Florilegium of Thalassemia

Author

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This book has been written to provide general guidelines and not to treat patients.
Patients and parents are advised to consult their thalassemia specialist for treatment.
Doctors should consult text books before arriving at any therapeutic decision.

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Preface

Thalassemia is one of the most common inherited blood disorders in India and an estimated over 10,000 new thalassemia major patients are born every year. Most of them are dying due to lack of facilities either because of shortage of blood, unavailability/unaffordability of chelating agents or insufficient/ineffectively managed transfusion centres. There are over 60 thalassemia associations in different parts of the country. In cities where thalassemia associations are active and were able to garner the support of clinicians and blood bank, the treatment has improved resulting in improved quality of life of thalassemics. Some of these clinicians update their knowledge by attending National and International conferences, reading literature published by Thalassemia International Federation (TIF) and are proactively taking a lead role in further improving management facilities. Many thalassemia associations in-spite of being very active and enthusiastically working hard to improve facilities in their cities have not been able to involve clinicians to support them. Though TIF has published a lot of material on each and every aspect of thalassemia which is available to all free of cost on internet as well as hard copy, busy doctors do not access them due to lack of time. This creates lack of confidence amongst them to treat thalassemia patients. Not only educated thalassemia parents and patients but now each one has understood that 'knowledge is the power'. They all want to know more about what is feasible and how they can improve life span and quality of life. For most of them understating TIF guidelines is beyond their scope.

The effort has been made to prepare a concise book which can be read and understood both by the patients/parents and doctors who wish to start thalassemia center with basic knowledge. This book is primarily based on TIF Guidelines for the Clinical Management of Thalassemia 2nd revised edition. The rich experience I gained under the guidance of Dr V.P. Choudhry & Dr Jagdish Chandra and my personal interaction with patients in last 22 years were the predispositions to conceptualize this book.

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About the author

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Dr. J.S. Arora did his MSc in Haemoglobinopathy, University College London and Training course on Haemoglobin Disorders at Belgium

He is Founder President, National Thalassemia Welfare Society (established 1991), General Secretary, National Thalassemia Welfare Society since 1994, Founder General Secretary, Federation of Indian Thalassemics, an all India body of all the Thalassemia Societies of India since 1994. He has been instrumental in establishing many new Thalassemia associations

He is PFPS (Patients For Patient Safety) Champion since 2007 under Patients for Patients Safety programme of SEARO, WHO. Member, Ethics Committee IIT Delhi. He has been Co-ordinator, Thalassemia Cell, Directorate of Health Servises Govt. of Delhi, Member, Hospital Advisory Committee, DDU Hospital and Member Delhi State VAT Advisory committee, Govt. of Delhi

He has received "Life Time Service Award" from PHO Chambers of IAP

He is Co-Author of the Books "Care & Control of Thalassemia: In the New Millennium" 2000 and "Perspectives in Thalassemia" 1994. Executive Editor of the "National Thalassemia Bulletin".

He has organized Six National Conferences, three symposiums and Four Workshops on Thalassemia

He was invited Speaker at "Regional Workshop on Patients for Patient Safety" under WHO, 2007, Jakarta, Indonesia, invited as an expert on Thalassemia at the Fourth International Symposium on Genetics, Health & Disease at Guru Nanak Dev University, Amritsar. He has been regular guest speaker at "Counselling Course for Happy Married Life" organized by Centre for Community Medicine, AIIMS. Guest faculty at various National and International Conferences. Invited as regular guest speaker in Thalassemia updates organized by IAP/IMA branches and Thalassemia Associations in many cities of India.

He is member of Delhi Society of Haematology, Delhi Society for Prenatal Diagnosis & Therapy and Indian Society of Blood Transfusion & Immuno-hematology.

INTRODUCTION

What is thalassemia?

Thalassemia is a type of blood disorder in which body does not make appropriate type of haemoglobin. The life of red blood cells (RBC) which contain haemoglobin is 10 to 20 days compared to normal life span of 120 days.

An adult hemoglobin molecule is a formed by symmetric pairing of α and β globins chains with iron molecule in the center. In thalassemia, synthesis of either α chains or β chains is reduced. In β Thalassemia, there is defective synthesis of β chains and the manifestations are due to the excessive α chains. In α Thalassemia, α chains are reduced and excess of β chains causes reduced survival.

α thalassemia is of two types α^+ and α^0. α^+ is mild and its inheritance is not of much clinical significance. α^0 is a severe variety. In India α^+ is common.

In our country β Thalassemia is very common and hence the term Thalassemia is used to represent β Thalassemia.

DIAGNOSIS

How to suspect thalassemia major in an infant or a child?

A newborn child with thalassemia major does not present any signs or symptoms and is difficult to diagnose clinically or with routine laboratory tests. Around 90% to 95% thalassemia majors start showing symptoms within 3 months to 24 months. A thalassemia major presents with persistent and progressive pallor with poor appetite, weakness, lethargy and delayed milestones. On examination child will have anemia of moderate to severe degree along with enlarged liver and spleen.

Children diagnosed at later age have typical thalassemic facial features (frontal bossing, prominence of facial bones, forward protrusion of upper teeth and depression of nasal bridge). Inadequately transfused thalassemia major also show similar signs and symptoms.

How to diagnose a thalassemia major patient?

If there is any suspicion of thalassemia in a child, following investigations are required to confirm the diagnosis.

Complete blood count (CBC) on automated blood cell counter will reveal haemoglobin (Hb) level <7gm/dl. WBC counts are mildly elevated, MCH and MCV are reduced & MCHC is normal.

Peripheral blood shows microcytic hypochromic picture along with anisocytosis, poikilocytosis, broken red cells and target cells. Large number of nucleated RBCs are usually present.

Hb electrophoresis or Hb HPLC will divulge HbF 70 - 99% depending upon the genetic mutation. HbA2 levels are variable. Unconjugated bilirubin may be high. Serum iron, transferrin saturation and serum ferritin may be normal in early infancy but are elevated if diagnosis is made late.

All these tests should be undertaken before the 1st transfusion. Transfusion should never be given to an infant or child before ruling out thalassemia syndrome by Hb HPLC.

Parental studies for thalassemia/haemoglobinopathy status by CBC & Hb HPLC is required to correlate and establish the diagnosis of thalassemia/haemoglobinopathy in the child.

How to diagnose a thalassemia major patient if transfusion has already been given?

If the child has already received couple of transfusions, the original picture can never be retrieved and the HbF levels may be low or within normal limits. In that case laboratory tests should be performed before the next blood transfusion and correlated with that of parents. Presence of clinical and haematological picture and raised HbA2 levels in both parents may be considered to support the diagnosis of thalassemia major in transfused child. Diagnosis is further confirmed by DNA mutation studies.

How to diagnose thalassemia intermedia?

Thalassemia intermedia is a clinical diagnosis which may be missed as nutritional anaemia at initial stages. Anaemia may vary from mild to moderate not requiring regular transfusion. It is a group of Non Transfusion Dependent Thalassemias (NTDT) resulting from various permutations and combinations of mild & severe thalassemia genes and with other haemoglobinopathies. Transfusion requirement in patients with NTDT varies from few transfusions every year to once in several years.

Children often present late (3 to 13 years or even later) with pallor associated with mild to moderate hepato-splenomegaly, and in older children the puberty may be delayed. The Hb drops during stress such as pubertal growth & infections. Thalassemic facies are common in Thalassemia intermedia. These features can also be seen in thalassemia major children who are being undertransfused.

CBC picture and peripheral smear are similar or slightly milder to that of thalassemia major. Hb concentration varies between 6-9 gm/dl. HbF level is increased, varying between 20-50%. Serum ferritin & iron levels may be normal or elevated and are essential for monitoring therapy. Confirmed diagnosis is based on the clinical history Hb electrophoresis/ Hb HPLC and DNA mutational studies of the patient and both parents.

What is thalassemia minor/carrier or trait?

Thalassemia minors are heterogygous and are symptom free with mild or no anemia. However, the hemoglobin level may reduce under stress such as puberty, pregnancy or infection and may require treatment. Thalassemia carriers may have iron deficiency thus may require treatment with iron supplementation. Thalassemia carrier pregnant women require iron as much as non thalassemia carrier pregnant women.

How to diagnose thalassemia carrier?

CBC - red cell counts, are higher for a given Hb concentration, MCV < 80 fl and/or MCH < 27 pg and microcytic hypochromic red cells in peripheral smear are suggestive of beta thalassemia trait (BTT). Major variance from iron deficiency anemia (IDA) is that in IDA, RBC count is also low in addition to reduced MCV & MCH.

Hb Electrophoresis/Hb HPLC confirms the diagnosis of BTT and other haemoglobinopathies such as HbD, HbE, HbS, HbO Arab etc. HbA2 is characteristically elevated, (>3.5%) in BTT. HbA2 may be normal in certain types of mutations such as silent beta thalassemia mutations

(-101 C $\rightarrow$ T , IVS 2-844 C $\rightarrow$ G, +33 C $\rightarrow$ G) and mild beta thalassemia allele (IVS 1-6 T $\rightarrow$ C, CAP+1 A $\rightarrow$ C, poly A T >C).

In some cases of BTT with severe IDA, the HbA2 levels may be low which rises to diagnostic level after correction of iron deficiency anemia so serum iron studies & serum ferritin level should also be done alongwith.

If MCV and MCH are low and RBC counts are high in relation to Hb level and HbA2 is normal or borderline co-existence of alpha thalassemia is suspected. DNA studies may be done to confirm the diagnosis.

What is the need to diagnose thalassemia carrier?

1. To inform the couples about the risk of having a Thalassemia major child.
2. To prevent unnecessary long time treatment with iron therapy to improve the haemoglobin.

TREATMENT OF THALASSEMIA MAJOR

What is the treatment of thalassemia major?

Broadly speaking treatment of thalassemia major can be divided into two categories

1. Conventional Management
    a. Life-long transfusion therapy
    b. Iron chelation
    c. Treatment of complications
2. Curative
    a. Stem cell transplantation
    b. Gene therapy

What is the objective of life long repeated blood transfusion?

The aim of the transfusion therapy is to maintain adequate oxygen supply to the tissues by keeping the haemoglobin level near normal. The current management is repeated blood transfusion of packed cells (RBCs) to maintain pre-transfusion Hb level above >10gm/dl (9.5-10.5gm/dl). Transfusions should be given at 2-4 weekly intervals. Efforts should be made to adjust with the academic and professional schedule of the patient and family. It helps in achieving sustained standard growth.

Every effort should be made to collect blood from carefully selected, voluntary, regular non- remunerated donor and tested for hepatitis B, hepatitis C, HIV (human immunodeficiency virus) and other infections as per national blood transfusion policy.

When should one start blood transfusion?

