

CLINICAL GUIDELINE TITLE**Paediatric Thalassaemia Disorders****1) SUMMARY**

1. The initial management of a newly diagnosed patient
2. Management of acute clinical presentation of a child with thalassaemia on treatment
3. Red cell transfusions in children with thalassaemia (see also [Paediatric Transfusion Guidelines](#))
4. Iron chelation - see [Imperial Iron Chelation for children guidelines](#)
5. Endocrine complications
6. Outpatient management and annual review
7. Thalassaemia intermedia
8. Blood and Marrow Transplantation

2) INTRODUCTION

The diagnosis of a child with thalassaemia (see Scope' for definition) should be timely and accurate. Thereafter patients need close monitoring to determine the likely clinical course and the family need full and accurate information with sensitive support from experienced professionals. A individually tailored management plan must be agreed and implemented. Infants with β and E/ β thalassaemia will be monitored carefully for clinical signs indicative of the need for transfusion. Transfusion will be started promptly when there is sufficient clinical evidence of severe anaemia, failure to thrive, and/or thalassaemic bone deformity. Infants and children with a thalassaemia intermedia phenotype will be identified clinically and not subjected to regular transfusion inappropriately.

3) DEFINITIONS

A&E	Accident and Emergency department
ALT	Alanine aminotransferase
BMT	Bone Marrow Transplant
CCG	Clinical Commissioning Groups
CNS	Clinical Nurse Specialist
CRP	C-Reactive Protein
DEXA	Dual Energy X-ray Absorptiometry
ECG	Electrocardiogram
GP	General Practitioner
HDU	High Dependency Unit
HPLC	High Performance Liquid Chromatography
ICHT	Imperial College Healthcare NHS Trust
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
NHSBT	NHS Blood and Transplant
PSSU	Paediatric Short Stay Unit
SHO	Senior House Officer
SpR	Specialist Registrar
UK	United Kingdom
U+E	Urea and Electrolytes

4) SCOPE

Patients: The term 'thalassaemia' in this guideline refers to all children with β -thalassaemias (β -thalassaemia major, β -thalassaemia intermedia, Haemoglobin E/ β -thalassaemia) and α -thalassaemias (HbH disease and rare cases of regularly transfused α -thalassaemia major). This guideline does NOT cover:

- i. Sickle- β -thalassaemia as this is a sickling disorder and patients are managed using the Imperial College Healthcare NHS Trust (ICHT) Paediatric Sickle Guidelines; or
- ii. Patients with α -thalassaemia trait or β -thalassaemia trait as these are silent carrier states and not diseases.

Staff: All consultants, junior medical staff and nursing staff in Paediatric Haematology, Paediatric Accident and Emergency Department, Paediatric Inpatient and Daycare wards, Paediatric Outpatients Department.

5) FULL GUIDELINE

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THE INITIAL MANAGEMENT OF A NEWLY DIAGNOSED PATIENT

Most children who are presenting as a new diagnosis will have been identified as part of the antenatal and newborn screening programme. The regional laboratory will usually have confirmed the diagnosis by HPLC but molecular analysis to identify the genotype will not usually have been performed. Parents of the vast majority of children who are diagnosed in this way will already have received specialist information and some counselling including the diagnosis, inheritance, options for prenatal diagnosis and the effects of thalassaemia on the child and the family. It is unusual for a new diagnosis of thalassaemia major or intermedia to be made in the present day without some prior knowledge by the family. This is now mainly occurs where there is a pregnancy in a patient who has recently arrived in the UK prior to delivery or has arrived in the UK with the child being born in another country. However, it often takes a long time for families to understand and accept the full implications of the diagnosis. It is essential to consider this in all of the early visits of the child and their family to the Paediatric Haematology clinic.

1. Emergency presentation

The child may present with anaemia and failure to thrive or, rarely, as a medical emergency due to severe anaemia. The child should be treated for symptoms and transfused if necessary. A senior member of the medical and nursing team should see the family on the day of presentation if the child is acutely ill and symptomatic from the anaemia and the Paediatric Haematology Consultant on call should also be informed.

2. Non-emergency presentation

This is usually when the diagnosis is anticipated by antenatal screening and established by prenatal testing, neonatal testing or the newborn screening programme. In this situation, the baby should be seen preferably within the first two weeks (without any delay even if clinically well) and in the unit where most of the care will be provided, which will be our unit for local patients. The local haemoglobinopathy counsellors may see some of the babies identified by newborn screening at home initially, especially if there is a previous relationship established from discussions in the antenatal period.

3. Tests to establish haematological and DNA diagnosis

- Full blood count, reticulocytes and blood film examination
- Haemoglobin analysis by high performance liquid chromatography (HPLC) and electrophoresis
- Genetic analysis for β thalassaemia mutations, α thalassaemia genotype and *Xmn1* C->T polymorphism.

Initial discussions with the family will centre around explaining the unpredictability of the clinical course and the need for close monitoring to assess the need for transfusion. The arrangements for care will be discussed and children who are being treated at a local centre will be seen in our unit for annual review.

Contact details of the Haemoglobinopathy Clinical Nurse Specialist are given to the families along with a local information leaflet. A written summary of the discussion and follow-up arrangements is sent to the local centre, GP and the patient's family. We strongly recommend that families join the UK Thalassaemia Society who not only provide very helpful literature for families but also a very useful Patient-Held Record which we are happy to use, and a user-friendly website. Membership is free for families of affected children.

4. Decision to start regular transfusions

The decision to start regular transfusions, although aided by information about the globin genotype, is mainly a clinical one as the severity of the phenotype can vary significantly in children. Children should be monitored at least monthly from the age of 4 months at the local clinic and/or Centre.

a) Clinical assessment should include:

- Height and weight measurement at each clinic visit
- Detailed history of feeding, sleep and level of activity, developmental milestones
- Spleen and liver size
- Evidence of extramedullary haemopoiesis, including head circumference
- Symptoms and signs of cardiac failure
- Full blood count, reticulocytes and film

A decision to transfuse should be based on the presence of anaemia (Hb < 70g/L) which is accompanied by inappropriate fatigue, poor feeding, developmental delay or regression, faltering growth or any symptoms or signs of cardiac failure, after accounting for correctable problems like iron deficiency, intercurrent infection or compounding factors like G6PD deficiency.

Occasionally an un-transfused child may present with an 'acute' anaemia. Causes might include intercurrent viral infection. It is therefore reasonable to give a single transfusion initially, and then wait and reassess whether the indication for transfusion recurs as the haemoglobin falls again. If it does, it is reasonable to assume longer-term dependency, and to plan for regular transfusions. The benefits and risks of transfusion must be explained to the family and written information provided, including information about the help and support available from the UK Thalassaemia Society (see above and references for contact details).

5. Investigations at Diagnosis (prior to first transfusion) and on annual basis

Specialty	Investigations
Haematology	Serial Hb measurements, reticulocytes, G6PD screen + assay if low
Transfusion	Full red cell phenotype [C, c, D, E, e, K, k, Jka, Jkb, Fya, Fyb, Kpa, Kpb, MNS, Lewis]
Biochemistry	LFT, U+E, calcium, phosphate and baseline ferritin assay
Microbiology	Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis B surface antibody, Hepatitis C antibody, HIV 1 and 2 serology, CMV IgG

6. Immunisations prior to starting transfusions

- Serology for hepatitis B if mother was not tested. If mother was tested antenatally in the UK and was clear then there is no need to test baby.
- If hepatitis B serology shows absence or inadequate previous vaccination, start hepatitis B vaccination programme (see BNF-C).

