

A Clinical Guideline on the Management of Adult & Paediatric Patients with Thalassaemia (guidance from the North Middlesex Regional Haemoglobinopathy Centre)

For Use in:	Clinical areas where patients with thalassaemia are treated
By:	Clinical staff caring for patients with thalassaemia
For:	Patients with thalassaemia
Division responsible for document:	Medical
Key words:	Thalassaemia; haemoglobinopathy; haemoglobinopathies
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Date of approval:	29/07/2022
Ratified by or reported as approved to (if applicable):	Clinical Safety and Effectiveness Sub-Board
To be reviewed before: This document remains current after this date but will be under review	29/07/2025
To be reviewed by:	Dr Suzanne Docherty
Reference and / or Trust Docs ID No:	16290
Version No:	1.1
Description of changes:	No changes
Compliance links:	Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, UKTS
If Yes - does the strategy/policy deviate from the recommendations of NICE? If so why?	No

Norfolk & Norwich Hospital is part of a Regional Haemoglobinopathy Network in which the North Middlesex Hospital is our Haemoglobinopathy Specialist centre. The North Middlesex Hospital provides Outreach clinics and specialist advice when required for haemoglobinopathy patients across the East of England regional hospital network. These clinical guidelines are provided by the North Middlesex Hospital to be used across their local haemoglobinopathy network.

It should be noted that clinicians at Norfolk & Norwich Hospital who need advice about patients with thalassaemia should contact the NNUH Haematology Registrar or Consultant directly for any advice, or to refer a patient with thalassaemia

- Adult patients presenting with problems that primarily relate to their haemoglobinopathy (including, but not limited to, painful crisis, chest crisis, infections, and transfusion reactions) should be triaged to Haematology.
- Adult patients presenting with other problems that require urgent management by another team (e.g. stroke, myocardial infarction, emergency surgery) may be triaged appropriately, but should be discussed with a Haematologist.
- The NNUH Haematology Consultant will liaise with the Regional Haemoglobinopathy Consultant at North Middlesex Hospital if necessary.
- Paediatric patients with haemoglobinopathies will be cared for by Paediatricians, with input from Haematology as needed.

Contact numbers for Haematologists at NNUH:

Haematology SpR on call:	DECT ext. 2919
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Thalassaemia Guidelines

Policy Number	CG - 000099
New or Revised Policy	Revised Clinical Guideline
Version:	8.0
Published:	April 2019
Review Date:	January 2022
Expiry Date:	April 2022
Policy Executive Owner:	Medical Director
Policy Owner	Service Manager Haematology Dr Arne de Kreuk Dr Marilyn Roberts-Harewood
Policy Author/s	Dr Anne Yardumian
Ratification Committee	Haemoglobinopathy Service (Local Service Meeting)
Date ratified:	January 2019
Approval Committee:	Haemoglobinopathy Service (Network Service Meeting)
Date approved:	March 2019
Agreement Committee	Drugs and therapeutic / medicines Committee
Date agreed:	October 2018
Target Audience:	Medical and nursing staff
Linked Policies:	
Key Words:	Thalassaemia, Thalassemia, Haematology, Transfusion, Iron Chelation
Name of other committees & meetings consulted	Reviewed and compliant to 'Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK' 3 rd Edition 2016
Designation of Individual Staff Members or staff groups consulted	Consultant Haematologist, Allied Health Professional, Nursing, Haemoglobinopathy service manager.

This is a Controlled Document. Staff must refer to the Intranet version of this document to confirm the most up to date version of this policy. If older versions are in circulation, they must be either returned to the author above or destroyed.

Clinical Guideline Ratification Sheet

Clinical Guideline Title	Thalassaemia Guidelines.
Version of Clinical Guideline	Version 8
	Last reviewed: November 2018
	Next review: January 2022
Speciality	Haematology. Transfusion. Thalassaemia. Iron chelation. Paediatrics.

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Management of Thalassaemia in children and adults: clinical guidelines

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β thalassaemia major – transfusion dependent children and adults.

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Last reviewed:

November 2018 , A Yardumian, M Roberts-Harewood, O Wilkey, K Madgwick, A Cummins, A de Kreuk, M Mirfenderesky

Plan next review:

November 2021 Introduction

At NMUH we look after a small number of **children**, and a much larger number of **adults** with beta thalassaemia major and thalassaemia intermedia. This guideline covers their general management in the Paediatric and Adult Haematology Clinics including specialist annual review, the arrangements for Day Care blood transfusions, monitoring and management of iron overload, referral to other specialist clinics and management of other acute and chronic complications.

Transition from Paediatric to Adult Haematology Services is the subject of a separate guideline: Transitional care for haemoglobinopathies.

Section 1: General management and arranging transfusions.

a The first clinic visit - infant.

In most babies with beta thalassaemia major, the diagnosis will have been anticipated by antenatal screening of the parents, who should have been offered prenatal diagnosis, PND. Some will have had this test and decided to proceed with the pregnancy. Newborn screening will detect the majority of infants with beta thalassaemia major, but it is acknowledged that not all will be identified. If the diagnosis is made when the baby has become symptomatically unwell, this should be reported to the lead consultants at NMUH and the Screening Programme for information / investigation.

At NMUH by the time an infant attends clinic, the family will have been visited at home by one of the George Marsh Centre specialist nurses, and the family will have been given initial information [verbal and printed] about their condition. The baby may also have been seen at their local hospital. However, the family will often want to hear about the condition again from the specialist doctor / nurse here – this initial discussion may be lengthy and cannot be hurried. They should be seen by a Consultant at this first visit.

Usually it will not be possible at this stage to know how soon regular transfusions are going to be necessary, if at all, and the main message is of supportive watchful waiting. While some families like to know about every possible future complication, it is probably sensible to confine initial discussions to how the decision regarding the need for transfusion will be reached [see c], and some general consideration of iron overload. Some may want information about current or future treatment options including bone marrow transplantation and ‘gene therapy’ etc.

- Convey the sense that while this is undeniably a serious long term condition, it is eminently treatable, and well managed children have a near normal quality of life and – probably – life expectancy, with every likelihood that they will go through school/ further education / have jobs and families like everyone else. Positive messages at this stage are really valued.
- Examine the baby, especially noting liver and spleen size.
- Start a height and weight centile chart. Measure / record parents height also.
- Some babies will need confirmatory blood tests taken at this time, + the other ‘pre-transfusion’ tests [see c].
- Introduce them to the Children’s Specialist Nurses for thalassaemia and sickle cell, who will be their ‘key contact’.
- Give the “Welcome to the Thalassaemia Service” Information leaflet.
- Ensure that the family has all appropriate written information about our service, and about the condition, and recommend that they contact the UK Thalassaemia Society [0208 882 0011] which they will find a very useful resource.

- Discuss ongoing outpatient arrangements, which might be for all treatment at NMUH including transfusions and outpatient visits, or routine outpatients and transfusions at their local hospital, with clinic visits at NMUH [or by outreach review by specialist team at linked hospitals] at least once a year, for Annual Review.
- Give the information leaflet about the National Haemoglobinopathy Registry, and request verbal consent to enter details.

At the end of the consultation, a letter outlining the care arrangements should be sent to the GP, with a link to the resources at the UK Thalassaemia Society [www.ukts.org] and the NHS Choices pages on thalassaemia [<http://www.nhs.uk/conditions/Thalassaemia/Pages/Introduction.aspx>]; this must also be copied to the parents and the local hospital paediatrician, if we are not their local provider.

b Indications for first transfusion in infants with thalassaemia.

From the baby's genotype, which should be available from PND or first diagnostic samples, it should be possible to have some idea of likely transfusion dependency, but this is not absolute. If the genotype is not available, it should be requested. The decision to transfuse should only be taken by a consultant; it is a clinical decision to be weighed carefully after discussion with the family. The child's activity level, achievement of developmental milestones, growth, any facial bone changes, and degree of hepatosplenomegaly should be taken into account, as well as Hb level. A first transfusion is often given if there are any concerning clinical features + the Hb has fallen below 70 g/l especially if the reticulocyte count is low [possible viral infection]. Other causes of reversible anaemia [intercurrent infection, iron deficiency etc] should be excluded and after a first transfusion it should not be assumed that regular transfusion will become necessary. A period of close watchful waiting, with Hb checks at intervals determined by the rate of fall, should occur to decide whether long term transfusion is inevitable.

Transfusions will be given on the Paediatric Day Assessment Unit (PDAU).

See operational policy PDAU and Blood Transfusion Ward Policy for specific guidance. Only staff trained and competent can cannulate and supervise transfusions.

c Investigations / vaccinations prior to first transfusion

- Hb levels, followed serially
- G6PD screen / assay if low;
- Full red cell phenotype (refer to local guidance - consider age of child > 3 months and consider genotype rather than phenotype)
- LFT and baseline serum ferritin level
- Hepatitis B screen: HBsAg, HBcAb, HBsAb, also Hepatitis C Ab and HIV ab.
- If Hep B negative, start a course of Hepatitis B vaccination as soon as possible: 1st dose immediately, 2nd after 1 month and 3rd after 2 months. Check an antibody level after a further month.
 - If antibody > 100 u / l – protective. Plan one further booster dose after 5 years.
 - If antibody level 10 - 100 u/l, give another booster dose and recheck level. If now > 100 u/l – single booster dose at 5 years.
 - If antibody level < 10 u/l, arrange another set of three doses at 0, 1, 2 months and recheck level.
 - If still < 10 u/l – non responder, do not give further doses
 - If 10 – 100 u/l, try one final booster dose.
 - If antibody level now above 100 u/l – one final booster after a further 5 years.

d The first clinic – older child or adult previously treated elsewhere

Sometimes a new patient joins the clinic, because they have moved into the area from elsewhere in the UK or, more commonly, from abroad. Where possible they should be allocated a double clinic slot, as there will be much to catch up on! They may bring records from their previous hospital.

