

<b>CLINICAL GUIDELINE TITLE</b>	<b>Clinical Management of Thalassaemia in Adults</b>
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## 1) SUMMARY

This guideline covers the management of thalassaemia major,  $\beta$ -thalassaemia intermedia and haemoglobin H disease and is directed at all clinical staff involved in the care of adults with these conditions.

Thalassaemia disorders are associated with multiple clinical complications, the effective management of which requires a multidisciplinary approach. Iron overload and infection are important causes of morbidity. All adults with thalassaemia disorders require regular follow-up to detect, prevent and manage disease-related complications. The patient and family should receive full and accurate information with support from experienced professionals.

## 2) INTRODUCTION

Thalassaemia disorders predominantly affect individuals of Asian, Mediterranean, Middle Eastern or African descent. Most patients with homozygous  $\beta$ -thalassaemia are identified through neonatal screening and monitored closely from infancy to determine the need for regular transfusion. Transfusion is started promptly where there is clinical evidence of severe anaemia, failure to thrive, and/or thalassaemic bone deformity (see ICHT Guideline Paediatric Thalassaemia Disorders). Whereas patients with thalassaemia major are transfusion dependent from infancy those with thalassaemia intermedia do not generally require regular transfusion and may present at all ages. All new patients who present in adulthood with suspected thalassaemia should be fully assessed to confirm the diagnosis, determine clinical severity and agree an individual management plan.

## 3) DEFINITIONS

A&E Accident and Emergency  
 CNS Clinical Nurse Specialist  
 CMV Cytomegalovirus  
 CRP C-reactive protein  
 CXR Chest Radiograph  
 ECG Electrocardiogram  
 eGFR Estimated Glomerular Filtration Rate  
 FBC Full Blood Count  
 GP general practitioner  
 Hb Haemoglobin  
 HIV Human immunodeficiency virus  
 ICHT Imperial College Healthcare NHS Trust  
 LIC Liver iron concentration  
 IV Intravenous  
 LFT Liver Function Test  
 NHSBT National Health Service Blood and Transplant  
 SAG-M Saline Adenine Glucose-Mannitol  
 SpR Specialist Registrar  
 TRV Tricuspid regurgitant jet velocity

#### 4) SCOPE

This guideline is directed at all clinical staff involved in the care of adult patients with thalassaemia. The term 'thalassaemia' used in the guideline refers to all patients with  $\beta$ -thalassaemias (including  $\beta$ -thalassaemia major,  $\beta$ -thalassaemia intermedia, Haemoglobin E/ $\beta$ -thalassaemia) and  $\alpha$ -thalassaemias (Haemoglobin H disease and rare cases of regularly transfused  $\alpha$ -thalassaemia major). It should be read in conjunction with Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK 2008.

The guideline excludes:

- Sickle  $\beta$ -thalassaemia, a sickling disorder which should be managed according to the Imperial College Healthcare NHS Trust (ICHT) guideline Clinical Management of Sickle Cell Disease in Adults
- Patients with  $\beta$ - or  $\alpha$ -thalassaemia trait as these are carrier states and not clinically significant

The following aspects of care are described:

Initial management of newly diagnosed thalassaemia patient

Management of acute complications

Transfusion therapy

Iron chelation

Endocrine/Skeletal complications

Outpatient management and annual review

Management of thalassaemia intermedia

Transition from paediatric to adult service

## 5) Full Guideline

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**Cooley's Anemia Foundation\***

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Web site: <http://www.thalassemia.org>

\* The CAF web site has an extensive range of information materials that patients and carers may find useful

**INITIAL MANAGEMENT OF NEWLY DIAGNOSED THALASSAEMIA PATIENT**

Most adults with thalassaemia will have been identified in childhood and have a confirmed diagnosis and care plan at the point of transfer to the Adult service. Patients presenting *de novo* should have the following investigations to establish/confirm the diagnosis:

Full blood count, reticulocytes, blood film and HbH preparation (if HbH disease suspected)

- Haemoglobin separation by high performance liquid chromatography (HPLC) +/- electrophoresis
- Genetic analysis for  $\beta$ -thalassaemia mutations and XmnI polymorphism (in  $\beta$ -thalassaemias) and  $\alpha$ -thalassaemia genotype (in all cases) - performed by Imperial Molecular Pathology Laboratory (extn 32177)

Contact details of the Haemoglobinopathy Clinical Nurse Specialist (CNS) and a Haemoglobinopathy card should be given to the patient. Patients are encouraged to join the UK Thalassaemia Society which provides information materials for patients/families, a patient-held record and has a user-friendly website.

**Clinical assessment should include:**

- Detailed history of anaemia symptoms Whether patient had a splenectomy or cholecystectomy
- Transfusion history
- Vaccination history
- Spleen and liver size
- Evidence of extramedullary haemopoiesis
- Evidence of iron overload
- Symptoms and signs of cardiac failure

**Investigations**

Haematology - FBC, reticulocytes and film, G6PD assay

Blood Transfusion - Extended red cell phenotype (including C, c, D, E, e, K, k, Jk<sup>a</sup>, Jk<sup>b</sup>, Fy<sup>a</sup>, Fy<sup>b</sup>, Kp<sup>a</sup>, Kp<sup>b</sup>, M, N, S, s, Le<sup>a</sup> and Le<sup>b</sup>). If the patient has been recently transfused the red cell phenotype should be obtained from the referring hospital and if not available blood group genotyping should be arranged with Red Cell Immunohaematology, NHSBT, Filton, Bristol via the Transfusion Laboratory (extn. 34772 or 34790).

Biochemistry - LFT, renal and bone profile, ferritin, glucose, LH and FSH, oestradiol/testosterone, thyroid function, vitamin D, parathormone, IGF-1

Virology - Hepatitis B surface antigen, Hepatitis B surface and core antibody, Hepatitis C antibody, HIV 1 and 2 antibody, CMV IgG

## **MANAGEMENT OF ACUTE COMPLICATIONS**

Management of patients with thalassaemia is mostly undertaken in the Outpatient or Day Care setting. Patients do however present unexpectedly to their GP, clinic, or the A&E Department when they may be seriously ill warranting prompt assessment, management and often hospital admission. Assessment is facilitated through patients carrying a record e.g. clinic letter/annual review listing their diagnoses, recognised complications and recent investigation results. Some problems are common in this group of patients and awareness of these is essential for prompt diagnosis and appropriate treatment.