MANAGEMENT OF ACUTE CLINICAL PRESENTATION OF A CHILD WITH THALASSEMIA ON TREATMENT

1. Background

Most of the management of children with thalassaemia can take place in out-patient clinics and Paediatric Haematology Day Care. Occasionally, however, patients present unexpectedly to their GP, clinic, or the A&E Department. When they do so they may be seriously ill and need prompt assessment and management, often requiring hospital admission. Assessment can be facilitated by patients carrying health records listing their diagnoses, recognised complications and recent investigation results. Some problems are common in this group of children and awareness of these is essential for prompt diagnosis and appropriate treatment.

2. Indications for immediate admission

- Fever >38° C, tachycardia, tachypnoea, hypotension
- Acute abdominal pain or distension, jaundice (many children will have chronic, mild jaundice)
- Altered consciousness or convulsions
- Symptoms or signs suggestive of central venous catheter infection.

3. Admission procedure

During working hours children with thalassaemia are identified by triage staff in A+E and the Paediatric Haematology Team informed via bleep 2261 (Paediatric Haematology SpR with responsibility for haemoglobinopathies and referrals). Children are seen in the paediatric A&E by the Paediatric Haematology SHO or SPR. Out-of-hours during the evening (up to 20.00 h) patients are seen by the Paediatric SpR with responsibility for Paediatric Haematology and thereafter by the paediatric on-call SHO. The relevant doctor should see the patient as soon as possible and certainly within 1 hour. The Paediatric Haematology SpR (or out of hours the Paediatric SpR) and the Paediatric Haemoglobinopathy CNS should be informed of all children admitted and children should be transferred to the ward as soon as possible.

Children may be admitted to PSSU when inpatient admission is thought not to be required but they require monitoring for a short period of time – this decision is taken in conjunction with the Paediatric Haematology team. The Paediatric Haemoglobinopathy CNS should also be informed of all children attending A&E and discharged without admission so that follow up can be arranged. During working hours families are encouraged to seek early advice from the Paediatric Haemoglobinopathy CNS who can arrange for an assessment in day-care or PSSU if appropriate.

4. Clinical assessment

All children presenting acutely should have a full history and examination carried out, keeping in mind specific problems more likely in children with thalassaemia, including infections and endocrine, cardiac and hepatic complications.

5. Specific clinical problems in children with thalassaemia

- a) *Yersinia enterocolitica* infections are particularly common in these patients as the organisms thrive in an iron-rich environment and should be suspected in any regularly transfused child with fever, diarrhoea and abdominal pain. Treatment in young patients may need discussion with microbiology/ ID as first choice therapy options include tetracyclines and quinolones. Tetracyclines are contra-indicated in under 12 years and quinolones are not licenced, but used in some situations. Chelation therapy should be suspended until results of blood and stool cultures are obtained or abdominal symptoms subside. *Klebsiella* can also present in this manner.

- b) Splenectomised patients are at risk of overwhelming pneumococcal sepsis and should be vaccinated appropriately ([DoH Green Book – immunisation of individuals with underlying medical conditions](#) , [Pneumococcal immunisation, Green book](#)) and receive penicillin prophylaxis (refer to BNF-C for dose). Despite this, they are still vulnerable to gram-negative sepsis and should be assessed with a high index of suspicion and treated promptly with broad spectrum antibiotics.
- c) Children with sepsis and indwelling central venous catheters are at risk of gram-positive infections and should have vancomycin added to their regime (or teicoplanin if patient to be treated as a ward attender or at home by community nurses). Antibiotics should be administered via the central line to reduce colonisation within the device.
- d) **Children on deferiprone are at risk of agranulocytosis or neutropaenia and should have an urgent full blood count every time they present with an acute problem to the hospital or GP** to look for evidence of neutropaenia and should be treated as per the febrile neutropaenia policy if found to be neutropaenic, in which case deferiprone should be stopped at once. Patients on deferasirox require assessment to exclude renal hepatic toxicity.
- e) Abdominal pain and/or jaundice may be caused by infection, but cholelithiasis is common and biliary colic or obstruction, with or without infection, should also be considered.
- f) Patients with transfusional cardiac iron overload may present with symptoms and signs of cardiac dysrhythmias or cardiac failure secondary to ventricular dysfunction.
- g) Endocrine problems secondary to iron overload, may also cause acute presentations, such as diabetes mellitus and, rarely, hypoparathyroidism or hypothyroidism.
- h) Those who have hepatitis due to viral infection, usually complicated by iron overload, may occasionally present with decompensated liver failure and hepatic coma.
- i) For most presentations, patients on regular desferrioxamine treatment should have this continued, the exception being suspected *Yersinia enterocolitica* infection.
- j) When acutely unwell, patients may not tolerate any degree of anaemia and should be transfused to a haemoglobin of >120 g/L. Transfuse with caution if a rise in Haemoglobin of > 4-5g/L of transfused blood is required.

6. Investigations to be performed on a child with thalassaemia presenting acutely unwell (those starred * depending on clinical presentation)

- FBC, group and antibody screen, direct antiglobulin test, U+E, LFT, LDH, CRP, calcium and phosphate, glucose, thyroid function, amylase*
- Venous blood gas*
- Blood cultures, urine culture, culture of stool*, CSF*
- ECG*
- CXR*
- Echocardiogram*
- Ultrasound of abdomen*

RED CELL TRANSFUSIONS IN CHILDREN WITH THALASSAEMIA

The aims of regular transfusions in children with thalassaemia are to promote optimal growth and well-being and to prevent complications of undertransfusion.

Blood transfusions, given regularly every 2-4 weeks, should enable normal growth and development of children with transfusion-dependent thalassaemia syndromes (see definition, above). A haemoglobin level maintained above 95 – 100 g/L is sufficient to inhibit bone marrow expansion and minimize transfusion-related iron loading. Transfusions need to be given safely with minimum disruption to everyday life. The risks associated with regular transfusion include acute transfusion reactions, allo-immunisation to red cell antigens, transmission of viral infection and, in the long-term, iron overload (see [Imperial Iron Chelation for children guidelines](#)). Serious reactions due to misidentification can be minimized by meticulous attention to protocols in transfusion practice.

1. Provision of red cell transfusion units

- Red cell units which are matched for Rh (D, C, c, E, e) and Kell (K) blood group antigens are selected (all patients should have extended red cell phenotyping done prior to their first transfusion).
- Large volume units are chosen, preferably greater than 300 mL (for children when one or more full unit is required), and wherever possible units should be less than 2 weeks old.
- Irradiated cellular products should be used for patients in preparation or undergoing stem cell transplantation.

2. Pre-transfusion testing

The patients attend Paediatric Haematology Daycare Ward for pre-transfusion testing, i.e. blood grouping and crossmatching, 2 - 3 days before the actual transfusion. **Cross match samples must be collected no more than 72 hours prior to each transfusion.** An adolescent service is in place (5pm-7pm on two Tuesdays per month) to enable these children to attend out of hours for testing. School age children are offered transfusions late in the afternoon and evening to minimise disruption to their everyday life.

