result in a severe thalassemic condition, of which approximately 30,000 have BTM and 3500 pass away during pregnancy due to hydrops fetalis syndrome. [20]

CLASSIFICATION OF THALASSEMIA



2.1 Alpha Thalassemia [AT]

Among the most common genetic abnormalities of hemoglobin is AT [21] The main flaw is the decreased or nonexistent synthesis of alpha globin chains, which make up the moieties of various hemoglobins (Hb), including the minor component HbA₂ (alpha₂ delta₂), the fetal HbF (alpha₂ gamma₂), and the adult HbA (alpha₂ beta₂). [22] AT is prevalent in tropical and subtropical regions of the world, where malaria was and is still endemic, much like other common globin gene diseases. Carriers of hemoglobinopathy are believed to be comparatively protected in a malarial environment. [23] Despite a great deal of investigation, the nature of this protection has not yet been determined. Note that the prevalence of the numerous genetic abnormalities that cause alpha-thalassemia varies throughout populations, and that the prevalence of the clinically relevant types, such as HbH illness and Hb Bart's hydrops fetalis syndrome, also varies. [24] Alpha-thalassemia is now a fairly frequent clinical condition in North America, North Europe, and Australia due to recent significant

population shifts. [25] The overproduction of beta globin chains due to decreased or missing alpha globin chain production is the cause of alpha thalassemia. Two genes on each chromosome 16 regulate the expression of the alpha globin chain. [26] Usually, the deletion of one or more of these genes results in the decreased output. The alpha thalassemia silent carrier state, which is asymptomatic and has typical clinical and hematologic findings, is caused by the mutation of a single gene. [21] Alpha thalassemia trait (minor) with microcytosis and typically minimal anemia is caused by the loss of two genes. Hemoglobin H (HbH), a beta₄-structured hemoglobin that functions poorly, is produced symptomatically when three genes are deleted. [26]. Hemolysis, splenomegaly, and microcytic anemia are the outcomes of alpha thalassemia intermedia, often known as HbH sickness. When four genes are deleted, hemoglobin Bart's (Hb Bart's), which has a gamma structure, is produced symptomatically. Because of hydrops fetalis, alpha thalassemia major (Hb Bart's) typically causes fetal mortality. [27]

Clinical classification of Alpha Thalassemia [28]

1. Silent Carrier State
2. Alpha Thalassemia Trait
3. Hemoglobin H Disease
4. Hydrops Fetalis

2.2 Beta Thalassemia

Excess alpha chain is the result of reduced or nonexistent beta globin chain production, which causes beta thalassemia. One gene, found on both chromosomes 11, controls the production of beta globin. [13] Patients may create different amounts of alpha globin chain in comparison to beta globin chain synthesis, depending on the amount of beta globin chain produced (from almost normal to none). [30] A gene mutation might result in beta thalassemia trait (minor), which is symptomless and manifests as microcytosis and very less anemia. [29] A patient has BTM (Cooley anemia) if their beta globin chain synthesis is either completely absent or drastically diminished. [13] Due to HbF, patients with BTM are nearly always asymptomatic during birth however, symptoms begin to appear at 6 months of age, when the beta globin chains are required. [31] The patient has beta thalassemia intermedia if the reduction in beta chain synthesis is less severe [29]. These patients may not need lifetime transfusions to survive past the age of 20, and their symptoms are less severe. [32]

Beta-thalassemias is classified as: [29]

- Thalassemia major [BTM]
- Thalassemia intermedia [BTI]
- Thalassemia minor
- **Beta Thalassemia Major [BTM]**

The signs of thalassemia major will first arise between 6 and 24 months of age; during this time, affected infants will exhibit poor growth.[33] Feeding difficulties, diarrhea, irritability, recurring acting febrile conditions, and growing abdominal distension due to splenomegaly and hepatomegaly may occur.[34] The symptoms of thalassemia major include poor growth, jaundice, generally poor musculature, genu valgum, a liver condition, ulcers in the legs, due to extramedullary hematopoiesis, and skeletal deformities due to bone marrow expansion. Thalassemia major is often poorly treated and transfused in developing countries where resources are scarce. [35] Long bone abnormalities in the legs

and common craniofacial modifications (head bossing, nasal bridge depression, eye mongoloid slant, and maxillae hypertrophy, exposing the maxillary teeth) are among the skeletal changes. Growth and development will typically proceed normally for ten to twelve years if a planned transfusion program is initiated that aims for an acceptable Hb concentration should be 9.5 to 10.5 g/dL. [36] Patients who have received transfusions may experience iron overload-related problems [37]. Growth latency (failure to attain predicted heights) and/or failing or delay of sexual development are among the issues that children who are iron overloaded may have [38]. Subsequent iron overload complications may include hepatic (cirrhosis and fibrosis), cardiac (dilated cardiomyopathy or occasionally arrhythmias), and endocrine (diabetes mellitus, hypogonadism (inability to develop secondary sexual characteristics), as well as deficiencies in the parathyroid, thyroid, anterior pituitary, and, adrenal glands). [39,40] Additional contraindications involve HIV infection, venous thrombosis, osteoporosis, hypersplenism, and persistent hepatitis brought on by the hepatitis B and/or C viruses. [41] Patients with iron excess and a viral infection of the liver are at a greater risk of getting malignant hepatoma. [42] The frequency and severity of iron overload-related problems are mostly determined by adherence to iron chelation therapy (described later). [43] People who don't get transfusions often die prior to they reach their second or third decade of life. [44] Patients can live past the age of 40 if they receive regular transfusions and the right chelation to cure iron excess. [45] Heart illness brought on by myocardial siderosis (iron buildup in the heart) is the most severe and clinically significant sign of iron overloading from beta-thalassemia. [46] 71% of individuals with BTM die from heart problems brought on by iron excess. [47]

