IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

An Overview On Thalassemia

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Abstract: Thalassemia, which means "sea," and haema, which means "of blood," are the Greek terms from which thalassemia is derived. Globally an estimated 300-400 thousand infants are born each year with significant hereditary haemoglobin disorders, and about 80 million are beta- thalassemia carriers. As per the 2011 Census of India , the average prevalence of b-thalassemia trait in India is 3-4%, meaning that there are 42 million carriers out of 1.21 billion persons. Population screening has revealed a greater frequency of carrier status in some populations, including tribal groups in Odisha and Gujarat, as well as Sindhis, Punjabis, Gujaratis, Bengalis, Mahars, Kolis, and Lohanas .Hemoglobin E (Hb E) is another type of thalassemia. A missense mutation at codon 26 is the cause of Hb E thalassemia. Co-inheritance of thalassemia and Hb E is prevalent in countries like southeast Asia, India and Bangladesh. Patients with Hb E or beta thalassemia have higher risk of pulmonary hypertension or vitamin D deficiency.

Hemoglobin H can induce chronic hypochromic microcytic anemia and hemolytic anemia, which can exacerbate during times of oxidative stress. This can be successfully broken down into inefficient erythropoiesis and enhanced hemolysis. Microcytic hypochromic anemia is caused by diminished alpha chain synthesis and cell hyperhydration, which impairs hemoglobin production. It is unclear what causes hyperhydration in alpha thalassemia. According to one explanation, the K-Cl cotransporter stops early, preventing the regular loss of K-Cl and water during red blood cell remodeling.

Patients with non-transfusion-dependent thalassemia are individuals who, under specific conditions, such as pregnancy, surgery, or infection, occasionally need a red blood transfusion. Patients with hemoglobin H illness and certain cases of hemoglobin E/β-thalassemia, as well as those with moderately severe thalassemia, are included in the NTDT group. Previous research has shown that patients with thalassemia experience a number of disease-related complications.

Thalassemia treatment depends on the type and severity of the disease. The sort of treatment a person receives is determined by the severity of their thalassemia. The more severe the thalassemia, the less hemoglobin the body has, which can lead to severe anemia.

These article is given for the awareness of thalassemia.

***Index Terms*:** beta-thalassemia, Haemoglobin, hypochromic microcytic anaemia, hemolytic anaemia, erythropoiesis, hyperhydration, NTDT group.

INTRODUCTION

Thalassemia, which means "sea," and haema, which means "of blood," are the Greek terms from which thalassemia is derived.[1]

A varied collection of genetic illnesses known as thalassemias are caused by a reduction in the production of either the alpha or beta chains of hemoglobin (Hb). The oxygen-carrying protein in red blood cells is called hemoglobin. There are two proteins in it: an alpha and a beta. [2]

• **Alpha thalassemia:** One of the most prevalent hemoglobin genetic disorders, alpha-thalassemia is brought on by either decreased or nonexistent alpha globin chain synthesis.
On a molecular and clinical level, alpha-thalassemia is highly variable. It is known that there are four clinical disorders of higher severity: hemoglobin Bart hydrops fetalis syndrome, which is fatal in utero or shortly after birth; alpha-thalassemia trait; silent carrier state; and the intermediate type of hemoglobin H sickness. [3]

• **Beta thalassemia:** A genetic defect in the synthesis of beta-globin chains characterizes the beta thalassemia syndromes, a group of inherited illnesses. When a person has homozygous beta thalassemia, also known as thalassemia major, they experience severe anemia that requires transfusions. The beta thalassemia trait, or thalassemia minor, results in mild to severe microcytic anemia in the heterozygous form.
The beta thalassemia category of illnesses includes hemoglobin (Hb) E, a frequent variation of Hb found in Southeast Asia that is linked to a beta thalassemia phenotype. [4]

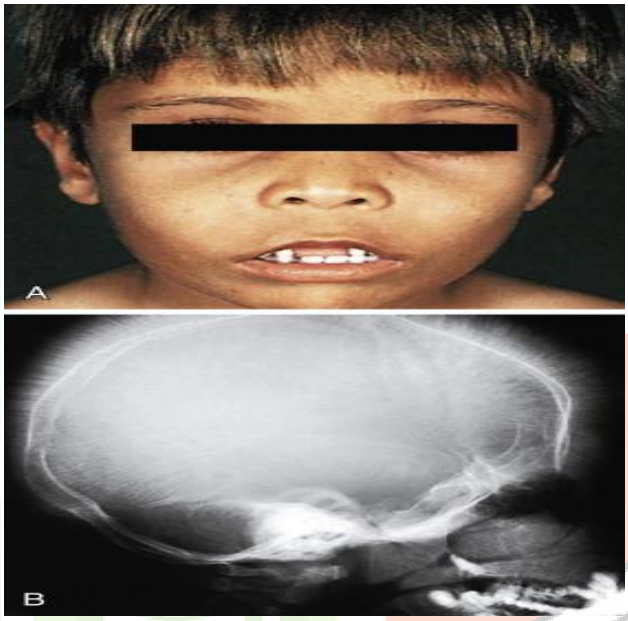


Fig.1: beta thalassemia- an overview [5]

However, today thalassemia is also prevalent in many countries where it was not recognized before, such as Northern Europe, North Central and South America, and Australia, perhaps due to an improved and fast transport system with immense population migration. [6]
It is unknown how many patients are impacted. In many other nations, children die from the more severe transfusion-dependent disorders before they are even diagnosed, and very few countries keep a patient register. [7]

EPIDEMIOLOGY

Globally an estimated 300-400 thousand infants are born each year with significant hereditary haemoglobin disorders, and about 80 million are beta- thalassemia carriers. Three thalassemic clinical states have been recognised, with the disease intensity increasing with time. These three conditions are thalassemia major, thalassemia intermedia and beta thalassemia carrier status.
The population with thalassemia carrier status varies from country to country. It is approximately 6-12 % of the population in Bangladesh, approximately 6.8-12.8 % of the population in Malaysia, and about 40 % of the population in Thailand. Multiple studies reported that nearly 23,000 as thalassemia major and 90 % of these children are born in low or middle-income countries (LMICs). [8]

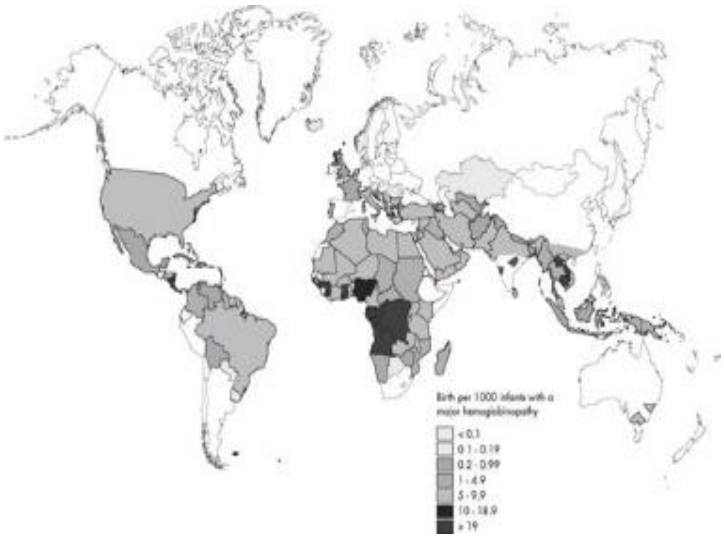


fig.2: global prevalence of thalassemia [9]

As per the 2011 Census of India, the average prevalence of b-thalassemia trait in India is 3-4%, meaning that there are 42 million carriers out of 1.21 billion persons. Population screening has revealed a greater frequency of carrier status in some populations, including tribal groups in Odisha and Gujarat, as well as Sindhis, Punjabis, Gujaratis, Bengalis, Mahars, Kolis, and Lohanas . The precise number of b-thalassemia characteristics is still unknown, though. B-thalassemia cases have been reported in all states of India; however, the eastern and western portions of the nation are the most impacted. The disease's frequency varies throughout the cities in each state and occasionally even within a single city, as in the cases of Kolkata, Chennai, and Indore.[10]

India has a high incidence of hemoglobinopathies, with thalassemia being the most common. In Central India, β-thal trait was found in 1.4% to 3.4% of the population, and 0.94% of anaemia patients had β-TM. The frequency of β-thal trait ranged from 8.50 to 37.90% in South India, while β-TM was found to be between 2.30 and 7.47%. The thalassemic load was higher in the states of Northern and Western India. The prevalence of β-thal trait (0.00-30.50%), β-TM (0.36-13.20%), and other hemoglobinopathies [Hb E (HBB: c.79G>A)/β-thal] (0.04-15.45%) was greater in tribal groups in Eastern India than in nontribal populations. β-thal also had an impact on other backward strata with low socioeconomic position and low literacy rates, such as scheduled tribes and castes.