3. Administration of blood

Transfusion is administered via an intravenous cannula or indwelling intravenous catheter in children on long term transfusions. Elective transfusions are always administered on the Paediatric Haematology Daycare Ward with input from nursing, medical staff and play specialists.

4. Transfusion plan

- Pre-transfusion haemoglobin levels are reviewed by the Paediatric Haemoglobinopathy CNS and the Paediatric Haematology SpR responsible for Paediatric Haematology Daycare Ward in order to plan appropriate transfusions.
- Transfusion intervals vary from child to child but will usually be every 3 - 5 weeks.
- The pre-transfusion Hb level should be maintained at 90 – 95 g/L and post transfusion not greater than 140 g/L. At these levels, optimal energy and growth are achieved with no more iron loading than is unavoidable.
- Blood supplied by the National Blood Service is SAG-M blood which comprises packed red cells in preservative (saline, adenine, glucose and mannitol), and has a haematocrit between 0.5 - 0.7.
- Calculation of required blood volumes is done using the following formula:
 - Volume of SAG-M blood required = required rise in Hb x wt (kg) x 4*
- (* may be x 5 or 6 in some patients: will depend on the result of previous transfusions- this should always be discussed with the Paediatric Haemoglobinopathy Consultant)
- Transfusions are administered at the rate of 5 mL/kg/hr and usually take 4-6 hours to be completed.

- If the pre-transfusion Hb is persistently below 90 g/L, the recorded volume of blood received with each transfusion should be reviewed and the Paediatric Haemoglobinopathy Consultant. The volume of blood required may need to be increased or the frequency of transfusions may need to be increased.
- Annual red cell requirements should be calculated at the Annual Review by the Paediatric Haemoglobinopathy Consultant.
- Splenectomy may need to be considered in children with hypersplenism or increased red cell requirements (>250-275 mL/kg/year of SAG-M, buffy coat-depleted red cells with a haematocrit of about 60% as currently supplied by the National Blood Service). Otherwise splenectomy is rarely required in regularly transfused thalassaemia major patients. For indications for splenectomy in thalassaemia intermedia- see section 6.

IRON CHELATION FOR CHILDREN WITH THALASSAEMIA

Iron overload in thalassaemia major, if untreated, is usually fatal in the 2nd or 3rd decade of life. The majority of deaths, even when effective iron chelation therapy is available, are due to iron related cardiomyopathy, presenting as cardiac arrhythmias and cardiac failure. Iron overload causes morbidity to a significant number of patients even when adequately treated and therefore careful monitoring is paramount. In addition, to cardiac damage, iron toxicity also causes hypothalamic and pituitary damage resulting in growth hormone and gonadotrophin deficiency, presenting as short stature, delayed or absent puberty, and infertility. Other endocrine abnormalities include glucose intolerance, diabetes mellitus, hypothyroidism and hypoparathyroidism. The liver is also an important site of iron toxicity: hepatic fibrosis can occur early in childhood eventually leading to cirrhosis, liver failure and hepatocellular carcinoma. Complications are accelerated in the presence of chronic hepatitis C virus infection.

1. Iron chelating drugs

THE MOST COMMON PROBLEM WITH IRON CHELATION IS INADEQUATE COMPLIANCE! CHECK AND DISCUSS EVERY VISIT. There are many reasons for poor or erratic compliance, including psychosocial reasons. It is important to offer families every available form of psychological support (via the Paediatric Haematology psychologist or Paediatric Haemoglobinopathy CNS). Help from the Haemoglobinopathy Social Worker may also be beneficial.

a) Desferrioxamine

Given as subcutaneous infusion on 5-7 days per week over 8 -12 hours at a mean dose of 20 -30 mg/kg [range 20 -50 mg/kg/day]. Its use has been accepted as chelation regime for over 30 years with substantial amount of data on efficacy and side effects. The main problem is compliance as mode of delivery which has consistently shown a major negative impact in quality of life. "Thumb-tack" (Thalasset) type sub-cutaneous needles, psychosocial support and disposable pre-filled elastomeric infusers can aid in adherence to treatment.

- Side effects include vertebral dysplasia leading to disproportionate short trunk, pseudo-rickets and genu valgum, high-tone sensorineural hearing loss and retinopathy. These are predicted by therapeutic index > 0.025.

$$\text{Therapeutic index} = \frac{\text{mg/kg/day}}{\text{serum ferritin } \mu\text{g/L}}$$

The presentation of fever, diarrhoea and abdominal pain may represent *Yersinia* or *Klebsiella* infection which is increased in patients on desferrioxamine treatment.

Vitamin C enhances mobilization of iron from intracellular store and should be prescribed at a dose of 100-200 mg orally daily on the days of desferrioxamine treatment.

Patients with severe iron load or who require a fast reduction can receive intravenous continuous desferrioxamine infusion 30 to 50 mg/kg/day via a Port-a-Cath with a disposable pre-filled elastomeric infuser. In circumstances where intravenous is inappropriate combination treatment of desferrioxamine subcutaneously with the deferiprone or deferasirox can be used as decided by the Paediatric Haematology consultant.

b) Deferiprone:

This was the first readily available oral chelating agent and is given at a dose of 75 – 100 mg/kg/day in three divided doses. It is very effective in reducing myocardial iron loading; improving and normalizing cardiac function due to its ability to effectively cross the cellular membrane because of its small size and lack of charge. As monotherapy it fails to control liver iron over the long term. Gastrointestinal disturbances, intermittent elevation in ALT and hepatic impairment, zinc deficiency and increased appetite are known side effects.

Serious side effects include neutropaenia (neutrophil count $0.5 - 1.5 \times 10^9/L$) in 2 – 10%, agranulocytosis (neutrophils $< 0.5 \times 10^9/L$) in 0.5 – 1% and arthropathy in 5 – 15% cases. All patients on deferiprone need to have a weekly FBC, receive advice regarding neutropaenic fever and be given a letter explaining to other health professionals the serious side effects of deferiprone treatment. **Deferiprone should NOT be used in patients with Diamond Blackfan anaemia.**

Patients with severe iron load, particularly affecting the heart and the liver may benefit from combination treatment with desferrioxamine sc 30 mg/kg four nights a week and deferiprone 75 mg/kg/day in three divided doses.

- **Deferasirox:** This oral chelating agent is given as a single daily dose of 20 to 40 mg/kg. Comparable to desferrioxamine in efficacy in achieving a negative iron balance, and with efficacy in controlling hepatic and cardiac iron loading. Adverse effects include self-limiting skin rash (10.8%), gastro-intestinal symptoms (15.2%) and drug induced hepatitis. An important side effect is a dose-dependent increase in serum creatinine in 38% of the patients, equivalent to a mean fall of 25% in creatinine clearance. This generally occurs in the first month of therapy and remains at a stable level during continued therapy. Patients who initiate treatment with deferasirox or have a dose increase should have weekly U+Es and LFT performed for a month as it may be necessary to institute a dose reduction or interruption of treatment. Intermittent proteinuria may also occur with or without changes in serum creatinine. Patients have a urinalysis performed on the days of crossmatch and dose interruption should be considered for persistent proteinuria.