### **1. Indications for immediate admission:**

- **Fever >38° C, tachycardia, tachypnoea, hypotension**
- **Acute abdominal pain or distension**
- **Worsening jaundice (mild/moderate jaundice common in steady state)**
- **Altered consciousness or convulsions**
- **Symptoms or signs of central venous catheter infection**

### **2. Admission procedure**

The haematology inpatient service is based at the Hammersmith Hospital. All patients under regular follow-up have been issued with an access passport with information on how to contact and access the haematology triage service if they require urgent assessment for problems related to thalassaemia. Patients should call the triage service which is staffed 24/7 by a nurse bleep holder on 020 3311 7788 and will be directed to attend either the ambulatory care service located on the Haematology Day Care Unit in the Catherine Lewis Centre (Mon - Sun, 8am - 8pm) or to the Specialist Medicine Assessment Centre (SMAC) on B1 ward. The patient will be advised to dial 999 if clinically indicated (see below). On ambulatory care, patients are first assessed by the triage nurse and then the Haematology Day Care SpR or SHO (Bleep 9077). The patient must be assessed medically within 1 hour and if admission is deemed necessary transferred directly to a haematology ward or to SMAC if a haematology bed is not immediately available. The Red Cell SpR/SHO should be informed of all admissions from the Day Care Unit. Patients attending SMAC directly will be seen by the Red Cell SpR (Bleep 9240) or SHO (Bleep 9078) within working hours, and by the on call SHO covering haematology outside working hours. If the Red Cell team or on call SHO are unable to attend immediately then the acute medicine team will assess the patient, prescribe initial treatment and monitor the patient until the haematology team arrives.

If a patient is very unwell they should dial 999 and present their access passport to LAS. They will be taken preferentially to Hammersmith Hospital, SMAC with the LAS team giving advance notification of their arrival. If a patient requires immediate treatment for a medical emergency they will be taken to the nearest hospital with an A&E service, usually St Mary's or Charing Cross Hospital.

All patients presenting acutely should be discussed with the Red Cell/On call SpR or Red Cell Consultant. A full history and examination should be undertaken, keeping in mind specific problems encountered in thalassaemia, including infective, endocrine, cardiac and hepatic complications.

### **3. Specific acute complications**

When acutely unwell, thalassaemia patients may tolerate anaemia poorly and require transfusion (see below). In this situation a target haemoglobin (Hb) of 120 g/L is recommended.

### **Investigations if acutely unwell**

- FBC and reticulocytes
- Coagulation screen
- Group and antibody screen +/- direct antiglobulin test (DAT)
- Renal profile, LFTs, CRP, calcium and phosphate, glucose
- Blood and urine culture

### **If clinically indicated:**

- Serum amylase
- Atypical respiratory serology, sputum/throat culture, NPA for virology
- Urine for Pneumococcal + Legionella antigen
- CXR
- US abdomen
- Lumbar puncture
- ECG +/- echocardiography
- CTPA

### **a) Infection**

Sepsis – Patients with thalassaemia are more vulnerable to infection including gram-negative sepsis. Splenectomised patients are at risk of overwhelming infection particularly with the capsulated bacteria species *Pneumococcus*, *Haemophilus influenzae b* and *Neisseria meningitidis*. In patients with iron overload there is an increased risk of infection with siderophilic organisms e.g. *Yersinia enterocolitica* and *Vibrio vulnificus*.

PROMPT treatment of severe sepsis saves lives and appropriate empiric antibiotics should be started as soon as possible and definitely within 1 hour. Where possible send appropriate investigations (eg blood, urine cultures) prior to giving first dose, but if severely ill do not delay therapy (see sepsis management matrix in ICHT Clinical Guidelines section on intranet). If penicillin-allergic discuss with Microbiology/ID team.

Antibiotic therapy should be tailored when suspected origin of sepsis is identified – see relevant sections of ICHT Adult treatment of infection policy.

#### Community acquired infection

- Ceftriaxone 2g iv od +/- metronidazole 500mg tds iv
- In severe sepsis add amikacin 15mg/kg od iv (adjusted in renal impairment - see ICHT Adult treatment of infection policy)

#### Hospital acquired infection

- Piperacillin/tazobactam 4.5g iv tds + Amikacin 15mg/kg iv od (adjusted in renal impairment - see ICHT Adult treatment of infection policy)
- If MRSA suspected/colonised or patient has indwelling central venous catheter add Vancomycin iv to above regimes (see ICHT Adult treatment of infection policy for dosing)

Splenectomised patients should be vaccinated appropriately and receive long-term prophylaxis with penicillin V 250mg bd po or erythromycin 500mg bd po if penicillin allergic. They are also at increased risk of malaria and should take effective prophylaxis if they visit an endemic area. See [ICHT Guideline Infection prevention for adult patients with an absent or dysfunctional spleen](#)

Yersinia - Patients with thalassaemia are more susceptible to infection with *Yersinia enterocolitica* which thrives in an iron-rich environment. This diagnosis should be suspected in any regularly transfused patient with fever, diarrhoea and abdominal pain. Klebsiella infection can also present in this manner. Appropriate antibiotic therapy (Ciprofloxacin 400mg bd iv or ceftriaxone 2g iv od if G6PD deficient) should be started on clinical suspicion and chelation therapy suspended until results of blood and stool cultures are obtained or abdominal symptoms resolve. The blood culture request must indicate the possibility of infection with *Yersinia enterocolitica* as this requires specific culture conditions. In severe sepsis give ceftriaxone 2g od iv + amikacin 15mg/kg (adjusted according to renal function – see ICHT Adult treatment of infection policy) stat iv then od iv.

Patients on deferiprone are at risk of agranulocytosis or neutropenia and should have an urgent full blood count every time they present with an acute problem to the hospital or GP. If T>38.0°C for 2 readings 1h apart, or one reading >38.5°C and neutrophil count < 1x10<sup>9</sup>/l then antibiotics should be instituted as per the febrile neutropenia policy (see ICHT Adult treatment of infection policy), treatment with deferiprone discontinued immediately and G-CSF administered.

