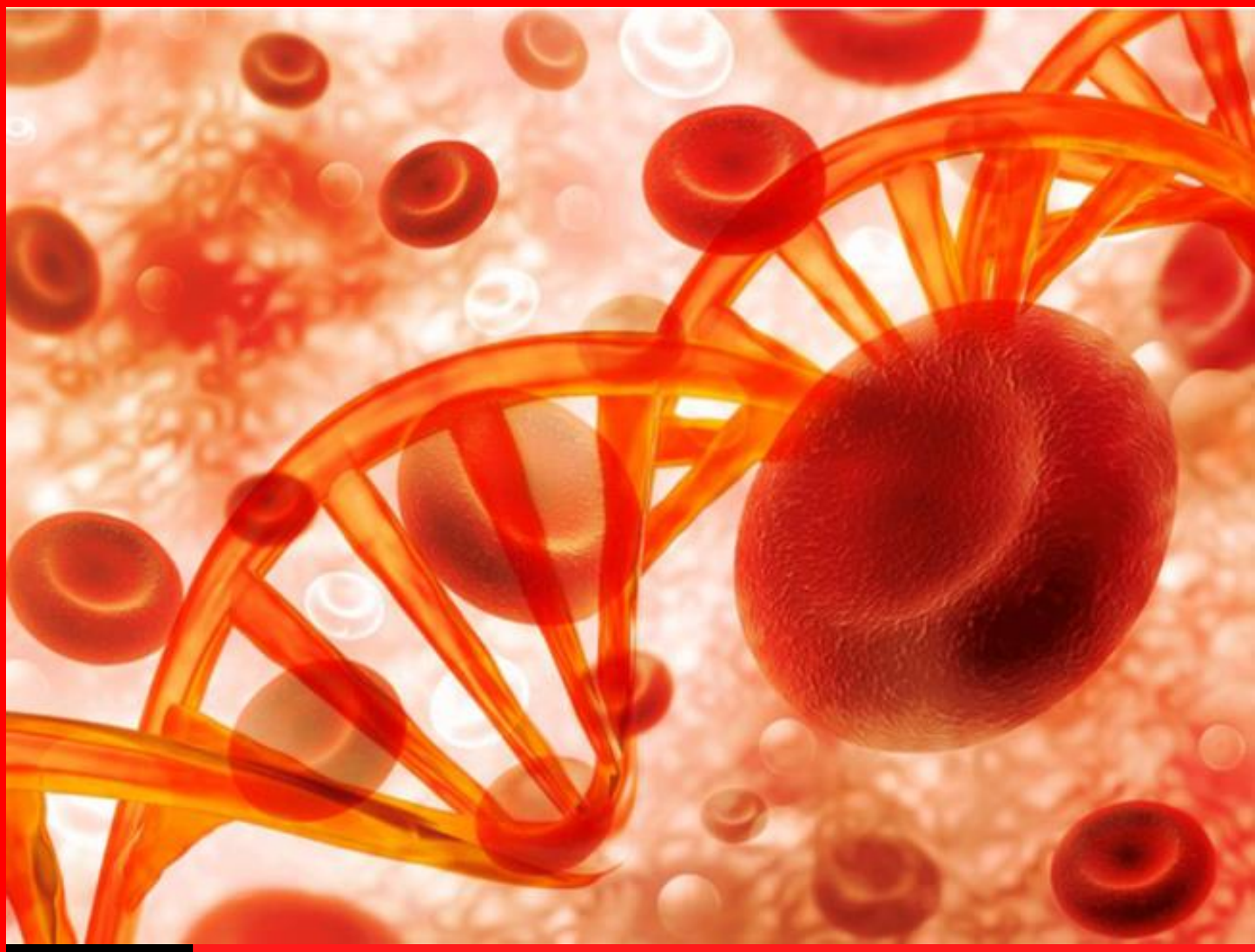

2022

MANAGEMENT OF TRANSFUSION DEPENDENT THALASSAEMIAS IN THE MALDIVES

Maldivian
Blood Services

MANAGEMENT OF TRANSFUSION DEPENDENT THALASSAEMIAS (TDT) IN THE MALDIVES

Management of Thalassaemia in a Multidisciplinary Approach

A practical guide for management of patients at all levels of health services in the Maldives

AUTHOR: Ahmed Faisal, Paediatrician, IGMH

REVIEWERS: Ahmed Umar, Paediatrician, MBS

Gulisthan Easa, Clinical Nurse, MBS

DOCUMENT NUMBER: MOH-MBS/G/22/110-0

Table of Contents

About this guide

Introduction

Thalassemia is very common in Maldives and there is a lot of mortality and morbidity. Beta thalassemia trait is present in 16 percent of population. This results in every 30th of marriages occurring in between 2 carriers.

What is this guideline about?

This guideline is a contextual summary of Thalassaemia International Federation's (TIFs) guideline for the clinical management of Transfusion Dependent Thalassaemia (TDT), guideline for the management of management of thalassaemia and Short guide for the management of Transfusion Dependent Thalassaemia (TDT). It will provide guidance for paediatricians, physicians, nurses, psychologists and medical officers on management of TDTs, early detection and management of complications. This guide will also include management of TDTs by multidisciplinary approach and when to refer patients for specialized care. As the patients grow, they should be counseled that management goes beyond transfusion and chelation but various expertise needs to be incorporated for the holistic managements.

How to use this guideline?

All health professionals treating thalassemia patients are required to follow this guideline. Maldivian Blood services must orient the health professional to this guide. Annual refresher course should be provided online to all health professionals. Every patient should be followed up according to the reference given in the guideline.

Chapter 1

ABOUT THALASSAEMIA

Definition

Thalassaemia is a group of blood disorder characterized by decreased or absent synthesis of normal globin chains. According to the chain whose synthesis is impaired, the thalassaemia is called α-, β-, γ-, δ -, δβ-, or εγδβ-thalassaemias. Thalassaemia comes under the broad spectrum of genetic blood disorders known as haemoglobinopathies. Clinical picture of haemoglobinopathies can vary from patients who require occasional blood transfusions (such as HbE-Beta thalassaemia) to patients who require regular lifelong blood transfusions (such as Beta thalassaemia major). Thalassemia is very common in Maldives. Any child present with severe anaemia should be investigated for both thalassemia and iron deficiency anaemia.

Genetic basis of thalassaemia

Most thalassaemia is inherited as autosomal recessive traits. The Figure 1 below gives the risk categorization of affected children from different partner matches.

Carrier combination chart

	Beta carrier	Alpha zero carrier	Alpha plus carrier	Sickle carrier	HbD carrier	HbE carrier	Non-carrier
Beta carrier							
Alpha zero carrier		Hydrops fetalis	HbH disease				
Alpha plus carrier		HbH disease					
Sickle carrier							
HbD carrier							
HbE carrier							
Non-carrier							

Figure 1: Carrier combination chart for all types of thalassaemia

Pathophysiology of beta thalassaemia

Each haemoglobin molecules is made up of 4 globin chains. This include 2 chains of α group chains (α or ζ) and 2 chains of β group chains (β, γ, δ or ε). The type of chains varies at different level of human development as shown in the figure 2 below. The chain has to be balanced to make a stable haemoglobin.

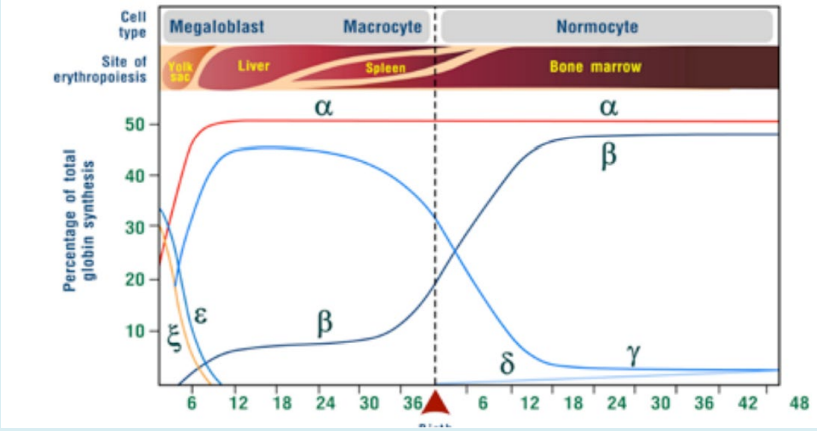

Figure 2: Types of haemoglobin and different stages of human development

In the embryonic haemoglobins in the 3rd to 10th week of gestation, it is either 2 ζ with 2 ε chains, 2 ζ with 2γ or 2 ζ with 2β chains. In the foetal stage it is called foetal haemoglobin where there are 2α and 2γ chains. After birth these haemoglobins are replaced mainly with adult haemoglobin called HbA haemoglobin which consists of 2α with 2β chains. From the total haemoglobin, about 2.5 percentage are HbA2 haemoglobins which consists of 2α and 2δ chains.

In β-thalassaemia there is decreased or absent production of β-globin chains with relative excess of α-chains causing imbalance in haemoglobin and increasing cell rigidity resulting in marked increase in peripheral haemolysis. These excess α-chains can also precipitate in the erythroid precursors within bone marrow which leads to immature death of erythroid precursors causing ineffective erythropoiesis. The result of this peripheral hemolysis and ineffective erythropoiesis is anaemia. The body responds to anaemia by increasing erythropoiesis causing erythroid hyperplasia in bones. This results in skeletal deformities, osteoporosis, extra medullary masses and hepatosplenomegaly. Non-transfused thalassaemia major patients have retarded growth, cardiac enlargement and sometimes severe cardiac failure. Anaemia also causes increased iron absorption.

Diagnosis and registration

Clinical manifestation

Children with TDT major presents usually around 4 to 6 months but may present as early as 2 months and as late as 24 months. Affected infants fail to thrive and become progressively pale. Feeding problems, irritability, recurrent bouts of fever may occur. There will be pallor, jaundice, and hepatosplenomegaly. Skeletal changes include deformities in the long bones of the legs and craniofacial changes such as bossing of the skull, prominent malar eminence, depressed bridge of the nose and hypertrophy of the maxillae.

Diagnosis

Deoxyribonucleic Acid (DNA) testing should be carried out for infants suggestive of thalassemia. Sampling is preferred before transfusion; however, post transfusion samples can also be used. DNA testing can be done from Society of Health Education (SHE). Maldivian Blood Services (MBS) do electrophoresis for carrier screening for people above 12 years of age. Once diagnosed, patients need to be registered at MBS.

Patient registration

Health professional should check parents' thalassemia screening cards by themselves. Often parents do not know or even may produce a wrong card. When screening test result is inconclusive person is asked to do a DNA test to confirm the status. Many times, people do not go for DNA test due to the cost and other reasons. All patients diagnosed with any type of thalassemia need to be registered in MBS.

Chapter 2

BLOOD TRANSFUSION

Goal of transfusion therapy

The major goals of blood transfusion therapy include:

1. Optimize hemoglobin for appropriate growth and development in children
2. Optimize hemoglobin to allow for normal daily function of patient
3. Safe transfusion in terms of blood borne infections and adverse events
4. Transfuse the blood with optimal half-life (fresh blood).

