Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK

3rd Edition, 2016

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The content of the document is evidence based, as far as available evidence allows, and reflects the experience and opinions of its authors. However they, the UK Thalassaemia Society, and the UK Forum on Haemoglobin Disorders can take no responsibility for clinical problems arising in individual patients managed in line with the contents.

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Foreword to the 3rd edition

From the Department of Health

I am really pleased to see an update of the standards for the delivery
of care to patients with thalassaemia and I strongly support it. The document has benefited from the involvement of patients in the development and the process of implementation. Empowerment of patients and the public is an essential aim of the NHS and the thalassaemia community should be proud of their leadership role in this. Clinicians embracing these standards will see improvements in their services and the Peer Review process is also key.

This document should be an invaluable source of information to commissioners when developing future services for patients. Well done to the Editor and authors. This is an important piece of work.

Professor Dame Sally C Davies FRS FmedSci
Chief Medical Officer for England

From the UK Thalassaemia Society

I am honoured and delighted to be writing this foreword to the 3rd edition of the Standards. When the second edition was published in 2008, as an ordinary member of UKTS I had no idea of the tremendous amount of work which goes into producing a book of this kind. Now that it has been my privilege to be President of the Society since 2010, however, I am all too aware that it is a tremendous undertaking; which took well over a year of very hard work from all who were involved. We are extremely grateful to all the authors who contributed their time and expertise, on an entirely voluntary basis; with particular thanks of course to the Editor Dr Anne Yardumian, who has given up most of her annual leave and rare leisure hours to this project for the first half of 2016. Thanks also to our National Coordinator Elaine Miller, without whose dedication this book would not have reached publication. Another essential contributor was Dr Matthew Darlison, whose incomparable technical expertise has allowed us to produce both a printed book and an interactive on-line version which can be accessed via the UKTS and UKFHD websites (www.ukts.org and www.haemoglobin.org.uk).

Like many of my peers who have thalassaemia, I will be requesting a copy of the book so that I can compare my own treatment with the guidelines; but I know that I am fortunate to have been treated all my life in a specialist centre. The excellent care I have enjoyed has given me access to a normal life – higher education, a career, marriage and very recently fatherhood, with the birth of my twin sons in April 2016. I am extremely thankful for all the skill and care that has kept me fit enough to enjoy these privileges. However, I am all too aware that not everyone with thalassaemia is as fortunate.

In early 2016 UKTS carried out a national survey of adult thalassaemia patients; and some of the reported outcomes made rather uncomfortable reading. Despite the progress that has undoubtedly been made due to better chelation, networks for care and peer reviews of services, people living in the UK today with thalassaemia are still suffering from social stigma, discrimination and in some cases, inadequate access to specialist care. It is our job as a patient Society to try to address the medical and social barriers which keep some of those who have thalassaemia from achieving their goals. We will also continue to work with clinicians and health care planners to improve and refine the networks for care. In the UK we have some of the world's leading authorities on thalassaemia treatment; and networks for care should mean that every individual has access to this expertise. Finally, services designed to fit around the patient's working life are still the exception; and this needs to change if people with thalassaemia are to become fully integrated, contributing members of society. This is a goal we will continue to pursue – until health care planners recognise that we cannot become fully independent, productive people if our health care is still being delivered as though we were invalids with no commitments or responsibilities.

I hope that this new edition of the Standards will be useful to all those involved in the planning and delivery of thalassaemia care; and to my fellow "patients" – I encourage you to use this book, learn about your condition, ask questions, be active and engaged in your treatment. We have set the Standards; now let's work together to deliver them.

Gabriel Theophanous
President, UK Thalassaemia Society

Summary of Standards

3: Networks for Care and Commissioning

■ All regions must deliver care for people with thalassaemia through a clinical network incorporating local haemoglobinopathy teams (LHT) and one or more Specialist Haemoglobinopathy Centres (SHC).

■ Established pathways within the network should ensure that all patients have access to an SHC – for their regular management if living nearby and for a comprehensive review of their condition and care at least once a year, at an 'annual review visit', if they live more distantly and receive their regular care from an LHT.

■ Specialist clinical advice should be available from the SHC at all times, for patients who present acutely to their local centre with complications the local team may not be experienced in managing. There should be the facility for urgent transfer of a patient to the SHC for complex care.

■ The network should have sufficient resources (health care professionals, management and administrative staff) to function effectively, and should develop systems for information sharing, clinical governance, accountability and staff development.

■ A 'key contact' health professional will be designated for each patient.

■ Patients and carers should receive regular education, supervision and support in thalassaemia care, chelation therapy and other home treatments.

■ All health providers within the network – primary care teams, LHTs and SHC – should record and exchange information relating to clinical events, monitoring investigations, and changes in treatment. Correspondence should always be copied to patients/carers.

■ Consent should be sought from all patients for entry of their details on the National Haemoglobinopathy Registry, and data entered in a timely fashion to assist audit and assessment of good quality outcome information.

■ Patients and carers should be involved in making decisions about management and delivery of care.

■ Patients and carers should have access to peer support groups.

4: Annual Review at Specialist Haemoglobinopathy Centre

■ Every person with thalassaemia will have the opportunity for their care and condition to be reviewed at least annually with a team of health care professionals who have particular experience in caring for thalassaemia disorders. This can take place during a visit to the Specialist Centre, or at an outreach clinic where members of the Specialist Team visit the local centre at which the person receives their routine care.

■ The assessment should cover all aspects of care including educational and lifestyle factors that may affect health or influence adherence to treatment.

■ Discussion of treatment options should include any new information which has become available, and an individual treatment plan for the next 12 months will be agreed.

■ A copy of the annual review consultation including the care plan will be copied to the patient or, for children, their parents as well as health professionals involved in their care.

■ Data should be entered into the annual review screens of the NHR for consented patients.

■ People in families affected by thalassaemia should be able to meet and gain support from other affected families at the Centre or in the community.

5: Quality Assessments

- An independent external peer review of thalassaemia services should be completed every two-three years.
- Results from this should be made available to the inspected services, to NHS Commissioners and NHS England.
- Commissioners should designate clinical networks, support the establishment and ongoing running of the networks and review outcome data from the network at least annually.
- Specialist haemoglobinopathy centres should have fail-safe mechanisms for enrolling all newborns with thalassaemia into clinical care.
- Specialist and local haemoglobinopathy centres should have enough medical and nursing time to care for patients with thalassaemia, and experienced support staff, aware of the issues facing patients with thalassaemias.
- There should be a clear process for transition from paediatric to adult care.
- There should be access to appropriate out of hours services.
- Adequate information should be provided for patients, and readily available comprehensive clinical guidelines for staff.

6: Psychosocial Issues in Thalassaemia

- Consideration of the psychosocial demands and support needs of living with thalassaemia is a key role and responsibility for all professionals involved in the provision of care for people with this condition.
- Consideration of the family context and developmental/life stage of the person with thalassaemia is key to ensuring that care and treatment recommendations are individually tailored and appropriate for each patient.
- Psychosocial support alongside specialist psychological care should be provided as a standard part of thalassaemia clinical care, in both paediatric and adult services.
- Core staffing of Specialist Haemoglobinopathy Centres should include a clinical psychologist with a special interest and experience in thalassaemia.

7: Initial Management of the Newly Diagnosed Infant

- Diagnosis of a child with a serious thalassaemia syndrome will be timely and accurate. It should be established as soon as possible after birth, and should include globin genotype.
- The neonatal heel prick test is a screening, not diagnostic, test and early confirmation is required.
- The child must be monitored closely to determine the likely clinical course.
- The family should be informed fully and sensitively from the outset once the diagnosis is confirmed, by appropriately experienced professionals, with the use of a culturally-appropriate health advocate if necessary, and with the opportunity for full discussion. Suitable written information should be given to them.
- A management plan tailored to the individual child must be agreed and implemented.
- The family will meet their 'key contact' within the clinical team, and given contact numbers for subsequent use.
- The family should be informed about the National Haemoglobinopathy Registry and asked to give consent for the child's details to be recorded on it.
- The family should be given the contact details for the UK Thalassaemia Society and any local support group.

8: Decision to Start Regular Transfusion

- Infants with β thalassaemia will be monitored carefully for clinical signs indicative of the need for transfusion. Transfusion will be started promptly when there is clinical evidence of severe anaemia, failure to thrive and/or thalassaemic bone deformity.

- Infants and children with a milder 'thalassaemia intermedia' phenotype will be identified clinically and not subjected to regular transfusion inappropriately.

- Extended red cell phenotype and genotype should be performed before starting regular transfusions to ensure compatible blood is transfused and to reduce the risk of alloimmunisation.

- Before a first transfusion, a course of hepatitis B vaccinations should be started, and completed if possible.

9: Red Cell Transfusion

- Trough haemoglobin levels should be maintained ~ 90-105g/l.

- Blood must be ABO compatible and antigen negative for any clinically significant antibodies the patient is known to have, or to have had previously identified even if not currently detectable. It should be fully matched for all the Rh antigens and K.

- Units should be less than 2 weeks old and, in adults, of larger volume where possible.

- There should be a clear record of patient's transfusion requirements outlining volume, frequency and target haemoglobin.

- Transfusions will be given on each occasion in a designated age-appropriate area with suitable facilities, experienced regular named nurses and familiar supervising medical team.

- Cannulation will be undertaken by an experienced nurse, doctor or phlebotomist.

- Pre-arranged transfusions should be started within 30 minutes of the patient's arrival.

- Good transfusion practice must be observed.

10: Monitoring and Management of Iron Load

- A protocol for iron chelation therapy in children and adults should be shared between the Specialist Haemoglobinopathy Centre and Local Hospital Teams within the clinical network, and reviewed at regular intervals. This should be based on current published evidence, expert opinion, and national specialist commissioning guidance.

- Decisions about initiating and changing chelation therapy should be made by the thalassaemia specialist, taking into account the preferences of the patient and carers, and the views of other involved health care workers.

- Patients and carers should be informed about benefits and possible adverse effects of each option and offered information in formats appropriate for age, language and literacy, with health advocacy as needed. 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 including clinic doctors, nurse specialists, clinical psychologists, and play therapists for children. Peer support should be encouraged.

- Adherence should be monitored regularly, and problems carefully identified and addressed in a non-judgmental manner.

- All patients should have access to Cardiac MRI for assessment of myocardial iron overload and cardiac function, and to liver MRI for assessment of liver iron concentration. The MRI methodology should be standardised and validated.

- Patients should be carefully monitored for side effects of iron chelation therapy, and treatment interrupted or reduced promptly to avoid serious toxicity.

- The outcomes of chelation therapy within local clinics and the clinical haemoglobinopathy network should be audited regularly.

11: Referral for Blood and Marrow Transplantation

■ The families of all children with thalassaemia should have the opportunity to discuss the option of BMT with the team at a transplant centre with experience in undertaking the procedure for this indication, whether or not there is currently a matched sibling donor.

■ They will be fully informed about all the potential risks and benefits of the procedure, in the immediate, middle and long term.

■ For those with an appropriate donor who choose to proceed with transplant, it must be undertaken at a centre with specific experience and expertise of managing thalassaemia transplants.

12: Growth, Development and Endocrine Function

■ Iron loading should be kept to a minimum, by careful monitoring and the use of effective chelation treatment, to reduce the risks of endocrine damage.

■ Paediatric and adult specialists in bone metabolism and endocrinology, with interest and expertise in managing the particular complications encountered, should be involved in the care of children and adults with thalassaemia, ideally in a joint clinic setting.

■ Children should have growth and development monitored regularly from diagnosis until they have achieved full sexual maturity and final adult height. Any change in expected growth and development should be identified, investigated and treated promptly.

■ Where paediatric endocrine input has been necessary then careful transition plans should be made at completion of puberty and linear growth. Ideally such transition should take place in a combined clinic. A detailed clinical summary and discussion should take place to ensure there is no disruption to treatment at this critical stage of adolescence.

■ Adults and children should be routinely assessed, at least annually, for evidence of disturbance of the hypothalamo-pituitary axis, for calcium and bone homeostasis, and thyroid function.

13: Transition from Paediatric to Adult Services

■ Support and education will be given to the young person and their parents or carers over time to nurture independent, informed young people who can take responsibility for their health and choices.

■ Each young person requires a named/key worker for transition and the transition process should commence by 13 years of age.

■ Adult and paediatric teams will work collaboratively with the young person and their parents or carers to provide a timely and smooth hand-over. Primary, secondary and tertiary health care providers and community teams should be involved in the process, and in the young person's ongoing care.

■ Any anxieties that the young person and their parent(s) or carer(s) may have, arising from the change from paediatric to adult health providers, will be addressed.

■ Psychosocial stresses that may negatively impact on adherence with their transfusion regime, medication and/or and self-care will be identified and managed.

■ Close monitoring of thalassaemia treatment should continue over the transition period, with particular attention to monitoring of iron stores and adherence to iron chelation therapy.

14: Fertility and Management of Pregnancy

- Each Specialist Centre will identify a paediatric endocrinologist with experience in the management of thalassaemia.
- Pubertal development, growth, and endocrine function will be closely monitored in boys and girls with thalassaemia, and prompt referral made if there is any suspicion of problems.
- Women contemplating pregnancy will be assessed for possible risks to themselves and their babies and this evaluation up-dated as needed.
- At any time when the patient wishes she/ he should be referred to a fertility / endocrine / assisted conception clinic with experience of thalassemia patients, to allow discussion about treatment options; culturally appropriate advocacy will inform these discussions.
- Women will be jointly managed during pregnancy and delivery by a 'maternal medicine' obstetrician experienced with haemoglobin disorders, and by their haematologist.