While β-thal has been detected in almost every state in India, it is primarily found in the eastern and western regions of the nation. β-thal was found in almost all Indian states, with a higher concentration in the east and west. [11]

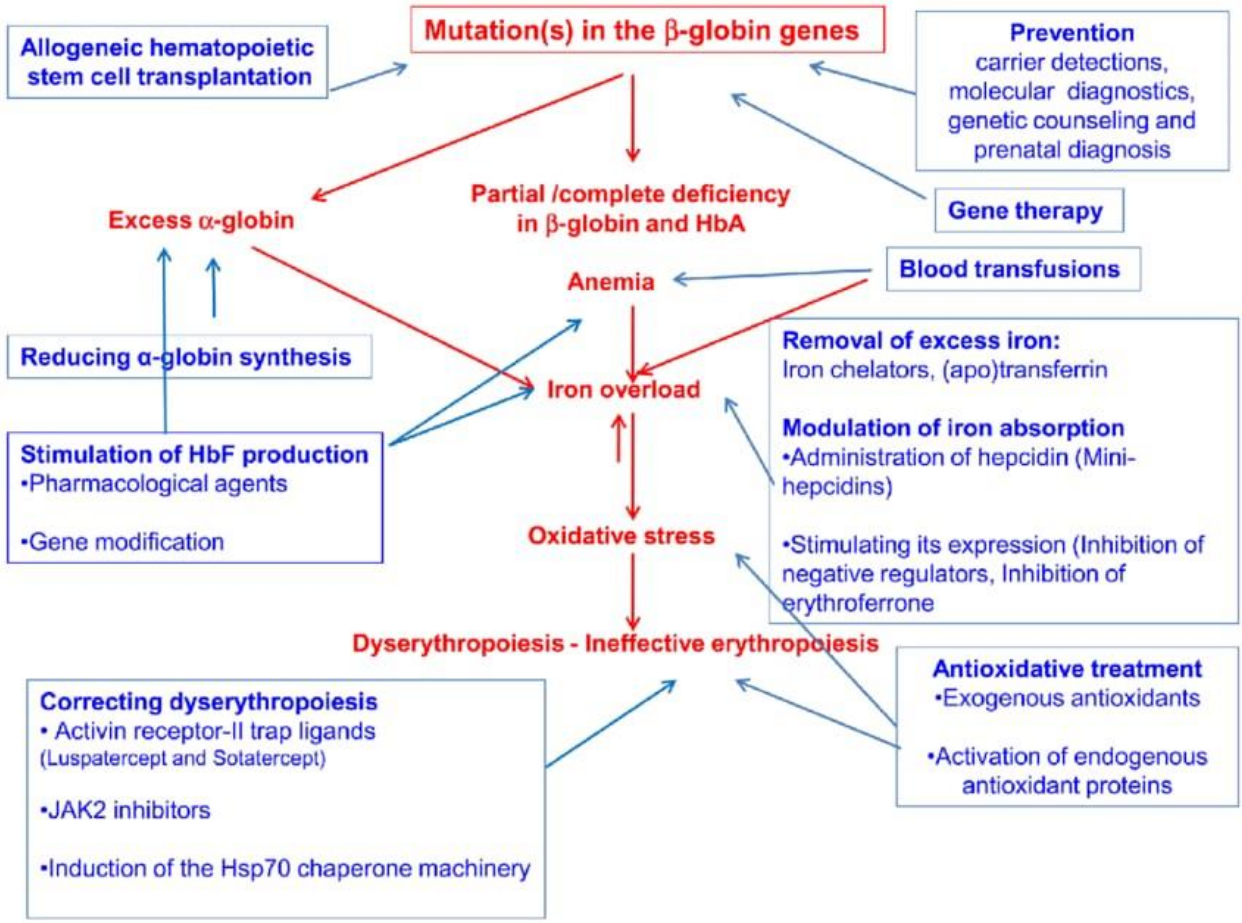


fig.3: beta thalassemia: epidemiology [12]

The prevalence of β-thal trait in Central India ranged between 1.4 and 3.4%, while 0.94% β-TM was reported among the patients with anemia. In South India, the prevalence of β-thal trait was between 8.50 and 37.90% and β-TM was reported to be between 2.30 and 7.47%. Northern and Western Indian states had a higher thalassemic burden. In Eastern India, tribal populations had a higher prevalence of β-thal trait (0.00-30.50%), β-TM (0.36-13.20%) and other hemoglobinopathies [Hb E (HBB: c.79G>A)/β-thal] (0.04-15.45%) than nontribal populations. [13]

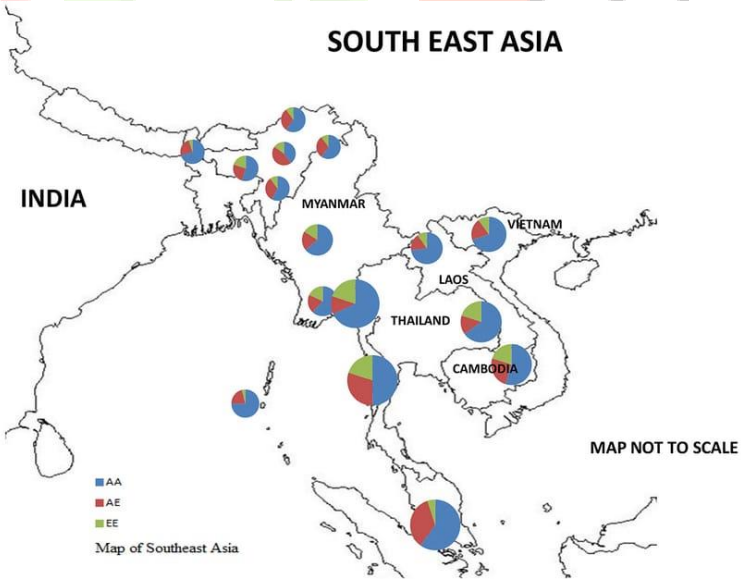


fig.4:- thalassemia distribution in southeast asia[14]

ETIOLOGY

Mutations in the DNA of the cells that produce hemoglobin, the component of red blood cells that transport oxygen throughout your body, are the cause of thalassemia. Children inherit the thalassemia-related mutations from their parents.

The alpha and beta chains that make up hemoglobin molecules are affected by mutation. Alpha or beta thalassemia can be caused by a reduction in the production of either the alpha or beta chains in thalassemia.
The quantity of gene mutations you receive from your parents determine the severity of your alpha thalassemia. Thalassemia will be more severe if you have more mutated genes.
Level of beta thalassemia severity is determined by the specific part of the hemoglobin molecule that is impacted. [15]

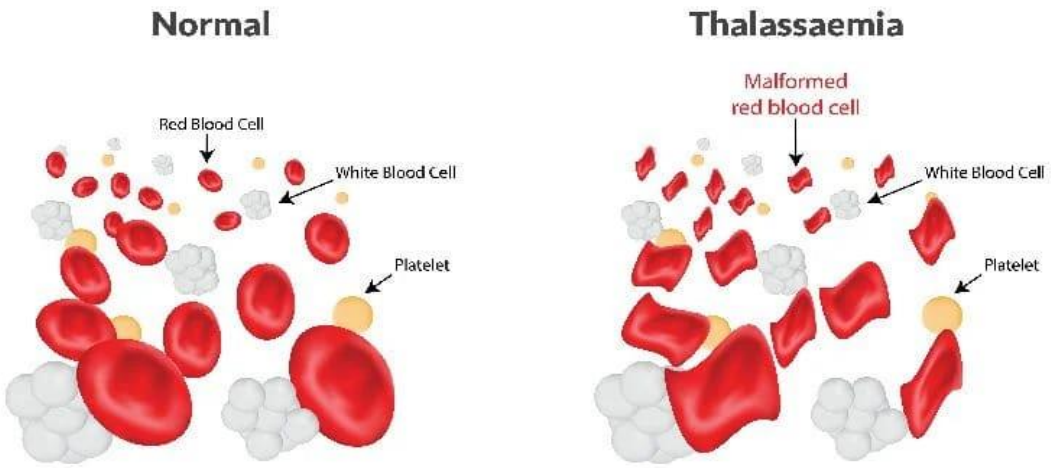


Fig.5: - causes of thalassemia [16]

Reduced synthesis of at least one globin polypeptide chain (beta, alpha, gamma, or delta) causes thalassemia, which leads to imbalanced production of haemoglobin. Thalassemia is inherited in an autosomal recessive manner.
Defect in three of four genes severely restrict the creation of alpha-chains, leading to the formation of tetramers of gamma chains (Bart's Hb) or excess beta chains (HbH) during infancy.
Defects in all four genes are fatal if a child is not given blood transfusions while still in the womb. This is because alpha-chain-deficient hemoglobin is unable to carry oxygen.
Hemoglobin E (Hb E) is another type of thalassemia. A missense mutation at codon 26 is the cause of Hb E thalassemia. Co-inheritance of thalassemia and Hb E is prevalent in countries like southeast Asia, India and Bangladesh.
Patients with Hb E or beta thalassemia have higher risk of pulmonary hypertension or vitamin D deficiency. [17]

