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Thalassemia and Its Management – A Review Article

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Abstract

Thalassemia is a hemoglobinopathy burdening India, making it earn the title of thalassemia capital of the world. Studying the last decade, the overall prevalence worldwide and incidence rates have declined, but prevalence rates were high in East and Southeast Asian countries. Screening for carriers and affected individuals and genetic counseling are promising approaches for reducing soaring cases and reducing the further spread. Thalassemia affects various organs due to iron overload and haemolysis leading to cascade of complications ranging from physical deformities to fatal outcomes like heart failure. Continuous monitoring of is requires with multidisciplinary approach to handle the adverse reactions of treatment modalities and deal with complications. The treatment of thalassemia ranges from conventional blood transfusions and chelation therapy to curative, i.e., bone marrow transplant and gene editing and newer drugs targeting ineffective erythropoiesis and production of foetal haemoglobin. The chronic nature of the disease affecting the quality of life of children makes nurses teaching them self-care management techniques more essential. The role of nursing strategies for managing thalassaemic children is through holistic approach that is addressing their developmental needs as per their age. Various governmental and NGO initiatives and programs has made a significant impact, but a multisectoral approach is needed to tackle the emerging cases.

Keywords: Thalassemia, self-care, quality of life, genetic screening, bone marrow transplant.

INTRODUCTION

Hemoglobinopathies are the most frequently occurring inherited genetic disorders of RBCs worldwide. It is an significant reason for morbidity and mortality; imposing a huge burden on families and the health sector in the country [1].

Thalassemia is derived from the Greek word *thalassa*, meaning "sea". It constitutes inherited blood disorders characterized by deficiencies in the amount of production of specific globin chains in hemoglobin [2].

BURDEN OF THALASSEMIA

"*Thalassemia Belt*" includes countries around the Mediterranean Sea. More than 30 million people are carrying defective genes, with 3–17% in different populations [3].

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WHO in 2006 recognized thalassemia as a global health problem and reinforced preventive strategies by adopting WHA63.17 by low and middle-income countries [4].

Studying the last decade, worldwide prevalence and incidence rates have declines, but prevalence rates were high in the East Asia and Southeast Asian countries [5].

India is now the thalassemia capital of the world. 8 Monthly, 40 million carriers and 100,000

thalassemia majors requiring blood transfusion are documented. With the absence of national registration of cases, precise number are not known, but approximately 25% of global β-thalassemia cases are seen in India [6].

Causes

A defect in the gene that helps control the production of alpha or beta globin causes thalassemia [7].

Risk Factors

- Family history.
- Asian, Chinese, Mediterranean, or African- American ethnicity [8].

TYPES OF THALASSEMIA

Alpha and Beta

Two alpha-globin and beta-globin protein chains make up haemoglobin. Alpha and beta are the main forms of thalassemia.

The terms "symptomatic," "mild," "moderate," and "major" were used to reflect the degree of disorder. With alpha thalassemia:

- When a gene or genes related to the alpha globin protein are missing or mutated.
- This type of thalassemia is characterized by low or absent alpha globin chains.

Beta Thalassemia

- The "same gene defect" affects beta globin protein synthesis.
- Beta globin group is absent or deficient in this type of thalassemia (Figure 1) [9].

Coinheritance & Coexistence

Beta thalassemia: This is due to the less severe alpha-beta chain asymmetry. People with comorbid alpha thalassemia therefore have a milder clinical outcome. Beta thalassemia is a severe form of hemoglobinemia associated with sickle cell syndrome. Prevalent Hb variation in Southeast Asian populations. HbE is associated with the beta-thalassemia phenotype (Tables 1–2) [10].

Table 1. Timing for screening.

Newborn	Early detection of disorder
Adolescence	Screening of carriers before selection of partner for marriage.
Pre-marital	Provides prospects to a carrier to make an informed decision before marriage.
Preconception Antenatal and prenatal screening and diagnosis	• If the fetus is affected. Carrier testing can effectively terminate a pregnancy. (if allowed) • Couples with access to the facility can receive genetic diagnosis before implantation. • Give carriers the opportunity to avoid being affected children [11].

