Child India

Monthly e-Newsletter of Indian Academy of Pediatrics

May 2021

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Editor's Note

Dear friends,

May greetings from Child India, your monthly IAP e newsletter.

This month we dedicate to the children and families under our care who are growing with Thalassemia as we celebrate the International Thalassemia Day ON May 8th. The Thalassemia International Federation's (TIF) theme for 2021 is 'Addressing Health Inequalities Across the Global Thalassaemia Community'. This theme is directly associated with the "Global Thalassaemia Report", an ambitious work the TIF has been developing these past few months which documents the current state of provided healthcare to patients with thalassaemia across the world and highlights the vast inequalities and unmet needs that afflict them.

In India, every year 15,000 children are born with thalassemia which accounts for approximately 10% of the total world incidence of thalassemia-affected children and one in eight of thalassemia carriers live in India – it is estimated that nearly 42 million in India have β-thalassemia trait. Communities in which it is more prevalent are Sindhis, Punjabis, Gujaratis, Bengalis, Mahars, Kolis, Saraswats, Lohanas, and Gaurs. In West Bengal and Northeastern states, specifically Hb E, a variant of hemoglobin, significantly contributes to the disease burden.

Community level and facility level are the two levels of child screening under RBSK. Facility-based screening includes newborn screening done at public health facilities – primary health centres, community health centers, and district hospitals conducted by medical officers, staff nurses, and auxiliary nursery midwives. Community-level screening includes a screening of newborn done by mobile health teams at Anganwadi centers and government schools. We need to advocate universal screening. We must go further and ensure facility for chorionic villi sampling for prenatal diagnosis and legalise abortion laws so as to reduce the burden of thalassemia in the Indian scenario.

Safeguarding equal access to safe and high-quality blood supply, creating a 'Haemoglobinopathy e-registry', supporting organisations like Federation of Indian Thalassemics andThalassemics India, creating local Thalassemia support groups are priority. There are robust laws and policies like RPWD Act 2016 and NHM in place but implementation in Indian States must improve and we need to help formulate a National Thalassemia Policy as directed by the Hon'ble Supreme Court of India.

We are thankful to Indian Academy of Pediatrics and the IAP Pediatric Hematology Oncology (PHO) Chapter in particular for creating an awareness of the issues related to thalassemia in India, their efforts in helping these wonderful children have an exciting future and for contributing to this issue of Child India.

Let us together become Thalassemia advocates

Jai India, Jai IAP,

Dr Jeeson C Unni
Editor-in-Chief

President's Address

Dear colleagues,

Greetings!

The May issue of Child India is dedicated to International Thalassemia Day – May 8th - the theme for 2021 is 'Addressing Health Inequalities Across the Global Thalassaemia Community' and IAP needs to pitch in to make this theme a reality.

It is estimated that India has roughly one lakh persons with thalassemia, 42 million carriers of the β-thalassemia trait, only 20% being diagnosed, very few among them being optimally managed, and even fewer having the wherewithal to undergo allogeneic stem cell transplant.

A feasible option for control is to promote education and awareness programmes, intensify screening in all the states with micromapping to assess the true burden, and develop adequate facilities for genetic counselling and prenatal diagnosis in public sector institutions. Government and non-government organizations have been working towards this goal for the last 3 to 4 decades but community control in a vast and diverse country is challenging and a national programme reaching all rural regions where almost 70% of the population resides is yet to begin.

Awareness among professionals, school and college students, pregnant women, NGOs and the population at large has been attributed to the success of prevention programmes in the Mediterranean region.

Data for 456,646 ever-married women aged 15-49 years, analysed from the National Family Health Survey (NFHS)-4 conducted in 2015-16 showed an overall consanguineous marriage prevalence of 9.9% in India; the South region (23%) and North-East region (3.1%) showed the highest and lowest prevalences, respectively. This figure needs to be pegged down drastically to reduce the burden of this autosomal recessive disorder.

World Asthma Day is organized every year by the Global Initiative for Asthma on the first Tuesday of May – May 4th this year – the theme for 2021 is "Uncovering Asthma Misconceptions". The theme provides a call to action to address common widely held myths and misconceptions concerning asthma that prevent persons with asthma from enjoying optimal benefit from the major advances in the management of this condition.

This month let us put our efforts into programs dealing with these two conditions that cause considerable childhood morbidity.

Warm regards,

Piyush Gupta
National President, IAP 2021

Secretary's Message

Dear all,

Greetings from Indian Academy of Pediatrics!

The Indian Academy of Pediatrics has done a very spectacular job this month. One of these to mention is 'initiating the process of agreement with Ministry of Women and Child Development, Govt. of India for services to Child Care Institutions'. As the Secretary General of the Indian Academy of Pediatrics, I would like to thank the Hon'ble Smt. Smriti Irani Ji, Minister, Ministry of Women and Child Welfare, Government of India. There is no doubt that we will do a great job together for the welfare of children in India.

On behalf of the Indian Academy of Pediatrics, I heartily congratulate our esteemed President Dr. Piyush Gupta Ji for this achievement. His tireless work and perseverance are truly commendable.

I am also happy to inform you that, India is hosting the conference of the International Pediatric Association (IPA) in 2023. The President of the conference is Dr. Bakul Jayant Parekh and the Chairperson of the scientific program of the conference is Dr. Santosh Soans. Congratulations to both of them for this honor and for making the name of the Indian Academy of Pediatrics across the seas and wish them success in their future endeavors.

A team is needed to carry out any task successfully and I think the Indian Academy of Pediatrics is very lucky in this regard. I thank all our Office Bearers, Executive Board Members, Committee Members who work day and night to complete any task.

We had a very successful Administrative Meeting via Video Conferencing with the IAP Office Bearers Meeting on 11th May 2021. My heartfelt thanks to everyone involved for participating in this meeting.

We have had many other committees that met this month like IAP SOP Committee Meeting which was held on 3rd May 2021, IAP Child Welfare Committee Meeting also various Zonal meetings regarding ongoing Mission Co-Win Uday Programs. We also had the Periodic Review Meeting of CIAP staff on 2nd May 2021.

Secretary's Message

This month we have started virtual workshops of our flagship program Mission Co-Win Uday. We are organizing virtual events all over India. So far, we have conducted programs in Delhi, Punjab, West Bengal, Odisha, Jharkhand, Maharashtra, Gujarat, Karnataka, Kerala, Tamilnadu, Telangana, Uttar Pradesh, Northeast, etc.with. a total of 25 programs have been conducted. There are many more such programs in the pipeline for upcoming days.

We have conducted other programs like West Zone ToT module "Transport of Sick kids (Task module)" on 22nd May, ToT East Zone "Transport of Sick kids (TaSK module)" on 15th May 2021, West Zone ToT module "Transport of Sick kids (Task module)" on 22nd May. "Childhood Allergic Diseases Education Module (CADE Module)" on 07 May 2021 & 08 May 2021. There will be many programs of WAR Module, CADE, module, Dysbiosis Module, etc. in the pipeline.

Last but not least, it is worth mentioning the efforts and hard work of Indian Academy of Pediatrics Central Office staff in handling all these programs successfully. I would like to thank and congratulate all the office staff for keeping the office running smoothly and accurately even during the current COVID 19 Pandemic.

Overall, the month of April has been very fruitful and focused on academic growth for members and we look forward to having more such activities in the coming months.

Thanking you!

Jai IAP!! Jai Hind!!

Sincere Regards,

Dr G V Basavaraja
Hon. Secretary General 2020 & 21
Whats app no: 82770 21754

World Asthma Day message

Uncovering Asthma Misconceptions

Prof. Subramanya N K
President, IAP National Respiratory Chapter

In 2021, India ranks 2nd with 37.8 million population suffering from Asthma. But what concerns more is the mortality/death rate where India ranks 1st in world map with 42% contribution to global overall mortality cases.

Is it that we do not have the right medicines to treat asthma?

Are we resource crunched to control the mortality rate?

The answer to is **NO**

With wide range of drugs & devices widely available, the *ASTHMA CONTROL* in India should have been in good state. But then, what makes it difficult to achieve. The probable answer is – **Lack of right knowledge about the disease among patients & caregivers.**

Globally, GINA has announced the theme for 2021, on the eve of world asthma day, (5th May2021) "Uncovering Asthma Misconceptions" IAP national Respiratory Chapter conducted various programmes on the theme like Quiz, ATM trainings, posters dissemination, TV shows, news and media dissemination and so on.

Still in India today, inhalers are perceived as taboo, hence asthmatics most of the times do not accept the therapy. It is the myth & misconception surrounding Asthma which makes it difficult for an asthmatic lead a normal life.

Here is the list of some common myths uncovered with facts backed up by evidence & research; you may add a few from *your experience* as well!

Myth	Fact
Asthma is uncommon, my child may not be the one	Nearly more than10% population have asthma, we are no exception!
Everyone with asthma experiences the same symptoms	Not only do symptoms of asthma differ from one patient to the next Symptoms can also vary from episode to episode in the same person One patient might have several symptoms including cough, wheezing, and chest tightness Another might only have shortness of breath
All asthma is same.	There are multiple variants of asthma and they all have different triggers. For example, non-allergic asthma can be triggered by things like cigarette smoke, extreme weather, or even stress Exercise-induced asthma is triggered by physical activity. Asthma also varies in severity

Should I call it Asthma, Allergic bronchitis, Hyper reactive airway disease?	Reactive Airways Disease" (RAD) – highly non-specific with no clinical meaning. Reactive airways dysfunction syndrome (RADS) is different diagnosis as well. Let us use only ASTHMA
Asthma is an adult disease	Asthma can affect people of any age. Asthma prevalence is higher in children (9.4 percent) than in adults (7.7 percent)
Asthma cannot be diagnosed in young children	Asthma can be diagnosed at any age.
Children outgrow their asthma	Asthma symptoms may improve with age, but it's a lifelong condition. As a chronic condition, there is no cure for asthma and symptoms can resurface at any time
Asthma is due to an infection, it is contagious, infectious	People feel that one should stay away from an individual with chronic cough. That it may be TB Asthma can be caused by both hereditary and environmental factors. It is not due to infection and it is not contagious.
Asthma can't be fatal	Lack of adherence can lead to worsening of the situation. Stopping inhalers on their own can be dangerous. A 16 yr old boy collapsed from a severe asthma attack after a school physical education class. Class did a mile run. Was taken to nearby hospital ED. The H/o wheeze was known to the school but he never had a severe wheeze. He was declared brought dead. Asthma can kill irrespective of severity level 1/3rd deaths are in those with mild asthma 1/3rd deaths are in those with moderate asthma 1/3rd deaths are in those with severe asthma
Asthma has nothing to do with allergies	70% of people with asthma have allergies. Allergies increase lung inflammation and cause coughing and wheeze. Treatment of allergies can alleviate asthma symptoms
If I'm not wheezing, it's probably not asthma	Asthma can have variable symptoms. One doesn't always have to be wheezing, to have asthma. A few people wheeze, some cough, some are short of breath, and some have a combination of symptoms Wheezing usually occurs when airways are constricted The absence of wheezing doesn't mean asthma is inactive. Wheezing could be audible but sometimes it can only be heard with a stethoscope The absence of wheezing may occur if the flare is very severe and prevents any air movement in part of the lung Wheezing is tip of iceberg!

Diagnosis of asthma requires investigations to confirm	Asthma is a clinical diagnosis. Wherever possible and feasible do PFTs
Asthma doesn't require treatment	Asthma is the cause hospital admissions and suffering, needs to be treated
I can't control my asthma	With scientific advice, asthma can be controlled, although it can't be cured.
Child with asthma shouldn't exercise	Exercise can be a trigger for some people With asthma, but the right treatment regimen can keep symptoms under control With good control of asthma, You can be winner in all sports! As long as their asthma is controlled, there is no reason children with asthma can't be physically active What exercises are best for people with asthma? • Swimming. Swimming is one of the most recommended exercises for people with asthma • Walking. As a low-intensity activity, walking is another great choice. ... • Hiking • Recreational biking. ... • Short-distance track and field. ... • Sports with short bursts of activity. Tips for children with exercise-induced asthma • If symptoms start, don't exercise until they stop • Warm up before exercise to prevent chest tightening. (Warm-up exercises can include 5–10 minutes of walking or any other light activity, plus stretching or flexibility exercises.) • Take rescue inhaler as close to the start of exercise as possible • Breathe through the nose during exercise • Take brief rests during exercise and use quick-relief medicine, as prescribed, if symptoms start • Cool down after exercise to help slow the change of air temperature in the lungs • Best not to exercise outside during very cold weather. If playing outside when it's cold, wear mask or a scarf over the mouth and nose • If air pollution or pollen are triggers, exercise indoors when air quality is poor or pollen counts are high. Avoid exercise when having • upper respiratory infection • Always have access to their rescue inhaler. Keep extras on hand and be sure to check all supplies so child is NOT carrying an empty inhaler

Asthma can be cured.	Asthma has no cure. It can be controlled by medications.
I can take oral drugs, not inhalers	Inhalation therapy is best, locally acting, very low doses, safe, no addictive, effective, affordable and easy to lean
I can take directly from inhaler device	No. You must use spacer with meter dose inhalers to ensure proper drug delivery even in adults Use of inhaler without a spacer - most of the medicine ends up inside mouth or stomach, instead of lungs The spacer acts as a holding chamber where the medicine sits as a fine mist that you can then breathe in very slowly
I can use nebulizers at home	You may end up using only relievers and not control the disease at all!
A rescue inhaler (SABA) is the best treatment you need for asthma.	Short-acting or rescue inhalers are just acute flare ups, not for long term use The treatment might also include long-term ICS
You only need to treat your asthma flare up once you're having trouble breathing only	You must take long term medications, mainly inhaled corticosteroids
Inhalers are addictive and lose their effectiveness over time.	Inhalers are not addictive and are generally safe. More often than you're used to, it doesn't mean the medicine isn't working anymore. It means that your asthma may have become more severe or it might not be the right medication for you. The chronic nature of asthma requires a specific routine of long-term medication use. This does not mean these medications are addictive
Regular usage of asthma medications will lead to tolerance and the drugs will not have effects on you.	Different medications work differently. Some medicines work only when you take them every day and some work when you take them to treat symptoms. Results of studies show that prolonged treatment with therapeutic doses of inhaled beta-adrenergic bronchodilators does not result in drug tachyphylaxis, which is in accord with the clinical experience that there is no loss of effect of the preparations during their continuous administration.
Steroids!	Inhalation steroids are safe and do not have any side effects in low to medium doses which most asthmatics require
Steroids used in asthma are dangerous	Inhaled corticosteroids (ICS) are the preferred treatment for persistent asthma. When used at recommended doses for most patients, the benefits of ICS outweigh the risks. These steroids are NOT the same as the anabolic steroids some athletes use to build muscle Not using inhaled corticosteroids regularly results in potentially life-threatening asthma attacks