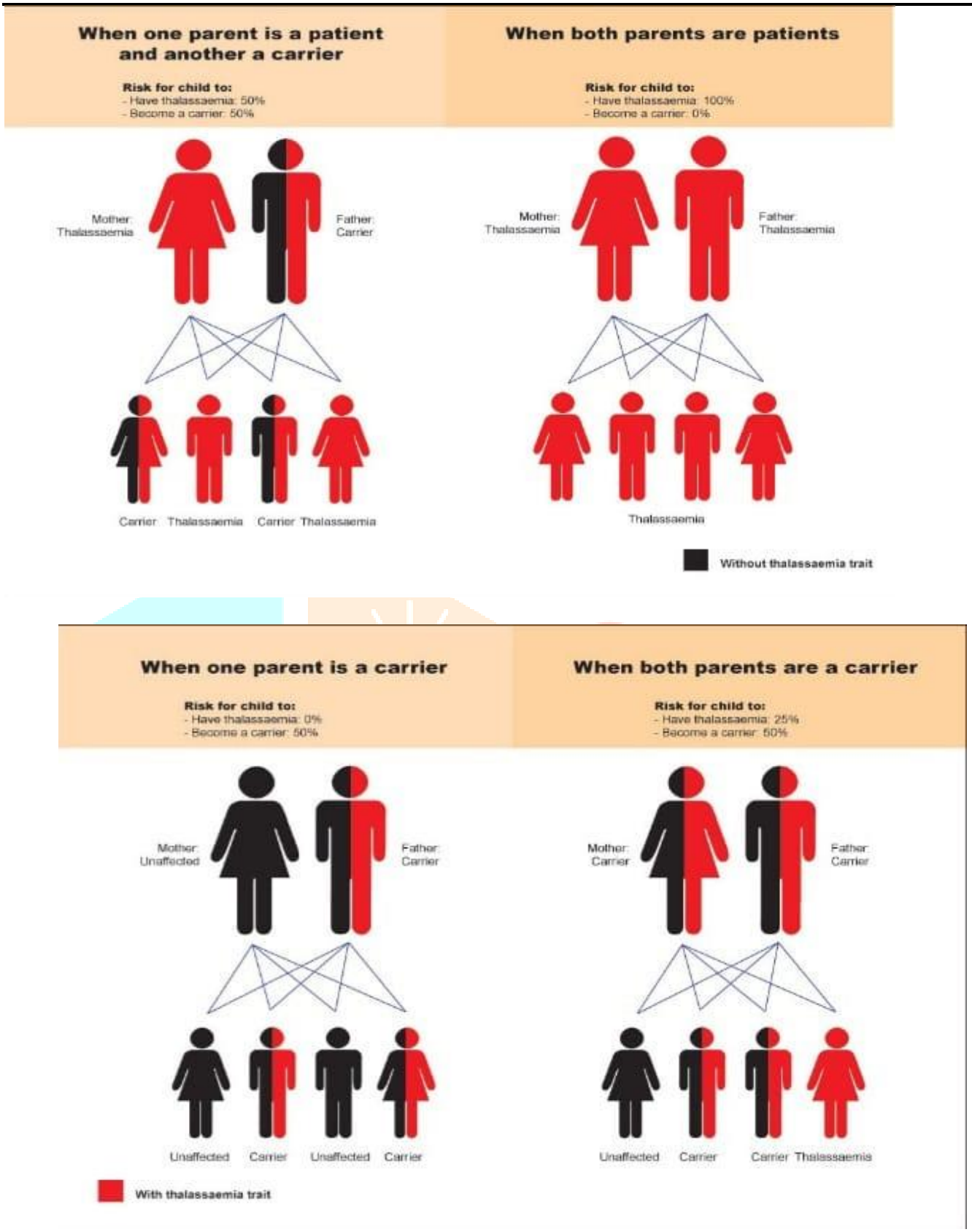


fig.6 :- causes of thalassemia in patient.[18]

PATHOPHYSIOLOGY

Mutations in the DNA of the cells that produce hemoglobin result in thalassemia, a blood illness. Patients may experience symptoms like weariness as a result of this, which lowers the quantity and capacity of red blood cells to transport oxygen throughout the body. [19]Hemoglobin H can induce chronic hypochromic microcytic anemia and hemolytic anemia, which can exacerbate during times of oxidative stress. This can be successfully broken down into inefficient erythropoiesis and enhanced hemolysis. Microcytic hypochromic anemia is caused by diminished alpha chain synthesis and cell hyperhydration, which impairs hemoglobin production. It is unclear what causes hyperhydration in alpha thalassemia. According to one explanation, the

K-Cl cotransporter stops early, preventing the regular loss of K-Cl and water during red blood cell remodeling. [20]

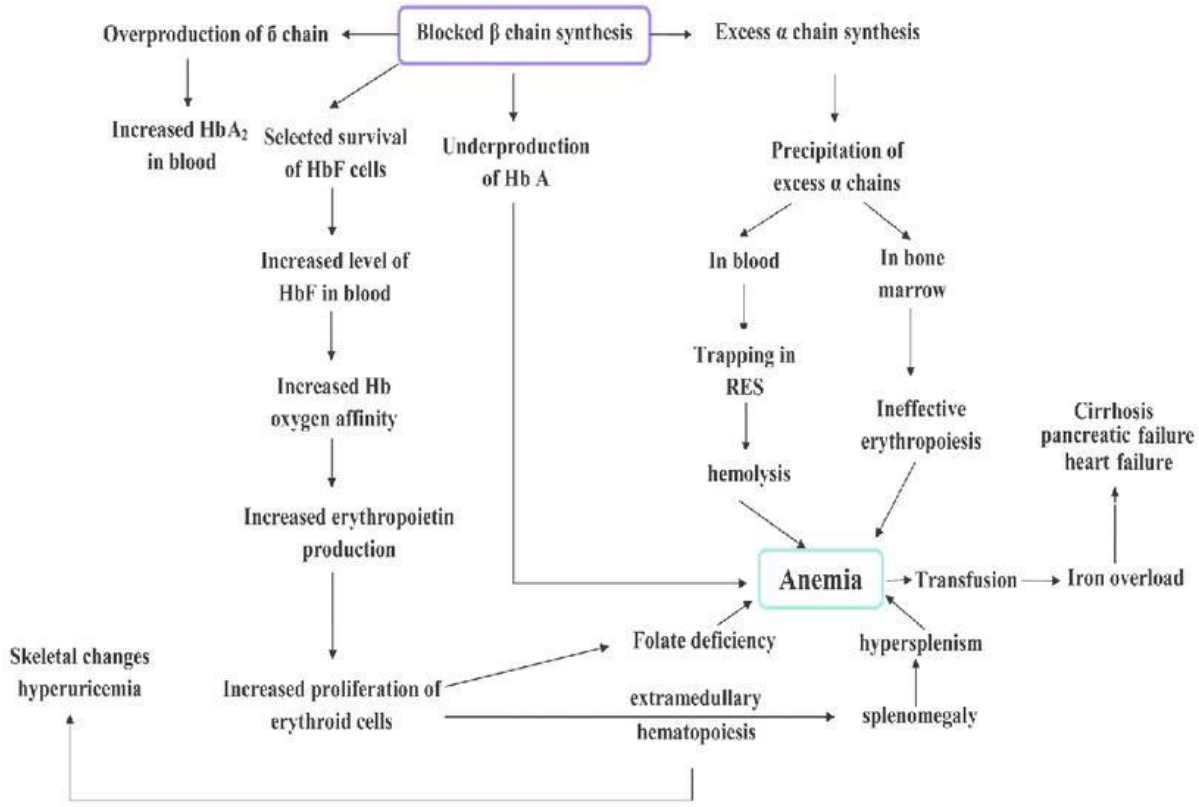


fig.7: - pathophysiology of thalassemia [21]

ALPHA THALASSEMIA

Genes that control the synthesis and structure of various globins are arranged into two distinct clusters. The alpha-globin genes are located on chromosome 16, while the gamma-, delta-, and beta-globin genes are on chromosome 11. Healthy people have four alpha-globin genes, two on each chromosome 16 (αα/αα; see image below). Alpha thalassemia syndromes are caused by a lack of expression of one or more of the four alpha-globin genes on chromosome 16, and are distinguished by the absence or diminished synthesis of alpha-globin chains.

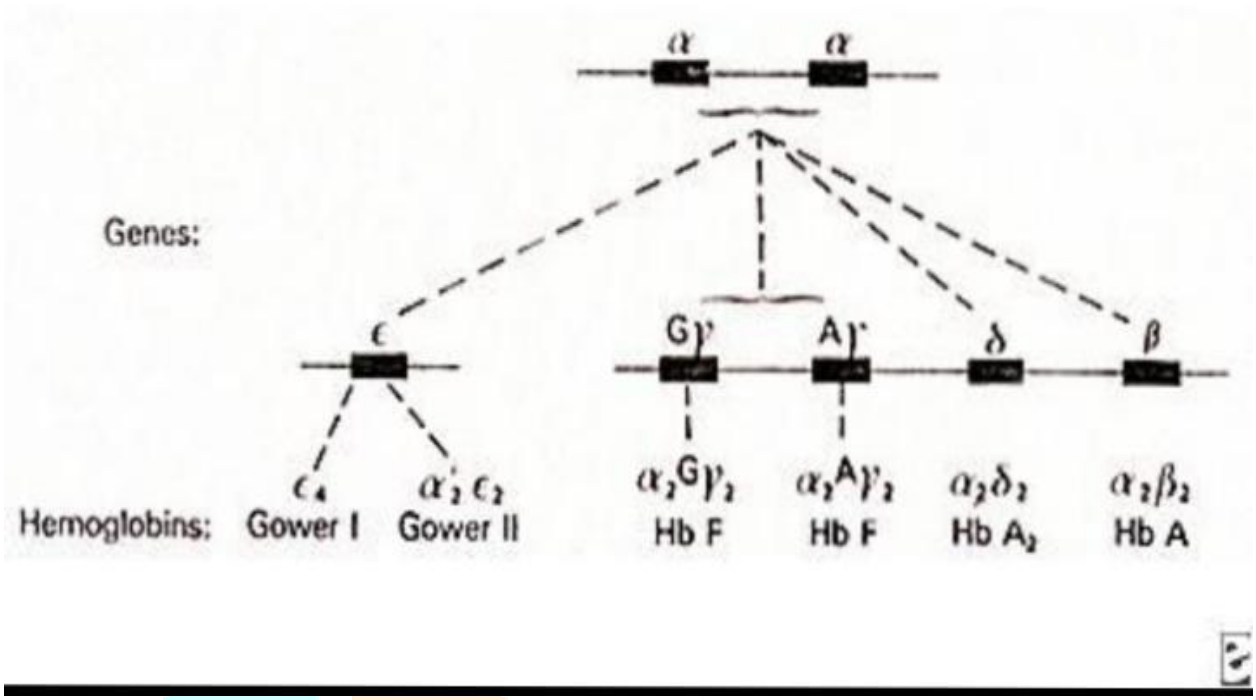


fig .8 :- alpha -thalassemia: pathophysiology [22]