They should be seen by a Consultant at this first visit, and the patient and / or family should be asked for a full background history including diagnosis, age of first transfusion, transfusion frequency, chelation history, any operations, immunisations, symptoms such as palpitations or menstrual disturbance / erectile dysfunction, and any children with or without assisted conception.

Record all current medications, to review after receiving initial investigation results and decide if appropriate.

Record a full physical examination including temperature, pulse rate, BP, oxygen saturation on air, weight and height

- Enquire where they have been previously transfused: our laboratory will contact the relevant transfusion laboratory for previous phenotype results and any previously detectable antibodies found if possible / contactable [may be difficult if outside the UK].
- Work through the 'annual review' proforma [see Section 7 and Appendix 1].
- Request a full set of monitoring blood tests, including: FBC, ferritin, U&E, LFT including ALT and γ GT, calcium, PTH, vitamin D level, glucose, TFT, in children from age 12 FSH, LH, testosterone / oestradiol, hepatitis B screen including HBsAg, HBsAb and HBcAb; also HCV IgG and HIV ab [after getting verbal consent] and β globin genotype – after signing the required consent form [Appendix 2] .
- Request urine for protein:creatinine ratio.
- For **young children, request full red cell genotype or phenotype** to inform selection of units for the future to minimise risk of alloantibody formation. Multi-transfused adults who have not already formed antibodies are unlikely to do so and this may not be necessary.
- Give the request forms for all of the above, and guide where to go to have the blood tests taken after the consultation.

- Take time to answer any questions they may have and for children, ensure that referral for bone marrow transplantation has been discussed.
- Give the "Welcome to the Thalassaemia Service" Information leaflet.
- Ensure they are aware of / have contact details of the UK Thalassaemia Society www.ukts.org.
- It will be useful for the patient and family to spend some time with the Children's Nurse Specialist for sickle cell and thalassaemia [if under 16] or Adult Red Cell Haematology CNS and / or Transfusion Practitioner [if 16 years or over] – who will be their 'key contacts' – to talk through the logistics of coming for pre-transfusion samples, and for attending for transfusions; they will make the first bookings at appropriate intervals with the appropriate Day Unit. If time, they may be taken to see the Day Unit and introduced to staff there.
- Give the information leaflet about the National Haemoglobinopathy Registry, and request verbal consent to enter details. They may already be registered at their previous treating centre if in the UK in which case check they agree to us informing the Registry of the change of centre – and do this.

After they leave the clinic, dictate a full summary letter to include all your findings and:

- If they are above the age of 10, refer to Cardiology at the UCLH, Dr Malcolm Walker, who will undertake an echocardiogram and also arrange for a T2* scan to quantify heart iron.

- If they are above the age of 10, refer to Chingford clinic for DEXA bone mineral density scan [the Haemoglobin Disorders data and network manager, or Haematology PA, will do this; cc into your letter].
- If the patient uses desferrioxamine or deferasirox chelation, refer for audiology and ophthalmology assessments.
- Make other referrals as needed eg to Endocrinology if there is growth delay, to Hepatology if they are known to have Hepatitis B or C infection.
- Send the full summary letter to GP, patient [or family if under 16 years], and previously treating hospital. Enquire about issues that have not been clear from the history, for example whether and when they had previous Pneumovax, other immunisations, splenectomy etc.
- Append all the Pathology results and ensure that any abnormal results have been noted and acted upon.
- If HBsAg, HbsAb and HBcAb negative, start a course of Hepatitis B vaccines as soon as possible: 1st dose immediately, 2nd after 1 month and 3rd after 6 months. This can be done on the Day Unit when attending for transfusions.

e Regular clinic checks and planning transfusion attendances – children.

Introduction

Below are some specific considerations to ensure good quality care for children with thalassaemia. It is not possible to be prescriptive as each child will be different and some will require closer monitoring than others for a variety of reasons which may include social reasons or problems with treatment compliance. For specific local information please refer to the appendices.

1) Outpatient clinic visits are usually every 3 – 4 weeks for the first several months after starting transfusions; when stabilised on a transfusion regimen, clinic visits can be every 2 – 3 months with blood samples otherwise being taken at family's convenience and pre-assessment check being made by Paediatric Day Unit Staff when they arrive on the day unit for the transfusion.

2) Children have height and weight recorded and any issues about their health or any other problems are discussed in clinic.

Ask about school attendance from age 4.

Once started on regular chelation [see section 2] enquire about how they are getting on with it / any difficulties managing. If there are problems with adherence, consider change in regimen [p6] and / or referral for psychology input

Record the size of liver or spleen every 3 months.

Check pubertal status at least yearly from age 10, refer to paediatric endocrinology [see Appendix X] if growth velocity falling or no pubertal development by age 13 [girls] or age 14 [boys].

3) A paediatric phlebotomist is on site in the Children's Outpatients Dept all day every weekday, including clinic day and can take samples for the next transfusion on the days they children are in clinic, for transfusion within the next 48 hours. After that time, samples can be taken in clinic by nursing or medical staff.

4) Dates for transfusion are arranged with the family by the Children's nurse specialists and the Day Unit Sister, who will also give request forms and arrange for pre-transfusion samples to be taken on the months the children are not seen in clinic.

Try to book the transfusions to fit around the child / family's other commitments.

Remember if there is any change of date (i.e. what is now planned is not what would be on 'cross match' request sent to lab) to telephone the transfusion laboratory x 2276 to make the change.

5) Write a prescription; many parents like the drugs delivered to the ward for when they are coming for transfusion rather than waiting in pharmacy. Indicate by 'please deliver to Paediatric Day Unit for (date)'.

You may need to include:

- Penicillin V [if splenectomised] up to 1 yr 62.5mg BD
1-5 yrs 125mg BD
>5yrs 250mg BD
Penicillin-allergic children should be given erythromycin, at the same doses.
- Desferrioxamine, deferiprone, or deferasirox – to be arranged but please note – where possible these are prescribed for home delivery by an external company, not throughout patient Pharmacy [VAT saving]. The home delivery company also delivers Thalaset needles, tape etc ie everything needed to administer the treatment. The application is made through the paediatric nurse specialists for children.
- Vitamin C (Ascorbic acid) orally (which is given with desferrioxamine after initial month or so of treatment to enhance iron excretion) just on 'pump days' - dose 50 mg if under 20 kg, 100 mg if 20 - 50 kg, 200 mg if > 50 kg body weight.
- Any others as needed e.g. analgesia.

6) Make next appointment for the Wednesday before subsequent planned transfusion date for infants still being seen frequently, or 2 – 3 months later once stabilised on transfusion.

7) Complete the Transfusion Prescription sheet, indicating the amount of blood to be given, and any other additional medication. Clip onto the front of notes.

f _____ Regular clinic checks and planning transfusion attendances – [adults](#).

1) Adults attend the Tuesday Haematology clinic, Clinic 4, and should be offered afternoon [2-5 pm, ADK4C] or evening [5 – 8 pm, ADK4E] appointments; evening appointments are usually for people in full time education or work.

On the first Tuesday of the month, young people aged 16-25 years including those who have recently transitioned over from Paediatrics [see guideline 'Transitional care of haemoglobinopathies'] are cohorted, to MRH4C and MRH4E.

Clinic visits are usually every 3 – 4 weeks for the first several months after a patient joins the clinic or starts on transfusions. When stabilised on a transfusion regimen, clinic visits can be every three months as long as monitoring results – often needed monthly, for example those on deferasirox – are being checked in between time.

Transfusions are given on Haematology Red Cell Day Unit, situated on Pymmes – 1

- Wednesdays 9 - 5
- Thursdays and Fridays 9 – 9pm,
- alternate Saturdays 9 – 5 pm.

2) For clinic: on arrival at the hospital patients go first to the OP Phlebotomy area, taking request forms (urgent marked on the forms) given at the previous attendance. The phlebotomists work until 18.45 on Tuesdays [and Thursdays]. After that, one of the clinical team can take samples any time until the end of the evening clinic.

3) The date of the last Annual Review is noted, and the next planned to fall close to the 12 month mark.

In between annual reviews, ensure actions arising from the last review have been completed, discuss

any new or ongoing problems, especially any difficulties with chelation medication, check recent blood test results. Other test results / clinic letters from tertiary specialist clinics are scanned onto the patient's electronic record, 'Haematology' section of CIP, so please check there for each patient you see.

4) Using the red file marked 'Red Cell Day Unit Diary' check that they are down for the time they are expecting to come on the week you are seeing them – this should have been entered at last clinic visit. Forward plan with them / enter their details in the diary for the next 2 – 3 transfusion dates until they are next due in clinic.