Cause of anaemia must be ascertained before first transfusion. If diagnosis of thalassemia major has been confirmed, first transfusion should be undertaken when Hb level falls <7gm/dl on two successive occasions at 2 weeks apart without any other contributory factor, or Hb level is >7gm/dl but there is poor growth, facial changes, fractures or extramedullary haematopoiesis.

What measures should be undertaken prior to putting the child on regular blood transfusion?

1. Red cell typing for ABO & Rhesus with extended red cell typing including C, c, E, e and Kell. Every effort should be made to transfuse full cross matched blood and screen for new antibodies before each transfusion.
2. Screening of patients for Hepatitis B, Hepatitis C and HIV.
3. Initiation of Hepatitis B vaccination for the patient and family members (if not vaccinated earlier). Three injections at 0, 1, 6 months produce upto 95% antibody response. One booster injection every 5 years helps in maintaining adequate antibody level in chronic diseases like thalassemia
4. DNA mutation identification of patient and family.

What target level of the haemoglobin to be achieved by blood transfusion?

The target should be to achieve pre-transfusion Hb level between 9.5-10.5gm/dl and care should be taken that post transfusion level should not be >15gm/dl. This regimen encourages normal growth keeping an arrest on bone marrow activity and minimizing iron chelation. If the child is already on low transfusion regimen it is better to change to high transfusion regimen as early as possible. It will require just 3-5 extra transfusions for 2-3 months depending upon the age and initial Hb levels. A higher pre-transfusion Hb level of 11-12gm/dl be maintained in patients who have associated heart disease.

What type of blood should be transfused?

Fresh packed red blood cells (not >7 days old) should be transfused to maintain maximum viability of red cells. Leucoreduction minimizes the transfusion reactions. Pre-storage filtration is best method to remove leucocytes from donor's blood followed by pre-transfusion laboratory filtration. If these techniques are not available with blood banks then bedside filters can be used. Washed red cells are indicated if repeated allergic transfusion reactions occur in spite of transfusing leucoreduced packed red cells. Saline washing of red cells does not substitute leucoreduction, instead it should be used in conjunction with filtration. Washed RBCs should be given to only those patients who develop repeated fevers with filtered blood or in IgA deficient patients. Allergic & febrile reactions should be managed appropriately.

Transfusions of the unit should be completed within four hours after it is removed from controlled temperature storage (CTS). Red cells units must not be warmed other than in an approved device nor left in sunshine or near a heat source. Once it is out of CTS the risk of bacterial proliferation increases with time, especially in a warm ambient temperature. Even a short period of exposure to high temperature may be deleterious.

How much blood should be transfused in one sitting?

Lecoreduced packed RBCs, 10-15ml/Kg body weight should be administered each time over 3-4 hours. Patients may require 1-3 units of packed red blood cells depending upon their body weight. In presence of congestive cardiac failure child should not be given more than 5 ml/Kg of packed cells at one time over 4-6 hours along with a diuretic.

How to evaluate transfusion therapy?

To assess the annual requirement, cause of reactions, tracing of transfusion transmitted infections and impact of transfusions, following information should be regularly recorded at each transfusion:

- Date of transfusion
- Bag number of the blood transfused
- Amount of blood transfused

- Height & weight of patient
- Liver and spleen size
- Transfusion reactions (details)

How would you assess the effectiveness of blood transfusion regime?

Clinically if child is growing well as per centile chart and there are no signs of extramedulary haematopoiesis or bony changes, it appears transfusion regime is optimum, atleast in growing age.

Average rate of fall of Hb is 1gm/dl/wk. It should not exceed >1gm/dl/week in splenectomised patients and not > 1.5gm/dl/week in non-splenectomised patients.

How to investigate increased blood requirement?

Increased red cell destruction from infections e.g. malaria or use of medicine like ribavirin (in hepatitis management), bleeding from gut or gums, transfusion of poor quality of blood, RBCs of shorter life span or low haematocrit are the main reasons for increased blood requirement. Hypersplenism, hepato-splenomegaly (enlargement of liver & spleen) also increases annual blood requirement. Alloimmunisation [antibodies to RBCs] is also one of the major cause of raised blood requirement if extended red cell typed blood is not transfused.

How can we make blood safe for transfusion?

Safety of blood transfusion starts from blood collection. Blood collected from voluntary, non-remunerated, repeat donor who has honestly answered a carefully prepared questionnaire (related to life style, medication, travel and medical history)and tested for all necessary infectious markers HIV, HBsAg, HCV, Syphilis & Malaria, is considered safe blood. Blood transfused from family members increases the risk of alloimunisation, thus should be avoided. There is increased risk of allo-immunisation if blood transfusion is started late (>3 years of age), hence it is more common in thalassemia intermedia.

What types of transfusion reactions can occur with blood transfusion?

Acute haemolytic reactions (AHR) a life threatening complication occurs immediately within 5-10 minutes after infusion of few ml of blood due to ABO incompatibility. The most common causes are errors in patient identification or blood typing and compatibility testing. Management requires intensive medical care. It can be prevented if protocol for screening for antibodies, full cross-matching of blood units and patient identification norms are followed.

Febrile non-haemolytic transfusion reactions (FNHTR) usually occur towards the end or after completion of transfusion. FNHTR occurrs due to reactions between leucocyte antigens in transfused blood and anti-leucocyte antibodies in the patient's blood. Symptoms are, increased temp by 1^0C or more without any other medical explanation. Incidence can be reduced by transfusing leucodepleted packed RBCs. If it occurs frequently, washed cells should be transfused. Washed cells must be used within 24 hrs.

Other possible transfusion reactions are beyond the scope of this booklet.

How to avoid blood transfusion problems?

i. Patients full name and date of birth should be clearly written on tube and data on transfusion application form be checked before the sample is drawn.

ii. A medical officer must visually check that there should not be any contamination e.g colour change to dark purple, clots or haemolysis and verify the blood has not expired.

iii. Compatibility between patient and the blood unit received must be verified i.e. patient's name, date of birth, blood group with parameters on the blood unit label.

iv. Identification details of blood unit to be transfused must be recorded in patient's record so that donor can be traced in case of need.

v. Transfuse only if the patient can be observed by clinical staff.

vi. Careful observation of patient's condition at initial stage of transfusion.

vii. Rapid transfusion of cold blood may be dangerous.

viii. In case of repeated transfusion reactions presence of irregular antibodies outside ABO & Rh system is recommended.

ix. If repeated FNHTR even after transfusing leukocyte depleted RBCs occurs, washed cells should be used.

x. All errors should be carefully noted, fully reported and lessons learnt.

Why does spleen enlargement (splenomegaly) occur in thalassemia patients?

One of the functions of the spleen in healthy persons is to remove damaged/abnormal cells. In NTDT patients most of the red cells produced are abnormal cells so they are trapped into the spleen and cause enlargement of spleen. Secondly, spleen becomes hyperactive to make red cells to compensate inadequate and abnormal formation of red cells (extramedullary hematopiesis) in NTDT patients and insufficient blood transfusions in thalassemia major on regular transfusion. NTDT Patients invariably develop splenomegaly due to extra-medullary haematopoeisis and retico-endothelial hyperplasia. Inadequately transfused thalassemia major patients may also develop splenomegaly if they are inadequately transfused for prolonged periods. Sometimes it may evolve into hypersplenism. It results in increased blood requirement, increased iron load & enhanced risk of transfusion transmitted infections. Children may develop leucopenia or thrombocytopenia and it becomes difficult to maintain pre-transfusion Hb near 10gm/dl. Some children may also have protruded abdomen.

How to manage splenomegaly?

In Thalassemia major initially when spleen is not much enlarged or has just started increasing in size, it can be reverted back by increasing the frequency of blood transfusion. Extra effort is to be made to keep pre-transfusion Hb above 10gm/dl. If above measures fail, then surgical removal of the spleen is the only option. In NTDT patients, it has to be dealt on individual basis whether to give hydroxycarbamide, put on regular transfusion, surgical removal or just wait and watch.

What are the indications of Splenectomy (surgical removal of spleen)

* Enlargement of spleen with fall in mean annual Hb concentration
* Increase of annual blood requirement by 50% or more over initial requirement.
* Packed red cell consumption of more than 250 ml/kg/year.
* Presence of leucopenia (reduction in leucocytes) or thrombocytopenia (reduction in platelets)
* Reduced red cell survival of 15 days or less by Chromium studies.
* Radionuclear evidence of splenic sequestration.
* Splenomegaly resulting in abdominal discomfort.

Are there any precautionary measure required before splenectomy?

Splenectomy should not be undertaken before the age of 5 yrs. Patient should be vaccinated with, Pneumococcal (Pneumovax 23), Meningococcal A & C and Haemophilus influenza B (HiB) vaccines at least 2 weeks prior to surgery. All these three vaccinations can be administered on same day at different sites.

Are any precautions required after Splenectomy?

In healthy individuals spleen prevents the body from infections by scavenging infectious organisms, therefore once the spleen is removed chances of infections increase manifold. Besides vaccinations as stated above, Penicillin prophylaxis (250 mg bd) or injection Benzethine Penicillin 6-12 lacs every 3 weeks life long or at least till 25 years of age is indicated to reduce the frequency and severity of infections. Those who cannot tolerate penicillin, erythromycin can be given. Post splenectomy infections should be dealt with broad-spectrum antibiotics immediately (Amoxicillin or Erythromycin from home) and then report to the doctor at the earliest.

Thrombocytosis does not carry much risk as it is balanced by reduction in platelet aggregation. It is advisable to give Aspirin 50-100mg/day if platelet count exceeds 8,00,000/mm^3.

IRON OVERLOAD

What is the cause of iron overload in thalassemia major?

In thalassemia major, due to increased erythropoiesis, body absorbs increased quantities of iron, as much as 3-4 mg/day depending upon severity of anemia. Absorption depends upon iron content in food & it may increase up to 10 mg/day if iron tonics are given.

On an average each unit of blood contains 200-250 mg of iron. A patient receiving 15-30 unit of blood/year receives between 3-6 gm of elemental iron i.e. about 3-6 times the normal annual iron requirement of 1gm.

How iron overload is toxic to the body?

Iron is non-toxic when it is bound to protein (ferritin, hemosiderin and transferrin). Iron toxicity begins when iron load exceeds binding and tissue storage capacity and enters labile or free pool. Though anterior pituitary is the first organ to be affected, liver is the primary site of iron storage. If liver iron storage capacity is exceeded, iron is deposited in other tissues of the body including heart. Heart failure is the major cause of death in Thalassaemia.

Labile plasma iron (LPI) is free plasma iron which produces harmful hydroxyl radical, capable of entering into cells specially hepatocytes & cardiomyocytes, the two most vital organs. It also increases the risk for developing other co-morbidities. As LPI is produced continually in conditions of iron over- load, the sustained presence of an iron chelator in the plasma may help avoid accumulation of excess iron, thereby preventing iron-related morbidity and mortality.

What are the toxic effects of iron overload?