- **Beta Thalassemia Intermedia [BTI]**

Patients with thalassemia intermedia will show up after those with BTM and may have less complications of anemia, from which they need blood transfusion or other therapy either not at all or just periodically [48]. Patients with thalassemia live on the severe end of the clinical spectrum, with symptoms presenting between the ages of 2 and 6 years, and although they can survive without regular blood

transfusion, they would be expected to demonstrate stunt growth and development.[29] The other extreme of the clinical spectrum would be individuals who have no symptoms and may only have mild anemia throughout maturity.[49] In the bone marrow uses extramedullary erythropoiesis, a compensatory strategy to get around the persistent anemic state of thalassemia, when patients with the condition exhibit hypertrophy of the erythroid marrow[29] This leads to characteristic features of bone and facial deformities, osteoporosis, and formation of erythropoietic masses that primarily affect spleen, liver, chest, and spine.[50] Splenomegaly develops due to the role of the spleen in removing abnormal red cells from circulation.[51] In the case of extramedullary erythropoiesis, patients may experience neurologic problems, for example, spinal cord compression leading to paraplegia or the presence of intrathoracic masses.[52] Due to dysfunctional erythropoiesis and peripheral hemolysis, gallstones may form in patients with BTI, and this occurs more frequently than in patients with BTM.[53] Patients with BTI often experience leg ulcers and are likelihood of acquiring thromboses compared to BTM patients, especially in the case of splenectomy.[54] Thrombotic events include deep vein thrombosis, portal vein thrombosis, stroke, and pulmonary embolism. Patients with BTI are exposed to higher concentration of iron as a result of intestinal iron overload.[55] In patients with thalassemia intermedia, hypogonadism, hypothyroidism, and diabetes are not common.[56] However, in the event blood transfusion are given while pregnant, patients who have never or minimal amounts transfused may develop isoalloantibodies against the transfused blood and erythrocyte auto antibodies.[57] Retardation of growth within the womb has been reported even with an adequate transfusion schedule.[58] Cardiac involvement in thalassemia intermedia is primarily due to a elevated output condition with hypertension in the lungs, and the systolic function of the typically, the left ventricle remains intact.[59] Patients with BTI have been documented to get pseudoxanthoma elasticum, a diffuse connective tissues. condition that affects the arteries due to calcium accumulation and the deterioration of the artery wall's elastic lamina. [60]

- **Beta Thalassemia Minor**

Iron deficiency must be figure out to be able to recognize beta-thalassemia minor since it can alter the normally elevated values of HbA2. Regardless on the underlying modification, large levels of HbF may also be present.[61] The RBC of a carrier will be hypochromic and microcytic. The majority of patients with beta-thalassemia minor enjoy a reasonable quality of life, and the condition is frequently medically mild. [62] While carriers are sometimes found to have enlarged spleen, modest bone abnormalities, leg ulcers, or cholelithiasis, the most of carriers do not have clinically significant anemia and do not need special therapy. In [63] Pregnant women who suffer from anemia may need transfusion therapy and 1–5 mg of folic acid per day (Hb 7 and the third trimester). [64] Couples, particularly those with close family members, compulsorily screened for atypical or silent α and β mutations. If found, medical assistance should be provided. [29].

3. Etiology

Thalassemia results in unequal hemoglobin synthesis due to reduced levels of minimum one globin polypeptide chain (beta, alpha, gamma, and delta). [13] Hereditary sequence for thalassemia is autosomal recessive. Beta thalassemia is characterized by decreased beta-polypeptide chain production. Heterozygotes with low to modest microcytic anemia (thalassemia minor) show no clinical signs. [65] In homozygotes with beta-thalassemia major, commonly referred to as Cooley's anemia, severe anemia and bone marrow hyperactivity are the results. AT results from decreased synthesis of alpha globin. When a genetic deficiency is heterozygous, the consequence is silent alpha thalassemia. [66] In When abnormalities in three of the four genes more significantly affect the formation of alpha chains, tetramers of excess beta chains (HbH) or, in babyhood, gamma chains (Bart's Hb) are generated.[67] In Since hemoglobin E (Hb E) is not connected to hemoglobin lacking alpha chains, abnormalities in all four genes are lethal until they undergo therapy with transplanted blood while still in gestation.[68] In addition to changing structure, the mutation decreases the rate of beta globin synthesis. As a result, Hb E trait and disease usually exhibit a modest Beta thalassemia phenotype. [13] In Bangladesh, India, and Southeast Asia, co-inheritance of thalassemia and Hb E is common. [69] The signs

of this Hb E/thalassemia compound heterozygote disease fluctuate between transfusion dependency to moderate anemia. The most important their genome, Hb E/Beta thalassemia, is responsible for half of all occurrences of severe beta thalassemia. [70] People who have Hb E/Beta thalassemia are prone to suffer from vitamin D deficiency or pulmonary hypertension. [71]

