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SPECIAL EDITION

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With
Best
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Dear Friends,

I am very pleased to address you through this special edition of Thalassemia Update. My memory goes back to the early years when we had no access to the printed material on Thalassemia. Pumps, needles, filters and deferal were arranged by thalassemia parents on their own. We never thought that we will ever have the oral chelating drugs, BMT options, books on Thalassemia and life saving equipments/drugs available in our country at subsidized rates.

Gene Therapy trials are in progress in a number of countries. A lot of support has come from the State Governments in the form of free chelation drugs and filters to our Thalassemia children.

We know, this is not enough. We would like all our thalassemia children to have access to the recommended treatment as per TIF’S guidelines. So far there is no prevention programme in our country. We are far behind in this area as compared to some of the countries where they have achieved nil birth of Thalassemia children. Although for the last 8 to 10 years, there has been some improvement on the awareness side, still we have to go a long way.

Thalassemics India, being the first Thalassemic NGO in the country, is proud to complete 25 Years of its selfless service to the society. We, as a group, have always put in best of our efforts. Sometimes we came across a number of difficulties, but we never looked back. We assure you that in future also we will keep doing the good work in the interest of our Thalassemia children and society at large.

A number of our thalassemic children are now ex-thalassemics. All thanks to our benevolent donors. Through this message, we would also like to thank our Doctors, Delhi Government and TIF for their continuous support. Today we are talking about marriages, demanding equivalent rights and expecting better treatment facilities. This is because of the work done by Thalassamia NGO’s in their respective States and Countries and also because of the Scientific Research taking place worldwide. We should all be proud of this fact.

We hope that you will find this issue useful and interesting. Do let us have your feedback.

Wishing you always the very best.

With warm sincere regards,

Shobha Tuli
Secretary, Thalassemics India
Thalassaemia major (TM) was known to affect a significant segment of population in Mediterranean countries, Middle and Far East, and West Africa. However, the alteration of migration has changed the geographic distribution and has made it a worldwide health problem in the 21st century. Our understanding of the pathophysiology of endocrine disturbances of Thalassaemia has changed significantly in the last five decades with advances in transfusion and chelation treatment as well as the total care. Treating patients with Thalassaemia major early with regular blood transfusions during the first decade of life has been shown to improve oxygen carrying capacity, cardiac status, systemic parameters of growth and development and overall well being (1).

Multiple transfusions in patients with TM result in iron overload. Iron accumulates in tissues with high levels of transferrin-receptors such as liver, heart and endocrine glands. The anterior pituitary is particularly sensitive to iron overload causing hormonal secretion abnormalities. Measuring levels of ferritin, serum iron, total iron binding capacity and transferrin saturation document iron accumulation. Magnetic resonance methods such as quantitative MRI and SQUID; biomagnetic liver susceptometry are recently available for measurement of iron deposition. Despite the improvement in chelation treatment yielding to important and progressive increase of life expectancy and decrease of comorbidities in recent years, clinical picture of thalassemia major is still characterised by consequences of iron overload and chronic hypoxemia, and the involvement of the endocrine system being one of the most frequent in these patients (2).

**Growth failure**

Children and adolescents with TM frequently present delay of growth and puberty with reduction of final height. Growth failure in TM has been recognised for many years, and has persisted despite major treatment advances. The child with TM has a particular growth pattern, which is relatively normal until age 9-10 years; after this age a slowing down of growth velocity and a reduced or absent pubertal growth spurt are observed. The growth plate fusion is usually delayed until the end of the second decade of life. Body disproportion between the upper (short) and lower body segment (normal) is observed in approximately 15-40% of TM patients. Spinal growth impairment starts during infancy and deteriorates progressively. During puberty hypogonadism further impairs spinal growth (3). The pathogenesis of growth failure is multifactorial. The fundamental problem is free iron and hemosiderosis-induced damage of the endocrine glands. However, other factors could contribute in aetiology of growth delay. Characteristically three phases of growth according to age of presentation are recognised which have different aetiologies as seen in figure 1.

First phase (infancy and childhood <5 years) In the first phase, growth disturbance is mainly due to ineffective erythropoiesis, anaemia, hypoxia and nutritional factors. Chronic anaemia leads to compensated erythropoiesis that causes bone marrow expansion. Skeletal changes due to chronic anaemia result after 12 months of age. In developed countries, chronic hypoxia is no longer a contributing factor in properly treated children and linear growth in this phase is disrupted only in a small percentage of patients. However, even with an optimal transfusion regimen, the bone marrow remains hyperactive, resulting in reduction of longitudinal growth of the long bones and subsequently the reduction of longitudinal growth of the child.

Second phase (childhood 5-10 years) During late childhood, growth retardation is mainly due to iron overload affecting GH- IGF-1 axis and other potential endocrine complications. It is well known that high serum ferritin levels during the first decade of life predict final short stature, indicating that appropriate iron chelation therapy can prevent or limit this complication. However, several studies showed high prevalence of short stature in TM patients.

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**Figure 1:** Three phases of growth according to age of presentation, which have different causes – the multifactorial origin of growth failure in Thalassaemia.
children and adolescence treated intensively with desferrioxamine (DFX). In addition, premature chelating therapy, between ages of 2-5 years, may have deleterious effects on growth. DFX is proven to inhibit cell proliferation, DNA synthesis, collagen formation and trace mineral deposition such as cooper and zinc. This complex mechanism results in platyspondylosis with flattening of the vertebral bodies and consequent shortening of the spinal height, resulting in truncal shortening, also in the presence of normal stature.

The hormonal cause of growth retardation in TM children is complex. Dysfunction of GH-IGF-1 axis is of a major concern because of its pathogenic role not only on their abnormal growth but also on cardiac and bone disease. Evaluation of GH-IGF-1 axis has given contradictory results, although most of the studies have shown reduced response to provocation tests with a variable prevalence. However, therapeutic response with rhGH administration in cases which GH deficiency is established, is often non satisfactory. Treatment with rhGH for 1 year seems to be effective in increasing growth velocity without causing adverse effects on bone maturation, glucose tolerance, serum lipids and blood pressure. The encouraging results described for the first year of rhGH treatment do not persist during the second and the third years. This is because increase in bone age with continued treatment is equal to or slightly greater than the height age increase. Prolonged therapy with rhGH could not improve final height; on the contrary a negative effect may be hypothesized (4, 5).

Third phase (peripubertal years >10 years) During the first decade of life the maintenance of haemoglobin levels above 9 g/dl together with adequate iron chelation therapy makes the children with TM indistinguishable from their non-thalassaemic peers (3). However, most patients now present after the age of 10-11 years with peripubertal growth deceleration. Delayed or arrested puberty is an important contributing factor to growth failure in adolescent TM patients. Sex hormones play an important role in pubertal growth spurt and TM patients with delayed puberty do not exhibit normal growth spurt; their GH peak amplitude is reduced as well as their nocturnal GH levels. Induction of puberty using androgen replacement or hCG in non-GH deficient boys with TM and delayed puberty produced a significant improvement in growth velocity.

Protocol for investigation of Thalassaemic children
2. Assessment bone maturation
3. Routine blood tests including liver function tests, ferritin, serum iron, total iron binding capacity and transferrin saturation, biochemical profile, and zinc
4. Urine analysis
5. Thyroid function tests (Free T4, TSH)
6. IGF-1 and IGFBP-3
7. Stimulation tests to assess GH secretion. At least two tests are required. Priming with sex steroids is necessary in boys older than 10 years with testosterone and in girls older than 9 years with estrogens.
8. IGF-1 generation test in patients with low levels of IGF-1 and IGFBP-3 and normal GH secretion to exclude GH resistance.

Pubertal disturbances and Hypogonadism
Puberty is the biological phenomenon, which results from the activation of the Hypothalamic – Pituitary – Gonadal axis and is clinically manifested by the appearance of sexual characteristics. Delayed puberty is defined as the absence of any pubertal sign in girls (breast enlargement) and in boys (testicular enlargement) by the age of 13 and 14 years respectively. Failure of sexual development by the age of 15 to 16 years in both sexes is defined as Hypogonadism. Secondary Hypogonadism appears later in life, and is manifested in women as Secondary Amenorrhea and in men as decline in sexual drive and azoospermia (6).

Hypogonadism still remains the most common endocrine and stressful complication in Thalassaemia major. Iron deposition on gonadotrophin cells of the pituitary leads to disruption of gonadotrophin production and consequently to delayed puberty and Hypogonadotropic Hypogonadism. Anterior pituitary function (GnRH stimulation test) correlates well with tissue iron deposition in the pituitary gland, as quantitatively determined by MRI measurements (T2*). The damage to the hypothalamus and pituitary is progressive, even when intensive chelating therapy is given and the appearance of Hypogonadism in both sexes is often unavoidable (9).

The association of susceptibility to develop Hypogonadotropic Hypogonadism with the genotype has already been proven (7). The contribution of the underlying molecular defect in TM to the development of endocrinopathies in TM and particularly Hypogonadotropic Hypogonadism is significant, because the patients with the more severe defects have a greater rate of iron loading through higher red cell consumption and probably a different vulnerability to free radical damage. Adolescent girls with TM often present with Primary Amenorrhea and boys fail to become well virilized. Most women with TM manifest Secondary Amenorrhea at some stage in their life and men develop hypogonadism in their 3rd decade after being normal for some years and even becoming fathers (6).
Protocol for investigation of pubertal disorders

1. Assessment of growth and puberty. The absence of any clinical pubertal signs in a boy (testicular enlargement) older that 14 years and in a girl (breast development) older than 13 years requires investigation.

2. Measure testosterone in the boy and oestradiol in the girl. (DHEA-S in both sexes is often helpful).

3. Measure basal levels of FSH and LH.

4. Perform the GnRH test to evaluate the pituitary capacity to secrete the gonadotropins FSH and LH.

5. Perform ultrasound of uterus and ovaries in girls

6. Bone age is helpful for the treatment decision options

Therapeutic approach in delayed puberty should mimic biological and biochemical pubertal changes, aiming on promotion of linear growth as well. Induction of puberty in boys can be achieved with Testosterone depot IM 25-50mg monthly for 6 months and reassessment. Pubic hair will appear and penile size will increase. In case where testicular volume indicates activation of the axis and release of Gonadotrophins (FSH and LH), where no further treatment is needed except for close observation. In case where testicular size is unchanged, then the therapeutic schedule is determined by the growth potential, clinical response and emotional factors. For testicular enlargement, the therapeutic regime is altered to the combination of hCG and hMG, both of which mimic the pituitary Gonadotrophins.