15: Acute Clinical Presentation

- Specialist Haemoglobinopathy Centre teams will offer education about thalassaemia-specific acute presentations to patients and health professionals across the network, including Emergency Department and Primary Care colleagues, with details of how to access specialist advice.
- Specialist haemoglobinopathy teams will make clear to their patients and to acute medical services at the local and specialist hospitals how they can be contacted for urgent clinical advice.
- Patients presenting with acute clinical problems will be assessed with consideration given to the range of thalassaemia-specific complications they might develop.
- If staff with appropriate knowledge and experience are not available on site, there must be urgent consultation with the specialist centre, and referral on after stabilisation where necessary.
- Appropriate management should be instituted as quickly as possible.

16: Management of Surgery

- Patients should be carefully assessed pre operatively with specific reference to complications relating to thalassaemia including cardiac, thrombotic, endocrine and metabolic disturbances.
- There should be close liaison between the surgical, anaesthetic, and paediatric/haematology teams in planning surgery, and shared care arrangements should be agreed prior to a surgical admission.
- Patients undergoing urgent surgery should always be discussed with the SHC team, during preparations for theatre.
- Patients should have been given adequate information regarding thalassaemia-specific and other issues related to surgery to allow informed consent.

17: Management of the Cardiovascular System

- Every patient must have access to a cardiology service with experience in the management of cardiac consequences of thalassaemia.
- Children should be referred for their first cardiac evaluation, including clinical assessment, ECG, echocardiogram and MR T2* between the ages of 7 – 10 years.
- Cardiology assessments thereafter should be at intervals guided by symptoms, adequacy of chelation and findings of previous assessments.
- A high risk time for development of cardiac problems is 16-25 years of age, and during this period assessments should be undertaken at least yearly.
- Patients with myocardial iron and left ventricular (LV) impairment with new-onset symptoms must be discussed with the SHC team, and reviewed urgently for consideration of inpatient intensive chelation.

■ Patients must be considered for anticoagulation if they have indwelling venous lines, or atrial fibrillation, including paroxysmal AF.

18: Management of Impaired Glucose Tolerance and Diabetes Mellitus

■ A paediatric and adult consultant diabetologist should be identified for each Specialist Haemoglobinopathy Centre.

■ Patients should be checked annually for impaired glucose regulation and diabetes from puberty, or from age of 10 years if there is a family history of diabetes.

■ Patients with diabetes should have a full annual diabetes review, including glycaemic control, cardiovascular risk factors, diabetic complications and sexual health.

■ Patients with diabetes should have access to a clinical health psychologist with experience in diabetes management.

19: Management of Bone Problems

■ Transfusion therapy will be initiated in time to prevent irreversible deformities associated with bone marrow expansion.

■ Doses of desferrioxamine will be kept in the range to minimise the risk of bone toxicity or reduce height velocity. Any bone changes possibly related to deferrioxamine toxicity should be suspected and investigated in children with bone/joint pain or short stature.

■ Management of the maturing skeleton should focus on achieving peak bone mass.

■ All patients should have vitamin D measured with supplements given if needed.

■ All patients should be advised of the need for adequate dietary calcium for healthy bones.

■ All patients should be advised on lifestyle changes that promote achieving peak bone mass and maintaining bone mineral density, BMD: smoking cessation, avoiding excessive alcohol consumption and undertaking weight bearing exercise.

■ Diagnosis of hypogonadism and other endocrinopathies should be prompt, and appropriate hormone replacement therapy given.

■ Adult patients should be monitored for low bone mass/osteoporosis.

■ Bisphosphonates and other bone specific agents should be considered in patients with deteriorating BMD/osteoporosis confirmed on DXA bone mineral density scanning, particularly if there have been fractures.

■ Osteoporosis treatments should be regularly reviewed.

■ If there is chronic severe bone pain, not amenable to corrective treatment, a patient should be managed together with a specialist pain team.

20: Management of Liver Problems

■ Liver function tests should be monitored at regular monthly intervals.

■ Liver iron levels should be maintained within safe limits to avoid hepatic damage, using the range of available chelation options and taking steps to encourage adherence to treatment.

■ Adjustments to chelation and other treatment should be made promptly if abnormalities of liver function are detected on routine monitoring tests.

■ Vaccination against hepatitis A and B virus infection should be ensured.

■ Liver disease should be managed jointly with a designated specialist hepatologist.

■ Management of chronic hepatitis C virus infection should include histological assessment of fibrosis on biopsy and/or non-invasive techniques.

■ Antiviral therapy aimed at sustained viral clearance should be planned and managed in collaboration with a designated specialist hepatologist.

■ Patients with established cirrhosis should have regular surveillance checks for hepatocellular cancer.

21: Management of Dental Problems

■ Adequate red cell transfusion in children with thalassaemia should be sufficient to prevent the development of marrow overgrowth and facial bone changes, and some of the associated dental problems.

■ All patients should access regular dental care to prevent oral infection and manage the potential orofacial features of thalassaemia.

■ Patients presenting with acute dental infections/abscesses should receive urgent dental care and antimicrobial therapy as required.

■ Close liaison with the haematology team is required to determine the potential complications when delivering invasive dental treatment, and to put measures in place to reduce risk.

■ All patients should ideally have a comprehensive dental assessment with their local dentist prior to the commencement of bisphosphonate therapy to ensure that they are as dentally fit as feasible.

22: Patients Previously Treated Outside the UK

■ Children and adults who have been receiving treatment outside the UK will be seen, as soon as possible after they arrive, at an established Specialist Haemoglobinopathy Centre for a thorough assessment.

■ Transfusion treatment will be re-started without delay.

■ Any complications which may have developed will be detected and discussed with the individual and family and management plans put in place.

23: Prevention Using Prenatal Diagnosis and Preimplanation Genetic Diagnosis

■ All couples at risk of having children with a thalassaemia disorder should be referred to specialist genetic counselling as soon as the risk is recognised.

■ Counselling is provided by a genetic specialist with specific experience in both prenatal diagnosis and preimplantation genetic diagnosis for haemoglobin disorders.

■ DNA analysis is provided for all at risk couples.

■ All at risk couples are informed of prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD) as options to achieve a healthy family.

■ A couple at risk of having a child with a thalassaemia disorder should be offered PGD if the female partner is under 40 years of age at the time of treatment, and there is no living unaffected child from the current relationship.

■ If the woman has a thalassaemia disorder, her treating haematologist should be involved in the management plan prior to PGD.

24: Management of Non-Transfusion-Dependent Thalassaemias

■ A comprehensive DNA diagnosis (β globin mutations, α globin genotype, $Xmn1$ C→T polymorphism) should be undertaken as soon as the diagnosis of thalassaemia has been established.

■ Parents, carers, and patients should be counselled at diagnosis, and as often as needed thereafter, about the likely course of the condition and therapeutic options available.

■ During the first 3-5 years of life, children with thalassaemia should be monitored carefully and systematically for evidence of thalassaemic features which may require regular transfusion therapy. Older children, adolescents and adults with a diagnosis of NTDT should continue to be monitored regularly, for consideration of indications for transfusion, and for iron loading, pulmonary hypertension, and extramedullary haematopoietic masses in particular.

■ Complications of NTDT should be identified at an early stage and treated promptly.

Introduction

1:   Context, and Aims of This Document

"Having access to out of hours transfusion has allowed me to achieve success academically and professionally, which means I pay more tax and live a normal life."

"Thalassaemia has never affected my education/career but I have never been able to build a relationship. My family think I am too ill."

"Thalassaemia has never hindered me doing the things I want to do, it has only limited the amount on occasions."

Thalassaemia in the UK

Modern treatment of thalassaemia in the UK is for the most part a success story. Children born in the UK today with thalassaemia are expected to survive to adult life in good health, to lead essentially normal lives in respect of career and family; and to live a normal or near normal lifespan. Unfortunately, this outcome is still not universal throughout the UK. Premature deaths still occasionally occur and children still develop complications such as growth failure and hypogonadism due to endocrine damage. These complications are related to transfusional iron overload and the ability to adhere to iron chelation therapy (Modell and Berdoukas 1984; Olivieri *et al.* 1994; Brittenham *et al.* 1994). Despite strenuous efforts by clinicians to develop networks for care, in order that all patients can access highly specialist care as needed, in 2016 outcomes and experience remain consistently better in a some areas than in the UK as a whole (Modell *et al* 2000; Porter and Davis 2002; WMQRS Review of Services for Haemoglobin Disorders for Children 2010-2011, WMQRS 2013).

Many thalassaemia patients in the UK are still managed in clinics of less than 10 patients (Modell *et al.* 2001; WMQRS 2011; WMQRS 2013), reflecting the patchy distribution of patients. Outside the North West of England, the West Midlands and some London areas, the majority of centres providing specialist care for haemoglobinopathy patients have a relatively small number of thalassaemia patients alongside a much larger population of sickle cell patients. Hence the number of centres which can realistically be regarded as providing specialist care for thalassaemia are few and far between. Further work is needed to ensure that the original aim of the first edition of the *Standards* (2005) is met – namely, that every patient, regardless of location, should have access to optimal, specialist management guidance and supervision, as well as local routine care.

Improving thalassaemia care

There have been a number of significant developments since the 2nd edition of the *Standards* in 2008. A National Haemoglobinopathy Registry was launched in 2008, with the aim of informing commissioning and healthcare planning by collecting information regarding numbers of affected people looked after at the various centres, and recording aspects of their clinical care and outcomes. Additionally, in 2010 the National Haemoglobinopathies Project produced a report on commissioning specialist haemoglobinopathy care; and an All Party Parliamentary

Group for Sickle Cell and Thalassaemia has been established, currently chaired by Diane Abbott MP. A Clinical Reference Group (CRG) for haemoglobinopathies which includes clinicians, commissioners, public health experts and service users was set up under the auspices of the National Programme of Care for Blood and Infection to advise NHS England on the best way these specialised services should be commissioned and provided. The CRG prepared the service specifications *Specialised Services for Haemoglobinopathy Care (All Ages)* (NHS England 2013) and has recently developed a clinical commissioning policy proposal for the treatment of iron overload in patients with chronic inherited anaemias, including the thalassaemias. The policy proposes that monotherapy with each of the three licensed iron chelator drugs – desferrioxamine, deferiprone and deferasirox, and the most frequently used combination of desferrioxamine with deferiprone, should be routinely commissioned for patients. It emphasises that MRI scans to quantitate tissue iron should be available for monitoring, that oversight of iron chelation should be undertaken by experienced clinicians at a Specialist Haemoglobinopathy Centre, and that decisions should take into account the clinical circumstances together with the views of the patients and carers. This policy is under consideration by the Clinical Priority Action Group (CPAG) and a decision is expected in summer 2016.

The NHS Screening Programme for Sickle Cell and Thalassaemia has been fully rolled out throughout England (2009); and Wales and Scotland have set up their own screening programmes. It should be noted however that some of the aims of the Screening Programme , which included early diagnosis of carrier couples and timely offer of prenatal diagnosis, have proved challenging; with only 40% of PND tests being carried out by 12+6 weeks gestation in 2014/15 (Public Health England 2014a). Work to address the complex issues surrounding the late detection of couples at risk is ongoing. Births of babies affected by clinically significant thalassaemias have remained consistent at between 20 – 30 affected births per annum(Public Health England 2014) A positive development from the work of the NHS Sickle Cell and Thalassaemia Screening Programme and the Newborn Outcomes Information Governance and Clinical Group has been the successful pathway into care for affected babies. Even though the detection of clinically significant thalassaemia is not a primary aim of the newborn screening programme, 99% of screen positive babies (both sickle and probable beta thalassaemia) were referred to specialist services by 8 weeks of age (Public Health England 2014).

The UK Forum for Haemoglobin Disorders, working with the West Midlands Quality Review Service (WMQRS) developed a comprehensive set of Quality Requirements drawn from the 1st edition of the Standards, and the parallel sickle cell disease care standards; and these have been used to introduce a system of 'peer reviews' to assess service provision across networks for care. Since 2008 three peer reviews have taken place: *WMQRS Review of Services for Haemoglobin Disorders for Children 2010-2011*, *WMQRS Review of Services for Haemoglobin Disorders for Adults 2012-2013* and *WMQRS Review of Services for Haemoglobin Disorders for Children and Adults 2014-2016*. The resulting reports (WMQRS 2011; WMQRS 2013; WMQRS 2016) highlighted a number of issues, of which the most worrying is the lack of resources in terms of experienced specialist medical and nursing staff. These highly complex patients cannot be successfully managed without a holistic, individually tailored treatment regime supervised by skilled and experienced clinicians. Networks for care and annual reviews by expert clinicians should have eliminated most of the inequalities in care which existed before the publication of the first *Standards* in 2005; and there is no doubt that improvements have been made. The majority of patients report that they are receiving their essential monitoring tests regularly, including heart and liver MRIs, DXA scans (UKTS national survey 2016) and this is to be welcomed. However there are still areas which do not seem to be adequately covered by the network system and patients who have never had an appointment with an expert clinician.

The internet and social media has opened up the world for everyone, and patients are better informed than ever before. They compare treatment and avidly research the latest developments, often becoming very knowledgeable and increasingly feeling equipped to become active participants in the management of their condition.

Organisational aspects of thalassemia care

The last ten years have seen radical changes in the treatment of thalassaemia. Since the introduction of the oral chelators deferiprone and deferasirox, the use of desferrioxamine has declined rapidly, and the fact that so many patients now use oral chelators has led to changes in how thalassaemia is perceived and experienced, for those living with the condition and for the numerous agencies involved in the management of their health and their lives. The new freedom from "the pump" has brought new responsibilities and expectations; more than ever before, people who have thalassaemia are expected to work full time to support themselves. Many do, but the services in many places have not adapted to accommodate their needs. For the most part, services are still organised on the basis that the thalassaemia patient has little else to do but attend hospital appointments. It would be worthwhile for every doctor and every nurse who looks after patients with this condition to stop and try to imagine how their own life would be if they were living with thalassaemia. Working full time, looking after a family, expected to keep performing at the same level for the entire month as the haemoglobin level gradually falls, trying not to get irritable with children, family members, colleagues – and then a nurse casually tells you your blood isn't ready and you should come back tomorrow, when your employers are already making irritable noises about the amount of time you have to take off! A person who has thalassaemia, however well qualified, however eminent in his or her profession, however meticulously organised in life, will always be dependent on the opening times of their day unit.