Organ affected	Clinical effect on body
Pituitary gland	Hypogonadotrophic hypogonadism, Delayed, missed puberty

Thyroid	Hypothyroidism,
Parathroid	Hypoparathyroidism, Bone disease
Pancreas	Diabetes,
Heart	Cardiomyopathy leading to heart failure
Liver	Cirrhosis, Liver fibrosis
Gonads	Primary hypogonadism, delayed/arrested puberty, infertility

How to measure iron overload?

Iron overload can be measured by various methods; each method has its own advantages and disadvantages. Regular monitoring of iron overload is required to minimize iron mediated morbidity & mortality and chelator mediated toxicity.

I Serum Ferritin:

Serum iron & total iron binding capacity (TIBC) are of little value to know iron overload. Serum ferritin reflects iron stores in the body tissues and thus is a good indicator of iron storage status. It is a useful prognostic marker. Sequential measurements of ferritin are used for monitoring trends in patient iron loading. Though maintaining serum ferritin level regularly less than 2500ng/ml reduces the risk of cardiac disease but keeping it < 1000ng/ml eludes most of the complications

Advantages - Can be measured repeatedly, widely available. Change in serum ferritin over time reflects change in liver iron concentration. Sequential evaluation of ferritin good index of chelation history, can be used for monitoring trends in patient iron loading.

Disadvantages - Correlation with liver and body iron is not linear. Different chelators may affect ferritin differently. Does not give reliable information on degree of patient iron loading. Serum ferritin levels are disproportionately increased in inflammatory disorders, infections, chronic liver disease, arthritis etc. and decreased in presence of vitamin C deficiency.

II Liver Iron Concentration (LIC)

Liver iron reflects total body iron more precisely, thus has become a standard reference. Total body iron is 10.6 x LIC mg/gm dry weight of liver (mg/gmdwl). LIC < 1.8mg/gmdwl (dry weight of liver) is considered normal, values above 7mg/gmdwl is toxic and level persistently >15mg/gmdwl is indicative of bad prognosis. Liver iron does not parallel heart iron in chelated patients because iron chelation is different in different organs and chelation removes iron from liver faster than heart.

a) Liver Biopsy:

Quantitative measurement of liver iron by liver biopsy is highly reliable but it is invasive and entails elevated risk of bleeding. It should be reserved only for special indications. Inadequate sample (<1 mg/gmdwl) or uneven distribution of iron, particularly in the presence of cirrhosis, may give deceptive results.

b) Liver MRI T2*

It is done on 1.5 or 3.0 Tesla machine using a special software T2* available at very limited centres in India. It is reported as < 2mg/gm normal, 2-7mg/gm mild, 7-15mg/gm moderate and >15mg/gm severe iron overload.

Ferriscan is a patented technique using R2 on MRI machine. To perform Ferriscan the machine must have phantom supplied by company and images are sent to company by internet for interpretation. It is neither available in India nor within the reach of Indian patients.

MRI T2* is now available in few major cities and affordable by many.

III Myocardial Iron Concentration (MIC)

Cardiac MRI T2*

Technique is same as done for liver MRI T2*. T2* values >20 ms (milli seconds) are normal and carry low chance of decreased left ventricle ejection fraction (LVEF), 10-20 ms depicts mild to moderate iron overload with 10% chance of decreased LVEF. T2* 8-10ms is moderate, 6-8 ms is severe and <6ms is very sever. MRI T2*predict decreased LVEF much before actual fall occurs, giving an early chance to intensify chelation. Now cardiac MRI T2* has been calibrated with myocardial

iron concentration (MIC). MIC <1.16mg/gm are normal, 1.16-1.65 mg/gm mild, 1.65-2.71 mg/gm moderate and >2.71mg/gm are indicative of severe cardiac iron overload.

MRI T2* measure only the storage form of iron. However increased labile iron will affect the cardiac function. Thus patients with low T2* can be asymptomatic as labile and storage iron can be compensated.

Estimation of iron with SQUID (Superconducting QUantum Interference Device), urinary iron estimation or labile plasma iron are of little practical value for monitoring iron overload or efficacy of iron chelation.

How to increase excretion of extra iron out of body?

There is no mechanism in the body that this extra iron is excreted out of body. Free iron (labile iron) causes tissue damage, therefore it is important to control iron overload from initial stages to minimize the damage caused by excess iron. There is always only a small portion of iron available for chelation at particular time. This Non Transferrin Bound Iron (NTBI) reappears immediately after the chelating drug has been excreted from the body. Thus 24 hour continuous controlled iron chelation is desired to minimize the toxic effect of free labile iron.

Worldwide three drugs Desferrioxamine, Deferiprone and Defrasirox have been licensed for use as iron chelator in human beings.

When to start Chelation?

Serum ferritin levels should be assessed after first 10-15 transfusions. Chelation therapy should be initiated when serum ferritin is above 1000ng/ml.

How to give Desferrioxamine and at what dose?

Desferrioxamine (DESFERAL - DFO) dose is 25-50 mg/kg/day

General Desferal dose recommendations

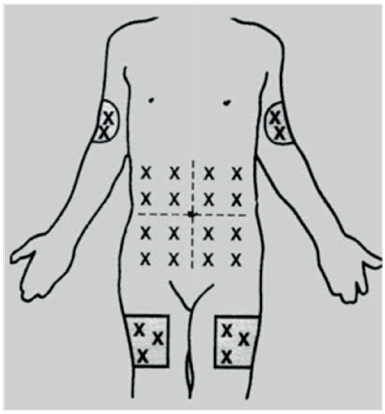
S.Ferritin	< 2000 ng/ml	25mg/Kg/day
S.Ferritin	2000-3000 ng/ml	35mg/kg/day
S.Ferritin	>3000 ng/ml	50mg/kg/day

Desferal should not be initiated before the age of 3 years and the dose should not be >30mg/kg during childhood, not >40mg/kg before

completion of puberty and not >50mg/kg in adults. Higher doses can be given only in expert hands.

How to administer Desferal injection?

Desferal does not absorb from the gut. Therefore it has to be administered as through parenteral route. It is given subcutaneous with the help of an infusion pump over 8-12 hours 5-7 days a week. Ten percent Desferal solution is prepared in water for injection i.e. one vial of Desferal (500mg) is dissolved in 5ml water for injection. If more than one vial is to be administered 2.5 to 5 ml of water for injection can be added per vial of Desferal. Desferal solution should not be stored for more than 24 hours. Subcutaneous Desferal can be given in abdominal muscles at one inch away from umbilicus, anteromedial aspect of thighs and at triceps in adolescents/adults also. It should be injected using a special 27G short needle and long tubing scalp vein sets. Butterfly needles are inserted at an angle of about 45 degrees to the skin surface, the needle tip should move freely when the needle is jiggled. Scalp vein sets in which needle can be inserted at 90° angle are also available but cost very high. Pumps and scalp vein sets are available with thalassemia societies at subsidized cost.



Desferal infusion sites should be regularly rotated.

Can Desferal be given along with blood transfusion also?

Desferal should never be added in blood bag. However, it can be given along with blood transfusion with the help of infusion pump in the same i v canula. If the pump is not available then Desferal solution can be further diluted in 50-100ml of 5% Dextrose or Normal Saline (NS) or Dextrose Normal saline (DNS) and given by separate line with help of 3 way canula together with blood transfusion alongwith diuretics. Desferal should not be directly dissolved in normal saline.

If patient is incapable of using subcutaneous Desferal due to local drug reactions like pain, tenderness or swelling, intravenous Desferal can be

given. However, intravenous Desferal should be administered only in consultation with referral center.

Continuous intravenous infusion can remove large quantities of iron and is very effective in reversing the cardiac complications. Intravenous infusions of Desferal are given very slowly. Rapid intravenous infusion may lead to collapse. Intermittent infusions of high-dose Desferal are less desirable than continuous infusions at low doses, particularly in high-risk patients.

Can Desferal be given during pregnancy and lactation?

Desferal should not be given during the first trimester of pregnancy but can be used in the second and third trimesters if required. It can safely be given during lactation.

What is the role of Vitamin C during Desferal therapy?

Vitamin C increases the availability of chelatable iron. It should not be administered until the treatment with Desferal has been in progress for 2-4 weeks. 2-3 mg/kg vitamin C should be given after setting the pump on. Desferal with high dose of vitamin C (500 mg) may cause cardiac impairment. However, this side effect is reversible on withdrawal of vitamin C. Vitamin C supplements are not necessary for patients who eat oranges or fresh orange juice regularly. One large orange contains on an average 75 mg of vitamin C & 100 ml of fresh orange juice contains 50 mg of Vitamin C.

What are the side effects of Desferal therapy?

1. Frequent pain, swelling, induration, erythema, burning, pruritis, and rashes at site of injection/infusion occasionally accompanied by fever, chills and malaise. Persistent local reactions may be reduced by diluting the solution.
2. If local reactions occur repeatedly or are severe, 5-10 mg of hydrocortisone may be added in the solution.
3. Intradermal infusion of Desferal may cause ulceration at the site of infusion.
4. High doses of Desferal especially in patients with low S. ferritin may lead to the visual & hearing side effects.

5. Higher doses may also cause platyspondily (flattening of spinal bones), growth retardation and rickets like deformity.
6. It also chelates zinc and copper.
7. Desferal increases susceptibility to Yersinia enterocolitica & Yersinia pseudotuberculosis infection.
8. Concurrent treatment with prochlorperazine (Stemetil) may lead to temporary impairment of consciousness.
9. Use of Desferal should be avoided during pregnancy if serum ferritin level is between 1000-2000 ng/ml. However in patients with higher serum ferritin levels Desferal can be given safely after 1st trimester.
10. Desferal infusion should be discontinued during fever, abdominal pain, diarrhea and infections.

How to monitor Desferal toxicity?

1. Hearing and visual checkup is must once a year during Desferal therapy.
2. Monitoring of height velocity, sitting and standing height twice a year.
3. Radiological monitoring of spine, forearm & knees annually.
4. Keep therapeutic index < 0.025.

   a. Therapeutic index = mean daily dose(mg/kg)/ferritin (ug/L). It should be <0.025

   b. Mean daily dose = actual dose received on each occasion x doses per week divided by 7

Toxicity is unlikely if doses do not exceed 40 mg/kg/day, not introduced at too young age, and the dose is reduced as iron loading falls.

What is the dose of Deferiprone (DFP/ Kelfer) and how to take it?

Dose of DFP is 75-100 mg/Kg/day given in two or three divided oral doses. It is available in 250 and 500 mg capsules. When child cannot swallow capsules, the capsule can be opened and medicine can be mixed with honey or sweetening agent and be given. It is excreted

through urine, hence urine becomes dark colored in patients on Kelfer therapy.

It is more effective if baseline serum ferritin is high (>2500 ng/ml). Various studies have shown that Deferiprone is more effective in chelating heart iron than liver iron in comparison to Desferal. DFP is more efficient in entering the myocytes, binds iron and removes it from the cell. It also binds free radicals generated from excess iron within the myocyte.