Alpha-thalassemia is caused by the genes HBA1 and HBA2, which are inherited in a Mendelian recessive pattern. Two gene loci
and four alleles exist. It is also associated with the deletion of 16p chromosomal αThalassemia reduces alpha-globin production, leading to an overabundance of ɣ chains in infants. Excess β chains generate unstable tetramers, known as hemoglobin H (HbH of 4 β chains), with aberrant oxygen dissociation curves. [23]

BETA THALASSEMIA

Beta-thalassemia results from an inadequate synthesis of beta-hemoglobin chains and an excess of alpha chains. Two genes on chromosome 11 are required to make the beta portion of the hemoglobin chain, and each is inherited from one parent. The number of gene mutations correlates with the severity of the condition as follows:

• One gene mutation causes minimal indications or symptoms, known as beta-thalassemia minor or alpha-thalassemia trait.

• Two gene mutations cause moderate to severe symptoms known as beta-thalassemia major or Cooley's anemia.[24]

The β-thalassemia trait results in a twofold increase in α-globin synthesis, indicating normal hematopoiesis with mild microcytosis and hypochromia of red cells. Individuals with thalassemia intermedia often have an α to non-α biosynthetic ratio of 3-4/1. This is due to residual capacity for β-globin synthesis and fluctuating γ-globin synthesis, which mitigates the effects of excess α-globin production. Individuals with β0-thalassemia mutations have severe symptoms due to a significant imbalance in chain biosynthesis.

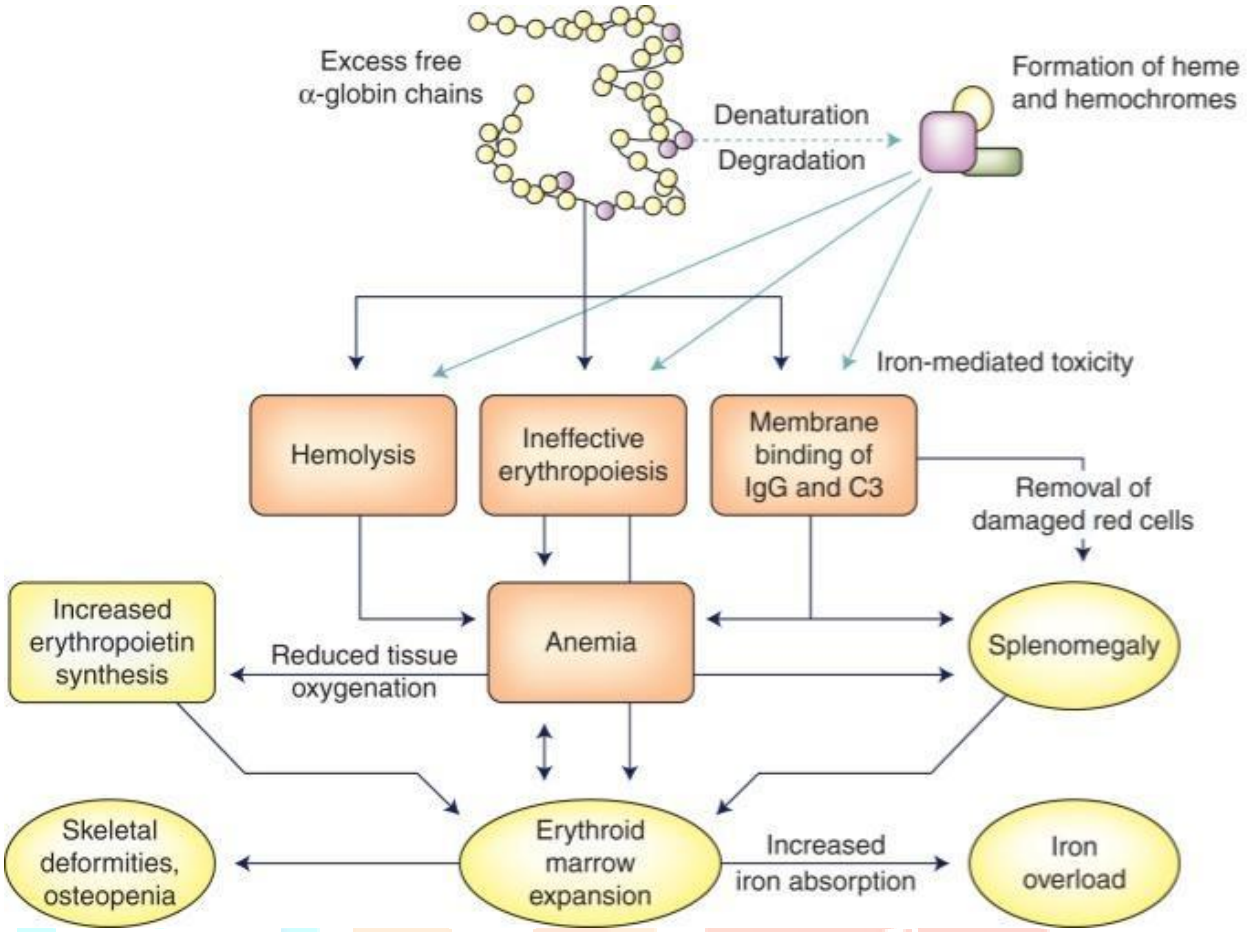


fig.9: - pathophysiology of beta-thalassemia [25]

SIGNS AND SYMPTOMS

• Iron overload:

Regular blood transfusion causes iron overload in the patient, which is one of the most frequent thalassemia-related problems. Excess iron can harm the liver, heart, and endocrine system.

• Enlargement of slpeen:

In addition to becoming accidental as a result of problems with blood flow and liver failures, spleen enlargement has numerous infectious, viral, and bacterial origins. The liver will crush the spleen when it gets inflamed. One of the illnesses that causes spleen enlargement is thalassemia. [26]

• defects in the face's bones
• Fatigue Failure to Grow
• Breathlessness
• Pale skin tone, or jaundice
• Small red blood cells are the only sign of alpha and beta thalassemia minor patients, who do not exhibit any symptoms.[27]

• Bone deformities:

This illness affects how the body develops. Consequently, it may manifest in individuals with Thalassemia. The majority of the time, the skull bone is visible. Skeletal anomalies are also caused by the thickening of the face and skull bones. [28]

