THALASSAEMIA INTERNATIONAL FEDERATION

The Maldives
WHO Mission August 2014

REPORT

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Executive Summary

- The Republic of the Maldives has one of the highest carrier rates of the beta thalassaemias in the world:
  Beta thalassaemia carriers 16-18%
  Alpha thalassaemia carriers 2.1%
  HbE carriers 0.9%, HbS carriers 0.13% and HbD carriers 0.43%
- A national register of thalassaemia patients has been kept over many years, which includes 563 currently living- this is roughly 1.6/1000 of the total population. 288 are living in the capital Male while roughly the other half live in atolls.

  According to the diagnosis the patients are divided into the following categories:
  - Transfusion dependent beta thalassaemia major – 459 patients(age distribution of these patients is provided in annex the eldest being 36 years old, median around 13 years)
  - Non-transfusion dependent thalassaemia – 88 patients
  - Of these Thalassaemia intermedia – 6 patients
  - HbE/beta thalassaemia -82 patients
  - Sickle cell syndromes -11 patients
  - Of these 10 patients have HbS/ beta thalassaemia and 1 patient has HbS/HbD
  - HbH disease (alpha thalassaemia) – 3 patients
  - Other haemolytic anaemias – 2 patients
- The beta thalassaemias are clinical entities that are lethal if no treatment is offered and shorten life if inadequately treated
- A situation analysis of current services thalassaemia was prepared based on information provided by local health professionals. This is in order to adapt international guidelines to the needs and the ability of the country to adopt them in the near future, since new technology is needed and organizational have to be addressed
- Issues that have to be considered include the difference in care of patients living in and near Male compared to those in the Atolls, the need for continued supplies of drugs and consumables and issues of collaboration between blood banks and between clinicians of the thalassaemia centre and the hospital when inpatient care is needed.
- The key to better care is the need to involve medical specialists in the monitoring and care of patients, especially when they reach adolescence when multi-organ involvement becomes prominent. The main need in specialities concerns:
  - Cardiology – there is a specialist keen to help but since at present he is alone on the islands he is busy
  - Psychological support for selected cases by a professional
  - Endocrinology – there is no specialist and the proposal is for a specialist to visit once or twice a year for consultation
  - Other specialties may be needed according to complications such as liver but these also may be offered by distance consultations
- The main tool for assessing iron overload is the MRI and since a new instrument is being installed then TIF will undertake to provide the necessary software for the measurements of iron in heart and liver

- The thalassaemia centre should be upgraded as the reference centre with facilities based on European standards for reference centres

Introduction

The archipelago has a population of 345,023 people (estimated for 2014). Birth rate 15.12/1000 and total births 5964. The largest city and capital in Maldives is Male, with an estimated population of 63,000. This is followed by Addu City (around 12,000) and Fuvahmulah (around 12,000). These are the only cities with a population surpassing 10,000.
The Maldives have one the highest prevalence rates of thalassaemia globally in both carriers and patients per 1000 population. This chronic and potentially lethal hereditary anaemia constitutes a major public health and social issue contributing to premature death in both children and young adults, and making increasing demands on the country's resources.

The health status of the population has been improving steadily over the years. Infant mortality has fallen from 18/1000 livebirths in 2002 to 9/1000, while the under-5- mortality has fallen from 23/1000 to 10/1000 over the same period. These indicators are characteristic of overall better health care for the population but also for the better care of thalassaemia patients since thalassaemia was a significant contributor to childhood mortality.

Improvements in health indicators are the result of a rising economy, with an income/ capita now at 5290 USD and a health expenditure per capita of 412 USD, which are higher than many of the SEAR countries. Despite these observations inequalities in both family income and health status exists between city dwellers in Male and people in the distant atolls. These inequalities are particularly acute in the case of the multi-transfused patients and those with chronic diseases who will thrive only if regular specialised care is provided. For this reason in addition to ignorance and poor income, atoll dwellers have to travel long distances to benefit from specialised care and even for a simple prescription. Another issue is that patients living in atolls are cared for by temporary expatriate staff and receive transfusions which are suspect in terms of quality since issues like the cold-chain are difficult to keep. The care of patients in the distant islands is an issue which health authorities need to address in order to reduce inequalities.