Some advances in treatment have led to unexpected developments. For example, before the first edition of the *Standards* was published in 2005, the thalassaemia community naïvely imagined that with the wide availability of oral chelators, the problem of adherence to chelation therapy would be solved finally and fully. This has not proved to be the case however, and the community has come to realise that, far from solving the issue, we have merely raised other questions about the interplay between the physical and the psychological. The international thalassaemia community faces a dichotomy between two groups of patients who are at risk of serious complications from iron overload – those who have no access to chelator medication, and those who, for poorly understood reasons, cannot take that same medicine even when it is made freely available to them, and often even delivered to their homes. In the UK we now have a cohort of beta thalassaemia major patients who are approaching their sixties. These are people who were told they would not survive beyond childhood, and who saw many of their fellow thalassaemia patients succumb to iron overload in the 1970s and 80s. Thanks to a modicum of luck and the persevering skill of a few pioneering clinicians, this lucky few remain to tell us about the days before chelation; when they were all too aware that every transfusion brought them closer to death from heart failure. They remember the dreaded, agonising "bolus" injections of desferrioxamine which were their only hope of survival, and how they welcomed the advent of the early pumps (as big as typewriters) as a less painful method of administration. The frustration of these older members of the thalassaemia community is tangible when they talk to a teenager who doesn't take deferasirox because it tastes chalky.

Thalassaemia patients in the UK for the most part 'have never had it so good' – with modern treatment, improvements in overall health and life expectancy, the ability to become parents, to enjoy careers and family life. The fear of early death has largely vanished; unlike their predecessors in the 1980s UKTS members do not open every newsletter to see obituaries of youngsters in their twenties. Patients no longer expect to die young, but with the decline of these fears new social concerns have arisen – peer comparison for growth and maturity, infertility, cultural problems such as being regarded as "sick" and therefore unmarriageable. Now knowing that they need not suffer an early death, people with thalassaemia quite reasonably want to live the same lives as their contemporaries, they want to look the same and act the same; and they find it harder and harder to accept any restrictions imposed by their condition. Most of these issues are beyond the scope of clinicians to resolve, but they are essential elements which contribute to the outcome of treatment for each patient. To examine all these issues we need expert psychology support and research; but the evidence from even the most recent round of peer review assessments of services is that psychology services for thalassaemia are among the most under resourced, and in many areas are practically non-existent.

Aims and scope of these Standards

In this document we have again outlined a model of care, and have defined standards for delivery of care, for patients with thalassaemia. We have addressed predominantly the needs of those who are transfusion-dependent (thalassaemia major), and, in a separate section those with non-transfusion-dependent thalassaemia, NTDT (Section D: Non-Transfusion-Dependent Thalassaemias). It is not intended to offer full clinical guidelines as these are well covered in other available published guidance. Overall our central focus is on the way in which services are structured and delivered.

In this edition, we have ordered the main chapters in line with a pathway for a person with thalassaemia, from birth into older adulthood. This works well in parts, but is to some extent artificial as many potential complications span the age ranges to varying degrees. Some chapters need therefore to be read together – for example chapters 12: Growth, Development and Endocrine Function , 18: Management of Impaired Glucose Tolerance and Diabetes Mellitus , and 19: Management of Bone Problems . Growth, development and endocrine function, as well as fertility issues, are now included in the 'Core Standards' section, in recognition of the importance of these aspects of care for patients and their families.

A chapter on Quality Assessments, peer review, has been added to Section A: Organisation of Thalassaemia Services and a number of new clinical chapters have been introduced: 18: Management of Impaired Glucose Tolerance and Diabetes Mellitus , 21: Management of Dental Problems, and 23: Prevention Using Prenatal Diagnosis and Preimplanation Genetic Diagnosis.

Appreciating the central role of the UK Thalassaemia Society in planning and implementing changes, we have as before included at the start of each section, a number of relevant quotations, derived largely from the 2016 national survey of adult patients organised by UKTS. We hope that these enliven the text, as well as giving insight into how patients experience their condition and prioritise the issues they face.

The document is aimed primarily at healthcare professionals who care for people with thalassaemia, and technical terms are mostly used without explanation in the text. However, we hope that it may also be of interest to patients and their families, and a Glossary is included (Appendix B) to help understanding of any unfamiliar terms.

Levels of evidence

Apart from the chapter on monitoring and management of iron load, which is fully referenced, the content of the standards is largely practical clinical and organisational guidance, most of which is not subject to formal trials or evidence base and in most areas, as previously, we have relied largely on published retrospective analysis of clinical data and non-randomised, non-controlled interventions, expert opinion, and the views of patients and families. For these standards we have adopted two grades of practical interventions:

- **Requirements** – being that which providers must do to ensure safe and adequate care: where omission could lead to poor clinical outcomes, and
- **Recommendations** – being that which would be beneficial and which providers should try to do, but which would be less likely to have a direct impact on clinical outcomes.

Conclusion

In summary, we feel that there is cause for real optimism in the way that services for the management of thalassaemia and sickle cell disease are developing in the UK. We trust that everyone working in thalassaemia clinics across the UK will read these standards and apply them locally. Additionally, we expect health service managers and commissioners to be fully aware of the challenges presented by managing these disorders and to work to ensure equitable, high quality care for all those affected. We hope that patients and user groups will also find the document helpful, supporting them in negotiating for the best possible care.

2: Thalassaemia – Clinical Features and Treatment

"You can never forget about thalassaemia because it's always there in the background. You need treatment at all times."

"I feel there is always someone in a worse situation than me so I just get on with it."

"Treatment has got better over the years and I am now 51 years of age. I usually see my haematologist every 6-8 weeks and she is very supportive."

Pathophysiology and geographical distribution

Beta (β) thalassaemia is a genetic disorder of haemoglobin production. It is inherited in an autosomal recessive pattern (apart from in very rare 'dominant thalassaemia' mutations), and is common in people originating from the Mediterranean, the Middle East, South Asia, South East Asia and the 'Far East'. In the UK, β thalassaemia major is more or less restricted to ethnic minority populations, the largest groups being Cypriot, Indian, Pakistani and Bangladeshi (Modell *et al.* 2001). The disorder is due to a range of mutations associated with the β globin gene, resulting in reduced or absent production of β globin, one of the constituents of the adult haemoglobin molecule (HbA). Reduced β globin production, leading to excess free alpha (α) globin chains, damages red cell precursors in the bone marrow. This results in ineffective erythropoiesis, severe anaemia and compensatory erythroid marrow hyperplasia.

Classification

Homozygous β thalassaemia can be broadly categorised clinically as:

- β thalassaemia major (*BTM* or *TM*), in which haemoglobin production is so reduced that normal growth, development and quality of life can only be achieved by regular red cell transfusions from infancy. Death at an early age is inevitable if no transfusions are given. Where the term 'thalassaemia' is used without qualification, it usually refers to β thalassaemia major.

- β thalassaemia intermedia (*BTI* or *TI*), in which a reduced amount of haemoglobin is produced, sufficient for growth and development without the absolute requirement for regular transfusions. Growth may fail, and other complications may develop in later childhood and adulthood, requiring regular transfusions.

However, there is a continuum or 'grey-scale' of clinical severity, with no absolute cut-off between the two. The term 'non-transfusion-dependent thalassaemia' NTDT is now commonly used to describe those who may require occasional, but not regular transfusion, in contrast to those whose haematology, symptoms and signs have required them to be treated with regular transfusions - 'transfusion-dependent thalassaemia' or TDT. The compound heterozygous states of β thalassaemia with a thalassaemic haemoglobin variant (including HbE, Lepore, Knossos) or

an alternative thalassaemic mutation (e.g. δβ thalassaemia) often result in NTDT, but can cause transfusion-dependent thalassaemia.

Haemoglobin H disease is a result of deletion of three of the four α globin genes or from non-deletional mutations which inactivate them. It is usually a mild condition with features typical of a chronic haemolytic anaemia, although a few individuals develop more severe problems, including transfusion dependency. If all 4 α globin genes are affected, the result is intrauterine anaemia and usually the early stillbirth of a hydropic infant (Bart's Hydrops fetalis) as α globin chains are required for fetal haemoglobin.

These standards apply chiefly to transfusion-dependent patients, and additional issues for those with non-transfusion-dependent thalassaemia are outlined in Section D: Non-Transfusion-Dependent Thalassaemias .

In a small number of cases worldwide to date, it has proved feasible, if prenatal diagnosis establishes that a fetus has α thalassaemia major, to give intra-uterine transfusion to sustain it until birth. This treatment needs to be started early, as otherwise serious disability results. After birth, such an infant will need to continue on a regular transfusion regimen as for BTM. Separate guidelines are necessary for the antenatal management of this condition.

Haemoglobinopathy screening

Population and antenatal screening to identify carriers of β thalassaemia is feasible within a health care system. Identification of a carrier parent, usually the mother, followed by testing of the partner allows identification of couples at risk of having an affected child. Having been counselled they can make informed choices about prenatal diagnosis and termination of an affected fetus. The effective delivery of this service has led to a great reduction in affected births in several countries. Systematic screening of pregnant women in England is now in place, through the NHS Sickle Cell and Thalassaemia Screening Programme for linked antenatal and newborn screening.

Newborn screening is primarily aimed at detecting babies with sickle cell disease, in whom early interventions can prevent fatal complications before clinical presentation. However, most babies with β thalassaemia major will be identified by the same screening test, and early diagnosis can reduce morbidity associated with late presentation, and anxiety for affected families.

Clinical features of untreated thalassaemia

Babies with homozygous β thalassaemia are initially asymptomatic, as the major haemoglobin at birth is fetal haemoglobin (HbF). As a result of the physiological switch from HbF to HbA, the latter becomes predominant by about four to six months of age, and it is from this stage onwards that infants with thalassaemia major can become symptomatic. Clinically, the presentation is insidious, with poor feeding, faltering growth, pallor, and increased susceptibility to infection. If untreated, progressive anaemia and metabolic stress eventually cause heart failure and death. There is enlargement of the liver and spleen. The ineffective expansion of the erythropoietic marrow results in bone thinning and deformity. Untreated, children with BTM die from heart failure or infection before the age of five years.

Standard treatment

Standard treatment consists of regular blood transfusions given every three to four weeks. Transfusions correct the anaemia, enable growth and normal activity levels, prevent enlargement of the spleen and inhibit the erythroid marrow expansion. The most important long-term problem associated with regular transfusions in thalassaemia is iron overload. Blood contains iron which cannot be excreted from the body, and a typical thalassaemia patient on a regular transfusion programme will accumulate 0.3-0.5mg/kg of iron per day. Excessive iron is toxic, the most vulnerable organs being the heart, liver and endocrine glands. Once the body has accumulated 12-24g of iron significant clinical manifestations of iron toxicity can be expected (Gabutti and Borgna-Pignatti 1994). Without treatment to remove the iron, the majority of patients developed cardiac problems and died of heart failure by the age of 20. Therapy to

remove or 'chelate' excess iron is therefore essential and this must be started within a year or so of starting regular transfusions.

The established regime requires subcutaneous infusions of the chelating agent desferrioxamine given 5-7 nights per week over 8-12 hours. This regime can stabilise the body iron load at an acceptable level in a majority of patients, and was shown to reduce the risk of cardiac disease, and to improve survival (Modell and Berdoukas 1984; Olivieri *et al.* 1994; Brittenham *et al.* 1994). Other complications of iron overload, such as short stature and hypogonadotrophic hypogonadism may also be prevented (Olivieri 1997). The main problem has been adherence to the regular subcutaneous infusions of desferrioxamine. The infusions are time consuming to set up, and require introduction of a subcutaneous needle on each occasion followed by continued attachment to an infuser device over 8 -12 hours. They are unpopular and often resisted, especially by older children and teenagers, because they can cause local discomfort and because having to undertake this onerous self-treatment sets the child apart from his or her peers. In large, well organised thalassaemia centres, physical and psychological problems with adherence can be addressed methodically, and excellent survival was seen in younger patients (Porter and Davis 2002). In the UK as a whole, however, survival did not improve to the extent hoped 30 years ago when desferrioxamine became available, and this is probably due to the problems thalassaemia patients experience in tolerating regular self-administered infusions (Modell *et al.* 2000).

Standard treatment now includes the possibility of using a licensed oral iron chelator, deferiprone (Ferriprox®, ApoPharma) or deferasirox (Exjade®, Novartis). These can help greatly where adherence to parenteral desferrioxamine infusions has been a problem, and have some additional therapeutic advantages which are described in chapter 10: monitoring and management of iron load. At least in part due to more tolerable and effective regimens using oral iron chelators, there is growing evidence that life expectancy across whole population has improved over the last two decades (Telfer *et al.* 2006; Borgna-Pignatti *et al.* 2006).

Constant monitoring for complications, and their timely treatment where possible, goes hand in hand with organising regular blood transfusions and managing chelation therapy throughout the patient's lifetime. As in other chronic lifelong conditions which demand a high level of medical intervention, it is not just the technical care that affects the patient's wellbeing, but also the way in which that care is delivered. Provision of patient-centred services is one of the most important factors, and clinics should take particular care to minimise disruption to education, employment and family life, allowing patients to live as fully and normally as possible. Such care can materially improve survival by enhancing adherence to difficult treatment regimens.