• Symptoms of Alpha thalassemia

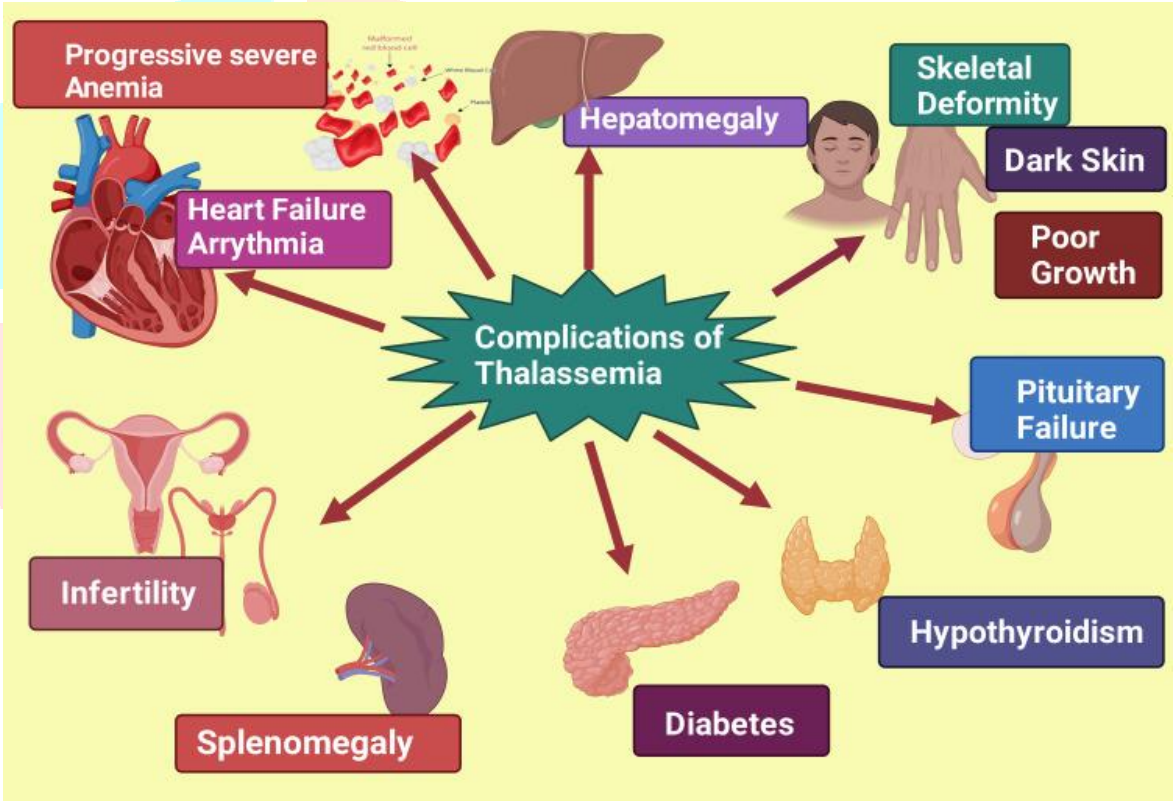
Silent carrier: In essence, silent carriers (-α/αα) do not exhibit any symptoms.
Alpha thalassemia trait: Those who have this characteristic (-α/-α or --/αα) do not exhibit any symptoms.
Hemoglobin H (HbH) disease: Severe pallor and anemic episodes are among the symptoms of HbH disease (--/-α).
Hydrops Fetalis: A Major Case of Alpha Thalassemia Hydrops fetalis (--/--) patients typically pass away in utero or soon after delivery; those who survive to give birth have severe anemia-related massive total body edema and high-output congestive heart failure, as well as massive hepatomegaly from heart failure and extramedullary hematopoiesis. [29]

• Symptoms of Beta thalassemia

Between the ages of six and twenty-four months, individuals with β-thalassemia major present with pallor as a result of severe anemia, poor weight gain, stunted growth, mild jaundice, and hepatosplenomegaly. There may be frequent episodes of fever, diarrhea, agitation, and feeding issues. [30]

COMPLICATIONS

fig.10: - various complications of thalassemia [31]



• Heart failure Arrythmia :

Aggressive iron chelation frequently reduces or eliminates arrhythmias in thalassaemia major. Many times, treating relatively
benign but symptomatic arrhythmias with medication might lead to more issues than the symptoms warrant. Since iron poisoning is the main cause of arrhythmias in thalassaemia patients, treating these conditions needs to be done with much thought. Reassuring the patient is usually appropriate for the majority of supraventricular arrhythmias. While couplets and non-sustained ventricular tachycardia are highly specific for iron cardiomyopathy and call for immediate attention to address the high myocardial iron load associated with them through intensified chelation, frequent premature ventricular contractions alone are not suggestive of iron toxicity. [32]

• Diabetes:

The interaction between diabetes risk factors and problems associated with β-thalassemia. Frequent blood transfusion causes iron overload and buildup in a number of tissues. Over-accumulation of iron reduces insulin production and increases insulin resistance, both of which help diabetes develop. Patients with thalassemia are more susceptible to developing diabetes at the outset of their condition due to obesity and other risk factors.

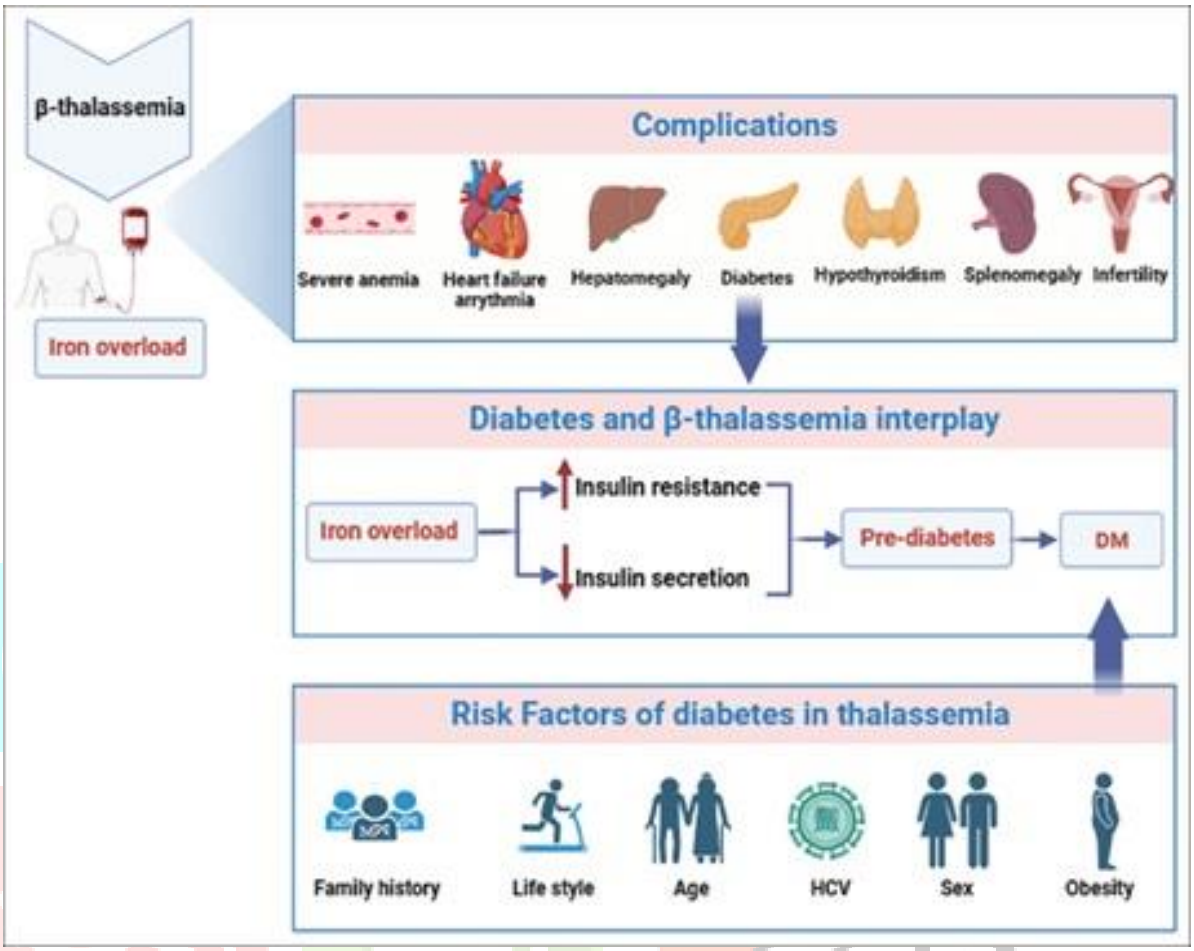


fig.11 :- the interplay between beta- thalassemia and diabetes risk factors.[33]

• Hypothyroidism:

Depending on the amount of TSH and FT4/T4, the frequency of primary hypothyroidism in TDT patients varies from 4% to 29% according to several reports. Subclinical hypothyroidism is generally more prevalent than overt hypothyroidism. Numerous factors, including the age and genotype of the patients, their ethnicity, and changes in the transfusion and chelation treatment regimens with notable variances in compliance and efficiency, have been implicated in this large heterogeneity. [34]
With reports of 5.6%–17% of patients, hypothyroidism is the second most common endocrine condition after hypogonadism. The primary factor causing harm to the endocrine glands, either directly or via the hypothalamic-pituitary axis, is iron accumulation. In thalassemics, splenectomy, high ferritin levels, and poor chelation compliance raise the risk of endocrinopathies.[35]

• Pituitary Failure

Concerns regarding endocrinological consequences are significant in patients with transfusion-dependent β-thalassemia (β-thal). In thalassemic patients, the primary cause of hormonal abnormalities is thought to be pituitary iron deposition. [36]

Thalassemia major can lead to the following complications:

• Jaundice and gall stones caused by hyperbilirubinemia
• Extramedullary hematopoiesis causes cortical thinning and bone deformation.
• High output heart failure due to severe anemia, cardiomyopathies, and arrhythmias – cardiac involvement is the leading cause of death in thalassemia patients.
• Hepatosplenomegaly caused by extramedullary hematopoiesis and excessive iron accumulation from recurrent blood transfusions
• Excess iron can cause primary hemochromatosis symptoms such as endocrine irregularities, joint difficulties, and skin discolouration.
• Neurological problems include peripheral neuropathies.
• Slow growth and delayed puberty.
•. Increased chance of parvovirus B19 infection. [37]

Patients with non-transfusion-dependent thalassemia are individuals who, under specific conditions, such as pregnancy, surgery, or infection, occasionally need a red blood transfusion. Patients with hemoglobin H illness and certain cases of hemoglobin E/β-thalassemia, as well as those with moderately severe thalassemia, are included in the NTDT group.

Previous research has shown that patients with thalassemia experience a number of disease-related complications.