The Ministry of Health has long been aware of thalassaemia problem and has made efforts to deal with the issues by providing the best possible care, under the difficult circumstances of a scattered population. One recent effort has been the preparation of a law to cover the aspects of prevention and clinical care (annex 1)

It is in this setting that this technical assistance has been requested as part of the Ministry of Health's effort to provide the best possible care to the growing, in both numbers and age, of the patient population.

Homozygous beta thalassaemia has two clinical manifestations:

- Transfusion dependent thalassaemia major (TDT), in which there is absence or severe reduction in the production of the beta globin fraction of the haemoglobin molecule. The poor production of this protein leads to an imbalance in the molecule due to normal

production of the alpha globin chains, which then become in excess and precipitate out, killing the red cell precursors and leading to ineffective haemopoiesis. Poor production of the protein is due, of course, to mutations on the gene, which controls its production.

- Non-transfusion dependent thalassaemia (NTDT) is due to 'mild' mutations on the beta globin genes which allow only a moderate production of the globin. In addition other genetic modifiers, such as the co-inheritance of an alpha thalassaemia gene, or mutations allowing more fetal haemoglobin production in post-natal life, will partially restore the chain imbalance in the molecule and reduce ineffective erythropoiesis. Double heterozygocity with variants such as HbE will also cause in most result in most cases with a NTDT syndrome.

Both these clinical entities are lethal if no treatment is offered, since anaemia, ineffective erythropoiesis, the need for regular blood transfusions and iron overload, cause complications which are life threatening. Complications appear later in NTDT, but premature death is still a problem. Both also seriously affect quality of life.
Sickle cell haemoglobin is a variant molecule, which in the homozygous form or in combination (double heterozygocity) with beta thalassaemia or other variants (such as HbC and HbD) will cause serious clinical effects. Sickle cell syndromes have a spectrum of severity, which is caused by genetic factors as well as environmental factors, and also require long term care in order to avoid suffering and premature death. Quality of life is severely compromised by pain and complications which result mainly from the variant molecule, which reduces the flexibility of the red cells and increases blood viscosity, causing rheological and vascular problems and reduced oxygen supply to vital tissues.

Understanding the molecular basis of these disorders and their pathophysiology, has led to medical interventions which result in long survival and a good quality of life. Basic care includes adequate and safe blood for transfusions, iron chelation, monitoring iron overload and complications, as well as the treatment of complications in vital organs. Such interventions however need to be delivered regularly and are lifelong, demanding adherence from patients and are a drain on health budgets especially in low resource countries.
For example the mean annual cost per patient in some countries able to provide optimal care is around $40000. Spending such a high price for individual patients is a serious challenge for both health authorities and for families. Yet in the absence of such investment the result is premature death or the more expensive treatment of complications. In reality the haemoglobinopathy syndromes, without treatment contribute to both infant mortality and under-5 mortality. Inadequate treatment will prolong life to adolescence or young adulthood leading to wastage of the resources already invested to manage the patient until that age. Optimum treatment will allow the patient to fulfill educational and employment goals and allow also marriage and reproduction with a satisfactory return on the 'investment' as well as a good of life for the patients.

Situation Analysis of the Maldives

The Republic of the Maldives is an island nation consisting 1190 islands, grouped in 26 atolls, scattered over a large geographical area. Only 201 of the Islands are inhabited.