For induction of puberty in girls oral Ethinylestradiol is preferred at the dose 100 ng/kg/d for 6 months, where increase in breast size and growth acceleration is noted. Therapeutic schedule is determined by the same factors as in boys. The adult dose is 400 ng/kg/d, where the uterine size is satisfactory increased for the induction of menarche. Induction of puberty can be successfully achieved by the transdermal use of Estrogens. Menarche is achieved by the addition of Medroxyprogesterone 10 mg/d for 10 days when the size of the uterus exceeds 5 cm. For maintenance of the menstrual cycle the use of Estrogens (Conjugated Estrogens 0.625 μg 1.25 mg, Ethinyl Estradiol 20 μg) from day 1st to 25th and Progesterone from day 14th to 25th is required. The transdermal use of Estradiol and Norethisterone is advantageous due to decreased liver toxicity.

Normal sexual activity and reproductive capacity have become demanding tasks for women with TM. Despite Hypogonadotrophic Hypogonadism and severe iron deposition, ovarian function may be preserved, as they are still able to increase oestriadiol level following gonadotrophin stimulation test. Women with TM who are regularly transfused and are well chelated can now become able to conceive after a closely monitored treatment. Ovarian Reserve Testing is based on indirect measures to evaluate the size of the residual ovarian follicle pool. Anti-müllerian hormone (AMH) emerges as an important biomarker for assessment of reproductive capacity in TM, demonstrating that fertility is preserved in the majority of those younger than 30 to 35 years. AMH can be useful in future studies aiming at improved chelation for fertility preservation (8).

Hypothyroidism
Primary hypothyroidism is one of the most common complications in patients with TM, usually appearing in the second decade of life related to iron overload. The reported prevalence varies depending on the number as well as on the age composition of the study population from 0-18% (9). The thyroid pituitary axis is less sensitive to iron induced damage than the gonadal and GH axis, and the thyroid gland appears to fail before the central components of the axis; thus secondary hypothyroidism due to pituitary haemosiderosis is rare. Damage of thyroid gland manifests mainly by increased thyroid stimulating hormone (TSH) along with normal or low thyroxin (T4) and tri-iodothyronine (T3), consistent with mild primary hypothyroidism. The progression of subclinical hypothyroidism to overt disease may take many years. Abnormal thyroid function may be reversible at an early stage by intensive chelation. Thyroid function tests should be checked routinely in all patients with TM.

Hypoparathyroidism
Hypoparathyroidism, which is a rare but severe complication in TM develops in late adolescence. Deposition of iron on parathyroid cells and tissue fibrosis are the main causes of hypoparathyroidism. The condition may present with the typical clinical picture of muscle cramps, pain and tingling, vibrating burning or numbness of the fingers, toes or face, carpopedal spasm (contraction, or tightening, of the muscles of the hands and feet) or neurological symptoms such as seizures. The biochemical picture of hypoparathyroidism is characteristic with low calcium, high phosphate levels. And inappropriately low or normal Parathormone (PTH) (9). Regular assessment and tight control of serum calcium level in all patients with TM is strongly recommended. Prompt treatment with oral calcium supplements and an active form of vitamin D can prevent the subtle and disturbing clinical manifestation of hypoparathyroidism and its neurologic complications.

Diabetes mellitus
Impaired glucose tolerance and insulin dependent diabetes mellitus (DM) are frequently observed in patients with TM. DM is uncommon during the first years of life and progressively increasing with age. Both liver and pancreatic β-cell siderosis and DFX toxicity may impair the glucose tolerance. The interplay between liver siderosis and hepatitis C facilitates and accelerates the progression to DM, at least in adulthood (10). In addition, insulin resistance is of central importance...
for the development of diabetes mellitus in patients with secondary haemochromatosis. Impaired glucose tolerance may start early in the second decade of life parallel to puberty. Pancreatic β-cells function in thalassaemia is characterised by the following steps: insulin-resistance with hyperinsulinaemia and normal glucose tolerance, insulin-resistance with IGT and progressive impairment of β-cell function with reduction of insulin secretion, and insulin dependent DM (10). Early recognition of glucose abnormalities is essential. OGTT should be done in every patient with thalassaemia after the age of ten or earlier if needed. Noetzli LJ et al demonstrated that pancreatic iron is the strongest predictor of beta cell toxicity and MRI of pancreas and fasting glucose/insulin are complementary screening tools, reducing the need for oral glucose tolerance testing, and identify high-risk patients before irreversible pancreatic damage (11). Screening for hepatitis infections and regular chelation therapy are important measures in preventing the development of diabetes. Initial management is based on special diet, regular exercise and intensive chelation therapy. Enhanced iron chelation therapy with DFX and deferiprone is effective to normalise β-cell function and may improve insulin secretion and reduce glucose intolerance and liver iron deposition (12). Introducing oral hypoglycemic drugs in the early stage of DM before dependence on Insulin may be beneficial, although limited data on the effect oral antidiabetic drugs are reported.

Bone disease
The prolonged life expectancy has subsequently resulted in the development of additional medical conditions, such as Bone Disease (BDT) or Osteoporosis / Osteopenia Syndrome (OOS). BDT may be found in 50-90% patients with TM worldwide and has become a major cause of skeletal complications (13). The pathogenesis of bone disease in TM is multifactorial and remains unclear. Several contributing factors seem to be involved, acting independently or in concert. The primary disease causes bone marrow expansion due to ineffective erythropoiesis, leading to mechanical interruption of bone formation, cortical thinning, increased distortion and fragility of the bones. Iron overload and direct iron toxicity on the bone impairs osteoid maturation and inhibits mineralization. DFX toxicity on bone results in skeletal abnormalities and cartilage alterations. Failure to progress normally through puberty is associated with failure of adequate bone mineralization and achievement of peak bone mass. Additional possible etiological factors for thalassaemia-induced osteoporosis include: GH and IGF-1 deficiency, parathyroid gland dysfunction, DM, hypothyroidism as well as liver disease (14). A study by our institution showed that 89.5% of the patients was found to have Osteopenia/Osteoporosis at the spinal region and 84.2% at the femoral site. This high prevalence was in accordance with previous reports and indicates the necessity of understanding the pathophysiology of this disorder, so that preventive measures could be designed in order to halt the continuous and probably inevitable bone loss (13).

There is a gender difference not only in the prevalence but also in the severity of BDT. Our study demonstrated that male patients were more frequently osteopenic/ osteoporotic compared with females. Moreover, the severity of bone disease based on BMD values was more prominent in males (13). Sex steroids regulate skeletal maturation and preservation in both men and women, therefore the impact of gonadal insufficiency on skeletal integrity has been widely recognised in both genders.

The contribution of other than sex steroid hormones on the acquisition and maintenance of bone mass is well known. Thyroid hormones stimulate both bone absorption and formation, so that low BMD values are expected to be present in patients with thyroid dysfunction. Vitamin D deficiency, which may start early in Thalassaemia potentially contributes to low bone mass. There is a possible role of DM in the pathogenesis of BDT, as 80% of diabetic patients with TM had severely low bone mass, compared with 41% of those with normal glucose tolerance in the report by Jensen et al (15).

TM patients have spinal degenerative skeletal changes, which can be detected only by MRI and most likely interfere with BMD values, resulting in false diagnosis of BDT. It seems therefore that DEXA scans fail to provide accurate and precise information and probably explains the discrepancy between the findings of the reported studies. An additional contributing factor that interferes with BMD readings by DEXA in Thalassaemia is the short stature, which is common in these patients, because DEXA measurements are influenced by size. BMD represents a measurement of bone area rather than volume and is influenced by body size, thus underestimating bone density in individuals with short stature. Since DEXA may fail to provide accurate information of BD in Thalassaemia, other methods, such as Quantitative Computed Tomography, High Resolution Computed Tomography and Single Energy Quantitative Computed Tomography should be considered as being more sensitive and reliable to detect bone disease (13).

Epilogue
Endocrine complications in TM have been well known for many years. During the last decades therapeutic progresses resulted in a prolonged life expectancy in TM patients. However, despite significant advances in transfusion programs and regimens, chelating agents and hormonal replacement, iron overload is still a major consequence leading to endocrine dysregulation. Growth retardation and hypogonadism continue to be a significant challenge.
in TM patients due to interrelated factors, affecting their social adjustment and quality of life. Close follow up, early recognition and proper management is crucial for every patient. During the last 25 years, investigators have made great strides in developing new iron chelators for the treatment of iron overload in thalassaemia. Many candidate drugs have been screened, but only a few have had the physicochemical and biological properties suitable for potential clinical application. Some of these are now under intensive investigation. Patients may ultimately benefit from having a choice between several chelators, including orally active drugs. New strategies of chelation, such as combination therapy and organ-targeted chelation, may soon have a considerable impact on the therapeutic outcome and quality of life of patients with thalassemia. In the meantime, gene therapy appears defiantly exigent and particularly challenging.

References


The thalassaemias are no longer primarily diseases of childhood, but, with the development of good clinical care, have been associated with a remarkable improvement in outlook for affected individuals, the world over. Regular transfusions with good quality blood products and co-ordinated multidisciplinary medical care mean that the number of thalassaemic patients reaching adulthood is increasing and the nature of the clinical problems are changing. With the need for regular blood transfusion comes the complication of tissue iron overload. Where the heart is concerned, chronic iron overload may produce life threatening severe heart failure, but is remarkable as a heart condition (cardiomyopathy) by virtue of being potentially completely reversible, in this case by iron chelation therapy. The are few other conditions in cardiac medicine where hearts so severely compromised can be treated so successfully to restore not only function, but also years of normal life.

Once clinical evidence of cardiac failure is apparent in iron overloaded hearts, the clinical situation becomes urgent to avoid a poor outcome and permanent heart damage. At this point aggressive chelation is required, in our experience this means constant (24 hr x 7 days per week) intra-venous chelation with desferrioxamine, sometimes in combination with the oral chelator deferriprone. In managing patients with thalassaemia the imperative is therefore to identify iron-overloaded hearts early, before severe heart failure has a chance to occur. In the past this has been difficult. The development of the magnetic resonance imaging parameter, named the T2* (cMR T2*) provided a non-invasive method to measure tissue iron accumulation and has transformed our ability to adequately risk stratify the thalassaemic patient population. In our own UK population this has been associated with a more than 80% reduction in cases of fatal heart failure, an experience that has been replicated in Cyprus, in Italy and other countries. Overall care has improved. A recent analysis of our patients with more than 10 years follow up revealed that only 23% now have any evidence of heart iron accumulation (T2* < 90 ms), compared to 60% of patients 10 years ago, with only 7% having severe iron overload (T2* < 10 ms), compared to 17% a decade ago.