4. Pathophysiology

The pathology that underlies the various forms of thalassemia is similar, despite the fact that clinical spectra differ based on the co-inheritance of other genetic modifiers. [72] This disorder is defined by impaired preparation of Hb and survival of red blood cells (RBCs) because of an excess of undamaged globin chains that precipitate as inclusion bodies as unstable homotetramers. [73]. Due to their greater instability, the β homotetramers in β -thalassemia precipitate earlier in the RBC life span than those in α -thalassemia. This causes considerable RBC injury and severe bleeding associated with extramedullary hemolysis and inefficient erythropoiesis (IE). IE

results in larger marrow cavities that press against good bone in severe thalassemia, causing the face, long bones, and skull to be deformed. Additionally, excessive erythroid activity in extramedullary hematopoietic locations can result in extramedullary malignancies, extensive lymphadenopathy, and hepatosplenomegaly. A lack of oxygen and chronic anemia also increase the uptake of iron in the gastrointestinal (GI) tract. [74,75] If transfusion support is not offered, over 86% of patients with severe homozygous thalassemia will die from severe anemia by the time they are five years old. [76] As serum transferrin saturation rises above 70%, free iron species, including labile plasma iron, have been found in the plasma and labile iron pool in the red blood cells. [77] Reactive oxygen species, which ultimately lead to tissue damage, organ dysfunction, and death, are mostly caused by these iron species. [78] To date, there have been unsuccessful attempts to use antioxidants to reduce thalassemic blood cells under oxidative stress. [79] Iron chelation treatment has been found to be the sole means of reducing morbidities and improving lifespan during the fourth and fifth decades of life. [80]

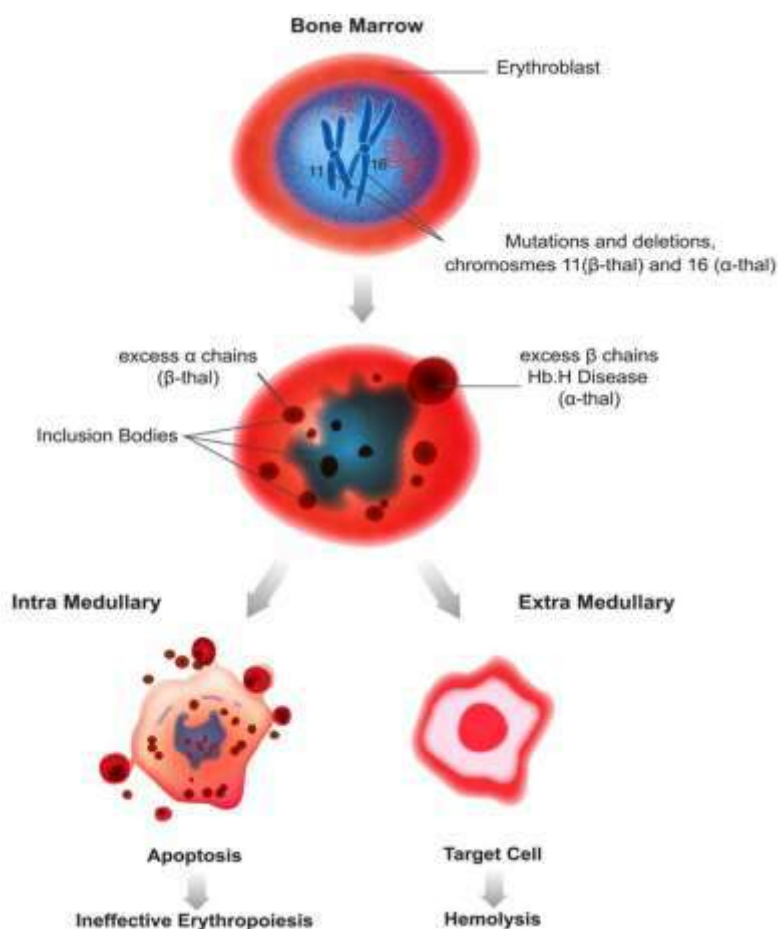


Figure no.1

4. Sign and Symptoms

Iron overload: Frequent transplants of blood can cause iron overload, one of the most common adverse effects of thalassemia that can damage the liver, heart, and endocrine system. [81] Infection: Person with thalassemia are an easy target for getting ill, which can harm their bodily systems. [82] Bone deformities: These disorders impact the body's development. Then, thalassemia patients may show it. Most of the time, the skull bone is visible. Also, the swelling of the skull and face bones leads to skeletal anomalies. [83] Spleen enlargement: Numerous bacterial, viral, and infectious causes might contribute to this illness. Additionally, it may happen unintentionally as a result of blood flow problems and liver failure. [84]