A national register of thalassaemia patients has been kept over many years (started in 1993-4) which has recorded 803 cases. Of these, 563 are currently living- this is roughly 1.6/1000 of the total population. 288 are living in the capital Male while roughly the other half live in atolls. According to the diagnosis the patients are divided into the following categories:

1. Transfusion dependent beta thalassaemia major – 459 patients(age distribution of these patients is provided in annex the eldest being 36 years old, median around 13 years)
2. Non-transfusion dependent thalassaemia – 88 patients
   Of these Thalassaemia intermedia – 6 patients
   HbE/beta thalassaemia -82 patients
3. Sickle cell syndromes -11 patients
   Of these 10 patients have HbS/ beta thalassaemia
   1 patient has HbS/HbD double heterozygocity
4. HbH disease (alpha thalassaemia) – 3 patients
5. Other haemolytic anaemias – 2 patients

Those living in Male are treated at the National Centre for Thalassaemia and other Haemoglobin disorders. Those living in atolls are transfused in regional hospitals (there are three) while some are transfused in smaller island health units. Some patients come to Male for check- ups but many cannot afford the trip or find it difficult because of distance. Doctors in the regional hospitals are mainly expatriates who stay only for 1-2 years and so there is a high turnover and so lack of expertise.

Sickle cell patients have been officially assigned as the responsibility of the centre.
MTS estimates around 5 thalassaemia deaths per year.

Available services:
The Maldivian Blood Services [MBS] is a service run by the Ministry of Health, in a centre which is housed in a building separate from the hospital. MBS provides the following services:

1. The National Centre for thalassaemia and other haemoglobin disorders:

This includes:

- The day transfusion centre
- The outpatient clinic for haemoglobinopathy patients
- A screening laboratory serving the national effort for prevention or limitation of new affected births.

2. The National Blood Transfusions Services:

Blood transfusion is a basic necessity for thalassaemia patients and their dependency on donated blood as well as the complications of transfusion which arise more frequently in this situation, require a blood service that follows international standards for blood banking. The end product reaching the patients must be adequate to meet their needs as well as safe, with procedures followed to minimise dangers.
In the current Maldivian situation the following observations are made:

- Blood shortages do occur and it may be necessary to postpone a transfusion. This despite the facilitation of blood donation drives by means of mobile units through which 3 camps are organised each month. Each camp usually collects 35-40 units of blood although occasionally up to 120 units may be collected.
- Blood donation is by a replacement system with only around 10-30% voluntary donations and no paid donors. Family members are avoided as donors. Despite the allocation of the MBS as the National Blood Centre, there is no cooperation of the various blood banks in other hospitals, such as the Indira Gandhi Memorial Hospital (IGMH), which could alleviate shortages, especially when a rare blood type or a an antibody free donor blood is being sought. This lack of networking further adds to delays in finding a suitable donor for a patient and allows a drop in pre-transfusion haemoglobin (Hb).
- Although the intention is to keep the pre-transfusion Hb within the limits recommended in international guidelines, this is not always possible because of lack of cooperation between banks, low stocks and failure of families to find a donor in time for the next transfusion.
- Extended blood group phenotyping (antigen identification) is not practiced and is confined to ABO and Rh typing. This is inadequate for multi-transfused patients since it increases the chance of reactions which are indeed frequent. Emerging antibodies are not identified
- Allergic reactions e.g. urticaria, are frequent but even though each case is managed for those with frequent reactions, the practice of preparing washed red cells offered.
- All patients receive packed red cells.
- Donor blood is serologically tested for HCV, HBV, HIV and VDRL. There no HCV positive patient among the 563. The HCV carrier rate in the donor population is quite low and HBV is virtually eliminated by infant vaccination..
- Pre-storage filtration is not yet practiced. However there is bedside filtration at each transfusion.

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3. Patient care in the centre:

- The centre is open from 8am to 8 pm each day allowing patients to be transfused outside school or working hours.
- The day transfusion unit has adequate beds and serves 20-30 transfusions per day. There is a separation of paediatric and adult patients currently being constructed.
- There are amenities in the centre for patient use such as WiFi, and TV.

4. Iron chelation

Iron chelation is basic to long survival provided that it is uninterrupted. In the Maldives the following issues were noted, affecting the reduction of iron overload:

- All three chelating agents are available (Desferal, Asurna and Kefler) and there are no restrictions to medical prescriptions. The drugs are provided free of charge to all patients.
- For Desferal, an infusion pump is provided but there has been difficulty in supplies which is now being corrected by efforts from the Ministry, the Ministry of Islamic Affairs and

MTS. There is also a problem with servicing and repairing pumps locally. Pump shortages contribute to non-adherence to prescribed treatment.

