THALASSAEMIA FEDERATION PAKISTAN

March 2006

Thalassaemia Handbook

01

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Introduction

The Thalassaemias are a group of genetic disorders with variable expression. The genetic mutation causes decreased synthesis of the globin chain. Many different types of thalassaemias have been described, of which ß -thalassaemia are the most common in our country. It has been estimated that over 100,000 people are living with homozygous ß-thalassaemias in the world [1]. In Pakistan over 5 -6% of our population is a carrier. This translates to approximately 3000 new cases of thalassaemia major each year [2].

Without proper diagnosis and treatment most patients with severe thalassaemia die before the age of 5 years. But with the recommended treatment the prognosis can be greatly improved. Patients can live a normal life span with a relatively good quality of life.

As with all chronic illnesses prevention is the ultimate goal. Currently prenatal diagnosis is available in our country and should be employed wherever possible. Early detection of carriers with prenatal diagnosis will help eradicate the presence of thalassaemia major in our country.

The road towards a thalassaemia-free Pakistan is a long one with many bumps and obstacles. Therefore while we are traveling this long tedious path we need to develop standards of care for our

thalassaemics patients. So that whether our patient live in Lahore or Karachi, Jhang or Sukkur, Quetta or Peshawar, they receive the same quality care that they would receive anywhere else.

To deal with our patients appropriately we must set up centers which can cater to the needs of the population of thalassaemics in our country. We must ensure that at least one medical doctor is a permanent employee who is well versed in thalassaemia and has a good rapport with all patients and their families.

In our country thalassaemics are cared for by many NGO's who work hard to make sure that these children get the best possible care they can in the current situation. Through this book we would like to acknowledge their valued hard work and efforts.

This handbook is the first step towards developing uniform standards of care for our thalassaemics countrywide. It provides guidelines for diagnosis, chelation and management of complications. It is meant to provide our healthcare workers with the information they may need in order to provide the best care possible to our thalassemic patients with our limited resources and improve their quality of life.

1. Thalassaemia International Federation. Guidelines for the Clinical Management of Thalassaemia. Italy ; April 2000
2. Ahmad S. An approach for prevention of Thalassaemia in Pakistan [Ph.d. thesis]: 1998: London University

Chapter 1:-

Genes & Pathophysiology

Thalassaemia is an Autosomal recessive disease with phenotypic heterogeneicity. As in all autosomal recessive disorders one will have a 1 in 4 chance of having a homozygously affected offspring in every pregnancy.

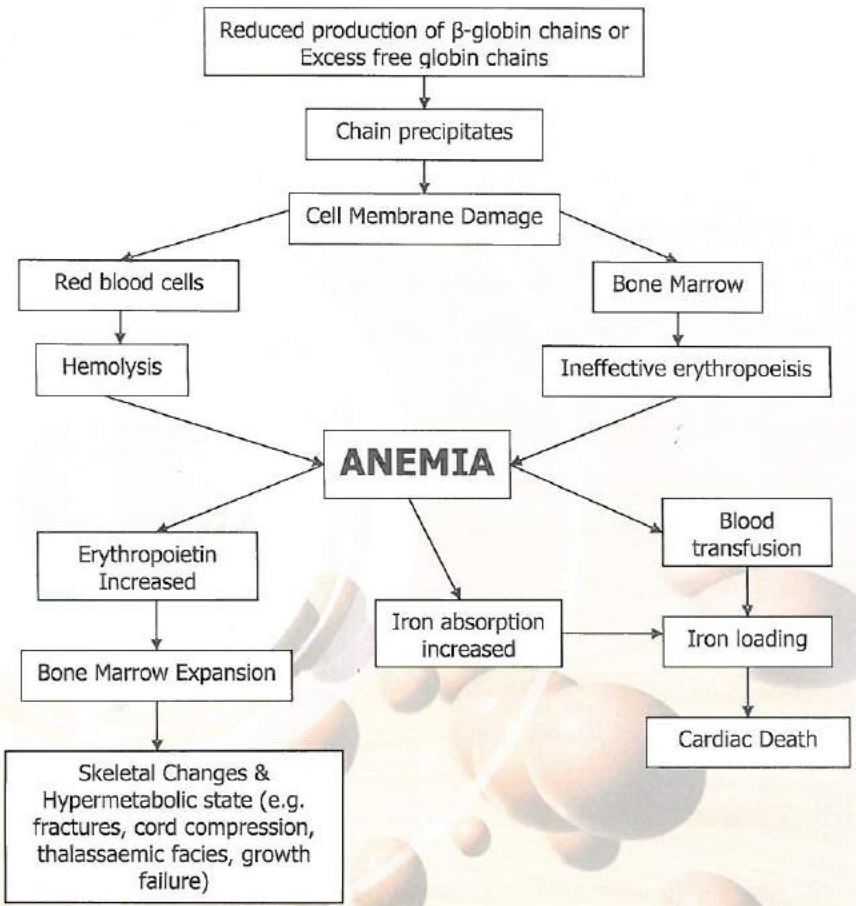
The genes for thalassaemia are on Chromosome 16 and 11, α and β respectively. The commonest β-globin gene mutations detected in our population are as follows

Table 1.1: *β-globin gene Mutations commonly found in Pakistan in 1200 CVS samples*

Mutation	No	%
IVS1-5	113	27
Fr8-9	158	37.8
Fr41-42	54	12.9
Fr16	2	0.5
Del619	34	8.1
Cd15	42	10
Cd30	12	2.9
Cap+1	3	0.7
Total	418	100

This genetic disorder causes a quantitative defect in the production of β-chain of haemoglobin resulting in an imbalance between α and β chains hence rendering the RBC's to haemolyse and resulting in anaemia.

Figure 1.2: Effects of excess production of free α-globin chains



Chapter 2:- Diagnosis of Thalassaemia

Case Diagnosis

Diagnosis is based on History, Clinical Features and Lab diagnosis none of which can be used in isolation.Most common clinical features are progressive pallor, lethargy, irritability, frequent infections and failure to thrive. Other important points are

- Age of onset of anaemia
  - Early Infancy – points towards Thalassaemia Major
  - Late Infancy or childhood – more commonly in Thalassaemia Intermedia.
- A child ≤ 1yr who has received two or more blood transfusions at different health care facilities.
- Unresponsive anaemia to haematinics
- Facial abnormalities
- Visceromegaly
- Chronic leg ulcers – occurs in Thalassaemia intermedia
- Family history of Anaemia, Jaundice, Gallstones

Lab Diagnosis

1. The initial investigations should be Haemoglobin level total RBC count MCV, MCH, RBC morphology and reticulocyte count. All cases of β-thalassaemia major and 95% of β thalassaemia traits have MCV <75fl and MCH <25pg (hypochromic, microcytic anaemias). Reticulocyte counts are usually high

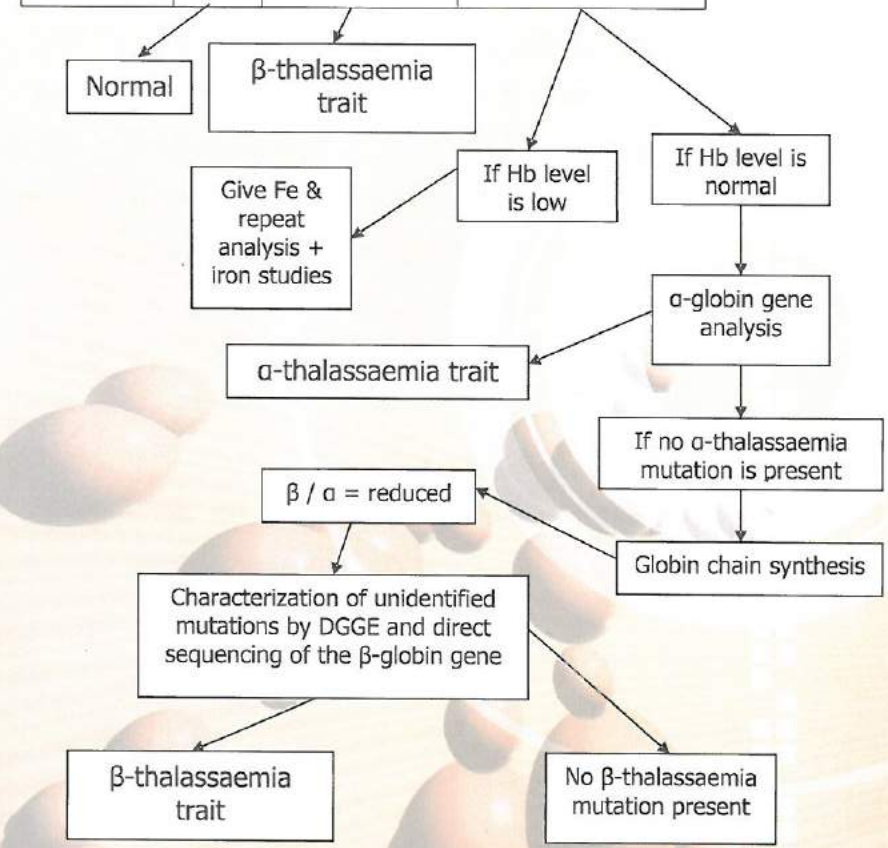
>4%. A small number of silent β-thalassaemia carriers and α-thalassaemia carriers may have RBC indices in the normal range. The results of haemoglobin estimation must always be interpreted in conjunction with MCV and MCH (<75fl & <25pg respectively) in β-thalassaemias.

2. *Haemoglobin Electrophoresis* In Hb electrophoresis the adult haemoglobin can vary from 0-80%. Fetal haemoglobin is usually as high as 50 - 80% in thalassaemia major and generally less than 50% in thalassaemia intermedia. Hereditary persistence of Fetal Haemoglobin (HPFH), these are thalassaemia like syndromes in which there is a lack of production of β-globin and α-globin chains. (See Table 2.1 at the end of the chapter)

3. *DNA diagnosis* when ever possible should be done for β-thalassaemia, α-thalassaemia and Xmn1 Polymorphism.

Figure 2.1: Flow Chart for thalassaemia screening in Pakistan[1]

MCV (fl)	>78	<78	<78
MCH (pg)	>27	<27	<27
HbA_2%	<3.0	>3.4	<3.5
HbF%	<1.5	Varies 0-5%	<1.5



1 Adapted from the Cyprus role model for Thalassaemia screening

- Homozygous Hb δ (δ/δ) have normochromic, normocytic anemias
- Patients with δ/β have hypochromic, microcytic anemias with raised A_2
- HbH is the most commonest, unstable and fast moving haemoglobin on an electrophoretic plate in Pakistanis. It is best seen in fresh blood samples. HbH inclusions are also seen in reticulocyte preparations.
- A_2 is >3.4% in typical carriers and helps diagnose carriers as well as helps in different situations as below. Atypical carriers can have normal levels of A2
- Occasionally one is faced with a child who has been recently transfused before electrophoresis or has presented after becoming transfusion dependent. In these cases Hb electrophoresis of both parents is helpful to demonstrate them as high A2 carriers. In certain cases a silent or β+ thalassaemia trait, Cap+1 mutation present in Pakistan can pose a problem. These patients will have a normal MCV, MCH and A_2. Patients with silent β- thalassaemia and those with coincidental α and β thalassaemia traits are best identified by PCR.

Hereditary Persistence of Fetal Hb

	Hb F	Anemia	Features	Genetic
Heterozygous	10 – 40%	Normal	Normal	Nondeletional
Homozygous	100%	Mild Anemia	Mild Microcytosis	Deletional

Table 2.1 Differences between heterozygous and homozygous hereditary persistence of fetal Hb.

Chapter 3:-

Blood transfusions in Thalassaemia Major

Blood transfusion is started once a definitive diagnosis of severe thalassaemia is made and haemoglobin is below 7gm/dl on two occasions more than two weeks apart. Before blood transfusion, extended blood group typing for ABO, Rh and if possible minor blood group antigen should be documented. Special care should be taken to identify A & A_2 subgroups as it can be done in our setting. If the facility exists, screening for new antigens and antibodies should be done before every transfusion.