5. Prevention

Offering prospective genetic counseling and informing carriers of the dangers of intra marriage are crucial in nations with high thalassemia incidence. [85] Attempts to use this strategy have so far been largely unsuccessful. As a result, programs for prenatal diagnosis have received a lot of attention. [86] Due to the easy identification of thalassemia carrier states, affected fetuses can be diagnosed. Recent efforts have concentrated on early diagnosis by using embryonic fluid cells for fetal genetic testing or chorionic villus collection. [87] Further, oligonucleotide probes to identify particular mutations have greatly improved the accuracy rate of prenatal diagnosis. Because of this, research is being done on removing fetal tissues from the blood supply of the mother. [88] Management during pregnancy: For everyone with thalassemia, preconception genetic counseling is highly recommended. One in four children born to two parents with β thalassemia trait will have β thalassemia major thus, three out of four will either have thalassemia trait or be normal. [89] The inheritance pattern of people with alpha thalassemia trait is more intricate. The result will change depending on whether both faulty genes are located on the same or separate chromosomes. [21] Babies with beta thalassemia can be identified by chorionic villus sampling that uses PCR technique. [90] Alpha thalassemia trait carriers should think about getting a pregnancy diagnosis due to Hb Bart's raises the risk of postpartum hemorrhage and toxemia. When combined with in vitro fertilization, pre-

implantation genetic diagnosis is becoming accessible. [91]

TREATMENT

6.1 Blood transfusion

People with BTM need frequent blood transfusions throughout their lifetimes to sustain a normal development and hemoglobin concentrations higher than 9.5 g per dL (95 g per L). The need for blood transfusions may arise as early as six months of age. For those with BTI, the decision to transfuse is a more personalized clinical judgment. [92,93,94] An individual may require episodic transfusions if their hemoglobin levels are insufficient for a healthy life. [95] Alpha thalassemia intermedia, another name for HbH illness, is characterized by light to serious hemolysis. Sometimes transfusions are necessary, depending on how severe the clinical situation is. [96]

6.2 Chelation

Patients who are transfusion-dependent experience iron overload because their bodies are unable to eliminate excess iron from repeated transfusions. [97] Because of this, they need to be treated with an iron chelator from the age of five to eight. The preferred treatment is deferoxamine (Desferal), administered intravenously or subcutaneously. [98] This therapy is costly and time-consuming, despite being comparatively nontoxic. The alternative treatment oral deferasirox (Exjade) was recently approved by FDA. [99] There were no reported cases of agranulocytosis, and deferasirox's side effects were gastrointestinal in nature and temporary. [100]

6.3 Stem Cell Therapy (SCT) and Gene Therapy

Stem cell therapy is still the only treatment option for TM, despite advancements in treatment that have improved survival and quality of life. [101] Even though 80–90% of patients who receive SCT from a related donor who shares the same human leukocyte antigen are disease-free and over 90% of them survive, there are still questions about how the potentially fatal but curative procedure can be used for adults, and patients with a matched unrelated donor. [102] The main drawback of SCT is that most affected patients (70–75%) do not have an HLA-identical sibling donor. [103] All thalassemia patients

may eventually be cured through gene therapy, which could solve the issue of donor availability.[104] Patients with beta-thalassemia are showing encouraging results from extensive clinical and molecular research on the treatment of thalassemia and the creation of targeted therapies (such as gene therapy, cell therapy, and reactivation of HbF production).[105] To manage this growing global health burden, however, efforts must continue to be made to establish universal health services that include screening, counseling, and prenatal diagnosis.[106]

6. Future Prospect

Informatics channels can be used to implement thalassemia education. As DNA analysis becomes more affordable, it may potentially be utilized as the initial screening method. [107] By employing microchip technology, which is intended to detect all recognized alpha- and beta-thalassems in addition to genetic variations that aid in phenotypic prediction, it is possible to circumvent the initial blood evaluation [108]. Technological developments in the methods of fetal DNA or fetal cell examination in mother's plasma may enable future clinical use of this important noninvasive approach. [109] The biggest difficulty for the coming years is the implementation of national prevention campaigns in areas like the Middle East, the Indian subcontinent, where thalassems are prevalent. [110] Many of the aforementioned problems currently impede the execution of such programs. [111]

CONCLUSION

Millions of people around the world suffer from thalassemia, a dangerous hereditary blood condition. Even though therapies like iron chelation and blood transfusions have helped patients, genetic counseling and carrier screening are still necessary for prevention. Hope for a cure is offered by developments like gene therapy and bone marrow transplantation. To lessen the effects of thalassemia and enhance the lives of those who are impacted, research, early diagnosis, and ongoing awareness are crucial. To ensure comprehensive care and eventually move toward the eradication of this preventable genetic disorder, cooperation between clinicians,