What are the adverse effects of Kelfer?

Nausea, vomiting, diarrhoea, abdominal pain & distension in about 5% patients. In a country like ours where GIT infections are common, one should exclude them before ascribing the symptoms to DFP intake. All these symptoms are mild and subside on continuation of therapy. Addition of antacids and/or anti-emetics (drugs to control vomiting) help in reducing these symptoms. Arthropathy (pain & swelling of joints and bones) is observed in 10-20% of cases. Pain and swelling of large joints specially knees and difficulty in squatting are main symptoms of Kelfer induced arthropathy. Abnormalities of the lower end of ulna are recently reported. Incidence decreases with reduction of dose (upto 50mg/kg/day) or on withdrawal of drug. Pain killers (NSAIDS, non-steroidal anti-inflammatory drugs) along with Glucosamine help in relieving the symptoms. If symptoms are not tolerable, the drug should be temporarily withdrawn. It may be started again after some time.

Cytopenia (reduction in total leucocytes, neutrophils, platelets) has been observed in 1-2% of cases. It is reversible on discontinuation of therapy.

If Deferiprone can be given during pregnancy and lactation?

Deferiprone should not be given during pregnancy and lactation. If a lady is planning for pregnancy Deferiprone should be stopped.

How to monitor patients on Deferiprone?

i) Complete blood counts (CBC-Hb, TLC, DLC, Platelet counts) should be performed at 2-4 week interval or whenever there is any sign of infection.

In case of infection, Deferiprone should be stopped immediately and

CBC should be checked. Deferiprone should be stopped if there is leucopenia (white blood cell count <3000mm^3) Neutropenia (absolute neutrophil count <1500mm^3) or thrombocytopenia (platelet count < 1,00,000mm^3). It may be re-started after counts return to normal but under close supervision of the doctor. However in case of recurrent neutropenia, leucopenia or thrombocytopenia Deferiprone should not be re-started. In case of agranulocytocis (absolute neutrophil counts <500mm^3) the child should be reffered to a referral center. Deferiprone should not be restarted if the above side effects are noted because of this drug.

ii) Liver function test (SGOT/AST , SGPT/ALT, GGTP, Billirubin total & direct) should be done at least once in three months, more frequently if ALT is raised.

Can Desferal and Kelfer be given in combination therapy?

Desferal is more efficient at binding liver iron, leading to biliary iron excretion, whereas deferiprone binds cardiac iron more readily. Both chelators are able to bind iron released from the dying RBCs. Presumably, there is no competition between the two drugs for chelating iron, rather the 'shuttle' effect may lead to synergism.

Shuttle effect: Orally absorbed DFP enters the intracellular compartment, binds iron, brings to the extracellular compartment for excretion, there concomitantly administered DFO binds to the iron attached to the DFP and excretes iron through urine and feces.

Combination therapy of Desferal and Kelfer is indicated, if patient:

1. can not tolerate full dose of Desferal and Kelfer due to any reason.
2. is highly iron overloaded and had not used adequate chelation for long.
3. have cardiac or endocrine problems secondary to iron overload, pre- and post- hepatitis treatment.
4. is preparing for bone marrow transplantation or pregnancy with high serum ferritin.

It should be given in consultation with the referral center.

Dose

* It should be individualized based upon the patient's condition and several other factors.
* Generally Desferal is given in dose of 35-50 mg/kg/day 2-4 times a week.
* Deferiprone is given in 50-75 mg/kg/day daily in 2-3 divided doses.

How Defrasirox (DFX) works and What is its dose?

DFX is rapidly absorbed from the gut and hence can be given orally. It forms highly stable complex with iron even at low concentration thus prevents redistribution of iron. It does not chelate copper and zinc but binds with aluminium. It has 24 hour control over labile iron thus needs to be given just once a day. The tablet is not to be swallowed or chewed but taken empty stomach after making suspension in water or apple/orange juice. Non-metallic container and stirrer should be used to dissolve the drug. It chelates both liver and myocardial iron. Patients on DFX chelation show ferritin trend parallel to liver iron and liver function parameters improves as ferritin reduces. Defrasirox can access myocardial iron and reduce free radical formation in the cardiac muscle.

It is excreted mostly through feces, therefore unlike Deferiprone and Desferal it does not cause dark coloration of urine.

Dose:- Flexible, 20-40mg/kg depending upon iron overload and transfusion regimen. In non transfusion dependent thalassemia (NTDT – thalassemia intermedia) even lower dose may be required. Defrasirox can be started as early as from 2 years of age.

What are the adverse effects with Defrasirox therapy?

DFX is generally well tolerated.

1. Minor GI symptoms - abdominal pain, diarrhoea, can be managed by dose adjustment and change in the time of treatment to the evening or after a meal.
2. Skin rash pruritic, usually develop within first two weeks of initiation of therapy. The dose need to be reduced in mild to moderate rashes and interrupted if the rash is severe and involve the whole body.

3. Increased serum creatinine - non progressive increase in creatinine has been reported. If 2 consecutive values are above the upper limit of normal, drug need to be stopped. No patient developed either acute or chronic renal failure in long term studies.
4. Raised AST (SGOT), ALT (SGPT) mandate to reduce the dose.
5. No effects on growth or sexual development in children.
6. No drug-induced agranulocytosis, neutropenia or arthropathy has been reported during clinical trials.

DFX is contraindicated in patients with liver or renal failure.

If Defrasirox can be given during pregnancy and lactation?

Defrasirox should not be given during pregnancy and lactation. If a lady is planning for pregnancy Defrasirox should be stopped.

Monitoring of Patients on DFX

CBC (complete blood count), ALT, AST, Urea, Creatinine, Urine protein before start of treatment and then every month. Visual and hearing examination should be done before start of treatment and then once a year.

ENDOCRINE COMPLICATIONS

What are the endocrine problems faced in thalassemics?

Following is the incidence of endocrinopathies in patients with thalassemia:

Pitutary dysfunction	80%-90%
Bone disease (Osteopenia and osteoporosis)	60%-70%
Diabetes	5%-15%
Hypo or hyper- parathyroidism	5%-10%
Hypothyroidism	3%-5%
Primary gonadal failure	1%-2%

How growth is affected in thalassemics?

Healthy infants grow around 30-35cm in 2 years. In childhood there is constant growth of 5-7cm/year and followed by growth acceleration in puberty.

In thalassemics, optimum transfusion and chelation usually results into normal growth pattern till 9 years of age. But despite medical advances, impairment in growth and puberty remains significant problems in thalassemics during adolescence. Growth impairment may be due to chronic anaemia, under-nutrition, iron-overload, hypogonadism and growth hormone insufficiency. Hypothyroidism, zinc deficiency and psychosocial factors also play an important role. Chelation toxicity (Desferal over dose) is not an issue in India.

How to monitor growth?

Growth deficiency may be diagnosed by maintaining growth chart from early childhood with serial measurement of height and weight every

three months, preferably by the same investigator, same machine and plotted on the same growth chart.

How to calculate the target height?

Target height is measured based on parental height.

Target (midparental) height boys = (mother's height in cm +father's height in cm +13) / 2

Target (midparental) height girls = (mother's height in cm +father's height in cm -13) / 2

Target range = +/- 4.5cm

Midparental height is plotted at 18 years and patient's presented height is compared with this. It should be remembered that height among thalassemics keeps increasing even upto 20-22 years.

How to treat growth retardation?

To achieve optimum growth in pre-pubertal stage following measures should be undertaken from early childhood.

- Hyper-transfusion i.e. maintaining pre-transfusion Hb level between 9.5 to 10.5gm/dl
- Optimum chelation to keep serum ferritin <1000ng/ml without endeavoring chelator toxicity with overdose (of Desferrioxamine)
- Diet rich in protein, calcium and other micro nutrients

What is the role of growth hormone treatment in stunted growth?

Diagnosis of growth hormone deficiency is a complicated (need to take several blood samples) uncomfortable and risky. It is non-physiological and the cut off level is arbitrary. Even though the growth hormone insufficiency has been established, there is limited evidence that growth hormone treatment will have an impact on final adult height.

When and how to suspect pubertal impairment in a Thalassemics?

In healthy individuals puberty begins between the age of 10-11 years in girls and 11-12 years in boys. Girls usually complete puberty by 15–17

years of age, and boys by the 16–17 years of age.

If pubertal development does not take place by the age of 13 years in girls and by the age of 14 years in boys it is known as delayed puberty. Pubertal failure i.e. absence of breast development in girls and testicular volume less than 4ml in boys by the age of 16 years is known as hypogonadism. Arrested puberty is known by non-progression of pubertal development for over a year or longer after initial changes. In this case, testicular size remains 6-8 ml and breast size is in B3 (Tanner's Classification).

How to assess pubertal growth?

To assess growth and development during puberty, 5 stageTanner chart is standard practice.

Males

Tanner 1 (Pre-pubertal)

Height- increases at basal rate, 5-6 cm/year

Testes-smaller than 4 ml or long axis <2.5 cm

Pubic hair-not coarse, pigmented

Penis-no growth

Tanner 2 (age 9.5 -14 years)

Height- increases at basal rate, 5-6 cm/year

Testes-size 4 ml or long axis 2.5 to 3.2 cm,

Pubic hair-minimal coarse, pigmented hair at base of penis

Penis-slight increased length and width

Tanner 3 (age 10-15.5 years)

Height-increases at accelerated rate, 7-8 cm/year

Testes-size 12 ml or long axis 3.3 -4.0 cm

Pubic hair-coarse, dark curly hair spread over the pubis

Penis- increased length and width

Other changes-gynecomastia, voice breaks, muscle mass increases

Tanner 4 (age 12-16 years)

Height- increases at peak rate, 10 cm/year

Testes- length long axis 4.1 to 4.5 cm

Pubic hair- of adult quality, not spread to junction of medial thigh with perineum

Penis-continued growth in length and width

Other changes-axillary hair, voice changes, acne vulgaris

Tanner 5 (age 15-17 years)

Height- no further height increases after age 17 years

Testes- length long axis >4.5 cm

Pubic hair-adult typedistribution,spreads to medial thigh

Penis-mature genital size

Secondary sexual characteristics-facial hair, mature male physique, gynecomastia disappears

Females

Tanner 1 (Pre-pubertal)

Height- increases at basal rate, 5-6 cm/year

Breast-papilla elevation only

Pubic hair-villus hair only, no coarse, pigmented hair

Tanner 2 (age 9-13.5 years)

Height increases at accelerated rate, 7-8 cm/year

Breast-buds palpable and areolae enlarge

Pubic hair- minimal coarse, pigmented hair mainly on labia

Tanner 3 (age 10-14 years)

Height- increases at peak rate, 8 cm/year

Breast-elevation of contour, areolae enlarge

Pubic hair-dark, coarse, curly hair spreads over mons pubis

Other changes- axillary hair develops, acne vulgaris develops

Tanner 4 (age 10.5-15 years)

Height- increases at 7 cm/year

Breast- areolae forms secondary mound on the breast

Pubic hair- of adult quality, no spread to junction of medial thigh with perineum

Tanner 5 (14.5 -16 years)

Height- no further height increases after age 16 years

Breast-adult contour, areola recesses to general contour of breast

Pubic hair-adult distribution, spreads to medial thigh, does not extend up linea alba

Other Milestones

Adrenarche: Age 6 to 8 years characterized by transient growth spurt. Some children develop axillary and pubic hair growth. No sexual development occurs. It is marked by secretion of steroids with androgenic activity by the adrenal gland.