Type of blood available:

Blood and blood products which are easily available in our setup are as below:-

1. Packed red cell ideally leucodepleted $<5\times 10^6$wbc/ L should be transfused. Leucodepletion may be done
    - Either by the blood bank
    - or by bed side filters (Sepacell, Baxter Leucofilters)
2. Washed red blood cells are especially useful in patients who experience blood transfusion reactions.
3. Fresh blood (In many places the only available blood is fresh blood which is hanged and settled RBC used. If possible hang the blood in a refrigerator as on a stand and when the red

blood cells settle, move it to the recipient without shaking. The RBC setting time is approximately 2 hours. It is also important to make sure that the blood transfusion set is attached to the blood bag prior to hanging.

In our country there are two types of blood transfusion regimens used.

High transfusion regimen

When the pre-transfusion Hb is maintained between 9.5 - 10.5 gm/dl. Although very few children benefit from this.

Low transfusion regimen

The Hb remains between 4-8gm/dl, and pre-transfusion Hb is 4 – 5gm/dl. This is the usual story and is a genuine problem especially in rare blood groups.

Once you decide to transfuse a child regularly you should maintain the child in high transfusion scheme. Any deviation from the recommended schedule can result in a low transfusion scheme (Hb between 6-10gm/dl). Thus to shift this patient into a high transfusion scheme it will require weekly blood transfusions for a short while. Patients maintained on a high transfusion scheme have a good rate of growth, no visceromegaly and ultimately have lower requirements of blood per year.

Safe transfusion:

Blood transfusion is considered to be safe if:-

1. Donor blood is carefully matched for ABO blood group, Rh sub type, and minor blood groups including, Kell, Duffy, and Lewis if available. Since minor grouping is not available at a majority of centres, therefore in patients with repeated acute haemolytic reactions blood grouping should be done by the Coomb's method rather than the slide method.
2. Properly screened for hepatitis B ,C HIV and malaria
3. Amount of blood volume to be transfused as appropriate.

Amount of blood

Fresh blood is transfused at a dose of 20 ml/kg at each visit and packed cell volume of 15-20ml/kg can be given according to the Hb level.

Rise in Hg in recipient	Hematocrit of donor blood 50%	Hematocrit of donor blood 60%	Hematocrit of donor blood 80%
	Amount of packed red blood cells required		
1gm/dl	4.2ml/kg	3.5ml/kg	2.6ml/kg
2gm/dl	8.4 ml/kg	7.0 ml/kg	5.2 ml/kg
3gm/dl	12.6ml/kg	10.5ml/kg	7.8ml/kg
4gm/dl	16.8ml/kg	14.0ml/kg	10.4ml/kg

Table 3.1: Recommended amount of blood to be transfused[3]

3 Thalassaemia International Federation. Guidelines for the Clinical Management of Thalassaemia. Italy ; April 2000

4. Duration of blood transfusion should be 3-4 hrs, however transfusion should be slower in cardiac failure i.e. 1-2ml/kg/hr
5. Proper records should be maintained including the following parameters
    a. Pre-transfusion Hb%
    b. Volume transfused on each visit
    c. Six and twelve monthly blood consumption calculations
    d. Adverse reactions (sign, symptoms and Rx given after a reaction).

A useful record form for blood transfusion monitoring is presented below.

Blood Transfusion Record

Date	Pre-Transfusion Hb	Volume Transfused	Post-Transfusion Hb	Date of Next Transfusion	Notes

Effective transfusion:

Effective transfusion should be able to

1. Promote normal growth & development
2. Allow normal physical activity
3. Suppresses erythropoeisis
4. Prevent bony changes
5. Prevent enlargement of the liver and/or spleen
6. Minimise iron overload

Intervals in transfusions

The intervals can vary between 2-5 weeks and should not exceed 20 ml/kg at any one time. They have to be adjusted according to the age, weight of the child and utility of quantity in one bag e.g. patient having wt.=12kg is normally given 12 ×15=180ml to adjust a full bag his interval can be increased to 5 weeks (12 ×20=240ml). Another example is a child wt.=30kg requires 30 ×15 = 450ml, he can be transfused one bag fortnightly i.e. 250ml fortnightly.

A rapid fall in haemoglobin may be due to

1. Hepatosplenomegaly (hypersplenism)
2. New antibodies against red blood cells
3. Low hematocrit of donor blood
4. Infections e.g. Malaria, gram –ve and gram +ve bacteria
5. Chronic blood loss
6. Auto-immune haemolytic reactions
7. Inadequate quantity of blood (Older children may require 2-3 bags at one time depending on their weight)
8. Acute illness in children especially with bacteria containing hemolysins e.g. β-haemolytic streptococcus, E. coli, etc. and malaria.

Common blood reactions

Adverse events associated with transfusions include the following:-

Non-haemolytic febrile transfusion reactions

- Can be prevented by leucoreduction by leucocyte filters.
- Pre-treatment with antipyretics

Allergic reactions

These may range from mild to severe which are mainly due to plasma proteins. These can be reduced by transfusions with packed cells and treated with steroids (I/V hydrocortisone 10-20mg/kg)

Acute haemolytic reactions

Such reactions are mostly due to mismatched blood transfusions. It is extremely important to ensure that the blood bags, serial numbers, blood types and names be properly checked prior to transfusions. These reactions will be associated with acute loin pain, anemia, jaundice and haemoglobinuria.

Autoimmune haemolytic anaemia's

These are common in patients who require chronic blood transfusions or who have started transfusion regimes later on in life as in Thalassaemia Intermedia. The cause of these reactions is mainly underlying alloimmunization (newer antibodies against minor blood antigens). Treatment includes steroids, immunosuppressive drugs and intravenous immunoglobulins. But it is usually very difficult

to treat and repeated blood transfusions leads to massive iron loads. These reactions are also associated with a fall in Hb sometimes lower than the pre-blood transfusion level as well as jaundice and haemoglobinuria.

Delayed transfusion reactions

Usually 5-10 days after transfusions patients may present with anaemia, malaise and jaundice. These are because of the inability to detect alloantibodies at the time of transfusions. This can be prevented by the continuing search and screening for newer antibodies as well as re-crossmatching of the last administered units.

Transfusion related acute lung injury (TRALI) and graft vs. host disease (GVHD)

These reactions are more common in patients who may be receiving blood from close relatives especially parents of the recipient. The symptoms commonly seen are dyspnea, tachycardia, fever and hypotension. Management of this reaction includes oxygen, I/V steroids, diuretics and assisted ventilation.

Transmission of infectious agents with blood transfusions

- Viruses
  - Hepatitis B, C
  - HIV
- Bacteria
  - Gram +ve

- In addition to usual infections suppurative arthritis, abcesses in various body planes and perinephric abscess are common in our population.

- Gram –ve
  - Septicaemias are common, pushing the patients into heart failure by making an existing cardiomyopathy overt. It is important to realize that the mortality in these types of infections is extremely high and any sign of septicaemia should alert the attending doctor. Diarrhea and Acute Respiratory Tract Infections are common illnesses which may prove fatal in these children.

- Malaria
- Yersinia Entercolitica
- Creutzfeldt-Jakob Disease (a very rare disease)

Chapter 4:-

Iron Overload & Chelation Therapy

One of the most serious complications of thalassaemia is iron overload. This mainly occurs because of multiple transfusions, ineffective erythropoeisis and increased iron absorption from the GI tract in Thalassaemia Intermedia.

With the recommended transfusion regimen iron stores may increase by an equivalent of 116-232mg/kg/yr of iron. Thus without proper chelation regimen patients may rapidly develop iron overload.

Iron chelation is a slow process mainly because only a small amount of body iron is available at any one time for chelation. Attempts to speed up this process by either increasing the dose of chelators or rapid infusions, poses a very high risk of toxicity therefore to get rid of iron regular chelation is the only way out.

The most widely used and known iron chelator is desferrioxamine (Desferal® 500mg/vial). It has a very short plasma half life approx. 0.3hrs and is rapidly eliminated from urine and bile. Because of this fact it requires to be given as a continuous subcutaneous infusion slowly 5 nights / week.

Iron chelation should be started either after the 1st 10-20 transfusions, when the ferritin level rises above 1000, or age is above 2yrs of age. The current recommended method is a slow SC infusion over 8-12 hours of a 10% desferrioxamine solution using an infusion pump 5 nights/wk. The desferrioxamine infusion should be constituted with distilled water only, not NS, thus decreasing the incidence of local reactions. Purer the distilled water preparation, lesser will be the incidence of local reactions. The dose for children is 25-40mg/kg /D, for adults up to 50mg/kg/D. Because of the difficulty in deciding whether acute reactions are due to I/V desferrioxamine or blood, it is no longer recommended that desferrioxamine and blood be transfused together. Doses maybe adjusted according to the ferritin level using the therapeutic index.

$$\text{Therapeutic Index} = \frac{\left(\frac{\text{Actual dose received on each occasion X doses/wk}}{7}\right)}{\text{Ferritin (µg/l)}}$$

* The aim is to keep the therapeutic index < 0.025 at all times.

For example if a child is getting a dose of 50mg/kg and chelates herself 7 times a week and her ferritin level is 1500µg/l then that means that

$$\text{Therapeutic Index} = \frac{\left(\frac{50 \times 7}{7}\right)}{1500\ (\mu g/l)}$$

The therapeutic index is 0.033. this means that she may be getting too high a dose a better option for her would be for her to get a dose of 35mg/kg 7 days a week which gives a therapeutic index of 0.023 which is in the safer range (<0.025).

Vitamin C increases the iron availability in the serum for chelation. Recommendations are to start Vitamin C after 1 month of chelation at 50mg in < 10yrs and 100mg in > 10yrs as a single dose within the 1st 1 hour of the start of the infusion pump of every chelation. Make sure that the patient is not taking a vitamin syrup containing Vitamin C at the same time.

Monitoring compliance is an important aspect of the chelation regimen. One way of monitoring compliance is by using the compliance index

$$\text{Compliance Index*} = \frac{\text{No. of days of treatment per year}}{\text{No. of days for which treatment is prescribed}}$$

* Ideal Compliance Index would be = 1

Side effects of Desferrioxamine

Side effects of desferrioxamine are dose dependant, hence dose of desferrioxamine has to be adjusted according to iron overload. Side effects should be quickly recognized and treated to enhance compliance .

Local reactions

1. Itching, erythema, redness, swelling and mild to moderate discomfort can be due to:-
2. Hypertonic solution may be one of the reasons– 500 mg must be dissolved in at least 5ml of distilled water.
3. Impure distilled water – if so change the brand
4. Wrong diluent – Only distilled water should be used for s/c route
5. Intradermal infusion can result in painful swelling and ulceration

Local reaction if not controlled by above mentioned measures can be adequately controlled by adding 5-10 mg of hydrocortisone to the solution .

Severe allergy to desferrioxamine

Severe allergy to desferrioxamine is rare and can be controlled by de-sensitization . Allergy to latex can also give rise to reactions in which case the patient will have no problem to I/v desferrioxamine but s/c administration will give rise to severe painful local reactions hampering compliance but this does not mean that it is an allergy to desferrioxamine.

Dose-related complications

Hearing Problems

Hearing problems are common in younger children and related to high dose therapy. Children can develop tinnitus, deafness and high-frequency sensorineural loss. Yearly audiometry is recommended.

Visual Problems

These are also related to dose and comprise of night blindness, impaired color vision, impaired visual fields and decreased visual acuity. These effects are more common with concomitant phenothiazine treatment and diabetes.

Skeletal Problems

Rickets like changes in metaphysis, vertebrae especially reducing the sitting height.

Growth retardation

Common when chelation treatment is started earlier than three years at higher doses. It can be arrested by reducing the dose to less than 40mg/kg/day in older children.

Rare complications seen in iron chelation are renal impairment and interstitial pneumonitis.

Rapid infusions can lead to shock, due to massive release of

histamine leading to flushing, vomiting and sweating or even collapse.

Continuous I/V infusions maybe considered in high risk cases such as those who have

- Ferritin levels > 2500ug/l for many months
- Significant cardiac dysrhythmias
- Evidence of decreasing ventricular function.
- Patients with active hepatitis C
- Patients planning bone marrow transplantation
- Persistent poor compliance or inability to use subcutaneous infusions

The recommended doses for continuous I/V infusions is 50mg/kg/24hrs. Distilled water or saline can be used but the amount of fluid is to be adjusted according to age, Hb level and cardiac status. Total amount of fluid to be given is reduced in cardiac disease due to the threat of cardiac overload.