All patients should be vaccinated against Hepatitis B and antibody levels checked at least every 5 years with booster doses given as required.

### **b) Abdominal pain and/or jaundice**

These may be caused by infection, but cholelithiasis is common and biliary colic or obstruction, with or without sepsis, should be considered. Patient presenting with symptoms of cholelithiasis should be referred to the Gastroenterology team via the SpR for ward referrals (bleep 9056) or if out of hours the Gastroenterology SpR/Consultant on call. If biliary sepsis is suspected antibiotic therapy should be instituted immediately in accordance with the current ICHT Adult Treatment of Infection Policy. ERCP referrals can be submitted electronically to [ercp.referrals@imperial.nhs.uk](mailto:ercp.referrals@imperial.nhs.uk) or if non-urgent booked on Cerner.

### **c) Cardiac**

Patients with transfusion associated iron overload may present with symptoms and signs of cardiac dysrhythmias or cardiac failure secondary to ventricular dysfunction. Cardiac failure is a medical emergency that necessitates rapid reversal of myocardial iron overload. Patients who present with acute cardiac symptoms should be discussed urgently with the Cardiology SpR on bleep 9064 or Consultant of the week via the hospital switchboard (020 3313 1000). If the patient is known to have pulmonary arterial hypertension urgent advice should be sought from the National Pulmonary Hypertension Service, Hammersmith Hospital. Between 9.00 am and 5.00 pm contact the Pulmonary Hypertension SpR on bleep 9045 or Pulmonary Hypertension Nurses Office on 38072/32330 Out of hours contact via bleep 9064.

### **d) Endocrine**

Endocrinopathy secondary to iron overload, may present acutely with diabetes mellitus and, less commonly, adrenal failure, hypoparathyroidism or hypothyroidism. All such patients should be discussed at the earliest opportunity with the Hammersmith Hospital Endocrinology SpR (bleep 9051/9050) or Consultant who can be reached via the hospital switchboard (020 3313 1000).

**e) Hepatic**

Patients with chronic viral hepatitis and/or iron overload may present with decompensated liver failure and hepatic encephalopathy. Patients with suspected hepatic decompensation require urgent assessment by Gastroenterology (SpR bleep 9056 or hepatobiliary team bleep 5251) with transfer to the Hepatology service at St Mary's Hospital if indicated. Specialist review at Hammersmith Hospital is provided by Consultant Hepatologists Dr Shahid Khan and Dr Belinda Smith.

## RED CELL TRANSFUSION

Blood transfusions, if given regularly every 2-4 weeks enable normal growth and development of children with transfusion-dependent thalassaemia (see ICHT Guideline Paediatric Thalassaemia Disorders) and once started are continued into adult life in the majority of patients. In patients receiving regular transfusion a pre-transfusion Hb level of 95 – 100 g/L is sufficient to inhibit bone marrow expansion and minimize iron loading. Transfusions should be given with minimum disruption to everyday life. To facilitate this the Haematology Day Care Unit (extn 34594) at Hammersmith Hospital operates extended hours from 8am – 8pm 7 days a week. Advance notice should be given to the Transfusion Laboratory (extn 34772/34790).

The risks associated with regular transfusion include acute transfusion reactions, allo-immunisation against blood group antigens, transmission of viral infection and, in the long-term, iron overload. Serious hazards are rare and minimized by meticulous attention to protocols in transfusion practice (see ICHT Blood Transfusion Policy for Adults).

### 1. Decision to start regular transfusion

The decision to commence a regular transfusion programme, though aided by knowledge of the underlying thalassaemia genotype, is primarily a clinical one as phenotypic severity varies even among patients of the same genotype. This should be based on the severity of anaemia (Hb < 70 g/L) and accompanying symptoms or evidence of cardiac failure, after taking account of correctable factors such as iron deficiency or infection. Serial Hb measurements should be assessed.

Patients who are not transfusion-dependent may present with an acute fall in Hb from their steady state. In these circumstances a single transfusion may be given in the first instance. If the Hb subsequently falls and no reversible cause e.g. intercurrent infection is identified long-term transfusion may be indicated.

### 2. Consent

The benefits and risks of transfusion must be explained to the patient and written information provided. Valid consent for blood transfusion should be obtained in accordance with Advisory Committee for the Safety of Blood Tissues and Organs guidance. This can be found at:

[http://www.transfusionguidelines.org.uk/docs/pdfs/bbt\\_informationresource\\_final\\_.pdf](http://www.transfusionguidelines.org.uk/docs/pdfs/bbt_informationresource_final_.pdf)

Patient information sheets are available from NHS Blood and Transplant at:

[http://hospital.blood.co.uk/library/patient\\_information\\_leaflets/leaflets/index.asp](http://hospital.blood.co.uk/library/patient_information_leaflets/leaflets/index.asp)

### 3. Immunisation prior to starting transfusion

All patients should be vaccinated against Hepatitis B if non-immune. Antibody levels should be checked at least every 5 years and booster doses given as needed.

#### 4. Selection of red cell units

NHSBT supplies SAG-M blood which comprises packed red cells in preservative (saline, adenine, glucose and mannitol) with a haematocrit of 0.5 -0.7. For transfusion in thalassaemia these should be:

- Matched for ABO, Rhesus (D, C, c, E, e) and Kell (K) blood group antigens
- Negative for blood group antigens to which the patient has developed alloantibodies
- Where possible less than 7 days old

#### 5. Pre-transfusion testing

Patients attend the Haematology Day Care Unit for pre-transfusion testing, i.e. FBC, blood group and cross match, before transfusion. Cross-match samples must be collected no more than 72 hours prior to transfusion.

All patients should have extended red cell phenotyping performed prior to their first transfusion or genotyping (see above) if they have been recently transfused and information on their red cell phenotype is not available. For patients previously transfused elsewhere, historical allo-antibody status should be ascertained even if no allo-antibodies are currently detectable.

#### 6 Administration of blood

Transfusion is administered via a peripheral venous cannula or indwelling intravenous device. It is recommended no more than 3 attempts at cannulation should be made by an individual practitioner. If initial attempts fail a more experienced practitioner should attempt cannulation.