2. Indications for chelation and monitoring of iron load

Children <5 yrs old should be started on subcutaneous desferrioxamine infusions (aiming to reach 20 - 30 mg/kg/day 5 times per week) after receiving 10 - 12 transfusions, and/or when the serum ferritin level is consistently greater than 1000 µg/L.

Iron load is monitored according to the following methods:

- **Serum ferritin:** persistent levels $> 2500 \mu\text{g/L}$ are associated with an increased risk of cardiac disease and death. Levels maintained in the $500 - 1000 \mu\text{g/L}$ over the long term carry a relatively low risk, but do not exclude severe tissue iron overload. Serum ferritin is an acute phase protein and therefore measurements need to be correlated with the clinical status of the patient and be done in conjunction with a CRP. Aim to keep ferritin in $1000- 1500 \mu\text{g/L}$ to avoid toxicity in patients receiving desferrioxamine and target $500 \mu\text{g/L}$ (but not lower) in patients receiving deferasirox.
- **MRI T2*:** Gradient-echo T2* sequences are very sensitive to magnetic properties of tissue iron. The technique is very accurate for quantitation of cardiac iron load and function. Left ventricular impairment becomes increasingly likely $< 20 \text{ ms}$ and nearly all patients with clinical evidence of heart failure have $< 10 \text{ ms}$. MRI T2* cannot be delivered at Imperial under GA, but there would be patients around 4 to 6 years of age that are able to tolerate it with the assistance of the play specialist.
- **FerriScan:** FerriScan® provides an accurate measurement of liver iron concentration (LIC) through a non-invasive, MRI-based technology and can be done on a standard MRI scanner, with data sent electronically to a commercial organisation for analysis. The process uses patented spin density projection R2-MRI imaging technology and provides sensitive and specific assessment of liver iron concentration enabling clinicians to monitor therapy. High LIC values have strong correlation with liver fibrosis and risk of cardiac death with cardiac iron overload. The following table shows the LIC thresholds in transfusional iron overload (adapted from Olivieri et al Blood 1997, 89, 739-61). FerriScan can be provided under sedation.

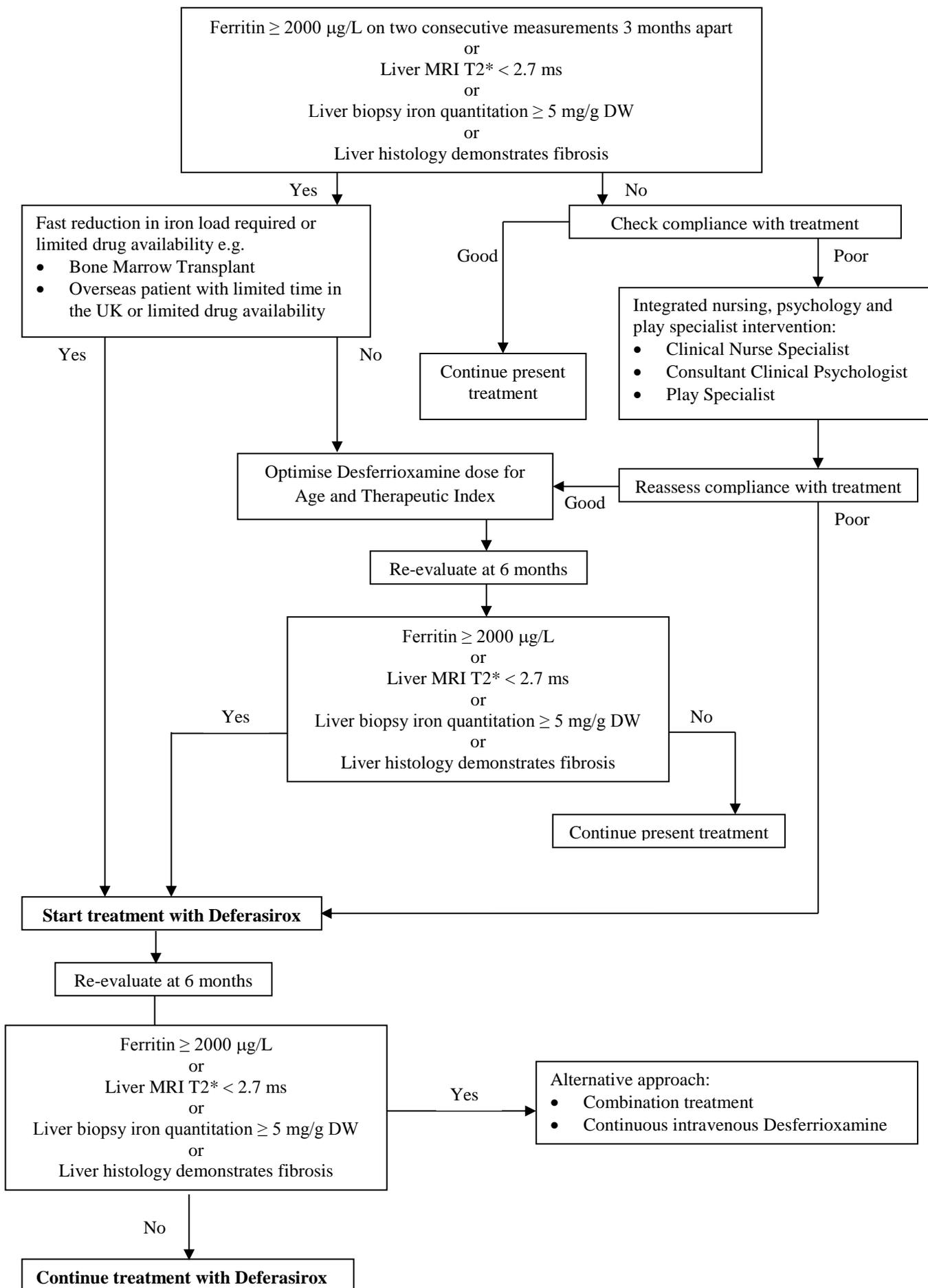
Liver iron concentration (LIC range) mg Fe/g dw	Clinical relevance
0.17-1.8	Normal range in non-disease patients in healthy population
3.2-7.0	Suggested optimal range for chelation therapy in transfusional iron overload
7.0-15.0	Increased risk of complications
>15.0	Greatly increased risk of cardiac disease and early death in patients with transfusional iron overload

- Liver biopsy:** ultrasound-guided percutaneous biopsy allows direct measurement of hepatic iron (as mg/g dry weight) which provides an accurate measure of body iron stores and allows for assessment of hepatic fibrosis (Ishak stage). The method is invasive, requires general anaesthesia and iron deposition can be patchy and show variable reproducibility. Levels < 3 mg/g DW are within the normal range, levels of 3 – 7 mg/g DW should not result in hepatic or endocrine toxicity. Levels > 15 mg/g DW are associated with an increased risk of cardiac disease. Aim to a level of 3 – 7 mg/g DW, but targeting the lower end as much as possible. The development of bridging fibrosis (initially focal) is significant and requires more intensive removal of iron load.