Steroids used in asthma will stunt growth.	Inhaled corticosteroids do not prevent children from reaching their full height. Studies have shown that children using inhaled corticosteroids will reach normal adult height, although it may cause some delays in their growth early on. It is possible that a child who suffers from asthma symptoms regularly may experience stunted growth. This is due to the fact that a sick child will not grow at the same rate as a well-child. In fact, evidence shows that children who are under-treated are shorter
Allergy immunotherapy can cure	Immunotherapy or allergy shots should be considered by experts in the field only exposure to unavoidable allergens. They are especially helpful when symptoms occur year-round or are not easily controlled with medication in spite of controllers
Can I take up alternative medicine like Ayurveda, homeopathy etc.?	They should not be substitute for sound scientific advice from your Pediatrician
Asthma is all in your mind.	Asthma is real. It takes place in the airways and lungs, not in the mind. Emotions, such as stress, crying, yelling or laughing hard, can act as asthma triggers causing already existing Asthma to flare up or become worse. Having a potentially life threatening disease such as severe asthma also increases anxiety and depression in many patients and may trigger panic attacks in some
Asthma happened because I didn't take care of the child	No. Some people are born with a predisposition toward developing asthma.
I can control asthma by avoiding triggers alone	No, you have to have multipronged approach. What actually triggers the disease can vary from person to person. Common triggers include: Indoor and outdoor allergens like Smoking, Air pollution, Pollen, Allergens from animals and insects, abrupt weather changes, biological contaminants such as mold, and viral infections.
I smoke outside, my children are safe	Tobacco and smoke: Studies show that children whose parents smoke are twice as likely to develop asthma as children of nonsmoking parents. Also, children whose mothers smoked during pregnancy tend to be born with smaller airways, which greatly increase their chances of developing the disease
I am normal when I don't have symptoms	Chronic symptoms may not be well perceived. The inflammation in airways will be persisting though you are free of symptoms
I don't get flare ups!	Acute flare ups are difficult experience which one gets in episodic fashion. However you can have chronic symptoms and may not perceive well and live with acceptance of compromised fitness.
There aren't that many people with asthma; it's just a bunch of media hype.	The prevalence of asthma is high, and significant

I need to suffer, sorry	You can win your asthma, if you control A good control is a cure
Asthma causes learning difficulties and school absence	Asthma is not the cause of LD Compared with children whose parents described their asthma as mild, those with severe asthma were three to four times more likely to have ADHD, depression or any behavioral or learning disorder School absenteeism due to uncontrolled asthma or any other chronic illness may contribute to scholastic backwardness Students with uncontrolled asthma are more likely to perform worse in all subjects than students with controlled asthma
Asthma only involves the airways only	Asthma is considered as a clinical and molecularly heterogeneous disorder. Systemic inflammation is suggested to play an important role in a group of asthma patients There is a subgroup of patients with asthma characterized by systemic inflammation
Asthma is not a big deal and it's easily controlled!	All asthma is serious and don't ignore the disease. Achieve control. Consult your Pediatrician

Dear all, Give your time, not prescription. We can, win over asthma and our children can breathe free!

Stay safe and stay free!

Molecular Basis and Molecular Diagnosis in Thalassemia Major

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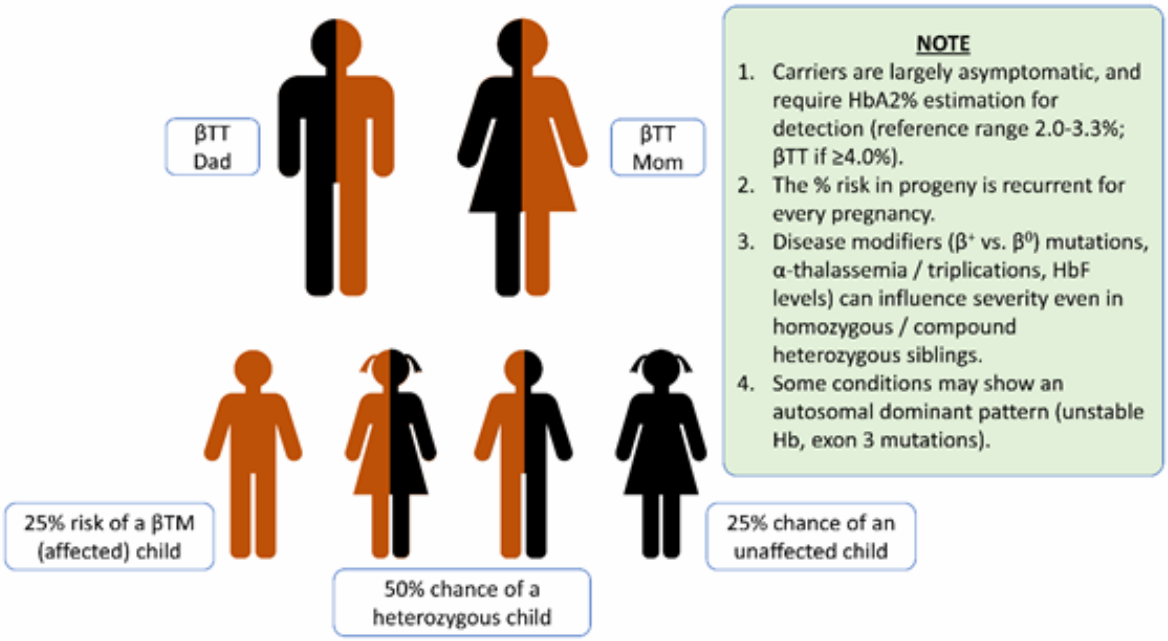
Introduction

- Hemoglobin (Hb) is an intra-erythrocytic tetrameric metalloprotein molecule that is involved in oxygen transport.
- It is composed of two pairs of dissimilar globin polypeptide chains (for e.g., α2β2 in adult Hb or HbA and α2γ2 in fetal Hb or HbF). Each of the chains is associated with an iron protoporphyrin IX group called heme.
- Thalassemias are genetic disorders characterized by reduced or absent production of an otherwise structurally normal globin chain.
- Based on the specific chain depleted, they are labelled α, β, γ, δ or δβ thalassemias (for e.g., the β-globin chains are deficient in β-thalassemia).
- Autosomal recessive in inheritance (Figure 1), they span a wide phenotypic spectrum and may be labelled clinically as thalassemia major, intermedia or minor. Hence, understanding the molecular basis is the key to understanding the phenotype in a particular patient. (Fig. 1)

Basics of the normal globin chain structure:

- The β-globin gene cluster is located on the short arm of chromosome 11 (11p15.5) and includes 5 functional genes, 5'-□-Gγ–Aγ-δ-β-3'.
- A locus-control region (LCR) located upstream of this cluster is a powerful enhancer of globin gene expression and regulates the fetal to adult Hb switch in the first year of life. Several polymorphisms in the LCR may elevate HbF even in adults, leading to beneficial effects in β-thalassemia.
- The β-globin gene (called HBB) consists of 3 exons (transcribed regions) separated by 2 introns or intervening sequences (IVS). The exonic segments when spliced together code for the final amino acid polypeptide chain. Mutations at splice sites are extremely deleterious for the protein.
- Exon 1 codes for non-heme-binding regions, exon 2 contains heme-binding amino acids and those responsible for ββ dimer formation while exon 3 contains amino acids involved in globin subunit interactions required for the Bohr Effect and 2,3-diphosphoglycerate binding.
- Like all highly expressed genes, HBB has 5' promoter regions along with enhancer sites. A 5'-untranslated region (UTR) distal to the promoter contains the CAP site marking the start of transcription of mRNA, and the initiation codon (ATG) indicating the start of translation of the polypeptide.
- A 3'-UTR between the stop codon (TAA) and the subsequent poly (A) tail is also of relevance in gene regulation.

Figure 1. The thalassemias show classical autosomal recessive inheritance patterns



- The 4 α-globin genes are located in pairs (HBA1 and HBA2) on the homologous chromosomes 16. They too contain upstream, intragenic and distal regulatory elements.
- In addition, for all genes (HBB, HBA1, HBA2), several trans-acting regulatory elements located outside of the α or β-globin gene clusters are known, including transcription factors ATRX, GATA1, EKLF/KLF1, NFE2, FOG1 etc.

Molecular basis of β-thalassemia

- The majority of β-thalassemias arise from point mutations involving one nucleotide (or a limited number of nucleotides) within the β gene or its immediate flanking regions. However, several less common exceptions are also known. Table 1 lists the major mechanisms of mutations causing β-thalassemia, their functional consequences and the 5 common Indian mutations.
- The quantitative defect in β-thalassemia may result in either complete (β0) or partial (β+) absence of β-globin chains. A primary modifier of β-thalassemia severity is therefore the type of β allele inherited (i.e., β0, β+, β++). Table 2 lists the modifiers of the disease.
- β-thalassemia major (βTM) usually results from the inheritance of two β0 alleles. Most patients with two β+ or β++ alleles (or their combinations) have a milder disease, labelled as β-thalassemia intermedia (βTI).
- Reduced β-globin production results in accumulation of excess α-globin chains in βTM and βTI that precipitate in the developing erythroblast, inducing intramedullary death. Phenotypic severity is therefore related to the extent of α- and non-α-globin chain imbalance. Coinheritance of α-thalassemia (by reducing free α-chains) ameliorates βTM or βTI. Coinheritance of α-globin gene triplications (i.e., extra copies) can induce a mildly symptomatic state (βTI-like) even in β-thalassemia trait (βTT).
- Co-inheriting an inherent ability to increase γ-globin chain production (like hereditary persistence of fetal Hb) also results in milder phenotypes in βTM or βTI, as the additional γ-globin chains combine with excess α globin to form fetal-type hemoglobin (HbF, α2γ2).

Table 1. Salient mechanisms by which HBB mutations lead to thalassemia

MUTATION	FUNCTIONAL CONSEQUENCE	ETHNICITIES PRIMARILY AFFECTED
POINT MUTATIONS AND SMALL INSERTIONS/DELETIONS		
I. Mutations that Alter Gene Transcription i.e., mRNA Synthesis		
Those affecting promoter regulatory elements		
−88 (C → T) or −101 (C → T)	β^{++} (silent &/or mild)	Asian Indians (esp. Jatt Sikhs) and Mediterranean
Those affecting the 5′ UTR		
CAP +1 (A → C)	β^{++} (silent & mild)	Asian Indian [it is a "silent" mutation, i.e., carriers have near-normal RBC indices as well as HbA_2 levels]
II. Mutants that affect mRNA Processing		
Affecting splice junctions		
IVS1-1 (G → T)*	β^0	Asian Indian, SE Asian, Chinese
Affecting consensus sequences splice sites		
IVS1-5 (G → C)*	β^0	Asian Indian, SE Asian, Melanesian
Creating/activating cryptic splice sites		
IVS2-837 (T → G) or CD10 (GCC → GCA)	?	Asian Indian
Affecting RNA cleavage—Poly A signal		
AATAAA → AACAAA or AATGAA or AATAGA	β^{++}	U.S. Blacks or Mediterranean or Malay respectively
III. Mutants that affect translation		
Involving the Initiation codon		
ATG→CTG or ATT	β^0	Chinese or Iranian respectively
Involving (creating/abolishing) the nonsense or termination codons		
CD15TGG → TAG	β^0	Asian Indian, Japanese
Leading to frameshifts in translation		
CD8/9 +G* or CD41/42 −TTCT*	β^0	Asian Indian, Japanese
DELETIONS OF THE HBB OR LARGER GENOMIC SEGMENTS		
I. Deletions restricted to *HBB*		
619 bp deletion involving the 3′ end of *HBB**	β^0	Asian Indian
II. Upstream Deletions and $(\varepsilon\gamma\delta\beta)^0$-Thalassemia		
Mutations that remove all or nearly all of the cluster, including the HBB gene and β-LCR	β^0	Asian Indian, Mediterranean, East Asian, Chinese
β-THALASSEMIA TRANSMITTED AS A DOMINANT TRAIT		
Hb Terre Haute, Hb Gunma, Hb Korea	β0	Sporadic, ultra-rare, exon 3 defects with very unstable β-globin chains, inclusion bodies in erythroblasts

**These 5 common mutations, i.e., IVS 1-5 G>C, IVS 1-1 G>T, Codon 41/42 (-TCTT), Codon 8/9 and the 619 bp deletion account for over 90% of the mutations in Indian β-thalassemia patients.*

Table 2. Genetic Modifiers of β-thalassemia

Primary modifiers:	*HBB* mutations (β0, β+ or β++)
Secondary modifiers *(influence α/non-α chain imbalance)*	- **Coinherited α-thalassemia** (ameliorates βTM and βTI). Degree of reduction in severity is proportionate to the number of α-globin genes deleted. - **Coinherited α-triplications or quadruplications** may exacerbate $\beta^+\beta^+$ state to βTM, or may induce symptoms in βTT. - **Elevated HbF** (due to co-inherited hereditary persistence of fetal Hb due to Xmn1Gγ polymorphism, polymorphisms in the βLCR, *BCL11A* gene or the *HBS1L-MYB* intergenic region.
Tertiary modifiers *(influence the onset and severity of thalassemia complications)*	- *UGT1A1* promoter polymorphisms (Gilbert syndrome) for unconjugated jaundice - *HFE* gene polymorphisms for iron overload and *APOE* for redox damage and heart failure - *TGFB*, *COL1A1* (collagen type A1) and VDR (vitamin D receptor) polymorphisms for bone disease - Factor V Leiden, *MTHFR* and prothrombin gene polymorphisms for thrombosis

Laboratory diagnosis of β-thalassemia:

Laboratory diagnosis of β-thalassemia:

- Quantitation of HbF% and HbA2% using cation-exchange high-performance liquid chromatography (HPLC) or capillary zone electrophoresis (CZE) are standard tests to identify βTT, βTM and βTI. Clinical background, hemogram correlation and absence of recent blood transfusions are vital to avoiding misleading results.
- Screening for βTT: A simple but non-specific and sometimes insensitive screening test is analysis of hemogram data (normal or mildly reduced Hb, low MCV and MCH, normal or high RBC count, and normal or near-normal RDW). This is falsely positive in cases with α-thalassemia trait, δβ-thalassemia trait, HbE trait or homozygosity, Hb Lepore trait, iron deficiency on therapy and iron deficient polycythemia vera. This may be misleadingly negative or equivocal in βTT with coexisting iron deficiency, α-thalassemia, or any cause of red cell macrocytosis.
- Silent βTT (i.e., one that is missed by screening studies) occurs when the red cell indices and the HbA2 percentage are both normal. Examples of silent mutations include –101 C>T and CAP +1 A>C in Asian Indians.
- Mutation analysis only commences after the screening tests, and is not required in all cases.

Indications for genetic testing in thalassemia:

- Children in whom the diagnosis is unclear. Circumstances in which this may occur include:

o The child is recently and/or continuously transfused and HPLC or CZE are not possible.