Elective transfusions are undertaken in the Haematology Day Care Unit. Transfusion should be commenced within 1 hour of the patient's attendance. Pre-transfusion haemoglobin levels should be reviewed by the Haematology Day Care SHO/SpR and at outpatient visits in order to plan appropriate transfusion. Transfusion frequency varies among patients but is usually every 3-5 weeks. Each patient should have an individual transfusion plan that is reviewed by a Red Cell Consultant at least annually or if there is any notable change such as a new alloantibody or a significant transfusion reaction (see also BCSH Guideline on the Investigation and Management of Acute Transfusion Reactions 2012).

The pre-transfusion Hb level should be maintained at 90 – 100 g/L and post transfusion Hb should not exceed 140 g/L. This limits iron loading and prevents complications of excessive transfusion. As a general guide, transfusing a volume of 4ml/kg will typically give an increment in Hb of 10g/L. The concept that one unit of red cells gives a Hb increment of 10g/L is only applicable in a 70-80 kg patient and should not be applied to patients of lower body weight. 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 volume of blood or the frequency of transfusion increased. In patients with normal cardiac function transfusion is administered at a rate of 2-3 hours per unit.

Annual red cell requirements should be calculated at the Annual Review outpatient visit. Splenectomy may need to be considered in patients with hypersplenism or high red cell requirement defined as >250-275 ml/kg/year of SAG-M filtered red cells with an average haematocrit of 0.6. Otherwise splenectomy is rarely required in regularly transfused thalassaemia major patients.

## IRON CHELATION THERAPY

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 endocrinopathies include glucose intolerance, diabetes mellitus, hypothyroidism and hypoparathyroidism. The liver is also an important target of iron toxicity: hepatic fibrosis can develop from an early age eventually leading to cirrhosis, liver failure and hepatocellular carcinoma. Hepatic complications are accelerated in the presence of chronic hepatitis C virus infection.

**The most common barrier to effective iron chelation is inadequate compliance. Check and discuss at every visit.** There are many reasons for poor or erratic adherence including psychosocial factors. It is important to identify these and offer support through the multidisciplinary team. This should involve the Haemoglobinopathy CNS, Community Nurse Specialist and where indicated Specialist Social Worker. Formal clinical psychology assessment is available through Dr Jeremy Anderson, Clinical Psychologist (extn 38119). **Significant changes in chelation treatment should be discussed with a Red Cell Consultant or at Red Cell MDT.**

### 1. Iron chelators

There are 3 drugs available with specific indications and licence - Deferasirox (Exjade<sup>®</sup>), Desferrioxamine (Desferal<sup>®</sup>) and Deferiprone (Ferriprox<sup>®</sup>).

#### **Deferasirox: ( Exjade<sup>®</sup>)**

Deferasirox is indicated for treatment of iron overload in the following patient groups:

- Adults with  $\beta$ -thalassaemia who receive frequent transfusions (>7ml/kg/month)

or when desferrioxamine inadequate or contraindicated in:

- Thalassaemia patients who receive infrequent transfusions
- Non-transfusion-dependent thalassaemia syndromes

This oral chelating agent is given as a single dose of 10 - 40 mg/kg daily. The usual starting dose is 20mg/kg increasing to 30mg/kg for patients receiving frequent transfusion e.g. thalassaemia major. Patients with severe iron loading not responding adequately to therapy may require a dose increase to maximum of 40mg/kg. Patients with non-transfusional iron overload that is not severe may respond to lower doses of deferasirox (10-15mg/kg/day). Deferasirox has comparable efficacy to desferrioxamine in achieving negative iron balance, and controlling hepatic and cardiac iron loading. Adverse effects include skin rash (7-11%), gastrointestinal symptoms (15-26%) and hepatitis. Gastrointestinal tolerability and compliance may be improved by taking in the evening, with food or in divided doses (bd). Other drugs associated with a risk of gastric ulceration should be avoided if possible. An important side effect is a dose-dependent increase in serum creatinine, seen in 38% of patients, equivalent to a mean fall of 25% in creatinine clearance. This generally occurs in the first month of therapy and in some cases is transient. Patients who commence treatment with deferasirox or have a dose increase should have weekly U&Es and LFT performed for one month. If the creatinine is >33% above baseline on two consecutive occasions dose reduction or interruption of treatment should be considered. Deferasirox is contraindicated if eGFR is < 60ml/min. Intermittent proteinuria may also occur with or without changes in serum creatinine. Patients should have urinalysis performed monthly and treatment interruption considered for persistent proteinuria.

### **Desferrioxamine: (Desferal®)**

Established as an iron chelator for over 30 years and licensed for first line use in children and adults with substantial data on efficacy and side effects. Normally given as subcutaneous infusion on 3-7 days (typically 5 days) a week over 8 -12 hours at a dose (mean over 7 days) of 20-40 mg/kg/day. Main limitation is compliance as mode of delivery has a major negative impact on quality of life. "Thumb-tack" type subcutaneous needles, psychosocial support and disposable pre-filled elastomeric infusers aid adherence to therapy.

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.

Therapeutic index = Average daily dose (mg/kg)/serum ferritin (µg/L).

Presentation with fever, diarrhoea and abdominal pain may represent Yersinia or Klebsiella infection the risk of which is increased in patients on desferrioxamine treatment. Iron chelation must be discontinued immediately and appropriate antibiotic treatment instituted (see above).

Vitamin C enhances mobilization of iron from intracellular stores and should be prescribed at a maximum dose of 100mg orally daily on the days of desferrioxamine treatment. It should not be started until the patient has been stable on desferrioxamine for 6-8 weeks and must be avoided in severe cardiac disease as it can be toxic.

Patients with severe iron overload or who require rapid reversal such as in cardiac disease/decompensation can receive intravenous continuous desferrioxamine infusion 40-50 mg/kg/day via a Portacath with a disposable pre-filled elastomeric infuser (see management of cardiac iron overload).