Monitoring Iron overload

Serum ferritin is a good and practical method to monitor iron overload but one has to keep in mind that it is also an acute-phase reactant. It should not be done during acute infections, hepatitis or vitamin C deficiency. Ferritin level will falsely be raised in hepatitis, acute infections and falsely decreased in Vitamin C deficiency. It should also be kept in mind that Ferritin tests should be carried out

from the same lab so that the results may be consistent and standardized. Ferritin levels should be monitored every 3 - 6 months. Ferritin levels in isolation maybe a poor indicator of iron overload but is most widely used. It has a better correlation with liver iron compared to cardiac iron overload in thalassaemia major. Accurate iron estimations may be done by the LIC (liver iron concentration) done on liver biopsies or for the heart by an MRI. Both methods need to be used in special cases but in our country they may not be used due to the first method being invasive, and the second method being expensive.

Oral Chelators

Deferiprone (Ferriprox®)

Deferiprone is an orally active iron chelator which is currently undergoing extensive clinical use. Although the most widely used drug is still desferrioxamine, deferiprone is a favoured oral therapy which may be used alone or in conjunction with desferrioxamine. It is seen to be more effective in removing iron from the heart when compared to desferrioxamine. It is also a life saver for those patients allergic to desferrioxamine. The daily dose of deferiprone which has been evaluated is 75mg/kg in 3 equally divided doses.

Important side effects to be considered are neutropenia, agranulocytosis, arthropathies, transient rise in ALT nausea and vomiting. Zinc deficiency and possible teratogenicity must also be considered. Thus while under treatment with deferiprone patients

should get weekly CBC's in addition to 3 monthly LFT's, RFT's and thyroid function tests.

In our country highly overloaded patients should be given both drugs simultaneously in sequential or concomitant therapy, with a close watch for side effects because combination therapy may cause a decrease in Zn^{2+}, Cu^{2+} and Ca^{2+} levels by aggressive chelation.

ICL670, Deferesirox (Exjade®)

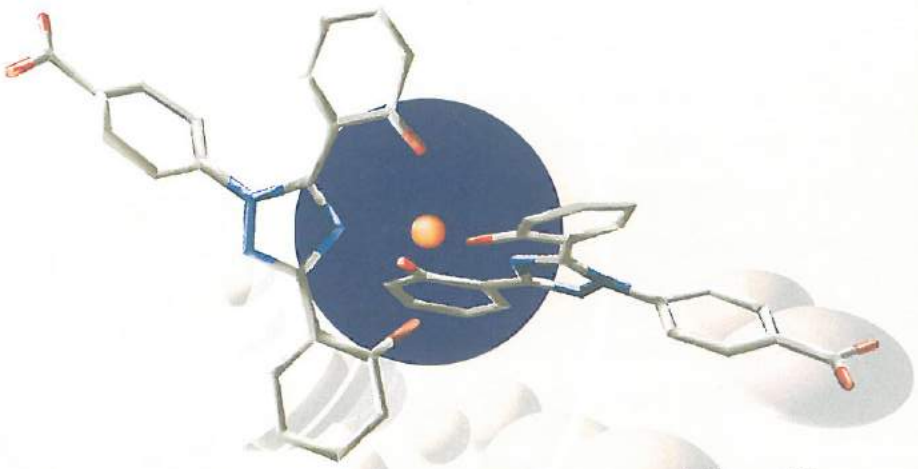


Figure 4.1:- Schematic diagram of ICL670 with an iron atom in the center.

ICL670 is another orally active chelating agent developed for the treatment of chronic iron overload. It represents a new class of iron chelators with a high specificity for iron and efficient and selective mobilization of tissue iron. It is more effective than deferiprone. It has been shown to be as effective as desferrioxamine with no side effects. Trials are currently underway and so far they

show good efficacy with no major safety concerns. There has been reported some transient nausea and vomiting but did not require cessation of treatment. It is available as a dispersible tablet, once a day on an empty stomach. Dosage is 10 - 20mg/kg/day.

Combined Chelation Therapy

With newer forms of iron chelators being researched, there is a hope for greater flexibility in the treatment of chronic iron overload. Combination therapy may provide the following benefits:-

- Access to different tissue iron pools
- Prevention of non-transferrin bound iron (NTBI) accumulation
- Increased efficacy
- Decreased toxicity
- Better compliance
- Improved quality of life

The combinations of desferrioxamine and deferiprone have showed a synergistic effect resulting in increased efficacy. Different combinations have been used but currently we recommend using desferrioxamine 4 days/wk and deferiprone 7 days/wk in patients of high iron overload. Both drugs chelate different tissue pools, liver and cardiac.

Chapter 5:-

Thalassaemia Intermedia

These are patients who present as a milder disease with no symptoms till adult age or at 2 – 6 years with retarded growth and development, typical facies and an emerging need for regular transfusions in the second decade of life. Some cases are diagnosed much later due to splenomegaly and signs of hypersplenism.

Diagnosis

A child presenting with moderate anaemia at more than 2 yrs of age with moderate to severe hepatosplenomegaly is a candidate for thalassaemia intermedia

Laboratory investigations

- Hb 8 – 10gm/dl reducing to lower levels in acute infections
- Reticulocytosis
- HbF between 10-50%
- $HbA_2 > 4\%$

Treatment

There are no clear cut guidelines for management of these patients, treatment strategy must be tailored for every single patient in a specialized center with strict clinical follow-up as well as considering local facilities for treatment of iron overload due to regular blood transfusions. Raising fetal Hb with hydroxyurea

25mg/kg/day once a day (can be used for some years in selected cases, by raising fetal Hb and delaying regular blood transfusions).

Transfusion-dependent Thalassaemia Intermedia

(Management is similar to thalassaemia major once the patients become transfusion dependent for a considerable length of time.) Patients who are more than 10yrs of age who have never or occasionally been transfused, may be considered candidates for splenectomies and can avoid regular blood transfusion scheme for a few years. In our country some patients present at more than 20yrs of age and become transfusion independent after splenectomy, though splenectomies are difficult due to massive sizes and multiple spleneculi in these cases.

As the age progresses complications like leg ulcers, thrombophilia, extramedullary haematopoiesis and severe osteoporosis (being the most commonest in our country) demands a regular blood transfusion therapy regimen. In any patient after 3 years of age the risk of red cell alloimmunization increases. Thus the 1st 3 – 5 transfusions should be covered with steroids to minimise reactions.

Transfusion-independent Thalassaemia Intermedia

These patients require 3 – 6 month follow-up with attention to clinical well being and the size of the spleen. In addition anthropometry as recommended for thalassaemia major, monitoring exercise tolerance, complete blood counts, serum ferritin levels and monitoring for complications of iron overload are mandatory.

Indications for transfusions in Thalassaemia Intermedia

- Growth failure
- Thalassaemics facies
- Osteoporosis / pathological fractures
- Cardiac complications
- Hypersplenism

Once regular transfusions are initiated, they must be administered as in thalassaemia major.

Iron Chelation in Thalassaemia Intermedia

Iron overload in thalassaemia intermedia patients is because of ineffective erythropoeisis, haemolysis and increased iron absorption. However the co-relation between serum ferritin and tissue iron is more unpredictable in thalassaemia intermedia patients. Transferrin saturation may be more reliable than ferritin in these cases. For these reasons initiation of iron Chelation should be considered as soon as the serum ferritin is moderately increased (>1000ng/ml). Desferrioxamine can be given subcutaneously 2 – 3 days a week with monitoring. Dosage is as in thalassaemia major. Thalassaemia Intermedia patients should be advised to avoid iron rich foods, and drink black tea with meals to reduce the absorption of non-heme iron from gut.

Splenectomies in Thalassaemia Intermedia

The principal indication for splenectomy is hypersplenism. Since gallstones are more common in thalassaemia intermedia, the

- Heparin especially in surgical operations or documented thrombosis

4. *Extramedullary Erythropoeitic Masses*

Management can be done via

- Transfusion therapy
- Radiotherapy
- Hydroxyurea

gallbladder must be explored during splenectomy along with macroscopic biopsy of the liver. If facility is available concomitant cholecystectomy should be performed. Thrombophilia is much more common in splenectomized patients but very few cases require anti-platlet drugs.

Complications

1. *Osteoporosis* is a much more severe problem in non-transfused thalassaemia intermedia than thalassaemia major due to ineffective haematopoiesis and progressive marrow expansion. Almost all patients with thalassaemia intermedia have a spinal bone mineral density at or near the fracture threshold. Osteopenic patients should be encouraged to

- Perform active exercises
- Increased dietary intake of calcium
- Avoid smoking
- Oral calcium and Vitamin D
- Bisphosphonates
- Sex steroids wherever needed

2. *Leg ulcers* can be treated with

- Regular transfusion if recurrent/persistent ulcers.
- Raise legs for 1-2 hours per day
- Raise bed end 10cm during sleep
- Hydroxyurea or erythropoietin

3. *Thrombophilia*

- Platelet anti-aggregates

Chapter 6:-

Splenectomy

Splenectomy is usually required in low transfusion thalassaemia major patients and all cases of transfusion-independent thalassaemia intermedia in the second or third decade of life.

Common indications for splenectomy are

1. Growth failure
2. Thalassaemic Facies
3. Mechanical discomfort of a large spleen
4. Hypersplenism

The earliest sign of hypersplenism is an increased annual consumption of blood greater than 220ml/kg/yr packed red cell volume. Late signs of hypersplenism are leukopenia and thrombocytopenia.

Thalassaemia intermedia patients who have recently become transfusion dependent may benefit tremendously from splenectomies. After the splenectomy they have a tendency to outgrow the need for regular blood transfusion schemes.

All cases of low blood transfusion schemes should be shifted to high transfusion schemes prior to surgery as it reduces the size of the spleen and demand for blood. This may delay the surgery as well as result in a less hazardous per & post-operative course. In addition prior to surgery the patient's hepatic function & cardiac status should be evaluated thoroughly including an echocardiogram.

All children should be immunized 2 – 4 weeks prior to surgery with three vaccines

- Pneumoccocal Vaccine
- Meninngococcal Vaccine
- Haemophilus Influenza type B

Till such time that the oral form of penicillin becomes available in the country, erythromycin should be used 125mg BID under 10yrs or 250mg BID for above 10yrs of age. Long acting penicillin is not recommended for post-splenectomy patients. Chemoprophylaxis should be continued for 3 – 5 years post-splenectomy. Post-operative thrombocytosis (>10,00,000/mm3) should be treated with aspirin 80mg/kg/day. Post-splenectomy sepsis should have a high index of suspicion and following steps should be followed

1. Evaluating the patient, including a complete physical examination
2. Obtaining blood and other cultures as indicated

Beginning treatment with an antimicrobial regimen effective against most encapsulated gram +ve and gram –ve organisms.

Chapter 7:-

Cardiac Complications in Thalassaemia

Cardiac complications are the leading cause of morbidity and mortality in thalassaemics. In four different 10yr follow-up studies 95% of all deaths in thalassaemia occurred due to cardiomyopathy. In the absence of effective iron chelation patients rapidly develop iron-induced myocardial damage. Symptoms of cardiac failure, arrhythmias, congestive heart failure and sudden death may occur.

There is a poor correlation of serum ferritin with myocardial iron content, fibrosis and cardiac functional impairment. Liver iron and ferritin levels do not co-relate with the cardiac iron content therefore the most useful parameter is not to let the serum ferritin increase above 2500ng/ml in the patient's lifetime.

The three most important presentations of iron overload causing damage to the myocardium are:-

1. Pericarditis
2. Cardiac arrhythmias
3. Congestive heart failure secondary to myocardial siderosis

Clinical Manifestations

Common symptoms include palpitations, syncope, shortness of breath, epigastric pain, decreased exercise tolerance and peripheral oedema. Symptoms of heart disease usually indicate advanced disease and a poor prognosis. Once the ventricles have enlarged, cardiac arrhythmias are common, generally atrial in origin but may also present as ventricular tachycardia.

Important feature of heart dysfunction in thalassaemia is that if detected early it is reversible with appropriate iron chelation therapy. Irreversible damage can occur if the serum ferritin is > 2500ng/dl for a considerable time.