- Children in whom both parents have βTT, but differential diagnoses other than βTM/TI are not excluded; for e.g., suspected CDA (may also show severe anemia, mild jaundice, hepatosplenomegaly, inappropriately low or normal reticulocyte counts), JMML, inherited bone marrow failure (both can have high HbF as well as some clinical overlap).
- Incongruent clinical phenotype vis-à-vis HPLC/CZE findings (for e.g. very high HbF but few or no symptoms; HPLC suggesting βTT but the child is symptomatic; variable clinical phenotypes between siblings with similar HPLCs)

• Prenatal diagnosis in couples at risk (i.e., where both partners have βTT and the lady is pregnant)

Genetic tests available

- Genetic testing is best planned in consultation with the laboratory, keeping in mind the specific clinical question(s) needing to be answered.
- Genomic DNA from peripheral blood mononuclear leucocytes is sufficient for all the routine molecular analysis.
- β-thalassemia mutations can be detected using the following techniques:
  - Automated DNA sequencing (Sanger sequencing): Rapid, broad application, requires expensive instrument.
  - PCR-based Amplification Refractory Mutation System (ARMS-PCR): Simple, cheaper than sequencing, tests one mutation at a time. Principle: A mismatch at the 3' end of one of the primers prevents the elongation of the primer by Taq polymerase.
  - Reverse dot-blot hybridization assay (inexpensive, screens for multiple mutations) and PCR-RFLP (available for specific mutations) are alternatives.
  - In cases where the mutation is not detected, methods like denaturing gradient gel electrophoresis (DGGE) or conformation sensitive gel electrophoresis (CSGE) have been used. Linkage analysis can be considered if mutation remains unknown.
- Genetic diagnosis of deletional α-thalassemia can be conveniently made by gap-PCR or MLPA (multiplex ligation dependent probe amplification). A multiplexed gap-PCR available permits testing for 8 common deletions in one test.
- Non-deletional α-thalassemia is most often diagnosed by Sanger sequencing.

Prenatal diagnosis

- Fetal sample-of-choice is the chorionic villous biopsy (CVS) sampled at 10-12 weeks of gestation. Lesser emotional trauma in case the fetus is affected.
- In the second trimester: option of amniocentesis and using fetal amniocytes as DNA source (14-18 weeks)
- Fetal blood sampling by cordocentesis (18 weeks onwards) is more complicated, less reliable diagnostically and hence, unpopular.
- Should discuss with the patient beforehand for all PND: Risk of pregnancy loss or limb defects (less than 1-2% with CVS), the family's personal attitudes to MTP if the fetus is found to be affected, minuscule possibility of an incorrect or inconclusive report due to non-amplification or maternal contamination.
- Pre-implantation Genetic Diagnosis (PIGD): Involves in vitro selection of unaffected embryos or less commonly, gamets, before pregnancy. The commonest PIGD sample is a

polar body or a single cell taken from 4-8 cell blastomere.

- Noninvasive prenatal diagnosis: This analyses fetal cells/cell-free fetal DNA from maternal blood.

Role of genetics in the post-stem cell transplant scenario

- The recipient's DNA specimen must be preserved by the lab for post-transplant chimerism analysis using STRs or VNTRs by fragment length analysis.

- Complete donor hematopoiesis is not mandatory for sustained engraftment. Mixed chimerism with even up to 30% of donor origin hematopoietic cells is not rare and may be sufficient to maintain disease-free red cell mass.

- Bone marrow/hematopoietic stem cell transplant may alleviate thalassemia in the index case, however the genetic risk of transmission to her/his offspring remains unchanged.

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Blood Transfusion in Thalassemia Major patients : General Guidelines

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Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. The purpose of transfusion is twofold: to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. However, once started, the transfusion-related complications become a major source of morbidity. Standards must be developed and maintained to ensure a safe and rational approach to the use of blood transfusions in the management of these rare disorders.

The decision to start transfusions is based on inability to compensate for the low hemoglobin (signs of increased cardiac effort, tachycardia, sweating, poor feeding, and poor growth), or less commonly, on increasing symptoms of ineffective erythropoiesis (bone changes, massive splenomegaly). The decision to institute chronic transfusion should not be based exclusively on the presence of anemia. The decision to initiate chronic transfusion therapy requires significant input from the patient, family, and medical team.

Decision of blood transfusion:

The decision to start regular transfusions is clear when the initial hemoglobin level is well below 6 g/dL. To assess a child's need for routine transfusions due to thalassemia, anemia caused by sepsis or viral infection must be ruled out. Assessment may be accomplished by withholding transfusions and monitoring weekly hemoglobin level. If the hemoglobin drops under 7 g/dL on two occasions, two weeks apart, then regular transfusions should be commenced.

Patients with a hemoglobin level less than 7 g/dL may sometimes require regular transfusions in the presence of growth impairment, marked skeletal changes, or extramedullary hematopoiesis.

Transfusions should generally be given at an interval of three to four weeks. (With aging patients, a transfusion every two weeks may be necessary.) Transfusions should be scheduled in advance and maintained at a fixed schedule. This enables patients and families to establish routines and will improve quality of life.

The amount of blood received on transfusion day is determined by pre-transfusion hemoglobin levels. The target is to maintain the pre-transfusion hemoglobin level between 9 and 10 g/dL. Attempts to maintain pre-transfusion hemoglobin at above 10 g/dL increase transfusion requirements and the rate of iron loading. Transfusions should be given in an outpatient setting with an experienced transfusion team that uses proper safety precautions. Blood should be transfused at 5 mL/kg per hour, and the post-transfusion hemoglobin should not exceed 14 g/dL.

In patients with severe anemia (hemoglobin less than 5 g/dL) or cardiac compromise, the rate of transfusion should be reduced to 2 mL/kg per hour to avoid fluid overload. Diuretics such as furosemide (1 to 2 mg/kg) may be necessary for some patients.

If cardiac insufficiency is present, higher pre-transfusion hemoglobin levels (10 to 12 g/dL) should be maintained with smaller volume transfusions given every one to two weeks.

The patient's weight and pre-transfusion hemoglobin and the volume of transfusion should be recorded at each visit. These values should be periodically reviewed to assess the volume of blood required to maintain the desired pre-transfusion hemoglobin level. Annual blood transfusion requirement in patients without hypersplenism is usually below 200 mL packed red blood cells/kg per year.

Quality of blood components:

To safeguard the health of the transfusion recipient, including patients with thalassaemia, blood should be obtained from carefully selected regular voluntary, non-remunerated donors and should be collected, processed, stored and distributed, in the context of dedicated, quality assured national blood transfusion centres.

Blood donation practices, donor selection (e.g., through questionnaire) and product screening constitute some of the most important strategies that contribute to the safety and adequacy of blood. Quality management system at the transfusion service needs to be maintained as per national standards & legal requirements.

Mandatory screening of blood for HIV, hepatitis B, hepatitis C, malaria and syphilis is to be ensured. Nucleic acid testing (NAT) is optional, but desirable to reduce the chance of transfusion transmitted infections.

Type of Blood component:

Patients with β-thalassaemia major should receive leucoreduced packed red blood cells with a minimum haemoglobin content of 40g.

Reduction to 1 × 106 or less leucocytes per unit (mean counts as low as 0.05 × 106 are achievable) is considered the critical threshold for eliminating adverse reactions attributed to contaminating white cells and for preventing platelet alloimmunisation. The various methods of leukoreduction are:

- Pre-storage filtration of whole blood is the preferred method for leucoreduction. This method of leucocyte removal offers high efficiency filtration and provides consistently low residual leucocytes in the processed red cells and high red cell recovery. Packed red cells are obtained by centrifugation of the leucoreduced whole blood.

- Pre-transfusion, laboratory filtration refers to the filtration at the blood bank laboratory of packed red cells, prepared from donor whole blood.

- Bedside filtration refers to the packed red cell unit which is filtered at the bedside, at the time of transfusion. This method, although equally sensitive to those above, may not allow optimal quality control because the techniques used for bedside filtration may be highly variable.

Compatibility Testing:

Development of one or more specific red cell antibodies (alloimmunisation) is a common complication of chronic transfusion therapy. Thus it is important to monitor patients carefully for the development of new antibodies and to eliminate donors with the corresponding antigens. Anti-E, anti-C and anti-Kell alloantibodies are the most common.

It is recommended that:

- Before embarking on transfusion therapy, patients should have extended red cell antigen typing that includes at least C, c, E, e and Kell, in order to help identify and characterise antibodies in case of later immunisation;

- All patients with thalassaemia should be transfused with ABO and Rh(D) compatible blood.

In addition, the use of blood that is also matched for the C, E and Kell antigens is highly recommended in order to avoid alloimmunisation against these antigens. Some centres use even more extended antigen matching.

- Before each transfusion it is necessary to perform a full crossmatch and screen for new antibodies.

If new antibodies appear, they must be identified so that in future blood lacking the corresponding antigen(s) can be used. A complete and detailed record of antigen typing, red cell antibodies and transfusion reactions should be maintained for each patient, and should be readily available when and if the patient is transfused at a different centre. Transfusion of blood from first-degree relatives should be avoided because of the risk of developing antibodies that might adversely affect the outcome of a later stem cell transplant.

Adverse transfusion reaction:

Blood transfusion exposes the patient to a variety of risks. Thus, it is vital to continue to improve blood safety and to find ways of reducing transfusion requirements and the number of donor exposures. Broad categorisation of immune-mediated transfusion related reactions and reported frequencies.

- Nonhaemolytic febrile transfusion reactions: These were common in past decades, but have been dramatically reduced by leucoreduction, especially pre-storage leucoreduction, which sharply reduces cytokine accumulation and leucocyte alloimmunisation. In the absence of effective leucoreduction, patients experiencing such reactions should be given antipyretics before their transfusions.

- Allergic reactions are usually due to plasma proteins and range from mild to severe. Milder reactions include urticaria, itching and flushing, and they are generally mediated by IgE. More severe reactions, such as stridor, bronchospasm, hypotension or other symptoms of anaphylaxis may occur. Occasional mild allergic reactions often can be prevented by the use of antihistamines or corticosteroids before transfusion.

- Acute haemolytic reactions begin within minutes or sometimes hours of beginning a transfusion and are characterised by the abrupt onset of fever, chills, lower back pain, dyspnea, hemoglobinuria and shock. These unusual reactions most commonly arise from errors in patient identification or blood typing and compatibility testing. The risk of receiving the wrong blood is greater for a patient with thalassaemia who travels to another centre or is admitted to a hospital not familiar with his/her case and medical history. Haemolytic reactions in these patients can still be avoided by (1) the use of optimal methods for identifying the patients and labelling of the sample when blood is obtained for crossmatch, (2) proper linkage of the sample to the donor unit in the blood bank, (3) adherence to standard protocols for screening for antibodies and carrying out the necessary full crossmatching of donor units and (4) use of multiple patient identifiers before transfusing the blood. In many transfusion units, two staff members check the identification of the unit and the recipient prior to beginning the transfusion.

If signs and symptoms suggest an acute haemolytic reaction, the transfusion should be stopped immediately and intravenous fluids should be administered to maintain intravascular volume. Diuretics may help to preserve renal function. The identification of the patient and the donor unit should be re-checked. The blood bank should also be alerted to the possibility of an undetected alloantibody.

- Delayed transfusion reactions usually occur 5–14 days after transfusion and are characterised by unexpected levels of anaemia, as well as malaise and jaundice. These reactions may be due to an alloantibody that was not detectable at the time of transfusion or to the development of a new antibody. A sample should be sent to the blood bank to investigate the presence of a new antibody and to repeat cross-matching of the last administered unit(s).

- Autoimmune haemolytic anaemia is a very serious complication of transfusion therapy that usually but not always occurs in patients with alloantibodies. Even red cells from seemingly compatible units (i.e., those units that do not contain the antigen to which there is a known alloantibody) may demonstrate markedly shortened survival, and the haemoglobin concentration may fall well below the usual pre-transfusion level. Destruction both of the donor's and the recipient's red cells occurs. The serologic evaluation by the blood bank usually shows an antibody that reacts with a wide range of test cells and fails to show specificity for a particular

antigen. Steroids, immunosuppressive drugs and intravenous immunoglobulin are used for the clinical management of this situation, although they may give little benefit.

- Transfusion-associated circulatory overload may occur in the presence of recognised or unrecognised cardiac dysfunction, or when the rate of transfusion is inappropriately fast. Signs and symptoms include dyspnoea and tachycardia, and the chest radiograph shows the classic findings of pulmonary oedema. Treatment focuses on volume reduction and cardiac support, as required.

- Transmission of infectious agents including viruses, bacteria and parasites, are a major risk in blood transfusion. Transmission of viruses HIV, HBV & HCV still occurs (window period, sensitivity threshold of tests). It is recommended to adopt NAT testing proactive along with serology testing.

Summary:

It is recommended for transfusion of thalassemia patients to have

- Careful donor selection and screening – voluntary, regular non-remunerated blood donation.

- Before initiation of transfusion therapy, confirm laboratory and clinical criteria.

- Before first transfusion, extended red cell antigen typing of patients at least for C, E and Kell.

- At each transfusion, give ABO, Rh(D) compatible blood. Matching for C, E and Kell antigen is recommended.

- Before each transfusion, full cross-match and screen for new antibodies.

- Use leucoreduced packed red cells. Pre-storage filtration is recommended, but blood bank pre-transfusion or bedside filtrations are acceptable alternatives.

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Monitoring of patients with Thalassemia Major

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The last few decades have seen major strides in the management of thalassemia. As a result, both the life span and health related quality of life (HRQoL) of patients living with thalassemia has improved dramatically. This, however, require optimal management of this condition. Ongoing monitoring is an integral part of optimal care of patients with thalassemia. It allows us to prevent chronic complications, detect them early and manage them optimally. It is only through meticulous monitoring that we can ensure optimal HRQoL of these patients.

Monitoring in patients with transfusion dependent thalassemia (TDT) is multidimensional and has many aspects.

- General Monitoring
- Monitoring of safety and adequacy of transfusion
- Monitoring for safety for adequacy of chelation
- Monitoring for chronic complications
- Monitoring for specific situations

General monitoring

As for all children and adolescents, growth should be monitored on an ongoing basis. Mid-parental height should be documented to ensure that the child is achieving his/her growth potential. Especially, pubertal development should be monitored regularly between the ages of 11-14 years. Specialist endocrinology input should be sought if puberty is not initiated spontaneously by 14 years of age. It goes, without saying that other aspects of healthcare such as immunization are also continued without interruption as for other healthy children. Specifically, these patients should receive hepatitis A and B vaccines with documented titers of Anti HbS. If Anti HbS titres are not in the protective range, patient must receive a booster dose. The degree of splenomegaly and facial changes, if any, should be documented and transfusion regimen optimized. It is also important to monitor that the child is attending school regularly and engaged in normal physical activity.

Monitoring for safety and adequacy of transfusion

It is recommended that all patients with transfusion dependent thalassemia undergo extended red cell phenotyping at diagnosis.

Though it may not be feasible for all patients to receive extended phenotype matched blood at present, this may at least be considered in the event of alloimmunisation.

Hemoglobin should be measured prior to each transfusion. Patients should maintain pre-transfusion Hb of 9.5-10.5. The quantity of packed red cells transfused should be documented to allow assessment of ongoing transfusional iron intake. In case of transfusion requirements in excess of 250 ml/kg/year, patients have to be evaluated for reasons for the same. Packed red cells transfused should be leucodepleted ideally at collection but if this is not feasible that bedside filters can be used. Any transfusion reactions should be documented.