Thelarche: The beginning of development of breast in girls (10.2 to 11.3 years). It usually precedes menarche by 24 months.

Menarche: The first menstrual period at a mean age of 12.7 years (10.8-14.5 years). It precedes by 12 months from regular menses.

Secondary amenorrhea: Cessation of menstrual periods after initial regular menses for few months/years. Poorly chelated thalassemia major females may develop secondary amenorrhea after initial thelarche.

When and how frequent one should look for pubertal growth?

Tanner staging should be recorded every 3 months from the age of 11yrs in females and 12yrs in males.

Bone age should be evaluated from Xray of the left hand and wrist by Tanner & Whitehouse method. X ray of left knee is advised to assess epiphysis fusion before intervention to check whether epiphysis is closed. This helps in appraisal of the factual position whether there is any potential of growth or not.

Pubertal complications need to be managed jointly by a thalassemialogist and an endocrinologist.

Can a thalassemia major plan to marry and have normal children?

Better understanding of thalassemia management, and improved facilities have made it possible to expect normal, reproductive quality life. Although spontaneous pregnancy can be envisaged in adequately managed thalassemics, many may require intervention by an expert in the field of reproductive medicine.

What precautions need to be taken before planning for family?

1. Check the thalassemia status of partner. If the partner is also thalassemia major (or have any other haemoglobinopathy) then all the pregnancies will be affected. If partner is thalassemia carrier (or of any other haemoglobinopathy) then there is 50% chance of having an affected child in each pregnancy. If partner is not even a carrier of thalassemia (or any other haemoglobinopathy) then all the children will be carrier.
2. Pregnancy should always be planned only after pre pregnancy counseling from experts.
3. Couple should always use barrier method for contraception before counseling session.
4. Complete health checkup including iron overload, chelation, heart, liver, endocrine, transfusion transmitted infections like HBV, HCV & HIV, bone health, thrombophilia etc is necessary before planning for pregnancy.
5. The cardiac load is increased during pregnancy so in case of reduced LVEF (left ventricular ejection fraction) or arrhythmia, it is not advisable to plan for pregnancy.

6. Oral chelators are contra-indicated in pregnancy so change to Desferrioxamine If iron overload is more, measures should be taken to reduce it before pregnancy. These measures may include high dose desferal infusions or use of combination therapy (Desferal and deferiprone or deferasirox).
7. Review treatment of other prevailing ailments like endocrinopathies, hepatitis B, hepatitis C, HIV status, osteoporosis, diabetes, thyroid, thrombophilia etc. Hormone replacement therapy, interferon, ribavirin, bisphosphonates, hydroxyurea need to be stopped 6 weeks to six month prior to planning for pregnancy. HCV should be treated before pregnancy and in case of HIV positivity antiviral treatment should be continued during pregnancy. Diabetic and thyroid treatment should be reassessed.

What crucial steps need to be taken during pregnancy in thalassemia?

a) Increase frequency of blood transfusion to maintain Hb>10gm/dl.

b) Quarterly cardiac, liver and thyroid checkup.

c) Desferrioxamine may be started from second trimester onwards including during lactation.

Fertility management in thalassemia essentially require multidisciplinary team consisting of a thalassemialogist, an endocrinologist, an obstetrician, a cardiologist and an expert in reproductive medicine to plan successful live birth.

What is the function of thyroid hormone?

Thyroid hormone controls the basal metabolic rate, stimulates lipid and carbohydrate metabolism. It is essential for growth, normal functioning of reproduction system, and development of the fetus & neonatal brain. It increases heart rate, cardiac contractility, cardiac output and has profound effect on mood.

How common is thyroid problem in thalassemics?

Hypothyroidism may be seen in under transfused and inadequately chelated thalassemics. Iron overload induced free oxygen radical cause lipid peroxidation damaging thyroid cells. It is more common in

females than in males. Hyperthyroidism is usually not predominant in thalassemia patients.

How to suspect and diagnose hypothyroidism?

Hypothyroidism may present with one or more of the varied symptoms like general weight gain, cold intolerance; dry, coarse, sparse skin; puffiness of face and extremities; hoarse voice, hair fall, growth retardation in children, slowness of thought & speech, lethargy, poor memory and suboptimal sensation in hands. Early diagnosis can be made by annual screening of TSH (thyroid stimulating hormone), free T3 and free T4 . Higher level of TSH with normal free T4 level indicate sub-clinical hypothyroidism while lower level of free T4 is diagnostic of frank hypothyroidism.

How to treat hypothyroid?

Hypothyroidism is treated by hormone replacement therapy using thyroxine. The drug should be started with the smallest dose which is 25-50 micrograms orally daily and increased every 2 - 4 weeks by 25 micro grams under strict medical supervision until thyroid function tests are normal. Monitoring should continue at 4 - 6 weekly initially and then 3 monthly. Aim of treatment is to get the TSH around mid range i.e. around 2 u/L.

How to prevent hypothyroidism?

Adequate transfusion & chelation from early childhood reduces the chance of hypothyroidism. Annual screening of thyroid function tests (TFT) from the age of 10 years helps in early detection. Abnormal TFT are reversible in the early stage with intensification of chelation.

What are the causes of bone disease in thalassemia major?

Chronic anemia leads to marrow expansion causing mechanical interruption of bone formation, leading to cortical thinning, distortion and fragility of the bones in thalassemia patients. It causes enlargement of cranial & facial bones, osteopenia or osteoporosis, spinal deformities, scoliosis and spontaneous fractures. The incidence of osteopenia and osteoporosis, the main cause of bone pains and pathological fractures in thalassemicsis around 40%-50%, even in well treated thalassemia

major patients.

Other factors responsible for bone disease include hormonal insufficiency, low vitamin D level, desferrioxamine toxicity and genetic factors. Aggressive desferrioxamine therapy can cause altered upper segment lower segment ratio and truncal shortening. Deferiprone also causes bone deformity and arthropathy.

What is osteoporosis?

According to the WHO, osteoporosis is a metabolic bone disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to compromised bone strength with enhanced bone fragility and a consequential increase in fracture risk.

How to diagnose osteoporosis/osteopenia?

Bone mineral density (BMD-DEXA) is the standard procedure to assess bone strength. It is measured as T score.

T score - 1 to +1 is normal BMD. Every one SD (standard deviation) decrease in T score is equal to10% to 15% decrease in BMD. Preferred site of measurement for BMD is spine or total body.

BMD T score> 2.5 SD below the young normal mean is osteoporosis. Every SD > -2.5 is indicative of further increase in fracture risk.

BMD T score >1.5 - 2.5 SD below the young normal mean is osteopenia. Osteopenia may behave like osteoporosis in presence of concomitant bone disease.

When standard deviation is age & sex matched with controls. it is known as Z score. International society for clinical densitometry (ISCD) recommends Z score instead of T score to diagnose osteoporosis/ osteopenia in children.

BMD in children is difficult to assess before 18 years because of growing bones so no validated data base is available. It carries a risk of over-diagnosis or under-diagnosis of osteopenia in children.

How to manage osteoporosis/osteopenia in thalassemia major?

Since causes of thalassemia bone disease are multifactorial, its management depends upon the age of the patient, the type of thalassemia, severity of clinical presentation, past history and associated endocrinal problems.

General principles are adherence to optimum transfusion & chelation, healthy diet, physical activity and treatment of other endocrinal complications like diabetes, hypothyroidism, hypoparathyroidism, and hypogonadism.

Calcium and Vitamin D supplements: Vitamin D-1000-1500IU daily (normal levels-25-120nmol/l; <25nmol/l is deficient, 25-50nmol/l -insufficient) with calcium 1-1.5gm daily (high dose can cause renal stone). If patient hasrenal calculus pure vitamin D (cholecalciferol/ calcitrol 20,000 units weekly) is the right choice.

Calcitonin: 100 IU x 3 times a week for 1 year in combination with 250 mg calcium daily has been used. With this treatment, bone pain disappears, radiological findings of osteoporosis improve and there is decrease in number of pathological fractures. Calcitonin has no major side effects. Minerals and trace elements must be given prophylactically to all.

Non-responders and poor-responders are subjected to second line treatment with bisphosphonates, under strict medical supervision. Bisphosphonates should not be given before 18 years of age. Dental checkup prior to bisphosphonate therapy is necessary as osteonecrosis of the jaw has been reported on long term use.

How to prevent osteoporosis in a thalassemia patient?

Adequate blood transfusions inhibit bone marrow expansion and appropriate iron chelation prevents iron toxicity in the bone. Calcium, zinc and vitamin D supplementation with regular physical activity increases bone mass thus prevents bone disease in thalassemics. Moderate and high impact activities should be encouraged only with support. Early diagnosis and treatment of diabetes mellitus is also important. Smoking increases risk of osteoporosis/osteopenia. Annual checking of BMD starting in adolescence helps in early diagnosis and treatment.

What is the cause of diabetes in a thalassemia patient?

The diabetes in thalassemia major is attributed mainly to insulin deficiency resulting from the toxic effects of iron deposited in the pancreas, and from insulin resistance due to iron deposition in liver and muscles. Initially body can compensate for this; pancreas secretes extra insulin in order to control blood glucose level. However eventually the increasing insulin level is unable to control blood glucose and levels start to rise up giving type 2 diabetes. Hepatitis C infection may also contribute to development of diabetes in thalassemics. The long term side effects of diabetes mellitus include retinopathy, nephropathy and neuropathy.

How to diagnose diabetes?

Symptoms of diabetes include increased frequency of urination, increased thirst and unexplained weight loss associated with random blood glucose $\geq$ 200 mg/dl

or

Fasting (no intake for 8 hours, plain water is allowed) blood glucose $\geq$ 126 mg/dl and/or post prandial (PP - 2hour after 75 gram glucose dissolved in water) blood glucose $\geq$ 200 mg/dl. For children, a dose of 1.75 g/kg to a maximum of 75 g is used.

Fasting glucose >100 below <126mg/dl and/or PP blood glucose 140 - 199mg/dl is impaired glucose tolerance. This is a pre-diabetes condition and a high risk factor for future diabetes and for cardiovascular disease. With intensive chelation and life style modifications pre-diabetes condition can be reverted.

Diabetes screening should be performed annually from the age of puberty.