Cardiac Examinations

- Medical history
- Physical examination
- 12-lead ECG
- Chest X-ray
- Echocardiogram
- MRI T_2 weighted imaging where ever possible

The ECG is usually abnormal, but the changes are non-specific. These include increased right ventricular voltage, changes in T-waves and ST segments. Occasionally, P-waves are also affected, indicating bi-atrial enlargement. Bundle branch blocks are also seen. Arrythmias may be picked up easily by ECG.

Echocardiography is a valuable tool to assess cardiac function. Other than the usual measurements of heart dimensions, ejection fraction and intracardiac pressures, Doppler measurements of intra-cardiac flow is very helpful. 24-hour holter monitoring is the standard method for detecting and monitoring arrhythmias.

Overall Management strategy

- Maintenance of pre-transfusion Hb level 10-12 g/dl once cardiac disease sets in.
- Regular iron chelation, continuous I/V infusion regimens of 50mg/kg/day over 24hrs.
- Surveillance of other causes of cardiomyopathy e.g. hypothyroidism, hypoparathyroidism, vitamin C deficiency, etc...

Despite effective regular chelation some patients may still develop cardiac complications, commonest being cardiac failure, less common complications are as below

Pericarditis

This is usually an acute illness which is self-limiting lasting usually 4 – 5 weeks. It occurs in more than ½ of all thalassaemics in the second decade of life. Management is usually supportive with salicylates and steroids.

Dilated Cardiomyopathy

Usually includes dilation of one or both ventricles. It is usually restrictive in nature. It may present with a sudden onset of an arrhythmia like SVT or VT, fulminant pulmonary oedema or a CVA (cerebrovascular accident).

Cardiac Arrhythmias

Chronic iron overload may present with many different forms of arrhythmias. The key to treating the arrhythmias is to treat the underlying cause, in this case iron overload.

Physical Activity

Only patients who have severe cardiac impairment and are symptomatic require restriction of physical activity. Those having normal or moderate cardiac dysfunction do not require any restriction.

Medications

Diuretics

These are usually the first line of treatment. The role of diuretics is to provide symptomatic treatment to those patients with pulmonary congestion or right heart failure. Loop diuretics produce a reduction in intravascular volume thus resulting in a significant decrease in preload. They should be used with caution as they may

cause hypotension and a sudden fall in cardiac output. Constant intravenous infusions of loop diuretics maybe required in severe congestive heart failure. In these cases urine output must be religiously monitored to prevent excessive diuresis. The use of spironolactone in conjunction with loop diuretics has shown good results. It reduces potassium depletion and counteracts hyperaldosteronism

Angiotensin Converting Enzyme inhibitors

ACE Inhibitors have been seen to reduce mortality in non-thalassaemic patients with established cardiomyopathy. Thus using this finding ACE Inhibitors are being used with promising results. Precautions that need to be taken while using them are

- Patients should be well hydrated
- Start at low doses
- Dose should be increased to the maximum level only limited by hypotension
- Patients who complain of chronic cough may be treated with an angiotensin II receptor antagonist e.g. losartan.

Digoxin

Digoxin should not be used in early stages of cardiomyopathy. It maybe used as an ionotropic agent or to maintain reasonable ventricular rates in established atrial fibrillation. It is contraindicated in complete heart block or cardiac tamponade.

Anti-arrhythmic agents

The decision to treat arrhythmias in thalassemics must be carefully considered keeping in mind that iron toxicity is the main cause. Intensive treatment has demonstrated a reduction in arrhythmias. Most arrhythmias are supraventricular.

β-blocking agents

These agents can be used to control many arrhythmias. Dosages should be low at first with gradual upward titration. One should use it cautiously because of its negative ionotropic effect.

Amiodarone

This drug has a wide spectrum of effectiveness against supraventricular and ventricular arrhythmias. Intravenous preparations are available for acute conditions It is available as a 3 ml ampule containing 150mg of amiodarone. The tablet form is available as 200mg of Amiodarone HCl. The dose of amiodarone is a loading dose of 10-15mg/kg/day in 1-2 divided doses for 4 – 14 days followed by a dosage reduced to 5mg/kg/day given once daily. This dose may be further reduced, if there are no further arrythmias, to 2.5mg/kg/day for several weeks. An important side effect to be considered in thalassemics is thyroid function disturbance. Thus because of its side effects it is recommended that routine TFT's, eye examination by an ophthalmologist and LFT's be done.

Chapter 8:-

Endocrine complications

Endocrine complications are common after the 1st decade of life in poorly chelated patients, though delayed sexual maturation and impaired fertility is often present in well chelated children.

	International Data	Pakistan's Data
H-P Dysfunction	90-95%	90%[3]
Hypothyroidism	3-5%	27%[1]
Hypoparathyroidism	5-10%	37%[2]
Diabetes	30-40%	-
Osteopenia & Osteoporosis	70-80%	85 – 90%[4]

Table 8.1:- Comparison of incidence of different endocrine abnormalities seen in thalassaemics in Pakistan to the rest of the world.

In Developing countries the main causes are chronic anaemia, iron overload and late onset of chelation therapy.

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1 Naveed S. Prevalence of Hypothyroidism in multitransfused thalassaemic children [Dissertation]. Lahore: Sir Ganga Ram Hospital

2 Chaudry S. Prevalence of Hypoparathyroidism in multitransfused thalassaemic children [Dissertation] Lahore: Sir Ganga Ram Hospital

3 Hassan S. Prevalance of Hypogonadogonadism and Delayed Puberty in Thalassaemia [Dissertation] Lahore; Sir Ganga Ram Hospital

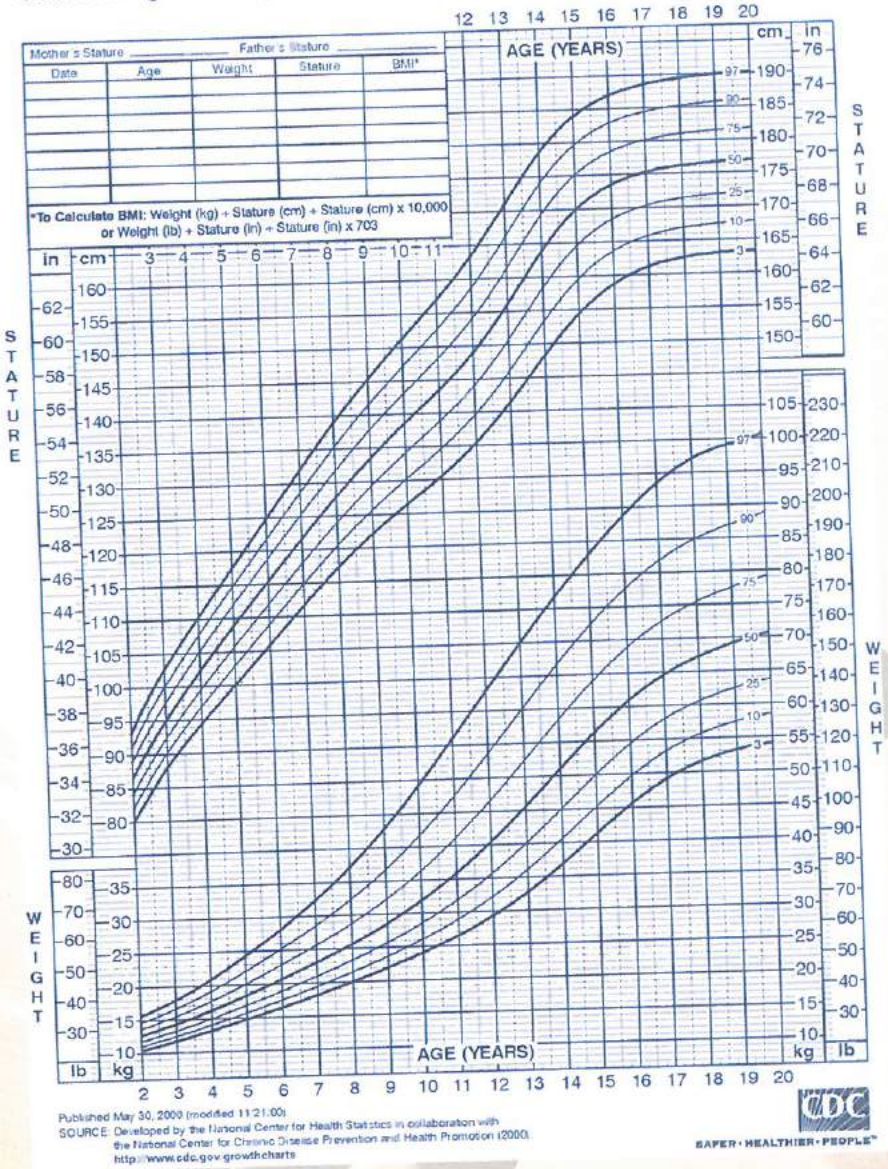
4 Statistics compiled from 850 pateints followed at the Thalassaemia Society of Pakistan, Sir Ganga Ram Hospital, Lahore

THALASSAEMIA FEDERATION PAKISTAN

2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Published May 30, 2000 (modified 11/21/00)
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
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THALASSAEMIA FEDERATION PAKISTAN

2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

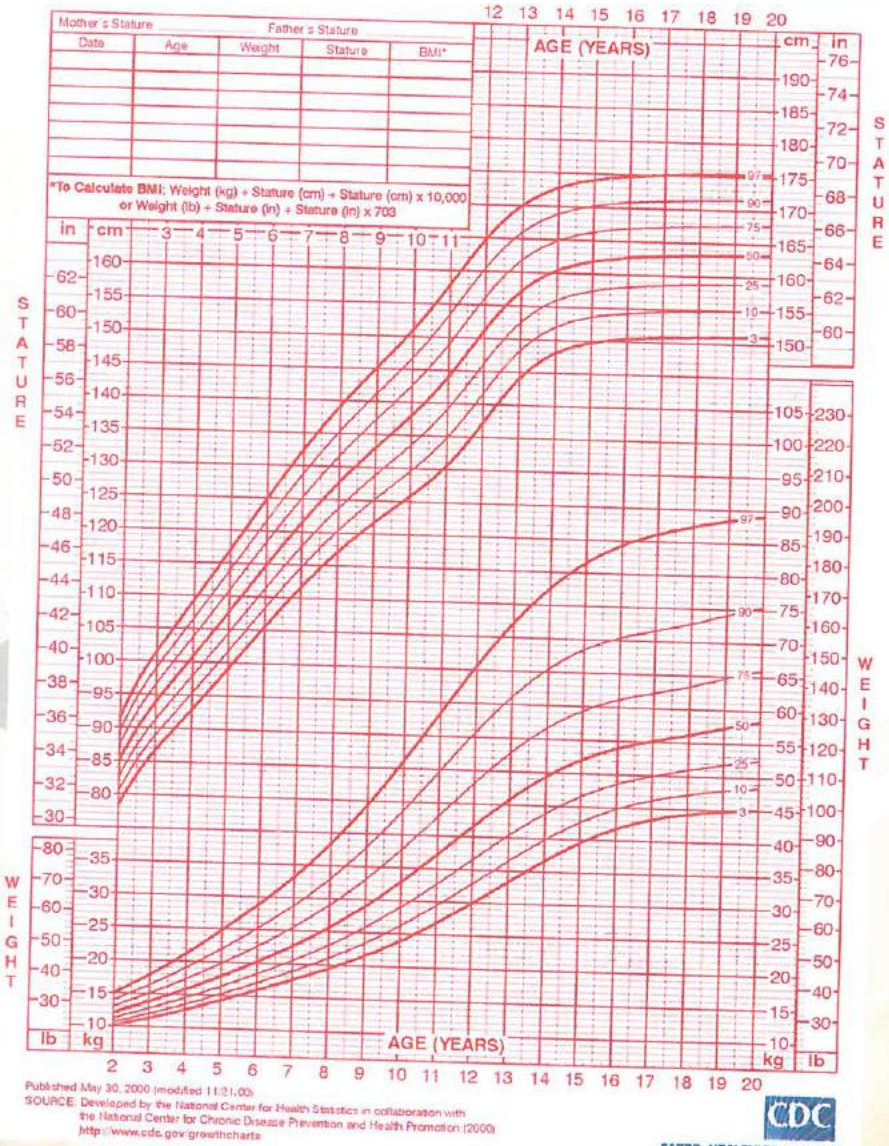
NAME _____

RECORD # _____

Mother's Stature _____ Father's Stature _____

Date	Age	Weight	Stature	BMI*

*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



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SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000)
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Investigations

- Bone age
- T3, T4, TSH
- Sex Hormones
- Glucose tolerance curve
- Calcium, Phosphorus and $AlkPo_4$
- Zinc
- Growth hormone(GH) – GH studies are difficult in our country and 99% of our population cannot afford treatment with growth hormone. Studies should only be performed after discussing with parents the cost of treatment.