Section A:
Organisation of Thalassaemia Services

3: Networks for Care and Commissioning

"We desperately need more specialist doctors and nurses outside London, there are not enough experienced medical and nursing staff in other areas."

"I don't rely on my local centre for expert thalassaemia related queries as we don't have anyone there who is a specialist."

Aims

To optimise care for all patients, wherever they live, by giving access to complex acute care and regular specialist multi-disciplinary input, while ensuring that routine treatment is given as conveniently as possible, close to the patient's home.

To provide a service emphasising prevention, early detection and management of complications, and improved quality of life.

To ensure good communication between patients and families, and the various agencies involved in their welfare, including the team in the Specialist Haemoglobinopathy Centre (SHC), the Local Haemoglobinopathy Team (LHT), Primary Care and, where relevant, social services and education.

Standards

■ All regions must deliver care for people with thalassaemia through a clinical network incorporating local haemoglobinopathy teams (LHT) and one or more Specialist Haemoglobinopathy Centres (SHC).

■ Established pathways within the network should ensure that all patients have access to an SHC – for their regular management if living nearby and for a comprehensive review of their condition and care at least once a year, at an 'annual review visit', if they live more distantly and receive their regular care from an LHT.

■ Specialist clinical advice should be available from the SHC at all times, for patients who present acutely to their local centre with complications the local team may not be experienced in managing. There should be the facility for urgent transfer of a patient to the SHC for complex care.

■ The network should have sufficient resources (health care professionals, management and administrative staff) to function effectively, and should develop systems for information sharing, clinical governance, accountability and staff development.

■ A 'key contact' health professional will be designated for each patient.

■ Patients and carers should receive regular education, supervision and support in thalassaemia care, chelation therapy and other home treatments.

■ All health providers within the network – primary care teams, LHTs and SHC – should record and exchange information relating to clinical events, monitoring investigations, and changes in treatment. Correspondence should always be copied to patients/carers.

- Consent should be sought from all patients for entry of their details on the National Haemoglobinopathy Registry, and data entered in a timely fashion to assist audit and assessment of good quality outcome information.
- Patients and carers should be involved in making decisions about management and delivery of care.
- Patients and carers should have access to peer support groups.

Background

Hospital care is, for the majority of patients with thalassaemia, inevitable – for transfusions, for often complex clinical and diagnostic assessments and their interpretation, and for decisions about chelation and other necessary medications. Ensuring that routine hospital care can be accessed locally, at times to suit the patient and family, while meeting the need for every patient to have access to skilled specialist healthcare professionals with particular interest, experience and knowledge of the condition, has led to the development of care networks.

The hospital services within the networks consist of Local Haemoglobinopathy Teams, LHTs, where much routine care should be delivered, linked to a large Specialised Haemoglobinopathy Centre, SHC, where a multi-professional specialist team is based, overseeing services and individual patient management at all the linked LHTs. This is because best practice guidance changes continually, particularly about iron chelation regimens and the management of specific complications, as clinical trials and studies mature and results are disseminated and discussed. All patients should benefit from the chance to discuss their care with professionals who are highly experienced and keep themselves comprehensively informed about the condition and its management.

The intention is that every patient should be known to, and seen at least once a year by, the SHC team, at an 'annual review' visit to ensure their management is in every aspect updated and appropriate. The content of the annual review, and arrangements for its delivery, are the subject of the next chapter. SHCs are required to agree with their LHTs an additional list of issues for which consultation in between annual reviews is required.

Additionally, every patient should have access to specialist advice at any time – day or night - they present with acute clinical problems, which may not be within the range of experience of their local clinicians.

Hospital services for children and adults with thalassaemia, sickle cell, and other inherited anaemias, have been commissioned by NHS England as specialist services since April 2014 (Specialised Services National Definition set no 38). Commissioning is a process by which health needs are identified and services bought to meet those needs. Where possible, an evidence-based approach is used in procuring services and in monitoring their delivery. Specialist services are designated as those which are low volume and high cost or are very complex to deliver.

Clinical Reference Groups (CRGs) bring together groups of clinicians, commissioners, public health experts, patients and carers to advise NHS England on the best ways that specialised services should be provided (www.england.nhs.uk/commissioning/spec-services/npc-crg/), and there is a CRG specifically for haemoglobin disorders services. CRGs lead on the development of clinical commissioning policies, service specifications and quality dashboards. They also provide advice on innovation, conduct horizon scanning, advise on service reviews, identify areas of unexplained clinical variation and guide work to reduce variation and deliver value. CRGs, through their Patient and Public Voice (PPV) members, also help ensure that any changes to the commissioning of specialised services are co-produced with patients and the public.

The service specification B-08 (NHS England 2013) describes the aims and objectives of the service and pathways of care. Care will be delivered by a specialist haemoglobinopathy centre (SHC) acting in a hub and spoke model with other linked providers. The SHC, working with linked providers, is expected to deliver a network of care for all patients in the geographical region. The aim is to reduce levels of morbidity and mortality and improve the experience of all haemoglobinopathy patients by reducing inequities and improving timely access to high quality expert care.

In summary, in relation to thalassaemia in particular, the specifications include:

- Clinical leadership.
- Managing the results of newborn screening and ensuring timely entry into care.
- Management of complex patients using a multidisciplinary team approach.
- Initiation, modification and cessation of long-term transfusion regimes.
- Initiation, modification and cessation of iron chelation.
- Monitoring of complications including access to cardiac and liver MR scanning to quantify tissue iron.
- Acute management of severe and life threatening complications including:
  - Heart failure and cardiac arrhythmias.
  - Infection prevention and control.
  - Post-splenectomy sepsis.
  - Acute endocrine disturbances
  - Acute hepatic decompensation.
- Long-term specific therapy for complications (complex long-term conditions management) including:
  - Endocrine dysfunction.
  - Cardiac dysfunction.
  - Chronic liver disease.
  - Bone and joint problems including osteoporosis.
  - Gallstones.
  - Ankle ulceration.
  - Iron overload.
  - Pulmonary hypertension.
  - Thrombosis.
  - Chronic pain.
- Peri-operative management of thalassaemia patients requiring surgery.
- Management of pregnant women with thalassaemia.
- Timely access to critical care (not always at the SHC for paediatrics, but pathway to another).
- Access to Bone Marrow and Stem Cell Transplantation (pathway to a recognised centre)
- Clinical Governance and Audit including
  - Reporting all adverse events to commissioners and the National Haemoglobinopathy Registry (NHR)
  - Undertaking an agreed number of clinical/quality audits.
  - Participating in any peer review process.
  - Reviewing all clinical guidelines and protocols across the network including those produced by community providers.
  - Reviewing and amending pathways to promote integrated care.
  - Ensuring the quality of care provision and delivery.
  - Supporting local and national benchmarking.
- Overseeing compliance with care pathways and standards for all patients in the network.
- Providing expert care and advice at all times.
- Patient and carer engagement.
- Data collection, management and submission.
- Clinical education and training across the network.
- Leading on research and development.

Quality Standards for the delivery of care are outlined in the service specification and have been developed by the UK Forum on Haemoglobin Disorders in conjunction with the West Midlands Quality Review Service for assessment by the peer review programme (WMQRS 2016).

There is no recommended size, in terms of the numbers of patients managed, for a Specialist Centre. The demographics of people living with thalassaemia are such that very large centres exist only in the North West England, West Midlands and North and East London. Centres outside these areas who manage relatively small patient numbers are encouraged to liaise with the larger Centre teams for staff training rotations, and for discussion of complex or atypical case presentations. The idea of a national 'MDT' for discussion of such individual patients is being considered through the Clinical Reference Group, in conjunction with the UK Forum for Haemoglobin Disorders.

It is recognised that to provide all of the Service Specifications across a whole clinical network places a great deal of responsibility on the members of the Specialist Team, and requires much additional work. How this can best be supported by the commissioning process is under current review. Recommendations for appropriate staffing are given in a workforce review (Ryan 2015).

Although a degree of hospital dependence is inevitable, much routine care such as the administration of iron chelation and other medication is undertaken by the patient and family at home. People who understand fully their condition, are involved in every care decision, and are guided and supported in self-care by primary and community care staff as well as hospital teams, become truly expert patients and this helps in ensuring optimal adherence to treatment, and maximising quality of life and longevity. Focus on education and support for the family from the time of diagnosis, and throughout life, is critical.

A designated 'key contact' health care professional, with whom the family will become familiar and comfortable, is essential for streamlining access to services, clinic appointments, transmitting results of investigations and troubleshooting medical and psychosocial complications as they occur.

Regular transfusions each month are the mainstay of treatment for those with thalassaemia major, but if the organisation for delivery is poor and inflexible, this causes great inconvenience to the patient and family, and impairs quality of life. A well planned process is required, delivering treatment close to the patient's home or work. Many patients prefer to arrange their transfusions during the evening or overnight, in order not to interfere with school/college/work commitments. Revised guidance by 'SHOT' (serious hazards of transfusions) that 'transfusions should be given with the same attention paid to observations whatever the time of day or night', over-riding their previous guidance that transfusions should only be given out of hours where clinically urgent, should help units to work toward this provision (Bolton-Maggs 2014).

Communication is a key element in efficient functioning of a care network. When a patient is being treated by multiple agencies, relevant information needs to be meticulously shared to avoid omission or duplication and to optimise treatment. This is more challenging but perhaps particularly important where there are communication or language difficulties. Patient-held records can be an effective way of transmitting information between clinical staff in different clinics, and patients and families, although in practice they have never become very popular or routinely used in the UK.

Collecting systematic records of all affected individuals is essential in planning, commissioning, delivering and monitoring care for long term conditions. The National Haemoglobinopathy Registry (NHR – www.nhr.nhs.uk) is an established platform for collection of all necessary data. It is being continually updated and refined to maximise its use for delivery and audit of services. Every patient with thalassaemia should be given information about the NHR, and asked for consent for their details – including any adverse events and results from annual reviews – to be entered on it. Once consented, timely data entry will support many of the governance and audit requirements of the network.

Requirements

◆ Once the diagnosis of thalassaemia is established, the parents must be given the diagnosis by a knowledgeable professional, often a specialist nurse, who can start to explain the condition

and offer some written information, and provide contact details of the UK Thalassaemia Society and any local support groups.

◆ This should be followed up by an early clinic appointment, usually with a Paediatrician, Paediatric Haematologist, or Haematology Consultant with experience of looking after children with the condition. This may be at the LHT but, if local experience is limited, should be at the SHC. Further discussion of the condition will include the subtleties of whether regular transfusions are likely to be necessary, when they might start, and the implications of this. The importance of the family as central care-givers should be emphasised.

◆ If the initial clinic visit is not at the SHC, a referral to the SHC should be made with a view to the family seeing the specialist team early, and before transfusion has been necessary if at all possible.

◆ It is important to check that the information given is understood by the family, and when needed, to use health advocates who can communicate in the appropriate language and cultural context.

◆ The family should be given the details of their 'key contact' at the LHT and SHC, and meet them as soon as possible.

◆ The patient's primary care team should be offered information about the condition and advised about possible acute presentations and their significance.

◆ Once regular care is established, arrangements are made for regular review by the SHC team at least once a year, and between times as necessary.

◆ Clinic letters and investigation results must, throughout the care pathway, be exchanged between the LHT, SHC, and primary care team, with the patient/family copied into all correspondence.

◆ LHTs will offer pre-transfusion compatibility testing, and organise and deliver routine transfusions once the need for them is established by the SHC. The LHT will provide regular prescriptions for medications as agreed with the SHC, check the child/adult before each transfusion in the clinic or day care setting, organise some if not all of the routine assessment checks, 'troubleshoot' any symptoms or problems, and offer support to the patient and family.

◆ For patients living close to the SHC, routine and specialist care will be delivered there.

◆ Out of hours/weekend phlebotomy, clinic appointments, and transfusion facilities should be available especially for older children and adults in full time education, and adults in employment.

◆ The SHC will draw up and communicate with the LHTs a list of indications for which they should be contacted, in or out of hours, for advice about a patient's condition, acute presentation or any other concern and/or for possible transfer of a patient to the Centre for complex care. The list will not be exhaustive, and the local teams are free to contact the specialist team at any time they have queries or concerns.

◆ At the SHCs, robust arrangements must be in place to provide expert consultant advice at all times. Hospitals with single-handed consultants should consider new appointments, and all should consider the need to make formal arrangements with other centres to cover out of hours periods when the haemoglobinopathy consultant is not on call, and for times they are on leave or other absence.

◆ Adequate numbers of sufficiently trained staff must be available at each point of care across the pathway

◆ Transition arrangements for passage from paediatric to adult services need to be considered at both the LHT for regular care, and the SHC for specialist reviews.

Recommendations

These figures assume a mixed patient group, including those with thalassaemia and sickle cell disorders, with a preponderance of the latter. In centres where there are larger numbers of thalassaemia patients, additional time is likely to be needed in the job plan.

Medical Staffing

Staff	LHT	SHC
Designated Consultant Paediatrician and/or Haematologist (depending on age spread of patients) providing a lead for the service. Thalassaemia will be a major interest and responsibility. The number of consultants will depend on the size of the Centre.		✓
Designated Paediatrician and/or Haematologist (depending on age of patients)	✓	
Named deputy for each	✓	✓
Middle grade cover (SpR/ST3 or above/Staff Grade) and consultant cover available out of hours	✓	✓

As a guide, suitable PA allocation for lead consultants would be:

- 1.5 PA for every 50 patients for direct clinical duties* made up as:
  - Clinics including specialist annual review (2.0 hours/week)
  - Ward rounds (1.5 hours/week)
  - Day unit attendance and ad hoc consultations, on call (1.0 hour/week)
  - Clinical administration and MDT meetings (1.5 hours/week)
- 0.25 PA for every 50 patients for supporting activities: NHR and data collection, audit, teaching, patient liaison, network participation
- 0.25PA CPD per consultant

Nursing Staffing

The key contribution of hospital and community based nurses to the acute and chronic disease management of sickle cell and thalassaemia patients should be acknowledged and numbers should be brought into line with those of other long term condition.