Optimal management of individuals needs close co-operation between clinicians of widely different specialties, probably best orchestrated by the prime provider of care, the haematologist. Regular assessments of the burden of iron overload are necessary for successful care, but cMR can be a scarce resource in certain communities, particularly in the developing nations. Thus good clinical judgement is required to marshall available funds, allied to a program of regular cardiovascular assessment using all the currently available diagnostic tools of cardiovascular medicine, especially high quality echocardiography (ultrasound scanning).

Although there have been remarkable advances in the management and survival of these patients, clinical problems remain common and new issues are beginning to become more prevalent, including atrial fibrillation (AF) in non-iron overloaded patients. Atrial fibrillation is a common rhythm disturbance in medicine, seen in many adults with diverse forms of heart problems, from high blood pressure to coronary artery disease. The rhythm may be intermittent (paroxysmal AF) or more persistent. In some patients AF is permanent. During AF the low pressure cardiac chambers (the atria) cease to beat regularly (fibrillate) and the overall beating of the heart often is rapid at the outset and is irregular in timing and irregular in the power of the pulse. For the patient this may be sensed as a fast, often irregular, heart beat. The efficiency of the heart is diminished, by about 15 to 20 %, which can be tolerated by those with good pump function, but can precipitate heart failure if the heart muscle in the ventricles is weakened. In the past, AF was commonly the harbinger of severe heart failure in heavily iron overloaded patients and thus gained a very ominous prognosis. Now the commonest presentation is decades after the resolution of cardiac iron overload, in thalassaemic patients with a very good outlook. Thus AF has moved from being a clinically severe and dreaded complication of iron overload, to a more benign outlook, requiring management, but not being associated with dire outcomes in those with no iron and good heart function.

A major complication of AF in other medical conditions is stroke. The risk varies according to the underlying clinical condition, but may lie between 1 to 10 % per year. Thalassaemia patients often have an associated abnormality of coagulation and potentially would be at higher than average risk. The risk is minimal for AF that is of short duration (< 24 hr) and intermittent, but requires formal anti-coagulation as a precaution against stroke if permanent, or frequent and more than transient (> 24 hr episodes). Drugs to prevent attacks of AF have been disappointing in their success rates. There are few drugs than can be used to successfully prevent AF attacks.
and each must be used with care to prevent side effects; a cardiologist familiar with their use must monitor these medications. In recent years non-invasive techniques have been developed to treat AF and prevent recurrences. These non-surgical electro-physiological techniques are performed by specialised cardiologists (EP specialists) and consist of catheter-based methods to alter the electrical characteristics of the atria. Success rates of catheter ablation of AF are in the region of 70 to 80% with recurrences requiring repeat procedures in about 15% of cases. Our experience suggests that success rates are lower and the difficulty of the procedures is higher in the thalassaemic population, due to the multi-focal nature of AF in this patient group. It is likely that in the future, as experience increases, the success of ablation will improve and patients will be referred earlier, rather than waiting until the rhythm is firmly established.

Thus although there is much to be confident about in patients with thalassaemia there still remain challenges to provide optimal quality of life to this population.

Special Thanks

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With improvement in basic care in transfusion and chelation therapy, thalassaemia patients are expected to have a longer life span. Thus emphasis has now shifted from survival to attaining a better quality of life. Multiple endocrinopathy is seldom life threatening, but causes significant morbidity.

Hypothalamic-pituitary (H-P) dysfunction or hypogonadotropic hypogonadism (HH) resulting from transfusional iron overload, continues to be the commonest endocrinopathy in thalassaemia patients. If untreated, it causes infertility, osteoporosis in later life. It occurs at an early stage and progresses in an irreversible way despite intensive chelation therapy. HH can affect patients at all age groups, especially the peripubertal children and post-pubertal adolescents. The commonest cause of retardation of growth and sexual development is HH, which affects 80-90% thalassaemia patients worldwide. Unless such deficiencies are corrected promptly and early, the final height is always lower than the patient’s height potential. Even if patients mature normally, they are vulnerable to develop primary or secondary amenorrhea (females) and infertility and sexual dysfunction and osteoporosis at a later age. In addition to the physical deficiency state, impaired growth/puberty, infertility are sources of considerable embarrassment and hinders social integration of affected thalassaemics leaving them isolated from the community at large. Early intervention and appropriate treatment is important to prevent irreversible damage to hypothalamic pituitary axis and offer the best quality of life to the children and adolescents with delayed growth and puberty.

Pathophysiology in relation to stages of life: Birth to adulthood

Growth failure in TM has been recognised for many years, and has persisted despite major treatment advances. The child with TM has a particular pattern, which is relatively normal until age 9-10 years; after this age a slowing down of growth velocity and a Characteristically 3 phases of growth according to age of presentation are recognised which have different aetiologies. (Fig 1) The first phase of childhood growth disturbance is mainly due to hypoxia, anaemia and nutritional factors. The second phase is due to anaemia and iron load affecting growth hormone-IGF axis. The hormonal cause of growth retardation in TM children is complex. It has been apparent that GH-IGF-1 axis plays a role in their abnormal growth besides hypogonadism and hypothyroidism.

However most patients now present after the age of 10-11 years (3rd phase) with peri pubertal growth and pubertal disturbance with absence of growth spurt, arrested and absent puberty with growth retardation. This is usually due to iron load affecting H-PG axis. GH-IGF axis may also be affected.

Characteristically patients frequently present with severe delay/absence of puberty with reduction of final height. Chronic hypoxia is no longer a contributing factor nowadays in properly treated children. Linear growth in childhood is disrupted only in a small percentage of children due to anemia, ineffective erythropoiesis and iron overload. During the first decade of life the maintenance of haemoglobin levels above 9 g/dL together with adequate iron chelation therapy makes the children with TM indistinguishable from their non-thalassaemic peers. Zinc deficiency is probably a concomitant factor in growth failure phase 1 and 2. The effects of zinc supplementation on growth velocity were assessed in 22 patients with biochemical evidence of zinc deficiency. The mean height velocity of zinc supplemented children was significantly greater that of normal children. The crucial role of zinc deficiency however was not confirmed by other studies.

It is well known that high serum ferritin levels during the first decade of life are associated with final short stature, indicating that appropriate iron chelation therapy can prevent or limit this complication. However, several studies showed high prevalence of short stature in TM children adolescence treated intensively with desferrioxamine (DFO). It may also contribute in phase 3.

Hypogonadotropic hypogonadism:

Gonadotrophin insufficiency or hypogonadotropic hypogonadism (HH) resulting from transfusional iron overload continues to be the commonest endocrinopathy which affects 70-80% of thalassaemic patients worldwide causing sexual infantilism, osteoporosis and infertility. Although it is seldom life threatening, HH phenotype causes severe impairment of quality of life. Early diagnosis and intervention is mandatory to offer best chances of attainment of peak bone mass, growth and puberty with restoration of fertility potential for a better quality of life.

Hypogonatotrophic hypogonadism in Thalassaemia is related not only to iron toxicity on gonadotroph cells but also to iron toxicity on the adipose tissue thus changing the physiological role of leptin in sexual maturation and fertility. Leptin is a polypeptide hormone that is produced in fat cells due to the expression of the ob
gene. In girls leptin levels increase dramatically as puberty develops and stimulate the Hypothalamic-Pituitary-Gonadal axis.

There is evidence that this hormone acts as a permissive signal allowing puberty to precede. The impaired synthesis of leptin in Thalassaemic patients seems to be related to transferrin receptor levels and therefore iron toxicity but further research will be required to elucidate this critical issue (59, 60).

Gonadal iron deposition occasionally occurs usually at a late stage when irreversible damage to H-P axis has occurred (Chatterjee 2000). The iron deposition on the gonads is a rarer condition. In the majority of patients gonadal function is normal as most women with amenorrhea are capable of ovulating with HMG- HCG treatment with successful outcome (Bajoria and Chatterjee 2009) and similarly men with azoospermia become fathers.

Role of hypogonadism and peak bone mass:

The overall frequency of bone disease in hypogonadal patients with TM is increased compared with those of normal gonadal function. Sex steroids regulate skeletal maturation and preservation in both men and women, therefore the impact of gonadal insufficiency on skeletal integrity has been widely recognised in both genders. BMD normally rises at a steady rate throughout childhood until around the age of 12, and then there is a sudden acceleration of bone mineral accretion that coincides with the onset of puberty and the pubertal growth spurt. Failure to progress normally through puberty is associated with failure of achievement of peak bone mass, which is a contributing factor to the ultimate bone disease in Thalassaemia.

Investigations for growth disturbance for thalassaemic children under 10 years

1. Current height (both standing and sitting in cm) must be plotted on the growth chart. Target height is based on mid-parental heights. Comparison with previous measurements is done to estimate the growth velocity. Growth and pubertal status (Tanner staging are noted by the same observer. Bode mass index is calculated (kg/sqm). Physical disproportion (truncal obesity) and waist: hip ratios are also calculated. Nutritional, emotional and social statuses are also reviewed.

2. Bone maturation is assessed by X ray of left hand and wrist (Tanner and Whitehouse.

3. Routine blood tests include liver function tests, serum ferritin + other markers of iron load (cardiac and hepatic MRI 2*, biochemical profile, and zinc

4. Urine analysis

5. Thyroid function test (Free T4, TSH). Vitamin D, PTH must be measured as well.

6. IGF-1 generation test is done in patients with low levels of IGF-1 and IGFBP-3 and normal GH secretion to exclude GH resistance.

7. Stimulation tests to assess GH secretion, where at least two tests are required. Priming with sex steroids (testosterone depot 100 mg IM in boys and ethinyl oestradiol 10 mg orally for 3 days in girls 72hrs before GH testing may be necessary in children who are prepubertal and have a bone age of 10 years (Chatterjee et al., 1993). GnRH priming may be used as well (Soliman).

Goal of therapy- to improve growth velocity and attain target height in patients with retarded growth

Dose and duration of therapy

Treatment with recombinant GH (rhGH) is recommended when GH deficiency is established.