Role of Nurse in Genetic Counselling

The predictive nature of genetic data, effect on other family members, tough choices made by people and ethical considerations involved, it is imperative to assess risk and educate about family planning while providing emotional support [12].

Genetic counselling and screening programs can significantly reduce the burden by expanding knowledge and understanding of genetics [13].

Table 2. Tests for screening.

Test	Description
NESTROFT	One-tube red blood cell osmotic fragility testing was performed visually to select samples for Hb HPLC.
CBC	CBC determines Hb and RBC level parameters to assess the type of anemia.
Peripheral smear/general blood picture	In cases of TI and severe thalassemia, GBP is quite specific and strongly supports the diagnosis.
Sickling test	HbS/0thal and HbS/+thal are two basic functional tests to differentiate between Hb S disease.
Serum ferritin by ELISA	To detect co-existent iron deficiency or to rule out iron deficiency.
Hb HPLC/newborn HPLC	Separation of Hb fractions was performed using automated high-performance liquid chromatography, which is used to detect thalassemia dried blood samples were collected from newborn babies.
IEF	Iso electric focusing is cost effective alternative to HPLC.
PCR based DNA analysis	• Reverse dot blot hybridization and amplification refractory mutation system is a confirmatory test. • Mutations detected by DNA sequencing.

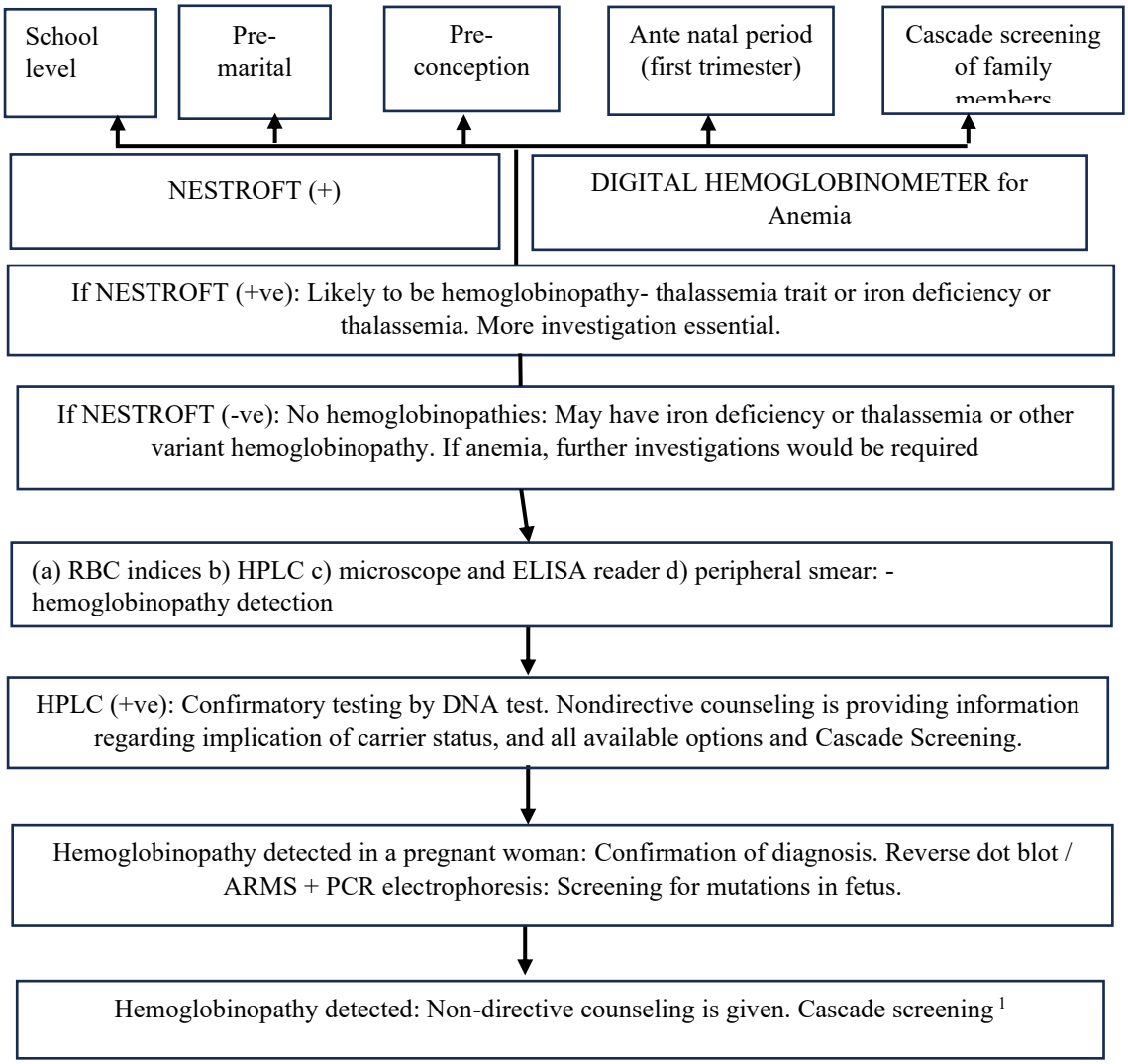

Figure 1. Target screening.

Main objective of genetic counselling is to evaluate which cases are clinically silent and which cases would require invasive tests. The information available in literature concerning the methodology for counselling by thalassemia centres is limited [14].

Nurse counsellors can do the risk assessment, screening and helping people making best possible health choices [15].

Alpha Thalassemia

Disorder in production of α-globin from any/all 4 genes encoded on chromosome 16 [16].

Causes

Mutation in DNA producing hemoglobin and inheritance [2].

Pathophysiology