Chronic Infections like urinary tract infections, malabsorption syndromes like celiac disease and lactose intolerance should also be considered in growth failure as these are common treatable causes in our setup.

Treatment

One should start treatment of growth retardation whenever diagnosed. Treatment in our setup should initially concentrate on treating chronic anemia, osteoporosis, thyroid replacement and sex steroid replacement.

Growth Retardation

Factors responsible in affecting the growth rate are as follows

1. Genetic factors
2. Chronic Anaemia
3. Hypogonadism
4. Hypothyroidism
5. Growth hormone deficiency or resistance
6. Chelation toxicity
7. Hypersplenism
8. Folate deficiency
9. Chronic liver disease
10. Zinc deficiency
11. Psychosocial stress

Diagnosis and Investigations

Growth curves and tanner staging should be done to establish growth velocity and signs of common endocrine deficiencies. Growth charts are available on the following pages for reference. In order to decide whether a child is growth retarded or not one must plot the predicted height of the child using the following formulas

$$\text{For males predicted height} = \frac{\text{Fathers height + mothers height}}{2} + 13 \text{ cm (2 SD)}$$

$$\text{For females predicted height} = \frac{\text{Fathers height + mothers height}}{2} - 13 \text{ cm (2 SD)}$$

If a child is < 2 SD (standard deviations) below the predicted height, then the child should be considered to be growth retarded.

e.g. Height = 140cm, predicted height at 14yrs of age = 162cm = 50%ile and 147cm = 3%ile.

Then 2 SD is 162 – 147 = 15, thus 1 SD = 15/2 = 7.5

Difference in height of child is 162 – 140 = 22, 22 / 7.5 = 2.9 SD

Desferrioxamine toxicity may cause a short trunk resulting in a smaller upper segment i.e. reduced sitting height. It may also cause pseudo-rickets (rickets like lesions of the extremities) due to metaphyseal flaring.

Treatment with growth hormone should be started when:-

- growth has been retarded / arrested at > 10yrs as per growth charts
- Chronological age – bone age > 2 yrs and epiphysis are not fused

Delayed puberty and hypogonadism

Delayed puberty is labelled in girls at 13 years and boys at 14yrs if there is a complete lack of pubertal development i.e. Tanner stage 1. Puberty failure in thalassaemics falls in the classification of hypogonadotrophic hypogonadism. Hypogonadism is defined in boys if the testicular size is less than 4 ml and is measured by orchidometry (figure below) In girls hypogonadism is defined by the absence of breast development at 16 yrs of age.

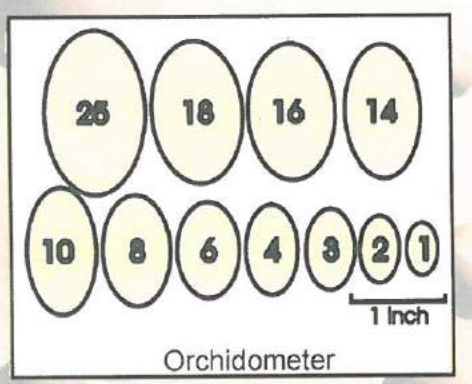


Figure 8.1:- Orchidometer used in determining the testicular size

Tanner Stage	Mean	STD
1	4.7 ±	2.76
2	6.4 ±	3.16
3	14.5 ±	6.54
4	19.8 ±	6.17
5	28.3 ±	8.52

Table 8.2:- Variaton of testicular volume with tanner stage

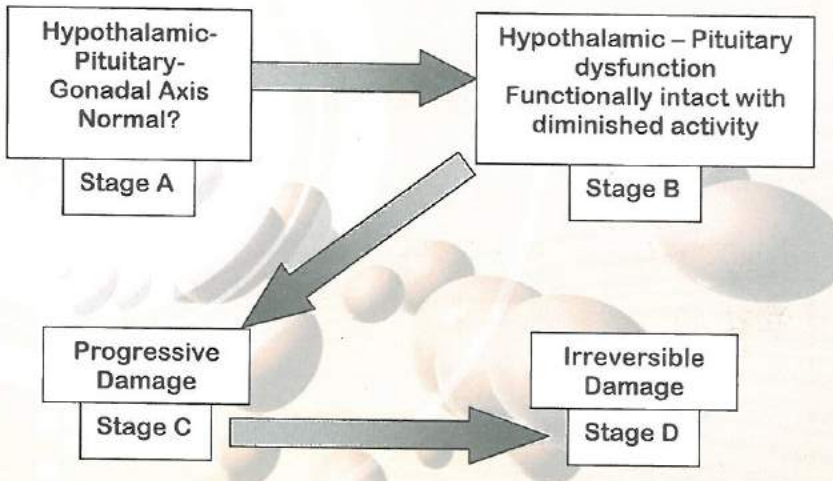


Figure 8.2:- Stages of Hypothalamic-Pituitary-Gonadal Dysfunction.

Important to remember that H – P dysfunction is treatable in stage B & C once stage D is reached there is irreversible damage.

Arrested Puberty

Lack of pubertal growth over a year or longer is called arrested puberty. Tanner staging (sexual maturity rating (SMR)) should be done 3 monthly. Below is the Tanner / SMR chart which may be used to stage the pubertal development of children.

Females					
Stage	**1**	**2**	**3**	**4**	**5**
Breast	Pre-pubertal	Budding	Small Adult Breast	Areola and papilla form secondary mound	Adult Breast
Pubic Hair	Pre-pubertal	Sparse growth of Hair	Darker, coarser, beginning to curl and spread over the symphysis	Hair has adult characteristics but not adult distribution	Adult

Table 8.3:- Female Tanner Staging

Males					
Stage	**1**	**2**	**3**	**4**	**5**
Testis and Scrotum	Pre-pubertal	Enlargement of testes and scrotal reddening	Increasing length more than width of penis, further scrotal enlargement	Further penile enlargement, darkening of scrotal skin	Adult
Pubic Hair	Pre-pubertal	Sparse growth of Hair	Darker, coarser, beginning to curl and spread over the symphysis	Hair has adult characteristics but not adult distribution	Adult

Table 8.4:- Male Tanner Staging

Investigation

- Growth parameters, height, weight, height velocity
- Bone age – AP X–ray of the left hand with abducted fingers is useful in most cases for hypogonadism.
- TSH, T4
- Sex steroids e.g. LH, FSH and testosterone levels.
- GnRH stimulation test for LH, FSH. This is considered to be very expensive therefore in our setup LH, FSH compared with pelvic USG in females for uterine dimensions and ovarian size is

helpful. In males levels of testosterone compared with testicular size is helpful.

- Pelvic ultrasound for ovaries and uterus in females is a useful modality
- Growth hormone stimulation if required
- IGF-I (this is usually not feasible in our setup)

Monitoring

1. Serial monitoring of growth and puberty as early as 10 years.
2. Sitting and standing height (monthly) throughout childhood and yearly till adulthood.
3. Bone age (x-ray of Left hand & wrist) and monitor epiphyseal fusion (left knee) biannually after the age of 10 years
4. Standing x-ray spine to exclude microfractures (annually)
5. Pubertal staging with testicular size in males (Tanner / SMR) at 3 month intervals

Treatment

For delayed puberty in males initially IM testosterone proprionate (Testoviron depot) 25mg/m2 is given monthly for 6 months. Testosterone proprionate 100mg IM can be given monthly as well. In patients with hypogonadotrophic hypogonadism, testosterone proprionate at 50mg/m2 monthly can be used until growth rate wanes. The final virilizing dose of 50 – 75mg of testosterone proprionate IM can also be given every 7 – 10 days.

For girls with delayed puberty, Premarin (conjugate ester) 0.3 – 0.6mg/day; ethinyl estradiol (stilbesterol) 2.5 – 5µg daily is recommended for six months. During treatment monitor bone age and growth yearly. If puberty does not occur, then increase the dose of Premarin (conjugate ester) 0.6 – 01.2mg/day; ethinyl estradiol (stilbesterol) 5 – 10µg daily. Do monthly pelvic ultrasounds to monitor uterine size. When the uterine wall size is greater than 45mm then add progesterone to induce menarche. If uterine bleeding does not occur then replacement hormone treatment with estrogen-progesterone combination should be given.

Hypothyroidism

Investigations for hypothyroidism should be preformed annually after 10yrs of age routinely and earlier if suspected. Bone age, Free T4, T3 and TSH. Majority of patients have primary thyroid failure, secondary is rare. TRH can be done in some cases.

Treatment of Hypothyroidism

Patients with normal biochemical tests but marginally raised TSH should be observed along with intensive chelation therapy. Once the thyroid function shows low values, with elevated TSH and an exaggerated TSH response to TRH patients should be treated with L-thyroxine (3-8 µg/kg/day single dose in the morning). Optimal dosages may vary in individuals and adjustment of dose may require

frequent monitoring. Monitoring is done with 6 monthly thyroid functions and yearly bone age along with monitoring of growth.

Hypoparathyroidism

Hypocalcemia due to hypoparathyroidism is a complication recognised at a very early age in our population as compared to the west. This is not surprising at all as hypocalcemia and rickets is a common finding in Pakistani children due to widespread protein energy malnutrition and expensive dairy products. Younger patients usually present with tetany, seizures or cardiac failure.

Investigations

Investigations should begin from 10yrs or when the first symptoms appear, serum calcium, serum phosphate, and alkaline phosphatase. In cases of low serum calcium and high phosphate, Parathormone should be measured.

Treatment

In acute cases of tetany and fits, intravenous administration of calcium gluconate 10%, 5 – 10ml at a rate of 0.5 - 1ml/min is slowly given intravenously to control the seizures with cardiac monitoring. Calcitriol 0.25 - 1mg twice daily can be given weekly blood tests are required and maintenance dosage varies between 0.01–0.10ug/kg/24hrs to a maximum of 1 – 2 micrograms/24hrs. Once normocalcaemia is achieved Vitamin D2 can be given in a dose of 1.25 – 2.50mg once a day. Monitoring is done by quarterly calcium,

phosphorus levels and 24hr urinary phosphorus levels (urinary phosphorus levels are rarely available in our setup). In patients with high phosphate levels, phosphate binders except aluminium can be given. Adequate intake of calcium should be ensured 800mg of elemental calcium daily can be given in adolescents and adults. Foods with high phosphate content e.g. eggs, cheese, and milk should be reduced. If hypercalcaemia develops therapy should be discontinued and restarted with lower dosage.

Impaired carbohydrate metabolism

Pathogenesis resembles type II diabetes, diagnosis is done according to WHO criteria of impaired glucose tolerance and diabetes mellitus

- A fasting venous plasma glucose concentration of 8 mmol/l (144mg/dl) or greater is diagnostic of diabetes.
- Two hour venous plasma glucose greater than 11 mmol/l (198mg/dl) is indicative of diabetes
- Two hour venous plasma glucose below 11 mmol/l (198mg/dl) but greater than 8 mmol/l (144mg/dl) is diagnostic of impaired glucose tolerance.

Oral glucose tolerance test should be performed annually from pubertal age

Treatment

Impaired glucose tolerance may be improved by strict diabetic diet and intensive iron chelation therapy. Metformin is helpful in early stages of diabetes in thalassaemics.

In symptomatic patients insulin treatment is required for life as endocrine glands once damaged do not recover.

Monitoring Diabetes and its complications

- Blood glucose, urine glucose
- Ketones where ever needed and available
- Fructosamine estimation or HbA_1C (glycosylated Hb) according to availability.

After a few years of established diabetes the following tests should be done for complications

- Renal function tests
- Serum lipids
- Urinary protein
- Opthalmoscopic examination for retinopathy

Chapter 9:-

Osteopenia & Osteoporosis

The complication has been recognized as a metabolic disorder called "Thalassaemic Bone Disease", present in 80 – 90% of patients. This term had to be coined because osteoporosis is a very severe problem in thalassaemia major & intermedia patients with poorly understood pathogenesis and very difficult to treat.