How to monitor diabetes in thalassemia?.

At the time of diagnosis: Complete clinical & biochemical evaluation should be done which will include height, weight, blood pressure, urine routine & micro-albuminurea, liver function tests, kidney function tests, lipid profile, serum ferritin, HCV, thyroid function tests, baseline neurological and cardiovascular examination, vision and fundus examination.

Monitoring: Blood sugar (fasting and postprandial) should be monitored regularly. Frequency of monitoring depends upon compliance and blood glucose level. HbA1C is not a reliable marker in thalassemics because of red cell transfusions. Fructosamine reflects last two to three weeks glucose level and is a suitable marker for monitoring diabetes in thalassemics. Target should be to achieve < 300 μmol/l level. Urinary ketones and microalbumin, serum creatinine, foot examination and annual review by an ophthalmologist are required to diagnose and treat diabetic complications at early stage.

How to manage diabetes in thalassemia?

Life style modification-diet rich in low glycaemia index food, exercise, and weight control should be advised. Intensify chelation to bring serum ferritin <1000ng/ml. Initially treat with oral antidiabetic drugs such as sulphonylurea, metformin, acarbose, voglibose etc. If not controlled by the above drugs, may need to add insulin.

Treat associated disorders like hepatitis C, thyroid, cardiac problems etc.

CARDIAC COMPLICATIONS

What are the cardiac manifestations in thalassemia major?

Overall survival of thalassemia major patients have significantly improved in recent years as a result of better management. Still many patients continue to develop iron overload in the heart, which is the major cause of death.

Iron-induced myocardial damage results in cardiac failure, cardiac arrhythmias, progressive congestive cardiac failure and sudden death in thalassemics. The average age of presenting cardiac symptoms in a nonchelated thalassemic is 11 years with the range 6-18 years. Over 60% of these develop heart failure by 16 years of age, 50% of those who develop cardiac failure die within one year if left untreated.

What are the signs and symptoms of cardiac disease in thalassemia?

Even after considerable iron overload in the heart many patients remain symptom free. Once myocardial dysfunction develops, symptoms become visible. Early signs are confusing with natural history of thalassemia like palpitation and breathlessness during exercise may be due to chronic anemia. If left untreated or misdiagnosed heart failure may present with sever breathlessness on minimum exertion, oedema (fluid retention) of limbs and congestion of lungs & liver.

How to investigate cardiac disease in a thalassemia major?

ECG shows changes in T waves and ST segments of anterior chest leads. Sometimes R & S waves are also affected suggesting biaterial enlargement. Conduction disturbance in the form of bundle branch block may be seen.

Treadmill ECG or Holter (24 hour ECG in normal working atmosphere) may contribute to indicate cardiac arrhythmias at an early stage.

Echocardiography provides valuable information on cardiac status

on heart dimensions, ventricular function, left ventricular ejection fraction, estimated pulmonary artery pressure and doppler analysis of intra-cardiac flows. If serial echocardiography is routinely done before scheduled transfusion, it obviates the clinical effect of transfusion.

Cardiac Magnetic Resonance Imaging (MRI) provide both structural and functional information and also quantitate cardiac iron overload. Interpretation of cardiac iron load by MRI T2* has been described in *"How to measure iron overload?".*

How to manage cardiac complications in thalassemia major?

Palpitation, ectopic rhythm (irregular heartbeat), dizziness and fainting must be investigated and treated at early stage.

Maintain pre-transfusion haemoglobin level 9.5-10.5 g/dl from the begining, and 10-11 g/dl in patients with heart disease. Intensify iron-chelation with continuous (i.v./s.c.) desferrioxamine infusion. Clinical trials have revealed significant reversal of cardiac complications if combination of desferrioxamine (i.v./s.c.) and deferiprone is administered simultaneously over a long period.

Even after significant effects on heart muscle, including symptoms of heart failure, aggressive iron chelation can revert the symptoms. It requires sustained co-ordinated effort of thalassemialogist and cardiologists experienced in dealing with cardiomyopathies over a long period to achieve complete recovery.

Co-morbidities such as hypothyroidism, hypoparathyroidism, renal dysfunction, coincidental valve or structural heart disease, vitamin C deficiency should be managed simultaneously. Patients should be advised to observe healthy life styles, quit smoking, avoid/reduce alcohol consumption and increase physical exercise.

General guidelines

A) Asymptomatic patients with normal heart condition

- No restrictions to physical activity and body exercise.

B) Asymptomatic patients with moderate cardiac impairment

- No restriction to physical activity
- Medication

i. ACE inhibitors

ii. Beta-blockers, especially if arrhythmia is a problem.

C) Symptomatic patients with severe cardiac impairment

* Restriction of physical activity
* Slow blood transfusion with diuretics
* Digitalis, if in atrial fibrillation

Management of cardiac complications should be under the guidance of referral center.

NUTRITION

What are the diet restrictions for thalassemia major patients.

Thalassemia major patients on adequate regular transfusion and optimum chelation do not require any dietary restrictions. In general high calorie, high protein nutritious diet helps in normal growth. Following measures are beneficial in reducing the iron overload and intake of necessary nutrients

1. Iron tonics, iron containing multivitamin syrups and market food products containing iron should never be taken.
2. Foods rich in iron e.g. meat, liver, kidney, egg yolk, green vegetables, jaggery should be avoided.
3. Food should not be cooked in iron pots.
4. Meals should include bread, cereals, milk, moong dal, soya bean etc. to reduce the iron absorption.
5. Vitamin C rich fruits e.g. citrus fruits should be avoided along with meals.
6. Strong tea/coffee taken along with meals helps reducing iron absorption.
7. Milk and milk products should be frequently taken. It helps in restoring calcium level.

Thalassemia patients on low transfusion regimens or NTDT patients have increased folate consumption and require folic acid supplementation. Patients on high transfusion regimens does not need folic acid supplements. Low dose vitamin D and calcium supplementation increases bone mass.

Does alcohol or smoking have any role in thalassemia management?

Alcohol can expedite the oxidative damage of iron and aggravates the effect of HBV and HCV on liver tissue. Alcohol consumption also results in decreased bone formation and is a risk factor for osteoporosis. In addition, alcoholic drinks may have unexpected interactions with medication. Cigarette smoking may directly affect bone formation thus a risk factor for development of osteoporosis.

VIRAL INFECTIONS

How liver dysfunction affects thalassemia?

Liver is primary source of iron storage in thalassemics. It causes liver dysfunction which affects the body in many ways.

Liver fibrosis: Even if there is no other factor, fibrosis can occur once the liver iron concentration exceeds 16mg/gmdwl (dry weight of liver).

Hypothyroidism: Liver is responsible for conjugation and excretion of hormones and metabolites. If the liver is damaged it will cause abnormal endocrine clearance and may contribute to hypothyroidism.

Metabolic bone disease: Due to iron overload in the liver, vitamin D hydroxylation in the liver is disrupted giving rise to low vitamin D and secondary hyperparathyroidism. It leads to metabolic bone disease (Hepatic Osteodystrophy).

Diabetes: Liver dysfunction causes hyperglycemia followed by insulin resistance that leads to impaired glucose tolerance and diabetes mellitus.

Viral hepatitis: Hepatitis B and C viruses transmitted through blood transfusion, if left untreated may cause liver fibrosis, cirrhosis of liver, hepatic cell carcinoma (liver cancer), liver failure and death.

How to diagnose hepatitis B (HBV) infection?

Presence of HBsAg (Australia antigen) in the blood is the screening test for hepatitis B infection. Symptoms include mild jaundice and flu like symptoms. Less than 1% of hepatitis B infected people develop acute severe infection. Only around 5% progress to chronic infection.

Carrier stage is marked by the presence of HBsAg and anti-HBc in the blood. Carriers can be active carriers, who are diagnosed by HBeAg or anti-HBe antibodies in the blood with raised liver enzymes. They can spread infection to others. Inactive carriers, have normal ALT & AST and positive anti-HBe antibody.

Patients who are also infected with hepatitis C are more prone to chronic

liver disease. Iron loading increase the risk of developing cirrhosis of liver. Liver cancer (Hepatocellular carcinoma) is a known complication of chronic hepatitis B infection.

All patients are advised annual HBsAg test for early diagnosis and treatment. Viral load is assessed by HBV DNA quantification test.

How to prevent hepatitis B infection?

All newly diagnosed thalassemia patients be vaccinated against hepatitis B. Three injections (at 0, 1 and 6 months) are given in normal individuals but in thalassemics one booster dose is advised every 5 years to sustain the immune level. The vaccine is ineffective in those who are already infected with hepatitis B.

HBV is highly infectious through close contact so family members should be vaccinated without delay. Common daily use items like nail cutter, razor, combs, tooth brushes etc should not be shared. It is also transmitted through sex so barrier contraceptive methods are advised to prevent transmission of infection in partner.

Besides hepatitis B, hepatitis C and HIV infections are also transmitted through blood transfusions. No blood transfusion is safe but blood collected from voluntary, non-remunerated, repeat donor who has honestly answered a carefully prepared questionnaire and tested negative for all necessary infectious markers is considered safe. Nucleic Acid amplification Test (NAT) in donors' blood further reduces the chance of transfusion transmitted infections.

How hepatitis C (HCV) affects thalassemics?

Acute HCV infection is not severe and usually without any symptoms. In 70-80% patients it leads to chronic liver disease. 5 to 35% develop cirrhosis of liver depending upon other co-factors. Cirrhosis of liver is a condition in which liver cells undergo irreversible damage and replaced by scar tissue resulting into liver failure and death. It takes 20-30 years from acquiring HCV infection to progress to cirrhosis. 1-5% HCV infected persons further advance to hepatocellular carcinoma. Iron overload and co-infection of hepatitis B & HIV increase the risk of complications. Co-infection of HIV & HCV synergistically worsen the prognosis of both the infections, leading to more severe fibrosis, cirrhosis, and mortality.

How to diagnose HCV infection?

All the thalassemics are advised HCV antibody screen by ELISA once a year. Positives are confirmed by HCV RNA quantification.

How to treat hepatitis B and C infection?

Treatment of HBV and/or HCV depends upon various factors like age of patient, acute or chronic stage of infection, viral load, genotype, co-infection of HIV etc. Prognosis depends upon iron overload, genotype, condition of liver etc. Oral chelators are not advised during treatment of HCV and/or HBV so intensive chelation should be given before embarking upon anti-viral therapy. Strict monitoring is required during treatment. Blood requirement may increase during treatment.

Treatment of HCV and HBV should be jointly undertaken by a thalassemialogist and an expert in liver diseases.

How to prevent hepatitis C infection?

There is no vaccine available for hepatitis C infection. Blood safety measures mentioned above in the prevention of HBV infection also reduce infection of HCV.

What is the risk of transmitting HIV (Human Immuno-deficiency Virus) in thalassemics?