Therapeutic response with rhGH administration in cases with GH deficiency, is often non satisfactory. Often supra physiological doses of GH are required to obtain therapeutic response due to partial GH insensitivity. In poor responders such treatment should be discontinued. Treatment with rhGH for 1 year seems to be effective in increasing growth velocity, IGF levels without causing adverse effects on bone maturation, glucose tolerance, serum lipids and blood pressure. The encouraging results described during the first year of rhGH treatment do not persist during the second and the third years.

This is because increase in bone age with continued treatment is equal to or slightly greater than the height age increase. Prolonged therapy with rhGH might not improve final height; on the contrary a negative effect may be hypothesized (52).

Growth acceleration is mostly promoted with sex steroids in children with pubertal delay as sexual complications present a significant issue in thalassaemics.

All patients should be monitored carefully for diabetogenic response (GTT) of GH therapy specially those with severe iron load

II/ H-P-G axis and diagnosis and management of disturbances of Puberty + Growth velocity

Clinical phenotypes of HH

Pubertal complications in TM present the commonest endocrine complication in almost all studies. These include:

(a) Failure in initiation of puberty:

Absence of gonadarche in males by 14 years and thelarche in
females by 13 years

(b) Arrested Puberty - and Hypogonadism. Arrested puberty is defined as the absence of further pubertal progression -once puberty has started -for more than one year, where testicular volume in boys never progressed beyond 6 to 8 ml and breast size in girls remained unchanged.

(c) Primary amenorhoea- Failure in menarche by 18 years

(d) Secondary amenorhoea- Absence of periods for >12 months after menarche

Delayed puberty or failure in initiation of puberty in TM is almost always due to HH, which still remains the most common complication of haemosiderosis. Iron deposition on gonadotrophic cells of the pituitary leads to disruption of gonadotrophin production

Protocol for investigation of peri pubertal disorder with / without growth disturbance

• Clinical:

Anthropometry: Assessment of growth: height (sitting and standing), weight, BMI, hip: waist ratio, height velocity, PHV centile chart.

Serial monitoring of growth (3- 4 monthly)) as early as 10 years and puberty (6 monthly) from 12 years must be done Sitting and standing height (3 monthly) throughout childhood and adolescence is also undertaken specially those n DFO

Puberty
Clinical signs of puberty: Tanner staging

Breast development in girls: thelarche
Testicular enlargement in boys: gonadarche

Pubic hair: adrenarche (DHEAS) strictly is not a sign of puberty must be checked as well

Biochemical: Assessment of H-P-G axis include the following:

- Basal FSH, LH, sex steroids, TFT
- Dynamic testing of the H-P-G axis- GnRH test
- Spontaneous assessment of H-P axis- Ultradian gonadotropin profile
- MRI: pituitary (only in selected cases as it is still a research tool)
- GH-IGF axis – See before
- Dissect gonadotroph from somatotroph damage by sex steroid priming
- Straight x-ray of spine to exclude micro fracture

GnRH test to evaluate the gonadotrophin reserve

Gonadal stimulation test to check gonadal reserve – HCG in boys and HMG in girls (Chatterjee 2000)

Bone age is helpful for the treatment decision options

Criteria for intervention for induction/ acceleration of puberty

1. Failure in initiation of puberty or arrest of puberty
2. CA- Bone age = > 2 years
3. Epiphysis– not closed (if growth increment is desired)

Therapeutic approach

Physiological puberty

If H-P-G axis is functionally intact with normal LH and FSH and sex steroid response to GnRH + normal or subnormal LH and FSH pulses (ultradian gonadotrophin profile) options are sex steroid priming, or pulsatile GnRH infusion can be used to induce physiological puberty (Chatterjee 2000). Although GnRH infusion is safest with no thrombogenic, hepatic or other metabolic effects, it is often difficult to advocate as H-P axis is irreversibly damaged in many patients. However, we have shown 80% success rate with this therapy if advocated at an early stage of HH (Chatterjee 1987). (See fig for GnRH infusion)

If H-P axis is irreversibly damaged pseudo puberty with sex steroids or gonadotrophins can be given (Chatterjee 2000)

If there is combined damage to H-P-G axis (Chatterjee), sex steroid replacement therapy is the only option to induce pseudo puberty.

Aims of treatment

In delayed puberty the aim is to mimic biological and biochemical pubertal events with promotion of sexual maturation and linear growth as well.

Induction of physiological puberty in boys for 6 months with sex steroid priming in boys this can be achieved with testosterone depot IM 25-50mg monthly for 6 months following reassessment. Pubic hair will appear and penile size will increase. Increase in testicular volume indicates activation of the H-P-G axis and release of gonadotrophins (FSH and LH), where no further treatment is needed except for close observation GnRH testing and ultradian profile may confirm maturation of H-P-G axis

Pseudo puberty

In cases where testicular size is unchanged, treatment is continued for 6 months and subsequently the dose is increased to 100 mg monthly for one year. The dose may be increased to 250mg im after Tanner 3-4

Therapeutic schedule is determined by the growth potential, clinical response and emotional factors. For testicular enlargement, the therapeutic regime is altered to the combination of HCG and HMG or rec FSH, both of which mimic the pituitary gonadotrophins. The final adult dose of testosterone depot is always individualized and usually 50mg/weekly IM or alternatively trans dermally in patches 5 mg/daily. The oral route (testosterone undeconate)
Induction of physiological puberty in girls
Oral ethinyl oestradiol is preferred at the dose 100 ng/kg/d for 6 months, where increase in breast size and growth acceleration is noted. Maturation of H-P G axis is also assessed from spontaneous and dynamic tests (increased gonadotrophin pulse frequency/amplitude (ultradian gonadotrophin profile) and augmented FSH and LH response to IV bolus GnRH test).

Pseudo puberty
Oral Ethinyl oestradiol dose is continued for additional 6 months and is increased to 200 ng/kg/d for the subsequent year. Therapeutic schedule is determined by the same factors as in boys. The adult dose is 400 ng/kg/d, where the uterine size is satisfactorily increased for the induction of menarche. Induction of puberty can be successfully achieved by the transdermal use of oestrogens too.

Menarche is achieved by the addition of Medroxyprogesterone 10 mg/d for 10 days (or nor ethisterone 10 mg for 10 days) when the size of the uterus exceeds 5 cm. When menstrual bleeding occurs spontaneously during oestrogen treatment, the regime should be adjusted. For maintenance of the menstrual cycle the use of oestrogens (Conjugated Estrogens 0.625 mg, Ethinyl Estradiol 20 μg) from day 1st to 25th and Progesterone from day 14th to 25th is required. The transdermal use of oestradiol with norethisterone is advantageous in iron loaded subjects due to decreased liver toxicity and is preferred in most cases as it obviates first pass effect.

Ovarian and testicular reserves are usually preserved in HH patients, as they are still able to increase oestradiol or testosterone levels following gonadotrophin stimulation test to produce ova or sperms in females and males respectively.

Women with TM who are regularly transfused and are well chelated can have successful pregnancies by gonadotrophins. Males who have normal gonadal function maintain their spermatogenic ability and therefore, frequently become father children with gonadotrophin support.

Other hormone treatment
Other hormonal deficiencies (thyroid, parathyroid and Vitamin D) must be treated with adequate dose of hormone replacement therapy.

Other management issues include haematological (transfusion and chelation) Nutrition- diet, exercise and lifestyle issues and psychological support must be provided adequately.

Reference

Thank You!

We would like to thank our benevolent donors for helping five of our Thalassemia major patients in response to our appeals for their Bone Marrow Transplant.
My Experience
Shivika Gadodia

Yes, I m… I m a special child of GOD. And we all are who have Thalassemia. I will prove you how???

If you compare us from the general people in the world I am sure that you will find that we thalassemic children are spiritually and emotionally stronger than the general people. Before coming to this world god told us “see this role is a tough one, I hope you all will be good actors and performers on the stage of life, at the place called world.” We smile and said “tension na lo aap, we will be the Amitabh and Aishwariya of the world.” And here we are…. Children like me have more faith in God and their parents.

Another proof of being strong is that when we get a report of any blood test we have done….you will not see that tension and panic or even traces of it on our faces which you can find in the 95% of the general public who have given their blood test…instead we smile and take the blood reports.

But one thing is for sure you will surely see faces full of tension, when we children take our report cards in the school ;-) Our biggest assets are our smile which you can see all the time. Once when I went for the blood transfusion, there was a boy who was going to put cannula. As his vein were punctured, sister was having a little difficulty in putting it. But that boy was so strong that even though it was pricked twice he dint cry. He did close his eyes because of pain, but he dint let his single tear fall… Finally when the cannula was pricked, instead of making faces, he smile….that was the time I realized that we can bear the pain with our smile 😊

We all do have a better understanding of everything and at a very early age. May be this is God gift. I have also noticed while interacting with many other children who have Thalassemia, that we are very practical in life, we all know the reality and face it with confidence. We start understanding things in general in very early age. We are more responsible that general children. I remember that when I was very small 7 – 8 yrs then someone asked me will you have apple and that time my mummy wasn’t around. I said “I am sorry but I can’t have apple as I am not allowed to. Because there a lot of iron content in it and I should avoid having things that have iron as they will affect my health”. Those people were shocked by seeing such a small child knowing so much and being so responsible for health. When my mummy came they told her that your daughter is brilliant… my mummy had a wonderful smile on her face which I can’t forget till today….and no doubt today also I m brilliant….as I m special.

One thing I like to request the world by this article of mine that some people who come to know about us shows too much of sympathy. Please stop showing too much of sympathy in front of Thalassemia children as we hate sympathy. If you really feel bad for us then do something for us, for the society, for those who couldn’t afford the treatment. But please don’t say this on our faces “poor child” or “poor baby” because it cuts our soul and makes us realize that we are not normal…

Another thing I also wanted to say to those who are like me as I call special child of God “Buddies please never lose hope and always be strong and positive as life gives chance only to those who are dare devils and not to the cowards who quit with a tear rolling the cheeks…chak de buddies!!!

These all are my personal views and I m really sorry if I have hurt you from any of the above lines.

Be Deaf, To World’s Negativity
By: Jyoti Arora, Author of Dream’s Sake

There’s a story that I have come across more than once on internet. Let me relate it here:

‘Once, there was a group of little frogs. One day, they decided to run a race. In haste of running, some frogs fell down in a deep pit.

The other frogs standing on the top started crying, ‘Oh, poor friends, you are as good as dead. You will never come out of this deep, dark hole.’

The frogs in the pit tried jumping and climbing the walls of the pit. But it was really too hard. They heard their friends’ cries from the top and believed that there really was no way to get out. So they stopped trying, fell back, and died.