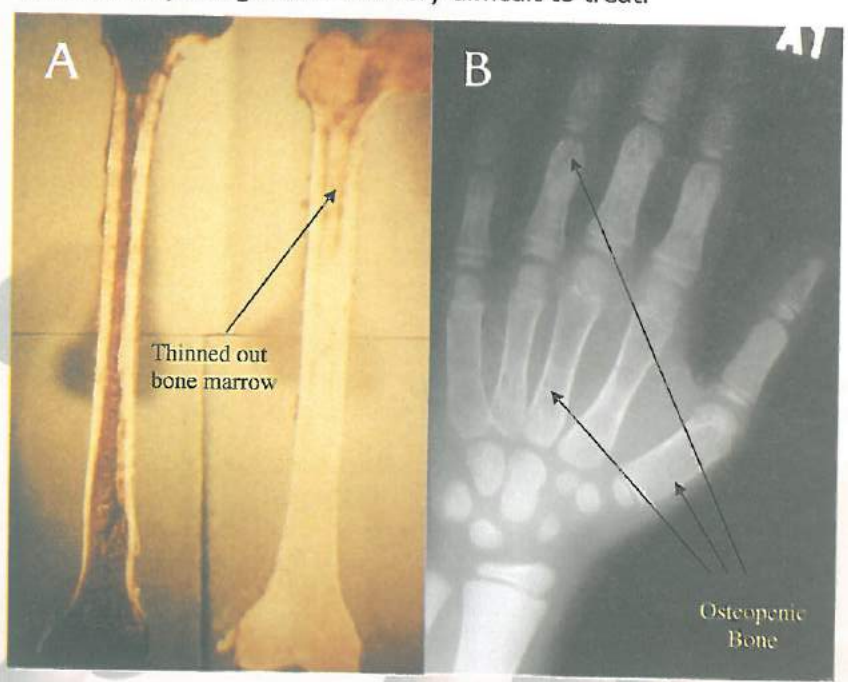


Figure 9.1:- **(A)** Shows Thalassaemic Bone Disease in an autopsy specimen, **(B)** Shows Osteopenic bone, in an X-ray of the left hand.

According to WHO (1994) criteria osteoporosis is strictly defined as

- a T-score on bone density tests (DEXAscan) of below -2.5 SD (standard deviations) below the young normal mean (T-score)
- a Z-score of less than 2.5 SD in relation to a patients age
- A milder form characterised as a T-score of between -1.5 to -2.5 below the young normal mean is called osteopenia.

Dexascans are available only in the major cities for our patients.

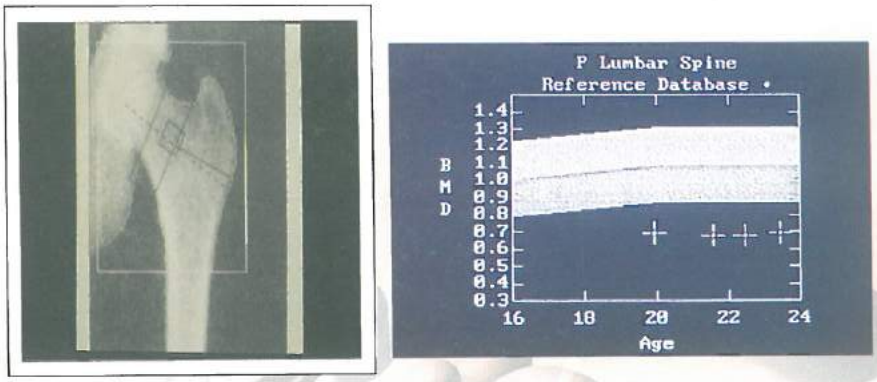


Figure 9.2:- **(A)** Bone Density measurement of the right hip on X-ray, the inner square indicates the area where the bone density is measured. **(B)** Bone density measurement of the lumbar spine on a normogram, notice that the four points marked by + are below the acceptable normal.

Contributing factors to osteoporosis are

- Hypogonadotrophic hypogonadism
- Low levels of Ca2+ Vit D and parathormone
- Hypothyroidism

- Chelation
- Anaemia
- Genetic Factors (three candidate genes for osteoporosis are colia-1, VDR, ERG.)

Factors affecting non-thalassaemic patients like alcohol, diet, smoking and sedentary lifestyles can also contribute to the severity of osteoporosis.

Recommended Investigations

- Endocrine
  - FSH, LH, T3, T4, TSH
- Bone Profile
  - Calcium, phosphorus, 25(OH)Vit D, Parathormone
- 24hr Urinary Calcium
- LFT's
- Spinal X-ray A/P and lateral
- DEXA spine-hip and radius-ulna annually

Treatment

It is of utmost importance to prevent and treat osteoporosis since children may develop recurrent pathological fractures and may become severely debilitated. All patients should be given a calcium rich diet and vitamin D, oral calcium supplementation should be carefully given due to an increased risk of renal stones in these patients. Regular exercise is a must. Smoking should be discouraged.

All patients should be treated for hypogonadism for two years before going to Bisphosphonates. Available bisphosphonates in our country include Clodronate (Bonefos 400mg capsules), Risedronate (Actonel 5mg tablets), Alendronate (Fosamax 10mg tablets). These bisphosphonates should be used only for 2 – 4 years due to its possible toxicity. Pamidronate 1mg/kg (Aredia) a third generation bisphosphonate can be used monthly for 6 years.

Chapter 10:-

Bone Marrow Transplantation

This is the only curable treatment for thalassaemia present at the moment and has become available in the country. It should be offered to all HLA identical siblings who are 100% matched, but assessment according to Lucarelli's classification is important. Class I patients should be offered the treatment and at present class II & III patients should be very carefully counselled. High morbidity and mortality due to inappropriate selection of cases will undermine the importance of this emerging treatment. Three parameters are used for classifying

- Inadequate chelation therapy
- Presence of liver fibrosis
- Hepatomegaly

	Class I	Class II & III
Inadequate chelation therapy	Regular	Irregular
Presence of liver fibrosis	Absent	Present
Hepatomegaly	Absent	Present

Table 10.1:- Lucarelli's Classification for Bone Marrow Transplant candidates

Class I patients have 97% chances of long term survival, disease-free survival of >10 years in 100% cases with a recurrence rate of disease of 8% and a 3% mortality. Class III patients have 30% mortality, 10 times the mortality of Class I hence parents and patients have to be carefully counselled.

The rate of recurrence of disease is greater in younger children whereas older patients receiving bone marrow transplants have increased mortality rates. The steps involved in bone marrow transplantation include the following:-

1. Pre-transplant conditioning regimens
2. Bone marrow is harvested from HLA identical donors and infused.
3. Transplantation is then followed by cyclosporine & steroids therapy for one year to prevent GVHD (Graft vs. Host Disease).

The post-transplant weeks can have bacterial, viral and fungal infections because of the immunomodulatory medications. This can be prevented by drugs, immunoglobulins, and G-CSF. Strict isolation in uncomplicated cases can be up to 2 weeks, but care is to be taken up to one year in order to avoid contacting infections. Post transplantation patients may still need to eliminate their excess iron load. This may be done by either phlebotomy (5cc/kg in one sitting) or by desferrioxamine

Post-transplant Complications

- Non-infective complications
  - Acute & Chronic GvHD
  - Graft Rejection
  - VOD Liver
  - Hypertension
  - Generalized fits
  - Haemorrhagic cystitis
  - Cardiac Tamponade
- Infective complications
  - Bacterial sepsis
  - CMV infections
  - Fungal infections
  - Tuberculosis
- Endocrine abnormalities
  - Hypothyroidism
  - Pancreatic Insufficiency
  - Gonadal Hormone deficiencies
  - Growth retardation
- Drug related complications (e.g. cyclosporine)
  - Hirsuitism
  - Hypertension

Recent specific conditioning regimes have improved the survival. The patients should be counselled to have 3 – 4 months time at their hand for complete treatment, they should also be informed about the chances of sterility due to treatment. Total cost of the treatment at present is 12 – 15 lakhs.

Chapter 11:-

Genetic Counselling of Thalassaemia

In Pakistan counselling if done at all is mostly done by the physician dealing with the patient. Doctors in our setting are in a habit of making decisions for their patients. Most of the times patients and their families are given very little or no information regarding the disease. It is important for the patients and their families to know about the disease, its prognosis, available treatment regimes and the availability of preventive facilities. The importance of talking to patients as an integral part of the management of patients and their families, particularly in inherited disorders like Thalassaemia, cannot be stressed enough.

Currently majority of the patients do not get adequate treatment. The current socio economic condition of the country reveals that Pakistan, as a country may not be able to adequately treat all of its Thalassaemics. Therefore the only viable solution is a national program that stresses upon preventive strategies such as screening and prenatal diagnosis.

The Genetic Counselling Clinic

The ability to communicate well is essential in genetic counselling. Not only does the counsellor provide information but he or she also has to be receptive to the fears and aspirations, of the person being counselled.

The settings should be agreeable private and quiet with ample time for discussion and questions. Questions should be answered openly and honestly. Information must be presented in a clear, sympathetic and appropriate manner.

Often an individual or a couple is extremely upset when first made aware of a genetic diagnosis like Thalassaemia. The counsellor should consider the socio cultural setup of our society in mind. It is important to invite members of the family who in our social and cultural setup are decision makers or can influence the decision of the couple coming for genetic counselling. These family members include mother-in-law, father-in-law, brother-in-law, etc.

The advantage of having these people also present at the counselling session is that the family as a whole can understand the disease, benefits of optimal treatment and the importance of prevention through prenatal diagnosis and carrier screening of extended family members. It is seen that counselling more members of the family helps not only the couple but also the family as a whole in understanding the disease and helps them cope up with the disease burden.

Genetic counselling involves the following steps:

1. Diagnosis
2. Risk calculation
3. Communication
4. Discussing the options
5. Long term contact & support

1. Diagnosis

The first step in genetic conselling is that of establishing the diagnosis. An incorrect diagnosis can result in potentially tragic consequences. A genetic counsellor needs to take a proper history of the patient and family. History taking involves drawing a family tree (pedigree) inorder to gain insight about family relationships, other affected members, carriers in the family and the mode of inheritance.

The genetic counsellor also needs evidence that the family to be counselled has already seen a qualified doctor, relevant laboratory tests have been conducted and a definite diagnosis of Thalassaemia has been made.

2. Risk Calculation

Thalassaemia is an autosomal recessive inherited disorder and calculation of recurrence risk is relatively straight forward (Figure 1.1) It is very important that the information which is provided is understood by the family in order to help them reach their own decision.

Inheritance Pattern Figure

For calculation of risk for thalassaemia let us consider two sorts of married couples;

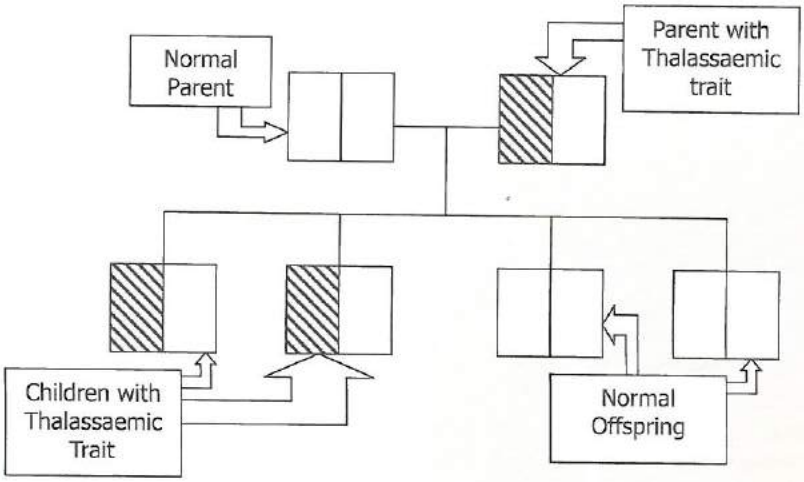


Figure 11.1 Genetic inheritance of normal parents with parent with thalassaemic trait.