The study included 433 patients in total (254 females and 179 males). There were 306 cases of non-transfusion-dependent thalassemia and 127 cases of transfusion-dependent thalassemia, respectively. In patients with TDT, the mean hemoglobin was 7.1 ± 1.3 g/dl, while in individuals with NTDT, it was 7.7 ± 1.2 g/dl. In patients with TDT, the mean serum ferritin levels were 2,250 ± 2,313 ng/ml, while in patients with NTDT, the levels were 1,483 ± 1,530 ng/ml. Complications from the condition were present in every TDT patient. Of the patients with NTDT, fewer than half (126 patients, 41.2%) had no prior history of problems associated to the condition.

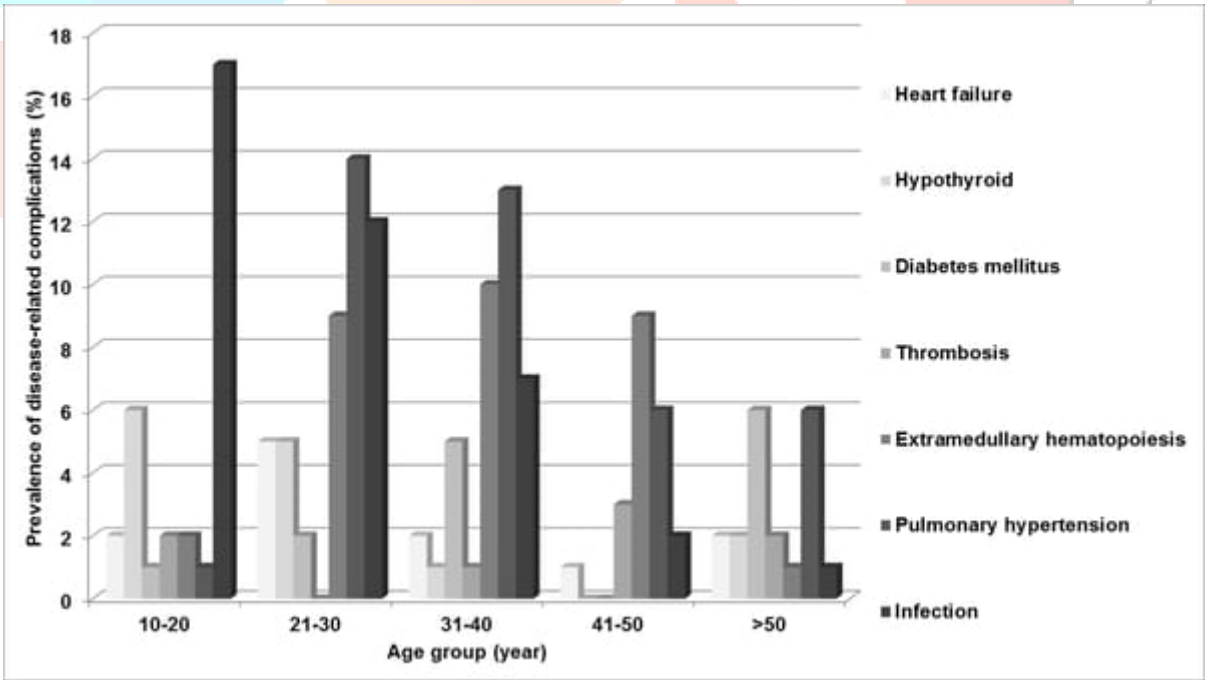


fig 12: - prevalence of the disease-related complications by age group in the 433 patients with thalassemia.[38]

Heart disease (heart failure and arrhythmias), persistent liver hepatitis (which can progress to cirrhosis and, in rare cases,
hepatocellular carcinoma), endocrine issues (hypogonadism, hypothyroidism, diabetes, hypoparathyroidism), stunted growth, osteoporosis, thrombophilia, and pseudoxanthoma elasticum are among the complications that are still frequently encountered. Younger cohorts of patients receiving blood transfusions that have undergone viral screening are experiencing fewer problems, in part because of the development of novel oral iron chelators and improved imaging techniques. More effective management of iron overload is made possible by precise monitoring of iron deposits. Therapy is also offered for a number of problems. Treating individuals with thalassemia requires a high level of specialized competence. [39]

Chronic hypoxia, bone marrow growth, iron overload, and desferrioxamine neurotoxicity are all potential causes of neurological complications. In most situations, neurological involvement does not immediately manifest with significant signs or symptoms (i.e., is subclinical) and can only be diagnosed during neurophysiological or neuroimaging examination. [40]

TREATMENT

Thalassemia treatment depends on the type and severity of the disease. [41].

The sort of treatment a person receives is determined by the severity of their thalassemia. The more severe the thalassemia, the less hemoglobin the body has, which can lead to severe anemia. [42]

Mild thalassemia (Hb: 6 to 10g/dl):

Signs and symptoms are generally mild with thalassemia minor and little if any, treatment is needed. Occasionally, patients may need a blood transfusion, particularly after surgery, following childbirth, or to help manage thalassemia complications.

Therapy	Advantages	Disadvantages
Blood transfusion	• Suppresses ineffective erythropoiesis, thus limiting downstream pathophysiological complications • Regular transfusion plus iron chelation therapy is associated with improved long-term survival in TDT • Role in ameliorating certain morbidities in observational studies with NTDT	• Lifelong transfusions required every 2–5 weeks in TDT • Risks of blood-borne infection, alloimmunization, and iron overload
Iron chelation	• Long-term use improves liver and myocardial iron levels and function, and improves endocrine function in TDT • Can reduce systemic and hepatic iron burden in NTDT • Oral formulations now available	• Not effective for all patients • Frequent side effects that require regular monitoring • Demanding regimen of parenteral formulation • Poor adherence among some patients • High cost
Hydroxyurea	• May improve haematological outcomes in specific NTDT populations • Low cost	• Lack of robust evidence of benefit
Splenectomy	• May improve growth, QoL, and haemoglobin concentration, thus avoiding transfusions for some patients	• Risk of sepsis • Increasing awareness of other risks from NTDT studies, including venous thrombosis and other vascular manifestations • May reduce ability to scavenge toxic free iron species, as evident from NTDT studies
HSCT	• Potentially curative for patients with TDT • 90% survival rate in patients; disease-free survival rates > 80% in TDT • Improves HRQoL of children with severe disease • Long-term cost-effectiveness	• Appropriate only for a subset of patients ○ Young age ○ Compatible sibling donor • 5–10% risk of mortality ○ Intensive myeloablative conditioning required, graft-versus-host disease, and graft failure • Potential impairment of fertility • Requires access to technology at major treatment centre • Substantial one-off cost of procedure

fig.13 :- advantages and disadvantages of treatment[43]

Non – Pharmacological Treatment

• Diet and Exercise:

There are reports that tea consumption helps to lessen the digestive tract's absorption of iron. Hence, tea could be a beneficial beverage to regularly consume for those with thalassemia. Vitamin C aids in the stomach's removal of iron, particularly when combined with deferoxamine. However, there is an increased risk of deadly arrhythmias when utilizing large doses of vitamin C without concurrent deferoxamine administration. Therefore, it is advised to utilize iron chelators (deferoxamine) in conjunction with low doses of vitamin C. [44]

• Stress related to the treatment of thalassemia:

It has been discovered that moms experienced emotional and physical strain, disregarded their own illnesses, and failed to take the necessary action because they were pressed for time. According to a study conducted

on mothers of thalassemia-affected children in Jordan, moms experience a variety of stressors, including social isolation, non-physical and cognitive stress, and worries about their children's future. These stresses are made worse by a lack of information and financial strain.
It Is imperative that family members, friends, neighbors, and medical professionals help these moms by offering counseling to increase their understanding of self-care. [45]

Pharmacological treatment

• Blood transfusion:

people with more severe forms of thalassemia frequently need blood transfusions on a regular basis, sometimes even every few weeks.
In addition to monitoring and suppressing extramedullary hematopoiesis, the aim is to maintain hemoglobin levels at approximately 9 to 10 mg/dl in order to provide patients with a sense of well-being.
Red blood cells (RBCs) that have been cleaned and packed at a rate of 8 to 15 ml. cells per kilogram (kg) of body weight over a period of one to two hours are advised in order to reduce transfusion-related problems. [46]

• Chelation therapy:

Iron overload occurs when the intake of iron is increased over a prolonged period of time and is commonly seen in patients with hereditary or refractory anemias (e.g. β-thalassaemia major, sickle cell anemia and myelodysplastic syndromes) who receive frequent blood transfusions. The iron excess is initially stored in the reticuloendotelial system, which has a capacity of about 10–15 g, and then in all parechymas, resulting in life-threatening complications, namely cardiopathy, liver and endocrine dysfunction and reduced patient's survival. Iron excess also increases cell concentration of iron-binding proteins such as ferritin and haemosiderin complexes in lysosomes [47]. Depending on how much iron is overloaded after transfusion, each patient's dose duration is unique. For thalassemia patients who are dependent on transfusions, the recommended starting dose of deferoxamine is 30–40 mg/kg per week, and for teenagers and adults, it is 40–50 mg/kg and 60 mg/kg, respectively. After 20–25 RBC units are transferred between the ages of 2 and 4, chelation therapy is started.
The digestive system absorbs deferiprone, which has a half-life of 1.5–4 hours in plasma. It is advised to take 75 mg/kg of the
medication orally three times a day during mealtimes. This amount may be increased to 100 mg/kg daily. [48]

Property	Deferasirox	Deferiprone
Route	Oral	Oral
Usual dose	20-30 mg/kg/day	75 mg/kg/day
Schedule	Once a day	in 3 divided doses daily
Side effect	Gastrointestinal Renal failure	Gastrointestinal Agranulocytosis/ neutropenia Arthralgia
Advantage	Oral and daily use	Effective in cardiac iron excretion
Disadvantage	unavailability of complete information	blood count monitoring

fig.14 :- general properties of iron chelation therapy [49]

• Gene Therapy:

Gene therapy holds promise repairing one's own bone marrow cells by transferring the normal b-globin or g-globin gene intohematopoietic stem cells (HSCs) to provide permanent erythropoietic effect. Since 2000, the introduction of gene transfer usinglentiviral vectors has succeeded to repair beta thalassemia gene in a mouse model. However, the oncogenic risk of lentiviral vectorintegration is a long-term concern. [50]

• Splenectomy:

To reduce the quantity of transfusions needed, patients with thalassemia major frequently have a splenectomy. When the annual transfusion demand rises to or above 200–220 mL RBCs/kg/year with a hematocrit value of 70%, a plenectomy is typically advised. In addition to reducing the need for transfusions, splenectomy also slows the spread of extramedullary hematopoiesis.