### **Deferiprone (Ferriprox®)**

This was the first readily available oral chelating agent licensed in 1999. It is licensed for use in patients with Thalassaemia Major in whom desferrioxamine is inadequate or not tolerated. It is given at a dose of 75 – 100 mg/kg/day in three divided doses. Due to its small molecular size, lack of charge and resulting ability to cross the cell membrane Deferiprone is very effective in reducing myocardial iron loading and can improve or normalize cardiac function. As monotherapy it may however fail to control liver iron accumulation 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 neutropenia (neutrophil count 0.5 – 1.5 x 10<sup>9</sup>/L) in 2 – 10%, agranulocytosis (neutrophils < 0.5 x 10<sup>9</sup>/L) in 0.5 – 1% usually in the first year of treatment and arthropathy in 5 – 15% patients. FBC should be performed weekly. Patients receiving deferiprone should be advised to attend hospital immediately if they are febrile (T>38.0°C for 2 readings 1h apart, or one reading >38.5°C) or unwell and be given a letter explaining to other health professionals the serious side effects of deferiprone.

### **Combination therapy**

Patients with severe iron overload, particularly affecting the heart and the liver may benefit from combined chelation therapy. Studies have shown this to be more effective than monotherapy.

Examples of combined chelation regimes include desferrioxamine sc 30 mg/kg 3-4 nights a week + deferiprone 75 mg/kg/day, deferasirox 20-40mg/kg/day + deferiprone 75mg/kg/day and desferrioxamine 30mg/kg 3-4 nights a week + deferasirox 30mg/kg/day. The decision to recommend combined chelation therapy should be taken by a Red Cell Consultant, bearing in mind previous chelation therapy/compliance/side-effects and any underlying comorbidities. Patients receiving combined chelation therapy must be monitored closely.

**If a patient is acutely unwell for reasons unrelated to iron overload chelation therapy should be suspended**

## **2. Indications for starting chelation therapy**

Iron chelation therapy should be initiated after 10 - 12 transfusions (>20 red cell units) and/or when the serum ferritin level is consistently greater than 1000 µg/L.

The aim of chelation therapy is prevention NOT rescue.

All patients should be referred for Ophthalmological assessment and Audiometry prior to starting treatment and at least annually thereafter.

## **3. Monitoring of iron load.**

### **a) Serum ferritin**

Persistent levels > 2500 µg/L are associated with an increased risk of cardiac disease and death. Levels maintained in the 500 – 1000 µg/L over the long term carry a low risk, but do not exclude clinically significant tissue iron overload especially in patients who are not transfusion dependent. Serum ferritin is an acute phase protein. Values should be correlated with the clinical status of the patient and CRP. Aim to maintain ferritin at 500-1500 µg/L to avoid chelator toxicity. Consider stopping chelation if ferritin falls below 500 µg/L.

### **b) Liver biopsy**

Ultrasound-guided percutaneous biopsy allows direct measurement of hepatic iron (as mg/g dry weight) and allows for assessment of hepatic fibrosis. The method is invasive and iron deposition can be patchy and show variable reproducibility. This is not routinely performed in adults and is reserved for individual patients e.g. suspected cirrhosis, or concomitant Hepatitis C infection in consultation with the Hepatology team.

### **c) Cardiac and hepatic T2\* MRI**

Gradient-echo T2\* sequences are highly sensitive to magnetic properties of tissue iron. This technique provides accurate quantitation of cardiac iron load and function, and estimation of hepatic iron load though is not quantitative. There is poor correlation between cardiac iron overload and serum ferritin or liver iron. The risk of impaired left ventricular function increases at T2\* values < 20 ms. Nearly all patients with clinical evidence of cardiac failure have a T2\* < 10 ms.

### **d) FerriScan® – R2 MRI**

This is the preferred and only validated method for non-invasive quantitation of liver iron concentration (LIC). Results are unaffected by inflammation, fibrosis or cirrhosis unlike T2\* MRI. Dual analysis of cardiac T2\* and FerriScan can take place at the same visit to the MRI unit. These are booked separately on Cerner.

### **e) Interpretation of liver iron concentration (LIC)**

A LIC < 1.8 mg/g dry weight is normal. Levels of up to 7 mg/g dry weight do not usually result in organ damage or endocrinopathy. A LIC >15 mg/g dry weight is associated with an increased risk of cardiac disease. The aim of chelation should be to achieve a LIC of 3-7 mg/g dry weight. At a LIC < 3 mg/g dry

weight there is a greater risk of chelator toxicity and dose reduction or treatment suspension should be considered.

**f) Schedule for monitoring of iron overload**

	Transfusion-dependent	Non-transfusion dependent
Serum ferritin	3 monthly	Annually
Cardiac T2* MRI	Annually (2 yrs if good compliance and no previous cardiac iron overload)	If ferritin > 1500 ug/L
	6 monthly if cardiac T2* < 10ms	
	3 monthly if cardiac T2* < 10ms and evidence of cardiac impairment	
FerriScan	Annually	If ferritin > 1500 ug/l
	6 monthly if LIC > 10 mg/g dry weight or change in treatment	

**4. Management of cardiac iron overload**

The choice of treatment should be decided on an individual basis by a Red Cell Consultant and discussed at the Red Cell MDT. Compliance must be monitored closely.

**Cardiac T2\* 10-20 ms**

- Monotherapy with Deferiprone/Deferasirox at maximum tolerated dose **or**
- Desferrioxamine + Deferiprone
- Reassess cardiac T2\* at 6 months.

**Cardiac decompensation**

- Desferrioxamine 40-50mg/kg/day by continuous iv infusion iv via Portacath
- If clinical improvement after 1-2 weeks consider dose reduction and combination therapy with deferiprone
- Reassess cardiac T2\* and LVEF at 3 months

**ENDOCRINE/SKELETAL COMPLICATIONS**

Endocrine/skeletal complications in thalassaemia are multifactorial, contributory factors including ineffective erythropoiesis, iron overload and chelation therapy. All patients with thalassaemia major should have a full endocrine screen and assessment by a Consultant Endocrinologist (Dr Jeannie Todd - extn 34823) at least annually. Any new or suspected endocrine complications that develop should be discussed with the Endocrinology team with arrangement for specialist review according to urgency. Adults with evidence of hypogonadism should receive hormone replacement therapy, under the guidance of a Consultant Endocrinologist/Reproductive Endocrinologist (Professor Stephen Franks – extn 21486).