3) Ask if they need any medication, and complete a prescription, so that the medication is waiting for the patient when they attend for transfusion. All the prescriptions are dropped into Pharmacy the following morning by the Haem PA's / CNS. who gets a 'receipt' for them – in case of prescriptions 'misplaced' in Pharmacy.

4) Ensure a prescription has been prepared for the blood transfusion.

5) dictate a summary letter to the GP summarising problems, medication changes, anything else discussed, remembering to cc the patient and anyone else you are referring to – it saves secretarial time if you do a single letter making any necessary referrals by way of copy letter.

g _____ Annual Specialist Review for patients with thalassaemia – **children and adults.**

Once a year, a longer and more in-depth review of progress should be undertaken, in a longer clinic appointment, and with prior warning to the patient to expect this.

This applies to those who receive all their care at NMUH, and those treated in linked hospitals being managed on an out-reach basis or attending NMUH for specialist input; for some milder intermedias, this is the only time we see them per year. Patients coming for annual review from linked hospitals are seen by the Consultant. Annual review can be undertaken by the clinic registrar (after training) for local patients, as they will be seen by the Consultant at their next visit.

Please read this guidance in conjunction with the proforma 'Thalassaemia annual review', Appendix 1A [children] 1B [adults] which is to be completed at this visit and is to a large degree self-explanatory.

If the patient is not already registered on the NHR, please briefly introduce this, give them the information leaflet, answer any questions they may have, and take verbal consent to enter their details.

At end of review, please dictate a letter to the GP, indicating that this individual had their annual review visit today, detail important outcome of discussions including any suggested changes in transfusion or chelation regimen, and list any actions required, copying letter to:

- Referring linked hospital consultant, if a non-NMUH patient
- The patient and / or parents [depending on age] – this is important as it constitutes their 'care plan' for the coming months.
- Any specialist consultants who need to see the person for example if cardiology review needed, cc Prof Malcolm Walker at UCLH Cardiac Care Clinic [see relevant contacts list]
- If relevant, health visitor / school nurse.
- As you sign out your letter, check through and append the results of all blood and / or urine tests. This is to ensure that you note, and manage as needed – or bring to the attention

of the team at the linked hospital with advice for management - any abnormal results as soon as they are available .

- A copy of all annual review letters is sent to the data and network manager for uploading details onto the NHR - for any patients who have not consented to their details being stored on the NHR the data manager will record that an annual review has been done for data quality purposes but the details of the review will not be recorded on the NHR.

h Optimal haemoglobin levels.

Haemoglobin level should be recorded before every transfusion, aiming for no lower than 95 g/l. If the level is regularly lower than this, consider:

- Decreasing transfusion interval
- Increasing transfusion volume [for younger children, more frequent transfusion usually better]
- In children, ensure spleen is not enlarging.

Post transfusion Hb should not exceed 140g/l. This is not measured routinely, but is helpful after every 2 or 3 transfusion especially in the early months to ensure appropriate levels are being achieved. At these levels, optimal energy and growth are achieved with no more iron loading than is unavoidable.

i Frequency of monitoring investigations.

Other investigations should be routinely undertaken as follows:

- Before every transfusion – FBC and antibody screen.
- NB. Weekly FBC for those on deferiprone is recommended but it is acknowledged that many patients cannot keep up with this frequency of monitoring. Always ensure however that people on this medication understand **that if they develop symptoms of infection / fever of 38 C or above they must present PROMPTLY to the Emergency Department if out of hours, or as arranged after discussion with members of the Red Cell Haem Team within hours, for a full blood count check. This is because NEUTROPENIA / AGANULOCYTOSIS** is a recognised side effect of this drug.
- Every 3 months - ferritin, U+Es and LFTs including ALT, random glucose
- Monthly U+Es, LFT including ALT and urine protein:creatinine ratio on for those on deferasirox

The checks to be undertaken regularly are all on the annual specialist review proforma [Appendix 1]:

- Annually at least (more often if at all abnormal for close monitoring/ if known complication such as diabetes mellitus, hypothyroidism, hypoparathyroidism and on treatment, to monitor appropriate management) -
 - oral GTT [from age 10 if FH diabetes, done on PDAU, or from age 16 otherwise, on Day Unit preceding transfusion; remember to tell come fasting for this!]
 - Thyroid function tests from age 10
 - Calcium / phosphate levels from age 10
- Ophthalmology review for patients on desferrioxamine [yearly] or deferasirox [every two years].
- Audiology from the age of 4 years for patients on desferrioxamine [yearly] or deferasirox.
- Cardiac assessments once a year by Prof Malcolm Walker, consultant Cardiologist UCLH / National Heart Hospital from the age of 10 yrs. He will recommend frequency of follow up after a first visit, depending on the degree of cardiac iron loading. In children under the age of 10, if ferritin constantly > 2000 ng/ml, consider earlier referral.

- Paediatric endocrine referral if there is any concern about growth velocity or delayed puberty [no pubertal development by age 13 [girls] or age 14 [boys].
- All patients at NMUH are reviewed in the thalassaemia endocrine clinic at least annually.
- DEXA bone density scanning should be undertaken every 18 – 24 months from age 10 years.
- Check hepatitis B serology HBsAb titre annually; if titre < 100 u/l, arrange booster dose of hepatitis B vaccine at next transfusion.
- Check hepatitis C serology if transaminases are raised [consistently or intermittently], and otherwise 3 yearly.
- Calculate mls / kg red cells transfused, mg / kg midyear body weight. If this is > 250-275 ml/kg/year consider if splenectomy would be appropriate.

j Managing bone thinning.

Bone thinning is common.

Steps to reduce the risk are

- Not smoking
- Not consuming alcohol in excess of recommended limits
- Regular weight-bearing exercise
- Good calcium / dairy intake in the diet

and it is good to remind patients of these at frequent intervals.

Key to bone health is **adequate vitamin D** – we aim to keep levels about 80 nmol/l in these patients with supplementation if the levels are low –

- Prescribe **colecalfiferol 40,000 units once weekly for 7 weeks** then maintenance dosing **OR ergocalciferol 50,000 units weekly for 6 weeks then maintenance dosing**. (Ergocalciferol should only be prescribed if patients do not want colecalciferol – most preparations containing gelatin - due to religious reasons or if a vegan). Maintenance doses of vitamin D are not kept in the hospital pharmacy and the patient should buy these over the counter.
- Adequate **hormone replacement** should be prescribed in any who patients who have hypogonadism.

On the basis of the DEXA scans, it may be decided to add in a bisphosphonate which can be oral – eg alendronic acid 70 mg weekly, or pamidronate 30 – 60 mg iv pre-each transfusion, or zometa 4 mg iv every 3 months. This decision will be guided by the reporting Rheumatologist, and the Consultant Haematologist after discussion with the patient.

If patients are treated with bisphosphonates for a period of years, it is good to give them a ‘bisphosphonate holiday’ for 1 – 2 years every 5 years or so.

Because of the risk of osteonecrosis of the jaw (ONJ), patients should consult their dentist prior to start with a bisphosphonate and have any major dental work done beforehand. Also, ask about thigh pain in patients on these drugs, as they can cause an atypical thickening at the femoral cortex which is brittle and may result in atypical horizontal fracture. If there are any symptoms – stop the bisphosphonate and X ray the femur.

k Splenectomy

If blood consumption is high, the increased transfusion volumes / frequency will lead to increased blood donor exposure – so possible increased risk of transfusion transmitted infections as well as antibody formation, and increased iron loading. Calculate mls / kg red cells transfused, mg / kg mid-year body weight. If this is > 250-275 ml/kg/year then consider / discuss if splenectomy would be appropriate. Splenectomy usually reduces consumption, and lessens these risks.

This possible gain has to be set against the long term risk of infection post-splenectomy, increased iron loading from the gut, and the increased risk of thrombo-embolic disease. The decision needs to be

taken by a consultant from the specialist team, after careful discussion with the patient and family of the pros and cons. As early full transfusion tends to reduce spleen growth, and as iron chelation regimens become easier, fewer children / adults with thalassaemia major proceed to splenectomy, but it still has its place for some. The situation in thalassaemia intermedia is different – see Section 4.

If it is decided to proceed to splenectomy:

- Immunisation:
 - Ensure that the child has been immunised according to national schedule, including the 12-month boosters
 - Give an additional dose of Hib/MenC and the first dose of MenB vaccine, along with the pneumococcal polysaccharide vaccine (PPV23)
 - Give a dose of MenACWY conjugate vaccine one month after surgery and the second dose of MenB two months after the Hib/MenC booster
- before the procedure, an abdominal ultrasound scan should be done to detect gall stones. If present, a cholecystectomy at the same time should also be considered.
- Penicillin V twice daily for pneumococcal prophylaxis, should be prescribed to start immediately post splenectomy and continued at least until early teens, after which treatment dose [500 mg qds at the first hint of infection or low grade fever < 38 C] may be preferred. If penicillin allergic, Erythromycin at the same doses.
- Advise that if there is fever of > 38 C, and / or if symptoms are not getting better after 24 hours on Penicillin at treatment dose, then they must come to the hospital for further assessment and broader spectrum antibiotics.
- Lifelong vigilance and early treatment for infection, together with 5 yearly boosters of Pneumococcal vaccine are required.
- Patients who did not receive Prevenar as part of their primary vaccinations should receive a single dose, at least 6 months before or after any Pneumovax immunisation.
- Post splenectomy thrombocytosis is frequent but usually not associated with thromboses in children. In adults, thromboprophylaxis should be considered for those with persistently elevated platelet counts.