• Cholecystectomy:

Following a cholecystectomy, patients may experience cholelithiasis as a result of accelerated hemoglobin breakdown and gallbladder bilirubin accumulation. Patients who experience symptoms should have a cholecystectomy performed concurrently with a splenectomy. [51]

• Stem cell transplant:

An allogeneic stem cell transplant (allo-SCT) remains the only curative option for the majority of patients with β thalassemia major. The use of allo-SCT is rapidly Increasing in India and other developing countries and is hence the most widely available and accessible curative therapeutic strategy for this condition. The central concept revolves around the ability to replace the hematopoietic stem cells (HSC) from a donor to a recipient resulting in a new donor derived hematopoietic system in the recipient.[52]

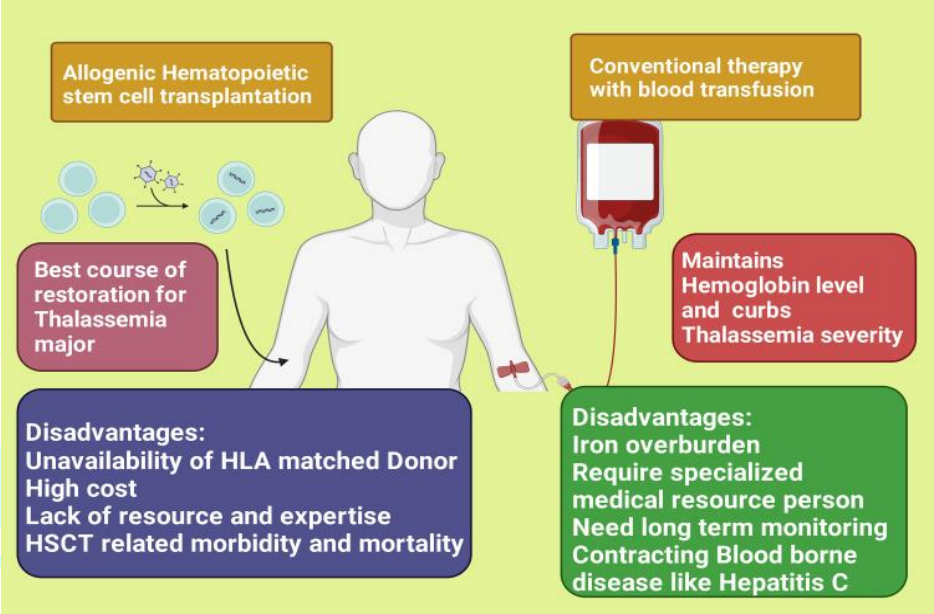


fig.15 :- showing the advantage and disadvantages of the different treatment options for thalassemia hla: human leukocyte antigens; hsct: hematopoietic stem cell transplantation. [53]

• Antioxidant Therapy

Based on the idea that unmatched globin chain accumulation damages erythroid Precursors and RBCs via oxidant injury, there have been trials of antioxidant agents.
The trials have used combinations of vitamin E, acetyl cysteine, and deferiprone. The results from the largest trials are not available.

•Endocrinopathies :

Endocrinopathies are quite common in thalassemic patients. One study found Hypogonadism in 22.9% of boys and 12.2% of girls, hypoparathyroidism in 7.6%, Hypothyroidism in 7.7%, and short stature in 39.3% .[54]

Treatment of β-thalassemia.

Novel therapeutic approaches β-thalassemia. Normal erythroblasts have balanced Caspase 3/1 cleavage and HSP70 protective function in the nucleus, which controls GATA1 levels. Erythrocytes that are healthy and functional are therefore created. GATA1 is cleaved by Caspase 3/1, resulting in fewer functional matured erythrocytes, however in β-thalassemic erythroblasts, the absence of functional β-globin chains causes buildup of free α-globin chains, which restricts HSP70 distribution to the cytoplasm.

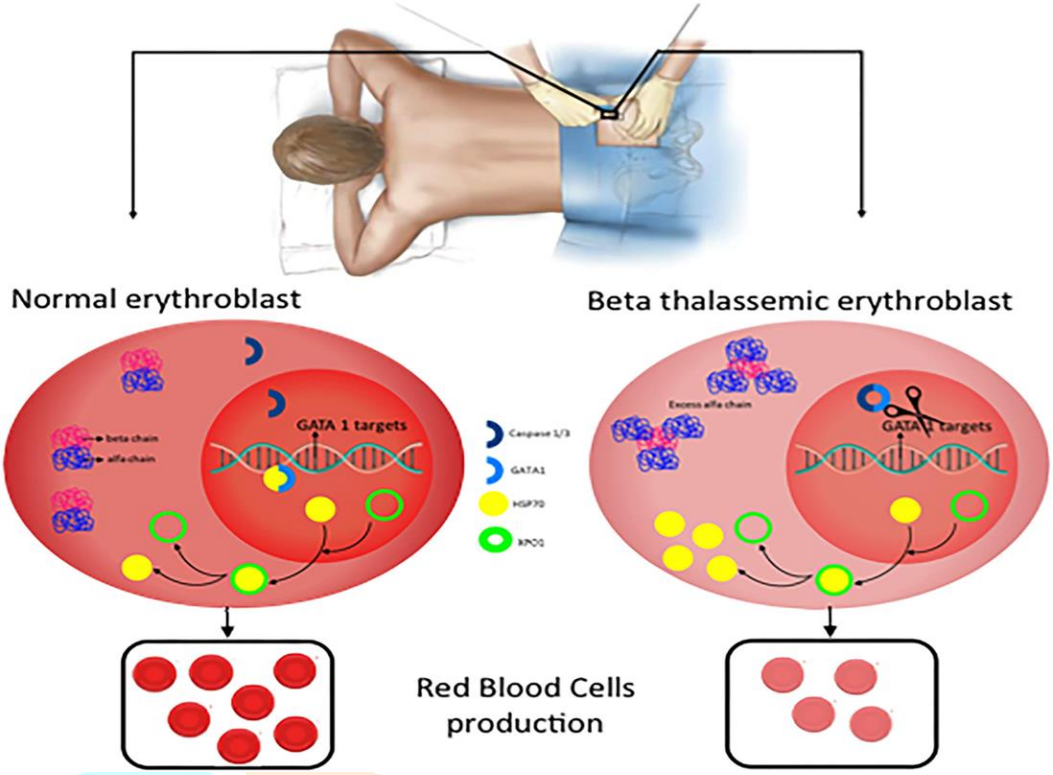


fig.16 :- new potential treatments for β-thalassemia. [55]

• Drugs:

• Hydroxyurea (HU):

It is a sickle cell disease HbF inducer licensed by the US Food and Drug Administration. Patients with β-thalassemia who have inconsistent treatment responses are now using HU. Because HU delays or eliminates the need for repeated blood transfusions, it has been shown to improve clinical and hematological outcomes in thalassemia patients.