Functional point mutations, nonsense mutations, frame shift mutations, and chain termination mutations occur in and round coding sequences of α-globin gene cluster leading to inhibition of protein synthesis [17].

TYPES OF A THALASSEMIA

1. *Hemoglobin H*: Formation of α-chains is absent resulting in extra production of γ- globin chains in fetus and newborn or in children β- globin chains. β-globin chain tetramers make unstable precipitates, forming insoluble inclusions called heinz bodies resulting in damage to erythrocyte precursors causing ineffective erythropoiesis.
2. *α thalassemia major*: Functional depletion of all pair of α -globin genes due to around 20 mutations, leading to development of hydrops fetalis or hemoglobin bart
3. *Silent carriers:* Functional deletion of 1 out of 4 α globin genes caused by more than 15 mutations result in reduced formation of α -globin.
4. *Alpha trait*
   - Alpha thalassemia trait (heterozygous state) only has two genes for alpha globin, so they make slightly lower amounts of hemoglobin.
   - Children remain asymptomatic hhaving no /mild anaemia [18].

Clinical Manifestations

- Anaemia.
- Pale skin.
- Weakness.
- Fatigue.
- Hepatosplenomegaly.
- Heart defects.
- Urinary system or genitalia abnormalities.

Hb Bart syndrome causing complications in pregnancy like

- High BP.
- Abnormal bleeding.
- Premature delivery.
- Jaundice [19].

MANAGEMENT

Blood Transfusion

Depending on age, weight of child and other factors, frequency of transfusions varies every 2–4 weeks. Packed RBC (<2 weeks old) are the component of choice.

- Packed RBC15 ml/kg body weight at rate of 5 ml/kg/hr.
- Child may require 1–2 units of pRBC's, or even more depending upon body weight and pre-

transfusion Hb.

Iron Overload

Patient receiving significant numbers of blood transfusions (15–30 units pRBC/yr) need chelation therapy to eliminate excess iron from body [20].

Monitoring of patients with thalassemia in a day-care center (Table 3).

Table 3. Monitoring of patients with thalassemia in a day-care center is shown below.