Indications for regular blood transfusions

1. Confirmed diagnosis of thalassemia
2. Symptomatic anaemia
3. Haemoglobin level less than 7 g/dl on two consecutive occasions more than two weeks apart (excluding all other possible causes).
4. Haemoglobin > 7 g/dl with any of the following:
    a. Facial changes
    b. Poor growth
    c. Clinically significant extramedullary haematopoiesis

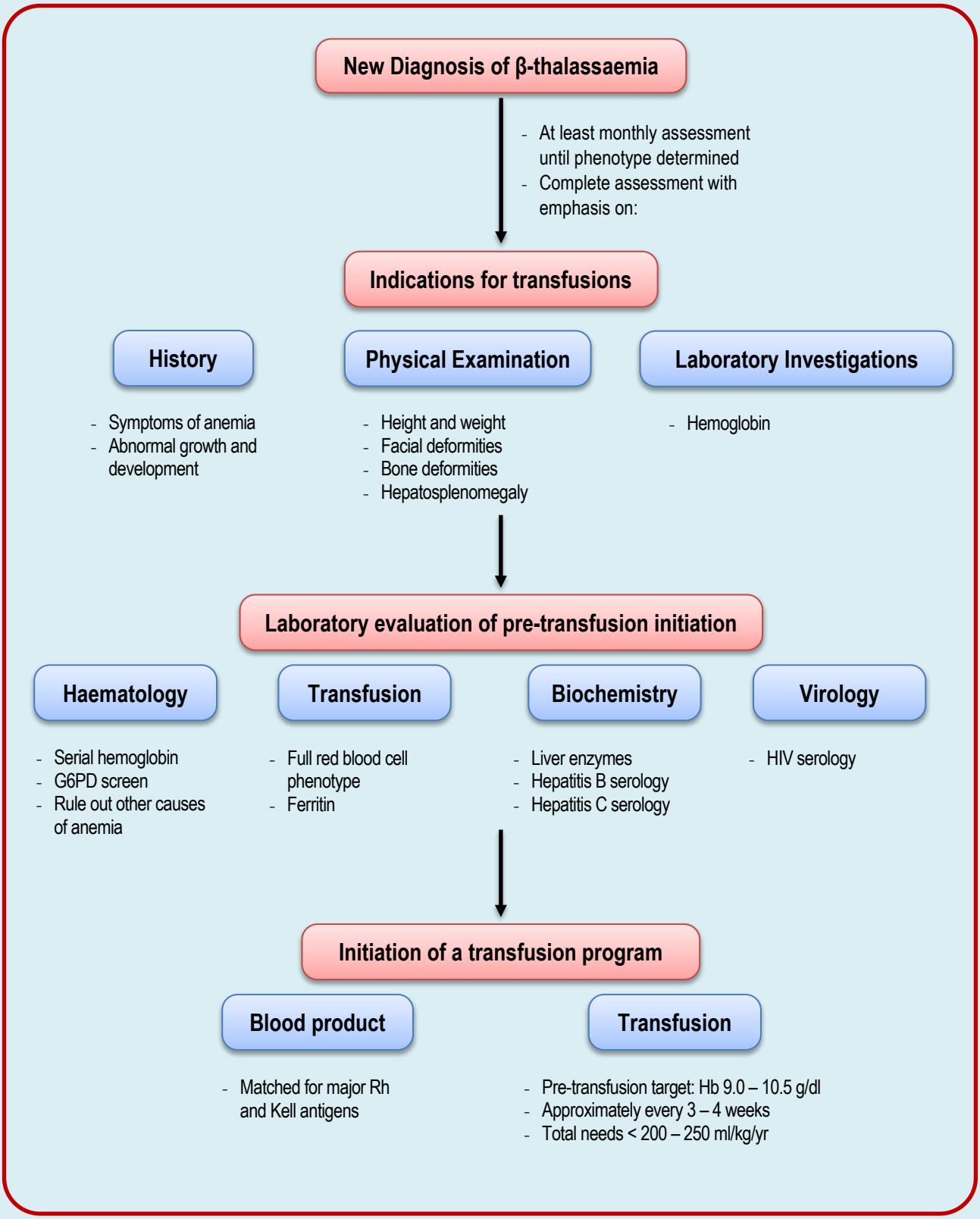

Figure 3: Clinical and Laboratory Aspects When Deciding Appropriateness of Initiating a Transfusion Program

Recommended blood product

Leukoreduced packed red blood cells

It is important to reduce leukocytes in donated blood before transfusion. Leukocyte can be removed from donated blood at 3 different stages. These include;

1. Just after bleeding from donor but before storing in blood bank
2. After storage but before issuing to patient
3. At bed side using blood filters. Some leukocytes might have lysed and released chemicals such as interleukins that can cause fever and some unwanted effects. Filtering at bedside is easier but there is no method to ensure quality of it.

Other blood products required in special population

1. **Washed Red blood cells** are used for patients who have recurrent severe allergic transfusion reactions or for patients with immunoglobulin A (IgA) deficiency.
2. **Red cells obtained by donor apheresis** helps in decreasing donor exposure. This procedure is done in MBS.

Compatibility testing

Alloimmunization is a common complication of chronic transfusion. To prevent this, it is important to identify red cell antigens (C, c, D, E, e and Kell). Therefore, before embarking on transfusion therapy it is important that patients are tested for red cell antigens (C, c, D, E, e and Kell). If the patient has already been transfused, it is important to do antigen typing using molecular rather than serologic testing. All patients should receive ABO and red cell antigens (C, c, D, E, e and Kell) compatible blood. These antigens can be tested at MBS and Indira Gandhi Memorial Hospital (IGMH).

Transfusion of blood from first-degree relatives should be avoided because of the risk of developing antibodies that might adversely affect the outcome of a later stem cell transplant and the risks of transfusion associated Graft versus Host Disease (GvHD).

Transfusion program

How much to target for pre-transfusion haemoglobin level?

The aim is to keep pre-transfusion Hb above 9-10.5 g/dl. This transfusion regimen promotes normal growth, allows normal physical activities, adequately suppresses bone marrow activity in most patients, and minimizes transfusional iron accumulation. A higher target pre-transfusion haemoglobin level of 11-12 g/dl may be appropriate for patients with clinically significant heart diseases.

How much blood volume is required?

For calculation of this we should know Hb or PCV of both donor pack and recipient. Volume of blood to be transfused can be calculated using the formula. The guideline for calculating how much to be transfused is summarized in table 1.

Volume to be transfused (ml) = (Desired – actual Hb) x weight x 3/haematocrit of transfused unit

Table 1: the guideline for calculating volume to be transfused

		Haematocrit of donor red cells			
		50%	**60%**	**70%**	**80%**
Target increase in Haemoglobin level	**2g/dl**	12ml/kg	10ml/kg	8ml/kg	7.5ml/kg
	3g/dl	18ml/kg	15ml/kg	12ml/kg	11.2ml/kg
	4g/dl	24ml/kg	20ml/kg	16ml/kg	15ml/kg

How much safe is to increase Hb with transfusion?

Post-transfusion haemoglobin should not be greater than 14-15 g/dl.

What rate should the transfusions be given?

In patients without any cardiac complication a unit of blood can be transfused within 4 hours with strict monitoring. In patients with symptomatic and possible cardiac complications, transfusions must be done with low volume (5ml per Kg) with close monitoring.

Process of blood transfusion

The following should be ensured before, during and after transfusion

1. **Before transfusion**

Counseling has to be given to patient and care giver regarding risks and benefits of transfusion. Blood is preferred to be less than 10 days old. Storage temperature should be at 2 to 6 degree Celsius. Transfusions should be done in where usual transfusions take place. There should be enough staff available to observe the patient and monitor for any adverse transfusion reactions. It is also important follow 30 minute and 4-hour rule discussed in figure 4 to ensure the quality of transfused blood remain safe.

Role of the nurse and pre transfusion checks

Nurses play major role in care of patients including transfusing blood to them. Since nurses take the final step in transfusion of blood, which is irreversible, safety largely depends on nurse's role. To reduce the adverse transfusion reactions, it is vital to follow the three checks as described in figure 5.

30 minute and 4-hour rule

REMEMBER

*Blood should be commenced upon arrival to the clinical area (after pre-transfusion checks) Blood may be returned to Blood Bank Controlled Storage within 30 minutes

*Blood that has remained in the clinical area for more than 30 minutes **MAY STILL BE TRANSFUSED** to the patient as long as the total transfusion time is **WITHIN 4 HOURS**

Why do you have to return unused blood to blood bank within 30 minute

1. Returning blood unit within 30mins helps to decrease wastage.
2. They can be returned to controlled storage in the blood bank refrigerators
3. The unit can be used for another patient
4. If the unit is returned to the BB after 30mins have elapsed, blood bank staff have no option but to discard them.

Can blood that has been left on the ward for >30 minutes be transfused? YES, you have up to 4 hours to complete a blood transfusion.

1. RBCs that have been left at room temperature in the clinical area (i.e. hung on an IV pole, sitting in the medication room etc…) may still be transfused provided the transfusion is complete within 4 hours from release from the blood bank. For example: If a unit of RBC is left sitting in the ward for 1 hour, you can still transfuse this unit to your patient, provided that you complete the transfusion within the next 3 hours (i.e. 1 hour + 3 hours = 4 hours' total time out of the fridge)
2. Red cells 60-180 minutes per unit.
3. Remember to perform the PRE-TRANSFUSION CHECK on any blood BEFORE it is connected to the patient.

Does blood have to be transfused within 4 hours?

YES, A transfusion must be completed within 4 hours

WHY? The risk of bacterial proliferation greatly increases when blood remains at room temperature for >4 hours.