...
Only one little frog continued his struggles. Again and again he slipped down, but at every time, he climbed up again, at each attempt going a little higher as the wall of the pit became familiar to him.

From outside the pit, the frogs kept on crying, ‘Leave it, little frog. Why are you troubling yourself? It’s no use. You’ll never come out of this deep, dark hole.’

But the little frog paid no heed, and kept on climbing higher and higher. Finally, after a lot of hard work, he managed to step out of the pit and stand on the open ground.

The frogs all gathered around the little frog and congratulated him for his success. They all said ‘We really believed that nobody can come out of that dark pit. But you proved us wrong. You just kept on trying despite our telling you it was no use. Didn’t you hear us?’

It turned out that the frog hadn’t heard a word of his friends’ negative warnings, because he was deaf. So their negativity had not penetrated his mind as it had penetrated the minds of other frogs in the pit. The negativity and discouragement had made other frogs in the pit to lose hope and give up too soon. But the deaf frog had only his courage to lead him, and no negativity to push him down. So he succeeded.

So would we all if we too become deaf to what the world says we can’t do. On no account must we let the world’s negativity push us down. For we have a right to climb up too, and we will, if we keep on trying.

Life with Thalassemia is much like the deep, dark pit in which some of the frogs fell. Coming out of it is a struggle. And too many would shed tears of pity for us and think our situation hopeless. And yet, I suppose by now enough of us have proved that it is not so. We Thalassemics too can succeed and build for ourselves a happy life and successful career.

Just refuse to accept the negativity that people throw your way. Just don’t let people dictate what you can, or cannot do. Nobody has a right to set limits to your dreams and aspirations. Don’t allow anyone that right. Follow your own heart, make your own trials, and keep pushing, keep trying and most of all, keep hoping.

Had I given up on my hopes and dreams when I stopped going to school after class seventh, I would never even have tried to achieve what I have achieved today. There was a time when being a Thalassemic was all the identity I had, and nobody expected me to be anything else besides that. But I refused to let my disease become my identity. I struggled on.

The path hasn’t been easy. Sometimes I felt as if I was holding on to my hopes just by the skin of my fingernails. But I held on. And today, I am a published novelist, author of Dream’s Sake, and that’s an identity I proudly accept. I won a contest and became a blogger for Samsung. I earned the title of Samsung Mobiler. And that’s an identity I proudly accept. I’m a freelance writer, a resume editor for a recruitment firm, a book reviewer at a well known blog, and a still striving, still aspiring dreamer. I am so much more than my disease.

Thalassemia is a part of my life, I’d be glad if the world sees it as just that. And if the world cannot, and if people would still insist on looking at me with pitiful eyes, let them. I am blind to their glances and deaf to their words. My eyes see only my dreams and I hear only what my heart says, just like the little frog.

Had the deaf little frog lost hope of coming out in the world, he would have stopped trying like his other friends did. But he stayed hopeful and determined and struggled on to success.

So, don’t let anybody or any circumstance of life kill your hope and endeavour, because when these die, life loses its purpose and degenerates into mere existence. And really, in the absence of life, existence is not so easy to bear as it may sound.

So, hope on, strive on, and don’t give up. Never give up.

---

Thanks

We hereby extend our heartfelt thanks to the below mentioned Organizations & Individuals for arranging Blood Donation Camps for our thalassemia children.

- Lifestyle, Ghaziabad
- Lifestyle, Ambience Mall, Vasant Kunj
- Lifestyle, Metro Polis, Gurgaon
- D.D.U. College, Moti Nagar
- Huges, Gurgaon
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• All names are listed in alphabetical order by surname.

Address all correspondence to:
Shobha Tuli
Secretary, Organising Committee

Thalassemics India
A-9, Nizamuddin West, New Delhi-110013
Tel(O): 41827334, Telefax: 46595811 • E-mail : thalcind@yahoo.co.in • Website: www.thalassemicsindia.org
Over the last 25 yrs, since the inception of Thalassemics India, several advances have been made in all the basic principles of management which have resulted in improved survival, better quality of life and now children with Thalassemia major are entering in third and forth decade of life. Currently thalassemic children are serving the nation as professionals such as engineers, doctors, advocate, IAS officers etc. and some of them are having married happy life.

In the present article some of the advances in the conventional therapy which have resulted in significant decreased morbidity are being reviewed.

Basic Principles of Management include:
1) Correction of the anemia by regular transfusion therapy
2) Removal of iron with use of iron chelating agents
3) Treatment of complications of the disease and therapy
4) Bone marrow transplantation

Transfusion therapy in Thalassemia has two major goals:
1) To prevent anemia
2) To suppress endogenous erythropoiesis to avoid ineffective erythropoiesis & bony changes.

Blood transfusion is the mainstay of therapy for all children with Thalassemia major and for those children with Thalassemia Intermedia who cannot maintain their hemoglobin at 7gm/dl. Patients who have progressive evidence of growth retardation, severe bony changes, and significant hepatosplenomegaly.

Regular red cell transfusions forms the mainstay of treatment.

**Packed Red Cell Transfusion (RBC)**
Transfuse these children with comb's "cross matched packed RBCs. It is preferred to give leukodepleted red cell which can be done either by bed side filters or by prestorage leukoreduction systems as several reactions due to white cells are reduced. Pre storages filtration is better than bed side filters as cytokines released from the white cells are not present. Blood from near relatives should be avoided to prevent alloimmunization and for possible bone marrow transplantation in future.

**How much to transfuse**
The ideal transfusion regimen is hyper transfusion regime in which the aim is to maintain mean hemoglobin levels at 12.5gm/dl and pre-transfusion hemoglobin levels should vary between 9.0 -10.0gm%. This regimen permits normal growth and development, prevents skeletal abnormalities and gastrointestinal iron absorption. It’s also prevents the liver & spleen enlargement and development of hypersplenism. The advantages of this therapy are given in table 1.

**Safe Blood Transfusion**
Complication of repeated blood transfusions include increased frequency of non-hemolytic febrile reactions; transfusion transmitted infections such as hepatitis B or C, HCV, HIV, malaria etc. Screening of the blood for HIV, HBV, HCV, malaria etc. is mandatory to prevent these infections. Screening of blood with the advent nucleic acid testing (NAT) for various viral infections have reduced the window period. This test is very sensitive & specific but its cost is high. The comparison of various screening tests for specificity, sensitivity and their window period are given in table II.

Over the last 25 years there has been a major effort to ensure safe blood. Initially the screening test were done
by ELISA 1st generation & presently most blood banks are testing by ELISA 4th generation which is highly sensitive & specific with shorter window period. Advent of NAT test has further ensure safer blood but the cost of testing is high and only few blood banks have adopted this test.

**Immunization**
All Thalassemic children should receive all the immunization to prevent various infectious diseases as other normal children. These children should receive first dose of hepatitis B vaccine before their first blood transfusion while other two doses of hepatitis B vaccine can follow. Children who are already on transfusion therapy should also receive hepatitis B vaccine if they are negative for hepatitis B surface antigen. Hepatitis B booster dose is further advised at every five year intervals.

**Transfusion Transmitted Infection**
With the advent of ELISA iii & IV, NAT testing the blood transfusion have become very safe. Efforts are on to bring the Transfusion transmitted infection prevalence to zero. But addition of other tests increases the cost of blood testing. eg testing hepatitis B core antigen, serum transaminasis levels, P-24 antigen level for HIV etc. The National policy by NACO looks into the cost effectiveness of screening testing, blood collection etc. However the corporate hospitals have added additional tests to ensure safe blood transfusion & screening blood by NAT testing. The policy of hepatitis B vaccination before first transfusion has further reduced the risk of hepatitis B infection through blood. Leucodepletion of blood before transfusion has further reduced the risk of infections transmitted through leucocytes.

**Iron Over Load and Chelation Therapy**
Two factors contribute to iron overload in a Thalassemic children
A. Transfusion iron overload
B. Enhanced gastrointestinal iron absorption.

Each unit of pack cell releases 180-200 mg of elemental iron. The body accumulates nearly 200 mg/kg of iron every year. One mg of iron is absorbed daily from the gut in a normal person while in a Thalassemic child it may be as high as 10mg/day. However, iron overload from gut is minimal. Transfusion iron overload leads to deposition of iron in the heart leading to multiple heart problems. Its deposition in the pancreas causes diabetes, while in the liver and spleen may results in hepatosplenomegaly, hepatic fibrosis and cirrhosis of liver. The iron overload in the pituitary gland causes growth retardation, delayed puberty. Iron deposition in others glands causes their dysfunction. Its deposition in the skin leads to black discoloration.

**Monitoring for Iron overload**
Iron levels of Thalassemic can be monitored by serum ferritin levels which are readily available and easy to monitor. When its level is above 1000 ng/ml, the chelation therapy should be initiated. Level of serum ferritin above 10,000 ng/ml is found to be associated with significant organ dysfunction. The limitation of serum ferritin is that its levels are falsely very high in presence of infection, Vitamin C deficiency, hepatic damage, hemolysis and ineffective erythropoiesis. Till date serum ferritin still remains most practical test to access the iron overload. The trends in serum ferritin levels over a period (rise or fall) serve as a good indicator of body iron burden.

Other methods to detect iron overload are Liver biopsy, MRI and SQUID & Star 2 images of heart. Liver biopsy is the gold standard but it is invasive, expensive, & associated with the risk of internal bleeding. Presently this is used for research only.

SQUID (Superconducting Quantum Interference Device) is an imaging modality & it directly measures the body ferritin and hemosiderin. However it is not preferred to evaluate myocardial iron.

MRI provides a non-invasive, quantitative method of measuring tissue iron concentration indirectly. Liver iron levels determined using MRI shows excellent correlation with liver iron. MRI has the ability to evaluate the entire organ. It is a more accurate method to measure liver iron content. Presently Ferrisean has been developed using MRI which is simple & effective method to assess iron overload in different organs & total body iron. The advent of T2* MRI has become the new gold standard for measuring liver & cardiac

<table>
<thead>
<tr>
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<th>HBsAg tests</th>
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<td>P24 antigen test</td>
<td>4.4 week</td>
<td>4.4 days</td>
<td>7-12 days</td>
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**Table II:** Window period of Screening test

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**THALASSAEMIA UPDATE**

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**Article**
Ascorbic acid deficiency increases iron overload. In general, the lower the T2* value, the risk of cardiac dysfunction is high, and T2* value below 8 ms is suggestive of severe cardiac iron overload.