Each Transfusion	Monthly Transfusion	Every 6 Months	Every Year	After 10 yrs	Physician's Order
• Pre transfusion haemoglobin • Liver and spleen size • Transfusion reaction	• Amount of blood to transfuse • Pre-transfusion Hb • On deferasirox • SGOT, • SGPT, • BUN, • Serum Creatinine, Urine R/E • On deferiprone-CBC • Subsequent transfusion	• S. Ferritin • SGOT • SGPT • BUN • S. Creatinine • Calcium • Phosphorus • Height • Weight	• HCV IgG antibody • Anti HBs antibody • HIV 1 & 2	• FBS/ GTT • TSH • ECG • MRI - Heart/ liver • DEXA Scan	• Cortisol • Testosterone • Estradiol • LH • FSH • PTH • Holter monitoring [21]

Medications

- *Folic Acid:* FA-8(oral)/ folvite (injectable) for treating / preventing low folate levels.
- *Deferexoamine:* (Desferal)/ deferasirox as iron chelator [22].

Surgical Management

- Increased transfusion requirements indicate need for splenectomy.
- Skeletal deformities of maxilla and skull resulting from erythroid hyperplasia require surgical/orthodontic correction.
- Bone marrow transplant can cure the disorder [23].

Psychological Care

- *Counseling:* It is needed to deal with the stresses of lifelong treatment adherence and inevitable complications and problems like employment, marriage and other difficulties [24].
- *β thalassemia:* Partial or complete lack in production of β chain. In India, first case of β-thalassemia was reported by Dr. Mukherjee from Calcutta in 1938 [25].
- *Forms:* Beta thalassemia occurs in 4 forms:

Two Heterozygous

1. *Thalassemia minor:* generally asymptomatic silent carrier state.
2. *Thalassemia trait:* produces mild microcytic anemia.

Either Heterozygous/Homozygous

Thalassemia intermedia: causes moderate to severe anemia and splenomegaly.

Homozygous

Thalassemia major (Cooley's anemia): results in severe anemia with transfusion support [26].

Pathophysiology

- Compensatory increase in synthesis of alpha chains and gamma chain production, resulting in

formation of defective hemoglobin causing anemia.
- Compensating hemolytic process increased erythrocytes are formed unless bone marrow is suppressed by transfusion therapy, leading to iron overload from transfusion and increased iron absorption [27].

Clinical Manifestation

β-thalassemia major

At birth remain asymptomatic and become symptomatic by 4–6 months after birth developing severe anemia.
- Pale skin due to anaemia and jaundice from hyperbilirubinemia. Bronzed, freckled complexion (iron overload).
- Deformity due to erythroid hyperplasia with intra-medullary expansion and cortical bone thinning.

Bone Changes
- Enlarged head.
- Prominent frontal (frontal bossing) and parietal bones.
- Prominent malar eminences.
- Flat or depressed bridge of the nose.
- Enlarged maxilla.
- Protrusion of lip and upper central incisors and eventual malocclusion.
- Generalised osteoporosis.
- Heart examination may show cardiac failure and arrhythmia due to severe anaemia or iron overload. The children may feel fatigued, weakness and shortness of breath.
- Retarded growth (small stature) in severe illness is related to hemochromatosis, possibly because endocrine glands are sensitive to iron toxicity, and can produce organ dysfunction.
- Delayed sexual maturation are common findings, thought to be caused by pituitary failure.
- Cholelithiasis and hyperbilirubinemia because of hemolytic state. Urine may be dark in color.
- Hepatomegaly and chronic hepatitis due to repeated blood transfusion and iron overload resulting in cirrhosis or portal hypertension.
- Splenomegaly due to extramedullary hematopoiesis or massive hemolysis.
- Endocrine dysfunction especially affects pancreas, testes, and thyroid due to iron toxicity [28].

β-thalassemia Intermedia

Moderate to severe anemia with associated problems, such as bone deformities and splenomegaly. β-trait will be asymptomatic or can have mild anemia.

Thalassemia Minor

It is usually characterized by mild anemia [29].

Diagnostic Evaluation
- History collection.
- Physical examination.

Blood Test

Microcytic, anisocytosis, poikilocytosis, target cells and basophilic stippling of various stages. CBC reveals anemia, Low Hb and hematocrit.

Hb Electrophoresis

It shows the level of HgF and HgbA2 as it separates different Hb fractions used for finding

thalassemia.

DNA Analysis

Mutational defects can be detected by amniocentesis and molecular diagnostic tests that can determine a mutation presence after 8 weeks of gestation [30].