Patients should be screened annually for Hepatitis B, C and HIV

Monitoring for Adequacy and safety of Chelation

Adequate chelation is the most important aspect to prevent development of other chronic complications. Chelation must be initiated once S. ferritin is above 1000.

The chelator of choice is Deferasirox (DFX). It is important to remember that this agent has dose-dependent pharmacokinetics and a minimum dose of 30 mg/kg must be administered to achieve negative iron balance. A dose of 20 mg/kg is expected to achieve neutral iron balance. For tight control of iron overload, S.Ferritin should be monitored 3 monthly along with SGOT, SGPT, S.Ferritin and urine for microalbuminuria.

The gold standard for monitoring of cardiac and liver iron overload is T2* MRI. This is usually feasible only after the age of 7 years or so as younger children would require sedation to undergo this procedure. This should be done annually, where available.

If optimal chelation is not achieved with Deferasirox or for patients who are unable to tolerate deferasirox for any reason, the options chelators are Desferroxamine (DFO) and Deferiperone.(DFP). Either of these can be given in combination with Deferasirox or alone. For patients receiving Deferiperone, patients should be assessed for arthralgias and CBC should be monitored fortnightly in view of the rare but catastrophic complication of agranulocytosis. Patients receiving Deferoxamine should undergo auditory and ophthalmic evaluations annually

An important aspect of ongoing monitoring for patients with thalassemia is ensuring compliance with the chelation regimen. As with all other chronic conditions, it can be appreciated that patients may lose enthusiasm to comply with a treatment regimen whose benefits are not evident immediately. Regular discussion regarding this aspect can go a long way to ensure adequate compliance

Monitoring for chronic complications

Patients with transfusion-dependent thalassemia are at risk of developing a number of chronic complications which are largely attributable to inadequate transfusion and chelation. Patients should be monitored for growth and pubertal delay.

All patients should undergo LFT and Calcium/ Phosphate assessments once in 6 months.

Above the age of 10 years, patients should be screened annually for hypothyroidism, hypoparathyroidism, hyperglycemia and gonadal function.

An echocardiogram annually after the age of 10 years can further substantiate adequacy of cardiac function.

Finally, osteopenia and osteoporosis are commonly seen in adolescents and adults with TDT. It is ideal that a Bone densitometry (Dexa scan) is done annually or once in two years to monitor bone health.

Monitoring for specific issues

Monitoring for Patients with increased transfusion requirement

Monitoring of Hb and volume of transfused packed red cells allows clinicians to determine if the transfusion requirements are higher than expected. The possible causes are:

- Alloimmunization
- Massive splenomegaly
- Micronutrient insufficiency

Patients can be screened for these. In case of alloimmunization, it is common to develop antibodies to C, E and Kell antigens and blood negative for these antigens can be given blood negative for these antigens.

Monitoring of Splenectomized patients

Fortunately, splenectomy is required infrequently for patients on optimal transfusion regimen. For those who have undergone this procedure, we must ensure compliance with pencillin prophylaxis, ideally lifelong, but for a minimum of five years following the procedure. We must also ensure:

- CBC 6-12 monthly. In case of thrombocytosis > 800,000 low dose aspirin should be given to the patient
- Influenza vaccine annually
- Pneumococcal vaccine every 5 years

In summary, regular monitoring is an essential part of optimal management for patients with transfusion dependent thalassemia. Tables 1 and 2 depict the parameters required for close monitoring in a tabular form.

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Table No 1: Monitoring for all patients

Genotype	At diagnosis
Transfusion regimen	
Current Medication	
Pre-Transfusion Hb	At Every visit
CBC	Fortnightly if on DFP
Growth	3 Monthly
Ferritin	3 monthly after 10th transfusion
SGOT / SGPT	3 monthly if on DFX otherwise 6 monthly
S. Creatinine	3 monthly if on DFX otherwise annually
Urine for micro albuminuria	3 Monthly if on DFX
Ca,PO4,Alk phos, Vit D3	6 Monthly
HBs Ag	Annually
Anti HBs	Annually
Anti HCV	Annually
HIV (ELISA)	Annually
Auditory evaluation	Annually if on DFO
Ophthalmic evaluation	Annually if on DFO

Table 2: Additional monitoring for patients for over 10 years of Age

PUBERTAL STATUS	Every 3-6 months till puberty completed
T4, TSH	Annually
GTT	Annually
LH/FSH	As indicated
Testosterone	As indicated
2 D ECHO	Annually
DEXA SCANS	Annually
T2 STAR MRI	Annually

Chelation therapy in transfusion -dependent thalassemia major

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Introduction

Thalassemia major is one of the most common hemoglobinopathies in India, with an estimated 10000 new births each year. Treatment of thalassemia major includes packed red blood cells (PRBC) transfusion every 3 – 4 weeks to maintain pre-transfusion hemoglobin above 9 g%. There is a serial and progressive accumulation of iron in tissues with proportionately increasing transfusions. The accumulated iron results in progressive organ damage, particularly affecting the heart, liver, and endocrine organs. Chelation of iron is an essential component in the management of thalassemia major. This article highlights the complications related to iron overload, techniques for detecting and estimating iron overload, and optimal chelation.

Transfusion and iron overload

Each unit of packed red cells delivers an estimated 200 mg of iron. The iron per ml of blood can be calculated using the formula 1.16 x hematocrit of the transfused product. Consequently, transfusion of 100-200 ml/kg of PRBC each year delivers an estimated 116-232 mg/kg/year of iron to an individual transfusion-dependent patient.

Non-transferrin bound iron (NTBI) or 'labile' iron

Iron overload, particularly in transfusion dependant thalassemia major, is associated with saturation of the transferrin in the body. The excess iron remains in the form of non-transferrin-bound iron. This labile iron is the predominant form of iron that causes tissue damage. The uptake of NTBI varies between organs, dependent upon the organ's capacity to respond to labile iron reflected by the calcium channels within the tissue. Consequently, myocardial tissue, hepatocytes, and endocrine organs accumulate NTBI rapidly as compared to other tissues. Iron is stored as ferritin or hemosiderin within the tissues.

Pathophysiology of tissue damage in iron overload

Iron is a highly reactive compound and generates significant free radicals while transitioning between the ferric and ferrous states. The reactive oxygen species and hydroxyl radicals generated are responsible for activating cytokines and inflammatory markers, including TGF-B1 and caspase. The resultant lipid peroxidation leads to organelle and DNA damage and subsequent apoptosis and cell death. Free radicals also form a bed for increased risk of infections.

Iron accumulation causes cardiomyopathy, cirrhosis, and endocrinopathies. The most commonly seen endocrine disorders are panhypopituitarism, hypogonadism, short stature, hypothyroidism, diabetes mellitus, osteopenia, osteoporosis, and infertility.

Techniques of measurement of iron overload

Serum ferritin is the most widely available, easily accessible, and inexpensive tool for measuring iron overload. As soon as the child completes 10 to 15 transfusions, we need to start serial ferritin estimation. Ferritin levels need to be maintained between 1000 to 2000 µg/L during chelation therapy. Ferritin is an acute-phase reactant, and we often

observe a falsely high value during periods of inflammation and infections. Serum ferritin may be low despite high tissue iron. Therefore, monitoring the trend in serum ferritin values is more reliable than a single estimate.

Liver iron concentration

Liver iron concentration (LIC) is the most reliable indicator of iron overload. Average values are up to 1.8 mg/g dry weight of the liver. Methods to detect LIC include biopsy, SQUID (superconducting quantum interface device), and MRI.

Cardiac iron concentration

Echocardiography to assess left ventricular ejection fraction (LVEF) has been used to evaluate cardiac function; however, it cannot measure tissue iron concentration. MRI T2* is a more reliable tool to assess cardiac iron and, inferentially, cardiac function. MRI T2* values of >20 milliseconds (ms) are expected, and 10 to 20 ms and <10 ms suggest moderate and severe cardiac iron overload. MRI T2* is the most widely used technique for the measurement of liver and heart iron concentration. Radiofrequency magnetic pulse targeted onto the heart and liver results in protons taking up energy. This energy uptake alters the spin rotation, and we calculate the relaxation time to the original state in T1 and T2 sequences. The relaxation in T2 correlates with the tissue iron concentration.

Management of iron overload

Management of iron overload in thalassemia major can be of three types; preventive therapy when we commence iron chelation before end-organ damage; rescue therapy where there has been a significant iron overload in tissues with changes in end organs; and emergency therapy, mainly when the patient presents with cardiac failure secondary to unchecked cardiac iron overload. Thalassaemia International Federation has recommended guidelines for optimal chelation. We need to initiate chelation when the serum ferritin is above 1000 µg/L, after > 10 - 20 blood transfusions, or once the child is above two years of age.

The purpose of the iron chelator is to increase the solubility of the iron, thus ensuring excretion in the urine. Iron chelators bind specifically to the labile iron, which is in a constant state of production. Therefore, a steady level of chelator is essential to optimize efficacy in binding to the available labile iron. Daily administration of chelators helps provide continuous iron-binding. An ideal iron chelator should be an oral preparation with no toxicity and not expensive.

Desferrioxamine

Desferrioxamine is a trivalent iron chelator licensed for use in children above two years of age. We administer desferrioxamine either subcutaneously or via the intravenous route at a dose of 20-40 mg/kg/day. One vial of 500mg of desferrioxamine when diluted in 5ml of water for injection results in a 10% solution. The recommended dose is a slow subcutaneous infusion over 8-12 hours of a 10% solution with an infusion pump for a minimum of 5 days a week. It can be administered as bolus subcutaneous doses once or twice a day or as a continuous intravenous infusion through a balloon pump. In children, the mean daily amount should not exceed 40mg/kg/day. The half-life of desferrioxamine is extremely short, and we can increase its efficacy with a continuous infusion.

The adverse effects include hearing abnormalities, cataracts, night blindness, decreased visual acuity, and reduced bone growth. There is also an increased risk of infections due to Yersinia enterocolitica and Klebsiella pneumonia. In case of local reactions to the injection, dilution can be increased to more than 5ml of water for injection, with a change in sites for injections and application of local steroid cream.

Desferrioxamine effectively decreases liver and cardiac iron concentration and helps reverse impending cardiac failure, improve cardiac function and LVEF when administered as a continuous infusion. For patients with mild to moderate cardiac iron overload, as measured by MRI, subcutaneous doses of desferrioxamine have shown to decrease cumulative myocardial iron and improve functions. Desferrioxamine is the chelator of choice for patients presenting with cardiac failure because of iron overload. Desferrioxamine can be used as a continuous infusion to reduce iron overload before pregnancy or hematopoietic stem cell transplantation. Vitamin C increases the availability of iron, thereby increasing iron available for desferrioxamine to chelate. Vitamin C is administered concomitantly with desferrioxamine at a dose less than 2-3mg/kg/day.

Deferiprone

Deferiprone is a bidentate oral iron chelator licensed for use in children above the age of 6 years. It is administered at a dose of 75-100 mg/kg/day in two to three divided doses, with a maximum amount of 33 mg three times a day. The main adverse effects include nausea, vomiting, epigastric pain, arthropathy, arthralgia, neutropenia, and agranulocytosis. Due to renal excretion, urine is red-colored. Neutropenia can occur in the first year of therapy. Arthropathy is a significant adverse effect ranging from mild joint pain to joint erosions, predominantly affecting the knee, wrist, and ankle joints. It is recommended to decrease the dose on the initial manifestation of joint symptoms and stop the drug in persistent symptoms. Monitoring complete blood count every 2 to 3 weeks is essential with the use of deferiprone. Deferiprone has greater efficacy in decreasing cardiac iron as compared to other chelators.

Deferasirox

Deferasirox is a tridentate oral iron chelator licensed for use in children above two years of age. The drug is administered once a day at a dose of 20-40 mg/kg/day, preferably before a meal. We need to disperse the drug in water or apple juice using a non-metallic stirrer. The adverse effects include nausea, vomiting, diarrhea, and skin rash. Deferasirox has known renal and hepatic toxicities, including elevation in creatinine and liver enzymes and proteinuria. Serum creatinine and SGPT need to be monitored regularly, preferably once in 2 to 3 months. In case of deranged values, the drug needs to be withheld and restarted when normalized and tolerated. Loss of zinc and calcium in the urine necessitates concomitant zinc and calcium supplements. Deferasirox reduces liver iron concentration across all LIC values and is non-superior to desferrioxamine for chelating cardiac iron.

Deferasirox film-coated tablets are a recent addition that is long-acting with decreased gastrointestinal adverse effects. The film-coated tablet can be administered after meals and does not require any specific preparation. The recommended pediatric dose is 14mg/kg. It is, however, more expensive than available deferasirox.

Combination chelation

Combining two chelators either given simultaneously or sequentially has been studied over the years and has proven efficacy in decreasing iron overload. The simultaneous combination works on the "shuttle hypothesis," whereby one chelator mobilizes cell iron and the other chelates the iron in plasma. Desferrioxamine and deferiprone combination has been validated to reduce life-threatening iron deposition. The combination of deferasirox and deferiprone has been shown to reduce liver and cardiac iron with tolerable toxicity. In this combination, deferasirox can be administered in the morning and deferiprone in the afternoon and night, thereby improving efficacy and compliance and providing a means to reduce the dose of each drug.

Addressing compliance

Iron overload does not result in overt clinical symptoms. Hence, ensuring optimal chelation long term requires motivated families and caregivers. This is especially true of the injectable medications. The main issue in low and middle income countries is financial constraint and results in poor compliance in chronic disorders. Teenage is a particularly difficult time for patient families with mood swings and pressure from academic commitments results in poor compliance. The transition from paediatric to adult services results in an increase in ferritin levels due to lack of compliance. Innovator and generic brands are now available in all countries and the lower cost has resulted in increased access to these life saving medications. The average cost of chelation ranges from INR 3000 to 10,000 each month and increases with the weight of the child.

Conclusion

Iron chelation is pivotal to future health in patients with thalassaemia major. Single agent or combination chelation need to be dispensed with close supervision. Optimal chelation is the key to intact survival and the newer oral chelators have made strict compliance feasible for all patients with thalassaemia major.

Table 1: Iron chelators and their key points

Name of the chelator	Average cost for a 10 kg child per month	Route of administration	Dose	Efficacy	Specific monitoring
Desferrioxamine	INR 3000	IV/SC	20-40 mg/kg/day	Liver/ Cardiac	Visual field defects, high frequency hearing loss
Deferiprone	INR 500	Oral	75-100 mg/kg/ day	Cardiac	Agranulocytosis, arthralgia
Deferasirox	INR 1000	Oral	20-40 mg/kg/day	Liver	SGPT, creatinine, gastritis, dermatitis

Table 2: Deferosirox availability in India

Deferasirox brands available in India and available strength	Deferasirox film coated tablets available and strength
1. Asunra – 100mg/400mg 2. Desirox – 250mg/500mg 3. Defrijet – 250mg/500mg 4. Desifer – 100mg/400mg	1. Oleptiss – 90mg/360mg 2. Defrijet FCT – 90mg/360mg

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Endocrine complications in Thalassemia

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INTRODUCTION

Advances in medical management i.e regular transfusion and iron chelation have led to improvement in the survival of patients with thalassemia. Newer complications are being recognized as patients continue to age. Endocrine complications are the commonest cause of morbidity and mortality in these patients. The prevalence of various endocrine complications has been demonstrated in Figure 1. There is a wide variation in the prevalence in various studies due to differences in management protocols, compliance, and different diagnostic tests employed.