• Thalidomide:

Thalidomide is an immune modulator that has shown a considerable reduction in transfusion in patients with BTM and BTI. It is being investigated for its potential to induce HbF. Tumor necrosis factor and other inflammatory cytokines decrease the induction of nuclear factor-κB when taken with thalidomide, which may lead to an increase in HbF. Many studies have looked at the effectiveness of HU in treating β-thalassemia patients, and some have reported on the usage of thalidomide; however, very few, based on our search, have assessed the impact of taking both medications together. [56]

Test for beta thalassemia:

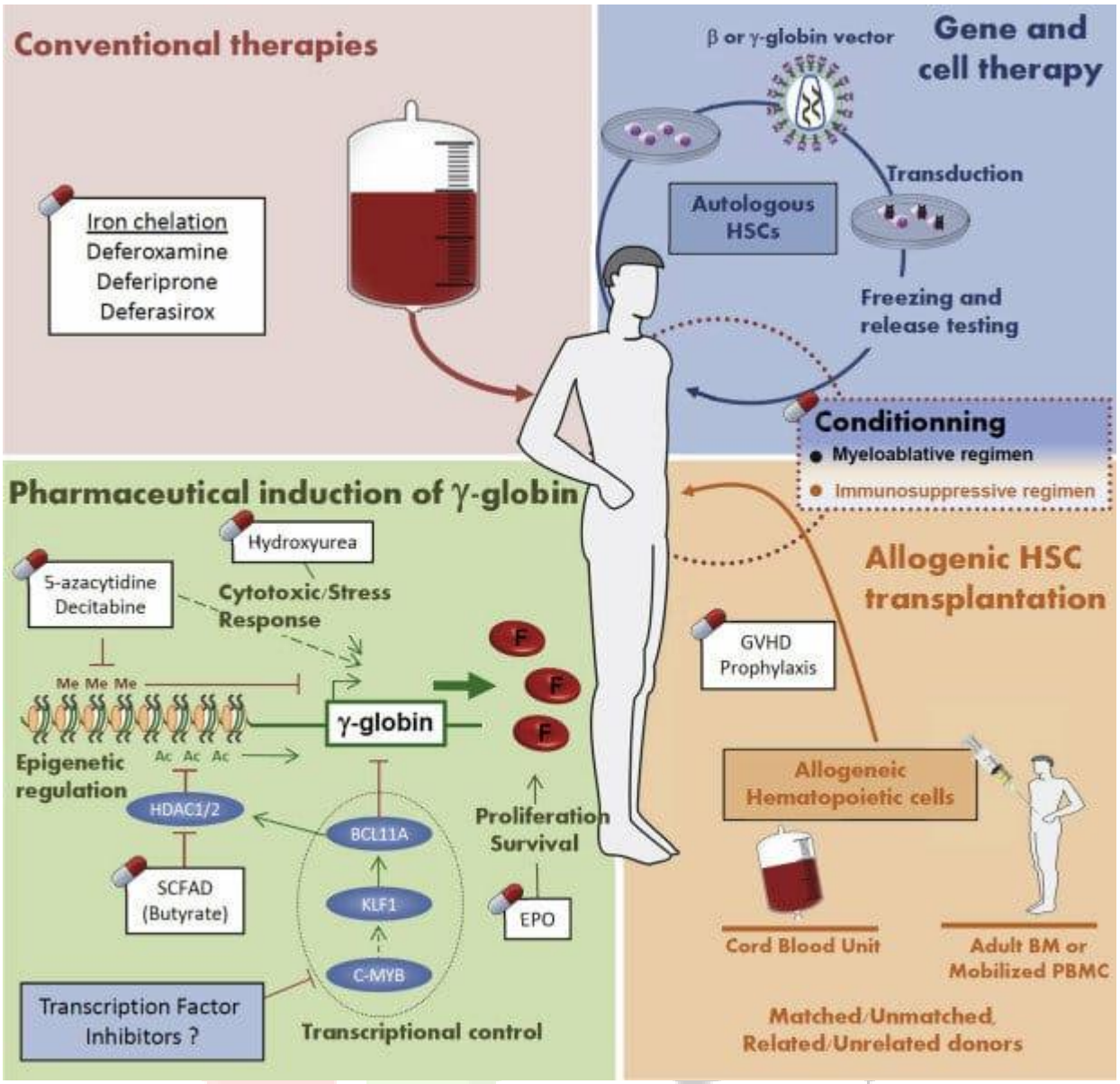


fig.17 :- current and future therapies for beta-thalassemia major. [57]

AWARENESS

In certain nations, prevention initiatives have decreased the birth prevalence of thalassemia and may have saved money on patient care. Planning and funding are needed for these initiatives to include genetic counseling to help couples make educated decisions, screening to find carriers, public awareness, and, in the end, making treatments like prenatal diagnosis available.

The attitudes of individuals about prenatal diagnosis, pregnancy abortion, and screening varied significantly. Each country must take into account cultural, religious, ethical, and legal factors. However, in this day of rising population diversity, it is also necessary to take into account the many views that exist among communities throughout the world while developing services.

Despite the cost-effectiveness of prevention, very few nations have implemented nationally coordinated initiatives.[58]

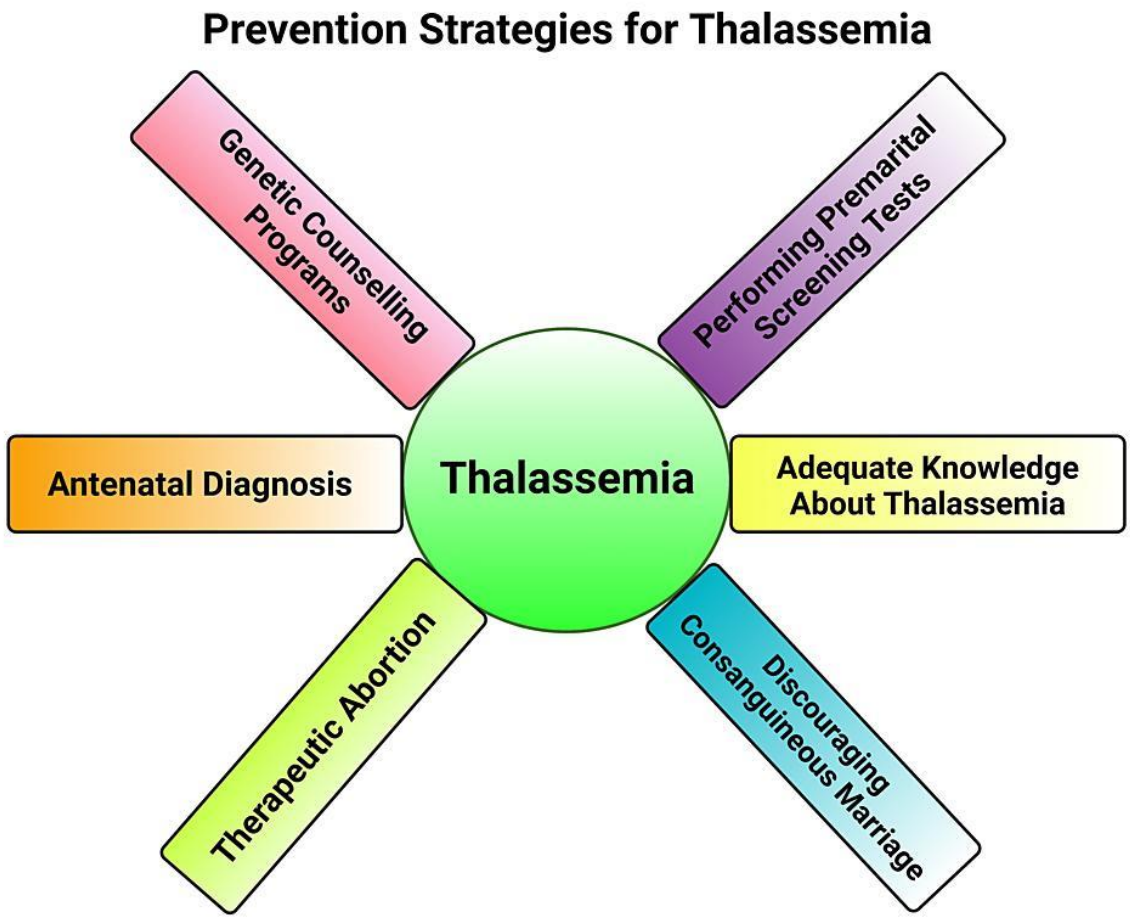


fig.18 :- prevention strategies for thalassemia.[59]

Successful and sustainable screening for α-thalassemia must include follow-up strategies to track patients and enter them into treatment programs. Importantly, follow-up strategies should be managed by primary care physicians and guided by factors that impact the local population, such as disease prevalence, ethnic variation, level of consanguinity, and the local healthcare system.[60]

• Hemoglobin variants can be accurately identified and so result in the well-known benefits of screening for sickle cell disease and epidemiological data on other variants can be obtained.
• Epidemiology of α-thalassemia can also be obtained through the detection of Hb Bart's.
• Thalassemia major can be identified in neonatal blood by using a cut off value of 1.5% HbA.

These tests are useful for secondary prevention and epidemiological studies, especially if supplemented by molecular studies. Other forms of technology such as tandem mass spectrometry may even be sensitive enough to identify β-thalassemia heterozygotes.[61]

CONCLUSION

Patients with thalassemia and their families face significant psychological, physical, and financial challenges. It is necessary to raise awareness by educating parents and other caregivers about thalassemia. It is necessary to provide educational programs to raise mothers' consciousness regarding self-care and caring for their sick children. For social support, raising awareness among close friends, family, neighbors, and the community would also be very beneficial. They need financial assistance in order to feel less stressed. In order to manage thalassemia and lessen the stress on patients and families, a multidisciplinary approach to the disease's management and psychosocial support is necessary.[62]

A hereditary condition known as thalassemia, beta thalassemia is very severe and manifests as mild to severe anemia. Diagnosis made by Blood smears, hemoglobinopathy, iron studies, prenatal testing using amniotic fluid genetic testing, DNA analysis (genetic testing), and complete blood counts (CBC) are among the tests that can be performed. Severe anemia patients are treated with iron chelation, bone marrow transplantation, splenectomy, and routine blood transfusions.

Prenatal testing, carrier identification, and premarital screening are the methods of prevention. With no treatment, the prognosis for β thalassemia major was exceedingly dismal; the natural history was death from

infections and cachexia by age five. Transfusion and chelation therapy were able to extend survival into the second decade, but it is clear that these interventions prevent heart disease in early childhood or adolescent. [63]

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