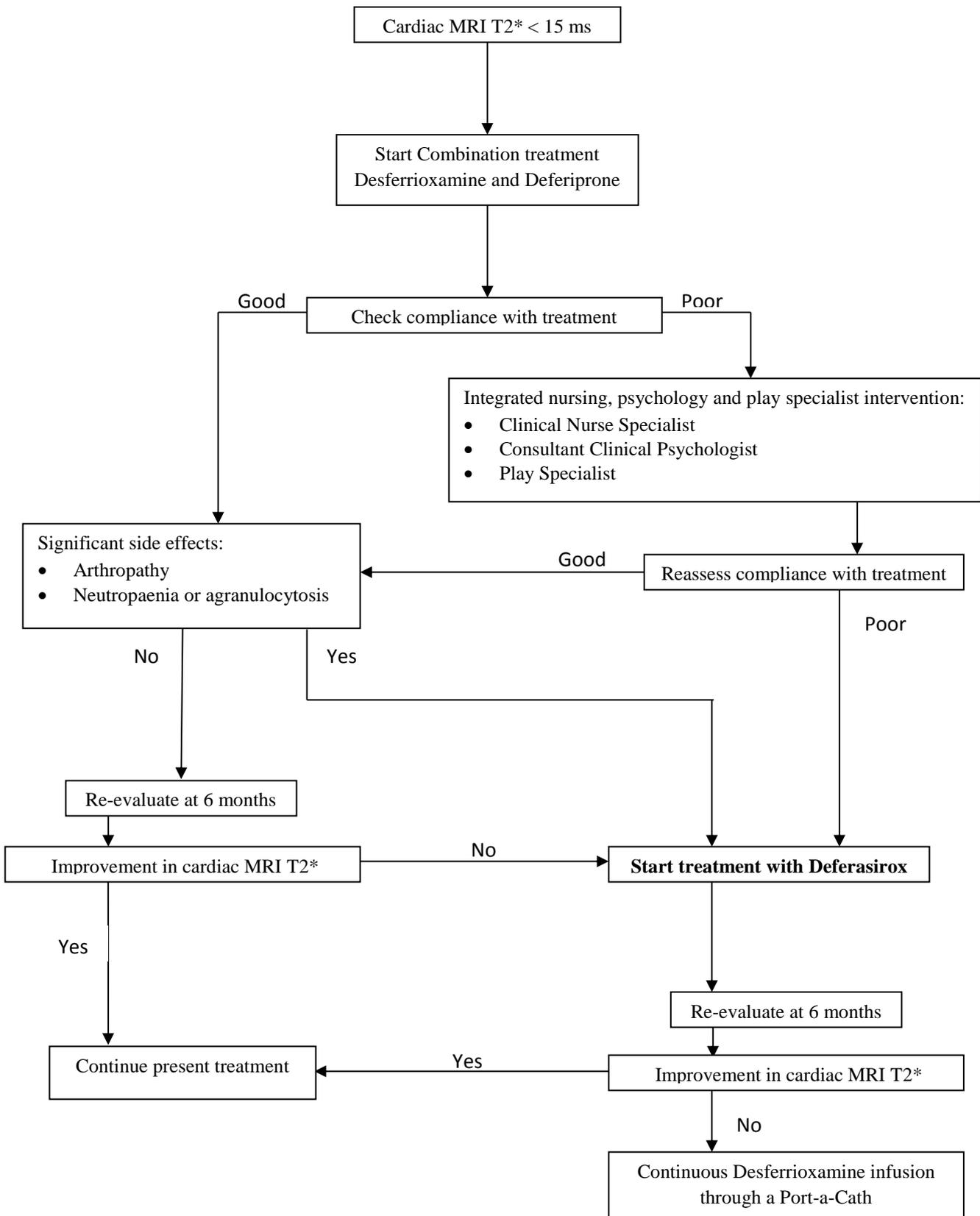
3. The schedule of iron load monitoring

	Transfusion dependent	Transfusion independent
Serum ferritin	<ul style="list-style-type: none"> every crossmatch 	<ul style="list-style-type: none"> annually
FerriScan	<ul style="list-style-type: none"> annually from 2 years of age every 6 months if LIC >10mg/g DW 	<ul style="list-style-type: none"> at 10 years of age and then every 5 years
MRI T2*	<ul style="list-style-type: none"> annually from 5 years of age every 6 months if heart <10 ms or liver < 2.7 ms every 3 months if heart < 10 ms and evidence of cardiac impairment 	<ul style="list-style-type: none"> if ferritin > 1500 µg/L at 10 years of age
Liver biopsy	<ul style="list-style-type: none"> If LIC >10 mg/g DW or MRI T2* < 2.7 ms or abnormal LFT After age 2 years if patient does not tolerate ferriscan 	<ul style="list-style-type: none"> If LIC >10 mg/g DW or MRI T2* < 2.7 ms or abnormal LFT

4. Modification of therapy for desferrioxamine treatment failure



5. Modification of therapy for cardiac iron overload



ENDOCRINE COMPLICATIONS

Endocrine complications in thalassaemia are multifactorial and are possibly due to the ineffective erythropoiesis, iron overload and chelation treatment. All patients with thalassaemia should have an annual review by a Consultant Paediatric Endocrinologist. There is currently a 3- monthly endocrine clinic run concurrently with the Haemoglobinopathy clinic on a Monday afternoon, (the Paediatric Haemoglobinopathy CNS co-ordinates this clinic). Appointments are also available at other times via other joint clinics, including the Late Effects Clinic.

- Regular assessments of growth, including weight and height (standing and sitting), should be recorded every six months from diagnosis until final adult height is attained with referral to the Paediatric Endocrinologist if there is any concern. Evidence of faltering growth (declining centiles for height and height velocity) is often apparent around the age 8-12. This should be investigated thoroughly with consideration given to desferrioxamine toxicity, and growth hormone deficiency. Under the direction of the paediatric endocrinologists, a growth hormone stimulation test may be administered, and if positive, growth hormone therapy instituted.
- Puberty should be systematically assessed annually from the age of 10, with referral to a paediatric endocrinologist if there is any suspicion of delay (no pubertal changes in girls by age 13 and boys by age 14) or arrested puberty. Adolescents with evidence of hypogonadism should be treated with hormone replacement therapy, under guidance from the Consultant Paediatric Endocrinologist.
- Glucose intolerance should be watched for, with random glucose levels every 3-6 months, and oral glucose tolerance tests annually from puberty or from age 10 if there is a positive family history. HbA1C is unreliable after transfusion, and monitoring fructosamine levels can give an indication of glucose control
- Calcium and phosphate levels should be checked every 3 - 6 months and 25-OH vitamin D level measured if low. In addition, parathyroid hormone levels measured from 12 years of age.
- Thyroid function should be assessed at least annually.
- Bone mineral density in the hip and spine should be measured every 18 - 24 months, more frequently if there is concern, by dual energy x-ray absorptiometry (DEXA) in all patients over 10 years of age. Established osteoporosis (Z score < -2.5 in either hip or spine) should be managed with advice about diet, exercise, hormone replacement therapy, and bisphosphonate therapy after advice by Consultant Paediatric Endocrinologist.

OUTPATIENT MANAGEMENT AND ANNUAL REVIEW

The paediatric haematology clinics are held weekly on Monday afternoons. Adolescent clinics are held monthly on Tuesday evenings, on the second Tuesday of every month. In addition, the psychologist and the paediatric dietician are often available.