researchers, policymakers, and communities is essential

REFERENCE

1. Hartevelde CL, Higgs DR. α -thalassaemia. Orphanet journal of rare diseases. 2010 Dec; 5:1-21.
2. Conley CL, Charache S. Inherited hemoglobinopathies. Hospital Practice. 1969 Oct 1;4(10):35-43.
3. Meri MA, Al-Hakeem AH, Al-Abadi RS. An overview on thalassemia: A review article. Medical Science Journal for Advance Research. 2022 Mar 1;3(1):26-32.
4. Peixeiro I, Silva AL, Romão L. Control of human β -globin mRNA stability and its impact on beta-thalassemia phenotype. Haematologica. 2011 Feb 28;96(6):905.
5. Recht M. Thrombocytopenia and anemia in infants and children. Emergency Medicine Clinics. 2009 Aug 1;27(3):505-23.
6. Mattiello V, Schmutz M, Hengartner H, von der Weid N, Renella R, SPOG Pediatric Hematology Working Group. Diagnosis and management of iron deficiency in children with or without anemia: consensus recommendations of the SPOG Pediatric Hematology Working Group. European journal of pediatrics. 2020 Apr; 179:527-45.
7. Hughes ML. Mediterranean, Malta or undulant fever. Macmillan; 1897.
8. Marengo-Rowe AJ. The thalassems and related disorders. In Baylor university medical center proceedings 2007 Jan 1 (Vol. 20, No. 1, pp. 27-31). Taylor & Francis
9. Schechter AN. Hemoglobin research and the origins of molecular medicine. Blood, The Journal of the American Society of Hematology. 2008 Nov 15;112(10):3927-38.
10. Brancaloni V, Di Pierro E, Motta I, Cappellini MD. Laboratory diagnosis of thalassemia. International Journal of laboratory hematology. 2016 May; 38:32-40.
11. Songdej D, Fucharoen S. Alpha-thalassemia: diversity of clinical phenotypes and update on the treatment. Thalassemia Reports. 2022 Nov 22;12(4):157-72.
12. Dronamraju KR, Francomano CA, editors. Victor McKusick and the history of medical

- genetics. Springer Science & Business Media; 2012 Jun 8.
13. Cao A, Galanello R. Beta-thalassemia. Genetics in medicine. 2010 Feb 1;12(2):61-76.
 14. Weatherall DJ. The genetic control of protein synthesis: The haemoglobin model. Journal of Clinical Pathology. Supplement (Royal College of Pathologists). 1974; 8:1.
 15. Kacian DL, Gambino R, Dow LW, Grossbard E, Natta C, Ramirez F, Spiegelman S, Marks PA, Bank A. Decreased globin messenger RNA in thalassemia detected by molecular hybridization. Proceedings of the National Academy of Sciences. 1973 Jun;70(6):1886-90.
 16. Lodish HF, Jacobsen M. Regulation of hemoglobin synthesis: equal rates of translation and termination of α - and β -globin chains. Journal of Biological Chemistry. 1972 Jun 10;247(11):3622-9.
 17. Hardison RC. Evolution of hemoglobin and its genes. Cold Spring Harbor perspectives in medicine. 2012 Dec 1;2(12):a011627.
 18. Shafique F, Ali S, Almansouri T, Van Eeden F, Shafi N, Khalid M, Khawaja S, Andleeb S. Thalassemia, a human blood disorder. Brazilian Journal of Biology. 2021 Sep 3;83: e246062.
 19. De Sanctis V, Kattamis C, Canatan D, Soliman AT, Elsedfy H, Karimi M, Daar S, Wali Y, Yassin M, Soliman N, Sobti P. β -thalassemia distribution in the old world: an ancient disease seen from a historical standpoint. Mediterranean journal of hematology and infectious diseases. 2017 Feb 20;9(1): e2017018.
 20. Shegekar T, Pajai S. A comprehensive review of pregnancy in sickle cell disease. Cureus. 2023 Jun 30;15(6).
 21. Galanello R, Cao A. Alpha-thalassemia. Genetics in medicine. 2011 Feb;13(2):83-8.
 22. Randolph TR. Hemoglobinopathies (structural defects in hemoglobin). Rodak's Hematology-E-Book: Rodak's Hematology-E-Book. 2019 Feb 22:394.
 23. Qidwai T, Qidwai T. Alpha-Thalassemia. Exploration of Host Genetic Factors associated with Malaria. 2021:29-42.
 24. Tamary H, Dgany O. Alpha-thalassemia.
 25. Musallam KM, Lombard L, Kistler KD, Arregui M, Gilroy KS, Chamberlain C, Zagadailov E, Ruiz K, Taher AT. Epidemiology of clinically significant forms of alpha- and beta-thalassemia: a global map of evidence and gaps. American journal of hematology. 2023 Sep;98(9):1436-51.
 26. Farashi S, Hartevelde CL. Molecular basis of α -thalassemia. Blood Cells, Molecules, and Diseases. 2018 May 1; 70:43-53.
 27. Elbedour L. The mechanistic role of cytoadherence in thalassemia's protection against malaria. Journal of Pain Management. 2019 Apr 1;12(2):87-100.
 28. Aggarwal R, Prakash A, Aggarwal M. Thalassemia: an overview. Journal of the scientific society. 2014 Jan 1;41(1):3-6.
 29. Galanello R, Origa R. Beta-thalassemia. Orphanet journal of rare diseases. 2010 Dec; 5:1-5.
 30. Kan YW, Schwartz E, Nathan DG. Globin chain synthesis in the alpha thalassemia syndromes. The Journal of Clinical Investigation. 1968 Nov 1;47(11):2515-22.
 31. Muncie Jr HL, Campbell JS. Alpha and beta thalassemia. American family physician. 2009 Aug 15;80(4):339-44.
 32. Vamvakas EC, Taswell HF. Long-term survival after blood transfusion. Transfusion. 1994 Jun;34(6):471-7
 33. Origa R. Beta-thalassemia.
 34. Israeli E, Bernstein CN. Gastrointestinal manifestations of systemic diseases. Yamada's Textbook of Gastroenterology. 2015 Nov 27:2399-439.
 35. Jagadisha S. Study of Cardiovascular Complications in β -Thalassemia Major Patients Attending a Tertiary Care Hospital (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).
 36. Basu I, Perry M. Initial Assessment of the "Head and Neck" Patient. In Diseases and Injuries to the Head, Face and Neck: A Guide to Diagnosis and Management 2021 Feb 17 (pp. 57-134). Cham: Springer International Publishing.
 37. Shander A, Cappellini MD, Goodnough LT. Iron overload and toxicity: the hidden risk of multiple blood transfusions. Vox sanguinis. 2009 Oct;97(3):185-97.