1. One parent is normal and other is Thalassaemia trait; all the children must inherit a normal gene from their normal parent. However they may inherit a normal or a Thalassaemia gene from their carrier parent. For each child there will be a one in two or a 50% chance of inheriting the Thalassaemia gene form their carrier parent; if this happens the child will be a Thalassaemia trait. There is also a one in two or a 50% chance of inheriting the normal gene from both the parents; if this happens the child will be completely normal. None of this

couples children can have Thalassaemia major. **Hence in a couple where one parent is genetically normal no prenatal testing is required.**

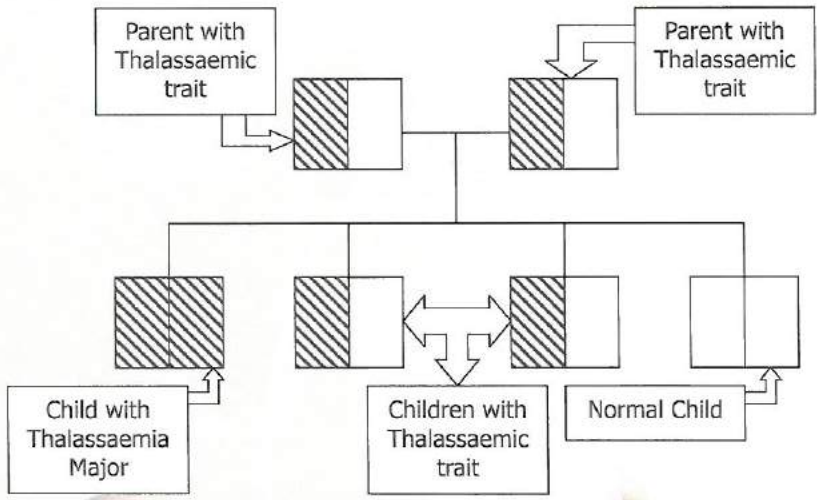


Figure 11.2 Genetic inheritance pattern of two parents with thalassaemic trait.

1. Both the parents are Thalassaemia trait; couples of carriers have one in four or 25% chance **in each pregnancy** of having a child with Thalassaemia major, a one in tow or 50 % chance of having a child with Thalassaemia trait; and one in four or 25% chance that the child will be completely normal. These chances are the same in each pregnancy. **Hence a prenatal diagnosis is required in every pregnancy.**

3. Communication

It is important that the risk of inheritance is clearly understood by the consultant. In Pakistan most families who are affected by thalassaemia, either do not properly understand the mode of inheritance or are given wrong information in this regard. Misinterpretation of risk quite often leads to tragic consequences to the family. It is genetic counsellor's duty to show the good side of the picture and do not act as prophet of doom. For example a couple faced with a probability of one in four or 25% that their next baby will have Thalassaemia major should be reminded that there are 75% or three in four chances that the next baby will not be affected, while also highlighting the importance of prenatal testing. When possible technical terms should be avoided or, if used, then should be fully explained to the family.

4. Discussing the options

Having established the diagnosis and discussed the risk of occurrence or reoccurrence, it is now essential to discuss all possible choices available to the family. This information will include the details of optimal treatment including, safe blood transfusion, iron chelation, bone marrow transplant and other matters related with treatment. The consultant should also be told about carrier screening and prenatal diagnosis. These issues should be approached with great care and sensitivity. For some couples the prospect of prenatal diagnosis followed by selective termination of pregnancy is unacceptable.The genetic counsellor should inform the parents about the Fatwa taken in this regard, according to which as Mufti Mehmood

Ashraf Ali from Darul-Fatwa Jamia Darul-Islam, Karachi, **"THE SOUL COMES INTO THE BODY AT 120 DAYS OF GESTATION (FOUR MONTHS OF PREGNANCY) AND IF AN ABNORMALITY IS DETECTED WHICH COULD BE FATAL TO THE CHILD OR THE MOTHER, TERMINATING THE PREGNANCY WILL NOT BE A SIN."** The family whould have ample time to think and make independent decisions.

Whatever the personal views of the counsellor, the family is entitled to make their own informed decision as they are the ones who have to live with their decision. The genetic counsellor must refer the family to the most appropriate laboratories, doctors and Thalassaemia centers for treatment and prevention purposes.

A very important part of the genetic counselling is assessing the financial status of the family and informing them of the costs involved in the treatment and prevention including prenatal diagnosis. In case they belong to a lower income group and cannot afford certain tests and treatments, the counsellor may try to assist them by referring them to centers where their financial circumstances are considered and they are helped accordingly.

5. Long term contact and support

Despite all these measures, a counselling session can be so intense and intimidating that many times most of the information discussed is quickly forgotten. For this reason giving the family a written summary of the topics discussed is helpful along with allowing them multiple opportunities to return to discuss any other fears or confusions which they may still have.

Chapter 12:-

Prevention: Screeening and Prenatal Diagnosis

Looking after a thalassaemics patient according to standard case management is tedious and very expensive. For a country like Pakistan all our efforts should be concentrated on prevention of disease. The 4 pillars of a successful preventive program are

1. Public awareness
2. Population screening for carriers
3. Genetic Counselling
4. Prenatal Diagnosis

Public awareness

Awareness Campaigns are targeted at:-

1. Medical Doctors
2. NGO's
3. Couples and families affected
4. General Public

Population screening for carriers

Carrier Screening which is possible in our country at present is:-

1. Targeted Screening of the affected families to screen for carriers in the family. Important to remember is that there is a

30 – 40% carrier rate in the extended family, due to complex consanguity.

2. One tube osmotic fragility test, is a cheap way to do mass screening.
3. Complete blood picture & Hb electrophoresis will give the final diagnosis of carriers.

PRENATAL DIAGNOSIS

The development of techniques for diagnosing genetic disorders in-utero is a major advance in medical genetics, and has altered the outlook for families at risk of having affected children. This has helped in preventing the birth of children with thalassaemia major in countries like Cyprus, Italy, and Greece which had a prevalence rate as high as 15 – 17 %.

The widespread use of screening test in pregnancy now means that most prenatal diagnosis is undertaken where there is no previous risk or expectation of a genetic disorder. In Pakistan the prevalence rate of Beta - Thalassaemia carrier status is 5 % and mass screening is not cost effective. The recommended protocol by the World Health Organization in countries with low prevalence is:-

1. Target Screening: This means targeting families who already have an affected child and detecting carriers in those families.

2. Counseling: Genetic counseling must examine certain basic factors. The most important of which is whether the couple concerned actively wish for a prenatal diagnosis, and whether termination of an affected pregnancy is acceptable to the couple. The risk of 25% of every pregnancy of two carrier couples being affected must be conveyed. The procedure of prenatal diagnosis and the risk of loss of pregnancy due to the procedure must be explained in detail.
3. Prenatal Diagnosis: Should be done as early as possible.
4. Termination of affected pregnancies.

Prenatal Diagnosis:

The various procedures used for prenatal diagnosis are:

1. Chorionic Villus Sampling.
2. Amniocentesis.
3. Fetal Blood Sampling
4. Fetal Cell analysis in maternal blood.
5. Pre implantation diagnosis

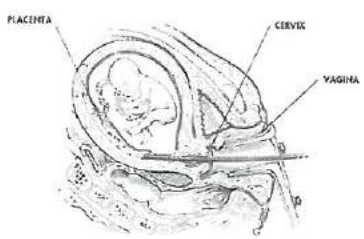
CHORIONIC VILLUS SAMPLING

Chorionic villus sampling is done in the first trimester of pregnancy. The best time is between 11 and 12 weeks of gestation. A sample of fetal tissue is taken from the placenta with a special biopsy needle under ultrasound guidance. Uncultured chorionic villi are the most satisfactory sample which can provide a rapid and accurate diagnosis for Beta Thalassaemia as the DNA markers for the majority of the

mutations are known. This procedure can be done through two routes.

Transcervical.

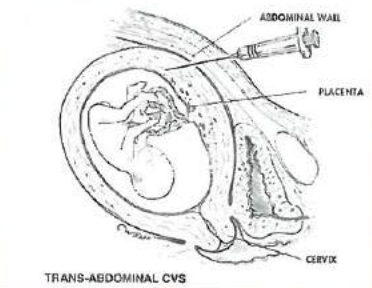
In the transcervical route a covered biopsy needle is passed through the cervix (opening of the uterus) under ultrasound guidance and a sample taken from the placenta. However, this route cannot be used after 12 weeks of pregnancy as the uterus becomes an abdominal organ.



TRANS-CERVICAL CVS

Transabdominal.

In the trans abdominal route the needle is passed through the abdominal wall under ultra sound guidance. This route can be used through out pregnancy



TRANS-ABDOMINAL CVS

As it is an interventional procedure it can cause complications like haemorrhage, infection and miscarriage. The rate of miscarriage is 2%. Limb reduction defects have been associated with this procedure if it is performed before 10 weeks of gestation.

Chorionic villus sampling is the preferred method for prenatal diagnosis of Beta Thalassaemia as it is done in the first trimester of pregnancy and termination of pregnancy in case of an affected pregnancy is easier and safer.

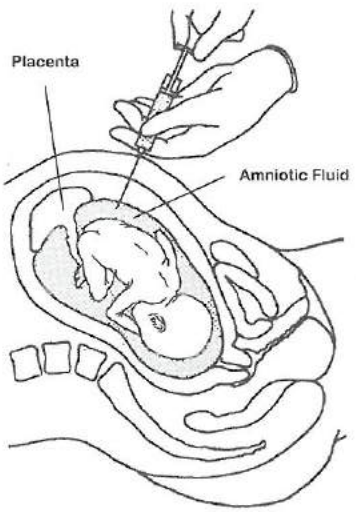
In patients who are Rhesus negative chorionic villus sampling should be followed by an injection of anti D immunoglobulin to prevent Rhesus immunisation.

AMNIOCENTESIS

Amniocentesis is a procedure by which a sample of amniotic fluid (the fluid around the baby) and its cells are taken from the uterus with the help of a spinal needle under ultrasound guidance. It is performed between 15 to 16 weeks of gestation. The results may take a week to ten days and in case of an affected pregnancy the termination of pregnancy might need to be done as late as eighteen weeks of pregnancy which is comparatively more difficult.

Amniocentesis is done trans-abdominally under ultrasound guidance. The placenta is localized and avoided while passing the spinal needle into the amniotic fluid. 20cc of clear fluid is aspirated. Only clear fluid which is not blood stained can give the best results.

AMNIOCENTESIS



The miscarriage rate in this procedure is 1% and lower than chronic villus biopsy.

An injection of anti – D must be given to women who are Rh negative after this procedure is performed.

Fetal Blood Sampling

Direct umbilical cord sampling under ultrasonographic control has superseded placental aspiration as a method of obtaining pure fetal

blood. It may have useful application for establishing haemoglobinopathies like thalassaemia in the baby where DNA analysis is not feasible. It is done after 18 weeks of pregnancy and being an interventional procedure has fetal miscarriage rate as high as 3%. It is not a recommended procedure as termination of pregnancy may have to be done between 19 – 20 weeks of pregnancy which is very late.

Preimplantation diagnosis

In this procedure couples who are thalassaemia carriers can avoid termination of an established pregnancy. It is now possible to undertake molecular analysis of cells of an early embryo produced by invitro fertilization, and to implant only unaffected embryos.

The disadvantage is the limited success rate for IVF in general and the high expense.

Fetal cell analysis of maternal blood

It has long been known that a small number of fetal cells or the baby cells pass into the maternal blood across the placenta. Techniques have been developed to identify them and separate them. This gives

the possibility of DNA analysis which sufficient to diagnose thalassaemia. A number of large scale studies are in progress, which are promising but still not sufficiently accurate for diagnostic use. However when this point is reached, there will be a radical shift in the overall pattern of prenatal diagnosis services as this will be a non – invasive approach.

In Pakistan the preferred method for prenatal diagnosis remains chronic villus sampling. The advantage is that it is done early in pregnancy and the result are available with in a week. Termination of pregnancy is easier and also follows the Fatwa which has been obtained which says according to the Quran **"the soul comes into the body at 120 days".** The fatwa says termination of pregnancy before 120 days is not a sin.

Chapter 13:-

Psychosocial Support

Like all chronic diseases, thalassaemia has important psychological implications. Culture sensitive psychological services make up an important part of the care plan for patients with chronic illnesses. Understanding and accepting the disease is a tremendous step towards facing the lifelong need for transfusion and chelation therapies.