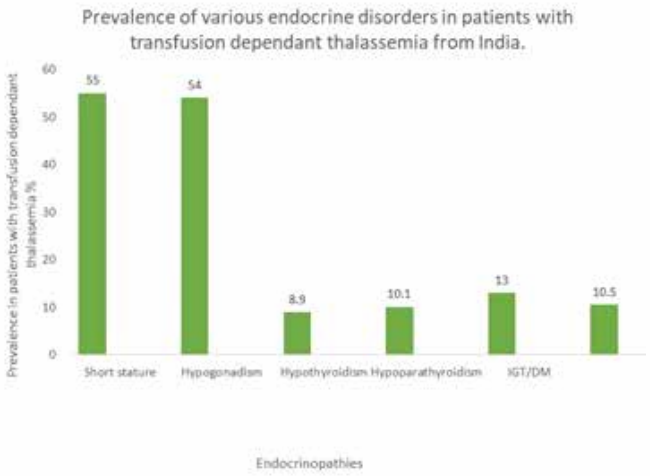

Figure 1: Prevalence of various endocrine disorders in adolescents with thalassemia major from India. IGT: Impaired glucose tolerance, DM: diabetes mellitus.

PATHOPHYSIOLOGY

The endocrine complications result from iron overload secondary to regular blood transfusions. The iron in the body is transported to red blood cells by transferrin and its receptors. Once transferrin is saturated, free iron is present in plasma as Non-Transferrin Bound Iron, (NTBI). NTBI is transported to tissues through the calcium channels, hence, explaining the affinity for cardiac muscles, hepatocytes, and endocrine organs. Iron overload-induced damage to the pituitary, pancreas, thyroid, parathyroid, and gonads results in various endocrine complications.

HYPOTHYROIDISM

Hypothyroidism results primarily due to iron deposition in the thyroid gland [primary hypothyroidism] or iron toxicity to Hypothalamic Pituitary Axis [secondary hypothyroidism]. Primary hypothyroidism is much more common than secondary. The degree of thyroid dysfunction is proportional to iron overload. A lower prevalence of hypothyroidism is found amongst patients in low iron overload and non-splenectomized patients. Annual evaluation of FreeT4 and TSH starting at 10 years of age [Figure 2].

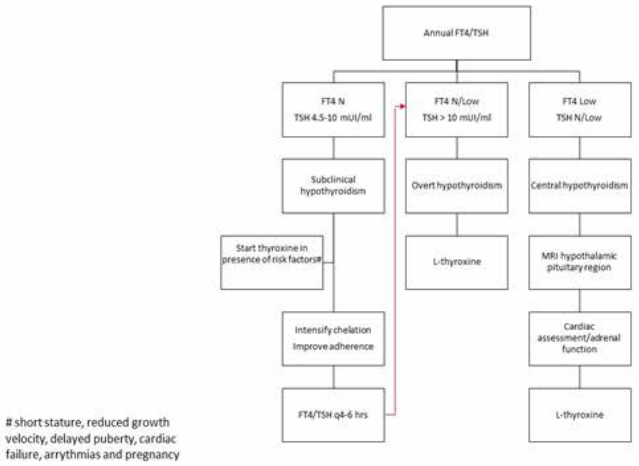

Figure 2: Diagnosis and management of thyroid dysfunction in thalassemia. FT4: free T4, TSH: Thyroid-stimulating hormone, MRI: Magnetic resonance imaging.

Subclinical hypothyroidism can be reversed by intensifying iron chelation and improving compliance. Thyroxine supplementation is recommended for patients with overt hypothyroidism.

Amiodarone-induced hyper-hypothyroidism: Amiodarone; an anti-arrhythmic drug can cause thyrotoxicosis as well as hypothyroidism. The mechanism of these is not completely understood. In patients with cardiomyopathy with sub-clinical hypothyroidism, amiodarone can further aggravate hypothyroidism resulting in worsening of cardiac function. Early intervention is indicated in patients with decreased growth velocity, short stature and delayed puberty, cardiac failure, and pregnancy. During pregnancy, trimester-specific reference ranges should be used [first trimester 0.1 to 2.5 mIU/, second trimester 0.2 to 3.0 mIU/L, third trimester 0.3 to 3.0 mIU/L].

Thyroid cancer: A higher incidence of thyroid cancer has been reported in thalassemia patients, thus, annual thyroid USG surveillance has been advised for adult thalassemia patients.

HYPOPARATHYROIDISM

Hypoparathyroidism [HPT] is characterized by low calcium [hypocalcemia] in association with low PTH levels. Hypocalcemia results in significant impairment in the function of important organs like the brain, muscles, kidneys, and heart. Hypoparathyroidism results from iron deposition in the parathyroid glands and other contributing factors include chronic anemia and magnesium deficiency and other endocrinopathies i.e; diabetes.

The prevalence of HPT is significantly higher in TDT as compared to NTDT and males than females. The symptoms associated with HPT include paraesthesia, tachycardia, tetany, cardiac rhythm disturbances, and cardiac failure. The onset of HPT is usually in the second decade of life. The following investigations should be done from sixteen years of age onwards: serum calcium, magnesium, phosphate.

Symptomatic hypocalcemia is a medical emergency and needs immediate administration of intravenous calcium. Vitamin D deficiency has to be corrected. The starting dose of calcitriol is 0.25-0.5 microgram twice daily to 0.5 micrograms four times a day for adults and 20 to 60 microgram/kg/day for children and adolescents. HPT needs lifelong supplementation with oral calcium and vitamin D. The goal of the treatment is to maintain serum calcium-phosphate product below 55 mg/dl and reduce 24-hr urine calcium excretion < 7.5mmol/dl. High phosphate can be managed by using phosphate binders. Kidney stones and nephrocalcinosis may be seen in patients overtreated with calcium and vitamin D.

SHORT STATURE

Short stature is defined as height less than the 3rd percentile or 2 standard deviation below the mean height for that age and sex.

Short stature can be found in nearly 30-50% of patients with thalassemia depending on the adequacy of transfusion and chelation. Various other factors also contribute to the growth failure in children and adolescents with thalassemia (Figure 3). Reduced spinal height resulting from flat vertebrae (platyspondylosis) has been seen in thalassemia. Desferrioxamine treatment in very young children < 5 years of age has been associated with reduced spinal height by inhibition of collagen formation. Growth hormone deficiency has been encountered in nearly 1/3rd patients with TDT.

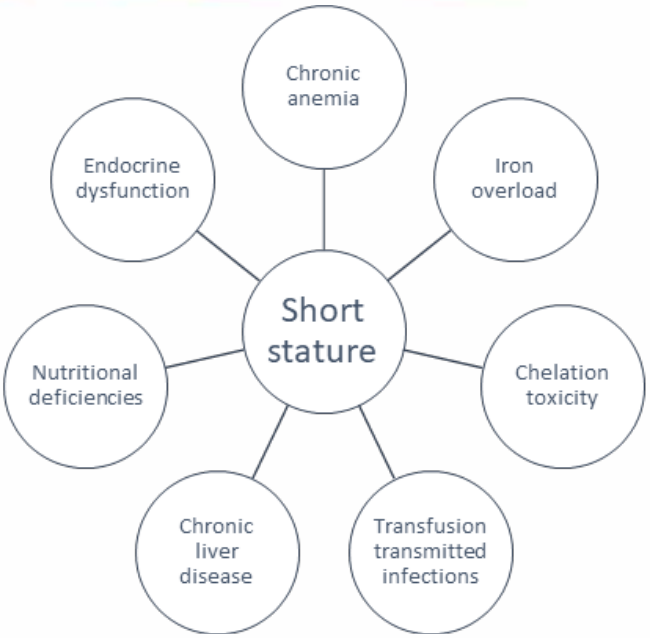

Figure 3: Factors contributing to short stature in thalassemia.

Assessment of a child with short stature includes a thorough history, physical examination, assessment of bone age, screening for other iron overload-related comorbidities, screening for coeliac disease before embarking on GH testing (Figure 4). Management of short stature involves optimization of transfusion and chelation regimen, correction of underlying nutritional deficiencies, and endocrinopathies. Growth hormone replacement therapy can be initiated in patients with established growth hormone deficiency along with replacement of sex steroids.

Approach to short stature in thalassemia

History	Physical examination	First line investigations	Second line investigation
▪Age of diagnosis ▪Mean pretransfusion Hb ▪Annual packed cell requirement ▪Chelation history from beginning : type and dose of chelator, compliance with therapy ▪Any other complications during the past	General examination : pallor, facial dysmorphism, skin pigmentation, signs of nutritional deficiency Anthropometry: wt , sitting and standing height SMR Features of extramedullary hematopoiesis	Serum ferritin Serology for HBsAg, Anti HCV, Anti HIV 1&2 FT4/TSH Fasting Blood Sugar Anti TTG Bone age assessment : X ray wrist and hand.	Growth hormone testing if Ht < 3rd centile and delayed bone age LH, FSH, Estrogen/ testosterone MRI of hypothalamic pituitary region

Figure 4. Approach to short stature in thalassemia. Wt: weight, Ht: height, SMR: Sexual maturity rating, TSH: Thyroid-stimulating hormone. TTG: Tissue transglutaminase, MRI: Magnetic resonance imaging, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone.

HYPOGONADOTROPHIC HYPOGONADISM

Hypogonadotropic hypogonadism [HH] is the most common endocrine complication in adult thalassemia patients. The prevalence of HH from countries without specialized clinics may be as high as 100%. The damage to gonadotrophs in the anterior pituitary is considered the major factor failing to produce gonadotrophins, LH and FSH. Timely diagnosis and appropriate management of HH play a vital role in imparting a good quality of life, improved bone health, and making it feasible for patients to produce offspring. Delayed puberty is defined as a complete lack of pubertal development in males by age of 14 years and females by 13 years. Hypogonadism in males is defined as the absence of testicular enlargement <4ml and in girls as the absence of thelarche [breast bud development] by age of 16 years. A two-step approach is recommended while evaluating a child with HH along with regular growth monitoring from childhood and progression of puberty by SMR staging every six months starting at 10 years.

The 1st step is to rule out causes of growth failure as depicted in Figure 4, followed by evaluation of the hypothalamic-pituitary axis (LH/FSH and estrogen/ testosterone) (Figure 5).

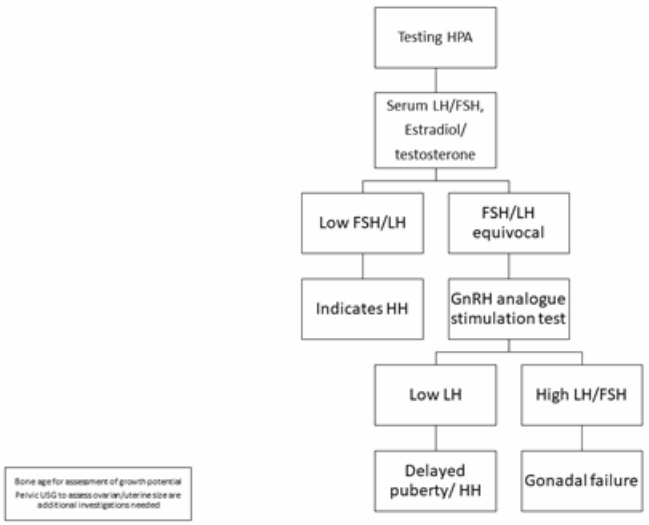

Figure 5: Evaluation of hypogonadotropic hypogonadism in thalassemia. LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, GnRH: Gonadotropin-releasing hormone.

Pubertal induction is indicated in girls with

bone age > 11 years and boys > 12 years. Pubertal induction should not be delayed beyond the bone age of 14 years as it adversely affects the growth potential and bone density. Pubertal induction in boys can be started with depot testosterone injections 30-50 mg given monthly and then increased to 100 mg every 10 days once growth rates start decreasing.

In girls priming with Ethinyl estradiol is started at a low dose of 2.5-5 mcg/day for 6 months which can be doubled if spontaneous puberty does not occur in this period. Estrogen and progesterone combination is recommended for patients who do not attain menarche after 12 months.

IMPAIRED GLUCOSE HOMEOSTASIS

Disorders of glucose homeostasis like impaired glucose tolerance and diabetes mellitus are commonly encountered in patients with TDT. The pathophysiology of IGT/DM in TDT is complex and is characterized by both insulin resistance as well as insulin deficiency. Iron-mediated insulin resistance is mediated by secondary hemosiderosis in the liver and skeletal muscle. Pancreatic β cell dysfunction gradually ensues due to deposition oxidative damage by iron species leading to insulin deficiency. Chronic hepatitis C, family history of diabetes, zinc deficiency, and genetic factors also contribute to the development of diabetes in India. The diagnostic criteria for the assessment of glucose homeostasis are mentioned in Table 1.

Table 1. Diagnostic criteria for assessment of abnormalities of glucose homeostasis.

Abnormality	Criteria for diagnosis
Diabetes mellitus	A random blood glucose ≥ 200 mg/dl with classical symptoms of hyperglycemia
	Fasting blood glucose ≥ 126 mg/dl
	2 hr plasma glucose after oral glucose challenge ≥ 200 mg/dl
	HbA1C ≥6.5%
Impaired glucose tolerance	Fasting plasma glucose between 100-125 mg/dl
	2 hr plasma glucose after oral glucose challenge between 140-199 mg/dl
	HbA1C between 5.7-6.4%

Patients with diabetes are at high risk of developing cardiac dysfunction and arrhythmias along with other endocrine dysfunction, hence should undergo screening for thyroid dysfunction and hypogonadism.

The management of impaired glucose tolerance and diabetes involves lifestyle modification, intensification of iron chelation therapy, oral hypoglycemic agents e.g metformin and insulin therapy. Patients on insulin therapy should monitor glucose levels at home. Screening for complications secondary to diabetes (nephropathy and retinopathy) is recommended routinely.

CENTRAL ADRENAL INSUFFICIENCY

Adrenal insufficiency is an emerging endocrine complication in patients with thalassemia major. It can be difficult to diagnose but pose an important threat during periods of stress.

The adrenal insufficiency could result from decreased ACTH secondary to pituitary iron overload. Biochemical adrenal insufficiency has been seen in 15-53.6% of children and nearly 32.1% of adults. Patients with advanced age, severe iron overload, poor adherence to iron chelation therapy, and multiple endocrine complications are at risk of CAI.

The suggested investigations in a patient suspected of CAI are single early morning plasma ACTH and serum cortisol values [before 9 AM]. Primary adrenal insufficiency is with low serum cortisol with increased ACTH. If ACTH is low, secondary or tertiary adrenal insufficiency should be considered.

The serum cortisol may be normal in presence of mild/ partial adrenal insufficiency. A serum cortisol >10 microgram/dl, rules out clinically significant HPA insufficiency when that is below 4.2 microgram/dl is likely due to adrenal insufficiency. An ACTH stimulation test may be done in patients with equivocal results on cortisol testing. Oral contraceptive and hormonal replacement therapy should be stopped at least six weeks before the stimulation test.