Figure 4: 30 minute and 4-hour rule

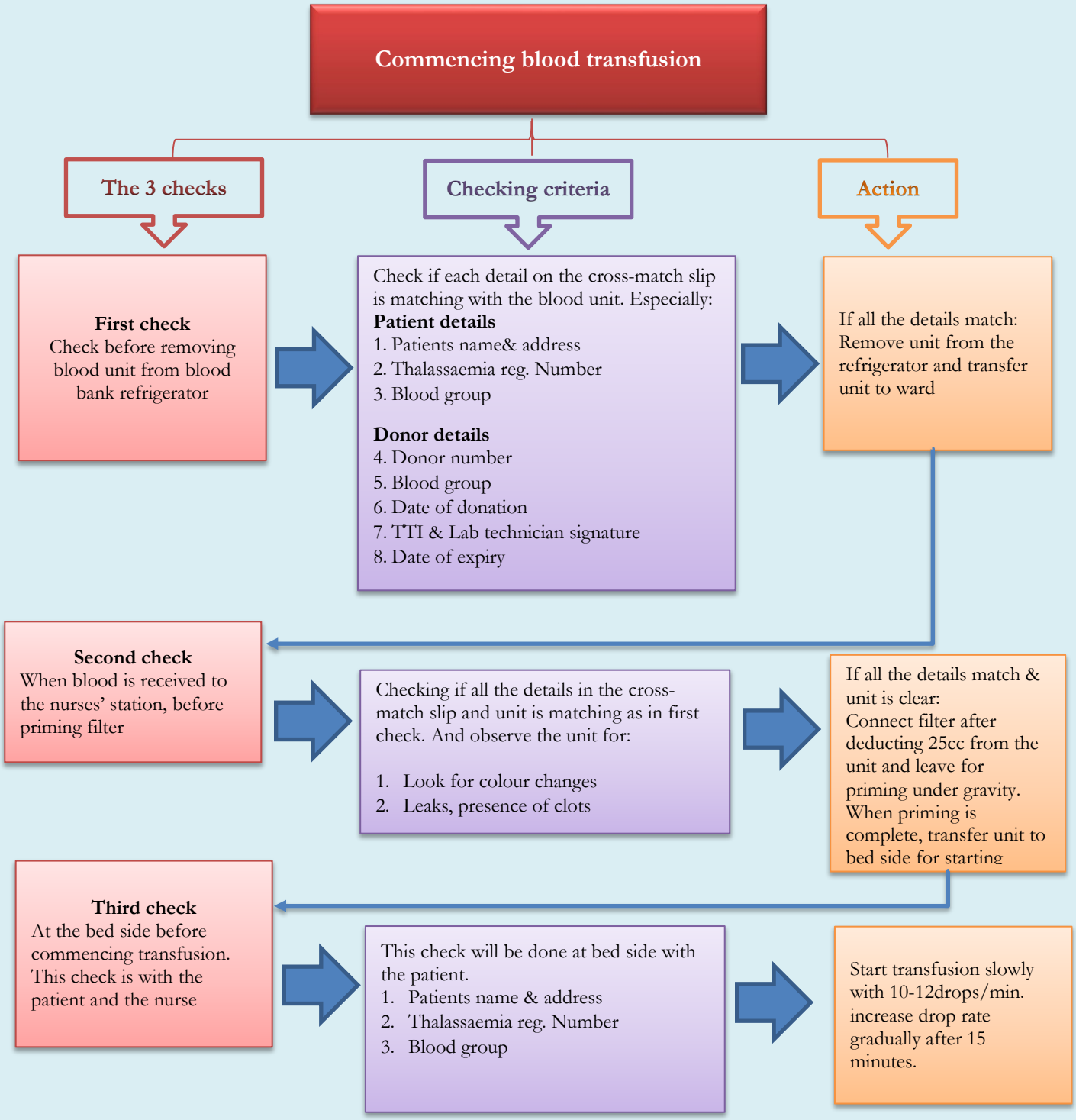

Figure 5: Getting ready for commencing blood transfusion

2. During transfusion

The patient is carefully observed over the course of the transfusion, particularly in the first 15 minutes when a transfusion reaction is more likely to occur. Blood components are transfused within the recommended time. Rapid transfusion of cold blood may result in complications. Observed reactions must be noted and reported. All serious complications should be investigated. Draw a post-transfusion sample and send it with the remaining blood bag and its administration set to the blood bank for serological incompatibility investigation and bacterial culture test. In case of repeated transfusion reactions, investigation for the presence of irregular antibodies outside the ABO and Rh systems is recommended. Efficacy of desferrioxamine co-administered with red blood cells through a Y-connection is doubtful. During transfusion the nurse practitioner should closely monitor all patients on blood transfusion for any symptoms/signs such as: fever, chills and rigors, tachycardia, hypertension, hypotension, pain in muscle, chest and abdomen, shortness of breath, nausea, feeling of unwell, respiratory distress, urticaria and rash.

When a transfusion reaction is suspected, inform head nurse and medical officer in charge and stop the transfusion, maintain venous access, monitor vital signs (temperature, pulse respiration and oxygen saturation). If resuscitation is required maintain airway, give oxygen, connect monitors. Normal saline 10ml per kg if hypotensive can be administered over 30 minutes. If the hypotension is prolonged, the patient may require inotropes. Recheck the identity of the patient against the unit. Monitor urine output. The first urine passed should be sent to the laboratory to monitor for free haemoglobin. Send blood specimen to the lab for repeat cross-match, full blood count, urea, electrolyte and liver function tests. The unit of blood should be returned to the laboratory with the giving set for further investigation.

Chapter 3

TRANSFUSION REACTION AND MANAGEMENT

Definition

Blood transfusion exposes the patient to a variety of risks and adverse effects. The adverse effects rage from mild to severe.

Non haemolytic febrile transfusion reactions

This is a common transfusion reaction and has decreased over the decades with the use of leukoreduction.

Management: If fever is present, hemolysis and infected blood products need to be ruled out. Send a peripheral smear to look for hemolysis. Paracetamol can be given for fever. Once the fever subsides and patient is stable, restart the transfusion.

Allergic reactions and anaphylaxis

Plasma proteins are usually causing allergic reactions in transfused patients. This can range from mild to severe. Milder reactions include urticaria, itching and flushing. They are generally mediated by IgE. It can be treated with antihistamines and steroids. This can be prevented with antihistamines or corticosteroids before transfusion.

More severe reactions such as anaphylaxis present with urticaria, stridor, bronchospasm, hypotension or other symptoms of anaphylaxis may occur, especially in patients with IgA deficiency.

Management: These need urgent treatment with securing airway, oxygenation, circulation intramuscular adrenaline (undiluted adrenaline of 0.5ml IM for adults, 0.3 ml for children above 6 months) followed with steroids and histamines. Adrenaline can be repeated every 5 minutes if response is poor but will need further management such as securing airway and maintaining breathing and circulation.

Acute haemolytic reactions

These reactions begin within minutes or sometimes hours of initiating a transfusion and are characterised by the abrupt onset of fever, chills, lower back pain, a sense of impending death, dyspnea, haemoglobinuria and shock. These unusual reactions most commonly arise from errors in cross matching.

Management: Transfusion should be stopped immediately and intravenous fluids should be administered to maintain intravascular volume. Diuretics may help to preserve renal function. The blood bank should also be alerted to the possibility of an undetected alloantibody. Patients' blood and blood bag need to be sent to blood bank for further analysis.

Alloimmunisation

This happens in 10-20% of TDT patients.

Management: A short cause of prednisolone 1mg/kg once a day for 7-10 days will be helpful.

Delayed transfusion reactions

Delayed transfusion reactions are extremely rare. These usually occur 5-14 days after transfusion and are characterised by unexpected levels of anaemia, as well as malaise and jaundice.

Management: A sample should be sent to the blood bank to investigate the presence of a new antibody

Autoimmune haemolytic anaemia

Here the haemoglobin concentration may fall well below the usual pre-transfusion level because of destruction of both the donor's and the recipient's red cells. The serologic

evaluation by the blood bank usually shows an antibody that reacts with a wide range of test cells and fails to show specificity for a particular antigen.

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

Transfusion-related acute lung injury (TRALI)

Severe complication that is presented as dyspnoea, tachycardia, fever and hypotension during or within six hours of transfusion. Hypoxemia is present and the chest radiograph shows bilateral infiltrates typical of pulmonary oedema although there is no reason to suspect volume overload.

Management: It includes oxygen, administration of steroids and diuretics, and, when needed, assisted ventilation.

Transfusion-associated circulatory overload

It may occur in the presence of recognized or unrecognized cardiac dysfunction, or when the rate of transfusion is inappropriately fast. Signs and symptoms include dyspnoea and tachycardia, and the chest radiograph shows the classic findings of pulmonary oedema.

Management; Stop transfusion, prop up the patient, examine the chest and vitals, monitor patient with saturation monitors, administer diuretics and oxygen as required. X ray will help in identifying intensity of fluid overload. Calculate amount of blood that has been transfused to ensure the cause of symptoms is due to over transfusion. Treatment focuses on volume reduction and cardiac support as required.

Transmission of infections

Transfusion acquired HIV, HBV, HCV and syphilis has been reduced to almost zero with the implementation of appropriate mandatory testing methods to screen the donated blood for

transfusion transmissible infections. However, the risk exists and stringent screening need to be carefully continued. Yearly screening of patients should be done for these infections. Positive cases should be managed with guidance from specific programs of Health Protection Agency (HPA). HPA runs programs for hepatitis, STD and HIV.

Transfusion associated graft versus host disease

Usually occurs within 1-4 weeks of transfusion and is characterized by fever, rash, liver dysfunction, diarrhoea, and pancytopenia due to bone marrow failure.

Table 2: Types of transfusion reactions and their cause with presenting symptoms			
Type of reaction	**Timing**	**Cause**	**Symptoms**
Febrile Non-Haemolytic Transfusion Reaction (FNHTR)	-	Reaction between leukocyte antigens in transfused blood and anti-leukocyte antibodies in the patient's blood. Some reactions believed to be due to transfusion of proteins called cytokines, produces leukocytes during storage.	
Acute haemolytic	Few minutes after initiation of transfusion	ABO incompatibility	Dyspnea, chest constriction, fever, chills, lumbar pain, hypotension shock and renal failure.
Anaphylaxis	-	Congenital deficiency in IgA	Skin flushing, hives, itching, dyspnoea, chest pain, hypertension, loss of consciousness and shock.
Air embolism	-	Air entering the system	Cough, dyspnoea, chest pain and shock
Bacterial contamination	Towards completion and after completion of transfusion	Transmission of bacteria through transfused blood	Fever, chills, vomiting, diarrhoea, hypotension, shock, renal failure and DIC.
Circulatory overload	-	Transfusion processing too quickly	Dyspnoea, cyanosis and increased systolic pressure.
Transfusion Related Acute Lung Injury (TRALI)	-	Reaction between transfused anti-leukocyte and patient's granulocytes.	Dyspnoea, cyanosis, cough and hypotension.
Allergic urticaria	-	Results from foreign allergens in the donor's blood reacting with patient's antibodies or vice versa.	Urticaria, rash, localized oedema.
Adopted from TIF publication 2007			

Chapter 4

IRON OVERLOAD AND CHELATION

PATHOPHYSIOLOGY OF IRONOVERLOAD

Iron overload occurs due to transfusions or in non-transfused NTDTs by increased iron absorption from gastrointestinal tract. Both of this occurs in thalassaemia major. Human body lacks a way to excrete excess iron patients' body. A blood unit has about 22 mg of iron while body only excretes 1-2 mg iron per day.

Iron accumulation is toxic to many tissues, causing heart failure, cirrhosis, liver cancer, growth retardation and multiple endocrine abnormalities such as diabetes, hypothyroidism, hypogonadotrophic hypogonadism, and hypoparathyroidsm and bone diseases. Careful dose adjustment is necessary to avoid under chelation and excess chelation. Annual calculation of iron load can be helpful. Using iron chelators is the only way to excrete the excess iron.

Annual blood requirement = Total volume of blood transfused in the year / weight of patient (in ml/kg/Year)

Annual pure red cell requirement = Annual blood requirement x packed cell volume

This is important to assess for blood requirement in looking for indication for splenectomy. As the annual transfusion requirements rise above 200 ml/kg/year of pure red cells, splenectomy may be considered.

Annual transfusional iron load = Annual pure red cell volume required x 1.08mg/mg

Initiation of iron chelation therapy

Iron chelation therapy starts when all of the following criteria meets:

- 10-12 transfusions or
- Serum ferritin > 1000µg/l on two consecutive occasions, the first taken two weeks before the second reading or
- Age > 2 years old

Monitoring of Iron Overload

Iron in the body is usually measured with Serum Ferritin in the blood, liver iron concentration and cardiac iron using MRI T2*.

Serum Ferritin

Trend of Serum ferritin (SF) is very useful rather than a specific value. A decreasing trend in SF is good evidence of decreasing body iron burden but absence of a decreasing trend does not exclude a decreasing iron in the organs such as heart and liver. However, an increasing SF trend implies an increasing iron burden but may also be due to infections, hepatitis, inflammatory conditions or even when compliance suddenly increase. Serum ferritin measured at least every 3 months (1-3 months). Target value is currently between 500-1000 µg/L.