Section 2 : Monitoring and managing iron loading in frequently or regularly transfused patients.

a General.

Anyone receiving frequent or long term transfusions will come to need **iron chelation treatment**, in order to control total body iron load and try to minimise related organ damage.

This usually needs to start after about 1 year of regular transfusion or when the ferritin level is climbing to ~ 1,000 ng/ml. The **decision to start iron chelation, which agent or combination of agents to use, and any subsequent changes of regimen, is only to be made by a Consultant on the specialist team** at NMUH [or by the team at outreach clinics in discussion with local Consultants for patients at linked hospitals], taking into account the informed preferences of the patient / carers.

Time is needed to explain the benefits and possible adverse effects of each option. The decision process should be recorded in the patient's records. Patients and carers should be supported in adhering to chelation therapy using a multi-disciplinary team approach which includes medical and nursing staff, clinical psychology, and – in children - play therapy.

Adherence should be monitored regularly, and problems carefully identified and addressed. Use of a treatment diary may assist with monitoring.

Patients should be carefully monitored for side effects of iron chelation, and treatment interrupted or reduced promptly to avoid serious toxicity. All professionals managing these patients and checking their monitoring investigation results need to be familiar with the issues, and aware of what to watch out for / escalate for discussion with the Consultant.

b Chelation therapy.

The aim of therapy with all chelation regimes is to attain and maintain annual average serum ferritin below 1500 ng/ml [ideally < 1000 ng/ml], liver iron below 7 mg/g dry weight [ideally below 5 mg/g dry weight], and cardiac T2* >20 ms.

c Indications for starting.

Chelation should be started after ~ 10 transfusions, or when then serum ferritin is, on repeat, nearing 1,000 ng/ml. Recent expert opinion suggests starting chelation as early as possible after regular transfusion commences, even before there is evidence of substantial iron loading.

d Which chelator?

There are three licensed chelator drugs, desferrioxamine ['Desferal', DFO], deferiprone ['Ferriprox', DFP], and deferasirox ['Exjade', DFX]. Desferrioxamine has to be given parenterally over long periods to be effective: typically sub-cut for 12 hours overnight on 5 nights per week in a fully transfused patient. The other two are taken by mouth.

Note!

- All prescriptions are undertaken by the hospital, NOT the General Practitioner as NMUH and / or the local hospital is monitoring and/or dose adjusting.
- Where acceptable to the patient / family, we prescribe home-delivered chelation.

Individual chelators and possible problems:

Desferrioxamine by subcutaneous infusion has been the standard starting chelator and remains the only one currently licensed for first line use in children under 6 years.

However deferasirox is licensed for children from aged 2 where desferrioxamine is 'contraindicated or inadequate'. On the basis that most children and parents struggle with subcutaneous infusions, and when not given almost every night chelation with desferrioxamine will be inadequate, it is common practice to start children on deferasirox from age 2, without a trail of desferrioxamine. This must be discussed with the parents – see below under **deferasirox** section.

Parents are taught how to administer desferrioxamine by the children's specialist nurses for thalassaemia and sickle cell, who will visit the home to demonstrate and help set it up, until they are confident to do so independently. They will also be given a booklet that they can refer to. Adults are taught how to administer DFO on the Red Cell Day Unit by one of the George Marsh Centre specialist nurses.

The dose for children is 20 - 30 mg/kg/day if given on 7 days per week, over 10 - 12 hours. It is more usually given on 5 days per week thus each dose slightly larger to achieve the same daily average. (In the starting weeks, it is often given on 3 days per week until they are comfortable and familiar with it.) More iron is removed by frequent use - daily is best - but realistically families are seldom able to maintain daily use.

The dose for adults is 20 - 50 mg/kg/day if given on 7 days per week, over 10 - 12 hours, but for those on high transfusion volumes, doses in excess of 50 mg /kg/day x 5 days a week may be required.

Where there are serious concerns about iron overload and organ damage, it can be given continuously, intravenously through a Port device or, more usually, subcutaneously, 24/7, sometimes in combination with deferiprone especially if there is evidence of severe cardiac iron loading or failure [see 'combination chelation treatment' below].

Some patients are allergic to desferrioxamine, and many find the route of administration difficult. Disposable desferrioxamine infusers and fine 'thumb-tack' type sub-cutaneous needles ['Thalaset'] aid adherence. It is also not ideal as a chelator because it is only effective at the time it is running so for at least 12 hours a day, in normal use, there is no active chelation going on.

At high doses it can cause audiological, ophthalmological and/or skeletal abnormalities in growing bones and thus monitoring for these side effects is required. Once the iron overload has been reduced satisfactorily (eg ferritin <1000 ng/ml in those with transfusion dependent thalassaemia / major, also taking into account the results of MR tissue iron quantitation results) the dose of desferrioxamine should be decreased.

It is important that a therapeutic index of < 0.025 is maintained at all times. Significant side effects as mentioned above are unlikely to occur when the mean daily dose (mg/kg) /current serum ferritin (microg/L) remains below 0.025.

If a patient receiving desferrioxamine develops abdominal pain, diarrhoea or unexplained sepsis, desferrioxamine must be stopped and stool samples taken as desferrioxamine increases susceptibility to **Yersinia enterocolytica** infection.

Iron excretion is reduced if there is ascorbic acid (vitamin C) deficiency, and supplementation should

be commenced one month after commencing desferrioxamine in patients with normal cardiac function; dose 50 mg if under 20 kg, 100 mg if 20 - 50 kg, 200 mg if > 50 kg body weight, taken orally just on the days the 'pump' is used.

Deferiprone has particular cardio-protective effects, and it is used singly or in combination with desferrioxamine where there are concerns about heart iron levels. The usual dose is 25mg/kg TDS ie 75 mg/kg/day, up to a maximum of 100mg/kg daily in adults with significant heart iron loading. Side effects include nausea and vomiting, abdominal pain, arthralgia and neutropenia. Zinc deficiency has been reported. In those found to be deficient, zinc supplements should be supplemented.

The most serious adverse effect of deferiprone is **agranulocytosis** and thus weekly monitoring of the full blood count with a white cell differential is recommended for the duration of therapy. Many do not attend for such frequent testing in practice, and **the most important safety message - repeat often! and write in the clinic letters - is that if the person has fever of 38 C or above, or other signs of infection, they must stop the medication and attend the hospital quickly for a blood count to exclude a significantly reduced neutrophil count.**

Deferiprone is available in 500mg tablets and 100mg/ml suspension.

Table 1

Body weight (kg)	Total daily Dose (mg)	Dose (mg) 3 times/day	Number of tablets 3 times/day
20	1500	500	1.0
30	2250	750	1.5
40	3000	1000	2.0
50	3750	1250	2.5
60	4500	1500	3.0
70	5250	1750	3.5
80	6000	2000	4.0
90	6750	2250	4.5

Deferasirox starting at 7mg/kg/day then adjusted in steps of 3.5–7 mg/kg every 3–6 months to a maximum dose of 28 mg/kg/day (usual maximum dose 21 mg/kg) can be used in children <6 yrs of age if desferrioxamine is 'contraindicated or inadequate', and can be used as first line chelation in children age >6 yrs and adults. Because of ease of administration, some patients greatly prefer it. For small children, after discussion with the parents about the fact that there is much longer experience with desferrioxamine, and an explanation that that is the only drug actually licensed for 'first line' use, deferasirox is sometimes now offered as initial therapy, as putting a child through the discomfort of sub-cut infusions several times a week to demonstrate that they cannot tolerate it is deemed unkind and unnecessary.

It is available in 90, 180 and 360 mg film coated tablets, which can be crushed for paediatric use; the usual starting dose is 14 mg/kg/day. Side effects include gastrointestinal symptoms, including severe indigestion and on occasion upper GI bleeding, skin rash, deranged liver and renal function.

Serum creatinine and liver function, and urine for protein/creatinine ratio must be measured on 2 separate occasions before initiating therapy, and weekly for 4 weeks after starting or increasing dosage.

It is contraindicated in those whose creatinine clearance is <60ml/min.

Once established on treatment, checks on U&E, LFT and urine PCR are required every month.

Do not administer NSAIDs to patients on deferasirox because of the added risk of upper GI irritation.

All three chelators are contraindicated in pregnancy

Patients who are / or appear to be having problems with adherence - for example who cancel or delay home deliveries, do not request repeat prescriptions, whose iron levels continue to rise despite high / appropriate dosing should be highlighted as part of a MDT approach and, if appropriate, asked to attend a MDT meeting to see if the team can offer help to assist in compliance. The ongoing use of positive reinforcement is critical and it is important to notice, record and praise good compliance. Use of graphs to track ferritin levels and or R2 / T2* monitoring can be helpful in showing patients the result of good, or poor, compliance.

e Monitoring iron loading.

Clinical assessments of iron loading are not helpful in routine practice: by the time there is obvious skin darkening, palpable hepatomegaly, cardiomegaly, or cardiac rhythm disturbance, iron loading is advanced and so investigations aiming to detect and enable correction of iron are required, on a regular basis, before these signs develop.