The Aims of the Clinic are to:

- Monitor progress of the children: medical, educational and psychosocial.
- Establish baseline observations for comparison in acute illness.
- Educate parents and children in the management of thalassaemia and iron chelation in particular
- Genetic counselling.

Routine clinic review (every 3-6 months)

- On arrival, FBC and reticulocytes.
- Weight and height; BP if aged ≥ 10 years. Each patient should have a growth chart.
- Document any ill health since last visit, immunisation up to date, school progress and attendances and holiday plans.
- Examination: check especially for jaundice, heart for size and murmurs, liver and spleen size (measure in cm).
- Any questions from parents, involve children as appropriate, any letters to be written.
- Prescribe any specialist medication (GP prescribes travel medication, e.g. malaria prophylaxis)
- Initiate (if first visit) or update the Transfusion Record (see Appendix 2)
- Make next appointment.
- Offer support from psychologist if indicated.

Annual review

See Appendix 3a for guidance on the format of the Annual Review appointment and Appendix 3b for the Annual Review Checklist

NON-TRANSFUSION DEPENDENT THALASSEMIA (NTDT)

Definition

Thalassaemia intermedia describes patients with thalassaemia who do not have an absolute requirement for regular transfusions for normal growth and development. It includes a wide spectrum of severity, from patients who only just manage without transfusions during childhood, to those who are virtually asymptomatic. At the severe end (10% of homozygous β thalassaemia, the majority of E/ β thalassaemia and a very small proportion of haemoglobin H disease), patients have anaemia, reduced exercise tolerance, mild to moderate bone changes, hypersplenism, poor growth during childhood, a delay in pubertal development and are likely to develop gallstones, extramedullary haematopoietic masses, and gradually accumulate iron, particularly in the liver, due to increased gastro-intestinal iron absorption. At the mild end of the spectrum (a small proportion of homozygous β thalassaemia, some with haemoglobin E/beta thalassaemia, and the large majority of haemoglobin H disease), the aim is surveillance of long-term complications: pulmonary hypertension, hypersplenism, gall bladder disease, and chronic ankle ulceration.

In addition to haemoglobin H disease the genetic determinants of thalassaemia intermedia are:

Homozygote (or compound heterozygote) for mild β -mutation (such as IVS1-6 T>C, Codon 9 C>T)	
Homozygote for severe β mutation but persistence of Hb F due to:	Homozygote for <i>Xmn1</i> polymorphism
	HPFH
	Other factors increasing HbF
Co-inheritance of β thalassaemia (heterozygote) and a thalassaemia-like Hb variant such as [these may result in a <i>major</i> or <i>intermedia</i> phenotype]	Hb E β thalassaemia
	Hb Lepore β thalassaemia
Co-inheritance of α thalassaemia mutations (homozygous α^+ or heterozygous α^0) with homozygous β thalassaemia resulting in decreased globin chain imbalance	
Co-inheritance of extra α gene(s) with heterozygous β thalassaemia resulting in increased globin chain imbalance	
Inheritance of a 'dominant thalassaemia' mutation (hyperunstable β globin variant)	

Management

- Patients should be monitored 3 monthly in the clinic although frequency can be reduced from 5 years of age if phenotype is mild. All patients should have as a minimum height, weight, spleen size, liver size, FBC, U+E, LFTs, CRP and ferritin.
- Patients should receive regular folic acid supplementation.
- **Indications for transfusion:**
 - **Sporadic transfusions:** episode of acute anaemia, for example after infection. The patient should be observed carefully for several months to determine steady-state symptomatology and haemoglobin level.
 - **Long-term transfusions:** symptomatic anaemia, falling growth velocity, delayed puberty, bone problems (facial deformities, recurrent fractures, premature epiphyseal fusion), pulmonary hypertension, symptomatic extramedullary haematopoietic masses, chronic ankle ulceration.
- The rationale for transfusion should be carefully discussed with the patient and/or parents and family, perhaps over the course of several clinic visits and requires the involvement of Consultant Paediatric Haematologist in all cases.

- **Iron load:** serum ferritin can be unreliable in thalassaemia intermedia, and tends to underestimate the degree of liver iron loading. Iron-related cardiomyopathy is unusual in children and young adults. All children with thalassaemia intermedia should have as a minimum MRI T2* and FerriScan® quantitation at 5 years, 10 years and 15 years of age. Chelation regimes for untransfused patients can be less intense than in thalassaemia major as it is easier to achieve negative iron balance because the rate of iron loading from the gut is much less than from regular transfusions.
- **Splenectomy:** indications for splenectomy include massive splenomegaly and hypersplenism. Many patients with lesser degrees of splenomegaly do benefit, with an improvement in haemoglobin level and a reduction in ineffective erythropoiesis so that transfusion dependence is delayed or averted. Removing the spleen can also improve growth velocity and pubertal development. However, the benefit is not always dramatic, and many will still eventually require regular transfusion. Risks of splenectomy in thalassaemia intermedia include a marked thrombocytosis, postsplenectomy sepsis, pulmonary hypertension, and possibly enhanced iron deposition in the liver. The risk of thrombosis, already increased in thalassaemia intermedia, is further increased after splenectomy.
 - Patients should be transfused for several months prior to splenectomy to reduce spleen size, suppress marrow activity, and reduce the numbers of circulating, pro-thrombotic thalassaemic red cells.
 - USS abdomen is performed prior to the procedure to detect gallstones in order to schedule a cholecystectomy at the same time.
 - An ultrasound guided liver biopsy should be scheduled at the same time.
 - The case should be discussed with the surgeons to assess the possibility of laparoscopic procedures and a PICU/HDU bed should be booked for post-surgical observation of all patients.
- **Hydroxycarbamide:** Responses to hydroxycarbamide are very variable, but it should be considered for alleviation of symptoms of anaemia, reduction in clinical jaundice because of decreased haemolysis, relief of bone pain, reduction in bone marrow and spleen enlargement and regression of extramedullary masses. Results are more effective for specific genotypes: E/beta thalassaemia, haemoglobin Lepore, and in some Middle Eastern patients and patients who are homozygous for the Xmn1 polymorphism or who have been splenectomised.
 - It should be started at a dose of 10-15 mg/kg/day, and the full blood count monitored weekly for the first month, then four to six weekly.
 - The maximal dose is unlikely to be in excess of 20 - 25 mg/kg/day as the risk of bone marrow suppression is greater than in sickle cell disease.
- **Pulmonary hypertension:** Pulmonary hypertension is prevalent in untransfused adults (23%), particularly those who have been splenectomised. Thalassaemia intermedia patients should have a minimum of 5-yearly echo from 15 years of age. Where echocardiography proves inconclusive with regard to pulmonary pressures, further investigation with cardiac MRI and right heart catheter studies should be considered to confirm the diagnosis. If pulmonary hypertension is found, treatment with regular transfusion should be strongly considered.
- **Growth and pubertal development:**
 - Growth should be carefully monitored with the use of growth charts from birth
 - All patients should have an annual review with the Consultant Paediatric Endocrinologist from the age of 10 until cessation of puberty.
 - Vitamin D levels should be checked annually and supplemented as necessary [Vitamin D Guideline](#)
 - DEXA scan should be performed 5 yearly from 10 years of age.
- **Extramedullary haemopoiesis:** Symptoms due to extra-medullary haematopoietic masses should be investigated, usually with MRI imaging, and treated with hypertransfusion or hydroxycarbamide. Radiotherapy can be considered if there is urgent need to reduce the mass; hypertransfusion and hydroxycarbamide act more slowly. Asymptomatic masses may require therapy depending on their position (e.g. if impinging on the spinal cord), but if not threatening vital structures, may simply be monitored.