Liver Iron Concentration (LIC)

LIC and extrahepatic iron is complicated by chelation therapy as iron tends to be accumulate initially in the liver and later in the heart but also is removed more rapidly from the liver than the heart by chelation therapy. Normal LIC values are up to 1.8 mg/g dry weight, with levels of up to 7 mg/g dry weight seen in some non-thalassaemic populations without apparent adverse effects. Sustained high LIC (above 15-20 mg/g dry weight) have been lined to worsening prognosis, liver fibrosis progression. LIC gives the most reliable estimate of body iron LIC unreliable as predictor of heart iron in chelated patients. MRI determination of LIC is unreliable above of 30 mg/g dry wt. LIC of 3-7 mg/g dw is an acceptable therapeutic goal in TM patients. It is recommended that levels are kept towards the lower part of this range. The frequency of LIC assessment should be guided by LIC and rate of change in LIC.

1. Stable levels in the range 3-7 mg/g dw: Every 1 or 2 years
2. Levels >7 mg/g dw: yearly
3. Levels falling rapidly or <3 mg/g dw; every 6 to 12 months

Myocardial iron estimation

The risk of developing heart failure is increased by 160 fold with T2* values <10ms, in the next 12 months. T2* more than 10 ms might have abnormal heart function but is less severe. Table 3 describes estimation of myocardial iron loading estimation using MRI T2*. However the frequency of cardiac MRI scan should be guided by myocardial iron level for example:

1. Stable T2* > 20 milliseconds: two yearly
2. T2* 10-20 milliseconds: yearly
3. T2* < 10 milliseconds: 6 monthly –
4. It is particularly important to measure left ventricular function when cardiac iron is high (e.g. T2* <10 ms).

Table 3: A grading scheme for assessing myocardial iron and guiding changes in chelation therapy.

Risk if untreated	MRI T2*
No cardiac iron, low risk of heart failure (HF)	≥ 20 milliseconds
Mild to moderate cardiac iron, low risk of HF	10 – 19 milliseconds
High cardiac iron, moderate risk of HF	6 – 9 milliseconds
High cardiac iron, high risk of HF	< 6 milliseconds

Adopted from TIF guideline 2017 (A short guide for management of transfusion dependent thalassaemias

Iron Chelation Therapy

Iron can be chelated at 3 stages of accumulation.

1. **Prevention**; when the target is to chelate iron before it deposits in organs. This is the best stage at prevention of iron overload.
2. **Rescue therapy**; When iron need to be removed from organs after it is been deposited in organs. This is a slow and sometimes ineffective process.
3. **Emergency treatment**; When iron overload cause heart failure, it requires continues intravenous desferroxamine. It should be given nonstop, 24 hours for at least 3 to 6 months. This may be combined with deferiprone.

When to start chelation

Iron chelation is usually started at the age of 2 years when child has received either 10 to 12 transfusions or when serum ferritin is greater than 1000 µg/l on two consecutive readings. For children transfused from a very young age, consideration might be given to starting earlier than this, if the serum transferrin saturation exceeds 90%, and/or when 1000 g of pure red cells have been transfused.

The first chelation drug to be offered is DFO by sub-cutaneous infusions. If there is failure of adherence or if the patient is intolerant to DFO, then DFX should be started as soon as possible to prevent worsening iron loading. The patient must be monitored very closely particularly in the first weeks after starting treatment. Table 4 discuss about different types of chelators available and their usage with possible adverse effects.

Table 4: Available chelators

	Desferrioxamine	**Deferasirox**	**Deferiprone**
Route	Subcutaneous or IV	Oral	Oral
Frequency	8-12 hours 5-7 days/week	Once daily	Three times daily
Half-life	30 minutes	12 -16 hours	3-4 hours
Dose (mg/kg/day)	30-60	20-40	75-100 (divided dosed)
Adverse effects	Ocular and Auditory Retarded Growth Skin reactions	Gastritis, Renal and liver impairment	Neutropenia, arthralgia
Precautions	Monitor the ferritin level If therapeutic index falls < 0.025, reduce DFO Do audiometry and retinal examination annually especially in low ferritin levels <1000 Sepsis with Yersenia Renal impairment	Renal and liver impairment Renal tubular acidosis	Neutropenia ANC <500 will need hospital admissions and cover with broad spectrum antibiotics Arthropathy Liver function
Contraindications			Neutropenia <1500/dl
Investigations to be done during therapy	Monthly ALT Annual Pure tone audiometry and Ophthalmology	Twice before start, then weekly during first month after initiation and change of dose. Thereafter monthly Creatinine, ALT and Urine analysis Annual Pure tone audiometry and Ophthalmology	Weekly Neutrophils Monthly ALT
Drug interactions	Interference of excretion of Radio isotope scan Gallium-67 can interrupt result	Midazolam Theophylline Galliam-67 results	Aluminium containing oral antiacids Zinc Diclofenac Sodium (allow 4 hours) Gallium-67results

Practical prescribing of individual chelators

Iron chelation is started usually after 10-12 transfusions or when ferritin level increases to more than 1000ng/dl which usually comes at age of 2 to 3 years of age. Monotherapy is preferred. Usually, desferrioxamine is started. Combination therapy is started when monotherapy fails to reduce iron. A switch to DFX can be considered if adherence to DFO infusions is difficult. Ferritin can be controlled with DFO monotherapy at 30-60 mg/kg administered as an 8-10 hour infusion at least 5 times a week. A consistently low level of below 1000 gives a good prognosis. 30 mg/kg/day is preferred in growing children as initial dose. It takes a year to decrease cardiac iron by 3ms with a dose of 40-60mg/kg/day (Porter 2005). When cardiac MRI T2* is < 10 ms, as with other iron chelators, it will take several years of sustained and compliant therapy to normalise myocardial iron (Porter 2002). For T2* values <10ms, Patient should be admitted and give continuous intravenous doses of 50-60 mg/kg/day typically normalise LVEF in a period of three months (Anderson 2004).

Desferrioxamine (DFO)

Desferrioxamine is the drug of choice for initiation of chelation. Skin reactions are common and is not a contraindication to continuation of therapy. The increased toxicity of DFO at low levels of body iron is well established. Dose reductions can be guided using the therapeutic index, which is equal to mean daily dose (mg/kg) divided by serum ferritin level in µg/L to keep this < 0.025 (Porter, 1989).

Use with vitamin C

When patient is under DFO for few weeks, Vitamin C can be started at a dose of 2-3 mg/kg/day. Patient should take vitamin C after connecting DFO.

Deferasirox (DFX)

DFX can be prescribed as monotherapy after 2 years of age. It is dispersed in water or juice using a non-metallic stirrer and consumed as a drink once daily, preferably before a meal but can be used even after a meal if patient has gastritis. Dosage is started at 20 mg/kg/day and increased up to 40

mg/kg/day. It can be adjusted 3 monthly according to ferritin. If the patient is unable to take DFX regularly for reasons of tolerability (e.g., high serum creatinine) or adherence, consider switching to either DFO or DFO/DFP combination. In exceptional circumstances where other options are not possible, DFX/DFO combination can also be considered (Aydinok et al, 2015). The latter has been shown to produce a rapid decrease in liver iron stores.

Deferiprone (DFP)

DFP is a small molecule which is quite unstable and thus it works well at higher doses. DFP at high doses (90-100 mg/kg) was found to increase the T2* more than conventional s.c. DFO 5 days a week (Pennell 2006b) and because combined DFP + DFO has also been found to improve T2* more rapidly than conventional doses of DFO (Tanner 2007).

Dose adjustments in iron chelators

Optimal levels of iron; serum ferritin SF) is 500 - 1500 µg, liver iron concentration (LIC) is 3-7 mg/g dw and myocardial iron T2* > 20 ms. It is usually the liver iron that starts increasing before cardiac iron. Dose adjustments is required when there is an increase or high total body iron stores even without increase in cardiac iron. Higher LIC > 7 mg/g dw shows increased total body iron. The aim of chelation therapy in this group is bring SF and LIC down to optimal levels. Before increasing the dose ensure adherence to prescribed dose. Patient on DFO can be optimized either by increasing the frequency of infusions to 6 or 7 times per week or increasing the duration of infusion to at least 12 hours. In adults, dose can be increased to 50 mg/kg per infusion. Consider switching to combination of DFP with DFO. Higher doses of DFX above 30 mg/kg/day should be considered if increasing trend of LIC and/or ferritin. Dose can be increased every 3 months within the range of 20-40mg/kg/day, in increments of 5 mg/kg. If the cardiac T2* is improving and the ferritin is also improving current regime can often be continued. If the cardiac T2* is worsening, carefully examine patient's adherence. If the patient is unable to tolerate DFX or the patient is already on maximum doses, consider switching to DFP 75 - 100 mg/kg/day, seven days per week with escalated dose.

In increased myocardial and high body iron stores (SF consistently > 1500 µg/l, and/or LIC > 7 mg/g myocardial iron, Cardiac T2* 10 - 20 ms, DFO-containing regimes are better tolerated. Options to be considered will depend on the direction of the T2*change (also ferritin and LIC). Escalating DFX at maximal dosage (35-40 mg/kg/day). Daily combination of DFO 40 - 50mg/kg,
(initially at least 4-5 infusions per week) plus DFP 75-100mg/kg/ day, seven days per week. The dose of DFP should be determined by the cardiac T2* value. Intensive DFO chelation at 50-60mg/kg, 6-7 days per week with optimal adherence. Continuous subcutaneous (SC) or continuous IV DFO infusion through an indwelling venous device would also be options.

In severe myocardial iron loading (Myocardial T2* < 10 ms), and low LVEF, DFO at a dose of 50-60 mg/kg should be started immediately via a peripheral line and given as a continuous 24 hour IV infusion. A long-term intravenous line should be inserted to facilitate long-term therapy. Simultaneous addition of DFP (75-100mg/kg/day) should also be considered (Porter et al, 2013).

Dose reduction when body iron is low

Dose reduction is generally preferable to dose interruption (e.g. DFO 10 - 20mg/kg per infusion 5 per week; or DFX 5 - 10mg/kg/day, or DFP 50 - 75 mg/kg/ day). The chelator dose should be reduced if there is a rapid SF decline (of > 500 µg/dl over a three month period at absolute levels < 1000 µg/dl, or when LIC is 20ms. With DFO monotherapy, it is the dose per infusion that should be reduced rather than the infusion frequency. With combination therapies containing DFO, the infusion frequency can be reduced. Conversion from DFO to oral chelation should be considered if SF is consistently in the range 500 -750 µg/l, or if LIC is < 3 mg/g. Special Monitoring at low iron loads. Table 5 describes guideline for monitoring of chelation therapy.