Job planning for specialist nurses must include adequate time to deliver RCN training competencies for hospital staff and to undertake audit and service development.

Staff to cover these roles are necessary:

Staff	LHT	SHC
Lead nurse for thalassaemia service, training, liaison, audit.		✓
Regular nurse(s) in ward area who can cannulate and start/supervise transfusions on day care unit, and also during evenings, overnight and week-ends	✓	✓
Specialist nurse outreaching into community (responsible for home visits, teaching parents to set up desferrioxamine pump etc.)		✓
Key contact - could be any of above, or an experienced transfusion practitioner.	✓	✓
Identified deputy for key contact.	✓	✓

Psychology Staffing

Staff	LHT	SHC
Clinical psychology, for children and adults.		✓
Access to named psychologists.	✓	✓

Other Specialist Staffing (not necessarily all on site)

Staff	LHT	SHC
Consultant Cardiologist.		✓
Consultant Paediatric and Adult Endocrinologist.		✓
Consultant Hepatologist		✓

Staff	LHT	SHC
Consultant Nephrologist		✓
Consultant Urologist		✓
Consultant Orthopaedic Surgeon		✓
Consultant General Surgeon		✓
Pulmonary Hypertension Team		✓
Fertility, contraception and sexual health services, including pre-implantation genetic diagnosis		✓
Consultant Obstetrician		✓
Dental team		✓
Allogeneic Bone Marrow Transplant team		✓

Access to other staffing and facilities

Staff	LHT	SHC
Appropriate laboratory support (transfusion and other, and access to molecular diagnostics).	✓	✓
Access to full range of diagnostic imaging including MR T2* and R2 (not necessarily on site).	✓	✓
Access to translation services	✓	✓
Access to Social Worker	✓	✓
Access to Dietician	✓	✓
Administrative support sufficient to ensure proper communication between patient and family/LHT/SHC/primary care teams.	✓	✓
Personnel to handle patient data and input to National Haemoglobinopathy Registry.		✓

Facilities

- Facilities for transfusion should be in a relaxed, preferable dedicated, day care area rather than in a conventional ward setting.
- For children, all facilities must be separate from adult services, and should be age appropriate, with availability of play therapy for younger children and entertainment/schoolroom facilities for older children.

4: Annual Review at Specialist Haemoglobinopathy Centre

"My consultant and specialist nurse both helped me create a suitable treatment plan for the coming year. I am pleased with the service I receive."

"The medical and nursing staff need to understand how thalassaemia impacts on our lives day to day and make sure we are referred regularly for all the necessary tests."

Aim

To ensure that all children and adults will have a comprehensive assessment by specialist healthcare professionals at least yearly, or more often if necessary, to optimise their care.

To ensure that patients and families are fully informed about their condition, are kept up to date about any possible treatment changes, and have a clear management plan for the year ahead.

Standards

■ Every person with thalassaemia will have the opportunity for their care and condition to be reviewed at least annually with a team of health care professionals who have particular experience in caring for thalassaemia disorders. This can take place during a visit to the Specialist Centre, or at an outreach clinic where members of the Specialist Team visit the local centre at which the person receives their routine care.

■ The assessment should cover all aspects of care including educational and lifestyle factors that may affect health or influence adherence to treatment.

■ Discussion of treatment options should include any new information which has become available, and an individual treatment plan for the next 12 months will be agreed.

■ A copy of the annual review consultation including the care plan will be copied to the patient or, for children, their parents as well as health professionals involved in their care.

■ Data should be entered into the annual review screens of the NHR for consented patients.

■ People in families affected by thalassaemia should be able to meet and gain support from other affected families at the Centre or in the community.

Background

Patients with these complex multi-system disorders require input from a range of specialist health professionals and access to investigations which may not be available everywhere. An individual case review by SHC professionals at least once a year will offer all patients access to optimal specialist care regardless of where they live. The annual review is intended to be a

comprehensive assessment of every aspect of the patient's treatment and condition to assess progress and identify any areas where treatment could be improved.

The National Haemoglobinopathy Registry (NHR) is a database for patients with thalassaemia and other inherited haemoglobin disorders and captures data including numbers of patients, adverse events, treatments and complications arising from transfusion, medication or iron overload. The annual review screens allow for collection of a consistent dataset. This national resource will provide information to help in future planning of service delivery and performance in relation to key outcomes of care. Participation is voluntary and all patients and their families should be given verbal and written information to enable them to give properly informed consent.

The NHS standard commissioning contract for specialised services for haemoglobinopathy care for all ages (B08/S/a) stipulates that a Specialist Haemoglobinopathy Centre (SHC)

- *will provide (or delegate) a multidisciplinary annual review for all patients living in its geographical area either on-site or as an outreach service. This annual review will include review of cardiac and liver MRI results for patients with thalassaemia.*

- *will register all consented patients in their geographical region on the NHR. For patients identified by the screening programme this will be at first paediatric review. The SHC are to ensure that individual records are complete and kept up to date, including adverse events and annual review data.*

Requirements

◆ The patient and family will usually visit the Centre for a pre-booked appointment. In some areas, a local agreement may be made for a Paediatrician and/or Haematologist from the SHC, often with a specialist nurse, to hold an outreach clinic. In areas where the designated SHC does not have specific thalassaemia expertise, arrangements will be made to link with another SHC with the appropriate experience.

◆ The SHC should agree with the patient's local team which investigations can be performed there and the results of these, together with information on clinical progress and treatment should be available at the time of annual review.

◆ At the visit, the consultation will be with the designated Paediatrician or Haematologist. Access to other specialist team members such as specialist nurses or clinical psychologist should be provided, ideally at the same visit, or at a separate consultation, if not possible.

◆ Assessment will be made of progress in general and a review made of the patient's and family's knowledge of the condition and they should have the opportunity to ask questions.

◆ The review should include:
  – Assessment of any new or ongoing symptoms.
  – Adverse events over the preceding 12 months
  – Transfusion management; assessment of pre transfusion haemoglobin levels, any transfusion related complications.
  – Results of monitoring tests for iron status.
  – Current iron chelation regimen, adherence, and consideration of whether it can be improved in terms of tolerability and efficacy.
  – Review of other medication.
  – Prophylaxis against infection for splenectomised patients (vaccinations and a supply of antibiotics).
  – Attendance at the appropriate specialist clinics (cardiac, endocrine, hepatology) for his/her age and clinical status. If not referral should be made.
  – Weight, sitting and standing height and review of growth charts (children).
  – Clinical examination with particular reference to heart, liver, spleen, pubertal status in relevant age group.
  – Education and work activities and aspirations, and lifestyle factors which may affect health.

– The issue of possible bone marrow transplantation, and consideration of referral to a transplant centre (see chapter 11: Referral for Blood and Marrow Transplantation). Once a discussion has taken place this should be noted and it is not necessary to repeat at each visit, unless the family wish to revisit the question or new circumstances have arisen e.g. pregnancy, birth of another sibling.

– Discussion regarding fertility and plans for conception/pregnancy, where relevant, including partner testing for any haemoglobin disorder.

– A measure of emotional and psychosocial wellbeing, and discussion of the possible value of referral for psychological assessment and support.

◆ After the visit the clinician should write a summary including any problems highlighted and recommended changes to management. Copies should be sent to the referring hospital, the GP and the patient/family.

◆ Where test results become abnormal between annual reviews, the local team should discuss them with the SHC team to decide on the need to refer/start additional treatment.

Recommendations

- Any specialist investigations should be planned so as to require the minimum possible number of hospital visits and, where logistically possible, should be combined with the annual review visit.

- It should be ensured that the patient/family has access to relevant written informational material. They should know how to access the UK Thalassaemia Society and be put in touch with any local support group or organisation. Ideally they should be able to meet other patients/families at the Centre.

- The annual review visit is also an opportunity to discuss with parents of an affected child plans for further pregnancies with reference to their choice regarding pre-natal diagnosis, pre-implantation genetic diagnosis, and testing/storage of cord blood.

- The patient's hand-held record, if used, can be completed at the end of the annual review visit.

- Following the visit data should be submitted to the NHR provided consent has been given.

5: Quality Assessments

> *"My life would be so much easier if only the day unit was open at weekends."*

> *"We need more specialist nurses and doctors – I cannot fault them for dedication but they are very overworked and don't have enough time for all our problems."*

Aims

To ensure that all patients with thalassaemia have access to appropriate clinical care, so as to optimise their chance of living a healthy, good-quality and long life with as few inconveniences and complications as their condition allows.

To provide an external independent review of thalassaemia services in the UK with the aim of highlighting any areas of sub-optimal care and improving quality and equity of care for patients.

To ensure findings from external review are presented to appropriate local and national bodies and are used to influence commissioning and policy development.

Standards

- An independent external peer review of thalassaemia services should be completed every two-three years.
- Results from this should be made available to the inspected services, to NHS Commissioners and NHS England.
- Commissioners should designate clinical networks, support the establishment and ongoing running of the networks and review outcome data from the network at least annually.
- Specialist haemoglobinopathy centres should have fail-safe mechanisms for enrolling all newborns with thalassaemia into clinical care.
- Specialist and local haemoglobinopathy centres should have enough medical and nursing time to care for patients with thalassaemia, and experienced support staff, aware of the issues facing patients with thalassaemias.
- There should be a clear process for transition from paediatric to adult care.
- There should be access to appropriate out of hours services.
- Adequate information should be provided for patients, and readily available comprehensive clinical guidelines for staff.

Background

Following the development of the *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK*, and similar standards for the management of patients with Sickle Cell Disease, the haemoglobinopathy community expressed a need to review services in the UK against these standards. The UK Forum on Haemoglobin Disorders, the UK Thalassaemia Society, the Sickle Cell Society, and the NHS Sickle Cell and Thalassaemia Screening Programme agreed that a peer review programme should be set up and worked with the West Midlands Quality Review Service (WMQRS) to develop this. The first programme of reviews of services for Children and Young People with Haemoglobin Disorders ran between 2010 – 11, reviewing 19 centres, and was followed by a review of Adult Services between 2012 – 13 which reviewed 32 teams. An

overview of both of these programmes of Peer Review and the report from each participating centre are available (www.wmqrs.nhs.uk/publications) This has been succeeded by a programme of joint reviews of children and adult services which commenced in 2014 and is nearing completion at the time of writing.

The first rounds of these peer reviews was intended to be developmental, aiming to improve the quality of services for children and adults with Haemoglobinopathies. Quality Standards were developed for the first peer review programme after extensive review by members of the UK Forum and patient groups and were modified for subsequent reviews. These were divided into standards looking at the following areas:

• Information and Support for Patients and their Families

• Staffing

• Support Services

• Facilities and Equipment

• Organisation of Services

• Guidelines and Protocols

• Service Organisation and Liaison with other Services

• Governance

Network and Commissioning Standards are also included in the latest review programme.

Peer reviewer training was provided for health professionals and patient representatives who were to be part of a review team, before each programme began. All specialist centres and non-specialist centres with a large population of haemoglobinopathy patients were offered the opportunity to take part in the programme and although participation in the programmes has been voluntary, all invited centres agreed to be visited.

Prior to the visit centres are asked to complete a self assessment against the quality standards and also to provide some background information on their service. The visit team comprises multidisciplinary health professionals (doctors, nurses, psychologists), managers, commissioners and patient and carer representatives. During the visit they review the evidence provided by the centre to demonstrate compliance with the standards, tour the facilities, interview staff and patients and assess the service against the quality standards, before producing a visit report. The programme is overseen by a steering group consisting of multidisciplinary health professionals, members of the WMQRS and patient representatives who meet regularly and review all reports.

While some findings of the peer review were local issues, several themes became apparent during the course of the review programmes. These included:

• The peer review programme supported national recommendations that haemoglobinopathy services should be provided by specialist haemoglobinopathy centres (SHCs) supported by local hospital centres (LHTs) providing care close to the patient's home, but found that there were few fully functional clinical networks and those that existed were informal and often based on historical referral patterns. LHTs were identified which did not have a robust link with a SHC and where referral patterns were poorly defined or non-existent.

• Data collection was poor and/or incomplete. Few of the centres reviewed during the initial visits were entering data systematically on the National Haemoglobinopathy Registry (NHR). In later visits many centres were enrolling patients on the NHR but few were routinely entering data for annual reviews or reporting all adverse events. The NHR is a valuable tool for data collection and once data is routinely entered will allow rapid and accurate collection of audit data.

• Some areas did not have 'fail-safe' arrangements to ensure that children identified by the screening programme accessed appropriate care and SHCs could not accurately enumerate all children for whom they had responsibility in the network. This led to a lack of audit of compliance with key standards for clinical care. Most SHCs had no formal data collection support and this role was performed by medical or nursing personnel.

• In almost every centre, services were provided by key medical and nursing personnel who were providing high quality care. The number of consultant and specialist nursing sessions was

rarely adequate to manage the number of patients cared for by the service and workload of specialist staff was often unreasonably high. Staff absence was not covered robustly leading to problems in providing consistent high quality care. Poor staffing levels resulted in a lack of training and often poor quality care outside of the haemoglobinopathy team. There was inadequate planning for staff support in areas with rapidly increasing patient numbers or where staff retirement was imminent.

• Provision of transition services was patchy with some services providing high quality support throughout transition and others having no transition programme.