- **Dental review:** All patients should have an annual review including the assessment of facial bone deformity.
- **Bone Marrow Transplant (see page 24):** stem cell transplantation should not be ruled out as many patients with moderate/severe thalassaemia intermedia have relatively poor quality of life, and many will eventually require transfusions and chelation therapy.

BONE MARROW TRANSPLANT (BMT)

BMT should be considered for all children with thalassaemia major and selected patients with β thalassaemia intermedia. The timing of discussion about BMT varies according to the needs and wishes of the family. It is extremely important that 'false hopes' are not raised and **detailed discussion of BMT should only be undertaken by an experienced Consultant in Paediatric Haemoglobinopathy or Paediatric Haemoglobinopathy BMT**. Particular care is needed where an affected child has no siblings, since current UK practice is to offer BMT to children with HLA-identical family donors. In some consanguineous families family members other than siblings may be HLA-identical. Haplo-identical transplants (where the donor is 50% match to the patient) is also being offered to selected patients with thalassaemia. These cases will need to be discussed in detail with the BMT clinical team.

ICHT is a paediatric haemoglobinopathy BMT centre and families seeking detailed information should be referred to the BMT clinic.

Disease	Allogeneic matched related	Allogeneic unrelated	Haploidentical related	Autologous blood or marrow
Donor specifics	10/10 sibling Other 10/10 related 9/10 related	10/10 adult 9-10/10 adult 4-6/6 cord	<9/10 related	
Stem Cell Source	BM/PBPCs/cord	BM/PBPCs/cord	PBPCs/BM	PBPCs/BM
Thalassaemia	Standard of Care	Clinical Option (requires careful assessment)	Clinical Option (requires careful assessment)	N/A

Directed cord collections

Mothers with children fulfilling the criteria for BMT carrying a new pregnancy from the same father may be candidates for directed cord donations. ICHT has a Human Tissue Authority License covering consent for directed cord donations and the maternity unit has a third party agreement for the procurement of cord with Stem Cells Services. It is extremely important that 'false hopes' are not raised and **detailed discussion of BMT should only be undertaken by an experienced Consultant in Paediatric Haemoglobinopathy or Paediatric Haemoglobinopathy BMT**, and that the feasibility of funding is pursued early from the relevant CCG.

6) IMPLEMENTATION

Training required for staff	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If yes, who will provide training:	N/A
When will training be provided?	N/A
Date for implementation of guideline:	N/A

7) MONITORING / AUDIT

When will this guideline be audited?	January 2016
Who will be responsible for auditing this guideline?	Kirstin Lund
Are there any other specific recommendations for audit?	No

8) REVIEW

Frequency of review	<p>Please indicate frequency of review: 2 years</p> <p>Person and post responsible for the review: Dr Kirstin Lund</p>
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9) REFERENCES

- Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK revised version 2008: UK Thalassaemia Society
- NHS Sickle Cell and Thalassemia Screening Programme programme, second edition, 2011.
- BCSH Transfusion guidelines for Children and Neonates, (2004+ Amendments 2005/2007)
- Blood transfusion guidelines for children and neonates:, ICHT Intranet.
- Iron chelation guidelines for paediatric patients requiring regular transfusions. ICHT Intranet.
- Chern JP, Lin KH. Hypoparathyroidism in transfusion dependent patients with beta thalassaemia. *Journal of Pediatric Haematology/Oncology* 24;291-3:2002.
- Chern JP, Lin MY, Lu Mv, Lin DT, Lin KS, Chen JD, Fu CC. Abnormal glucose tolerance in transfusion dependent beta thalassaemic patients. *Diabetes care* 24;850-4:2001.
- De Sanctis V. Growth and puberty and its management in thalassaemia. *Hormone Research* 58 Suppl1:72-9:2002.
- Jensen CE, Tuck SM, Agnew JE, Koneru S, Morris RW, Yardumian A, Prescott E, Hoffbrand AV, Wonke B. High prevalence of low bone mass in thalassaemia major. *British Journal of Haematology* 103;911-5: 1998.
- Porter JB, Davis BA. Monitoring chelation therapy to achieve optimal outcome in the treatment of thalassaemia. *Best Practice and Research Clinical Haematology* 15; 329-368:2002.
- Wonke B. Bone disease in beta thalassaemia major. *British Journal of Haematology* 103;897-901:1998.
- CCLG Stem Cell Transplantation guidelines: indications for transplantation (2012)
- Guidelines for the Management of Non Transfusion Dependent Thalassemia (NTDT) , Thalassemia International Federation, 2013

10) GUIDELINE DETAIL

Start Date:	October 2015
Approval Dates	Name of Divisional group: Date of ratification: Children's Quality and Safety Committee Meeting 08/10/15
	Name of Directorate group: Date of ratification: Quality Meeting Paediatric Haematology 28/08/15
Has all relevant legislation, national guidance, recommendations, alerts and Trust action plans been considered, and included as appropriate in the development of this guideline?	<p>Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK revised version 2008: UK Thalassaemia Society</p> <p>NHS Sickle Cell and Thalassemia Screening Programme programme, second edition, 2011.</p> <p>BCSH Transfusion guidelines for Children and Neonates, (2004+ Amendments 2005/2007)</p> <p>Blood transfusion guidelines for children and neonates:, ICHT Intranet.</p> <p>Iron chelation guidelines for paediatric patients requiring regular transfusions. ICHT Intranet.</p> <p>West Midlands Quality Review Service Quality Standards</p>
Have all relevant stakeholders been included in the development of this guideline?	<p>Dr Kirstin Lund: Lead Consultant for Haemoglobinopathy Service</p> <p>Dr Leena Karnik / Dr Josu de la Fuente: Deputy Lead Consultant(s) for Haemoglobinopathy Service</p> <p>Dr Josu De La Fuente: Paediatric Blood and Marrow Transplant Programme Director</p> <p>Dr Leena Karnik: Lead Consultant for Paediatric Haematology</p> <p>Catherine Mkandawire: Haemoglobinopathy Clinical Nurse Specialist/ MDT coordinator</p> <p>Marion Ong: Paediatric Haematology Day Unit Haematology Clinical Nurse Specialist</p> <p>Camilla Barratt</p> <p>Zita Noone: Specialist Social Worker for Haemoglobinopathy Service</p> <p>Becky Armstrong: Specialist Psychologist for Haemoglobinopathy Service</p>
Who will you be notifying of the existence of this guidance?	<p>Please give names/depts:</p> <p>Consultant Paediatricians including A&E and Ambulatory Care Unit</p> <p>Junior Paediatric Doctors including A&E and Ambulatory Care Unit</p> <p>Paediatric Nurses including those in the wards, A&E and Outpatients</p> <p>Will be available on the Source</p> <p>Pathology</p>

	Pharmacy
Related documents	Transition of haemoglobinopathy patients Operational Imperial College Healthcare NHS Trust Paediatric Red Cell Operational Policy
Author/further information	Name: Kirsten Lund Title: Consultant Paediatric Haematologist Division: W&C Site: St Mary's Hospital Telephone/Bleep: 02032127682 Trust email address: Kirstin.Lund@imperial.nhs.uk
Document review history	Next review due: October 2017
THIS GUIDELINE REPLACES:	Thalassaemia - Management of Children and Young People (Imperial)

11) INTRANET HOUSEKEEPING

Key words	
Which Division/Directorate category does this belong to?	Women & Children
Which specialty should this belong to when appearing on the Source?	Haematology

12) EQUALITY IMPACT OF GUIDELINE

Is this guideline anticipated to have any significant equality-related impact on patients, carers or staff?