Effects of Thalassemia on Children

Thalassemia can have significant effects on the developmental stages of children [31]. The following are areas to consider regarding the impact of thalassemia on the developmental stages of children:

Physical Development

Thalassemic children may experience stunted growth and delayed puberty due to chronic anemia and other complications associated with the disorder.

Cognitive Development

Chronic anemia can impact cognitive function and academic performance in children with thalassemia. Iron overload from transfusions can also affect cognitive development and lead to iron toxicity in the brain.

Emotional and Social Development

Physical and emotional challenges associated with thalassemia cause psychological effects like anxiety, depression, and stress may arise due to chronic nature of the disease and its impact on daily life [32].

Educational Challenges

Children with thalassemia may face educational challenges due to frequent absences from school for medical treatments, fatigue, and cognitive issues related to the disorder making special educational support and accommodation necessary.

Nutritional Needs

Children with thalassemia may have specific nutritional requirements due to issues like poor appetite, dietary restrictions, and nutrient deficiencies caused by the disorder and its treatments [30].

Overall, the effects of thalassemia on developmental stages of children can be multifaceted and require a holistic approach that addresses physical, cognitive, emotional, social, and educational needs [33].

Physical changes can affect self-esteem of children further by reducing QoL. Different age groups are affected in various domains of quality of life (Figure 2) [34].

MEDICAL MANAGEMENT

Iron Chelating Agents

Deferoxamine (IV) desferal chelates Fe by forming stable complex that prevents iron from going into further chemical reactions.

Oral chelating agent (Deferasirox) is major advance in long term therapy.

Caution

- Do not chew tablet; disperse tablet in water, apple juice, or orange juice.
- Take on empty stomach at least 30 minutes prior to food [35].

SURGICAL MANAGEMENT

1. *Bone marrow transplantation* is the cure available for thalassemic children and is more appropriately called hematopoietic stem cell transplant. Children younger than 16 years of age who undergo allogenic HSCT have a high rate of complication free survival.
2. *Splenectomy* may be done to decrease transfusion requirements. Post splenectomy complication is severe and overwhelming infection so, children are kept on prophylactic antibiotics with close medical supervision for many years [5].