• Support services are very important in providing high quality care, for example psychology support is key to achieving good adherence to therapy for adults and children with thalassaemia. Access to support services such as psychology and social work was variable and often not readily available.

• Most services could not provide planned care (transfusions, blood tests, clinics visits) outside normal working/school hours and this led to patients missing 1.5 to 2 days of education or work per month.

• The Quality Standards listed a range of patient information which should be available including description of services and information about thalassaemia and its treatment and complications. Whilst good quality information was available in some centres, in others it was limited or of poor quality.

• Engagement with service users and responsiveness to user feedback was variable between different services. This has been encouraged in the most recent round of peer reviews by provision of a patient survey which sites are expected to complete prior to their visit.

• A number of clinical guidelines were listed in the Quality Standards but were not available in all centres visited. These included:

    • Checklists for first out-patient appointment, routine monitoring and annual review

    • Transfusion guidelines including indications for transfusion, investigations prior to first transfusion and recommended number of cannulation attempts

    • Chelation therapy, including monitoring of iron overload

    • Management of acute and chronic complications of thalassaemia

    • Indications for referral for bone marrow transplantation

    • Management of non-transfusion-dependent thalassaemia

Requirements

◆ Each SHC should have clinical responsibility for a defined geographical area which has been agreed with the specialist commissioners. This clinical network should include SHCs designated for care of children and adults with thalassaemia, LHTs/linked providers and Community Care Providers

◆ Each SHC should monitor annual patient data from their network which should include as a minimum

    – Number of thalassaemia patients under active care

    – Number of new thalassaemia patients (newly diagnosed patients and transfers)

    – Number of thalassaemia patients having annual reviews performed

    – Numbers of thalassaemia patients on long term transfusion and on iron chelation

    – Adverse events in thalassaemia patients

    – Numbers of thalassaemia patients who died or became lost to follow up in the last year

    – This should be accompanied by patient enrolment onto the NHR and systematic reporting of annual reviews and adverse events.

◆ It is acknowledged that not all babies with thalassaemia will be identified by the newborn screening programme, but SHCs should have robust 'fail-safe' mechanisms for identified newborns and any other infants as they are diagnosed, into appropriate clinical care.

◆ Each SHC and LHT should have appropriate consultant, other medical, and nursing time for the number of thalassaemia patients under their care. This should include adequate cover for staff absence.

◆ Each SHC and LHT should have a clear transition process. This should include a named co-ordinator for transfer of care, guidelines for transition (with age of transition), joint meeting between children's and adult services, patient information about transition and arrangements for monitoring immediately following transition

◆ SHCs should have access to appropriate levels of support services (eg psychologists, social workers, play therapists) with an awareness of issues facing patients with thalassaemia

◆ SHCs and LHTs should provide facilities for out of hours transfusions, phlebotomy and out-patient clinics appropriate to the local population.

◆ SHCs and LHTs should have a full range of clinical guidelines to aid in clinical management of patients with thalassaemia. The LHTs should have access to all the guidelines developed by the SHCs, and can adapt these for local use if necessary. Alterations should be agreed by the SHC.

◆ Commissioners should agree the configuration of clinical networks and ensure that the SHCs have sufficient resource to support the network.

◆ Commissioners should ensure that all LHTs have formal links and referral pathways to SHCs so that all thalassaemia patients can be offered annual review, and management guidance as and when needed, by appropriate specialist clinicians.

Recommendations

• Commissioners should monitor the quality of care provided by SHCs and LHTs by reviewing their annual data outputs

• 'Fail-safe' mechanisms to enrol any newborns into care should be reviewed at least annually with the newborn screening laboratory.

• SHCs should have adequate resource to allow appropriate data collection which should include consent and entry, annual review and adverse reporting on the NHR.

• All Trusts should ensure that all patients with thalassaemia have appropriate access to support services including psychology, social work and play therapy

• SHCs and LHTs should have a full range of information available for patients and carers and should have mechanisms for receiving feedback from patients and responding to this feedback. An annual patient survey would be one way of meeting this.

• NHS England should ensure there is support for an on-going peer review programme.

Section B: Core Management Standards

6: Psychosocial Issues in Thalassaemia

"People don't and can't understand thalassaemia as they can't see from the outside how unwell you are and what you're going through every day of your life – especially when your haemoglobin is dropping before transfusion. It's like looking at a house, it might look OK on the outside but you can't tell what's happening on the inside."

"I wish they would offer counselling services to people who have thalassemia."

"Some people think you are diseased and don't have a right to the same emotions and relationships as everyone else. You are broken."

"I find it difficult to form relationships. The fear of negative attitudes from people plus my own lack of self-esteem and body image issues mean I am shy when meeting new people."

Aims

To promote the patient's capacity to adapt optimally to having thalassaemia.

To improve quality of life and emotional wellbeing among patients.

To support patients to manage their health alongside their normal lives.

To minimise the negative impact of thalassaemia on emotional wellbeing.

To reduce levels of emotional distress and the effect such distress can have on physical wellbeing and engagement with treatment.

Standards

■ Consideration of the psychosocial demands and support needs of living with thalassaemia is a key role and responsibility for all professionals involved in the provision of care for people with this condition.

■ Consideration of the family context and developmental/life stage of the person with thalassaemia is key to ensuring that care and treatment recommendations are individually tailored and appropriate for each patient.

■ Psychosocial support alongside specialist psychological care should be provided as a standard part of thalassaemia clinical care, in both paediatric and adult services.

■ Core staffing of Specialist Haemoglobinopathy Centres should include a clinical psychologist with a special interest and experience in thalassaemia.

Background

Living with physical illness can be difficult and upsetting (Christie and Khatum 2012). The physical and emotional disruption caused by illness, along with the potential demands and the toll ill health places on the individual can be substantial. Illness challenges our sense of health, control, stability and self, and impacts our day to day life and relationships with others. Chronic illness can have particularly life-changing effects: rather than involving a full return to health and normal life, it demands that the individual must adjust to and accept some level of ill health and manage periods of remission and exacerbation over time (Rolland 1984; Rolland 1987). Serious chronic illness requires permanent changes to normal life and an ability on the part of the individual to continually readjust and redefine goals and personal identity, making changes to his/her way of living and being (Fennell 2003).

As a chronic, lifelong and life-limiting condition, thalassaemia poses multiple and severe challenges (Anionwu and Atkin 2001; Politis 1998). Alongside the physical symptoms of thalassaemia, and its impact on family, relationships, emotional wellbeing and quality of life, the child or adult with thalassaemia must also cope with invasive, complex and demanding treatments, frequent hospital visits, and a lifelong reliance on health services. Thalassaemia has an impact on both physical and emotional functioning as the individual must adjust to the impact illness has on his/her physical wellbeing and on his/her hopes and ambitions for life. Feelings of difference, uncertainty, anxiety, helplessness and loss are common and the individual must make physical and emotional adaptations to build a life that incorporates illness, managing physical symptoms and treatments while struggling to maintain a sense of self-worth and normalcy (Atkin and Ahmad 2001; Georganda 1998).

Not only does growing up with a chronic medical condition present significant challenges to children in accomplishing developmental tasks (Eiser 1993; Immelt 2006) but high rates of depression and anxiety are consistently found among seriously physically ill adult populations (Royal College of Psychiatrists, 2012). Given that a number of psychosocial factors are known to influence patient adjustment and adherence (Goldbeck *et al.* 2000; Joshi 1998), failing to provide psychosocial care, as part of standard care, in thalassaemia runs the risk that higher levels of untreated emotional distress will lead to lower treatment adherence, poorer self-management and reduced clinical outcomes. Many patients acknowledge that the ways in which their doctors and nurses approach them, and the messages and expectations they convey in clinical interactions, are centrally important to the way in which they think about themselves and their illness, so the psychosocial wellbeing of the individual needs to be a significant concern for the whole team.

Requirements

◆ The psychosocial needs and challenges faced by thalassaemia patients at different stages of life should be prioritised, to provide comprehensive and effective care. Psychological support should be available to address a variety of challenges associated with thalassaemia including, but not limited to, adjustment difficulties, poor self-esteem, low mood, health anxieties, needle phobia, treatment compliance, school and work difficulties, relationship problems and cultural issues.

◆ Comprehensive care requires a multidisciplinary biopsychosocial team approach and regular multidisciplinary meetings.

◆ A clinical psychologist should be an embedded member of the multidisciplinary team.

◆ All specialist staff should be aware of the importance of psychosocial issues in providing care for people with thalassaemia and should have access to training, support, consultation or supervision from a psychologist with a special interest in thalassaemia.

◆ Patients should have access to specialist psychology services; they should have the opportunity to self-refer and, where there are people from within the same family using the service, patients should be able to seek support from another clinician if requested. The opportunity for individual, couple and family sessions should be available.

◆ Where psychological difficulties are suspected, a referral to a clinical psychologist should first be discussed and agreed with the patient.

◆ Psychology assessments and reviews should include an overview of psychological and social aspects of the individual including details of their development, life stage, mental health history, family, relationships, schooling, employment, understanding of thalassaemia, coping skills, health beliefs and issues of self-esteem and identity.

◆ Diagnosis of a child with thalassaemia is a challenging time for families and appropriate support should be available to enable the family to discuss the diagnosis, management and overall psychosocial impact on the child and family.

◆ Paediatric services should utilise a developmental framework and have regular multidisciplinary reviews of all children within the service. Reviews should take place at key developmental milestones and after important medical, life or family events.

◆ If cognitive or developmental problems are suspected, a referral should be made to clinical psychology for an initial assessment and a further referral made, if necessary, on to a specialist neuropsychologist.

◆ Transition from paediatric to the adult care is stressful for young adults and their families, and it is important to provide psychosocial support to ensure that optimal care continues throughout adult life. Paediatric and adult centres should collaborate to ease transition using a standardised process to ensure that the proper steps are taken to equip and prepare the young person. Transition should not take place during a time of acute illness or another period of stress.

◆ Where serious mental health difficulties or psychiatric problems are identified, referral to a secondary child or adult mental health service should be considered and, if possible, discussed with the team psychologist in a timely fashion.

◆ If issues of safeguarding or child protection arise in regard to the safety of a child or an adult during the course of clinical care (whether the person at risk is the patient of the service or not), staff should promptly seek guidance by referring to their local safeguarding and child protection policies and guidelines, and by discussing directly with their organisation's Safeguarding Lead.

◆ All specialist staff should be aware of the importance of cultural influences on health and have access to training in cross-cultural work. Access to professional interpreters should be available and staff should be experienced in working with interpreters.

◆ Information should be made available in a variety of formats, including verbal and written. Information given verbally should be adequately documented and written information should be provided in the patient's preferred language. Information should be age appropriate and given at repeated points during the course of the condition and at times when changes in treatment or in the course of the condition occur.

Recommendations

• Best practice should include a multidisciplinary assessment of all new patients and regular psychosocial review and discussion of all patients.

• Specialist psychological support should be made available at critical milestones in patients' lives including initial diagnosis, first transfusion, start of chelation, puberty, transition to adult care, and other major life events such as university, first employment, marriage, pregnancy, and parenthood.

• The opportunity for patients to meet one another at specialist facilitated support groups within the service should be provided as a standard part of care and on an ongoing basis.

• To promote adherence, recommended treatments should take into account the patient's developmental level, family structure, cultural ideas around illness and treatment, social context and life demands. The constraints imposed by treatment should also be considered and wherever possible some flexibility incorporated to accommodate any minor difficulties and issues. Patients should, whenever possible, be involved fully in decisions and details about treatment regimes. Changes in treatment should always be discussed fully, and the rationale

and reasons for any changes made clear. Information about treatment options, including the relative benefits or disadvantages and the potential consequences of non-adherence to should be made available to patients. Patients should also be involved in monitoring their progress, for example ferritin levels, and the results of imaging tests quantifying tissue iron, so that their understanding of the impact of adherence and non-adherence is enhanced. More regular reviews can prove helpful in initially establishing a routine for a new treatment regime.

• Planning for transition from paediatric to adult care settings should start several years in advance, educating the adolescent about the biological, medical, and psychosocial aspects of thalassaemia, and equipping him/her with the skills to become responsible and independent in caring for his/her health. To ease transition and reduce anxiety, the process works best if individualised to take into account the developmental stage and readiness of the patient and family to take on new responsibilities. Following transition, adult patients should be followed up routinely to ensure that they are receiving optimal care and appropriate psychosocial support.

• Standard annual reviews of patients should include a measure of emotional wellbeing to monitor psychosocial well-being among patients in order to identify any difficulties pro-actively, providing prompt psychological assessment and early support and treatment, if necessary.

• Wherever possible when breaking bad news the patient's support networks should be included. Staff should remain aware of the significant impact bad news can have on patients, and should be prepared for a range of emotional responses from the patient including anger, denial, shock or distress. Staff should be trained and supported in breaking bad news. They should be prepared to offer support in accepting losses associated with the bad news and in fostering realistic hope. Giving false promises should be avoided. Staff should remain alert to the possibility of depression in response to bad news, and the impact low mood can have on motivation to adhere to medical regimes. Where appropriate, support from or referral to the psychologist should be considered.

7: Initial Management of the Newly Diagnosed Infant

"Getting our daughter's diagnosis felt almost like a bereavement. It is like any loss or perceived loss, where only the passage of time and the realisation that your child can have a fairly normal life helps you get over it."

Aims

To establish the correct diagnosis in an affected infant promptly, and initiate an appropriate and timely management programme.

To ensure the family has a good level of understanding of the condition, and feels well supported in the early weeks after diagnosis, and to minimise distress by communicating information and advice in a way which is appropriate to their culture and language.

Standards

■ Diagnosis of a child with a serious thalassaemia syndrome will be timely and accurate. It should be established as soon as possible after birth, and should include globin genotype.