**Desferrioxamine (DFO/ Desferal)**

This was the first iron chelator introduced in the World in late 1960 and in India in 1970-1972. Desferrioxamine is a hexadentate. One molecule of DFO binds with one molecule of iron. It has short half life and is not absorbed from the gut. Therefore, it needs to be given continuously with the help of an infusion pump. Desferal should be started before the age of 2 years. It is given on daily basis for a minimum of 5 to 6 days per week, over 6 to 8 hours with the help of subcutaneous infusion pump. The daily dose of desferal is 30 to 50 mg/kg and its dose need to be tailored according to the need of the patient. It is advisable to keep the serum ferritin level between 1000-1500 ng/ml. Nearly two third of iron is cheated through stool and remaining through urine. It offers benefit to variety of organs such as liver, heart, endocrine glands. As it needs to be administered by slow subcutaneous or intravenous infusion, the compliance decreases with the advancing age.

It is fairly safe and has minimal toxicity. Its subcutaneous administration causes local pain, and redness. Visual abnormality may occur and includes decreased acuity of vision, peripheral field vision defects, and defective dark adaptation. High incidence of high frequency sensori-neural hearing loss has been observed. Auditory and visual toxicity are reversible if detected early. Therefore slit lamp and audiometry examination are advised annually. It was gold standard form of therapy but with advent new chelators its use is on decline. However it augments iron chelation when used in combination with deferiprone.

**Vitamin C**

Ascorbic acid deficiency increases insoluble iron hemosiderin. Vitamin C helps in conversion of hemosiderin into ferritin from which iron can be chelated. Addition of vitamin C 100 mg daily prior to DFO therapy increases iron excretion. It is given only with DFO therapy and not along with other chelators.

**Deferiprone (Kelfer)**

This was the first oral drug developed. It mobilizes iron from transferring, ferritin and hemosiderin. It has undergone extensive trials in USA, UK, Canada, India and several other countries. It has been found to be an effective and safe iron chelating agent. It is given daily in dose of 75 to 100 mg/kg body weight in three divided doses. It has been found to be more effective than DFO in mobilizing intracellular iron from heart. It has been termed as cardio protective. Nearly 20 percent of children develop gastrointestinal symptoms like nausea, vomiting, pain in abdomen and diarrhea. Advent of deferiprone has improved the compliance. Ten to twenty percent children develop arthropathy, which is reversible after reducing the dose or on stopping deferiprone. Absolute neutropenia and thrombocytopenia also has been reported in occasional cases. This drug alone is usually not very effective in bringing the serum ferritin levels around 1000ng/ml.

**Combination Therapy**

Desferal and Deferiprone have different actions. Both have been used together to improve the compliance, efficacy to reduce the side effects & cost of therapy. Deferiprone (75 mg/kg/day) is given for days in a week and desferal (30-40 / kg / day) is given subcutaneously 2-3 days a week. This combination has been found to be good and an acceptable regimen. Combination regimen is recommended for patients with high ferritin levels and patients having cardiac, hepatic or endocrine problems.

Studies on other combination of chelating drugs such as desferal with desferasirox or desferasirox with deferiprone are in progress and soon the result of these studies will be available. Author has personal experience of use of desferasirox and deferiprone in few children and observed that this combination is safe and very effective. However for general recommendation we need to learn the efficiency and safety of this combination from well planed studies.

**Deferasirox/ICL-670 (Exjade/ Asunra/ Desirox)**

ICL 670 is new class of tridentate which is a synthetic iron chelator. Two molecules of the chelator are required to form complex with ferric iron. It is twice as effective as DFO. The iron excretion is predominantly fecal. Chelated iron is cleared by the liver and excreted through the bile. It also has the ability to chelated iron, from the reticulo-endothelial cells (RE cells) as well as various organs. It is highly selective for iron and does not excrete zinc or copper. Its oral bioavailability is 70% and can be given once a day as it has long half life. In comparative studies 40mg/kg of Deferasirox is found to be as effective as 40 mg/kg of DFO. Maximum dose recommended is 40 mg/kg/day. The most common side effects noted are transient GI disturbances like abdominal pain, nausea and vomiting, diarrhea etc and skin rashes. In Indian children who require more blood transfusion, have high serum ferritin levels generally require Deferasirox in dose of 40 mg/kg /days to effectively reduce the serum ferritin levels.

**Splenectomy**

It has been proved that if the hemoglobin level is maintained above 10gm/dl, Spleen does not get enlarged & evidence of hypersplenism does not appear. However, in our country many children develop splenomegaly and hypersplenism because of poor facilities for management of Thalassemia. If the child has already developed splenomegaly and sign
of hypersplenism. Splenectomy is indicated if yearly requirement of packed cells is 200 cc / kg. (Table III) Splenectomy should be undertaken after 6 years of age.

**Table III: Indication of Splenectomy**

1. Large spleen with risk of rupture
2. Abdominal pain or discomfort due to large spleen
3. Red cell transfusion requirement over 200ml/kg/year
4. Presence of bi or pancytopenia
5. Evidence of hypersplenism on nuclear studies

All children needing splenectomy should receive pneumococcal, H influenza and meningococcal vaccine at least 3 to 4 weeks prior to surgery. Family should be counseled regarding the risks & benefits of splenectomy prior to surgery. Prophylactic penicillin therapy must be continued life-long after Splenectomy. Parents should start amoxicillin or ciproflox at start of fever at home. Child should be taken to the hospital the earliest. All infections should be treated promptly with broad spectrum antibiotics in the hospital under care of specialist.

**Bone Marrow Transplantation**

It offers permanent cure and better future for children. The credit of first bone marrow transplantation in Thalassemia major goes to E Donald Thomas who performed this procedure in 18 months old Thalassemic child in 1982 using HLA matched elder sister as donor. This child was cured of Thalassemia. Since then many centers in the world and few in India have initiated BMT facilities.

The principles of bone marrow transplantation include:

(a) To destroy and prevent regeneration of defective stem cells,
(b) To infuse normal HLA matched stem cells
(c) Sufficient immune suppression for good engraftment of donor

Bone marrow cell

(d) To prevent GVHD with high dose therapy of busulphan, cyclophosphamide, total and other modalities.

The three most important adverse prognostic factors for survival and event – free survival have been observed in large studies which include:

a) Presence of hepatomegaly (Hepatomegaly of 2 cm. below costal margin.)
(b) Portal fibrosis and
c) Irons overload (S ferritin > 1000 ng/ml).

Based upon these factors children have been divided into three classes. Class I when all above three factors are absent. Class II when one or two factors are present and children with presence of all factors are termed as class III. Results of bone marrow transplantation is best in class I children with event free survival of more than 95 percent of cases. The cost BMT in India is around 8 to 10 lacs and is regularly being done at Christian Medical College Vellore, Tata Memorial Hospital Mumbai, AIIMS in Delhi, SGPGI Lucknow & several other centres. With the advent of non myeloblastic BMT and newer pre-conditioning regimens the success of BMT and long term survivals have further improved.

**Key Messages**

1. Management of Thalassemia is lifelong and has become simple with the advent of recent advances.
2. Regular packed cell transfusion to maintain pretransfusion hemoglobin above 10gm/dl is most important.
3. It is essential to monitor serum ferritin levels regularly at 3-4 months interval.
4. Chelation therapy should be started as soon as serum ferritin level is >1000ng/ml.
5. Chelation treatment is necessary as long as child is getting blood transfusion.
6. Among various chelating drugs the Asunra / Desirox is most effective. It needs to be given once daily and is a total body iron chelator.
7. Dose & from of chelation therapy should be selected to maintain serum ferritin levels around 1000ng/ml.
8. Splenectomy should be undertaken with all precautions & only when indicated.
9. Regular monitoring of blood counts, liver & renal functions, serum ferritin, growth parameters are essential from beginning.
10. Yearly monitoring of endocrine function, HIV, hepatitis markers, ECHO of the heart, T2* images, bone mineral density (BMD) after 10 years of age is essential to detect early abnormalities for prompt management.
11. Bone marrow transplantation offers complete cure. It is only one time procedure.

**Thank You!**

We are thankful to all those who have contributed in this issue of Thalassaemia Update.

**Be a part of our Thalassemia Extended Family.**

**Become a member of Thalassemics India!**

**Change of Address**

Please inform Thalassemics India if there is any change in your postal address.

**Thalassemics India**

A-9, Nizamuddin West, New Delhi-13

email: thalcind@yahoo.co.in
Quality of Life with Thalassemia Major in India
Dr. Amita Mahajan

The life expectancy of patients with thalassemia major has improved dramatically in the last 30 years primarily because of regular blood transfusion therapy and effective iron chelating therapy. In the developed countries more than half of the patients are over the age of 30 years. In India also, now, we now have a large number of older patients with thalassemia who have their own hopes, dreams and aspirations. More importantly, a number of thalassemics have gone on to become high achievers and made us proud. It is indeed inspiring to see these children overcome all odds and excel as lawyers, engineers, architects and very recently as an IAS officer. As a physician, it is very gratifying to see our patients perform well in every sphere of their life. When I am asked what has really changed in thalassemia over the last few years, I feel it is really our attitude to this disease that has changed. Even as we work hard to prevent thalassemia, it is important to realise that with optimal management it is now possible for these children and young adults to live a longer life span with a much better quality of life.

With their increasing life span, it is essential that we must focus on improving their overall quality of life so that they can go on, as adults, to achieve their full potential. Whilst in the younger years, the focus is mainly on optimal transfusion and chelation, the older thalassemics in addition are grappling with issues relating to higher education, career, relationships and marriage. It is imperative that parents, physicians and support groups understand their needs.

The quality of life (QOL) is now considered an important index of effective treatment. An assessment of QOL differs from other forms of medical assessments in that it focuses on the patient’s own views of their well-being and assesses other aspects of life, giving a more holistic view of well-being. The four dimensions of quality of life are - physical, emotional, social, and role functioning which refers to how they perform at school, college and at work. The QOL of individuals with thalassemia major is influenced by many factors: impact of the diagnosis and treatment, having a chronic condition, appearance, treatment components like frequent hospital visits for transfusion, delayed puberty, complications of the disease and therapeutic interventions and uncertainties about the future.

There is also evidence that culture and education play a vital role in the way a family copes with thalassemia. Fortunately, for our patients the cultural values of our society are such that the patients continue to enjoy tremendous family support even as they grow to be adults. Even though, our systems are not perfect and there is really so much scope for improvement in terms of the delivery of healthcare to these patients, the family support they enjoy goes a long way to shape their lives. In addition, a number of support groups are working very hard to make things better.