- Glucose intolerance should be monitored for, with random glucose levels every 3-6 months, and oral glucose tolerance tests annually. HbA<sub>1C</sub> is unreliable after transfusion in which context fructosamine levels give a more reliable indication of glycaemia
- Calcium and phosphate should be measured every 3-6 months. Vitamin D levels and parathyroid hormone should be checked annually and vitamin D replaced as necessary according to ICHT guideline
- Thyroid function should be assessed at least annually

Bone mineral density in the hip and spine should be measured every 2 years in thalassaemia major, more frequently if there is concern, by dual energy X-ray (DEXA scan). Patients with osteopenia (T score between -1 and -2.5 in either hip or spine) or osteoporosis (T score < -2.5) should be managed with advice about diet, exercise, calcium and vitamin D supplementation and possible hormone replacement therapy. In established osteoporosis bisphosphonate therapy should be considered on Consultant Endocrinologist advice (caution in patients of reproductive age).

## **PREGNANCY**

Pregnancy in thalassaemia major is associated with increased maternal morbidity. Women with a history of cardiac complications and iron overload are at particular risk and should be referred for assessment by a Consultant Cardiologist (Dr David Lefroy or Professor Petros Nihoyannopoulos) before conception. Good control of iron overload should be achieved before pregnancy. Iron chelators are potentially teratogenic. Advice should be given on the need to discontinue iron chelation prior to conception or as soon as pregnancy is suspected if unplanned. Transfusion requirements typically increase in pregnancy. In patients with hypogonadism secondary to iron overload referral for assessment of fertility options should be made to the Assisted Conception Unit (Mr Stuart Lavery – extn 34152 )

Women with thalassaemia should be managed antenatally at Queen Charlotte's and Chelsea Hospital (QCCH) under the joint care of Mr Andrew McCarthy, Consultant Obstetrician and Dr Mark Layton, Consultant Haematologist. Patients are seen in the joint Obstetric Haematology clinic on a Monday morning and followed up at QCCH until after delivery. The clinic is located on the 2<sup>nd</sup> floor of QCCH in the Centre for Fetal Care (Tel: 020 3313 3998). If their haemoglobinopathy status is not documented the woman's partner should be offered testing. If the couple is at risk of having a child with a major haemoglobinopathy they should be offered genetic counselling including the option of prenatal diagnosis.

Contacts: Mr A McCarthy

Bleep 5116

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## **OUTPATIENT MANAGEMENT AND ANNUAL REVIEW**

Clinics for patients with haemoglobinopathies are held weekly at Hammersmith Hospital (Thursday afternoon) with a satellite clinic at St Mary's Hospital (Friday morning). The Haemoglobinopathy CNS, Specialist Social Worker and Clinical Psychologist attend the clinic on a Thursday afternoon.

The aims of outpatient review are to:

- Monitor progress: medical, and psychosocial
- Establish steady state parameters for comparison in acute illness
- Educate in the management of thalassaemia and iron chelation in particular
- Provide genetic counselling

### **Routine clinic review (every 3 months):**

- Document any ill health since last visit
- Check immunisations are up to date
- Record weight and BP
- Examination: check especially for jaundice, heart size and murmurs, liver and spleen size (measure in cm)
- All patients should have FBC, reticulocytes, LFT, renal and bone profile, ferritin, thyroid function and other endocrine investigations if indicated
- Offer support/referral to Clinical Psychologist where appropriate
- Prescribe any specialist medication
- Arrange follow up appointment

All patients with thalassaemia should have a comprehensive review on an annual basis, details of which are provided in Appendix 1.

Patients who develop new complications of thalassaemia or require review of management should be referred for discussion at the weekly Red Cell MDT meeting (See ICHT Red Cell Operational Policy).

## **THALASSAEMIA INTERMEDIA**

## 1. Definition

The term thalassaemia intermedia applies to patients with thalassaemia disorders in whom regular transfusion is not essential for survival, growth and development. The most commonly encountered forms are due to homozygous  $\beta$ -thalassaemia (due to less severe mutations or genetic modifiers), haemoglobin E/ $\beta$ -thalassaemia or haemoglobin H disease. These encompass a very wide range of clinical severity, from patients with severe anaemia to those who are virtually asymptomatic. At the severe end of the spectrum there may be symptomatic anaemia, mild/moderate skeletal changes, poor growth during childhood, pubertal delay, hypersplenism and extramedullary haematopoietic expansion. Patients with thalassaemia intermedia are prone to cholelithiasis and even in the absence of transfusion may develop iron overload, particularly affecting the liver, due to increased gastro-intestinal iron absorption. In all patients, even at the mild end of the spectrum, monitoring for these and other long-term complications including pulmonary hypertension, hypersplenism and leg ulcers is necessary.

## 2. Management

Patients should initially be seen 3 monthly in the clinic and the frequency reduced if the phenotype is mild. At each visit all patients should have as a minimum weight, spleen and liver size, FBC, renal and bone profile, LFTs, CRP and ferritin. Patients should receive supplementation with folic acid 5mg od po.

## 3. Indications for transfusion

Sporadic transfusions should be considered for episodes of acute anaemia, for example precipitated by infection. Long-term transfusion may be considered in thalassaemia intermedia for the following indications:

- Symptomatic anaemia
- Delayed puberty
- Skeletal abnormalities e.g. facial deformities, recurrent fractures, premature epiphyseal fusion
- Pulmonary hypertension,
- Compression syndromes due to extramedullary haemopoiesis
- Chronic leg ulcers

The patient should be observed closely over several months to determine steady-state symptoms and Hb before a decision on long-term transfusion is reached. The rationale for transfusion should be carefully explained if necessary over the course of several clinic visits and should always involve the patient's primary Consultant.

## 4. Iron overload

Serum ferritin is less reliable in thalassaemia intermedia, and tends to underestimate the degree of liver iron loading. Iron-related cardiomyopathy is unusual in children and young adults but may develop later in adult life even in untransfused patients. All patients with thalassaemia intermedia should have cardiac T2\* MRI and LIC quantitation by Ferriscan (R2 MRI) at least every 5 years or annually if on regular

transfusions. Chelation regimes for untransfused patients can be less intensive than in thalassaemia major. Negative iron balance is more easily achieved because the rate of iron accumulation from intestinal absorption is less than that due to regular transfusion.