Table 5: Monitoring iron chelation therapy			
	DFO	**DFP**	**DFX**
Neutrophil count	Not required	Weekly during therapy	Not required
Creatinine	Not required	Not required	Twice before start, then weekly during first month after initiation and change of dose thereafter monthly
ALT	Monthly	Monthly	Twice before start, then 2 weekly for the first month after initiation of therapy. Thereafter monthly
Urinalysis	Not required	Not required	Twice before start, then weekly during first month after initiation and change of dose. Thereafter monthly
Audiometry	Annual	6-12 monthly for combination DFO with DFP if not used as single agent	Annual
Ophthalmology	Annual	6-12 monthly for combination DFO with DFP if not used as single agent	Annual

Adopted from TIF guideline 2017 (A short guide for management of transfusion dependent thalassaemias)

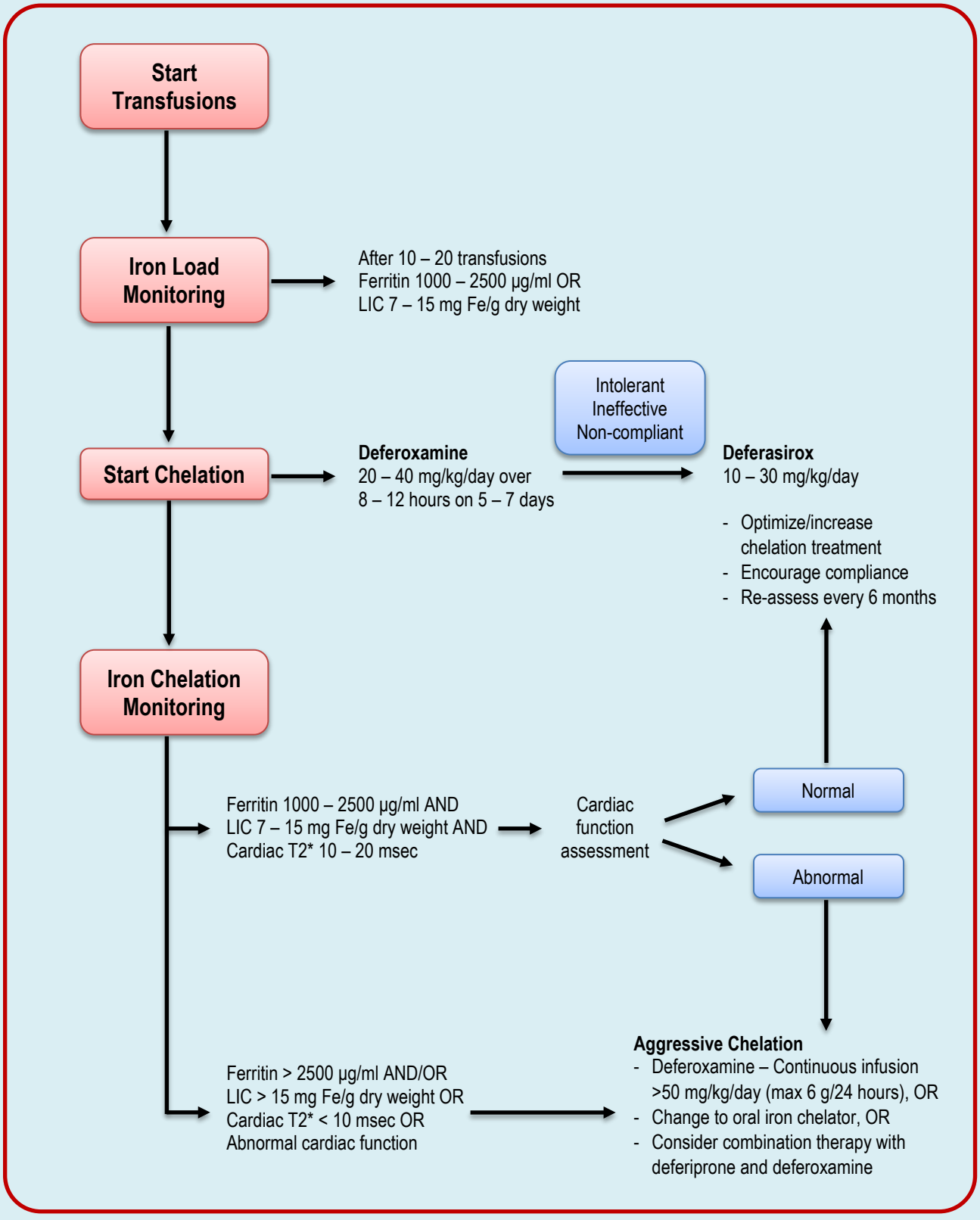

Figure 6: Monitoring of Iron Load and Appropriate Chelation Therapy

Chapter 5

COMPLICATIONS AND THEIR MANAGEMENT

Cardiac failure

Cardiac complications remain one of the major causes of mortality in thalassemia patients in the Maldives. Iron deposition in cardiac muscles cause myocyte failure, endothelial dysfunction, arrhythmia, pulmonary hypertension and to some extent vascular stiffening. Cardiac iron overload is reversible when continuous intravenous DFO is administered for months. However, the goal of chelation should always be to prevent iron deposition in the heart and if present to remove it before heart failure occurs. MRI T2* can identify cardiac iron before patient develops any cardiac failure symptoms. The development of heart failure implies generally advanced disease with poor prognosis. In addition to iron overload, deficiencies in nutrients such as carnitine, thiamine, vitamin D and selenium as well as endocrine disorders such as hypothyroidism, hypoparathyroidism and hypogonadism can also contribute to cardiac dysfunction

Clinical Manifestations

Patients with considerable cardiac iron overload may remain free of symptoms for long. Symptoms are generally related to the degree of ventricular impairment and may include left heart failure features (dyspnoea on exertion, orthopnoea, pulmonary rales) and/or right heart failure features (neck vein distension, hepatomegaly and peripheral oedema).

Assessment

1. Medical history with physical examination and 12 lead Echocardiography (ECG) and electrocardiography to assess cardiac function and possible pericardial effusion or pulmonary hypertension
2. Cardiac enzymes for possible myocarditis
3. D-dimers for possible pulmonary embolism in patients with right heart symptoms
4. Thyroid and parathyroid levels
5. Blood glucose
6. Cardiac CMR T2* should be performed as soon as practical. Cardiac dysfunction in the absence of a T2* < 20 ms should prompt alternative diagnoses. Contrast-enhanced cardiac MRI can also be used to screen for myocarditis.

Management of cardiac failure

Cardiac failure should be managed by cardiologist. Maintain a pre-transfusion haemoglobin of at least 10 g/dl and regular chelation therapy to maintain a CMR T2* >20 ms. A mild impairment of ventricular function merits aggressive escalation of iron chelation therapy, even if patients are completely asymptomatic. Combined therapy with deferiprone 75-100 mg/kg and desferrioxamine 40-50 mg/kg/day is the best option. Patients with cardiac T2* values below 6ms are at high risk for symptomatic heart failure (Kirk, 2009) and should be treated with intensive chelation, even if cardiac function remains normal.

1. All symptomatic heart failure patients should be managed in a tertiary care hospital. It should be communicated with doctors treating the patient in Maldivian Blood Services when patients are admitted in any hospital.
2. Use mild diuresis as over diuresis can precipitate acute renal failure. Furosemide drips can be easier to titrate than bolus diuretics.
3. Antihypertensive medications should be used cautiously thalassaemia patients typically has lower diastolic and mean blood pressures. Drugs for left ventricular dysfunction are angiotensin converting enzyme inhibitors (ACE inhibitors), beta-blockers and aldosterone antagonists, gradually titrated to the maximum tolerated according to heart failure guidelines.

4. Chelation in heart failure is continuous deferoxamine therapy at 50 mg/kg/day as long as they have adequate urine output. Deferiprone at 75 mg/kg/d, divided TID, should be added as soon as the patient is capable of tolerating oral medications. Heart function should be supported long enough for iron chelation therapy to work.
5. Ensure there is no arrhythmias
6. Maintenance of urinary output is imperative, since both desferoxamine and deferiprone are eliminated primarily by the kidney. Dialysis should be promptly initiated if kidney function fails despite optimal medical management
7. Heart transplant is the treatment of last resort.

Arrhythmias

Any arrhythmia associated with hemodynamic compromise, syncope or pre-syncope must be considered a medical emergency. Arrhythmias can be life threatening and difficult to control. Amiodarone is the drug of choice in the acute setting. Aggressive iron chelation therapy can reverse most of arrhythmias. Arrhythmias usually present as palpitations, but may sometimes be asymptomatic. In older patients, even without any evidence of current iron overload, there is a high incidence of Atrial Fibrillation (up to 40% of those over 40 years), which carried a high risk of stroke in this group of individuals who may carry increased thrombotic tendencies due to the main disease. Sudden death is rare in the modern era, but historical data suggests an association with increased QT dispersion, consistent with Torsades de Pointes as a possible mechanism. In poorly chelated patients complete heart block is relatively common.

Management of arrhythmias

1. Optimize chelation.
2. For most supraventricular arrhythmias, reassurance of the patient is generally appropriate.
3. Many arrhythmias reverse over time and thus antiarrhythmic therapy can often be short term (less than one year). Ventricular couplets and non-sustained ventricular tachycardia are highly specific for iron overload cardiomyopathy and require attention to address high myocardial iron load via intensified chelation.

4. Amiodarone is the drug of choice in the acute setting. Long term amiodarone therapy increases the risk of hypothyroidism because of pre-existing iron toxicity to the thyroid gland. Beta-blockers are generally well tolerated, if titrated slowly, and can be useful in controlling ectopic rhythms.

Atrial Fibrillation (AF)

AF occurring in an acute context, often precipitating heart failure, may be treated with immediate cardioversion by synchronized DC shock if its duration is less than 48 hrs. If hemodynamically stable, patient can be conventionally managed with anti-coagulation and introduction of parenteral amiodarone, simultaneously with intensive chelation. Cardioversion should be considered in patients who fail to revert to sinus rhythm with iron chelation therapy and pharmacological intervention. In patients with permanent or persistent AF radiofrequency isolation of the pulmonary veins may be considered. Anti-coagulation should be undertaken in all patients with significant episodes of AF.

Endocrine complications

Endocrine complications are common in iron overloaded patients. Even if asymptomatic screening for specific causes should start at the age specified below. If symptomatic screening should be done at the presentation. Prevention remains the first priority. Once endocrine complications have developed, management should focus on halting the progression of such complications and treating associated symptoms.

Growth failure and short stature

It is important that every patient must have a growth chart plotted every 6 months for height and weight. Growth standards are available at https://www.who.int/tools/child-growth-standards/standards.

Sex adjusted mid parental height

Boys: [Maternal height + Paternal height + 5 inches]/2

Girls: [Maternal height + Paternal height − 5 inches)]/2

In every 6 months assess for the following;

Growth rate (growth velocity expressed in cm/year, below 1SD for age and sex)

Growth failure is defined as a downward crossing of more than 2 percentile lines for height on the growth chart.

Short stature is defined as growing either below expected sex adjusted mid parental height or growing below −2 SD for age and sex.

Adolescent growth is associated with a decrease in growth velocity prior to the onset of puberty; this deceleration tends to be more pronounced in males. During pubertal development, sex hormones (testosterone and estrogen) are the primary drivers of growth and enhance growth hormone secretion, thereby facilitating pubertal growth acceleration. Girls typically experience growth acceleration during Tanner Stage 3 for breast development, whereas this acceleration occurs during Tanner Stage 4 for pubic hair development in boys.

Bone age

Radiograph of the left hand and wrist will be used by radiologist to assess for bone age.

A delayed bone age (skeletal age younger than chronological age) suggests catch-up potential for linear growth. Advanced bone age suggests a rapid maturation of the skeleton that may lead to earlier cessation of growth.

Pubertal age

Pubertal delay is defined as lack of pubertal development by age of 14 years in boys and by 13 years and/or no menstruation by age 16 in girls. Table 6 describes pubertal assessment according to tanner scale.