Conclusions: A child with thalassemia needs close and regular monitoring for endocrine complications

(Table 2). Early detection and management of these can help achieve a good quality of life in addition to a reduction in morbidity and mortality.

Table 2: Recommended screening tests for patients with thalassemia.

Effect	Monitoring	Frequency
Growth	Height (sitting/standing)	3 monthly
Sexual development	Tanner staging	6 monthly from 10 years
	LH,FSH Estradiol/ testosterone	Delayed puberty
Bone	Bone age	At puberty
Diabetes	GTT	yearly
Hypothyroidism	T4, TSH	yearly
Hypoparathyroidism	Ca, PO4, magnesium PTH Vitamin D	yearly
Adrenal insufficiency	Morning serum cortisol	yearly

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Hematopoietic Stem Cell Transplant in Thalassemia Major

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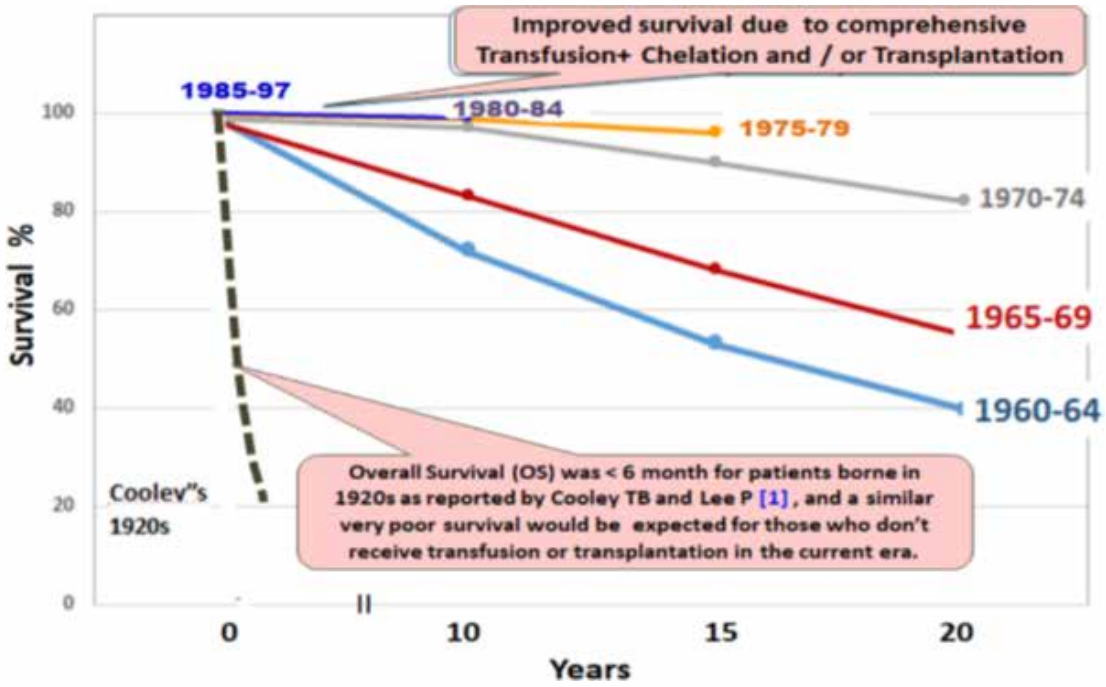
Introduction

- Thalassemia is the most common monogenic disorder caused by defect in globin gene encoding alpha or beta chains.
- Beta thalassemia is the most common among them associated with extreme morbidity and mortality due to severe anemia and progressive iron overload.
- More than 50,000 children are born worldwide each year with this condition adding to the disease burden.
- Survival rates of thalassemia major patients over the years1 are shown in figure 1
- There are two important treatment options for Thalassemia patients that improve survival and provide a better QOL :

1. Regular blood transfusion with pre-transfusion Hb target between 9 - 10.5 gm/dl along with effective chelation has been the mainstay of treatment since decades.
2. In the recent years, allogeneic stem cell transplantation has been the standard of care with curative intent in selected patients.

Challenges for an optimal comprehensive transfusion-chelation therapy:

- High cost which makes it unaffordable for people of developing countries.



- Lack of health care facility and blood bank services in many limited resource countries.2-4
- Increased risk of transfusion transmitted infections, mainly HCV, HBV, HIV and CMV .
- Alloimmunisation and transfusion reactions.
- Poor compliance to regular transfusion and chelation.2
- Poor QOL for both patients and families.

Hematopoietic stem cell transplant (HSCT) in transfusion dependent Thalassemia major:

- HSCT is the only curative options in Thalassemia Major; however some progress in gene therapy has been made recently as well.
- The best results for HSCT in Thalassemia is appreciated if performed at an early age, before complications of chronic anaemia or iron overload sets in and in the presence of a matched sibling donor. Siblings who are thalassemia carriers are accepted as donors for HSCT.
- However, access to this therapy is limited in more than half the patients due to-

- Lack of suitable donor
- Lack of Centers capable of providing bone marrow transplant services
- High cost of therapy

- Transplant related mortality and morbidity has decreased over a period of time with greater experience in transplant, use of novel conditioning regimens and more effective supportive care.

Risk stratification for predicting outcomes of HSCT:

- Age at transplantation and the severity of iron overload are two important indicators that directly correlate with transplant outcomes.
- There are different types of risk stratification used currently in clinical practice

1. In 1980s the Pesaro group developed a simple prognostic system shown in (table 1)-

$ OS has improved in Class III with Protocol 26 using preconditioning with Hydroxyurea, Fludarabine, Azathioprine with reducing dose of cyclophosphamide to 160 mg/Kg

- According to Pesaro, Class I and II were considered low risk and Class III high risk.
- Pesaro failed to recognise Class III very high risk (VHR) subgroup as such population hardly exist in western countries.

2. CMC Vellore classification7

o Recognised subset within Class III as high risk category to include patients aged >7 years old and liver size >5 cm. This subset has the worst outcome.

Pretransplant Evaluation:

- Iron overload assessment using either T2 Star MRI (liver, heart) or Liver biopsy
- Testing for Viral hepatitis

Risk factors	Class I	Class II (1 OR 2 Risk factor)	Class III
Hepatomegaly >2 cm	No	Yes/No	No
Liver fibrosis	No	Yes/No	No
History of inadequate chelation	No	Yes/No	No
Overall survival at 3 years	90%	87%	70- 85% $

- Cardiac function assessment using ECG and ECHO.
- Fertility preservation, where ever possible

Outcomes of HSCT in Thalassemia Major:

- As indicated by results from Pesaro group, optimal transfusion and regular chelation therapy pre transplant is the key to a successful transplant.
- Report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry,2000–2010, revealed best results, with OS (Overall Survival) and EFS (Event Free Survival)of 91 ± 1% and 83 ± 1%, respectively from HLA identical sibling donor transplant.8
- Transplantation done prior to 14 years of age showed better outcomes with an OS of 90–96% and EFS of 83–93%.8
- Studies have shown that pre-existing organ dysfunction, especially involving liver and hyperactive immune system due to repeated transfusions are important challenges to tackle.
- In high risk patients, reduced intensity conditioning regimens were associated with high risk of graft rejection while intensified regimens caused organ toxicities.
- Outcomes reported from India closely match the results from west if matched for the "risk" of the disease. However, in India there is higher proportion of patients presenting late with High Risk/Class III disease and hence compromising outcomes.
- Over the decades, several studies used modifications in conditioning regimens. The following modifications were known to improve outcomes in high risk patients9-13

o Reduction in the dose of Cyclophosphamide in conditioning.

o Usage of IV busulphan with therapeutic drug monitoring.

o Usage of less toxic myeloablative agents like treosulfan. Use of Treosulfan based conditioning protocols has led to improvement in high risk group by more than 10-15%.

o Pretransplant immunosuppressive therapy using fludarabine and dexamethasone.

Alternative donor transplants:

25-30% patients will have a fully HLA matched donor in their families. For the rest of the patients there are alternative donor options like-

Matched unrelated donor (MUD) transplants:

- MUD is an unrelated individual with the same HLA type as the recipient who are identified from Unrelated Donor Registries.
- In a 2005 study from the Italian, Bone Marrow Transplant Group (GITMO) in transplants in Thalassemia patients with MUD donors, overall survival in Pesaro Class I and II was 97% and in the high risk Class III, OS was 65% which was comparable to transplants with Matched Sibling Donors.14

Haploidentical Donor Transplants:

- These donors share one haplotype with the recipient. They are also called Mismatched Related donors.
- Our experience with Haplotransplant is from small case series rather than large studies all of which have reported considerable success, with some studies reporting even 90% OS using novel conditioning regimens. Pre-transplant immunosuppressive therapies lasting few weeks prior to HSCT has been a major contributor of improving outcomes. More experience is evolving in this type of transplant type and outcomes constantly improving.

Umbilical Cord Blood Transplant :

- Umbilical cord is a rich source of stem cell and can be given as a source of stem cells.

- This type of transplant has been in decline last few years in Thalassemia Major due to higher risk of rejection and delayed engraftment.
- Outcomes of related cord blood transplant are reported more than 80% however the outcomes of unrelated cord blood transplant have been reported in range of 50-70%.

Transplant related complications:

Early complications:

- Graft rejection/failure (recurrence of beta Thalassemia major)
- Regimen related toxicities, particularly liver dysfunction(Venoocclusive disease/ Sinusoidal obstruction syndrome)
- Life threatening infections
- Acute Graft Vs Host Disease (GVHD)

Late complications:

- Organ dysfunction (hepatic, endocrine and cardiovascular complications) related to
- Past and residual iron overload
- Regimen related toxicity
- Viral infections
- Chronic GVHD
- Solid organ tumours, infertility and gonadal failure
- Chronic GVHD
- Persistent mixed chimerism
- Iron overload acquired pre-transplant continues post-transplant as well and hence chelation 6 to 12 months post-transplant needs to be started till ferritin comes to normal levels. Venesection and/or iron chelators are used to achieve the above.

Conclusion:

- Allogeneic HSCT is the only curative method currently available in clinical practice.
- Outcomes and cure rates are better with matched sibling donor transplant compared to other alternative donor transplant.
- The development of novel conditioning protocols and GVHD prophylaxis for haplo identical transplant has resulted in high rate of survival that is similar or close to other types of transplant. However more experience is required with these type of transplants before they can be considered as standard of care.
- The biggest drawback of this novel therapy in India is high cost and lack of enough centres capable of providing this treatment.
- Post-transplant regular follow-up, prevention and management of complications will further improve outcomes.

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Prevention of Thalassemia


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Background

Thalassemia syndromes are a group of single gene disorders affecting haemoglobin molecule due to reduced or absent production of globin chains. Thalassemia syndromes are classified into alpha, beta and delta Thalassemia, depending upon the globin gene affected. Since beta thalassemia is more prevalent in our country, this article shall focus on prevention of beta thalassemia.

There are 2 genes encoding for beta globin chains in our body. When these genes are abnormal or mutated, the beta globin chains are either absent or deficient. If one gene is abnormal, it leads to the heterozygous state or thalassemia minor or carrier state. If both genes are abnormal or mutated, it causes Thalassemia homozygous state – either Transfusion dependent Thalassemia (TDT) or Non-Transfusion dependent Thalassemia (NTDT), depending on various factors such as the type of mutations, co-inheritance of other abnormalities related to hemoglobin molecule etc.

The worldwide prevalence of β Thalassemia carriers is around 1.5–7%. The overall prevalence of β-thalassemia in India is about 3-4%, with an estimated 40 million carriers and over a 100,000 people living with Thalassemia (1). Some ethnic groups like Sindhis, Kutchis, Lohanas, Punjabis, Bhanushalis, Agris, Mahars, Saraswats, Lingayats, Gowdas, Reddys, Neobuddhists and few Muslim groups as well as few tribal populations have a higher prevalence of Thalassemia carrier status (5-17%) (2)

Why Prevent?

Management of transfusion dependent Thalassemia includes lifelong red cell transfusions, iron chelation and monitoring of complications of the disease and treatment since the age of 6-18 months when the diagnosis is made. Besides, they need to undergo various investigations which include repeated painful pricks for blood collections associated with expensive tests such as endocrine work up, T2* MRI scan for iron overload determination in the heart, liver, pancreas and pituitary and DEXA scans to determine bone mineral density status. The birth of a child with Thalassemia thus, places substantial emotional, economic and psychosocial burden on affected child and family, besides the financial burden on the nation. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment available currently for individuals with Transfusion dependent Thalassemia in India. However, only limited patients can avail of this either due to non-availability of a suitable donor or its high cost. Gene therapy, which is now available in the West, is beyond reach for our Indian patients presently, but may become a reality in the future! Hence, prevention is a better option.

Is It Preventable?

Fortunately, beta-Thalassemia carrier state is easily detectable by performing a simple blood test for haemoglobin variant by high performance liquid chromatography (HPLC) once in a lifetime. Once the carrier state is known in an individual, he/she has to ensure that the spouse undergoes the test too, before starting their family.

Is Prevention Cost-Effective?

An Indian study has shown that the treatment expenses of a patient with thalassemia ranged from INR 41,514 to INR 151,800 annually at an average of INR 74,948. Nearly half of this was spent on medications(3). As we are aware, if there are no

prevention programs, there would be an addition of 10,000 - 15,000 children with thalassemia to the existing number annually. Additionally, with improved management, the longevity of people living with Thalassemia has increased considerably (50-55 years of age). This will lead to an exponential increase in the financial burden on the society as well as the burden of providing packed red cells on the blood banks. There are several studies which have shown that the cost for treating thalassemia is 10 times the cost for prevention by screening methods. In a study done in Iran, it was concluded that, the ratio of cost of treatment to prevention is 16:1.6. Therefore, it is cost-effective to prevent the birth of a child with thalassemia.(4)

How to Prevent?

Prevention strategies should include the following:

1. Population education and awareness

Educating community regarding

i. The inherited nature of the disease

ii. Possibility of detection of carrier state

iii. The chances of having a child with Thalassemia

iv. Management and complications of Thalassemia

v. How to prevent the birth of child with Thalassemia

This can be achieved through mass media campaigns, posters, quiz and competitions among adolescent and young adults and interpersonal communication related to various aspects of Thalassemia. Mass screening camps can be held in high schools, colleges, offices, at wedding venues etc. Primary prevention can be achieved by screening those individuals who are yet to start their families. As a nation, we must aim to implement primary prevention and reduce the births of children with thalassemia upfront.

Secondary prevention by screening the ensuing pregnancies in those already having a child with thalassemia, is an absolute must!

2. Mass Screening

a. Who should be screened?

- It is ideal to perform mass screening amongst all individuals before marriage, especially among those belonging to high-risk communities. However, in case, that has not happened, the next best option is to screen them after marriage, but before the woman conceives. Finally, if screening has not been done before conception too, one should at least screen the pregnant woman for thalassemia trait in first trimester.If she is trait, screen the spouse and counsel for prenatal diagnosis, if both are traits.

- All members belonging to extended family of an individual with Thalassemia major and/or trait should also be screened.

b. Which tests should be used for screening?