■ The neonatal heel prick test is a screening, not diagnostic, test and early confirmation is required.

■ The child must be monitored closely to determine the likely clinical course.

■ The family should be informed fully and sensitively from the outset once the diagnosis is confirmed, by appropriately experienced professionals, with the use of a culturally-appropriate health advocate if necessary, and with the opportunity for full discussion. Suitable written information should be given to them.

■ A management plan tailored to the individual child must be agreed and implemented.

■ The family will meet their 'key contact' within the clinical team, and given contact numbers for subsequent use.

■ The family should be informed about the National Haemoglobinopathy Registry and asked to give consent for the child's details to be recorded on it.

■ The family should be given the contact details for the UK Thalassaemia Society and any local support group.

Background

Learning that their infant has a serious blood condition inevitably comes as a shock to parents. Parents should have been made aware of their risk of having an affected child through screening and counselling during pregnancy. This counselling should have included information about inheritance, the option of pre-natal diagnosis and other choices, and the effects of thalassaemia and its treatment on the child and the family. It should be backed up by suitable written information.

If the risk was not identified during the pregnancy, affected infants may be identified through the newborn screening programme. This is a screening test, and not all cases of thalassaemia will be identified. If the test shows 'haemoglobin F only', follow up is necessary and diagnostic

confirmatory tests should be performed. If undiagnosed in the neonatal period, the child is likely to present with failure to thrive, poor feeding and other non-specific symptoms of anaemia and may have an enlarged spleen and liver. Depending on the level of haemoglobin at this time, initial red cell transfusion may be urgently required.

Whenever the diagnosis is made, the way in which it is conveyed to the parents, and the initial conversations they have with professionals, will colour their expectations and attitudes. The first discussions must therefore be accurate, unhurried, considered and sensitive.

The fact that there is a 'grey scale' of transfusion dependency should be explained, and parents should understand that it is usually not possible to predict the severity of the condition, or the need for transfusions, from the outset. Children need to be monitored carefully for signs of poor growth, failure to thrive, complications of anaemia and bone marrow expansion – clinical features indicative of the need for regular transfusion.

Genetic analysis usually, but not always, helps to predict the clinical phenotype. Routine DNA testing should therefore include β globin genotype, α globin genotype and a determinant of persistent fetal haemoglobin production (the *Xmn*1 C→T polymorphism) (Ho et al. 1998).

Requirements

◆ The diagnosis should be anticipated from antenatal screening, and established by prenatal diagnosis where requested or by neonatal testing. If not, affected infants may be identified through the newborn screening programme. The baby and parents should be seen for testing as soon as possible and preferably within two weeks. If the diagnosis has not been made at these stages, and the presentation is a clinical one, then assessment and treatment may be urgent, within one to two days.

◆ Haematological and DNA diagnosis should be established as soon as possible by the following tests:

– Full blood count and blood film examination.

– Haemoglobin analysis by electrophoresis or high performance liquid chromatography (HPLC), β and α globin genotyping and *Xmn*1 C→T polymorphism.

◆ Family studies may be informative, and the parents should also be tested if results are not available from prior screening.

◆ Once the diagnosis of thalassaemia is established, the parents must be given the diagnosis by a knowledgeable professional, often a specialist nurse, who can start to explain the condition and offer some written information as well as contact numbers for any urgent concerns or questions.

◆ This should be followed up by an early clinic appointment, usually with a consultant paediatrician, paediatric haematologist, or haematologist with experience of looking after children with the condition. This may be at the local clinic, with the LHT, but if local experience is limited, should be at the most convenient specialist centre, SHC.

◆ If the initial visit is at the local clinic, staff seeing the family should discuss details of the case with the centre beforehand, and set up an appointment for the family to be seen there soon after.

◆ It should be emphasised that the clinical phenotype cannot be predicted accurately in the early stages, and that the child will be monitored carefully for clinical signs indicative of the need to commence transfusion, when that might be, and the implications of this.

◆ The importance of the family as central care-givers should be emphasised.

◆ The arrangements for care should be discussed – wholly at the Centre if they live near, or based at the local linked hospital if more convenient – and the plan for regular, at least annual, review at the Centre with additional contact whenever required should be explained.

◆ Appropriate written information should be made available. The family should additionally be given the contact details for the UK Thalassaemia Society and any local support groups.

◆ The parents should meet and exchange contact details with their local key contact staff member/s, and the team psychologist, and offered support.

◆ After the visit a written summary, covering the discussion and follow up arrangements, should be exchanged between local clinic and specialist centre, and copies sent to the GP and the family.

Recommendations

• For babies identified by the screening programme, an initial home visit may be preferred. Where the parents already have a relationship with a specialist nurse counsellor, from discussions in the antenatal period, s/he may be the best person to make this contact. The nurse can then accompany the family to the first hospital consultation soon after.

• There should be no delay in referral following suspected diagnosis because the child remains clinically well: important information is given, discussions take place and investigations to confirm the diagnosis should be instigated at this stage.

• Ample time should be given to enable parents to ask questions and clarify issues. A professional interpreter is essential at this consultation if the family are not primary English speakers. If only one parent is present, it is advisable that a friend or relative accompanies them to help them to remember afterwards what was discussed. Strenuous efforts should be made to involve both parents from the start. When both attend, it is important to be sure that each has a chance to ask his/her own questions and discuss his/her own issues.

• The initial meeting is likely to be dominated by the family's need to understand the nature and implications of the child's newly diagnosed condition. Genetic counselling, with regard to options in future pregnancies, can be mentioned but it is better to arrange a further meeting to address this issue, although this should not be long delayed. At this meeting there should also be discussion of the implications of possible carrier status in siblings and other family members, who should be offered testing.

• During the early clinic visits, treatment options for the child in future should be discussed including the different options for iron chelation and the availability of stem cell transplantation.

• Families should be made aware of the need for frequent monitoring of growth, development, and blood test results.

• Where possible, the family should be given the opportunity to meet with other families who have children with thalassaemia.

8:   Decision to Start Regular Transfusion

"I remember the nurse coming to take her to be cannulated, my heart pounding, the tears, the screams and the little hands that wouldn't let go."

"Good clinical judgement cannot be replaced by any kind of clear instructions regarding decisions whether to transfuse a patient"

Professor Dimitris Loukopoulos,
Thalassaemia International Federation Conference,
Palermo, October 2003

Aims

To distinguish carefully, using clinical and DNA-based assessments, between infants with transfusion-dependent thalassaemia: thalassaemia major, and those who can maintain acceptable health and development without transfusion: intermedia or non-transfusion-dependent-thalassaemia (NTDT).

To initiate transfusion therapy in thalassaemia major before the infant/child develops complications of anaemia and of bone marrow expansion.

To avoid unnecessary transfusion in thalassaemia intermedia.

Standards

■ Infants with β thalassaemia will be monitored carefully for clinical signs indicative of the need for transfusion. Transfusion will be started promptly when there is clinical evidence of severe anaemia, failure to thrive and/or thalassaemic bone deformity.

■ Infants and children with a milder 'thalassaemia intermedia' phenotype will be identified clinically and not subjected to regular transfusion inappropriately.

■ Extended red cell phenotype and genotype should be performed before starting regular transfusions to ensure compatible blood is transfused and to reduce the risk of alloimmunisation.

■ Before a first transfusion, a course of hepatitis B vaccinations should be started, and completed if possible.

Background

The decision about when to start red cell transfusions in a child with β thalassaemia is a subtle and important one.

There will be some indication about likely clinical severity and likely transfusion dependency from the β globin genotype, but ultimately the decision is a clinical one. The difference between 'major' and 'intermedia' is not absolute or predictable. At a given untransfused haemoglobin level, some children apparently thrive, grow and have no clinical problems while others are clearly failing to thrive. A decision to treat cannot be made on haemoglobin level alone and

needs to include consideration if the child is thriving or not, taking into account the parents' opinions; also height velocity, weight gain and spleen size. In the past, some children have been transfused to the point of iron toxicity who would probably have been better without regular transfusion at all. The decision about starting transfusion must always be made by – or, if urgent, after discussion with – a clinician with specific experience in this area, in a Specialist Haemoglobinopathy Centre, after detailed evaluation of the child.

Usually, a decision to commence transfusion should be based on the presence of anaemia (below 70 g/l on two occasions 1 – 2 weeks apart) which is accompanied by inappropriate fatigue, poor feeding, developmental delay or regression, faltering growth, or any symptoms or signs of cardiac failure. It should be ensured that there are no correctable problems such as iron deficiency or intercurrent infection, or compounding factors such as G6PD deficiency. Into the balance should be included consideration of other factors such as age at presentation or first symptoms, increasing splenomegaly, any evidence of bony expansion or changing appearance of facial bones.

Sometimes there is an 'acute' anaemia, for example due to a viral infection, in a child who otherwise can maintain a satisfactory haemoglobin without regular transfusion. It is therefore reasonable to give a single transfusion initially, and then wait and reassess whether the indication for transfusion recurs. If the haemoglobin falls again promptly, it is reasonable to assume longer term dependency, and to plan for regular transfusions. Where possible, a decision to start regular transfusions should not be delayed until after the 3rd year, as the risk of alloimmunisation and of developing multiple red cell antibodies increases, with subsequent difficulty in finding suitable units for transfusion. In practice, in children who are going to need regular transfusion this is normally manifest sooner than the age of 3.

Where transfusion is started later because of fall in height velocity or bony changes (often intermedia) it should not be assumed that lifelong transfusion will then be necessary. After maximum height is achieved, and bones are fused, in some cases it is possible to 'wean off' and then stop regular transfusions entirely, although the patient still needs to be carefully monitored for other complications (see chapter 24: Management of Non-Transfusion-Dependent Thalassaemias).

Requirements

◆ After diagnosis, infants will be monitored regularly in the local clinic in liaison with the specialist centre. From the age of 3 months, these visits should be at least monthly, until the clinical phenotype is established.

◆ Monitoring will include history of any feeding concerns, infections, ill health and developmental delay. Examination will include an assessment of growth, bone expansion (including head circumference) and hepatosplenomegaly. Haemoglobin level should be checked at least monthly.

◆ The decision to initiate regular transfusion should be made by, or in consultation with, the designated clinician in the Centre.

◆ Before the first transfusion, the investigations in Table 8.1 should be carried out. It is assumed that DNA studies have already been undertaken previously, at diagnosis. If not, they should be sent prior to the first transfusion.

Table 8.1. Investigations prior to first transfusion

Specialty	Investigations
Haematology	Serial Hb measurements; G6PD screen and assay if low
Transfusion	Full red cell extended phenotype and genotype (C, c, D, E, e, K, k, Jka, Jkb, Fya, Fyb, Kpa, Kpb, MNS, Lewis)
Biochemistry	LFT and baseline ferritin assay
Microbiology	Hepatitis B surface antigen; Hepatitis C antibody; HIV antibody

9: Red Cell Transfusion

> *"Junior doctors need to listen to us when we tell them where to cannulate us and which cannula to use and not have the superior attitude that they know best. We know our own veins."*

> *"We need flexible services to accommodate work routines. If it were not for my consultant arranging weekend transfusion for me at another hospital I would have lost my job."*

Aims

To ensure that children are transfused to an appropriate level to promote growth and wellbeing.

To prevent complications of under-transfusion.

To ensure that transfusions are given safely and that the transfusion programme causes minimum disruption to everyday life.

Standards

- Trough haemoglobin levels should be maintained ~ 90 – 105g/l.
- Blood must be ABO compatible and antigen negative for any clinically significant antibodies the patient is known to have, or to have had previously identified even if not currently detectable. It should be fully matched for all the Rh antigens and K.
- Units should be less than 2 weeks old and, in adults, of larger volume where possible.
- There should be a clear record of patient's transfusion requirements outlining volume, frequency and target haemoglobin.
- Transfusions will be given on each occasion in a designated age-appropriate area with suitable facilities, experienced regular named nurses and familiar supervising medical team.
- Cannulation will be undertaken by an experienced nurse, doctor or phlebotomist.
- Pre-arranged transfusions should be started within 30 minutes of the patient's arrival.
- Good transfusion practice must be observed.

Background

Blood transfusions are essential in children with thalassaemia major enabling normal growth and development. In adults regular transfusions remain necessary to maintain life, and if given appropriately will minimise the symptoms of anaemia and allow a good quality of life. A haemoglobin level maintained above 90-105 g/l is sufficient to inhibit bone marrow expansion and minimise transfusion iron loading in most patients (Cazzola *et al.* 1995; Cazzola *et al.* 1997; Pasricha 2014). Occasional patients with cardiac disease, extramedullary haematopoiesis and/or inadequate bone marrow suppression benefit from higher transfusion thresholds of 110-120g/l although there is little published evidence on this. Transfusing to above a post-transfusion level of 150 g/l risks stroke, hyperviscosity symptoms and increases the iron burden and is not recommended.

Transfusions are usually given regularly every 2-4 weeks. However intervals vary from patient to patient and should be agreed between clinician and patient depending on the clinical response to anaemia/transfusions and pragmatic lifestyle decisions. In adults each unit of red blood cells is

usually administered over 1-3 hours. The volume in red cell units varies from approximately 220 to 320 ml. In adults units of larger volume (greater than 280 ml) can minimise the number of units required and thus donor exposure. Although there is no clear evidence for this, fresher units may reduce the frequency of transfusion therefore units less than 14 days old are preferred. For calculations of blood volumes to be given to children the following calculation can be used (adapted from New *et al.* 2016 for the BCSH):

$$\text{Volume to transfuse (ml)} = \frac{\text{Desired Hb (g/l)} \quad - \quad \text{actual Hb (g/l)} \quad \times \quad \text{weight (kg)} \quad \times 4}{10}$$

To reduce donor exposure, transfusions are not normally given to the nearest ml, so for example if the calculated volume is 330 ml and one matched unit is identified containing 305 ml, part of a second unit would not be necessary.