- For all three chelating agents stocks are low and because of this patients are given a prescription for a limited period: for 1 week if the patient lives in Male and for 2 weeks if the patient lives in an atoll. This creates difficulties particularly for patients living in atolls who need travel frequently to the centre to get their medications and often cannot afford the fair or the time off work. This results in inevitable 'gaps' in chelation therapy with devastating results in organ damage and long term effects (since during the period of interruption, free iron radicals are damaging cells of vital organs).
- Currently there about 268 patient taking Desferrioxamine, about 150 on this drug alone, while 82 in combination with Deferiprone and 36 in combination with Deferasirox. There are 31 patients on Deferiprone monotherapy and 82 patients on Deferasirox monotherapy. This means that there are 381 patients receiving chelation treatment. If the living patients are 563 and of these 459 have thalassaemia major plus most of the milder syndromes (est 547), this means that there are at least 166 are not being treated: whether this means that they do not need it (e.g. because of non-transfusion dependency) or because they are not being supplied has not been clarified yet. Doctors feel that these are patients from atolls who do not return for their prescriptions.
- Blood transfusions and chelating agents and some basic tests are provided free of charge. However additional tests such as hormones, DEXA etc have to be paid through the health insurance scheme or out of pocket.

5. Monitoring of patients

The success of modern treatment depends on identifying and quantifying iron load in vital organs early and removing this load to prevent irreversible organ damage. Successful monitoring depends on having the necessary tests available, but also in having medical specialists following the patients in collaboration with the treating physiciance at the thalassaemia centre. The following observations concerning this vital service in the Maldives:

- Medical staff consists of only one permanent physician who is assisted by three temporary medical officers (currently expatriates) who serve in the centre for a few weeks to up to three years. The permanent physician, providing continuity of care, (Dr Farzana) is near retirement, which means that a replacement must be found. There is an offer from the Thalassaemia International Federation (TIF), to provide a scholarship with training for such a replacement. It is of vital importance to establish continuity of care from at least one experienced physician.
- Adult thalassaemia, due to accumulated tissue and organ damage is a multi-organ disorder which requires experience to monitor and recognise organ involvement early and to respond correctly. Allowing patients to develop advanced heart, liver and endocrine complications, is dangerous and uneconomical.
- Management Protocol of Thalassaemia is a guideline document used in the centre, which was compiled by in 2003 based on an older version of TIF guidelines. New updated guidelines (2014) are to be adopted as issued by TIF international experts and made available to the thalassaemia centre of the Maldives. The purpose of this technical assistance is to introduce the basic elements of the 2014 guidelines to be adopted for the better care of Maldivian patients

- Despite many patients having reached adolescence and adulthood there is no multidisciplinary care to ensure early detection and treatment of complications. The oldest patient is 36 years old and many will have a poor quality of life (see the age distribution curve).
- There is no endocrinologist on the island.
- Patients have regular, annual, follow up by a cardiologist who uses echocardiography only.
- T2* cannot be supported but a new MRI instrument has been bought. There is need to install the software and again TIF is willing support this. Using MRI technology, iron deposition in heart and liver can be monitored and if above certain limits, then intensification of iron chelation can prevent further organ damage and even reverse serious complications such as heart failure.
- Patients keep their own records in the form of a hand held notebook. This is good practice. In the near future a mobile application will be available, from TIF, to replace the notebook and provided to patients free of charge; this will include reminders of treatment schedules as well as for tests.
- It was noted from patients who showed us their records, that ferritin values were varying in an unrealistic manner (e.g. from 2000 to 12900 in one patient within 2-3 months). These rapid changes are dangerous, inducing a doctor to frequently change chelation regime and to use various combinations of drugs. Coupled with the lack of MRI or biopsy assessments the iron overload status of these patients is not known and so realistic chelation control is not possible yet changes in individual regimes are frequent. Correct monitoring of iron overload is a matter which must be looked into and corrected urgently.