There are various screening tests including:

i. Red blood cell indices

ii. NESTROFT

iii. Various Discriminant functions derived from Red Cell Indices

Since a complete blood count is easily available today even in the remote parts of our country, Red cell indices continue to remain a valuable tool in screening for thalassemia trait. Low MCV, MCH coupled with a normal RDW and a high RBC count with a Mentzer index of < 13 (RBC/MCV) are a good indicator of thalassemia trait or carrier state. However, confirmation by Hb Epp or HPLC is mandatory.

Currently, NESTROFT is not recommended as routine screening test, except in special circumstances, where a CBC may not be available. Discriminant functions have a very low specificity and/or sensitivity and hence are not recommended anymore.(5)

c. Confirmatory tests

Hemoglobin Electrophoresis

HPLC for abnormal hemoglobin (Fig. 1)

Molecular tests

Hemoglobin electrophoresis or High Performance Liquid Chromatography (HPLC)

Hemoglobin Electrophoresis: This was conventionally done for confirmation of abnormal hemoglobins. It is based on the principle of mobility of ions in an electric field. Various types of electrophoresis are available. These include Capillary Electrophoresis – CE (most accurate), Paper / Cellulose Acetate and Gel – Starch/ Agar/Agarose/Polyacrylamide electrophoresis.

But today, automated machines are easily available for HPLC, making it one of the most preferred methods for confirmation of thalassemia trait. It can handle high volume of samples in a short time.

The diagnosis of thalassemia trait or carrier state is based on high HbA2 levels. The cut-off for HPLC is taken as HbA2 ≥4%, whereas HbA2 of 3.5 – 4% is considered borderline and needs to be repeated after iron supplementation in individual with iron deficiency anemia. In case, the value remains borderline, it may be confirmed by molecular tests (Silent carriers).

Molecular tests: Molecular tests used for DNA analysis of hemoglobinopathies currently are based on PCR methods to detect globin gene mutations. Presently, this is the only method to detect beta thalassemia silent carriers, who may be missed by all of the tests mentioned above.

3. Genetic counselling

Genetic counselling is an extremely important step in preventing the birth of a child with Thalassemia. The couples who are both Thalassemia carriers need to be counselled that there is a 25% chance in each pregnancy of having a child with Thalassemia (Fig. 2). They should be counselled regarding prenatal diagnosis and informed about options of terminating the affected fetus.

4. Prenatal Diagnosis

Prenatal diagnosis should be offered to all couples where both partners are Thalassemia carriers. Genetic mutations or the molecular defect in the couple should be identified well before pregnancy or as soon as they report during antenatal period for testing. This helps us to confirm presence or absence of mutations in the fetus. Various methods of collecting the fetal sample are available based on gestational age of pregnancy. These include:

A. Chorionic villous sampling –This is done between 10th and 14th week of pregnancy. It can be performed as a transabdominal or transcervical procedure.

B. Amniocentesis – This is performed between 15th and 20th week of pregnancy.

C. Cordocentesis – In case, the pregnant woman reports beyond 18 weeks, the fetal blood sampling can be done by cordocentesis.

Once the sample is collected, it is sent to a molecular lab and the result is obtained in 7 days, if genetic mutations in the parents are already identified and, in 14 days, if the genetic mutations are not identified.

Non-invasive prenatal diagnosis (NIPD): NIPD is a relatively newer technology implemented under research conditions. It involves detection of circulating fetal DNA in maternal plasma during pregnancy. Further testing to detect mutations is carried out on this fetal DNA. The drawbacks of this method are detection of paternal mutation in maternal plasma is feasible only in carrier couples with different mutations. the tiny quantity of fetal DNA may not allow detection of mutations.

Timely recognition of pregnancy carrying affected fetus assists in counseling the couple regarding the option of termination of pregnancy.

Pre-implantation genetic diagnosis (PGD):PGD is a recent advance in prenatal diagnosis for various genetic disorders. It involves in vitro fertilization using assisted reproductive technology. The cell from the embryo thus produced is tested for Beta-Thalassemia Homozygous state using molecular methods. Those embryos which test negative for Thalassemia homozygous are then implanted.

Is Prevention Feasible in Our Country?

Yes, it is feasible, provided, we have the political will, the dedication and determination to allay the suffering of those born with thalassemia and their families as well as to reduce the financial burden

on the nation. If Cyprus, Sardinia, Italy, Greece and various other countries can achieve, India too can achieve it. A concerted effort through an organized National Program for prevention can achieve the goal of zero thalassemia births in our country too!

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Fig. 1: HPLC showing HbA2 of 4.4% (Thalassemia Trait)

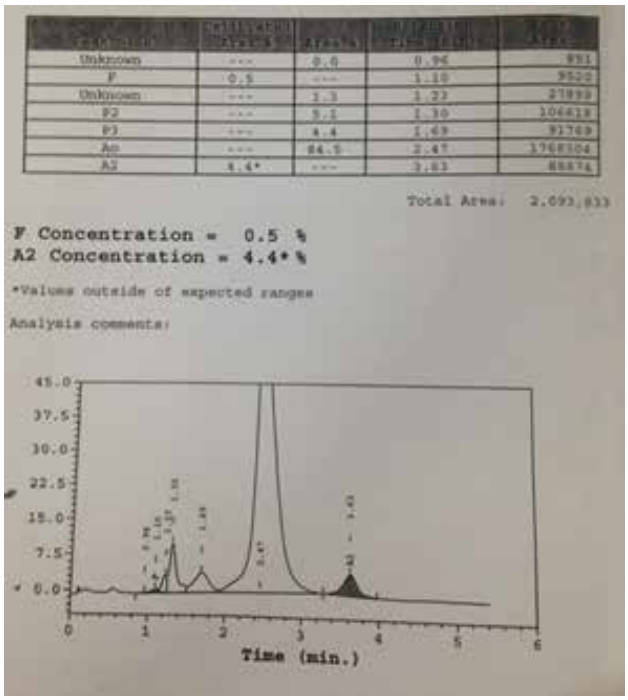
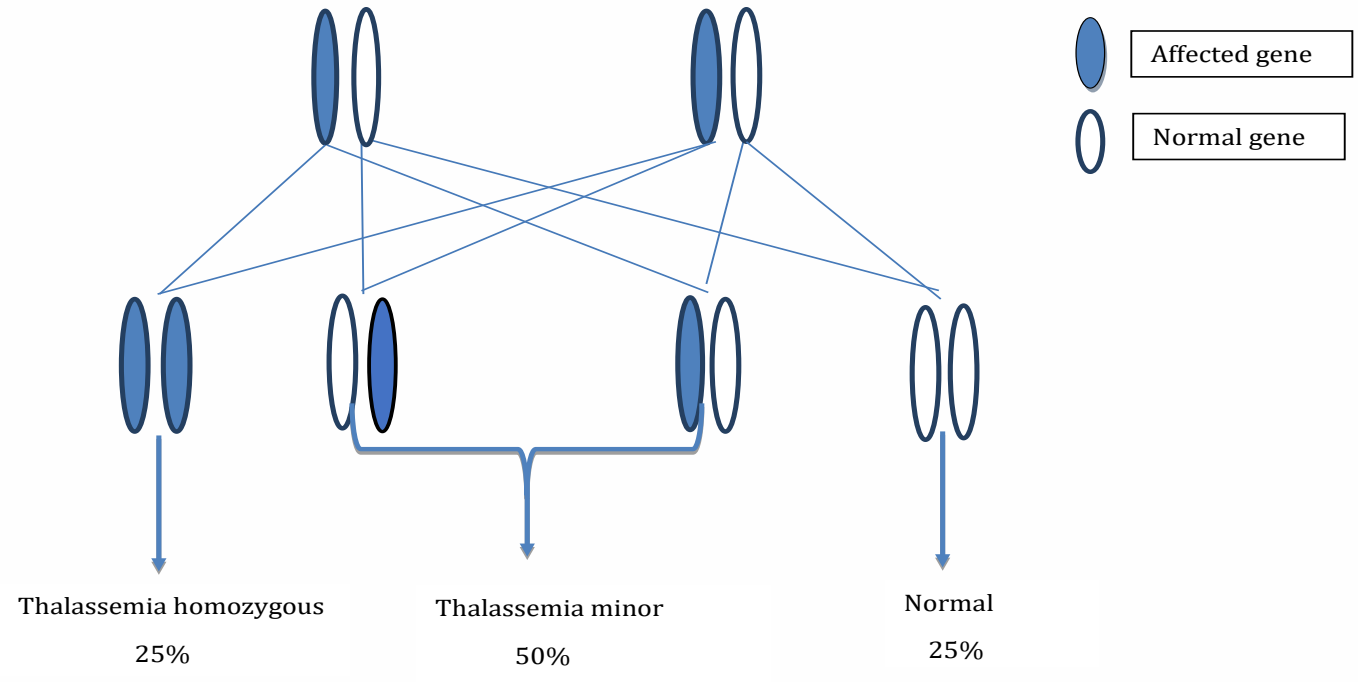


Fig. 2: Autosomal Recessive Inheritance pattern in beta-thalassemia

(Chance of giving birth to an affected child during each pregnancy)



Thalassemia and the ammended Persons with Disability Act 2016

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How does the blood disorder affect an individual in terms of her/his functioning – daily living, education, employment etc.?

Following issues are common in all three blood disorders Thalassemia, Sickle Cell Anaemia and Hemophilia:

- Repeated blood/factors administration for survival/prevention of complications.
- Repeated pricks for investigations and to infuse medicines or blood.
- Higher incidence of infections, inflammation and painful episodes.
- Higher incidence of transfusion transmitted infections like Hepatitis B, Hepatitis C and HIV.
- Repeated hospital visits for treatment or monitoring. Travel (100 – 500 km) for adequate/proper treatment.
- Even routine activities require micro planning according to health condition, next hospital visit, or sudden crisis. Life style is severely restricted and several activities are curtailed. This affects whole family.
- Mental health could also be affected.
- Loss of work days (education, employment or business).
- Because of anaemia, pain crisis, infections, hospital visits etc. they miss schools (may be exams too) so they have difficulty competing with their peers.
- Repeated hospital visits, anaemia, infections, pains also restrict their extracurricular activities and socializing. These further barricades their life.
- For higher education or better job prospects one has to move 200 – 2000 Km away from home town. Maintaining health with such a challenging treatment at a new place is extremely difficult to manage.
- Treatment is very costly not affordable by even upper middle-class family.
- Social stigma a big issue.
- Life expectancy always hovers the minds of affected persons and family.

What does The RPWD Act, 2016 have for persons with blood disorders?

The RPWD Act 2016 has recognised persons with blood disorders (Thalassemia, Hemophilia and Sickle Cell Disease) as 'persons with disabilities' under the Act. Those with 40% and above disability will be given a Disability Certificate.

The first and foremost benefit of The RPWD Act 2016 is non-discrimination. In the past many outstanding persons with blood disorders have been denied employment even though they were selected on merits. With this Act in place, such discrimination cannot happen. Moreover, the Act states denying reasonable accommodation (adjustment) will be also discrimination. Therefore, an organization should not deny any accommodation that a person may need.

The second most important benefit would be "Reservation in Higher Education". This will enable

the persons with blood disorders to pursue higher education of their interest.

The other benefits of the RPWD Act, 2016 are the right to equality, life with dignity, and respect for his/her own integrity equally with others.

Few more measures like appropriate healthcare measures, insurance schemes, rehabilitation programs and incentives to employer in private sector that provide 5% reservation for persons with benchmark disability to be undertaken by the Government will depend on how these are implemented.

What accommodations (adjustments) should employers and educational institutions provide?

Private and government establishments should not discriminate a person with blood disorder. Individualised accommodations should be provided. Some of the common accommodations are listed below (this is not an exhaustive list).

- Free education up to 18 yrs
- Time Flexibility: A person may need adjustment in work timings, for treatment and related issues, which should be provided.
- Extra Leave: A person may need extra leave (over and above what is entitled) for anaemia, pain crisis, infections, hospital visits etc.
- Relaxation in Attendance: Schools and colleges should provide relaxation in attendance and should not prevent a student with blood disorders from writing exams if the student does not meet the required attendance. If a student is unable to write an exam on a particular day, she / he should be given re-examination on another day.
- Extra time for exams and assignments (compensatory time): Some people may need to take breaks due to pain or other reasons related to their disability and hence may need extra time to complete their exam paper, which should be provided.
- Financial assistance for the affected person/caregiver to meet the medical expenses.
- Posting and transfers: Since optimum treatment is available in select cities only, preference in posting should be given to person with blood disorders and their parents.
- Inclusion in extracurricular activities: Some people may have difficulty participating in certain physical activities and they could be exempted. However, this should not lead to the student feeling left out. Some precautions can be taken in consultation with the person/parent, to make the activity safe for them. Inclusive extracurricular activities can also be planned.
- Ensuring no bullying/harassment at school/college/workplace: Organizations/schools/colleges should create adequate awareness so that there is no stigma and there is inclusion in all aspects of school/college/work/ social life. There should be policies to ensure zero tolerance for bullying/harassment/discrimination.

The District Disaster Management Authority is to record of PwD in the district and take measures to enhance disaster preparedness for the differently abled

Govt to conduct surveys in schools; first 2 yrs after revision of PwD Act and then every 5 yrs to identify differently abled children, their needs and the extent to which these needs are being met

Various social security schemes are also in the offing - Pension schemes – already available in 5 states – if annual income from all sources is less than Rs 1 lakh

Income tax concession

Allotment of land/flats

Loans for self-employment and start-ups

Health – infusion pumps, cannulas, syringes, blood transfusion sets, leukocyte-removal filters, irradiated blood, splenectomy and BMT at reduced cost; 400 BMTs have been done under CSR from Coal India (may not be a continuing project); priority cards for patients with thalassemia provided in certain hospitals; under CGHS select private hospitals are recognised for treatment for families from low socioeconomic strata so that long waiting lists in

Govt health facilities may be avoided (previously only unemployed girls >25 yrs could avail CGHS facility – with the amended PwD Act, unemployed boys are also eligible for claiming this facility)

Training of members of the District Disability Board regarding disability certification of patients with Thalassemia

Lot more needs to be considered?

Schemes for higher education

Insurance schemes

Employment in private sector

Free Fast Tag pass

Availability, Accessibility, Accommodations for appointments - transfusions on Sundays or public holidays and during night shifts, Affordability, Awareness

Article 21 of Indian constitution – Right to life with dignity (all needs to be taken into consideration)

Some of the government benefits are only for BPL families. There should be no income ceiling. If at all there is need to put income ceiling, it should be minimum Rs. 5,00,000/annum.

Empower the differently abled

Organisations working for children and families with thalassemia

National Thalassemia Welfare Society (NTWS) was formed by patients, parents, doctors and well-wishers in November 1991 at AIIMS. Since then it is dedicated to the cause of Thalassemia and Sickle Cell Anaemia. NTWS stimulated all Thalassemia Associations of India to come on a common platform and created FIT (Federation Of Indian Thalassemics) where all thalassemia societies can interact and work for the mutual benefits and common cause at national level. Federation of Indian Thalassemics is working for the cause of Thalassemia since its inception in 1994

Objectives

Strive for best possible care for existing patients, and prevent future generation from menace of Thalassemia and SCD.