Because of repeated life long transfusions thalassemics are highly prone to get infected with HIV, however by creating awareness in public overall prevalence in population has reduced to <0.3% and with improved screening techniques transmission has also reduced.

Though no blood is 100% safe but with introduction of NAT in donor's blood the window period (duration in days of catching infection and testing positive with a particular methods) reduces to just 5.3 days in HIV, 3.4 days in HCV and 15 days in HBV. It has been observed that during first 3 days of infection viral load is so less that transmission of HIV/HCV infection is almost negligible. That means if best testing method (individual donor testing with NAT) is applied along with good history taking on non-remunerating voluntary blood donors, we can reach to "Near" zero risk blood transfusion.

UK SHOT [serious hazards of transfusion] data revealed that there was

no transmission of HIV, just 2 cases of HCV and only 1 case/annum of HBV through blood transfusion from 1995-2004.

How to diagnose and monitor HIV infection?

Annual HIV antibody screening by ELISA is recommended in transfusion dependent thalassemics. CD4 cell counts should be measured at the time of diagnosis and every 3 to 4 months thereafter. CD4 cell count helps in ascertaining the stage of HIV disease and need for prophylaxis against opportunistic infections. CD4 count is most effective monitoring tool for initiation/adjustment of ART (anti retro-viral therapy) and to assess progression of disease.

How HIV infection affects the body?

In adults, it takes around 7-11 year for HIV infection to progress to full blown AIDS (acquired immnuno-deficiency syndrome). Age, viral load, other co-infections/diseases influence the progression of HIV infection. HIV infection causes progressive immune depression leading to depletion of CD4+ lymphocytes that renders the patient at risk for many types of opportunistic infections. HIV positive patients are at increased risk for significant morbidity from infections, because they are immune-compromised.

How HIV infection is managed?

Highly active antiretroviral therapy (HAART) has contributed to the survival and improved health of patients with HIV infection. HAART partially restores immune function, but not the HIV-specific response. Free treatment for HIV infections is available in most of the major hospitals all over India. Optimal control of iron overload with iron chelation is recommended in HIV-positive patients. Deferiprone has shown some antiviral properties in laboratory trails, but it should be used cautiously because there is an increased risk of neutropenia with deferiprone.

HIV infection is not exacerbated by HCV treatment, indicating that co-infected patients may be treated safely with combination of IFN and ribavirin.

What is the scope of haematopoietic stem cell transplant (HSCT) in thalassemia?

Currently haematopoietic stem cell transplant (HSCT) from HLA (human leucocyte antigen) matched sibling donor is the only method available to cure β-thalassemia major. The outcome is best if the transplant is performed as early as possible, because the less advanced the disease, the greater the likelihood of a favorable result

Who can be a donor for HSCT?

For best results 100%, HLA-identical sibling donors are recommended. The probability of having such a donor is just 15-30 %. Since now HLA matching is done by means of molecular genetics, the use of fully matched unrelated donors has been shown to be almost equivalent.

From where the stem cells are obtained?

Haematopoietic stem cell are obtained by withdrawing blood from hip bone of the donor or mobilized peripheral blood stem cells (PBSC) by drawing blood from arm with a special machine. Bone marrow is still the most preferable source of HSC. However, PBSC are easier to collect since stem cell apheresis can be done in an outpatient setting. Bone marrow collection invariably requires admission and general anaesthesia. PBSC engraft faster than bone marrow derived stem cells, however, they also increase the risk of GVHD.

In young children, stem cells extracted from umbilical cord blood (UCB) are a valuable option. The key advantages of UCB are, easiness to collect stem cells, opportunity to store in cord blood banks facilitating easy available at any time, less GVHD due to the immunological naivety of UCB cells and, a lower probability to pass on cytomegalovirus infections to the recipient. However, engraftment is significantly slower in UCB transplants putting the patient at risk for serious infectious complications due to prolonged neutropenia.

What is graft versus host disease (GVHD)?

GVHD may occur after a bone marrow or stem cell transplant in which someone receives bone marrow or stem cells from a donor. The new, transplanted cells regard the recipient's body as foreign. When this happens, the newly transplanted cells attack the recipient's body. GVHD

is less likely to occur, or symptoms will be milder, when the match is close. The chance of GVHD is:

- Very low when a person receives bone marrow or cells from an identical twin
- Around 30 - 40% when the donor and recipient are related
- Around 60 - 80% when the donor and recipient are not related

Chronic GVHD is one of the most serious consequences of BMT in thalassemia. Risk factors for chronic GVHD include cytomegalovirus infection, previous splenectomy, steroid prophylaxis for acute GVHD, and high CD34 cell count in the graft. Recipients of unrelated cord blood transplants are likely at lower risk for chronic GVHD.

What is the outcome of transplant?

Prof. Guido Lucarelli from Pesaro, Italy, has done maximum transplants in thalassemia. He has classified success rate on three factors

1. quality of chelation received for the entire life before transplantation
2. hepatomegaly (liver enlargement) and
3. the presence of liver fibrosis at pretransplant hepatic biopsy examination.

These factors are used to classify the patients into three groups

Class I : patient has none of the above factors i.e. patient has been adequately chelated before transplant, does not have hepatomegaly and there is no fibrosis (determined by liver biopsy). 87% class I patients were fully cured, they did not require transfusion after transplant. In 7% there was rejection i.e. they survived but not cured, they again became transfusion dependent. 6% died due to complications related to transplant.

Class II : (having one/two factors): 81% fully cured, 3% rejection and 16% deaths.

Class III : (having all the risk factors): 58% were fully cured, 12% rejection and 30% died.

In adult patients, transplant related mortality rate was 35%.

What problems can occur after transplant?

Ex-thalassemics (thalassaemics cured by HSCT) may still suffer from iron overload and its toxic effects after transplant. Hence, iron detoxification is a major concern after the transplant. It is done by regular venesection (taking out blood) or chelation therapy. Iron removal is usually delayed until the critical phase of post-transplant of 12-18 months is over.

Hypoadrenalism may occur in patients on prolonged corticosteroid therapy for GVHD treatment. Gonadal function is impaired lifelong in the majority of patients receiving conditioning prior to transplant. The major cause of gonadal damage leading to hypergonadotrophic hypogonadism is irradiation or chemotherapeutic agents. The ovaries are usually more vulnerable to chemotherapy than the testes.

Lifelong infertility is typical, but not universal after BMT. The exact incidence of fertility following transplant is difficult to establish, but the overall incidence of conception is rather low.

NON TRANSFUSION DEPENDENT THALASSEMIA (NTDT)/THALASSEMIA INTERMEDIA

What is the role of hydroxyurea (HU) in NTDT?

The clinical picture of NTDT can be greatly improved by an even partial reduction in the degree of the non - α to α globin chain imbalance. Hydroxyurea works by inducing HbF synthesis. Combination of hydroxyurea with L-carnitine can be more effective in improving haematologic parameters and cardiac status in patients with NTDT patients. Co-inheritance of α thalassemia, Xmn-1 polymorphism and the inherited β globin genotype may be predictive of a good response to hydroxyurea. Hb E/b thalassaemia patients generally have a good response.

HU has beneficial effects in conditions like extramedullary erythropoiesis, leg ulcers, anaemia and bone pains in NTDT patients. It increases the energy level, exercise tolerance and feeling of well-being. Good response is seen in >90% of the NTDT patients.

What are the side effects of hydroxyurea therapy?

HU can cause pancytopenia i.e. reduction in all types of blood cells. stomatitis, nausea, vomiting, diarrhea, difficulty in micturition, increased urea & creatinine.

Alopecia, rash, facial erythema, leg ulcers, headache, seizures and transient increase in ALT can occur during HU therapy. It is contraindicated in pregnancy, lactation and assisted reproduction treatment.

What are the indications of transfusion therapy in NTDT patients?

Occasionally anemia in patients with thalassemia intermedia gets suddenly worse, usually following infections, worm infestation, stress of examination, pregnancy, severe menorrhagia etc. One, two or more transfusions are needed to recover from such episodes.

Before deciding to put the patient on regular transfusion therapy, clinical picture and haemoglobin level needs to be observed for ~3 months. Regular transfusion therapy needs to be considered :

If patients show signs of failure to grow, thrive or develop. There is growth failure (height is better indicator than weight) or poor school performance, failure of secondary sexual development in parallel with bone age, severe bony changes, deformity, thinning or fracture of bones and extramedullary hematopoiesis with symptoms. If Haemglobin level falls < 50 g/l. alongwith profound enlargement of the spleen (at a rate exceeding 3 cm/year) specially during maximal growth and development.

Diminished exercise tolerance, thrombosis, pregnancy are other indications requiring long term transfusion therapy.

What are the indications for splenectomy in NTDT?

Poor growth and development - As an alternate to transfusion therapy, although the latter is preferred particularly where iron chelation therapy is available

Increased transfusion demand - Annual blood requirements exceed 1.5 times those of splenectomised patients, provided there is no other reasons for increased consumption (e.g. new alloantibodies, infection, or changes in the haematocrit of the transfused units). The rate of iron overload should also be taken into consideration. For patients who maintain effective chelation therapy despite increased blood requirements, splenectomy may be avoided.

Hypersplensim - Leucopenia or thrombocytopenia causing clinical problems such as recurrent bacterial infection or bleeding.

Splenomegaly - Accompanied by symptoms such as left upper quadrant pain or early satiety. Massive splenomegaly causes concern about possible splenic rupture.

What are the complications of splenectomy in NTDT?

Splenectomy in NTDT can contribute to an increased susceptibility to thrombo-embolic event and pulmonary hypertension (PHT). This increases NTDT related complications and the inherent risk of infection.

Peri-operative complications include bleeding, atelectasis (collapse of

lung tissue part or all of one lung preventing normal oxygen absorption to healthy tissues) and sub-phrenic abscess.

Post-operative thrombosis is common with platelet reaching 1000,000 – 2000,000/mm3. Since splenectomised NTDT patients have increased risk of thrombosis, low dose aspirin is advised to patients with high platelet count and anticoagulants for patients with past history of thrombosis

What precautions need to be taken before or after splenectomy in NTDT patients?

Pre and post-splenectomy precautions are same as already discussed above for thalassemia major patients.

How iron overload occurs in NTDT patients?

Iron loading in thalassemia intermedia patients is derived from two sources: increased intestinal absorption from gut and occasional transfusion therapy. Iron overload in NTDT patients develops more slowly than patients with thalassemia major. The initiation of chelation therapy in NTDT patients depends primarily on the extent of iron overload and rate of iron accumulation.

How to measure iron overload in NTDT patients?

Serum ferritin levels do not accurately reflect the level of iron overload in patients with NTDT patients. Assessment of liver iron concentration (LIC) by MRI T2* every 1-2 years is indicated in NTDT patients after the age of 10 years before.

Why serum ferritin is not reliable measurement in NTDT?