6. Psychosocial support

Family and patient support is provided by the staff of the centre and by the MTS. In the centre there is a counsellor employed for the last 8 years. This lady is not a qualified psychologist but has gained practical experience. She talks to the patients and provides advice and encouragement. However she may not be able to deal with some of the more severe cases and a referral to a professional depends more on the patient. The doctors and nurses also provide support and advice, but there is evidence that some patients need help from qualified psychologists. In addition members of MTS hold group meetings for patient support and several patients attend and find the meetings useful. Again enhancement by an experienced professional is advisable.

7. Stem Cell transplantation

Haematopoietic stem cell transplantation is conducted with assistance from Italian centres. Several cases were done in the past by the Pesaro group (Prof Lucarelli) and more recently in Pescara (Prof Locatelli). Cost is high although some cases were covered by Italian funds. The ‘cure2children’ foundation which is much cheaper is active in Pakistan and India and is soon to be established in Sri Lanka, which can serve the needs of the Maldives well, at a much lower price.

8. Prevention in the Maldives:

In the past the national prevention program was assigned by the government to an NGO. The SHE organisation provided awareness campaigns and screening, which included regular visits to all inhabited islands. Tests were performed in laboratories developed by SHE both for screening and molecular diagnostics. These services were supplemented by counselling thus providing a comprehensive programme. Prenatal diagnosis was not developed because of restrictions in pregnancy termination although many cases are referred to India. Since 2010 there has been a governmental decision to place all the preventive services under the wing of the Ministry of Health through the thalassaemia centre. The centre's laboratory has been encouraged to increase its output however the interruption in supplies has not allowed this goal to be reached. In addition molecular laboratory support is still in the SHE labs who are now having to charge both for screening and DNA analysis (500 rupias and 1000 rupias respectively) due to interruption of funding.

From the national screening results:
The Society for Health Education (SHE) has screened 121416 people from 1992- 2011. The results of this program will be sent to us soon. Overall beta thalassaemia carriers are just over 16%.
The national thalassaemia centre has been screening since 1998 and has tested 40450 people. From these the following results were obtained:
Beta thalassaemia carriers 18.07%
Alpha thalassaemia carriers 2.1%
HbE carriers 0.9%
HbS carriers 0.13%
HbD carriers 0.43%
The beta thalassaemia carrier rate is higher in the thalassaemia centre compared to the SHE results (see below). Could this be due to more family members of patients are tested at the centre? This is not documented.

There is considerable variation in carrier rates in the different atolls as well as the presence of HbS and HbE
From the screening results the following births of affected children are expected yearly without taking into account any effect of prevention:
Children with beta thalassaemia syndromes: 54 new cases (total for beta homozygotes and HbE/ beta thalassaemia)
Chilldren with sickle cell syndromes: 1 case per year

According to the recorded births the following new cases were detected:
2008 – 37 cases (31% prevention)
2009 -25 cases (53% prevention)
2010 – 22 cases (59% prevention)
2011 – 32 cases (41% prevention)

These figures are said to be worse than in previous years when well over 50 % of cases were prevented.

The results of screening must be presented to the court prior to marriage. If the even if the couple have been given counselling either at MBS or at SHE, the court will also counsel and give time to the couple to reconsider. However most couples will proceed with marriage and childbearing, despite counselling. Of 13 new affected births this year 11 new of their carrier status. Since many couples prefer prenatal diagnosis and travel to India at considerable expense, this service should become available locally. The molecular laboratory has the capacity for this and obstetricians have been trained in chorionic villus sampling. Legal and religious barriers need to openly discussed.

SHE has resumed the education campaign on thalassaemia for high schools and this includes taking samples for screening.

Consanguineous marriage is not common in the Maldives, however people marry within the atoll and so inbreeding may be a factor, evidenced by the different carrier rates and the mutations that characterise each atoll. Polygamy is practiced but what effect this may have on families with thalassaemia is not known.