Serum ferritin levels should be **monitored at least every three months**; levels maintained in the range 500-1500 µg/l over the long term carry a relatively low risk, best if around / below 1,000 ng/ml. Remember that ferritin levels are elevated during intercurrent acute infections, chronic inflammatory conditions and chronic viral hepatitis, and this leads to an overestimate of the degree of iron loading. Low levels may give a false reassurance, this is especially the case in intermedia [see section 5].

Magnetic resonance imaging (MRI).

Cardiac T2* MRI is the best available method for detection of cardiac haemosiderosis in thalassaemia. There is evidence that T2* can be used as a marker for cardiac risk, and the result allows adjustment of chelation regime to reduce myocardial iron load and avoid clinical cardiac disease. There is a relationship between low T2* [lower numbers indicating higher iron level] and impaired LV function; LV impairment becomes increasingly likely when T2* falls below 20 milliseconds (ms). Although not specifically designed to measure liver iron, the T2* also gives an estimate of liver iron content; aim for a level of < 7 mg/ g dry weight. T2* will be undertaken at the direction of Dr Malcolm Walker and team at UCLH, who see all our patients for their regular cardiac assessments. Refer from the age of 10.

As a guide, cardiac T2* MRI

- every 2 years if T2* >20 ms,
- every year if T2* 10-20 ms,
- 6 monthly if T2*<10 ms, and / or if any evidence of cardiac impairment.

R2 MR assessment scan [Ferriscan] is reported to be more accurate in quantifying liver iron levels. R2 should be requested via the Haematology PA, if:

- the T2* indicates some degree of iron loading in the liver
- the ferritin is consistently high, above 2,000 ng/ml
- liver function is abnormal without any other evident cause
- there is infection with hepatitis B or C, so that LFT and ferritin might be unreliable, and it is especially important to keep liver iron levels low.

In practice, having this additional scan is now becoming standard care, and all patients are now referred for Ferriscan, first at aged 8, and then at intervals according to load / compliance with chelation:

- yearly if the liver iron is over 15 mg/g dry weight, up to
- 3 yearly if liver iron is below 5 mg/kg dry weight as long as other indicators of iron loading remain stable and low [ferritin, liver iron on T2*].

f Modifying chelation regimen – **to be undertaken only by a Consultant.**

1 Patients with acceptable iron stores (Serum ferritin consistently 1000±500 µg/l,

liver iron < 7 mg/g dry weight, Cardiac T2* >20 ms.) If patients are content to continue regular desferrioxamine, switching is not necessary. Maintain desferrioxamine 20-30 mg/kg 5 infusions per week, up to 50 mg/kg/day for adults. Oral chelation should be offered if patients would prefer, and there are no contra-indications. This will usually be deferasirox 14-21 mg/kg/day. In older children and adults, if there are adverse effects to desferrioxamine and deferasirox, deferiprone 75mg/kg/day in three divided doses may be considered.

It is important that a therapeutic index for desferrioxamine of < 0.025 is maintained at all times. Significant side effects as mentioned above are unlikely to occur when the mean daily dose (mg/kg) /current serum ferritin (microg/L) remains below 0.025

2 Patients with increasing or high iron stores and normal Cardiac T2* (Serum ferritin consistently >1500 µg/l, and/ or liver iron >7 mg/g dry weight, Cardiac T2*>20 ms.)

Patient on desferrioxamine: Can try optimising dosage and adherence as far as possible, but usually this will have been tried: try switching to deferasirox if no contra-indications.

Patient on deferasirox: Optimise dosage and adherence to deferasirox. For patients treated with deferasirox, it may take years for ferritin and liver iron to reach target levels. Deferasirox should be continued provided there is a trend to decreasing iron levels with dosage increases as required within the licensed range (up to 28 mg/kg/day) in increments of 5 mg/kg as tolerated.

3 Patients with increased cardiac iron (Cardiac T2* <20 milliseconds.)

Increased cardiac iron and high liver iron stores: (Serum ferritin consistently >1500 µg/l, and/ or liver iron >7 mg/g dry weight, Cardiac T2*<20 ms.) Switch to combination desferrioxamine 30 mg/kg x 5 per week plus deferiprone 75 mg/kg/day seven days per week. The dose and frequency of desferrioxamine and dose of deferiprone should be determined largely by the cardiac T2* value, pushing to deferiprone 100 mg/kg /day if cardiac iron is substantial, and as many desferrioxamine infusers per week [ideally 24/7] as the patient can manage to use.

Increased cardiac iron and acceptable liver iron stores: (Ferritin consistently 500-1500 µg/l, and liver iron <7 mg/g dry weight.) Consider switching to deferiprone pushing to 100mg/kg/day seven days per week.

4 Chelation in patients with iron-induced cardiac failure

It is imperative for the management of decompensated cardiac failure that early input from a cardiologist with experience of acute management of cardiomyopathy in general and thalassaemia in particular is sought; refer immediately to Professor Malcolm Walker at UCLH cardiac clinic.

There is a consensus statement from the American Heart Association which outlines accepted best practice for this clinical emergency, in summary:

- 24 hour iv desferrioxamine [50 mg/kg/day]
- PLUS oral deferiprone pushing to to 33 mg/kg/day tds [100 mg/kg/day]
- Avoid inotropes – tolerate low BP if renal and cerebral perfusion is OK
- Maintain pre-load... *minimise* diuretics; filtration if need be
- Correct electrolytes

- Amiodarone for dysrhythmias, β blocker if BP allows
- Meticulous glucose control
- Hydrocortisone at replacement dose in case adrenal insufficiency
- Look for infection
- Maintain Hb 100 – 120 g/l

Cardiac function may recover relatively rapidly, but sustained compliance with an appropriate chelation regime over several years will be required for reversal of cardiomyopathy and normalisation of cardiac iron levels.

g Additional considerations - administering chelators and monitoring for side effects.

Desferrioxamine.

Parents and patients should be taught how to administer subcutaneous desferrioxamine infusions. The training and performance should be documented in the patient's records. Their technique should be assessed regularly. Children should be encouraged to participate in setting up and administering the desferrioxamine infusions at an early age. Initiation of desferrioxamine infusions in very young children is best done starting with 2- 3 infusions per week and gradually increasing to 5 infusions over a 3 month period. Means of facilitating the delivery of desferrioxamine such as Thalaset® needles, anaesthetic cream, disposable elastomeric pre-filled infuser pumps (not in very young children as the infused volumes are too large) should be offered to all children and adults: a majority of patients find home reconstitution and the mechanical syringe drivers inconvenient / heavy, and they receive home delivered pre-filled 'balloon pumps' ordered by the children's Haemoglobinopathy nurses for those under 16 years of age, or Transfusion Practitioner if above 16; see also comprehensive patient information sheet.

Ascorbic acid should be taken around the time of starting each desferrioxamine infusion, from about a month after starting to use regular desferrioxamine.

Offer / prescribe local anaesthetic cream to apply to the skin before needle insertion, for children and any adults who find it painful.

Monitoring for adverse effects should include

- 3 monthly sitting and standing height in children,
- annual audiometry [checking for high tone hearing loss] in all ages, and
- annual ophthalmology checks in all ages.

Desferrioxamine should be stopped if there are symptoms of gastrointestinal disturbance (abdominal pain, severe diarrhoea) or high fever. Patients should be aware of the risk of overwhelming infection due to Yersinia - see section 3 - and Klebsiella, and seek medical attention as soon as possible if they have symptoms or signs of severe infection

Deferiprone therapy [alone or in combination with desferrioxamine].

Patients should be monitored carefully for side effects of deferiprone, with **frequent blood counts (weekly counts are recommended – but see p 15 above) to detect neutropenia or agranulocytosis.** Patients should be regularly reminded of the side effects of deferiprone, and should understand that if they develop fever or symptoms of infection, they should **stop the medication and immediately attend for a blood count.** They should carry a treatment card indicating they take deferiprone, contact details of their treating doctor, and what action should be taken if they seek medical advice after becoming unwell. *Warning card in each box?*

Nausea / constipation may occur in the early weeks of use; if the child can persevere - at a reduced dose working up to full dose if necessary – these GI side effects often subside.

Joint pains or swelling are uncommon in children, but may occur in older children and adults. ANA / Rheumatoid factor should be checked. If the symptoms are severe, or there is any evidence of actual arthritis, more than just some discomfort, the medication may need to be stopped altogether and a different chelator regimen chosen instead.

Deferasirox

The current formulation is film coated, so is just to be swallowed with a drink, not necessarily on an empty stomach. For children it can be ground up and put into a spoonful of soft food such as yoghurt. Patients should be monitored carefully for side effects of deferasirox, with urine analysis for proteinuria [request protein creatinine ratio], serum creatinine and liver function testing at baseline (in duplicate) and renal function and liver function checks weekly for the first month, and after increasing the dosage. These tests should be done monthly thereafter.

Audiometry and ophthalmology checks should be done at baseline and bi-annually thereafter. **Deferasirox should be interrupted if serum creatinine rises to 33% above average baseline level or on appearance of significant proteinuria with no other cause [eg UTI] , or if transaminase rise is persistent or progressive.**

A florid rash can occur, which necessitates stopping the medication. GI side effects can sometimes cause the patient to request transfer back on to another agent. Avoid other medications which can cause gastric irritation such as NSAIDs.