Ensure free treatment to Thalassemics all over India.

Organize blood donation camps every year to support the blood banks.

Provide free drugs - iron chelating agents

Financial support for bone marrow transplant

Thalassemics India A non-governmental organization, Thalassemics India is working zealously across the country, operating in close association with doctors, drug/equipment companies throughout the country and abroad, hospitals, Thalassemia associations & thalassemia centers

Thalassemia patients advocacy group - Recognising the need and value of advocacy in the area of thalassemia, seven adult thalassemics accomplished in the fields of psychology, law, IT and education, came together to found Thalassemia Patients Advocacy Group (TPAG) under the aegis of Thalassemics India in 2017. Mission of this focus group is "To Protect the overall interests of Thalassemics and prevent Thalassemia." and Vision is "To advocate for a Thalassemia Free India where all Thalassemics are cured or healthy."

Thalassemia and Sickle Cell Society - Thalassemia and Sickle Cell Society (TSCS) is a registered NGO established in the year 1998 in Telangana with the pledge to help the Thalassemia patients.

The multicentre Jai Vigyan programme of the Indian Council of Medical Research on Community Control of Thalassemia helped to strengthen centres in different states particularly in medical colleges to initiate screening programmes and also to determine the prevalence of β thalassemia and other hemoglobinopathies in 6 states, Maharashtra, Gujarat, West Bengal, Karnataka, Punjab and Assam by screening college students and pregnant women.

The Ministry of Health and Family Welfare launched the second phase of "Thalassemia Bal Sewa Yojna" in Oct 2020 for the underprivileged Thalassemic - patients whose monthly family income is below Rs 20,000. The Hematopoietic Stem Cell Transplantation (HSCT) program was launched in 2017 and is funded by Coal India Corporate Social Responsibility (CSR). It will be extended for next two years from 2020. A total of 200 patients could avail a package cost not exceeding rupees 10 lakhs for the HSCT.

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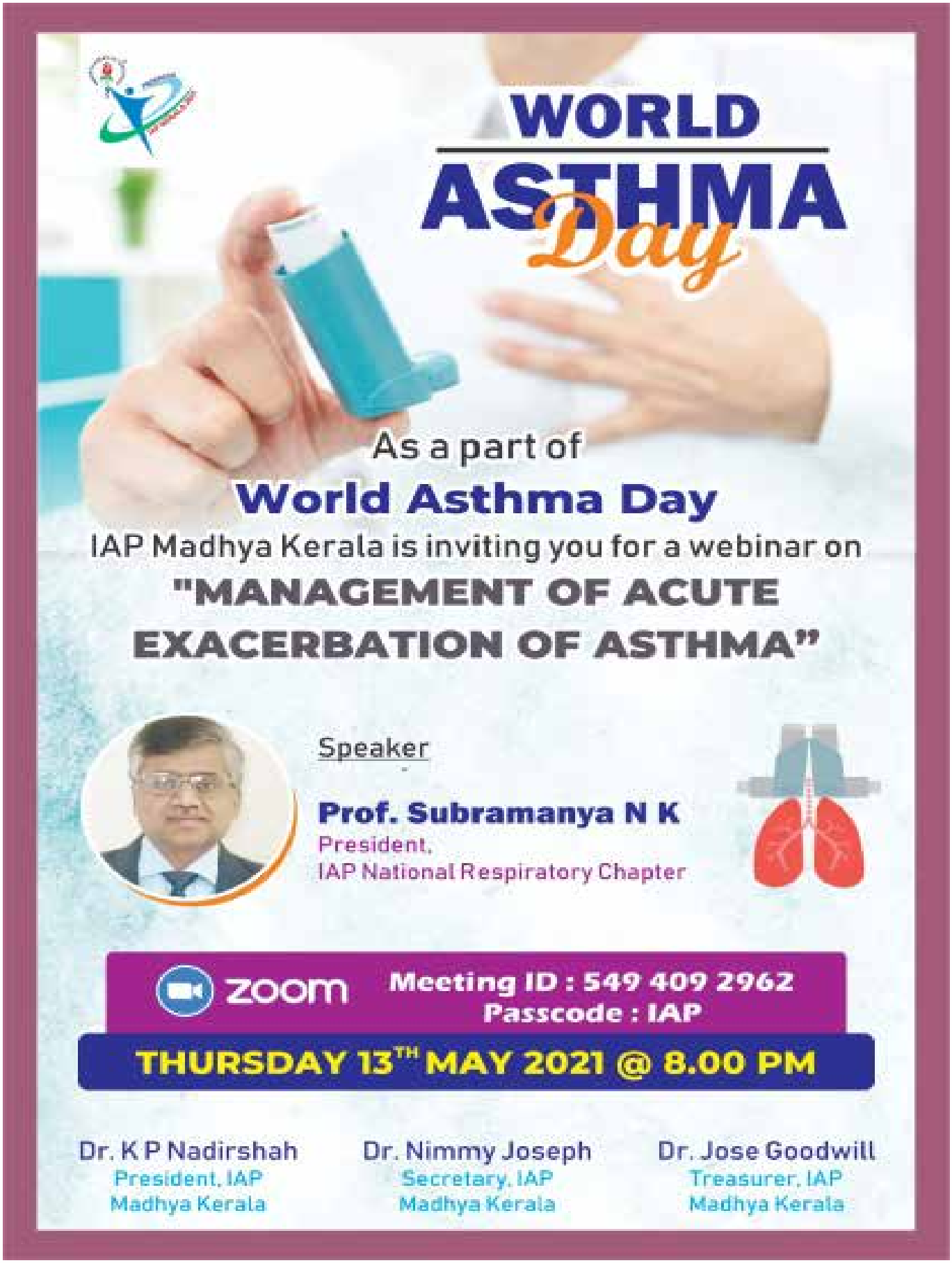
Time	Subject	Speaker
4.45pm	Welcome & plan of the day	Dr. Sanjiv Singh Rawat
4.55pm	Inaugural Address	Dr. N.K.Subramanya
5.00pm to 5.30pm	Difficult to treat Asthma : How to address ?	Dr. Andrew Bush, UK
5.30pm to 5.45pm	Discussion	Dr. Varinder Singh, Dr. Meenu Singh, Dr. Hema Mittal
5.45pm to 6.15pm	Genetics & Asthma : It's relevance to a practicing Pediatrician	Dr. Mahesh Babu, Singapore
6.15pm to 6.30pm	Discussion	Dr. Ankit Parakh, Dr. Jagdish Chinappa, Dr. Krishnamohan R
6.30pm to 7.00pm	Allergen specific Immunotherapy in Asthma : Current Understanding	Dr. Adnan Custovic, UK
7.00pm to 7.15pm	Discussion	Dr. K.Nagaraju, Dr. Indu Khosla, Dr. N.P. Modi
7.15pm	Vote of Thanks	Dr. Subashish Roy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IAP WAYANAD

IN ASSOCIATION WITH **IMA SULTHAN BATHERY**, **MPH WAYANAD** AND **WAYANAD O&G SOCIETY** INVITES YOU ALL TO A WEBINAR AS A PART OF

PRESIDENTIAL ACTION PLAN 2021- AEROSOL THERAPY AND WORLD ASTHMA DAY OBSERVATION

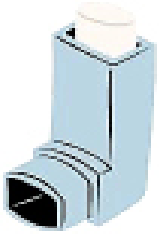
ON **14TH MAY 2021,FRIDAY AT 8PM**

GUEST SPEAKERS

DR. SURESH KUMAR E K

HOD PEDIATRICS, ASTER MIMS,KOZHIKODE

CHAIRPERSON AEROSOL THERAPY PAP 2021, IAP KERALA



TOPIC: AEROSOL THERAPY IN PEDIATRIC ASTHMA

DR. SIBY KURIAN PHILIP

CONSULTANT PEDIATRICIAN &ALLERGIST, GG HOSPITAL TRIVANDRUM,

SECRETARY ALLERGY & IMMUNOLOGY CHAPTER, IAP KERALA

TOPIC: WHAT'S NEW IN GINA GUIDELINES

ZOOM MEETING ID : 84523857286 PASSWORD: Wayanad

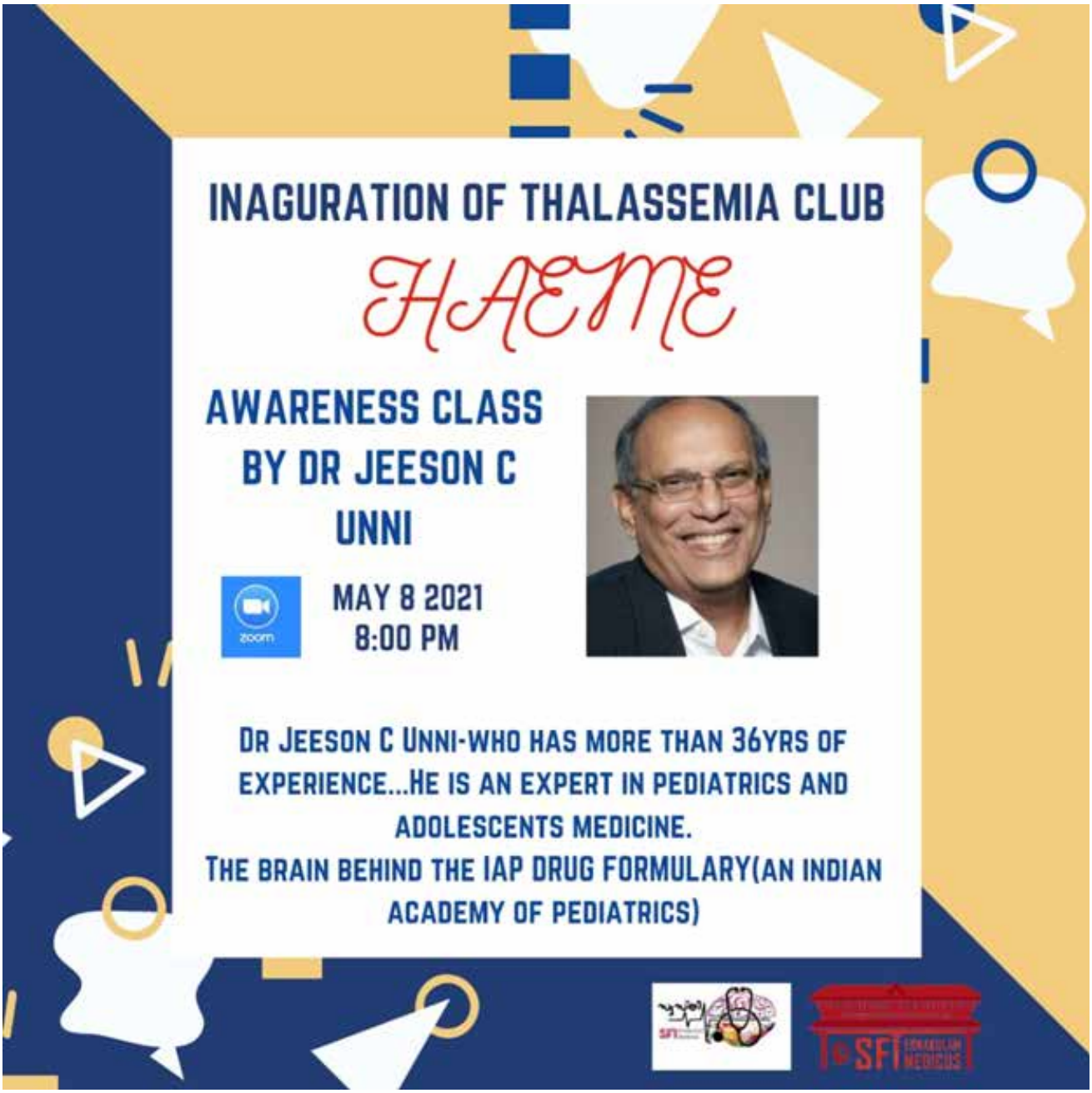
DR.VIJAYAN A
PRESIDENT
IAP WAYANAD

DR. ABDUL GAFOOR
PRESIDENT
IMA SULTHAN BATHERY

DR.OMANA MADHUSUDANAN
PRESIDENT
WAYANAD O&G SOCIETY

DR. SUMA VISHNU
DISTRICT COORDINATOR
MPH WAYANAD

DR.A M YASHWANTH KUMAR
SECRETARY
IAP WAYANAD


INAGURATION OF THALASSEMIA CLUB
HAEME
AWARENESS CLASS
BY DR JEESON C
UNNI
zoom
MAY 8 2021
8:00 PM
DR JEESON C UNNI-WHO HAS MORE THAN 36YRS OF EXPERIENCE...HE IS AN EXPERT IN PEDIATRICS AND ADOLESCENTS MEDICINE.
THE BRAIN BEHIND THE IAP DRUG FORMULARY(AN INDIAN ACADEMY OF PEDIATRICS)

Jodhpur Branch (Marwar IAP)

Marwar Paediatric Society

on the occasion of World Thalassemia Day
invites you

Scientific Session
Updates in Thalassemia Management

Date : 8 May 2021 | **Time : 8:30 pm**

Zoom Meeting ID: 875 7386 5024 | **Passcode: 606526**

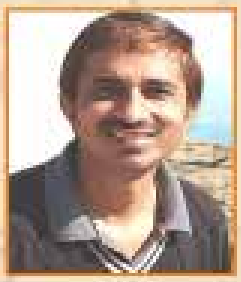
Chairperson

Dr. Pramod Sharma
Senior Professor
Ex. Head of Department
Department of Paediatrics
Dr. S.N. Medical College, Jodhpur

Speaker

Dr Satyendra Katewa
Head Pediatric Hematology Oncology
and Bone Marrow Transplant
Manipal Hospital Jaipur

Dr. Pradeep Jain
President MPS



Dr. Purushotam Dan
Secretary, MPS

Dr. S.R. Didel
Treasurer, MPS

NATIONAL RESPIRATORY CHAPTER

WORLD ASTHMA DAY CELEBRATIONS- 4th May, 2021

Theme: "Uncovering Asthma Misconceptions

Difficult to treat Asthma-Indian Experience

Programme Schedule

7.30-7.40pm	Welcome *Dr NK Subramanya , Dr SS Rawat*
7.40-9.00pm	My Difficult cases on Asthma- Case based session
7.40-8.00pm	My Difficult cases on Asthma- Case1 *Dr Gautam Ghosh*
8.00-8.20pm	My Difficult cases on Asthma- Case 2 *Dr Jasmeet Kaur Wadhwa*
8.20-8.40pm	My Difficult cases on Asthma- Case 3 *Dr Sarath Balaji*
8.40-9.00pm	Discussion on cases by Lead Discussants: *Dr Krishan Chugh, Dr Pallab Chatterjee ,Dr Barnali Bhattacharya*
9.00-9.05pm	Release of Poster on Public Education on Asthma *Dr NK Subramanya*
9.05-9.30pm	Felicitation of winners of PG quiz on Asthma *Dr NK Subramanya*
9.30pm	Vote of thanks *Dr Manjunath V*