Recommendations concerning patient care and clinical management

From the information received and the discussions that ensued, recommendations to be included in the new national guidelines were formulated having always in mind that survival of patients is the main motive for these recommendations although all difficulties, financial, geographic and practical are considered also. These recommendations are based on guidelines published by international experts and reviewed by peers. These guidelines are now in print and will be officially launched in November 2014.

Recommendations according to the latest international guidelines:

Guideline	**Available in the Maldives**	**Recommendations for the Maldives**
Diagnosis:		
Haematological	Yes	Both at MBS and SHE labs
Molecular	Yes/ done in some cases	Molecular confirmation of diagnosis will also indicate the existence of molecular modifiers which may affect treatment e.g. the co-existence of a-thal or Xmn polymorphism which may determine response to hydroxyurea. The SHE lab can provide this service
HLA typing before the first transfusion	Not done	This is recommended but is not a standard which all follow. Explore if SHE can take this over to facilit6ate future transplants
Blood transfusion:		
Voluntary blood donation	10-30%	This needs to be increased. Suggested that MTS and SHE in their education campaigns could

		contribute to this
Before the first transfusion: extended red cell antigen typing, at least for C,E, Kell	Not done	Guideline for future reaction management – strongly recommended
Before each transfusion: ABO, Rh(D) compatible blood	Yes	However matching for C, E, Kell is strongly recommended. Collaboration of blood banks, especially with IGMH will increase donor pool, facilitating the search for antibody –free blood for these difficult patients
Cross match and screen for new antibodies before each transfusion	Not done	Cross match is standard in MBS but search for antibodies is not. Should be done
Leukodepleted blood	Yes	Done by bedside filtration. Pre-storage filtration is strongly recommended
Washed red cells	No	Recommended for patients with severe allergic reactions
Red cells stored in CPD-A use within 1 week	Yes	But if stored in additive solutions can be used within 2 weeks of collection
Pre-transfusion Hb 9-10.5g/dl	Yes but not always possible	Not keeping to these levels is difficult since thalassaemia patients must find a donor to replace the blood they receive. Increasing voluntary blood donation is a priority for the MBS in collaboration with the Ministry, the MTS and other NGOs. This will increase safety as well as adequacy and reduce family anxiety. Increased cooperation between blood banks is an urgent requirement.
Pre-transfusion Hb 11-12g/dl for patients with heart complications	?	Short transfusion intervals are necessary to avoid circulatory overload while good oxygenation of heart muscle is achieved
Keep post-transfusion Hb below 14-15g/dl	Yes	
A record of reactions and annual transfusion requirements must be kept	Yes	A record of antibodies also should be kept – see above
Iron overload monitoring:		
Serum ferritin is measured every three months and indicates changes due to transfusion and iron chelation, usually. It is an approximate marker for liver iron concentration.	Yes	The hospital lab has been giving dangerously inconsistent results. The MBS lab has the equipment and should take over this vital test ensuring consistent and valid results based on which the doctor must make decisions on treatment. The limitations of ferritin measurements must also be noted: levels rise with inflammation and liver disease and also the test underestimates iron in NTDT
Keep ferritin levels below	Not done	Cooperation of suppliers, patients, families and