Yes

No

Appendix 1. Vaccination Schedule

Routine childhood vaccinations are recommended for all children with thalassaemia.

Please check National Guidelines as changes do occur:

<https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book>

<http://www.immunisation.nhs.uk/>

Approach to pneumococcal vaccination depending of age of presentation – From Green Book August 2015

VACCINATION SCHEDULE FOR THOSE IN A CLINICAL GROUP RISK

Patient age at presentation	Vaccine given and when to immunise	
	13-valent PCV (PCV13)	23-valent PPV
At-risk children 2 months to under 12 months of age (including infants who have asplenia or splenic dysfunction or who are immunosuppressed)	Vaccination according to the routine immunisation schedule at 2, 4 and 12 months	One dose after the second birthday.
At-risk children 12 months to under 5 years of age who have asplenia or splenic dysfunction or who are immunosuppressed	Two doses, with an interval of 2 months between doses	One dose after the second birthday and at least 2 months after the final dose of PCV13
All other at-risk children 12 months to under 5 years of age	One dose	One dose after the second birthday and at least 2 months after the final dose of PCV13
At-risk children aged 5 years and at-risk adults	PCV is not recommended unless severely immunocompromised (see below for advice for severely immunocompromised)	One dose (see below for advice for severely immunocompromised)

13-valent PCV = Prevenar 13[®] and 23-Valent PPV = Pneumovax II[®]

Hepatitis B Vaccine (mandatory for children receiving blood transfusions)

For doses see the current edition of the BNFC as doses vary per brand.

All children requiring blood transfusions, whether as an elective or emergency procedure should receive Hepatitis B vaccination. Hepatitis B antibody levels should be checked 2 - 4 months after 3rd dose to ensure an adequate response (>100 iu/ml). Thereafter, antibody levels should be checked every 5 years and a booster given if levels are sub-optimal.

BCG is recommended, preferably at birth. If this is not administered at birth, follow the RCPCH guidelines.

Malaria Prophylaxis is recommended

- Depends on area to be visited. Consult with GP or Infectious Diseases team.
- Check G6PD status
- To be commenced up to 1 week prior to departure and to be continued throughout visit and up to 4 weeks after return depending on the drug used. Patients going to live in malarial areas should be advised to stay on prophylaxis lifelong if possible.

General advice re preventing bites – mosquito nets, clothing, repellents should be given

Appendix 3a. The Annual Review - Outline

The Annual Review should include the following [each patient should have an Annual Review Checklist (Appendix 3) completed and filed in the case-notes every year] An electronic database is being developed by the Red Cell data manager and the Red Cell Consultant, and will be used henceforth. :

- Assessment of progress in general and a review of the patient's and family's knowledge of the condition.
- School attendance and progress
- Chelation- compliance, child and family attitudes to chelation, problem-solving
- Review of information provided – to include any investigations taken, treatment given, healthy lifestyle advice
- Clinical measurements – undertaken at visit or results of investigations since last visit reviewed
 - Clinical examination – heart, lungs, liver, spleen
 - Weight and height (plotted on centile charts)
 - Assessment of puberty
 - Blood pressure
 - Urinalysis
- Clinical review
 - Number of hospital admissions
 - Other complications e.g. line infections
- Review of transfusions
 - Annual red cell consumption
 - Splenectomy: review of need
 - Red cell allo-antibodies
 - Virology status and anti-hepatitis B antibodies
- Investigations: All patients should have U&Es, LFTS, oral glucose tolerance test, serum ferritin, thyroid function other endocrine investigations as indicated and virology- Hepatitis B S Ag, S Ab, Hepatitis C and HIV.
- Transition care: options discussed with all families (and children) (age >12 years)

Appendix 3b. The Annual Review Checklist

**ST MARY'S PAEDIATRIC HAEMOGLOBINOPATHY CLINIC:
Thalassaemia Annual Review Checklist: investigations and management**

Date of review:.....

Diagnosis:.....

Other diagnoses:

1.....

2.....

3.....

4.....

Consent for NHR given: Yes/No

Shared care centre (if applicable):

Transfusion record available Yes/No/Not complete

Observations:

Height (cm)..... Centile..... Weight (kg) Centiles.....

BP(mm of Hg).....

Transfusion:

On regular transfusions Yes/No (delete as appropriate)

Transfusion interval.....(weeks)

Transfusion total (ml/kg/year).....

Average pre-transfusion Hb (g/L).....

Red cell allo-antibodies- specify and specify if new.....

Other transfusion/chelation issues.....

Hospital Admissions in last 12 months:

Number of hospital admissions:.....

Any acute infective episodes:.....

Vascular Access: Good/Poor (delete as appropriate)

Peripheral cannula

Port-a-cath

Other.....

Name
Hospital Number

Chronic complications: (tick as appropriate)

- Pubertal delay Poor growth
- Osteoporosis
- Diabetes
- Hypothyroidism

Name
Hospital Number

Surgery in the last 12 months:

Medication:

On iron chelation Yes/No (delete as appropriate)

- Desferrioxamine Yes/No Dose (mg/kg).....
- Deferasirox Yes/No Dose (mg/kg).....
- Deferiprone Yes/No Dose (mg/kg).....
- Combination (desferrioxamine (DFO) and deferiprone (DFP)) Yes/No Dose (mg/kg).....

Other medication:

.....

.....

.....

Schooling and education:

Name of school.....Academic year.....

School attendance: Good/Average/Poor

Examination:

- Splenomegaly Yes/No Size(cm).....Hepatomegaly: Yes/No Size(cm).....
- CVS.....Respiratory.....
- Other (specify).....
-

Name
Hospital Number

Investigations:

Hb (g/L)..... and Reticulocyte count.....(x10⁹/L)... (if not on transfusion)

Bilirubin (µmol/l).....

Creatinine (µmol/l)..... Vitamin D(nmol/l).....

Most recent ferritin (µmol/l).....

TSH (iu/l).....T4..... -

Calcium (mmol/l).....Glucose (mmol/l).....

Hepatitis B serology: Anti HBs antibody (miu/l).....Protective/Not protective

HBsAg/antiHBc..... HepC Antibody.....

Bone mineral density if appropriate

Audiology review date.....

Ophthalmology review date.....

Ferriscan date:.....Result.....(mg/g dw).

T2* MRI of heart :date..... Result..... (ms).

T2* MRI of liver date..... Result..... (ms).

Management changes considered:

Psychologist Yes/No/Not applicable

Dietician Yes/No/Not applicable

Refer to other clinics Yes/No/Not applicable (specify if yes).....

Other (specify).....

Offered BMT: Yes/No/Not applicable

Name of person completing annual review.....