Table 2 summarises regular monitoring tests which should be performed for patients receiving chelation:

** indicates – as part of regular monitoring rather than for specific drug related side effect*

*** monitor more frequently again like this after dose change*

Medication	Test	Required prior to commencing treatment	Then @ frequency :	
Desferrioxamine Deferasirox Deferiprone	FBC	Yes* Yes* Yes	Pre –each transfusion Recommended weekly, in practice usually before each transfusion AND IF ANY FEVER OR SYMPTOMS / SIGNS OF INFECTION	
Desferrioxamine Deferasirox	Serum ferritin	Yes Yes	3 monthly Monthly	Reduce dose when ferritin below 1000ug/l Reduce dose when ferritin below 1000ug/l, interrupt if < 300 ug/l

Deferiprone		Yes	3 monthly	Reduce dose when ferritin below 500ug/l
Desferrioxamine	Serum creatinine	Yes*	Before transfusion	Deferasirox: dose adjustments per renal function tests – see table 3 below Deferasirox is contraindicated in patients with a creatinine clearance < 60ml/min. Return to checking weekly for 4 weeks after any dose adjustment.
Deferasirox	Serum creatinine [ctd]	Yes – on 2 occasions	Weekly for first 4 weeks, then monthly **	
Deferiprone		Yes*	Before transfusion	
Deferasirox	Urine protein : creatinine ratio	Yes	Monthly	For other chelators, uPCR not routine, only if concern about renal function, or symptoms, or other causes for proteinuria eg diabetes mellitus
Desferrioxamine	LFTs	Yes*	Before transfusion	Deferasirox: reversible mild increase in LFTs is a known side effect. Interrupt treatment there is a persistent or progressive increase in transaminases. Deferasirox is contraindicated in severe hepatic impairment [Child-Pugh class C].
Deferasirox		Yes	2 weekly for first 4 weeks, then monthly**	
Deferiprone		Yes*		
Deferiprone	Zn		Yearly	
Desferrioxamine Deferasirox	Audiology and ophthalmology testing	Yes Yes	Yearly Yearly	Consider alternative chelator if affected

Table 3 – deferasirox dose adjustment according to renal function tests:

Reduction of daily dose by 7 mg/kg/day (film-coated tablet formulation), <i>if following renal parameters are observed at two consecutive visits and cannot be attributed to other causes</i>			
Adult patients	>33% above pre-treatment average	and	Decreases <LLN* (<90 ml/min)
Paediatric patients	> age appropriate ULN**	and/or	Decreases <LLN* (<90 ml/min)
After dose reduction, interrupt treatment, if			
Adult and paediatric	Remains >33% above pre-treatment average	and/or	Decreases <LLN* (<90 ml/min)
*LLN: lower limit of the normal range			
**ULN: upper limit of the normal range			

Further reading:

1. Standards for the clinical care of children and adults with Thalassaemia in the UK 2016: <http://ukts.org/standards/Standards-2016final.pdf>
2. <https://www.england.nhs.uk/wp-content/uploads/2018/07/Treatment-of-iron-overload-for-transfused-and-non-transfused-patients-with-chronic-inherited-anaemias.pdf>
3. NMUH Blood transfusion ward policy

Section 3 Referral to other specialty clinics.

People with transfusion dependent and non-transfusion dependent thalassaemia can develop complications relating to

- iron load – including cardiac, hepatic and endocrine damage [including fertility problems]
- transfusion – transmitted infection, predominantly hepatitis B and C
- adverse effects of chelator drugs – hearing, ophthalmology, renal impairment, hepatitis, rash.
- less well understood complications including bone thinning / osteoporosis, extra-medullary haematopoiesis
- the difficulty of managing a chronic, demanding and sometimes painful long term condition.

[linked hospitals – please replace this list with your own local referral pathways]

We refer to colleagues in different specialties for joint management of these problems.

For some, assessment is routine / for all patients, on a regular basis as outlined elsewhere in these guidelines. For others, marked * referral is only if a complication has arisen requiring speciality input. We manage some endocrine problems [hypothyroidism, hypoparathyroidism] in adults from the Haematology Clinic, but request expert advice for the management of diabetes and hypogonadism.

Cardiology	Dr Malcolm Walker, Consultant Cardiologist, UCLH
Audiology	Dr A Thambapillai, Consultant Audiology, St Ann's Hospital
Ophthalmology	Miss J Raina [<16 yrs], Eye Dept NMUH Mr G Palexas [16 yrs and above], Eye Dept NMUH
Endocrine Reviews	Dr A Garg – sees all patients 16 years and over, Endocrine Clinic, NMUH
Hepatology *	Dr Baker, Hepatology, Kings College Hospital (<16yrs) Dr Andrew Millar, Consultant Hepatologist, NMUH

Diabetes*	16 years and above Dr Kapila at NMH (<18yrs) Dr A Garg, Consultant Endocrinologist, NMUH, 18 yrs and above
Renal*	Dr Singh , Paediatric Nephrologist, NMUH (<16yrs) Dr Dakshina Jayasena, Consultant Nephrologist, NMUH 16 years and above
Paediatric Endocrinology*	Dr Piyusha Kapila, Paediatric Endocrinologist, NMUH
Hypogonadism and male fertility treatment*	Dr Anukul Garg, Consultant Endocrinologist, NMUH
Fertility treatment in females*	Mr Liebermann, Gynaecology, Whittington Hospital
Counselling and psychology*	Child and Adolescent Psychology and Psychotherapy Team, NMUH < 16 years Ruth Marks, Clinical Psychologist, Red Cell Team >16 years

The highly specialist areas

- consideration of / referral for bone marrow transplant in children is outlined in Section 6
- the management of women with thalassaemia during pregnancy is the subject of a separate guideline 'policy on management of pregnancy, contraception and fertility in thalassaemia'.

Section 4 Acute presentations in people with thalassaemia

People with thalassaemia rarely present for non-elective care, but when they do they may be very sick and need urgent assessment and management. They should be referred urgently and directly to the Paediatric [< 16 years] or adult Haematology teams [16 or over] from A&E, at whatever time they present – even if it considered they may be able to go home.

Infection / sepsis – especially in those who have been splenectomised.

Implement 'sepsis six'; take blood cultures as well as baseline blood tests [FBC, chemistry, bicarbonate, lactate, coagulation, CRP] give iv fluids and high flow oxygen, monitor urine output; send MSU and sputum for culture and swab any possibly sites infection [especially any long lines] and START ANTIBIOTICS within 1 hour.

Antibiotics:

Sepsis of unknown origin

First line

- **Adult:** Ceftriaxone 2g IV od
- **Child :** Ceftriaxone 40 mg/kg if under 50 kg, [> 50 kg give adult dose]

IV-oral switch

- **Adult:** co-amoxiclav 625mg po tds
- **Child:** co-amoxiclav (see paediatric BNF)

Severe Penicillin allergy (anaphylaxis)

- **Adult:** Teicoplanin 400mg (6 mg/kg if > 70kg) IV BD for 3 doses then IV OD
AND
Gentamicin* 5mg / kg

- **Child** : Teicoplanin IV and clarithromycin IV/ po (see paediatric BNF for doses)

IV- oral switch

- According to source or speak with Microbiology

Additional Notes:

In the adult patient presenting with NO high or med-to-high risk factors for sepsis then

- Oral doxycycline 200mg loading, followed by 100mg bd is an alternative agent (requires safety netting). Review need at 48-72 hours. Maximum course 5 days.

Consider the additional need for atypical cover if severe chest sepsis suspected

- Doxycycline 200mg loading, followed by 100mg bd po / clarithromycin 500mg bd IV
- Use clarithromycin in paediatrics

In severe sepsis i.e. NEWS2 > 5 in adults

- **Adult:** ADD gentamicin* 5mg / kg (Max 450mg) until haemodynamically stable (Max 5 days)
Consider increasing Ceftriaxone to a max of 4g / day in divided doses
- **Paeds:** Add gentamicin

**Use actual body weight or corrected body weight if >120% ideal body weight. Requires therapeutic drug monitoring and dose adjustment in renal impairment. See MicroGuide app or gentamicin guidelines.*

Add Metronidazole if abdominal source likely (not required if patient is on co-amoxiclav)

- **Adult:** Metronidazole 500 mg IV tds
- **Child** : Metronidazole (see paediatric BNF)

If Yersinia enterocolitis suspected

- **Adult:** Levofloxacin 500 mg bd IV /po
- **Child:** Co-trimoxazole (see paediatric BNF)
Duration 5 days

For suspected community acquired pneumonia or urinary sepsis treat as per clinical guidelines or see MicroGuide app.

Yersinia enterocolitis

Yersinia enteritis is usually a mild self-limiting condition. However, people who are iron loaded and on desferrioxamine treatment are at much increased risk from infection, which can progress to fatal enterocolitis. Yersinia organism is mostly transmitted by the ingestion of contaminated food, meat, milk or water.

Enterocolitis may mimic acute appendicitis although, of course, people who are on desferrioxamine may have appendicitis, like anyone else. The diagnosis should be considered in anyone on desferrioxamine treatment who has a significant fever, abdominal pain and tenderness, with or without diarrhoea or vomiting. During the first 24 hours a trial of conservative management may be considered as long as there are no signs of sepsis, acute abdomen or clinical deterioration.

- Request an urgent abdominal ultrasound.
- Requires early haematology consultant and surgical review.