38. Tenuta M, Cangiano B, Rastrelli G, Carlomagno F, Sciarra F, Sansone A, Isidori AM, Gianfrilli D, Krausz C. Iron overload disorders: Growth and gonadal dysfunction in childhood and adolescence. *Pediatric Blood & Cancer*. 2024 Jul;71(7):e30995.
39. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. *Journal of cardiac failure*. 2010 Nov 1;16(11):888-900.
40. Schifter M, McLean M, Sukumar S. Disorders of the endocrine system and of metabolism. *Burket's Oral Medicine*. 2021 Aug 30:817-902.
41. Songtanin B, Chairimaneepan N, Mendóza R, Nugent K. Burden, outcome, and comorbidities of extrahepatic manifestations in hepatitis B virus infections. *Viruses*. 2024 Apr 16;16(4):618.
42. Kew MC. Hepatic iron overload and hepatocellular carcinoma. *Liver cancer*. 2014 Mar 4;3(1):31-40.
43. Entezari S, Haghi SM, Norouzkhani N, Saheb nazari B, Vosoughian F, Akbarzadeh D, Islampanah M, Naghsh N, Abbasalizadeh M, Deravi N. Iron chelators in treatment of iron overload. *Journal of Toxicology*. 2022;2022(1):4911205.
44. Vamvakas EC, Taswell HF. Long-term survival after blood transfusion. *Transfusion*. 1994 Jun;34(6):471-7.
45. Shander A, Sazama K. Clinical consequences of iron overload from chronic red blood cell transfusions, its diagnosis, and its management by chelation therapy. *Transfusion*. 2010 May;50(5):1144-55.
46. Koochi F, Kazemi T, Miri-Moghaddam E. Cardiac complications and iron overload in beta thalassemia major patients—a systematic review and meta-analysis. *Annals of hematology*. 2019 Jun 1; 98:1323-31.
47. Yadav PK, Singh AK. A review of iron overload in beta-thalassemia major, and a discussion on alternative potent iron chelation targets. *Plasmatology*. 2022 May; 16:26348535221103560.
48. Rachmilewitz EA, Giardina PJ. How I treat thalassemia. *Blood, The Journal of the American Society of Hematology*. 2011 Sep 29;118(13):3479-88.
49. Tefferi A. Anemia in adults: a contemporary approach to diagnosis. In *Mayo Clinic Proceedings* 2003 Oct 1 (Vol. 78, No. 10, pp. 1274-1280). Elsevier.
50. Al-Taki M, Nahle IS. Bones and Fractures. In *Hamilton Bailey's Physical Signs* 2016 Jan 7 (pp. 147-165). CRC Press.
51. Suttorp M, Classen CF. Splenomegaly in children and adolescents. *Frontiers in pediatrics*. 2021 Jul 9; 9:704635.
52. Sorsdahl OS, Taylor PE, Noyes WD. Extramedullary hematopoiesis, mediastinal masses, and spinal cord compression. *Jama*. 1964 Aug 3;189(5):343-7.
53. Borgna-Pignatti C, Gamberini MR. Complications of thalassemia major and their treatment. *Expert review of hematology*. 2011 Jun 1;4(3):353-66.
54. Taher A, Isma'eel H, Cappellini MD. Thalassemia intermedia: revisited. *Blood Cells, Molecules, and Diseases*. 2006 Jul 1;37(1):12-20.
55. Sankar V, Villa A. Hematologic diseases. *Burket's Oral Medicine*. 2021 Aug 30:627-64.
56. Origa R, Comitini F. Pregnancy in thalassemia. *Mediterranean journal of hematology and infectious diseases*. 2019 Mar 1;11(1): e2019019.
57. British Committee for Standards in Haematology, Milkins C, Berryman J, Cantwell C, Elliott C, Haggas R, Jones J, Rowley M, Williams M, Win N. Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories. *Transfusion Medicine*. 2013 Feb;23(1):3-5.
58. Warshaw JB. Intrauterine growth retardation. *Pediatrics in review*. 1986 Oct 1;8(4):107-14.
59. Aessopos A, Kati M, Farmakis D. Heart disease in thalassemia intermedia: a review of the underlying pathophysiology. *Haematologica*. 2007 May 1;92(5):658-65.
60. Baccarani-Contri M, Bacchelli B, Boraldi F, Quaglini D, Taparelli F, Carnevalia E, Francomano MA, Seidenari S, Bettoli V, De Sanctis V, Pasquali-Ronchetti I. Characterization of pseudoxanthoma elasticum-like lesions in the skin of patients with β -thalassemia. *Journal of the American*