Penile development	Breast development	Growth of pubic hair
Early puberty (Enlarged scrotum and testes, 4-5ml with little or no enlargement of testes)	**Early puberty** (Breast bud stage)	**Early puberty** (sparse growth)
Mid puberty (Enlargement of penis in length and breadth. Increased pigmentation of scrotal skin)	**Mid puberty** (areola and nipple project separately from the contour of the breast)	**Mid-puberty** (hair extends over the pubic junction)
Adult	**Adult** (Fully developed breast, the areola no longer projects separately from the breast contour)	**Adult**

Table 6: pubertal assessments according to tanner scale. Adopted from TIF guide: TIF guideline 2017 (A short guide for management of transfusion dependent thalassaemias

Etiology

The most common cause of for growth failure and short stature in TDTM are chronic anemia and complications related to hemosiderosis. However other causes need to be ruled out.

1. Variation of normal
    a. Familial short stature (plot gender based mid parental height and assess for bone age which is same as chronological age in this)
    b. Constitutional delay (delay in bone age)
    c. Delayed puberty (Tanner staging and delay in bone age)
2. Nutrition and gastrointestinal conditions
    a. Malnutrition (delay in bone age)
    b. Malabsorption syndromes (Celiac disease, Inflammatory bowel disease)
    c. Vitamin A deficiency
    d. Zinc deficiency
    e. Carnitine deficiency
3. Genetic conditions (rule out Turner Syndrome in girls)
4. Endocrine conditions (delay in bone age)
    a. Hypothyroidism
    b. Growth hormone deficiency
    c. Poorly controlled diabetes mellitus
    d. Poorly controlled diabetes insipidus
    e. Metabolic bone disease: rickets, hypophosphatasia
    f. Glucocorticoid excess
5. Psychosocial causes
6. Renal conditions
    a. Renal tubular acidosis
    b. Nephrotic syndrome
7. Medications
    a. Desferrioxamine excess above therapeutic index (therapeutic index = mean daily dose (mg/kg)/SF µg/L) to keep this < 0.025 to avoid growth retardation caused by desferrioxamine)

b. Glucocorticoids
c. Inappropriate sex steroid exposure
d. Antiepileptic medications

Investigation

1. Haemoglobin
2. Ferritin
3. MRI for Liver Iron Concentration and Heart Ion Concentration
4. Protein-calorie malnutrition,
5. Calcium Homeostatis (Calcium, Phosphate, ALP, Vitamin D level, PTH)
6. Bone age from Xray of left hand and wrist (Bone age to be done if above 6-7 years of age)
7. Bone mineral density during late childhood
8. Growth hormone level
9. Pituitary growth axis (insulin-like growth factor-I (IGF-I) for (Insulin Growth Factor Binding Protein-3 (IGFBP-3)
10. Liver profile
11. Hypogonadism (test GnRH, LH, FSH and hCG)
12. Thyroid profile (TSH and free T4)
13. Delayed Puberty (testosterone, estradiol, LH, FSH)
14. To exclude coeliac disease IgA transglutaminase antibodies

Treatment

1. Maintain pre-transfusion Hb >9gm/dl
2. Maintain ferritin <1000 ng/ml
3. Use of new iron-chelators with lower toxicity on the skeleton and with better patient compliance
4. Correction of nutritional deficiencies (protein-calorie, folate, vitamin D, vitamin A, zinc, carnitine) when suspected
5. Refer to endocrinologist for management of endocrine disorder (GH deficiency, pubertal delay, hypothyroidism and abnormal glucose homeostasis and diabetes mellitus, stimulation of GH-IGH axis). Age of 16 is ideal for reference.

Delayed Puberty and Hypogonadism

Delayed puberty is defined as the complete lack of pubertal development in boys by the age of 14 and in girls no breast development by age 13 and no menstruation by age 16.

Hypogonadism is defined in boys as the absence of testicular enlargement (less than 4 ml), and in girls as the absence of breast development by the age of 16

***Hypogonadotropic Hypogonadism*;** The GnRH pulse generator may be disrupted by hemosiderin. Excess prolactin, stress, chronic illness, malnutrition, or excessive physical activity.

Arrested puberty is a relatively common complication in moderately or grossly iron overloaded patients with TM, and is characterised by a lack of pubertal progression over a year or more. In such cases, the testicular size remains 6-8 ml, and breast size at B3. In such cases annual growth velocity is either markedly reduced or completely absent (Sanctis, 2013a). Hypogonadism in adolescents and adults with TM has prevalence of 38% in females and 43% in males

Constitutional delay of growth and puberty Patient is consistently short for chronological age but appropriate for bone age. The bones mature and grows as puberty arise later. Usually there is a family history of delay in puberty. Bone age is delayed. A bone age that correlates with the patient's pubertal status confirms it. Systemic examination is mostly normal except delayed dentition. No treatment is required. Watchful waiting is usually the appropriate course of action.

History

Assess the following

1. age
2. severity of iron overload
3. damage to the hypothalamopituitary-gonadal axis
4. chronic liver disease
5. psychological problems

Investigations

1. Thyroid function (TSH and FT4)
2. bone age (X-ray of wrist and hand)
3. bone mineral density (BMD)
4. Testing the hypothalamic-pituitary-gonadal axis (hypogonadotropic hypogonadism)- patients with TM and delayed puberty/hypogonadism have
5. Lower basal FSH and LH secretion. - Low LH/FSH response to GnRH (gonadotropin releasing hormone) and - Variable disturbance of the spontaneous pulsatile pattern of LH and FSH secretion. - Low basal sex steroid levels (estradiol and testosterone). - n some cases low testosterone secretion in response to human chorionic gonadotropin (HCG). •
6. Pelvic ultrasound to assess ovarian and uterine size in females

Treatment

For girls, therapy may begin with the oral administration of ethinyl estradiol (2.5-5 μg daily) for six months, followed by hormonal reassessment. conjugated estrogens (Premarin) at 0.3 mg daily for the first 6 mo and 0.625 mg daily for the second 6 mo (NELSON). If spontaneous puberty does not occur within six months after the end of treatment, oral oestrogen is re-introduced in gradually increasing dosages (ethinyl estradiol from 5-10 μg daily) for another 12 months. If breakthrough uterine bleeding does not occur, low oestrogen-progesterone hormone replacement is the recommended treatment.

For delayed puberty in males, low dosages of intramuscular depot-testosterone esters (30-50 mg) are given monthly for six months, followed by hormonal re-assessment. In patients with hypogonadotrophic hypogonadism, treatment at a dose of 50 mg per month can be continued until growth rates wane. The fully virilising dose is 75-100 mg of depot-testosterone esters every 10 days, administered intramuscularly after growth is almost completed and afterwards. The same effects can be achieved with topical testosterone gel. For pubertal arrest, the treatment consists of testosterone esters or topical testosterone gel, administered as for the treatment of delayed puberty

and hypogonadotrophic hypogonadism. It is important that the treatment of pubertal disorders is considered on a patient-by patient basis, taking account of the complexity of the issues involved and the many associated complications.

Hypothyroidism

All TDTM patients should undergo annual screen for hypothyroidism from 9 years of age or younger than that if symptomatic. Hypothyroidsm is defines as having high TSH with normal or low free T4.

Signs and Symptoms

Weight gain is mostly caused by fluid retention (myxedema), not true obesity. Myxedematous changes of the skin, constipation, cold intolerance, decreased energy, and an increased need for sleep develop insidiously. School performance usually does not suffer, even in severely hypothyroid children. Additional features may include bradycardia, muscle weakness or cramps, nerve entrapment, and ataxia. Adolescents typically have delayed puberty. Older adolescent females may have menometrorrhagia, and some may develop galactorrhea

Investigations

1. TSH
2. Free T4
3. In complicated cases need to rule out specific conditions mentioned above

Treatment

Levothyroxine (LT4) is the treatment for children with hypothyroidism. The dose on a weight basis gradually decreases with age. The daily once dose of LT4 are;

a. 1-3 yr, is 4-6 µg/kg
b. 3-10 yr, 3-5 µg/kg
c. 10-16 yr, 2-4 µg/kg
d. Above 16 yrs, 1.7 µg /kg (maximum dose is 300 µg)

Treatment should be monitored by measuring serum TSH with free T4 every 4-6 mo, as well as 4-6 week after any change in dosage. Dose should be adjusted to have normal TSH for age and free

T4 at upper half of range. In the initial days of treatment poor sleeping habits, restlessness, short attention span, and behavioral problems may develop. In people with **central hypothyroidism**, in which TSH levels by definition do not reflect systemic thyroid status, serum free T4 alone should be monitored and maintained in the upper half of the age-specific reference range.

Complications

In severe and selected cases of hypothyroidism, complications can include brady cardia, cardiac failure, pericardial effusion, delayed puberty, stunted growth, impaired lipid metabolism and bone demineralization.

Diabetes Mellitus (DM) and Impaired Glucose Tolerance (IGT)

IGT and DM are common in poorly chelated patients. However, it is also found in well chelated patients as well.

Sign and Symptoms

Polydipsia, polyuria, weight loss and enuresis are common. In undiagnosed cases diabetic coma causes vomiting, dehydration, abdominal pain, hyperventilation, drowsiness and coma. Screening should be done annually for those above 11 years.

Investigations

The oral glucose tolerance test (OGTT) should be done in every patient with thalassaemia after the age of eleven or earlier if needed

Diagnosis

1. fasting plasma glucose 5.1–6.9 mmol/L (92–125 mg/dL)
2. 1-hour plasma glucose 10.0 mmol/L (180 mg/dL) following a 75 g oral glucose load
3. 2-hour plasma glucose 8.5–11.0 mmol/L (153–199 mg/dL) following a 75 g oral glucose load

Note: OGTT to be significant when 2 values are deranged.

Treatment

1. Strict diabetic diet
2. Regular physical activity
3. Intensive chelation therapy
4. Oral hypoglycemic drugs: introducing oral hypoglycemic drugs in the early stage of DM before dependence on insulin may be beneficial
5. Insulin

Monitoring glycaemic control

1. Daily home capillary glucose monitoring
2. Urine ketones if blood sugar is above 250 mg/dl
3. Fructosamine estimation every month (HbA1c is not a reliable indicator of glycaemic control because of reduced red cell lifespan, ineffective haemopoiesis and frequent blood transfusions, all of which may potentially affect the validity of the HbA1c result)
4. Renal function
5. Urinary microalbumin and protein
6. Evaluation of retinopathy

Hypoparathyroidism (HPT)

These common complications present in patients after age of 16 years. Therefore, all patients turning to 16 should be investigated.

Clinical manifestation

1. Paraesthesia
2. Tetany
3. Seizures
4. Cardiac failure.

Investigations

1. Serum Calcium
2. Phosphate

3. Parathyroid hormone

Treatment

The aim of treatment is to prevent acute and chronic complication of hypocalcemia and to maintain normal phosphate level. Treatment include the following:

1. Oral Vitamin D (monitoring of serum calcium is needed to prevent hypercalcemia)
2. Calcitriol, 0.25-1.0 µg, twice daily (monitor plasma calcium and phosphate and 24 hour urinary calcium and phosphate level)
3. Phosphate binder if persistently high phosphate
4. Intravenous calcium for symptomatic hypocalcemia.
5. Instruct patient to take foods rich in calcium and low in phosphorous.

Adrenal Insufficiency

Sign and symptoms and management

Adrenal insufficiency is mostly subclinical and may manifest when patient is in critical condition. Symptoms include asthenia, muscle weakness, arthralgias and weight loss. Subclinical impairment of adrenocortical function in patients with TM is not uncommon; however, it is of little or no clinical impact under basal conditions but may have a potential relevance during stressful events. Accordingly, glucocorticoid treatment coverage might be advised only for stressful conditions.