If the surgical opinion is that appendicitis is likely and surgery is necessary, the diagnosis of enterocolitis may be made by the **inflamed appearance of the terminal ileum** plus abnormal appendix. In this case the surgeon should be requested *not to remove the appendix* as there is a risk of fistula and/or peritonitis from the appendix stump. If 'ordinary' appendicitis is found, then of course there is no contraindication to appendectomy.

Anyone on desferrioxamine treatment who has a significant fever, abdominal pain and tenderness, with or without diarrhoea or vomiting :

- admit for IV ciprofloxacin 4 – 8 mg / kg over 30 – 60 minutes bd [max 400 mg per dose]
- [once clinical improvement then oral ciprofloxacin 5-7.5mg/kg BD (max 750mg per dose)]
- Request urgent abdominal ultrasound
- Consultant Haematology early review
- Try manage conservatively for the first 24 hours, unless there are signs of an acute abdomen or symptoms or signs worsen in which case
- request an urgent surgical opinion

If the surgical opinion is that appendicitis is likely and surgery is necessary, the diagnosis of enterocolitis may be made by the **inflamed appearance of the terminal ileum** plus abnormal appendix. In this case the surgeon should be requested *not to remove the appendix* as there is a risk of fistula and/or peritonitis from the appendix stump. If 'ordinary' appendicitis is found, then of course there is no contraindication to appendectomy.

Iron chelation should not be restarted till the symptoms resolve.

Cardiac dysrhythmias / heart failure – If there is tachycardia in the absence of fever, or irregular pulse rate, or low blood pressure, or other signs of left or right sided cardiac failure:

Take ECG, if abnormal rhythm contact Med Reg out of hours / Cardiology in hours for guidance and in parallel make urgent referral to Dr Walker at UCLH.

CXR, urgent echo, any signs of failure start treatment as per AHA clinical management guidance, page 17 and urgent referral to Dr Walker's team UCLH

Endocrinopathies

Although routine screening should have led to a diagnosis before acute clinical presentation, these patients are also at increased risk of:

Diabetes, hypocalcaemia [hypoparathyroidism], hypothyroidism – if there are any grounds for clinical suspicion request urgent glucose / calcium / thyroid function respectively. If derangements are found please discuss with the Haematology Consultant

Acute hepatic derangement due to viral hepatitis is a rare – consider if the presentation is with nausea, jaundice and LFT's show marked transaminitis. Alternative considerations would be biliary problems, chelator toxicity, right sided cardiac failure. Call Consultant Haematologist.

Neurological presentations. Patients with thalassaemia, even well transfused, can develop bone marrow tissue masses outside the confines of the bones – extramedullary haematopoiesis. These are commonly along the paravertebral gutter at any level, or can be pre-sacral, but sometimes they grow within the spinal canal and can cause spinal cord compression.

If any patient with thalassaemia complains of unusual sensation in the limbs, difficulty with bladder / bowel sensation, even pains in the joints of the lower limbs – do a FULL neurological examination and if any abnormal findings request an URGENT MR scan of the spine at the appropriate level[s]. Even if there are no signs at all but symptoms are suggestive of nerve compression, request a 'soon' MR.

If identified, management may be with hypertransfusion, hydroxycarbamide, local radiotherapy or a combination of these and the decision will be made with the Consultant at the specialist centre, in or out of hours.

Referral to critical care should be considered for any patient

- whose vital observations are unstable or deteriorating as per the National Early Warning Score NEWS / 'track and trigger' guidance on our routine observations charts
- where initial management is failing to stabilise the situation or
- where interventions requiring the assessment / input of Critical Care team may be required: including need for inotropes, assisted ventilation, haemofiltration.

Referral 'in hours' is via the **Critical Care Outreach Team, bleep 522** and out of hours by bleeping the **ICU Registrar, bleep 311**.

Section 5 Management of non-transfusion dependent thalassaemias ['intermedia'] [including many with HbE β thalassaemia]

The term "thalassaemia intermedia" has been used to categorise patients with thalassaemia who do not have an absolute requirement for regular transfusions. It includes a wide spectrum of severity, from patients who only just manage without transfusions, to those who are virtually asymptomatic. Thalassaemia intermedia can be the result of inheritance of milder β globin gene mutations, allowing sufficient β globin chain production for some adult haemoglobin production. Additional genetic factors, such as co-inheritance of α thalassaemia, or enhanced fetal haemoglobin production, can also alleviate the severity of the thalassaemia. The clinical phenotype can usually but not always be predicted from α , β , *Xmn* genetic analysis.

People with the more severe forms are usually transfused, following the same guidelines as for thalassaemia major; the classification 'transfusion dependent thalassaemia' and 'non-transfusion dependent thalassaemia' is now often used.

a Moderate/severe thalassaemia intermedia.

This includes up to 10% of patients with homozygous β thalassaemia, the majority of those with Haemoglobin E/ β thalassaemia and a very small proportion of those with haemoglobin H disease (α thalassaemia intermedia). At the severe end are patients who can only just manage without transfusions, but who have severe anaemia, reduced exercise tolerance, mild to moderate bone changes, hypersplenism, poor growth during childhood, and a delay in pubertal development. They are likely to develop gall-stones, extramedullary haematopoietic masses, and gradually accumulate iron, particularly in the liver, due to increased gastro-intestinal iron absorption. The majority in this group are treated with regular transfusions as for thalassaemia major. Indications for long-term transfusions include 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.

For the clinical management of these patients, in terms of iron monitoring and chelation, follow the clinical guideline relating to the regularly transfused patient.

b Milder thalassaemia intermedia.

This group includes a small proportion of patients with homozygous β thalassaemia (usually predictable from genotype), some patients with haemoglobin E/beta thalassaemia, and the large

majority of patients with haemoglobin H disease. It is important to identify this mild group and to provide information tailored to their condition. Long-term complications can include pulmonary hypertension, the development of extra-medullary haematopoietic masses, bone thinning, hypersplenism, gall bladder disease, and chronic ankle ulceration.

The following guidelines relate mostly to the infrequently transfused patient.

c Indications for transfusion

Patients who are symptomatically well off transfusion much of the time may still need transfusion at intervals, for episodes of acute anaemia, for example after infection [almost any], puberty or during pregnancy. The need for transfusion under these circumstances is guided by consideration of the clinical condition of the patient, the haemoglobin level and reticulocyte count. Fall in haemoglobin accompanied by poor reticulocyte response - for example during infection with parvovirus B19 - most often needs early transfusion. Lethargy affecting school or work attendance or delayed puberty should also be taken into account although this is not common in this milder group.

d Monitoring iron levels.

The degree of iron loading in this condition relates in part to the number of transfusions received, but the condition is also 'spontaneously' iron loading, so even patients who have received very few transfusions can develop high iron levels. Assessment of iron stores should take into account the severity of the anaemia, number of transfusions received, and clinical evidence of iron-related toxicity (heart, liver and endocrine disease).

Serum ferritin is unreliable in thalassaemia intermedia, often significantly underestimating the degree of iron loading. An additional measure of iron stores should be undertaken using MRI T2* for the heart, and / or R2 for the liver. In the less transfused patient, T2* should be requested initially at age 15; then [depending on levels] 5 yearly is usually sufficient.

e Chelation regimes

Chelation for untransfused people can be less intense than in thalassaemia major. The choice of chelator drugs is as for the regularly transfused patient, depending on the degree of iron demonstrated in the heart and / or liver. Desferrioxamine remains an option, although deferasirox is licensed for patients with non-transfusion dependent thalassaemia and is often the chelator of choice for these patients. There is limited experience with deferiprone, which seems to be beneficial in Hb E thalassaemia, and would be indicated in any patient with identified heart iron, at least in combination with desferrioxamine.

f Splenectomy.

Careful consideration should be given to the risks/benefits of splenectomy in these patients. For a patient who has an enlarged spleen, whose haemoglobin is running low enough to cause symptoms and / or decreased growth velocity : treatment options are to start on regular transfusion – which is likely to shrink the spleen - or to try splenectomy, which may of itself allow the haemoglobin to rise to a level where symptoms are abolished and growth velocity improves back to normal. This possible gain has to be set against the long term risk of infection post-splenectomy, and the increased risk of thrombo-embolic disease. The decision needs to be taken by a consultant from the specialist team, after careful discussion with the patient and family about the pros and cons. Considerations may include if a person is returning to live in a country where blood safety is not assured, or chelation availability is not good, which would tip the balance in favour of splenectomy and away from ongoing long term transfusion.

If it is decided to proceed to splenectomy:

- Immunisation required:
 - Ensure that the child has been immunised according to national schedule, including the 12-month boosters
 - Give an additional dose of Hib/MenC and the first dose of MenB vaccine, along with the pneumococcal polysaccharide vaccine (PPV23) 'Pneumovax'
 - Give a dose of MenACWY conjugate vaccine one month after surgery and the second dose of MenB two months after the Hib/MenC booster
 - A single dose of Prevenar should be given, at least 6 months after the PPV23
- the individual 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
- prior to the procedure, an abdominal ultrasound scan should be done to detect gall stones. If present, a cholecystectomy should also be considered.
- twice daily Penicillin V prophylaxis, dose 125 mg bid if < 5 years, 250 mg bid if 5 years or over, , should be prescribed to start immediately and continued at least until early teens, after which treatment dose [500 mg qds at the first hint of infection or low grade fever < 38 C] may be preferred. Lifelong vigilance and early treatment for infection, together with 5 yearly boosters of Pneumovax, are required. Advise that if there is fever of > 38 C, and / or if symptoms are not getting better after 24 hours on Penicillin at treatment dose, then they must come to the hospital for further assessment and broader spectrum antibiotics.

g Other monitoring and treatment.