- Academy of Dermatology. 2001 Jan 1;44(1):33-9.
61. Colaco S, Nadkarni A. Borderline HbA2 levels: dilemma in diagnosis of beta-thalassemia carriers. *Mutation Research/Reviews in Mutation Research*. 2021 Jul 1; 788:108387.
 62. Sankar V, Villa A. Hematologic diseases. *Burket's Oral Medicine*. 2021 Aug 30:627-64.
 63. Fasano RM, Meier ER, Chonat S. Sickle cell disease, thalassemia, and hereditary hemolytic anemias. *Rossi's Principles of Transfusion Medicine*. 2022 Aug 23:326-45.
 64. Doshi HU. Anemia in Pregnancy. *Clinical Cases in Obstetrics & Gynecology*. 2021 Oct 30;1.
 65. Aswathi P, Anjana SR, Somesh Kumar R, Suravajhala P, Polipalli SK. Ascertaining Genetics of Beta-Thalassemia and Sickle Cell Disease using Molecular Techniques and Machine Learning Heuristics.
 66. Meri MA, Al-Hakeem AH, Al-Abeadi RS. An overview on thalassemia: A review article. *Medical Science Journal for Advance Research*. 2022 Mar 1;3(1):26-32.
 67. Josephson AM. Genetic disorders of hemoglobin formation. *Medical Clinics of North America*. 1962 Jan 1;46(1):151-63.
 68. McLintock C, Repke JT, Bucklin B. Hematologic disease in pregnancy. *de Swiet's Medical Disorders in Obstetric Practice*. 2010 Jul 6:61-3.
 69. Olivieri NF, Pakbaz Z, Vichinsky E. Hb E/beta-thalassaemia: a common & clinically diverse disorder. *Indian Journal of Medical Research*. 2011 Oct 1;134(4):522-31.
 70. Mehta V, Kirubarajan A, Sabouhanian A, Jayawardena SM, Chandrakumaran P, Thangavelu N, Cader R, Mettananda S, Bandara D, Khan S, Weatherall DJ. Leg ulcers: A report in patients with hemoglobin e beta thalassemia and review of the literature in severe beta thalassemia. *Acta haematologica*. 2022 May 30;145(3):334-43.
 71. Langer AL. Beta-thalassemia.
 72. Thein SL. Genetic modifiers of beta-thalassemia. *Haematologica*. 2005 Jan 1;90(5):649-60.
 73. Beutler ER, Lichtman M, Collier B, Kipps T. Hemoglobinopathies associated with unstable hemoglobin. *Williams Hematology* (5th ed), edited by. Beutler E, Lichtman MA, Collier BS, Kipps TJ. New York, McGraw-Hill. 1995:650-4.
 74. Sankar V, Villa A. Hematologic diseases. *Burket's Oral Medicine*. 2021 Aug 30:627-64.
 75. Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. *New England Journal of Medicine*. 1993 Dec 2;329(23):1691-5.
 76. Baird DC, Batten SH, Sparks SK. Alpha-and beta-thalassemia: rapid evidence reviews. *American family physician*. 2022 Mar;105(3):272-80.
 77. Brissot P, Ropert M, Le Lan C, Loréal O. Non-transferrin bound iron: a key role in iron overload and iron toxicity. *Biochimica et Biophysica Acta (BBA)-General Subjects*. 2012 Mar 1;1820(3):403-10.
 78. Dixon SJ, Stockwell BR. The role of iron and reactive oxygen species in cell death. *Nature chemical biology*. 2014 Jan;10(1):9-17.
 79. Fibach E, Rachmilewitz EA. The role of antioxidants and iron chelators in the treatment of oxidative stress in thalassemia. *Annals of the New York Academy of Sciences*. 2010 Aug;1202(1):10-6.
 80. Bruzzese A, Martino EA, Mendicino F, Lucia E, Olivito V, Bova C, Filippelli G, Capodanno I, Neri A, Morabito F, Gentile M. Iron chelation therapy. *European Journal of Haematology*. 2023 May;110(5):490-7.
 81. Saliba A, Taher A. Iron overload in transfusion-dependent thalassemia. *Hematology*. 2015 Jun 1;20(5):311-2.
 82. Prathyusha K, Venkataswamy M, Goud KS, Ramanjaneyulu K, Himabindu J, Raj KS. Thalassemia-A blood disorder, its cause, prevention and management. *Research Journal of Pharmaceutical Dosage Forms and Technology*. 2019;11(3):186-90.
 83. Adamopoulos SG, Petrocheilou GM. Skeletal radiological findings in thalassemia major. *Journal of Frailty, Sarcopenia & Falls*. 2020 Sep 1;4(3).
 84. Robertson JL, Newman SJ. Disorders of the spleen. *Schalm's Veterinary Hematology*. 2000:272.1