Results from patient questionnaires from younger patients and parents usually highlight issues related to organization of transfusions, insufficient options with chelation therapy, and poor communication. Practical measures are being taken to address these issues. The older patients now face newer challenges in obtaining higher education, securing employment and raising their own families. They are also confronted with other problems like bone disease, infertility. We therefore, have to work in tandem to tackle each of these issues better not so that they are fit to take up all the challenges and that they get a fair chance at job opportunities and are able to have meaningful relationships.

Today, thalassemia major is a completely different disease. The patients are transfused from early in life, so that bone deformities as well as splenomegaly are prevented. Transfused blood is safer. Previously daily infusions of desferal impaired the QOL of these patients. Both kelfer and deferasirox have helped the patients to have a better QOL. Many more patients are able to get chelation now than before. The access to bone marrow transplant has improved significantly as have the results of BMT in our country. However, not every child has access to these facilities. The primary focus for the next decade has to be to make these facilities available to all.

A number of hospitals are setting up thalassemia services. The importance of specialized skills in treating patients with thalassemia is increasingly being recognized. But we still have a long way to go. Psychosocial and counseling programs aimed at helping patients accept their illness, facilitating a normal lifestyle and providing a link between the patients, care givers, school and may go a long way in alleviating their difficulties. In addition, modification of healthcare services for children with thalassemia to make them more patient-centered, flexible and comprehensive may reduce time spent at hospitals and also improve patient outcomes, including the QOL of our patients.

A lot more needs to be done. It should be our endeavor that each and every child with thalassemia has access to optimal healthcare and can go on to achieve their full potential as adults. If we work together towards these goals, the quality of life of our children will get better with each passing year.
Thalassemia major is a commonest hemoglobinopathy resulting from ineffective erythropoiesis leading to severe anemia manifesting usually after 6 month of age. It leads to progressive hepatosplenomegaly, growth retardation and various other organ dysfunctions. These kids require lifelong blood transfusion (red cell) which subsequently leads to iron overload and risk of transfusion transmitted infection. Around 10,000 kids with thalassemia major are born every year in our country with a carrier frequency of 3% to 17%.

Currently, approximately 50,000 patients are undergoing transfusions in India. Most patients die at an early age secondary to disease or transfusion related complications, compounded by inability to afford medications.

Only definitive treatment for this disorder is allogenic bone marrow/stem cell transplantation. It requires HLA identical stem cell donor usually sibling or parents. The chances of getting full match with siblings are approximately 25% and there is 4-5% chance of parents being a full match with the child. Slight degree of mismatch is acceptable in today’s world and it gives results comparable to full match donor except slight increase risk of graft versus host disease and primary rejection. Alternative source of stem cells is either unrelated HLA matched voluntary donor or umbilical cord blood. The ideal age of transplant for thalassemia major is 2-5 yrs of age but it can very well be done till 20 years of age provided condition of the patient is fit for transplant. Transplant related complications such as (Graft versus host disease, sinusoidal obstruction syndrome, infection and risk of rejection however is relatively more as the age increases)

In India first Allogenic Bone Marrow Transplant for thalassemia was done at Vellore in early nineties. Since then 700 - 800 thalassemia transplant have been done across the country so far following which many patients have been cured. More than 95% of patients were treated with HLA matched sibling transplant. Few patients had undergone transplant using cord blood stem cell with variable results.

The success of BMT in thalassemia depends on risk stratification based on Lucarrelli’s classification which in turn takes into account: size of liver, iron chelation and liver damage secondary to iron overload. Based on these features they are divided into 3 classes: Class I with all three favourable factors having the best results and Class III with all three unfavourable having relatively poor success rate. The morbidity and morbidity increase in higher class. Unfortunately, in present scenario due to lack of awareness, most of the patients who come for Bone Marrow Transplant present at later age and fall in class III as per the Lucarelli classification.

The standard conditioning regimen for thalassemia Bone Marrow Transplant is Bu/Cy/ATG which carries higher risk of transplant related complication especially in class III patients, thus increasing the morbidity and mortality and decreasing overall and thalassemia free survival. A new conditioning regimen using Thiotepa/Treosulphan/Fludarabine has been shown to give good results even in class III patients.

Currently centres have maximum experience of BMT in thalassemia major in India is CMC Vellore. Other than CMC Vellore, good numbers of thalassemia transplant have been done at BLK Superspeciality hospital, New Delhi, Apollo Chennai and Narayana Hrudayalaya Bangalore. There are many more centres which perform thalassemia transplant in smaller numbers.

Conclusion
In India HLA identical sibling or family donor transplant is ideal curative treatment options for thalassemia major. The newer conditioning regimen (with treosulphan/thiotepa/fludarabine) gives promising results in adolescent and adult thalassemia major.

Dear Readers,
Tell us what you think of our newsletter, your suggestions are most welcome.

Contribute to Thalassaemia Update
Please send for publishing, news / articles you wish to share!

Editors
Every day millions of people require blood transfusion and in many conditions the patients suffer absolute transfusion dependency. Most transfusion saves lives, but they can also put a patient at risk if blood is contaminated by an infectious disease.

There is an increase in the incidence of HIV in general population both in urban and rural areas in India. There are approximately 2.5 million HIV infected cases in India. As per NACO (National Aids Control Organization) 1.86 % of the HIV infection transmission is attributed to blood transfusions. The incidence of HIV, HBsAg and HCV in blood donors in India varies in different states of the country and ranges from 0.1-0.9%, 0.86-9% and 0.98-0.53% respectively. Even after the most sensitive screening tests and the battery of tests that we employ for the detection of Transfusion transmissible infections, some residual risk always remains. Accordingly there is a need to frame strategies to ensure safe blood for the patient.

**Strategies for Blood Safety**

Blood safety revolves around three things:

- Safe blood donors
- Safe blood transfusion Practices
- Appropriate / Rational use of blood

**Safe Blood Donors**

Voluntary non remunerated repeat blood donor is a pivot for safe blood supply. A carefully screened voluntary donor, who answers medical history questionnaire honestly and is non-reactive to the available screening tests, is the best defense against TAI (Transfusion Associated Infections). Such donors give blood out of altruism, and are not under pressure to donate blood. On the whole, they are more likely to meet national criteria for low risk donors. And they are also more likely to be willing to donate blood on a regular basis and at properly-spaced intervals. subject to donor selection and deferral techniques. This is important for maintaining an adequate stock of safe blood. Blood coming from family (Directed Donations), replacement donors and especially paid donors is known to have a higher incidence and prevalence of transfusion-transmissible infections. The paid donors are banned for blood donation according to laws that govern our Blood Transfusion Services (BTS). Not only is the blood coming from a voluntary system likely to be safer, it cuts down on the discard rates, thereby minimizing the wastage of this precious commodity. This is extremely important in multiply transfused patient such as thalassemics, leukemia patients, solid organ transplant patients who are more prone to these TAI due to multiple transfusions.

**Safe Blood Transfusion Practices**

Safe blood transfusion practices have to be followed right from the donor selection, phlebotomy, preparation of blood components, screening for the infectious markers by highly sensitive and specific tests, blood grouping, screening for immune antibodies, cross matching, issue of blood, to the transfusion of the blood / blood component.

Good donor selection is an important part of the process of collecting blood. When donors present themselves at blood donation centers they need to be interviewed (counseled) by trained staff, so that those who appear to have a high risk of being infected, or appear to be paid donors, are excluded. Potential donors whose poor health or nutritional status makes them unsuitable should also be excluded, for the sake of their own health as well as the health of the recipients. Educating people about the importance and responsibility of being a blood donor is essential so that prospective donors can make the correct decisions to donate, to self-exclude, or to self-defer. Self-exclusion means excluding themselves if they know or think that their blood may be unsafe as a result of risk behaviour, or because of the state of their own health.

**Appropriate / Rational use of Blood**

Appropriate / rational use of blood / blood components is an important strategy for safety of blood / blood components. Blood is not to be considered as a tonic and accordingly the clinician are supposed to give due thought before prescribing any transfusion of blood / blood components to the patients. Transfusions are not always necessary or appropriate.

Minimizing unnecessary transfusions reduces the risk of transmitting HIV and other TAI, especially in places where there is inadequate blood screening. An informed consent prior to transfusion of blood or blood components is a must.

**NAT testing**

Nucleic Acid Testing (NAT) along with serological testing has reduced this residual risk to a great extent because it involves highly specific detection of an infectious agent with much higher sensitivity. With the introduction of NAT, the blood safety has markedly improved as it has reduced the window period for...
HIV to 5 days from 21 days, HCV to 3.5 days from 60 days and by several weeks earlier than serological tests in case of HBV. Given the high rate of sero-positivity of HIV, HCV and HBV in India and keeping in mind the high percentage of first time and replacement donors, addition of NAT needs to be implemented in the blood screening programme across the country to prevent the transmission of Transfusion Transmitted Infections.

**Leucoreduction**
The use of leucodepleted blood products is gaining importance because of the scientific evidence that filtered blood products to remove leucocytes prior to transfusion prevent or reduce the incidence and severity of a number of adverse transfusion effects like Febrile Non Haemolytic Transfusion Reaction, sensitization to blood products (HLA alloimmunization), refractiveness to platelet therapy and prevention against lymphotropic viruses including CMV. It has been seen that pre-storage leucoreduction is more beneficial than bed side filtration being followed in most patients in our country. There is evidence that once the blood is stored the leucocytes break down during storage & liberate the cytokines (biological modifiers) which can pass through the filters once transfused to the patients.

**Bacterial Contamination of Blood Components**
There is a growing awareness that bacterial contamination of blood and blood components especially platelets (as these are stored at 22 °C) across the globe. The most common source being the donor skin contamination followed by the infection present in blood. Interventions to reduce bacterial risks of transfusion include enhanced cleansing of the venepuncture site, diversion of the first 20 ml donation to flush out skin bacteria entering the venepuncture needle, screening blood components for bacterial contamination and pathogen inactivation/reduction technologies to disable contaminant bacteria, especially in platelet preparations.

Blood Safety can further be improved by decreasing the donor exposure to the patient by providing blood components i.e. platelets, plasma on cell separator etc. In neonates, the Sterile Connecting Device has made it possible for blood components to be issued in small aliquots and thus allowing the same unit to be further issued to the same child if needed.

Safe blood begins with safe donors. Despite improvements, efforts to recruit voluntary, non remunerated donors remain insufficient. Screening for infections transmissible through Blood transfusion is essential, but the safest donations come from the safest donors.