- Patients should receive regular folic acid supplementation.
- Growth should be monitored regularly, and pubertal development from the age of 10, and referral to the designated endocrinologist made if abnormalities are documented.
- A period of regular transfusion during the years of peak potential growth and puberty should be considered if there is any suggestion of falling growth velocity.
- Cardiac assessments should be undertaken 5 yearly [as long as no abnormal findings] from age 15 – refer to Prof Malcolm Walker at UCLH.
- Thalassaemia intermedia patients should have regular echocardiography from age 15; 5 yearly if measurements are satisfactory. Where echocardiography proves inconclusive in regard to pulmonary pressures, further investigation with cardiac MRI and right heart catheter studies should be considered to exclude pulmonary hypertension. If this is found, treatment with regular transfusion should be strongly considered, and referred to Dr Coghlan at PHT clinic Royal Free Hospital, or local pulmonary hypertension specialist clinic for linked hospitals.
- DEXA bone density scanning should be undertaken 5 yearly from age 15.
- Hydroxycarbamide therapy (see separate guideline) is beneficial in a small number of patients; it may result in an increase in baseline haemoglobin and a reduction in bilirubin / clinical jaundice.
- Symptoms due to extra-medullary haematopoietic masses should be investigated with MRI imaging, and treated. Radiotherapy is usually needed if there is urgent need to reduce the mass; hypertransfusion and hydroxycarbamide act more slowly. Asymptomatic masses may require therapy depending on their position (eg if impinging on the spinal cord), but if not threatening vital structures, may simply be monitored.
- Referral to a bone marrow transplant centre, with specific experience of transplanting for thalassaemia, should be offered to families, for detailed discussion of transplant as an option.

- Patients with all forms of thalassaemia intermedia should have an Annual Review visit; the proforma for thalassaemia major can be used.

Acute presentations in Thalassaemia Intermedia: follow the guidance given on pages 22-24, as for thalassaemia major.

Section 6 Referral for Stem Cell Transplant [SCT]

Transplant from an HLA-matched family member, usually a sibling, is offered for transfusion dependent children with thalassaemia. Early transplantation, before significant iron load has developed, has the best outcomes. It is often undertaken between the ages of 3 and 5 years.

The issue of SCT should be raised with all affected families. They may choose to have any existing siblings HLA-matched. It is recommended that even those who do not have a matched sibling can be offered an appointment at the Transplant Centre – refer Dr de la Fuente, Paediatric Haematologist Imperial Healthcare @ St Mary's Paddington - as any subsequent children may be a match for the affected child and the family may wish to know more about the pros and cons of the procedure in anticipation.

If the mother of a child with thalassaemia becomes pregnant again, discuss the possibility of cord blood collection, as a source of stem cells for later transplant; detailed advice and guidance is available from NMH Transfusion Practitioner Karen Madgwick.

Appendix 1A NMUH Thalassaemia CHILD Annual Review Proforma

Thalassaemia annual review - Children

Performed by _____ Date _____ NHR Y / N/ declined

Name _____ DOB _____ Hospital no. _____

<p>Diagnosis / genotype if known:</p> <p>Any current problems:</p> <p><input type="checkbox"/> Update PHR/Passport</p>	<p>Height _____</p> <p>Centile _____</p> <p>Weight _____</p> <p>Centile _____</p> <p>BP _____</p> <p>HR _____</p> <p>SaO₂ _____</p>
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Transfusion history:

_____ units/mls of red cells every _____ weeks

Cumulative volume transfused over previous 12 months _____ = mls / kg @ mid-year body weight

Average pre-transfusion Hb _____ g/dl need to consider splenectomy? Y N

Blood results:

Date _____ Hb _____ WCC _____ Plts _____ Ur _____ Cr _____ ALT _____ ALP _____ alb _____ cCa _____

PO₄ _____ TSH _____ fT4 _____ Average serum ferritin _____

Treatment:

Iron chelation currently receiving: DFO DFP DFX

Dose = _____

Difficulty adhering to treatment? Y N If yes, why? _____

Appropriate Y N If not, proposed change _____

Other medications: _____

Vaccinations:

Routine immunizations up to date? Y N

Hep B 1st dose date _____ 2nd dose date _____ 3rd dose date _____ HepCAb positive negative

Last HepBs Ab level _____ @ date _____ HepB booster due? Y N

Responder / Poor responder / Non responder (circle)

If splenectomised; Pneumovax given [last date] _____

Prevenar [if not given as primary immunisations] > 6 months from any Pneumovax dose _____

Education:

School attended _____

Attendance _____

Any concerns? _____

Lifestyle:

Growth adequate? Y N Diet and exercise history _____
 Pubertal staging _____
 Age at menarche _____ yrs Regular menstruation Y N
 Sexually active Y N N/A Contraception advice needed / given Y N
 Social concerns _____
 Travel plans over next year? _____ Advice re antimalarials / vaccination

Review of systems:**Surgery planned:**

Splenectomy Other _____
 If splenectomy : plans for immunisations: hospital / GP requested : [see clinical guidelines p 26]

Examination:

General CVS; HS I _____ II _____
 RS: GIT:
 CNS: Puberty staging:

Specialist Clinical Review in last 12 months:

Cardiac clinic: Date _____ outcome _____
 Endocrine review: Date _____ outcome _____
 Audiology: Date _____ outcome _____
 Ophthalmology Date _____ outcome _____
 T2* MRI heart Date _____ outcome _____
 T2* MRI liver Date _____ outcome _____
 R2 MRI liver Date _____ outcome _____
 DEXA scan Date _____ outcome _____

Plan:

Bloods: FBC U&E LFTs Bone profile Glucose GTT Ferritin TFTs
 HepBAb HepCAb other _____

Immunisations: PCV Hib MenC HepB Other _____

Referral to: General surgeons
 Ophthalmology from age 10
 Cardiologist from age 10
 Endocrinologist
 Audiology
 CAHMS
 Clinical psychologist
 Dietician
 Other:

Other investigations required:
 GTT from age 16 or 10 if positive FH
 DEXA bone mineral density scan
 T2*
 R2

Lifestyle information given

Transition plan:

Appendix 1B NMUH Thalassaemia ADULT Annual Review Proforma

Patient's Name:

Hosp No:

DOB:

Diagnosis / genotype if known:

Hospital:

Consultant:

NHR: Y / N / Declined

HISTORY					
Any subjective problems:					
Cardiac history (palpitations, shortness of breath)					
Endocrine history (menstruation, spontaneous or with HRT, erections)					
SOCIAL					
Education / Employment:			Smoking:		
Family planning:			Alcohol:		
TREATMENT					
Iron chelation currently receiving (ring and insert dose):					
Desferrioxamine: <i>Dose</i>		Deferiprone [Ferriprox]: <i>Dose</i>		Deferasirox [Exjade]: <i>Dose</i>	
Adherence: Y / N If no why?					
Appropriate: Y / N If not suggested change:					
Other medications: Zinc supplements oral contraceptive pill testosterone insulin					
1α calcidol oral hypoglycaemic agent Thyroxine Penicillin Folic Acid Vit C					
Any changes?					
Bone strengthening treatment: Calcium supplements Y / N Bisphosphonates					
Appropriate: Y / N If not suggested change:					
EXAMINATION					
Pulse:	BP:	O2 Sats:	Weight: kg	Height (if <18): cm	
			Stable?	Growth in last year:	
Heart			Tick which apply: Hypogonadotropic hypogonadism Hypothyroidism Hypoparathyroidism Diabetes mellitus Extramedullary haematopoiesis Hepatitis C infection Bone thinning VTE Other:		
Chest					
Liver					
Spleen					
Other					

SPECIALIST CLINICAL REVIEW IN LAST 12 MONTHS

Cardiac clinic date:	outcome:	Next review:
T2* MRI: Liver date:	result:	Next review:
Heart date:	result:	Next review:
R2 MRI: date:	result:	Next review:
Endocrine review date:	outcome:	Next review:
Audiometry date:	outcome:	Next review:
Ophthalmology date:	outcome:	Next review:
DEXA bone mineral scan date:	outcome: hip spine	Next review:
Other assessment / review (eg hepatology, psychological):		

RESULTS REVIEW

Transfusion History:		
Cumulative volume transfused over preceding 12 months:		Estimated lifetime total:
Average pre-transfusion Hb:		Average serum ferritin:
Other results: check normal over last year [if so, tick; if not – insert results]		
U&E, creatinine:	LFT:	Calcium:
Random glucose:	GTT result [date]:	TFT:
Urine protein: creatinine ratio:		
Any comments on results:		

Virology:	HepBsAg	HepBcAb	HCV IgG	Other:
Date / result:				
Vaccinations:				
HepBsAb level:		revaccination needed:		
Pneumovax (if splenectomised / IDDM)		revaccination needed (date):		
Prevenar – 1 dose if splenectomised, > 6/12 from Pneumovax -				
Influenza recommended: Y / N				

Summary of referrals agreed / management changes recommended:

- 1
- 2
- 3
- 4
- 5