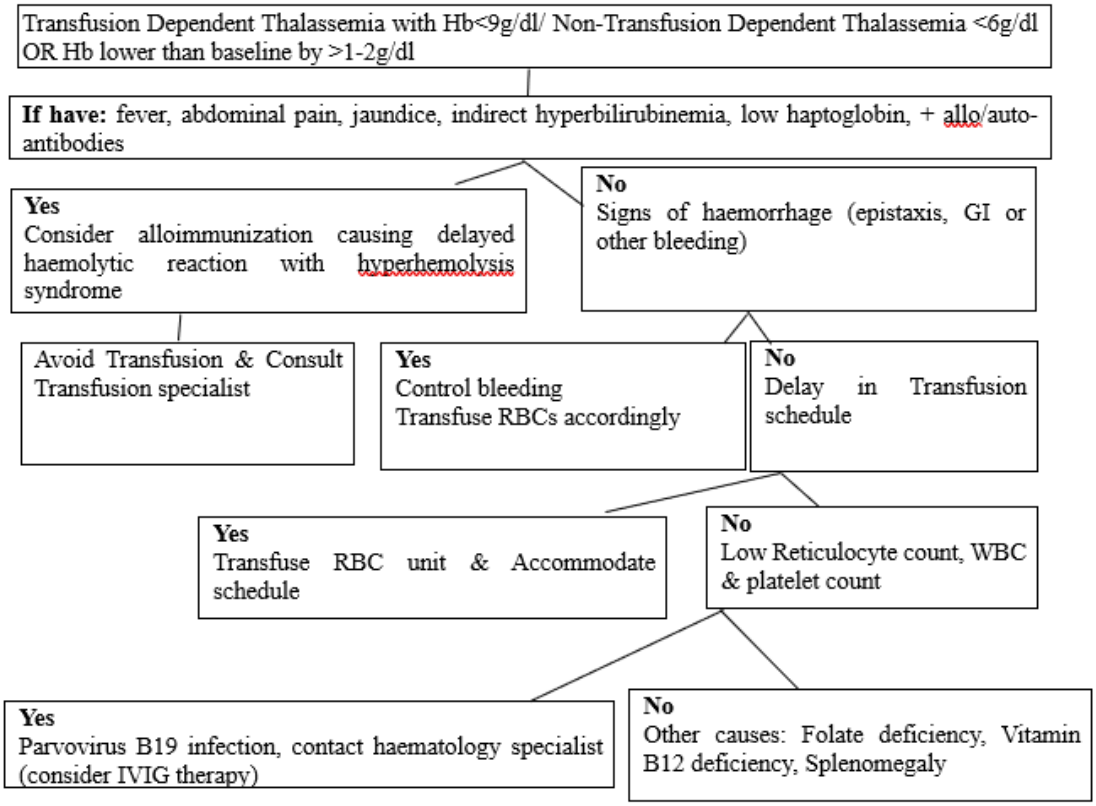

Figure 2. Emergency management of acute cases [36].

COMPLICATIONS

After diagnosis, treatment for thalassemia continues with stressors throughout like, Hb <5, surgery, infection, or pregnancy, accompanied by progressive changes throughout childhood like splenomegaly, growth failure, etc., leading to complications due to disease and treatment causing heart failure, CVA, haemolytic crises. This child cannot be put on conventional treatment and needs tailored transfusion therapy till resolution is achieved and checked for iron overload and alloimmunization. Hypersplenism or splenomegaly after 5 years of age calls for splenectomy, as there is a possibility of spleen rupture. The administration of hydroxyurea causes depletion of erythroid marrow and production of γ chain. Hydroxyurea can be used for alloimmunized and comorbidities cases and response can be checked every 6 months in terms of Hb function, QoL, and complications [37].

Recent Advancements

- Combination therapy (deferiprone and desferrioxamine) and organ targeted chelation may improve QoL [38].
- MRI is now used to assess cardiac iron overload [39].
- *Jak 2 inhibitors & Activin II receptor traps* used for ineffective erythropoiesis are currently in clinical trials. *Mini-hepcidins, exogenous transferrin and erythroferrone inhibitors* targets iron

dysregulation in preclinical studies [40].
- Mitapivat tablet increases level of enzyme for RBCs functioning [41].
- Isobutyramide is used for fetal Hb production [42].
- Erythropoietin administration increses fetal Hb [43].
- Wheat grass is given in hemoglobin deficiency and other chronic disorders considered as green blood [44].
- Indole compounds, namely choline, which known for antioxidants and also possess chelating property for iron overload disorders [45].

Gene Therapy

Gene therapy can replace an abnormal gene with a normal gene but is costly and often inaccessible to all members of the community [46].

Currently, infusion of autologous HSCs modified with a lentiviral vector into the erythroid progenitors of the patient is a promising approach holding non- zero risk for oncogenesis to completely cure β-thalassemia. Gene editing reversed the switch and restored foetal haemoglobin deputises for the adult one [47].

NURSING MANAGEMENT

1. **Assessment**

Assessing the impact of thalassemia on a child's general health and wellbeing and their physical, emotional and developmental needs.

2. **Treatment Administration**

Responsible for administering treatments, such as blood transfusions, chelation therapy, and other medications as prescribed by the healthcare team.

3. **Patient Education**

Teach families and children with thalassemia about the causes of the condition. Available treatments and self-care techniques.

4. **Emotional Support**

Provide a compassionate and understanding presence, listen to concerns, and help children and families navigate the emotional impact of the disease.

5. **Collaboration**

Participate in care planning, interdisciplinary meetings, and coordination of services to ensure comprehensive and coordinated care for the child.

6. **Monitoring & Evaluation**

Monitor the child's response to treatment, track progress, and evaluate the effectiveness of interventions.

7. **Advocacy**

Promote for the needs and rights of children with thalassemia, ensuring they receive appropriate care, support, and resources [48].

Pediatric nurses can act as a link between other health care workers, agencies, hospitals, and patients and their families, thereby contribute to improving the QoL and well-being of children living with

thalassemia [49]. Various studies have shown the role of nurse from awareness, screening, counselling, treatment, and prevention of complications in thalassemic children has been impactful [50]. Nurses should update their knowledge and skills in managing thalassemic children [51].