## 5. Splenectomy

Splenectomy leads to an improvement in Hb level and/or reduced transfusion requirement in many cases. Clear indications for splenectomy in thalassaemia intermedia include symptomatic splenomegaly and hypersplenism. Patients with lesser degrees of splenomegaly may also benefit. However, the improvement is not always dramatic and may not abrogate the need for transfusion. The potential benefits of splenectomy should be weighed against the risks on an individual basis. Adverse consequences of splenectomy in thalassaemia intermedia include thrombocytosis, risk of sepsis, pulmonary hypertension and possibly enhanced iron deposition in the liver. The thrombotic risk associated with thalassaemia intermedia, is further increased after splenectomy. Prior to splenectomy patients should be transfused for several months to reduce spleen size, suppress ineffective erythropoiesis, and reduce the numbers of circulating, prothrombotic thalassaemic red cells.

The feasibility of laparoscopic splenectomy should be discussed with the surgical team and an HDU/ICU bed booked for post-operative observation. If the patient has not undergone prior cholecystectomy ultrasound examination should be performed before a date for surgery is scheduled and if gallstones are present cholecystectomy considered at the same time. All patients should receive appropriate vaccinations at least 2 weeks prior to surgery (see ICHT [Guideline Infection Prevention for Adult Patients with an Absent or Dysfunctional Spleen](#)).

## 6. Hydroxycarbamide

Responses to hydroxycarbamide in thalassaemia intermedia are variable, but it may be considered for alleviation of symptoms of anaemia, reduction in jaundice due to haemolysis, relief of bone pain, reduction in medullary expansion or splenic enlargement and regression of extramedullary masses. Hydroxycarbamide therapy is more effective in specific genotypes including HbE/ $\beta$ -thalassaemia, Haemoglobin Lepore/ $\beta$ -thalassaemia and patients who are homozygous for the Xmn I polymorphism or have been splenectomised. It is not indicated in haemoglobin H disease. Hydroxycarbamide 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 exceed 20 - 25 mg/kg/day as the risk of bone marrow suppression is greater than in sickle cell disease. Guidance on counselling before and monitoring hydroxycarbamide therapy is provided in the ICHT Guideline Clinical Management of Sickle Disease in Adults.

## 7. Pulmonary hypertension

Pulmonary hypertension is prevalent in untransfused patients (23%), particularly those who have been splenectomised. Thalassaemia intermedia patients should have regular echocardiography (minimum of 5-yearly) from 15 years of age. If there is evidence of raised pulmonary artery pressure on echocardiography (TRV > 3.0 m/s or > 2.5 m/s if symptomatic) referral to Dr Simon Gibbs, National Pulmonary Hypertension

Service, Hammersmith Hospital for further assessment and consideration of right heart catheter studies should be arranged. If pulmonary hypertension is confirmed regular transfusion should be considered.

## **8. Endocrine/Skeletal**

For management of thalassaemia intermedia patients with significant iron overload at risk of endocrinopathy see section above on Endocrine/Skeletal complications in thalassaemia major.

Thalassaemia intermedia patients are at increased risk of osteoporosis. Management should follow the guidance above with the exception that in milder phenotypes without other risk factors e.g. iron overload DEXA scan can be repeated 5-yearly if bone mineral density is normal. All patients should have an annual review including the assessment of facial bone deformity.

## **9. Extramedullary haemopoiesis**

Patients presenting with symptoms due to extramedullary haemopoietic masses should be investigated, usually with MRI imaging, and treated with hypertransfusion or hydroxycarbamide.

Radiotherapy can be considered if there is urgent need for regression; hypertransfusion and hydroxycarbamide act more slowly. Asymptomatic masses may require intervention depending on their site e.g. if impinging on the spinal cord, but if not threatening vital structures may simply be monitored.

## ANNUAL REVIEW CHECKLIST

Patients should have an Annual Review checklist completed using Appendix 1 that includes:

- Assessment of progress in general and a review of the patient's knowledge of the condition
- Education/Employment
- Chelation-compliance, attitude to chelation, problem-solving
- Review of information provided – to include any investigations undertaken, treatment given, healthy lifestyle advice
- Clinical review
  - Number of hospital admissions
  - Other complications e.g. line infections
  - Review of transfusions/Annual red cell consumption /Red cell alloantibodies
  - Indication for splenectomy
  - Vaccination status
- Clinical examination
- Appropriate investigations to monitor for chronic complications

## **TRANSITION FROM PAEDIATRIC TO ADULT SERVICE**

A care plan should be agreed for all thalassaemia patients before they are transferred from Paediatric to Adult services. For adolescent and young adult patients attending ICHT this is developed jointly between the Paediatric Haematology and Adult Clinical Haematology teams in discussion with the patient during visits to the monthly Transitional Clinic held at St Mary's Hospital (see ICHNT Guideline Transition of Haemoglobinopathy Patients From Paediatric to Adult Services).

## 6) IMPLEMENTATION

<b>Training required for staff</b>	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
<b>If yes, who will provide training:</b> <i>Please give name/post</i>	Mark Layton Clinical Lead, Asad Luqmani, Consultant Haematologist and Lydia Alexander, Haemoglobinopathy CNS
<b>When will training be provided?</b> <i>Please give date</i>	Rolling programme of training for medical (including Haematology SHO and SpR induction), nursing and Acute Medicine clinical staff
<b>Date for implementation of guideline:</b> <i>(after the process of ratification)</i>	October 2015

## 7) MONITORING / AUDIT

<b>When will this guideline be audited?</b> <i>Please give approximate date</i>	October 2016
<b>Who will be responsible for auditing this guideline?</b> <i>Please give name/post</i>	Mark Layton
<b>Are there any other specific recommendations for audit?</b>	Monitoring and treatment of iron overload