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**Educational books and life saving equipments available at Thalassemics India**

**Educational Books**
- About Beta-Thalassemia – in Hindi
- About Sickle Cell Disease – in Hindi
- About Thalassemia – in Hindi
- TIF DVD in both Hindi and English.
- Compliance to Iron Chelation Therapy with Desferrioxamine (2000) (TIF Publication) in English
- Patients’ Rights (2007) (TIF Publication) in English
- Prevention of Thalassaemias and other Haemoglobin Disorders Vol.1 (2003) (TIF Publication) in English

*The above books are available free of cost with us in limited numbers.*

**Life saving equipments / drugs**
- Desferal
- Asunra
- Desirox
- Bio –R2 filter (for 2 units of blood)
- Thalapump-20 – Micrel Infusion pump of variable speed, made in Greece
- Venogliss G-27, short needle, length 60cm, made in Italy
- JMS G-27, short needle, length 80cm
- TI needle infusion line, Latex free, Tube: 60cm, 28 x 8 mm
Heartiest congratulations to Thalassemics India who have been serving the cause of Thalassemia for last 25 yrs with selfless dedication, commitment, hard work for improving the care of Thalassemic children not only in Delhi but for the entire country. A group of family member who had their children suffering with Thalassemia major. Their children were lucky as they belonged to highly educated, influential and rich families and were getting the best possible treatment. Their parents learnt the plight of poor thalassemic children, difficulties faced by them, availability of poor facilities, scarcities of blood which is a life line for these children and non existence of any day care centre for care of Thalassemia even in city of Delhi. These ground realities gave birth to Thalassemics India. Thalassemics India started functioning with prime following objectives.

a) To create the dedicated facilities for care of Thalassemics in Delhi and all over India.

b) To increase the awareness in community.

c) To import the filters, pumps and Desferal and other accessories to ensure their availability available at affordable cost.

d) To educate Thalassemic children regarding the current treatment.

e) To interact with the government & Institutions for exemption of duties and creation for dedicated facilities of care of Thalassemic children.

f) Interaction with local doctors in various parts of the country.

g) To bring the state of art care as available in the west through continuing medical education of doctors, Thalassemic children & Training of doctors.

h) To provide care to Thalassemic child through international experts.

i) To provide psycho social and even financial supports at special clinics.

j) Interaction of Thalassemics India with Thalassemia International Federation and various Thalassemic societies in India.

Thalassemics India have been marching ahead since its inception towards their objectives. A Preeti Tuli Thalassemia day care centre 8-10 beded unit was established at Sri Ganga Ram Hospital Delhi to provide a state of art care for thalassemic children. Presently it is providing facilities in three shifts. This is the largest Day care centre providing state of art care to over 250 Thalassemic children under abled guidance of Dr. V K Khanna a senior Pediatrician with extensive training & expertise for thalassemia care. They have special clinic where a team of doctors comprising Cardiologist, Gastroenterologist, Endocrinologist, etc to provide a comprehensive care at affordable cost. Presently many children are under their care who are above 30 years and leading normal life. Many of them are very well established in service, business and occupying professional jobs of excellence.

Thalassemics India have organized several International and National conferences in Delhi to provide recent concepts in management of Thalassemia. Thalassemics India have helped various states groups in different regions to form Thalassemia State Societies and for development of Thalassemia care facilities. In addition they made arrangements to supply the pumps & filters etc. To these Societies to promote state of art care to Thalassemic children. They encouraged the local societies to hold Medical education programmes for patients and doctors on thalassemia. In addition they encouraged the societies to hold special clinic. Thalassemics India started the News letter from 1989 which is being published regularly. This News letter is very informative on various aspects of Thalassemia care and in uniting the parents of various societies to provide better care for thalassemics.

Thalassemics India received the ‘Best Social Organisation Award’ in 1998 from the Ministry of Health. Thalassemics India interacted with central and State Government at various levels to promote the facilities for Thalassemia care, to increase the awareness and played a key role in interacting with various bodies to initiate the facilities for antenatal diagnosis and control of Thalassemia. Thalassemics India played a key role in formations of Federation of Indian Thalassemics to bring to all Thalassemia Societies in India under one umbrella for unified crusade against Thalassemia in India. Mrs. Shobha Tuli is currently the secretary of Thalassemics India playing a key role in representing the problems of Indian Thalassemic to Thalassemia International Federation (TIF). She has been representing India in TIF since 1996. Thalassaemia International Federation awarded her with George Englezos award after realizing her dedication, commitment and hard
work toward the cause of Thalassemic children not only in India but all over the world. She has played the major role in shaping the various activities of Thalassemics India. She has influenced life of every Thalassemic child in some or other way and is playing key role in shaping their life towards betterment and worthy citizen of India. Thalassemics India has been celebrating International Thalassemia day regularly every year by different innovative method along with Thalassemic children and their parents.

Mrs. Shobha Tuli & her dedicated executive members deserve very special thanks for their continued dedicated efforts & commitment towards the cause of Thalassemia in our country. Every Thalassemic is looking towards them with that one day government of India will initiate Thalassemia screening & control programme in India along with comprehensive care of Thalassemics.

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For your information

**Thalassemia Clinic at Apollo Hospital Inaugurated on 3rd May, 2012**

Children & young adults with Thalassemia major need comprehensive multidisciplinary input for optimal management in view of multiorgan involvement. The ideal way to provide this is the format of a joint multidisciplinary clinic enabling them access to all the specialties in a time-effective, cost-effective manner. To address the need of specialised care under one roof for Thalassemia management, Apollo Centre for Advanced Pediatrics (ACAP) is rolling out Thalassemia clinics involving multidisciplinary team for optimal patient care.

**Composition**

- Hematologist
- Endocrinologist
- Cardiologist
- Gastroenterologist
- Counselling Psychologist

**Clinic Fee**

A single consultation fee of Rs. 1500 will be charged. No fee will be charged to review the reports.

**Venue**

**Room 1108**

**Frequency**

Weekly, Thursday, 3-5pm, Starting 3rd May, 2012.

**Investigations**

- CBC
- LFT
- Creatinine
- Bone Profile (S. Ca. P. Aj. Phos)
- HbSAg, Anti HCV, Anti HbS, HIV
- X-ray Wrist for Bone Age
- Urine Routine
- T4, Tsh, LH, FSH, Testosterone, Estradiol, Blood Sugar-F and PP, Vitamin D3
- Dixa Scan
- HCV RNA PCR (Quantitative)-
- 2-D ECHO

**Special monitoring packages and discounts on all investigations.**

For appointments contact 9999251143 / 29871170/71

The contact details are as following:

- Dr. Amita Mahajan: 9810734137, mahajanamita1@gmail.com
- Dr. Anju Virmani: 9811278951, virmani.anju@gmail.com
- Dr. I.P.S. Kochar: 9910240919, inderpal_kochar@yahoo.com
- Dr. Vikas Kohli: 9958728855, vborah_md@yahoo.com
- Dr. Anupam Sibal: 9810114840, dranupamsibal@gmail.com
- Dr. Rakhi Anand: 9810361551, anand.rakhi@yahoo.com
- Dr. Ekta Soni: 9958290557, ekta_s@apollohospitalsdelhi.com
For your information

- 3rd Pan-European Conference on Haemoglobinopathies and Rare Anaemias 24-26 October 2012, Limassol, Cyprus.
- Share your experiences with Thalassaemia International Federation's office through email: thalassaemia@cytanet.com.cy
- If you wish to have information on MSc in Haemoglobinopathy or New TIF Publications or their Expert Patients Programme, please visit TIF website at www.thalassaemia.org.cy

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Thalassemics India Activities

Annual General Body Meeting held at St. Stephen’s Hospital

The Annual General Meeting was chaired by Dr. Gautam Bose, the Vice-President of Thalassemics India. The topics discussed were Marriages, Relationships, Education, Employment, Health Insurance and Thal Connect Project. The meeting was attended by 80 members. Details of Statement of Accounts for the assessment year 2011-2012 was presented by Mr. Arun Sehgal, the Treasurer of Thalassemics India. Report on Society Activities was presented by Shobha Tuli, the Secretary of Thalassemics India.

51 thalassemia major children were examined by both the doctors from 11 am till 6 pm each day.

Annual Picnic

Our Annual Picnic was held at Nehru Park, Chanakya Puri. It was attended by 130 thalassemia parents and children. They enjoyed the pleasant weather and had fun with a magic show, tattoos, hair braiding, makesups, tambola and a lucky draw with exciting gifts. The picnic was followed by snacks & lunch.

Table Calendar

2000 table calendars were printed with awareness messages. The calendars had beautiful pictures made by our thalassemia children.

Towards Awareness

- A talk was given by our adult thalassemic Pooja Nangia at Ambience Mall, Lifestyle, Vasant Kunj.
- Another talk was given by Jyoti Arora at Life Style, Ghaziabad.
- Awareness Camp was held at Gurgoan

We thank all of them for their creative efforts.
Kerala

Bangalore
Sankalp India Foundation, Applied Materials India and The Indira Gandhi Institute of Child Health Organize Walk to Raise Awareness for Thalassemia, its Treatment and Prevention. The 2.5 km walk began from Bangalore’s Cubbon Park to the Freedom Park, attracted over 500 people including students, working professionals and members of the medical fraternity.

Pune
The Indian Red Cross Society, Pune District Branch celebrated the Children’s Day with Thalassemic children. Over 100 Thalassemic children attended the program with their parents. The children enjoyed drawing and painting, expressing their skills with them. The program was also attended by the team of Red FM 93.5 who organized massive blood donation camps at the following blood banks, viz. Sahyadari Hospital Karve Rd., Janakalyan Swargate, Ruby Hall Clinic and KEM Hospital. Approx. 400 units of blood was collected through their awareness program on air. The Chairman of IRCs Mr. N.A.P. Nanavatti, Hon Secretary Prof. R.V. Kulkarni, counselors and Red Cross youths of IRCs were present on the occasion. Prof. R.V. Kulkarni thanked everybody for their cooperation.

Ajmer

The Editorial Committee reserves the right to change the text of the articles sent for publication where necessary, in good faith.

The Editorial Committee or Thalassemics India do not accept any responsibility for any inaccuracies or omissions.

The views expressed are not necessarily that of Thalassemics India.

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Ph : 91-124-4029300
Fax : 91-124-2398115
Toll Free Tech Support : 1800-180-1224
or + 91-9873177477
Website : www.bio-rad.co.in
e-mail : sales.india@bio-rad.com