1000microg/l in TDT Keep ferritin level below 800 microg/l in NTDT		doctors is needed.
Liver iron concentration (LIC) can be used to calculate total body iron. Methods: 1. Biopsy 2. MRI	Not available	MRI is the non-invasive method of choice which has largely replaced biopsy. MRI will become available in the country and T2* (which can calculate LIC) or Ferriscan (which can give direct result) can then be discussed. Each patient needs a measure annually after the age of 8 years.
Cardiac iron can be measured by MRI T2* and give early warning of heart accumulation which if successfully chelated will avoid cardiac complications. Has been shown to increase survival and is preferable to rescue treatment	Not available	MRI will need software for this and TIF will provide support for this, provided the radiologist agrees to give time to thalassaemia. This needs to be a validated method and regularly calibrated
Liver fibrosis can be estimated by: biopsy and an ultrasound instrument called the Fibroscan	Not available	Not yet urgent but will be needed later
Iron chelation:		
Chelation therapy cannot be effective unless taken regularly		Optimising adherence requires making the drugs easily available and by proper family and professional support
All three chelating agents registered	Yes	Desferrioxamine (DFO)- SC or IV Deferiprone (DFP) - oral Deferasirox (DFX) – oral
Chelation therapy free of charge	Yes	But patients need to travel frequently to get their prescription and supplies, and this results in interruptions, especially from atolls
Children aged 2-6 years are given DFO as first choice but DFX may also be given. DFP syrup is under trial for children but yet approved	Yes	DFO 20-40 mg/kg/day
For patients above 6 years all three are approved. Chelation should be tailored to individual patient needs and will vary with the current situation	Yes	DFO 40-60 mg/kg/day DFP 75 mg/kg/day in 3 divided doses DFX 20-40 mg/kg/day in a once daily dose but lower doses may be used in NTDT or SCD Response depends on dose and duration of exposure to the chelator
Combination of DFO + DFP And more recently DFO + DFX (not yet officially	Yes	Beneficial in high overload and may be given to intensify treatment in heart failure and other emergencies

accepted)		
Chelation can reverse heart dysfunction if given over 24 hour as IV DFO	Not done	Lack of collaboration of hospital physicians with thalassaemia experts.
Monitoring side effects:		
DFO: ❖ Audiometry annually ❖ Ophthalmology annually ❖ If fever stop therapy temporarily and establish organism (yersinia or klebsiella) ❖ Do not give prochorphenazine ❖ Stop if hypersensitivity ❖ Stop if pregnancy		
DFP: ❖ Neutrophil count every 1-2 weeks ❖ Stop if ANC <500 ❖ Patient to report if symptoms of infection and stop if fever ❖ Stop if joint pains ❖ Watch liver function ❖ Stop if pregnancy		
DFX: ❖ Avoid if renal disorder and creatinine clearance <60ml/min ❖ Avoid if liver impairment ❖ Monthly creatinine trends ❖ Monitor proteinuria ❖ Monitor liver function monthly ❖ Stop if pregnancy		
Cardiology management:		
All echocardiography and T2* should be reviewed by an cardiologist	Yes	T2* still to be installed. Until MRI is made available, cardiac systolic function can be used if serial measurements are recorded over time using standardised protocols: this can help to detect iron toxicity to the heart prior to heart failure. **The response is intensifying chelation to reduce the iron load to the heart.**

		Even mild decreases in ventricular function warrant aggressive and sustained intensification of treatment
Heart failure	?	This can be reversible in thalassaemia: the use of diuretics, pressors and anti-arrhythmic treatment are supplemented by continuous chelation. Also endocrine deficiencies, such as hypothyroidism, can contribute to heart failure and should be corrected, along with any other metabolic co-morbidities. **Futility of care should not be prematurely determined.** **Continuous intensive chelation could be IV DFO with or without DFP if the patient can take tablets.**
Pulmonary hypertension	?	Echocardiographic screening for pulmonary hypertension should be performed annually: if TR velocity is greater than 3m/s patient should have cardiac catheterisation. This is more common in NTDT
Liver Disease:		
Liver iron is best assessed by MRI	Not available	Biopsy is usually not necessary. Reversal of hepatic iron is a key objective
Diagnosis of HCV and/or HBV	Serology only	HCV RNA is important if positive serology. HBV DNA is needed to differentiate active from inactive infection
Chronic hepatitis	?	Treatment of chronic hepatitis requires attention to side effects e.g. ribavirin causes haemolysis requiring increase in transfusion. New oral drugs (nucleoside and nucleotide analogues) are now available. **Important to treat since danger of progression to cirrhosis and/or hepatocellular carcinoma**
Splenectomy	Yes	Indicated if excessive blood consumption
		Splenectomy can be avoided if transfusion regimen is strictly followed.
		Splenectomy has been linked to: thrombophilia, pulmonary hypertension, silent brain infarcts, DVT, sepsis etc.
	yes	Immunoprophylaxis: vaccination for Hib. Pneumococcus and Neisseria meningitides at least 2 weeks before op and 3-5 years after op
		Prophylactic penicillin depending on age of the patient
Infections:		Infection related mortality is the second leading cause of death after heart disease
If on DFO temporary	Yes	To avoid enhancing bacteria such as Yersinia or