## 8) REVIEW

<p><b>Frequency of review</b></p> <p><i>As a guide:</i></p> <ul style="list-style-type: none"> <li>• Drug related guidance should be reviewed every 2 years</li> <li>• Therapy related guidance should be reviewed every 5 years</li> <li>• Clinical treatment guidance should be reviewed every 3 – 5 years</li> </ul>	<p><b>Please indicate frequency of review:</b></p> <p>a) Clinical treatment guidance - 3 years</p> <p>b) Drug related guidance -2 years</p> <p><b>Person and post responsible for the review:</b></p> <p>a) Mark Layton, Asad Luqmani and Diana Hagger</p> <p>b) Stephanie Kirschke</p> <p><b>Next review due: October 2017</b></p>
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## 9) REFERENCES

Imperial College Healthcare NHS Trust (ICHT) (Dec 2014) Adult Treatment of Infection Policy

Imperial College Healthcare NHS Trust (ICHT) (Dec 2014) Infection Prevention for Adult Patients with an Absent or Dysfunctional Spleen

Imperial College Healthcare NHS Trust (ICHT) (Oct 2015) Paediatric Thalassaemia Disorders

Imperial College Healthcare NHS Trust (ICHT) (Aug 2014) Policy for Transition of Haemoglobinopathy Patients from Paediatric to Adult Services

Imperial College Healthcare NHS Trust (ICHT) (Aug 2014) Blood Transfusion Policy for Adults

Imperial College Healthcare NHS Trust (ICHT) (Jan 2014) Adult Treatment of Malaria

Imperial College Healthcare NHS Trust (ICHT) (October 2015) Red Cell Operational Policy

## 10) GUIDELINE DETAIL

Start Date: (date of final approval by CPG)	October 2015	
Dates approved by:	<b>Divisional Guidelines Group (if applicable):</b>	
	<b>Policies, Procedures and Ratification Meeting (PPRM)</b>	02.09.15
	<b>Directorate Quality and Safety Committee</b>	10.09.15
Have all relevant stakeholders (Trust sites, CPGs and departments) been included in the development of this guideline?	<p>Red Cell MDT</p> <p>Microbiology – Dr Kathleen Bamford</p> <p>Pharmacy – Stephanie Kirschke</p> <p>Obstetrics – Mr Andrew McCarthy</p> <p>Paediatrics – Dr Kirstin Lund</p>	
Who will you be notifying of the existence of this guidance?	<p>Divisional Directors</p> <p>Divisional Quality Leads</p> <p>Specialty Leads</p>	
Related documents:		
Author/further information:	<p>Dr Mark Layton</p> <p>Consultant Haematologist</p> <p>Surgery Cancer and Cardiovascular Division</p> <p>Hammersmith Hospital</p> <p>Telephone 31320</p> <p><a href="mailto:mark.layton@imperial.nhs.uk">mark.layton@imperial.nhs.uk</a></p>	
Document review history:	<p>Di Hagger August 2015</p> <p>Asad Luqmani September 2015</p> <p>Mark Layton October 2015</p>	

Next review due	October 2017
THIS GUIDELINE REPLACES:	RC-GL-002- Clinical Management of Thalassaemia in Adults (September 2012) <a href="http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/id_038315.pdf">http://source/prdcont/groups/extranet/@clinical/@guidelines/documents/ppgs/id_038315.pdf</a>

## 11) INTRANET HOUSEKEEPING

<b>Key words</b>	Thalassaemia Clinical Management Adult
<b>Which Division/Directorate category does this belong to?</b>	Surgery Cancer and Cardiovascular/Clinical Haematology
<b>Which specialty should this belong to when appearing on The Source?</b>	Haematology <a href="http://source/clingov/haematology/index.htm">http://source/clingov/haematology/index.htm</a>

## 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: Thalassaemia Annual Review

IMPERIAL COLLEGE HEALTHCARE NHS TRUST:

### Thalassaemia Annual Review checklist: investigations and management (Form 2)

Name:

DOB:

Hospital number:

Date of review:

Diagnosis:

Other diagnoses:

Consent for NHR given: Yes/No

Shared care centre (if applicable):

Transfusion:

On regular transfusions Yes/No

Transfusion interval (weeks)

Transfusion total (units per year)

Average pre-transfusion Hb (g/dl)

Red cell allo-antibodies (specify and if new)

Other transfusion/chelation issues

Vascular access: (tick as appropriate)

Peripheral

Portacath

**Hospital Admissions in last 12 months:**

Number of hospital admissions:

Any acute infective episodes:

Surgery in last 12 months:

Number of emergency attendances:

**Chronic complications:**

Diabetes: Y/N    Osteoporosis: Y/N    Hypothyroidism: Y/N    Cardiac: Y/N

Extramedullary haemopoiesis Y/N    Gallstones Y/N    Other:

**Medications:**

**On iron chelation:**    Yes/No    Daily dose and mg/kg/day

Desferrioxamine    Yes/No    Dose

Deferasirox    Yes/No    Dose

Deferiprone    Yes/No    Dose

Combination therapy    Yes/No    Doses

**Other medications:**

**Vaccinations:** (date given)

a) Hepatitis B

b) If splenectomy:

Pneumovax

Hib/Men C

Men ACWY

Meningitis B

Influenza

**Examination:**

Weight (kg)    Ht (m)    BMI

Splenomegaly: Y/N Size(cm)    Hepatomegaly: Y/N Size(cm)

CVS    Respiratory

Other (specify)

**Investigations:**

1. All patients

Hb            Reticulocyte count            (if not on transfusion)  
Bilirubin/ALT  
Creatinine/eGFR            Vitamin D            Calcium/Phosphate            Glucose  
Most recent ferritin/annual average  
Hepatitis B surface antibody  
Urine dipstick/ PCR  
Echo/TR jet velocity (5 yrly)  
DEXA scan (within last 18-24 months or 5 yrly if not on regular transfusion)

2. If Ferritin consistently > 500

TSH/T4            Zinc  
GTT (if fasting glucose > 6.0)            Parathormone  
FSH/LH            Testosterone/Oestradiol  
Cortisol+/-synacthen test  
Cardiac and liver T2\* (ms) on MRI  
Liver Iron Concentration (Ferriscan)  
Other imaging studies

3. Additional tests if on regular transfusions

Hepatitis B surface antigen            Hepatitis C            HIV

4. If on iron chelation therapy

Audiology review date  
Ophthalmology review date

**Management changes:**

**Name of person completing annual review:**