Management of thalassaemias is a team approach which includes doctors, nurses, social workers and the family. It is extremely important to keep open good lines of communication which is vital in successfully treating patients with thalassaemia.

Patients at times may feel as if they are different, limited or isolated. Their state of mind can quickly switch from anger to depression.

Rules of communication between doctors and patients are

- Listening - be interested in the patients emotional experiences
- Accepting - being respective of the patients point of view and be

sensitive of the patients feelings

- Sharing - being close to the patients positive and negative feelings as human being
- Maintaining boundaries - giving help and relief, but keeping in mind his/her role as a physician.

Psychosocial support must include discussions with patients at certain crucial periods during the ongoing treatment for Thalassaemia

- At the time of diagnosis
- At the time of 1st transfusion
- When chelation is first started
- During Puberty
- Genetic counselling
- If serious complications occur
- At the sad demise of a thalassaemic as they all live together as a family.

Social Services

In a poor country like ours where resources are scarce it is important to consider socio-economic support for these patients. This may be in the form of

- Bait-ul-Mal
- Zakat
- Personal Sponsorships
- Donation in kind

- Desferrioxamine
- Infusion pumps

- Fund-raising campaigns are necessary to support specialized care centers.

Also important for adolescents future is the consideration of the following issues

- Education
- Training
- Job Opportunities
- Stipends
- Job Placement

- Information given should be explicit and sincere at sessions
- Schedule repeat visits to allow time for the patients to absorb information.

Chapter 14:-

Nutritional Requirements & Exercise

Iron containing foods

Iron containing foods are to be restricted in thalassaemia intermedia. Chicken and fish should not be restricted as they contain other important nutrients. Administration of milk and milk products will reduce the absorption of iron but add calcium which again is very important to prevent osteoporosis. Restricting iron rich diets in patients with thalassaemia major is not advised since they are regularly chelated and the iron passed on with blood transfusions is tremendously more than that absorbed via dietary intake.

Vitamin C

No vitamin syrups or tablets should be given which contain vitamin C as high doses of vitamin C can release a lot of free iron and only recommended doses should be given in regularly chelated patients.

Vitamin E

Thalassaemics have high requirements for vitamin E and may be supplemented.

Zinc & Copper

In aggressively chelated patients with desferrioxamine and deferiprone, additional zinc and copper may be required.

Tea & Coffee

Black tea and coffee reduces iron absorption and should be advised to patients of thalassaemia intermedia.

Pickles and Vinegars

They should be discouraged in thalassaemia intermedia as they increase iron absorption.

Folic Acid

It should be given in all patients in thalassaemia intermedia and to low-transfused patients of thalassaemia major.

Calcium

Disease and therapy both put these patients on a risk of low calcium reserves which results in osteopenia and osteoporosis. Hence patients in their 3rd and 4th decades will have increasing orthopaedic problems. Liberal intake of milk and milk products should be encouraged to overcome these problems.

Physical Activity

Physical Activity improves the quality of life, protects against osteoporosis and helps with psychological problems of chronic illnesses. Children should be encouraged to have a regular walk of 30min daily. Physical activity should only be restricted in cases of severe cardiomyopathy.

Appendix A:-

List of Tables and Figures

Tables

Figures

- ***Figure 9.2:-*** **(A)** Bone Density measurement of the right hip on X-ray, the inner square indicates the area where the bone density is measured. **(B)** Bone density measurement of the lumbar spine on a normogram, notice that the four points marked by + are below the acceptable normal.
- ***Figure 11.1*** Genetic inheritance of normal parents with parent with thalassaemic trait.
- ***Figure 11.2*** Genetic inheritance pattern of two parents with thalassaemic trait.

Appendix B:-

Important Contact List

List of Registered Member Societies

Sr.#	Name, Designation & Address	Tele / Fax / E mail
1	Pakistan Thalassaemia Welfare Society, 22-Atta ul Haq Road, Westridge-1, Rawalpindi Lt Gen (R) Fahim Ahmed Khan (contact Person)	5462084 5566594, 5462227 (R) Fax: 5470668 pakthala@hotmail.com pakthala@yahoo.com
2	Abbottonians Medical Association, 11/12-D, Awan Plaza Mandian, Abbottabad Dr Noaman Siddique (contact person)	0303-7710485, 0992-382271 (R) ama_888@yahoo.com nooman888@yahoo.com
3	Fatimid Foundation (Peshawar Center) 310/D, Block & Street 65, Sector D-1, Hayatabad, Peshawar Dr Tahir Khan (contact person)	091-822708 Fax: 091-819810 fatimidp@psh.paknet.com.pk
4	Welfare Hand Organization, 4th Floor, Rahim Medical Center, Near Amin Hotel, GT Road, Peshawar Mian Atiq ur Rehman (contact person)	091-252924 0333-9149980 Fax: 091-2569182 Atiqus2003@yahoo.com
5	Thalassaemia Society of Pakistan, 146/1, Shadaman Colony, Jail Road, Lahore Dr Yasmin Raashid (contact person)	042-7573911 7596589 info@thalassaemia.org.pk
6	Fatimid Foundation (Lahore Centre), Blood Bank and Hematological Services 34-G Gulberg111, Lahore, Pakistan. Col. (R) Anwar Iqbal (contact person)	042-5853491 5863950 fatimidl@lhr.paknet.com.pk
7	Fatimid Foundation (Multan Centre), T-Chowk 26-J Shah Rukn-e-Alam Colony Multan. LT.Col. (R) Syed Abrar Hussain (contact person)	061-554520-21 Fax: 061-554520-21 fatimidm@mul.paknet.com.pk
8	Bilmillah Taqee Blood Diseases Centre, St-19, Block-5, Main Rashid Minhas Road, Gulshan-e-Iqbal, Karachi. Dr. Tahir Shamsi (contact person)	021-4812902-4 0345-2383956 btbdc@cyber.net.pk shamsi@super.net.com info@btihs.edu.pk
9	Burhani Medical Welfare Association, Street-1, Block- F, KDA Chowrangi, Near Saifee Hospital, North Nazimabad,	021-6644490 bmwa786@yahoo.com

	Karachi- 74700 Dr. Durriya Ijaz (Administrator) (contact person)	mfmilwa@hotmail.com
10	Husaini Trust, Thalassaemia Centre, 43- Rehmat Manzil, Bhurgary Road, Soldier Bazar, Karachi. Dr. Sarfaraz Jafry (contact person)	0345-2220554 021-5831171-3 husayni@cyber.net.pk hbb_sjafry@ammar .com.pk asadjafferiy2k@yahoo.com
11	Fatimid Foundation (Karchi Centre), Head Office393, Britto Road, Garden East, Karachi Gen. Moin ud Din (contact persons) Rumi Dossal Dr. Zia Ur Rehman	021-7225284, 7213323 fatimidk@khi.paknet.com.pk
12	Engro Thalassaemia Centre, Sukkur Blood & Drug Donating Society, Opposite Eidgha, Sukkur. Dr. Muhammad Naeem (contact person)	0715-615922 Fax: 0715-615375 0300-3116359 Sbdds_org@yahoo.com
13	Alsamad Medical Centre M.A. Jinah Road Opp. Casualty Civil Hospital Quetta. Dr. Nadeem Samad (contact person)	081-821598 0300-8380847 drnadeemsheikh@yahoo.com
14	Thalassaemia Welfare Society, Peoples Medical College Hospital Paediatrics Ward Nawabshah, Sindh. Dr. Muhammad Sadique Siyal (contact person)	0300-2706891 0244-366233 msadiqsiyal@yahoo.com msadiqsiyal@hotmail.com
15	Thalassaemia Day Care Centre, DHQ, Hospital, Sheikhupura. Dr. Sameera (contact person)	0300-9479815
16	Amna Welfare Society Multan, 5 Khan colony opp. Shell Petrol Pump, LMQ road Multan. Hafiz Muhammad Hanif (contact person)	061-4514023 0300-6301473 sohail_iqbal30@yahoo.com
17	Al-Fajar Foundation G.T. Road, Rahim Abad Swat. Mr. Ghaffar Administrator	0946-722305 al_fajar_foundation@yahoo.com
18	Ali-Zaib Blood Transfusion Centre, 16 Y.L, Madina Town, Faisalabad. Syed Shahid Ali Zaidi (contact person)	041-8715997 8722090 0300-8666468 alizaib@fsd.comsats.net.pk

19	Kshif Iqbal Thalassaemia Care Centre, Beecham Road, Liaqatabad, Deh Landhi, Karachi -75120 Mr. Muhammad Iqbal (contact person)	021-5021188 021-4515600 Fax: 021-5021188 0333-2295644 kitcc@gem.net.pk
20	Sundas Foundation, Lahore Jail Road Shadman Lahore., . Dr. Yaseen Khan (contact person)	0333-4211261 sundasfoundation@hotmail.com 042-7539232-3
21	Jamila Sultana Thalassaemia Welfare Trust 24 D 6th Road, Sattelite Town, Rawalpindi Ms. Sameera Khan	khansamera@hotmail.com 051-4422708, 4842184

List of Un Registered Societies

1	Thalassaemia Society, C/O Fazal Laboratory, Timergara-Dir (NWFP) Dr Fazal Rahim (contact person) 0935-821301 fazallab71@hotmail.com
2	Thalassaemia Blood Transfusion Center, Nawab Street, Banu City 0928-611742 savechild@hotmail.com
3	Kaim Khani Welfare Health Centre, A-7, Fourth Floor, Nimco Centre, Cambell Street, Karachi. Mr. Muhammad Hassan (contact person) 021-2628451-2 Fax: 021-2628450 mhr@vmytrading.com
4	Shahbaz Social Welfare Association, Near Government Primary (Boys) School Lahori Muhalla Larkana Sindh. (Head Office) Gulsher Mangi (contact person) 0741-454343 0741-446125 shahbaz_swa@yahoo.com shahbaz_tcc@hotmail.com
5	Ahsas Welfare Organization, H#1653 Mohalla Mulan Majeed, I/S Hushtnagri Peshawar City. Dr. Shahzad Rashid Awan (contact person) 0300-9598570 0300-5944838 091-2565094 shahzadrus@yahoo.com
6	Thalassaemia Patients and Parents Society of Pakistan, 9-10, PMA House, 2nd Floor, PMA trade centre, 66 Ferozepur road Lahore. M. Yaqoob Babar Rana (contact person) 042-7524586 042-7524577 tppsp@thalassaemia.org.pk
7	Frontier Foundation Welfare Hospital & B.T.S, 8 Khyber Colony, Tehkal Payan, Peshawar. Mr. Ijaz Ali (contact person) 091-5703463, 843642 0321-9006003 Fax: 091-5843642 Lifesaver_4u2000@yahoo.com
8	Human Welfare Thalassaemia Centre, Flate#404, Aslam Plaza Near Fawara Chowk Attock City. Prof. Dr. Maqsood Elahi (contact person) 057-2611020 0300-5490600 lifeglimp@yahoo.com

Filters:

- Pulse International, 199-A, Allama Iqbal Town, Neelam Block, Lahore; Tel no. 042-7843908, 0300-4175096

Pumps:

- Hospital Supply Corporation, 152-A, Shah Jamal Colony, Lahore, Pakistan, Tel: 042-7572693, Fax: 042-7588520, Email: hsc@hsc.com.pk; Website: www.hsc.com.pk
- Butterfly Infusion Systems, Al-Hafeez Technology, 604 Noman Tower, Marston Rd, Karachi, Tel: 0300-9666534, Website www.alhafeeztech.com Email: kashif@alhafeeztech.com

Distilled Water:

- Global Pharmaceutical, Redco Plaza, 2nd floor, E78 Blue Area, Islamabad Tel: 051-2870703, 051-2870704, 03009544199

Bone Marrow transplant centers

- Bismillah Taqee Institute of Health Sciences & Blood Diseases Center, St#19, Block#5, Rashid Minhas Road, Gulshan-e-Iqbal, Karachi, Tel: 021-4812902 – 4, Fax 021-4812900
- Armed Forces Bone Marrow Transplant Center, Rawalpindi Tel:- GHQ – 34011

Screening Center

- Hussaini Blood Bank, 43 – Rehmat Manzil, Burgary Road, Soldier Bazaar, Karachi, Pakistan. Phone. No. 92-21-2230529-31, Fax no. 92-21-2237735