discontinuation if fever and prompt use of antibiotics		Klebsiella. But put patient on oral drugs
If on DFP check ANC	Yes	If agranulocytosis stop DFP and use granulocyte stimulating factors as well as antibiotics
Possible septicaemia	?	ITU
Endocrine disorders:		
Growth	Yes	Keep growth chart throughout childhood
Deformities	Yes	Keep record of deformities and start transufions with Hb minimum at 9g/dl to stop further changes: important for quality of life and self image.
Tanner scale	No	Tanner scale for sexual development is kept at the clinic from age 8-9 years. If delayed puberty request endocrine consultation
Endocrine deficiencies	No	Even if basic tests are done only an endocrinologist can provide correct treatment. The most common is hypogonadic hypogonadism (40-5%)with manifestations in both sexes. Short stature (30%), Daibetes (10%), Hypothyroidism (7%), hypoparathyroidism (3%). These rates vary according to how well the patients have been chelated.
Bone disease (osteopororsis):		
Annual BMD	Yes	DEXA will determine if osteopenia or osteoporosis. 40-50% of patients affected
Treatment	No	• Adequate intake of Vitamin D and calcium • Encourage physical activity • Discourage smoking • Hormone replacement therapy when indicated by the endocrinologist • Bisphosphonates for 1 year and not longer than 2 years (preferably IV pamidronate or zolendronic acid)
Dental care	No	Increased risk of caries, periodontal disease and malocclusion. At least annual check up
Psychological support:		
Psychological wellbeing impacts on adherence to long term treatment and so survival	MBS & MTS	Patients and families are vulnerable and may need professional help
Cognitive defects have been detected few patients	No	Neuropsychological investigation
Approaches include: • Changes in		• Multidisciplinary teams essential • Expert psychological support has to be

institutional practices • Group sessions • Family therapy • Patient camps		available, tailored to children's needs, adolescents and adults • Behavioural and social science approaches • Holistic approach to the patient
Lifestyle:		
Physical activity	encouraged	Ergometry and cardiovascular assessment is recommended
.Calcium & Vit D supplements	Yes	Provide 2000IU vit D daily. Check Vit D levels every 6 months. Calcium rich diet: milk, cheese, fish etc
Folic acid	Yes	1 mg/day for all patients with low Hb
Zinc supplenents	No	Monitor levels. For cases with deficiency due to chelation, poor growth and reduced BMD, supplements may be given. Dose usuall 125 mg of zinc sulphate 1-3 times daily
Vitamin E		Vit E rich diet recommended: eggs, vegetable oils
Vitamin C supplements	Yes	Recommended only with DFO infusions at 2-3mg/kg/day or in proven deficiency
Dietary iron restriction		Recommended for patients on low transfusion regimens since they absorb increased amounts from the gut
Smoking, alcohol, drug abuse	yes	Prohibited!

The Thalassaemia Centre:

- Facilitates equal access to quality care for every thalassaemia patient
- Provides day transfusion at hours which facilitate patient education and work
- Collaborates with inpatient services for the best care of the patient
- Has close collaboration with the blood bank and other laboratory services
- Coordinates a multi-disciplinary team of specialists for holistic care and prevention of complications
- Follows evidence based guidelines and standards
- Maintains close collaboration with patient support groups
- Is an advocate for the rights of chronic patients and the development of services
- Provides information to families and patients concerning all aspects of the disease
- Decides on output measures which includes, Quality of Life measures since the aim of holistic care is independent existence and psychological wellbeing and not just survival.

ANNEXES

1. Recommendations
2. Age distribution curve of thalassaemia major patients 2014
3. Maldives Thalassaemia Policy
4. Multidisciplinary care Maldives