Osteoporosis

Osteoporosis is defined as BMD T-score <-2.5 leading to higher risk of fracture.

Osteopenia is defined as BMD T-score between - 1 and - 2.5. Normal BMD: T-score > -1.0.

T-score is defined as the number of standard deviations (SD) by which a patient's bone mass is above or below the mean peak bone mass for a 30-year-old healthy woman.

Diagnosis

Bone mineral density (BMD) measured by DXA scan is the gold standard for the measurement of bone mineralization. It is a non-invasive technique and can be performed at the hip, lumbar spine, and distal radius. Annual checking of BMD starts in adolescence.

Prevention and management of osteoporosis

1. Ensure enough intake of calcium, and supplement if low.
2. Vitamin D supplementation
3. Enough physical activity
4. Optimize pretransfusion Hb and iron chelation
5. Manage diabetes
6. Treat hypogonadism with transdermal oestrogen for females or human chorionic gonadotrophin for males.
7. Bisphosphonates

Fertility and Pregnancy

Although spontaneous fertility can occur in intact hypothalamic-pituitary-gonadal axis well-transfused and well-chelated patients with spontaneous puberty and normal menstrual function, the majority are subfertile mainly due to Hypogonadotrophic Hypogonadism (HH) as a consequence of transfusional haemosiderosis (Skordis, 1998). Those who fail to achieve pregnancy spontaneously require Assisted Reproductive Techniques (ART). Planned pregnancy is essential under a multidisciplinary team including, haematologist, the reproductive medicine specialist, the cardiologist and the obstetrician, in conjunction with the specialist nurse rule out other endocrine anomalies such as hypothyroidism and hypothyroidism. Evaluate the partner (Baseline testosterone and semen analysis for males)

Induction of ovulation should therefore only be undertaken by a specialist reproductive team, according to Human Fertilization and Embryology Authority due to risks such Ovarian hyperstimulation syndrome (OHSS).

Before pregnancy

1. If splenectomy done. All the vaccination to be completed
2. Rubella immunization if no IgG present against rubella.
    a. Both partners should be screened for haemoglobinopathies.
3. Is hypothalamic-pituitary-gonadal axis intact?

Counseling before pregnancy

1. Arrange genetic counselling if necessary
2. Pregnancy-specific complications such as ante-partum haemorrhage and preeclampsia, birth defects, miscarriage in thalassaemia are similar to that in the background population.
3. Risk of preterm delivery is twice high.
4. Pre-transfusion haemoglobin concentrations above 10 g/dl.
5. Cardiac load is increased during pregnancy by at least 25-30%.
6. Potential for premature death from cardiac failure in case of severe dysfunction and significant arrhythmias
7. Dietary habits, stop smoking and alcohol, and to commence supplements of folic acid, calcium and vitamin D.
8. Review of medications before and during pregnancy in thalassemia
    a. Folic acid supplementation 400mcg once daily to start 3 months prior to pregnancy
    b. If using Metformin, it can be continued, but may need to change oral hypoglycemic drugs to Insulin
    c. Calcium and Vitamin D supplementation during pregnancy and lactation (1000mg daily of Calcium with Vit D3 400-600 IU in the second and third trimester)
    d. Switch from oral iron chelators to subcutaneous desferrioxamine prior to induction of ovulation/spermatogenesis and stop DFX.
    e. Stop hormone replacement therapy at least 4-6 weeks prior to induction of gametogenesis.
    f. Stop bisphosphonates 6 months prior to conception and during breast-feeding
    g. Medications that should be discontinued for at least six months prior to fertility treatment include interferon, ribovarin and hydroxyurea.
    h. Ensure patients are euthyroid by increasing thyroxin

i. Switch carbimazole to propyl thiouracil.

Before pregnancy all female patients should be evaluated for

1. Routine investigations
    a. Full blood count
    b. Clotting factors
2. Iron status
    a. Serum ferritin
3. Degree of cardiac impairment using
    a. ECG at rest, with exercise and 24 hours for dysrhythmias.
    b. Echocardiography to aim for left ventricular ejection fraction >65% and fractional shortening >30%.
    c. Modified magnetic resonance imaging (MRI) using gradient T2* measurements, can quantify iron levels, and can accurately relate these to left ventricular dimensions assessed using the same technique. Aim for T2* of less than 20 ms
4. liver dysfunction
    a. liver function tests
    b. Ultrasound of the liver
    c. MRI liver for iron and fibrosis
5. Risk of vertical transmission of viruses.
    a. Screen for the human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C and rubella.
6. Bone heath
    a. Serum Calcium, Vitamin D levels
    b. Plain radiography of the spine
    c. Dual-energy x-ray absorptiometry scanning of the hip and spine
7. Endocrine anomalies
    a. Thyroid function
    b. RBS, PPBS, glycosated Fructose or HbA1C
8. Feasibility evaluation includes the following elements
    a. Hypothalamic - Pituitary - Gonadal axis

b. Assessment of ovulation
c. Ultrasound of the uterus and ovaries
d. Post coital test
e. Hysterosalpingography

During Pregnancy

1. Screened for gestational diabetes at 24 to 28 weeks with OGTT.
2. Serial ultrasound scans including anomaly scans at 18 to 24 weeks and growth scans in 3rd trimester usually after 32 weeks must be undertaken to monitor foetal growth.
3. Continue folic acid, calcium and vitamin D supplements.
4. Do not use iron supplements alone or in combination.
5. If cardiac function deteriorates during pregnancy, deferoxamine may be used with caution after the first trimester. Risk of fetal anomalies is not reported in humans but in animal studies it has been found. Low dose deferoxamine may be used during prolonged labour in patients with cardiac disease.

Contraception

All patients should be offered counseling regarding contraception. Intrauterine devices and estrogen-containing birth control pills should be avoided (Low dose estrogen can be used). Progesterone-only pills, injections (Depo-Provera), implants, Mirena, copper IUD, and barrier methods are safe and effective. The combined oestrogen/progesterone oral contraceptives can also be used with caution. Male patients with HH are not fertile spontaneously and therefore contraception is not required.

Chapter 6

HAEMOPOIETIC STEM CELL TRANSPLANTATION

Success of bone marrow heavily depends on

1. How regular and quality is the chelation through out
2. Hepatomegaly
3. liver fibrosis
4. age of child (young age is better)
5. Experience in the centre of BMT

Donors can be

1. compatible siblings
2. compatible sibling donor
3. Matched unrelated cord blood
4. Mismatched related donors

Post-transplant clinical follow-up of BMT is of particular importance.

1. Within the first year, monitor for
    a. hematological and engraftment parameters
    b. infectious complications
    c. graft versus host disease is essential
2. Appropriate immunization is necessary in the second year

3. Long-term follow up
    a. Multi-system assessment (iron overload, pubertal development, growth and endocrine deficiencies) related to the primary disease.
    b. Iron chelation; A number of reports indicate that iron overload, chronic hepatitis, cardiac function and endocrine deficiencies can be managed more easily after transplant, sometimes permitting the healing of severely damaged organs (Muretto 2002). It is also particularly important to remove excess iron after transplant. This can usually be achieved by repeated venesections (6 ml/kg blood withdrawn at 14-day intervals) (Angelucci 1997), or by chelation therapy. If venesections are not feasible, oral chelation can be proposed with standard dosing schedule. The reported agranulocytosis events with Deferiprone warrant caution when using this drug. All iron removal treatments should be started only once the graft is stabilized, and the patient free from any immunosuppressive treatment or prophylaxis, and in the absence of chronic GvHD. Endocrine dysfunction and infertility require specific expertise and follow up after HSCT, although several spontaneous and successful conceptions have been registered after HSCT in paternal and maternal treated subjects

Chapter 7

LIFESTYLE AND PSYCHOSOCIAL SUPPORT

As thalassemia is a chronic disease, management approach differs markedly at different ages. Psychosocial support varies at different ages.

Limitations that the disease imposes but also the effect that the treatment regimens have on the patients' lifestyle

Leading a "normal" life is an often-expressed priority for patients. This includes social integration, connecting and interacting with people and contributing to society, despite counter forces that the disease and its treatment bring, which can lead to isolation, and in some society's stigmatisation.

Counseling at point of diagnosis

What health professions should understand is that parents will undergo a series of changes after their child is diagnosed with thalassaemia (shock, denial, sadness/anger, adaptation, reorganization) (Drotar, 1975).

The following should be done;

1. Provide reliable information (will need to be repeated)
2. Teach tasks associated with caring for a child with thalassaemia.
3. Enough opportunities should be given to ask questions and share concerns.
4. Allow occasions to meet parents of older children diagnosed with thalassaemia, as this can help increase social support and confidence, while decreasing feelings of helplessness and hopelessness.
5. Access to psychosocial clinicians who can help them explore and manage their feelings of loss in a constructive manner.

6. Ensure parents accept and learn to effectively cope with their child's chronic medical condition.

Counseling at Start of blood transfusion

1. A developmentally appropriate verbal explanation of what the child will see, hear, feel, and smell during, before, and after the procedure.
2. Minimally threatening, but accurate information, as children who are given information that turns out not to be true (e.g., "you will not feel a thing" when in fact the child is liable to experience some pain), are more likely to develop a distrustful relationship with their parents and/or the medical team, which may negatively affect future interactions.
3. Teach parents distraction techniques such as parent company, use of visual aids (e.g., books, pictures, models, videos).
4. Medical play can help young children understand their therapeutic regimen
5. Time for the child to ask questions.

Counseling at Initiation of chelation

1. Encourage parent and child to carefully consider their chelation options, and determine which option best fits with their own capacities and their child's personality characteristics
2. use of incentives (verbal praise, stickers, or small toys or other incentives earned either immediately or over time are particularly useful for paediatric patients who don't yet understand the intrinsic value of adhering to an undesirable medical regimen.
3. Start from where the patient is at, gradually increasing goals, while working towards the ideal.
4. Need revision over time.
5. Provide age-appropriate education
6. Set alarms; use visual reminders
7. Work with the medical team to change the regimen to fit better with the patient's lifestyle
8. use a self-monitoring chart to document completion of tasks
9. Find ways to help minimize or cope with the side effects

10. Help the patient find activities to do to during the treatment
11. Engage the patient in treatment aimed at improving self-esteem
12. encourage the patient to meet other individuals with similar medical conditions
13. Increase adult involvement and monitoring
14. Work with family to understand their beliefs and when possible adapt treatments to fit within their values

Adolescence and transition to increased self-care

Because adolescents are vulnerable to having their decision making being driven by their desire to be independent and to fit-in with peers, parents need to continue to play an active role in monitoring adolescents self-care. Shared responsibility between the patient and caregiver has been found to be associated with better adherence

transition of responsibility has to be:

1. Done gradually over time, starting when children are young
2. Teach older patients how to take over responsibility such as checking when to go and see doctor, and get medicine from pharmacy.

Transition to adult Care and Adult thalassemia patients

Take every opportunity to orient the patient to an adult clinic and the adult care system. Ensure following;

1. Are they involved in activities such as sports?
2. Issues in social life
3. Ensure about no smoking and alcohol
4. Discuss about education and clinic visits interfere with the education program
5. Any need for clinic times adjustment
6. Employment – what jobs are they in
7. Marriage and family

Psychosocial support throughout the lifespan as part of standard care

This is best accomplished through a multidisciplinary team approach, which include nurses, social workers and psychologists who meet with the patient and families on a regular basis as part of their standard care.