85. Muthiadin C. Premarital screening and probabilities of genetic disease in premarital screening and probability of genetic diseases in couples preparing for marriage. *Tropical Genetics*. 2023 May 31;3(1):20-5
86. Lucas AO, Stoll BJ, Bale JR, editors. Improving birth outcomes: meeting the challenge in the developing world.
87. Traeger-Synodinos J, Hartevelde CL. Preconception carrier screening and prenatal diagnosis in thalassemia and hemoglobinopathies: challenges and future perspectives. *Expert review of molecular diagnostics*. 2017 Mar 4;17(3):281-91.
88. Dhallan R, Guo X, Emche S, Damewood M, Bayliss P, Cronin M, Barry J, Betz J, Franz K, Gold K, Vallecillo B. A non-invasive test for prenatal diagnosis based on fetal DNA present in maternal blood: a preliminary study. *The Lancet*. 2007 Feb 10;369(9560):474-81.
89. Weatherall D, Akinyanju O, Fucharoen S, Olivieri N, Musgrove P. Inherited disorders of hemoglobin. *Disease Control Priorities in Developing Countries*. 2nd edition. 2006.
90. Zahed R. Effective Utilization of Molecular Genetic Screening of Patients with Sickle Cell Disease and Beta Thalassemia Major in Saudi Arabia (Doctoral dissertation, University of Sheffield).
91. Deka D, Saxena R, Panigrahi I. Hemoglobinopathies in Pregnancy. *Obstetrics & Gynecology For Pgs Vol 1 (3 Edn)*. 2009:212.
92. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *New England Journal of Medicine*. 2006 Nov 16;355(20):2071-84.
93. Prathyusha K, Venkataswamy M, Goud KS, Ramanjaneyulu K, Himabindu J, Raj KS. Thalassemia-A blood disorder, its cause, prevention and management. *Research Journal of Pharmaceutical Dosage Forms and Technology*. 2019;11(3):186-90.
94. Lal A, Wong T, Keel S, Pagano M, Chung J, Kamdar A, Rao L, Ikeda A, Puthenveetil G, Shah S, Yu J. The transfusion management of beta thalassemia in the United States. *Transfusion*. 2021 Aug 28;61(10):3027.
95. Dugdale M. Anemia. *Obstetrics and gynecology clinics of North America*. 2001 Jun 1;28(2):363-82.
96. Fasano RM, Meier ER, Chonat S. Sickle cell disease, thalassemia, and hereditary hemolytic anemias. *Rossi's Principles of Transfusion Medicine*. 2022 Aug 23:326-45.
97. Ozment CP, Turi JL. Iron overload following red blood cell transfusion and its impact on disease severity. *Biochimica et Biophysica Acta (BBA)-General Subjects*. 2009 Jul 1;1790(7):694-701.
98. Irshad T. The social meanings and implications of the Beta-thalassaemia trait among South Asian women in England.
99. Gaál A. A COMPLEX STUDY ON ANTICANCER COPPER CHELATORS (Doctoral dissertation).
100. Stumpf JL. Deferasirox. *American Journal of Health-System Pharmacy*. 2007 Mar 15;64(6):606-16.
101. Hussen BM, Taheri M, Yashooa RK, Abdullah GH, Abdullah SR, Kheder RK, Mustafa SA. Revolutionizing medicine: recent developments and future prospects in stem-cell therapy. *International Journal of Surgery*. 2024 Dec 1;110(12):8002-24.
102. Sharma SK. Stem Cell Transplant for Hemoglobinopathies. *InBasics of Hematopoietic Stem Cell Transplant 2023* Jul 21 (pp. 443-478). Singapore: Springer Nature Singapore.
103. Symons HJ, Fuchs EJ. Hematopoietic SCT from partially HLA-mismatched (HLA-haploidentical) related donors. *Bone marrow transplantation*. 2008 Sep;42(6):365-77.
104. Thompson AA, Walters MC, Kwiatkowski J, Rasko JE, Ribeil JA, Hongeng S, Magrin E, Schiller GJ, Payen E, Semeraro M, Moshous D. Gene therapy in patients with transfusion-dependent β -thalassemia. *New England Journal of Medicine*. 2018 Apr 19;378(16):1479-93.
105. Karponi G, Zogas N. Gene therapy for beta-thalassemia: updated perspectives. *The application of clinical genetics*. 2019 Sep 23:167-80.
106. Bloom DE, Khoury A, Subbaraman R. The promise and peril of universal health care. *Science*. 2018 Aug 24;361(6404):eaat9644.

107. Agarwal RK, Sedai A, Ankita K, Parmar L, Dhanya R, Dhimal S, Srinivas R, Gowda A, Gujjal P, Jain S, Ramaiah JD. Information technology–assisted treatment planning and performance assessment for severe thalassemia care in low-and middle-income countries: Observational study. *JMIR Medical Informatics*. 2019 Jan 23;7(1): e9291.
108. Kumar A. Molecular Diagnosis of Beta Thalassemia.
109. Wright CF, Burton H. The use of cell-free fetal nucleic acids in maternal blood for non-invasive prenatal diagnosis. *Human reproduction update*. 2009 Jan 1;15(1):139-51.
110. Colah R, Gorakshakar A, Nadkarni A. Global burden, distribution and prevention of β -thalassemias and hemoglobin E disorders. *Expert Review of Hematology*. 2010 Feb 1;3(1):103-17
111. Taut SM, Alkin MC. Program staff perceptions of barriers to evaluation implementation. *American Journal of Evaluation*. 2003 Jun;24(2):213-26.

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