Quality of Life

Various studies have time and again emphasized the need to assess quality of life or health-related quality of life in thalassemic children as it affects the physical, mental, social, and emotional domains of QoL. The need for research exploring QoL in thalassemia affected children using culture appropriate tools are the need of the hour [52, 53].

Self-Care Management

Self-care management in thalassaemic children can improve QoL. Nurses can help improve self-care practices for better outcomes in the longer run [54, 55].

Prognosis

With ongoing medical care, it is recommended that children should be protected from infections by keeping up with the vaccines, such as HIB, hepatitis, meningococcal, and pneumococcal. Nutritious diet, regular exercise can help manage symptoms and lead to positive prognosis [56].

- Complications are still frequent and affect the patients' QoL [46].
- Most children with blood transfusions and early chelation therapy survive well into adulthood [57].
- Most common causes of death are heart disease, post splenectomy sepsis and multiorgan failure secondary to hemochromatosis [27].

POLICIES, PROGRAMMES & INITIATIVES

National Health Mission Policy for Prevention & Control of Hemoglobinopathies in India

In 2016, NHM came up with policy for prevention and control of hemoglobin in India as per the guiding principles of WHO report on services for preventing and managing genetic disorders in developing countries [1].

National Thalassemia Welfare Society

Under this all-thalassemia societies work for treatment of the disease and to educating families and doctors about the latest development in the field at national level [44].

Thalassemia Support Foundation

This organization organizes conferences, create awareness, and raises funds for research as well as the treatment of people [58].

Amendments to the Persons with Disabilities and Thalassemia Act 2016

People with leukemia are now considered "disabled persons" under the RPWD Act, 2016. People with a disability of 40% or more will receive a disability certificate and reservation of 5% with disability as per the standard.

Accommodation for children with disabilities is also stated ensuring education, employment and health benefits [59].

Thalassemic India

Thalassemia association, doctors, and hospitals join hands with the NGO thalassemia center as well as both domestic and international pharmaceutical and equipment companies [60].

Thalassemia Patients' Advocacy Group (TPAG)

This group gives platform to thalassemic to have their interests best represented on topics ranging from disability guidelines drafting and charter of patients' rights to policy on hemoglobinopathies [61].

Thalassemia & Sickle Cell Society

It is a registered NGO established in the year 1998 in Telangana. It helps aid by organizing blood donation camps, awareness programs, and 24-hour blood center and free medical camps. Also provide free medicines, record growth of children, specialized team of doctors, free BMT, blood transfusion, diagnostic, treatment, and genetic counseling [62].

Jai Vigyan Program

With the ICMR center program for community control of thalassemia disease medical colleges in various states able to screen pregnant women and students and estimate the prevalence of beta thalassemia and other hemoglobinemia diseases in six states [63].

Project Rainbow

Central and state governments along with the different NGOs and parents-patients societies as well as corporate houses work together for care of thalassemia patients in Punjab [64].

Thalassemia Bal Sewa Yojana

Its portal improves screening of disease, providing awareness and counselling opportunities and increase treatment facilities. This program has successfully performed multiple bone marrow transplants for thalassemia patients [65].

IAP-Guidelines

Guidelines explain meaning, classification, sign, and symptoms, treatment, complications and prevention of thalassemia. It explains parents' role and child expectations in school, vaccinations, marriage, and conception planning [45].

CONCLUSIONS

Thalassemia syndromes are inherited disorders with a complex pathophysiology and multi-organ involvement. Existing treatment modality may lead to prolonged survival and a good quality of life. Not all patients have access to comprehensive, high-quality care. Pediatric nurses can bridge this gap by teaching self-care and providing comprehensive care to the thalassaemic children. Emerging new treatment modalities, such as genetic therapy, are likely to benefit those able to afford and can avoid the struggle with conventional treatment of thalassemia. Screening of population and genetic counseling can be helpful in reducing disease burden. Various programs and initiatives have been taken in India and worldwide, but integration of information and services for reducing the soaring number of cases and provision of treatment to a larger population.

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