The combination of ineffective erythropoiesis and chronic anaemia/ hypoxia results in hepcidin suppression. This increases iron absorption from the gut and increased release of recycled iron from the reticuloendothelial system (RES). This results in depletion of macrophage iron, relatively low levels of serum ferritin, and preferential portal and hepatocyte iron loading leading to increased LIC.

Comparison of serum ferritin value with LIC (mg/gm dwl) in thalassemia major (TM) and NTDT patients

SF ng/ml		LIC in TM		LIC in NTDT
500	=	2.7	=	5.8
1000	=	5.4	=	11.6
1500	=	8.2	=	17.4
2000	=	10.9	=	23.2
600	=	3.2	=	7.0

How iron overload affects in NTDT?

During first and second decades there is abnormal stimulated LH (leutinising hormone) pituitary response and delayed menarche. Later in third and fourth decades diabetes, liver fibrosis, cardiac failure and hypopituitarism may develop.

When to initiate iron chelation therapy in NTDT patients?

Ferritin is not a good predictor of the extent of iron overload in NTDT patients. Chelation therapy in NTDT patients should be initiated when LIC exceeds 7 mg Fe/g dry weight of liver. Where LIC measurement is not possible or refused by patient, threshold serum ferritin values of 400–500 ng/ml are considered as an indicator for initiation of iron chelation therapy. Iron chelation therapy in patients with NTDT may not necessarily be life-long. Intermittent periods of iron chelation and careful assessment of iron indices are recommended.

NTDT patients may have positive iron balance from the age of 5 years, even in the absence of transfusions, iron chelation therapy be initiated in patients over this age to prevent on going accumulation.

What is the cause of leg ulcers in NTDT patients?

Leg ulcers are more common in older than in younger NTDT patients. The skin at the extremities of elderly NTDT patients is thin due to reduced tissue oxygenation, and this makes the subcutaneous tissue fragile and increases the risk of lesions from minimal trauma. It often starts from a bruise or a bang just above the ankle. Once an ulcer has

started to develop it is very painful and difficult to cure, although regular blood transfusions may provide some relief in persistent cases.

How to manage leg ulcers?

- Avoid injury over ankles.
- Wearing toweling (turned-down top) socks.
- Use wrist bands on the ankles.
- Raise foot end by 10 cm while sleeping.
- Raise lower limbs above the heart level at least 2 hours in a day while sitting.
- Zinc supplementation.
- Hydroxyurea also has some benefit, either alone or in combination with erythropoietin.
- Oxygen chamber can provide moderate relief, it ameliorates tissue hypoxia.

Monitoring of Thalassemia Patient at each Transfusion

Date							
Amount of Blood Transfused							
Pre- Transfusion Hbgm/dl							
TLC x 10^9/L							
DLC- Poly %							
Lymphocytes %							
Monocytes %							
Basophils %							
Eosinophils %							
Platelets x 1000							
Liver cm							
Spleen cm							
Transfusion Reaction if any							
Kelfer dose advised							
Desferal dose advised							
Next date							
Others							

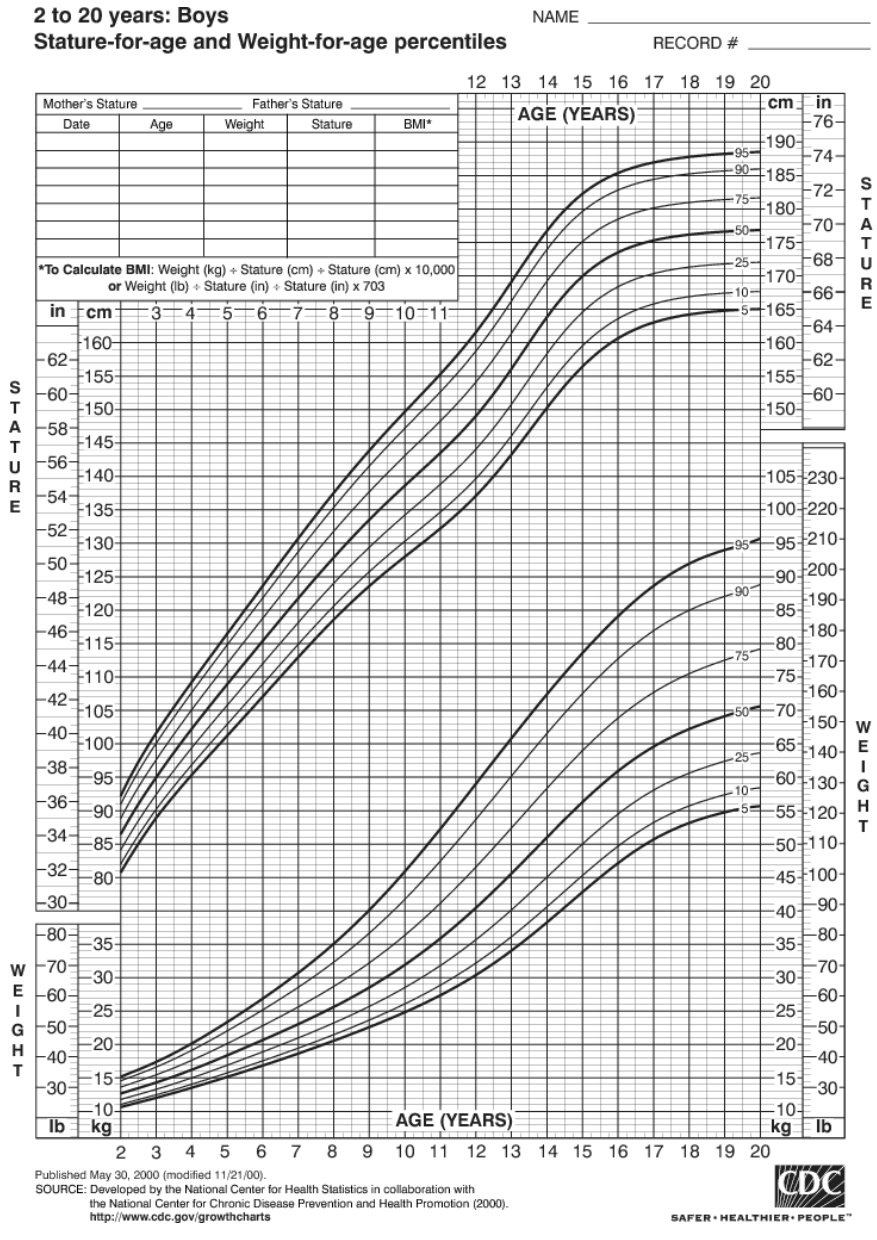
Monitoring- Quarterly

Date				
Ferritin µg/L				
Billirubin total				
Direct				
SGOT/AST				
SGPT/ALT				
ALP				
GGTP				
Proteins Total				
Albumin				
Globulin				
Urea				
Creatinine				
Uric acid				
Calcium				
Phosphorous				
Height				
Weight				

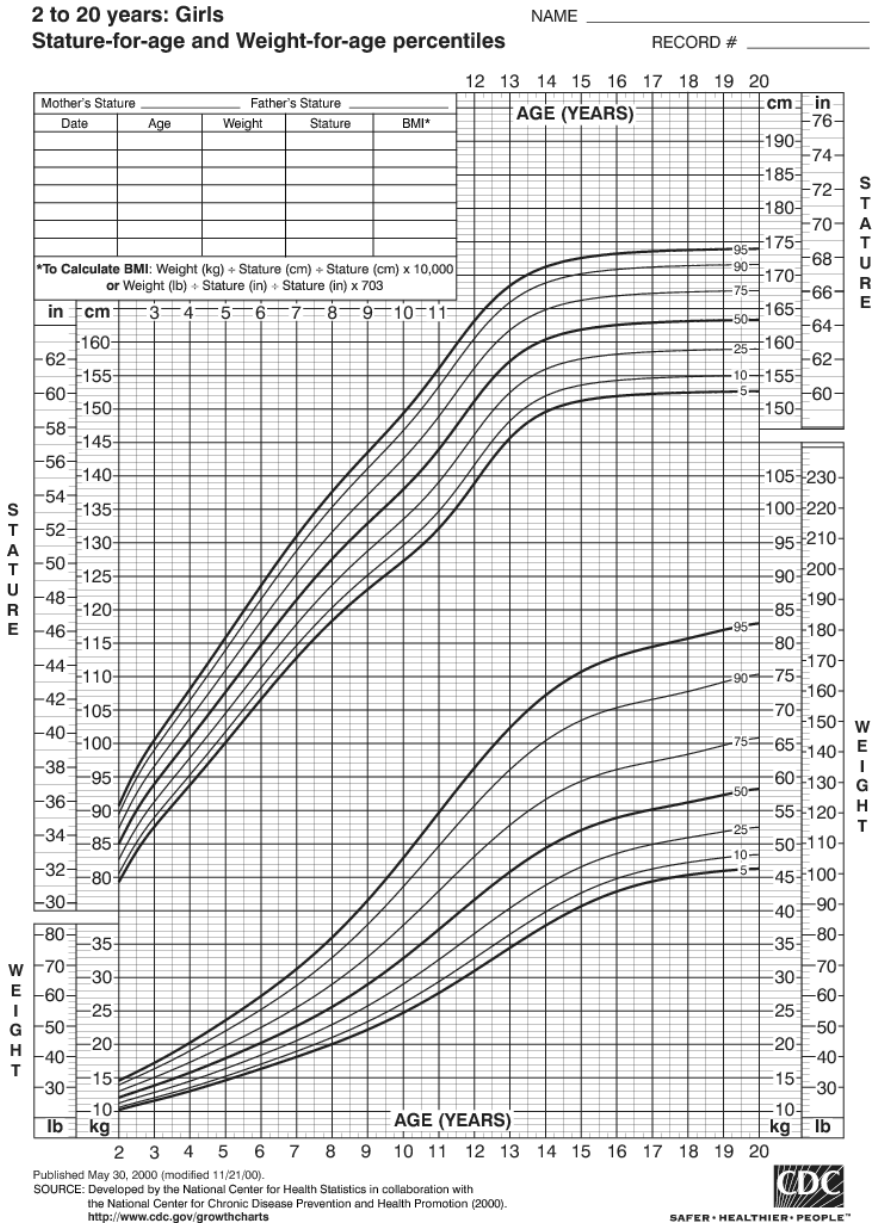
Monitoring- Yearly

Date			
HbsAg			
Anti HBs Ab			
HCV			
HCV RNA			
HIV			
Audiogram (if on Desferal)			
Ophthalmology check up (if on Desferal)			
Every alternate year after 10 yr of age or whenever required			
Blood Sugar F			
PP			
FT3			
FT4			
TSH			
ECG			
Echocardiography			
MRI T2* Heart/MIC			
MRI T2* Liver/LIC			
PTH			
LH			
FSH			
Oestradiol			
Testosterone			
Dehydro EpiandrosteroneSulphate			
Cortisol			
Bone Density			

Growth Chart - Boys



Growth Chart - Girls



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