Motivational facts

1. In a well-publicised case, a patient with thalassaemia major ran the London marathon on two occasions
2. Many have completed university education
3. Many ladies have conceived and have growing children
4. Many are employed

Nutrition

Iron

In regularly transfused thalassaemia major patients the contribution of dietary intake of iron is not significant when compared with transfusional iron intake.

Anemia also increases GIT iron absorption. Avoid falling of Hb below 7 to decrease gastrointestinal absorption.

Taking black tea with meals may reduce iron absorption, while foods rich in vitamin C will increase absorption

Zinc

Zinc is an essential element which in thalassaemia can be either removed by iron chelating drugs

The usual dose is 125mg 1-3 times daily

Calcium and Vitamin D

Calcium and vitamin D are the most commonly prescribed supplements for thalassaemia patients. Calcium homeostasis is intimately related to Vitamin D, and deficiency of this vitamin in thalassaemia ranges from 85%. Deficiency of calcium and vitamin D results in poor bone mineralization which contributes to thalassaemic bone diseases. Deficiency is also associated with muscle weakness, and more importantly can affect the heart muscle, causing left ventricular dysfunction associated with cardiac iron uptake (Wood 2008). Vitamin D and Calcium supplementation is recommended for all patients at a dose of 2000IU/day (Fung, 2011). It is also suggested that vitamin levels are monitored every 6 months in thalassaemia patients (Nakavachara, 2013 & Fung, 2011). A diet high in calcium, including milk, cheese, and oily fish is also recommended.

Folic acid

Patients on high transfusion regimes rarely develop folate deficiency, in contrast to those on low transfusion regimens folic acid supplements at up to 1mg/day

Vitamin E

Vegetable oils (e.g. olive oil, corn oil, safflower and sunflower oil), nuts and cereals.

Vitamin C

is known to promote the absorption of dietary iron, and even regularly transfused patients should control their intake of iron. Vitamin C increases labile iron and therefore contributes to iron toxicity. The increased availability of chelatable iron allows desferrioxamine to excrete more iron. In order to avoid toxicity, the vitamin is given at the time of desferrioxamine infusion at a dose not exceeding 2-3mg/kg. This benefit is not seen with the other chelating agents.

Oral Hygiene and Dental Care

In view of this, patients should be maintained closely on a preventive programme with regular follow-up. Oral hygiene instructions, dietary advice and preventive measures including prophylaxis, fluoride application, and fissure sealants should be implemented to minimize the need for invasive dental procedures. Dentists also need to be aware of the orofacial manifestations of thalassaemia so that they can be identified early and appropriately managed.

Immunization

Immunizations of all thalassemia patients are recommended for following even if not splenectomized.

1. Pneumococcal
2. Meningococcal
3. Haemophilus influenzae type B
4. Hepatitis B
5. Inlfuenza

Chapter 8

EMERGENCIES

Sepsis

Consider possible causes and investigations. Infections are typically bacterial and are often rapidly progressive and potentially fatal. Infections are the second most common cause of death in TM, after cardiac complications. Thalassaemia patients should be treated as if immunocompromised if they have a fever. Always admit in hospital. Organisms can be gram negative and gram positive as well especially Klebsiella and Yersinia (mainly GI symptoms).

Management

Investigate to look for a focus of infection. Provide early fluids (avoid overload since many patients have cardiac involvement due to iron toxicity - each case must be assessed according to cardiac status). Administer early antibiotics. Broad spectrum Cefotaxime and Amikacin should be used. Ciprofloxacillin is a good choice for adult patients. Monitor parameters e.g. mean arterial pressure, central venous pressure, lactate. Provide inotropic agents if indicated

Anemia

Sudden fall in Hb may result from:

1. delayed transfusion reactions
2. bleeding (e.g. GI from peptic ulcer)
3. infections such as parvovirius infection (B19) (may lead to Aplastic crisis)
4. delayed transfusion reactions
5. enlarged spleen (sub-acute)
6. folate deficiency
7. G6PD deficiency with haemolysis

Dyspnoea

Possible causes include the following.

1. ***Heart failure resulting from cardiomyopathy***: History includes rapid progression from severe to fatal. On examination the patient will have abdominal pain, peripheral oedema, low BP, rapid pulse, dysrhythmia is common, raised Jugular Venous Pressure (JVP), liver congestion, pericardial rub, faint sounds.

Investigations; cardiac MRI, echocardiogram

Treatment; Immediate iv DFO infusion unless contraindicated (allergy, suspected Yersinia infection) with a dose of 40-50mg/kg day as a continuous iv infusion dissolved in 100-500ml of saline.

2. Pericarditis
3. Pulmonary embolism
4. Pulmonary hypertension
5. Anaemia
6. Rib micro-fractures and splinting

Oedema

Possible causes;

1. Congestive heart failure
2. Venous thrombosis, more likely in TI. may present with typical leg DVT. other sites include mesenteric blood vessels. multiple small pulmonary emboli (PE).
3. Hypoalbuminemia renal protein loss - check urine protein. liver failure - check LFTS.
4. Acute renal failure

Chest Pain

Possible causes;

1. Pulmonary embolism (do dimer, high resolution CT)
2. Rib (micro) fracture palpate chest wall - pain on gentle pressure.
3. Pericarditis (listen for heart sounds, do ECG, echocardiogram.

4. Acute coronary syndrome (very rare)

Abdominal Pain

Consider possible causes and investigations.

1. Congestive heart failure may present as abdominal rather than chest pain, caused by distension of the liver capsule.
2. Cholecystitis due to pigment gallstones. (do abdominal ultrasound, serum and urine bilirubin, Alkaline Phosphatase, consider ERCP.
3. Yersinia infection is more commonly seen in patients receiving desferrioxamine. desferrioxamine should be stopped until diagnosis is confirmed
4. Portal vein thrombosis
5. Mesenteric infarction
6. Renal stone common in TM due to hypercalciuria (do USG KUB and urine RE for RBCs)
7. Peritonitis especially in splenectomised patients.
8. Gastroenteritis
9. Acute appendicitis.

Headaches

Consider possible causes and investigations.

1. Fever without focus (ask for associated symptoms, check for papilloedema and do septic screen)
2. Cerebral abscesses; Klebsiella may be the causative agent. Cerebral abscess commonly presents as headache, fever and/or neurological features, but often with a non-specific prodromal phase.
3. Meningitis - especially if the patient is splenectomised.
4. Sinusitis - more commonly seen in TI due to distortion of sinuses (extramedullary erythropoiesis).
5. Otitis media - more commonly seen in TI patients due to distortion of sinuses.
6. Extramedullary haemopoietic mass - rarely occurs intra-cranially.
7. Drug-related headaches (e.g. interferon, used in the treatment of chronic HC and/or HB).

Syncope and Altered Level of Consciousness

Consider causes include the following.

1. Tachydysrhythmias, such as atrial fibrillation or ventricular tachycardia (may result from iron-mediated cardiomyopathy, electrolyte disturbances such as hypocalcaemia)
2. pulmonary emboli - small pulmonary emboli are quite common in TI but may also occur in TM (red cells are prothrombotic in thalassaemia).
3. GI bleed drugs - e.g. non-steroidal (also take into account side-effects of iron chelation drugs, such as upper GI ulceration). varices - some older patients have varices secondary to portal hypertension.
4. Postural hypotension or vasovagal syndrome many TM patients have low resting blood pressure, and inadequate postural response may cause syncope.
5. Brain abscess
6. Hypovolaemia (fluid loss, acute severe anaemia)

Neurological Complications

Causes to consider.

1. Spinal cord lesions due to focal deficits due to extramedullary haematopoiesis - may occur anywhere but often results in spinal deposition with weakness, paraesthesia and sensory loss in the legs. Difficulty in bladder control or urgency may also be a presenting feature.
2. Cerebral abscess - bacteraemia may result in central brain abscess, often reported with Klebsiella pathogen. Symptoms may be non-specific, such as malaise and headache. Brain MRI is recommended where available.
3. Meningitis - more likely to be seen in splenectomised patients Spinal thrombosis - rare complication which presents with acute motor or sensory feature, often with a neurological dimension. MRI is the initial investigation of choice.
4. Deteriorating hearing or tinnitus. known side-effect of desferrioxamine overdosing - consider iron chelation regimen. stop desferrioxamine and seek audiometry assessment. Change in visual acuity or colour vision. known side-effect of desferrioxamine overdosing - consider iron chelation regimen. stop desferrioxamine and seek electro-retinography.
5. diabetic retinopathy, which may also result in sudden visual deterioration.

Back Pain

Causes to consider

1. Osteoporosis; Degenerative changes of the intervertebral disc - a common cause of back pain. More common in the lower thoracic and upper lumbar spine (compared to non-thalassaemic patients, more commonly affected in the two lower lumbar discs). Extramedullary haemopoietic masses may cause spinal cord compression. neurological signs of cord compression more likely to be present than pain. Flattening of the vertebral bodies (platyspondyly) in the lumbar and thoracic regions. Investigations exclude neurological deficit on examination. spinal X-ray and MRI (best method of assessing extramedullary haematopoiesis and also disc degeneration).

Trauma

In thalassaemia, be alert to possible;

1. Splenic rupture
2. Bone fracture

Involve surgeons early in the management

Chapter 9

SPLENECTOMY

There is a guarded approach to restrict splenectomy.

Before referring to splenectomy rule out;

a. Alloimmunization
b. Concurrent infections
c. Suboptimal transfusion therapy
d. Malignancy by peripheral blood smear

Indications for splenectomy

a. Increased annual transfusion requirement of more than 220 ml/kg/ year
b. Pancytopenia

Adverse effects after splenectomy are

a. venous thrombosis
b. pulmonary hypertension
c. infections (Spelenctomy should be avoid in children below 5 years as it predisposes to severe infection)

Planning Splenectomy

The following should be done

1. Peripheral blood smear
2. G6PD status if not done before
3. Vaccination should be done 2 weeks before splenectomy for following;
    a. Meningococcal
    b. Hemophilus Influenza B

   c. Streptococcus pneumonia
   d. Seasonal Influenza virus
4. Counsel the patient for appendicectomy in the same setting

Follow up and treatment after splenectomy

1. Thrombocytosis; Aspirin is recommended 3-6mg/kg/day if platelet is more than 1,000,000 /mm^3
2. 6 to 12 monthly echocardiography to screen for Pulmonary hypertension
3. Repeat vaccinations after 3 years for
   a. Meningococcal
   b. Hemophilus Influenza B
   c. Streptococcus pneumonia
4. Annual vaccination for Seasonal Influenza virus
5. Chemoprophaylaxis for splenectomized patients above 5 years should be given with oral Penicillin 250 mg BD for at least 2 years or lifelong. In case of allergy or non-availability of Penicillin, amoxicillin, trimethoprimsulfomethoxazole (if G6PD is normal) and erythromycin can be used.
6. Yearly scan for iron concentration of liver and heart

REFERENCES

Thein, S. L. (2005). Pathophysiology of β Thalassemia- A guide to molecular therapies. Haemoglobinopathies. Retrieved from https://ashpublications.org/hematology/article/2005/1/31/19297/Pathophysiology-of-Thalassemia-A-Guide-to.