Provision of red cell units for transfusion-dependent patients requires special considerations. Efforts must be taken to minimise the likelihood of antibody production, or alloimmunisation, which may delay the provision of blood and exposes the patients to the additional risk of a haemolytic transfusion reaction. Reported rates of alloimmunisation vary widely in the literature as do practices for the degree of matching red cells. For all patients with thalassaemia it is recommended that blood should be matched for all the Rh antigens (D, C, c, E, e) and Kell (K) to minimise this risk. The patient's full red cell phenotype/genotype should be determined before the first transfusion is given. Where patients have already been transfused samples can be referred to NHS Blood and Transplant (NHSBT) for genotyping. It is sensible for these patients to have genotype/phenotype records held by NHSBT where records can be accessed by all centres via the electronic reporting system (Sp-ICE).

The risks associated with regular red cell transfusion include acute and delayed transfusion reactions, alloimmunisation, transmission of microbial infections and, in the medium and long-term, iron overload. Serious reactions due to misidentification can be minimised by meticulous attention to good transfusion practice and by ensuring national guidance is followed (BCSH 2012a; BSQR 2005). Transmission of viral infections are uncommon in the UK; however, there is always a small risk of infection from units donated during the 'window-period' of infectivity: between the donor contracting the infection and developing the detectable antibody, or from blood-borne pathogens not currently tested for by the NHSBT. The greatest risk to patients receiving transfusion is human error within the transfusion process (SHOT Report 2014). This risk can be reduced by empowering these regularly transfused patients to understand the product that they should be receiving, and the checking processes that staff should undergo prior to and during the transfusion, and to challenge staff if they have any concerns. Patients or parents should be consented prior to starting blood transfusions to ensure they understand these risks, using the appropriate organisational policy and forms. Adverse event management and reporting is essential in maintaining good transfusion practice and identifying methods of risk reduction. Reporting errors and incidents in line with Blood Safety and Quality Regulations (BSQR 2005) to MHRA/SHOT is mandated and local incident reporting, for the purposes of learning, is highly recommended. In addition the National Haemoglobinopathy Registry encourages reporting of harm to patients with thalassaemia as a result of transfusion.

For the patient and the family, the organisation and efficiency of administering transfusions can have a major effect on the quality of life. The process includes attending for a blood sample, for pre-transfusion testing, usually within 72 hours of the transfusion, although this may be extended to seven days in some uncomplicated patients (BCSH 2012a). Availability of out of hours services, for phlebotomy and for transfusion, is greatly welcomed by patients and families. An intravenous cannula must be inserted which can be difficult and traumatic, particularly if the veins are hard to find. Cannulation done inexpertly increases anxiety and distress, and can damage veins, making future access more difficult. Patients may be extremely anxious about cannulation, and it is imperative to preserve the veins since the patient is dependent on life-long venous access. Anxiety about this key step may be an indication to refer to a psychologist or play therapist to assist with on-going management. Cannulation should be performed by

experienced staff with an understanding of the condition and good trust relationship with the patient. Indwelling catheters are not regularly used because as people with thalassaemia, especially if splenectomised, are at increased risk of venous thromboembolism. If considering their use, it is recommended that expect opinion is sought from the Specialist Haemoglobinopathy Centre, SHC, and consideration given to the most appropriate from of thromboprophylaxis.

The transfusion itself usually takes 4-6 hours. Each unit should be carefully checked ensuring all patients identification details match with observations and care during the transfusion being given in line with national and local guidance (NICE 2015; BCSH 2009).

Where families are able to fit blood sampling and blood transfusions conveniently around their other activities and the time taken at each visit is kept to a minimum, quality of life and motivation to adhere to treatment is enhanced. Transfusion away from a hospital setting is not usual; however where home care is considered there must be policies in place to ensure safe transfusion practice.

Requirements

◆ The patient should be reviewed prior to each transfusion by a trained and authorised health care professional. The pre-transfusion haemoglobin level must be checked, to ensure that the planned transfusion is appropriate, and there must be an opportunity for the patient/family to discuss any problems or issues.

◆ There should be a review with the designated clinician at least every 3 months in addition to the formal Annual Review visit at the SHC.

◆ Pre-transfusion haemoglobin level should be between 90 – 105 g/l; transfusion interval is usually between 3 and 4 weeks.

◆ ABO compatible red cell units which are matched for Rh (D, C, c, E, e) and Kell (K) blood group antigens must be selected.

◆ The patient's extended red cell genotype (or phenotype) should be determined before transfusions are given.

◆ Pre transfusion laboratory testing should be performed in line with national guidance (BCSH 2012a) and Blood Safety and Quality regulations (BSQR 2005).

◆ UK Blood Service, SaBTO or BCSH recommendations regarding the provision of special requirements should be referred to and followed where indicated. For example washed red cells may be beneficial for patients who have repeated severe allergic reactions, and irradiated components, cytomegalovirus (CMV) negative and/or hepatitis E virus (HEV) negative may be required in thalassaemia patients who have had or are to receive stem cell transplant. (BCSH 2012b; BCSH 2010; SaBTO 2012; SaBTO 2015).

◆ Hospitals involved with the routine care of patients with thalassaemia must have a written transfusion policy with specific reference to the transfusion and provision of blood for these patients. It should specify where the transfusions will usually be given, the procedures for checking red cell units, setting up the transfusion, maximum rate and volume of transfusion, monitoring for reactions and actions to be instituted if a reaction is suspected. Staff should be aware of the policy and should be given regular training, and adherence to the policy should be audited.

◆ Consent for transfusion should be recorded using the organisations policy for consenting long term multi-transfused patients (SaBTO 2011)

◆ Transfusions should be given in a familiar clinical area by regular staff who are experienced in setting up and supervising transfusions. No more than 3 attempts to site a cannula should be made by any one individual.

◆ Options for indwelling central venous access e.g. Vascuport or Port-a-cath should be discussed with the team at the Specialist Haemoglobinopathy Centre, if cannulation is or becomes difficult, although the risks of infection and particularly thrombosis need to be considered, and formal anticoagulation may be recommended.

◆ Facilities for out-of-hours provision are a key requirement, and become increasingly important for older children and adults in full time education or employment.

◆ A nurse should be in continuous attendance throughout the transfusion, at whatever time of day or night.

◆ Transfusion reactions should be investigated and managed according to the BCSH guideline on the investigation and management of acute transfusion reactions (BCSH 2012b)

◆ All adverse events and near misses should be externally reported to MHRA/SHOT in line with BSQR (2005).

◆ Laboratories providing components for transfusion should be accredited.

Recommendations

• It is good practice to measure a post transfusion Hb level occasionally and to have clearly documented details of transfusions given over the past year so that annual transfusional iron loading can be calculated

• Adverse events, especially if there is any element of human error, should additionally be reported through the hospital's incident reporting policy, for investigation and learning.

• There should be regular monitoring of patients to ensure transfusion intervals and volume is providing maximum health benefits while minimising the risks of iron loading and donor exposure, and is meeting their needs both physically and socially.

• All staff involved in the transfusion of patients with thalassaemia (laboratory and ward) should have awareness of these standards.

10: Monitoring and Management of Iron Load

"I am very good with my chelation and as a kid I used to be on the pump very religiously 6 nights a week 1 night off. Now I'm on Exjade a true godsend."

"I sometimes forget the pump, not deliberately but due to life, e.g. coping with the kids, wife, job, etc."

"I find chelation is a process that needs to have the flexibility to adjust to suit the health and circumstances of each person during different life stages."

"The treatment is inconvenient and painful. It's difficult but I am trying very hard to have it every day."

Aims

To monitor body iron stores accurately, minimise iron accumulation, and prevent tissue damage and organ dysfunction resulting from transfusion iron overload.

For patients who are already iron loaded, to reduce body iron load and minimise the toxic effects of intracellular and extracellular iron.

To monitor for adverse effects of iron chelator drugs, and to adjust therapy to minimise associated morbidity.

Standards

■ A protocol for iron chelation therapy in children and adults should be shared between the Specialist Haemoglobinopathy Centre and Local Hospital Teams within the clinical network, and reviewed at regular intervals. This should be based on current published evidence, expert opinion, and national specialist commissioning guidance.

■ Decisions about initiating and changing chelation therapy should be made by the thalassaemia specialist, taking into account the preferences of the patient and carers, and the views of other involved health care workers.

■ Patients and carers should be informed about benefits and possible adverse effects of each option and offered information in formats appropriate for age, language and literacy, with health advocacy as needed. 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 including clinic doctors, nurse specialists, clinical psychologists, and play therapists for children. Peer support should be encouraged.

■ Adherence should be monitored regularly, and problems carefully identified and addressed in a non-judgmental manner.

■ All patients should have access to Cardiac MRI for assessment of myocardial iron overload and cardiac function, and to liver MRI for assessment of liver iron concentration. The MRI methodology should be standardised and validated.

■ Patients should be carefully monitored for side effects of iron chelation therapy, and treatment interrupted or reduced promptly to avoid serious toxicity.

■ The outcomes of chelation therapy within local clinics and the clinical haemoglobinopathy network should be audited regularly.

Background

Introduction

Iron overload in thalassaemia major (TM) is usually fatal in the second or third decade of life if not treated. Toxic effects are attributed to non-transferrin bound iron (NTBI) in the plasma and toxic unbound iron in intracellular compartments. These accumulate when the normal physiological mechanisms which sequester iron are overwhelmed (Cabantchik, Breuer *et al.* 2005).

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 (Borgna-Pignatti, Rugolotto *et al.* 2004). 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 (Olivieri and Brittenham 1997). Other endocrine problems include glucose intolerance, diabetes mellitus, hypothyroidism and hypoparathyroidism (Cunningham, Macklin *et al.* 2004). The liver is also an important site of iron toxicity: hepatic fibrosis can occur early in childhood eventually leading to cirrhosis (Aldouri, Wonke *et al.* 1987), liver failure and hepatocellular carcinoma (Borgna-Pignatti, Rugolotto *et al.* 2004; Borgna-Pignatti, Garani *et al.* 2014). Hepatic complications are accelerated in the presence of chronic hepatitis C virus infection (Di Marco, Capra *et al.* 2008).

There is good evidence that the majority of complications can be prevented if iron stores are maintained within a safe range. In some situations, reversal of tissue damage is possible if intensive iron chelation therapy is instituted and adhered to. This is well established for cardiac disease (Anderson, Westwood *et al.* 2004; Tanner, Galanello *et al.* 2008) and there are also some data on improvement or reversibility of endocrine dysfunction (Farmaki, Angelopoulos *et al.* 2006). The expectation is that well monitored and chelated patients will have a near normal life expectancy.

Assessment and monitoring of iron overload

Transfusional iron loading

Estimating current iron stores, and monitoring their trends with time are essential for evaluating the likely risks of morbidity and mortality, and for making informed clinical decisions regarding chelation therapy. This requires knowledge of the transfusion history, and of past and present iron chelation. The annual transfusion requirement can be expressed in ml/kg/year of pure red cells using the estimated haematocrit of the transfused blood available from the blood transfusion laboratory. Average daily transfusional iron loading (expressed as mg/kg/day), can be calculated assuming 1 ml of pure red cells contains 1.08 mg of iron (Cohen, Glimm *et al.* 2008).

Patients whose transfusion iron loading is more than 0.3 mg/kg/day generally require higher doses of chelating agents to achieve negative iron balance (Cohen, Glimm *et al.* 2008). To assess the long-term effects of iron overload it is also necessary to know at what age chelation was started, and to ascertain the pattern of adherence to therapy and whether there have been periods of poor or absent chelation.

Serum ferritin (SF)

SF levels are an indirect measure of transfusion iron loading. Values up to about 4000 µg/l reflect macrophage iron, whereas levels above 4000 µg/l also reflect hepatocyte damage (Brittenham, Cohen *et al.* 1993). Ferritin levels are elevated during intercurrent infections, chronic inflammatory conditions and chronic viral hepatitis, and this can lead to an overestimate of the degree of iron loading. Conversely, low levels may give false reassurance. Long-term mean

ferritin measurements in the range 500-1500 µg/l have been observed in some patients who have severe cardiac iron loading and left ventricular impairment (Tanner, Galanello *et al.* 2008). This is probably due to accumulation of iron in the myocardium either during periods of poor adherence to desferrioxamine (DFO), or in the case of older patients, delay in starting chelation. Low vitamin C (ascorbate) levels also cause low serum ferritin readings in the presence of significant iron overload. As such, SF should not be used as an indicator of cardiac iron concentration.

SF and Iron chelation

The interpretation of SF levels and trends in SF also depend upon the iron chelator drug. With DFO, persistently high levels (>2500µg/l) are associated with an increased risk of cardiac disease and death (Olivieri, Nathan *et al.* 1994), and levels maintained in the range 500-1500 µg/l over the long term carry a relatively low risk (Telfer, Prestcott *et al.* 2000; Borgna-Pignatti, Rugolotto *et al.* 2004). In the case of deferiprone (DFP) and deferasirox (DFX), levels fall concurrently with reductions of liver iron (Cappellini, Cohen *et al.* 2006; Pennell, Berdoukas *et al.* 2006; Tanner, Galanello *et al.* 2007). Ferritin levels fluctuate markedly, and a rise seen from one month to the next should not prompt an immediate change in therapy. Trends in SF apparent over a period of at least 3 months are a more reliable indicator for adjusting therapy.

Other serum markers of iron overload

Iron is transported in the plasma predominantly bound to transferrin. Regular transfusion progressively overwhelms the normal body storage and transport mechanisms. As a result, transferrin quite quickly becomes fully saturated and non-transferrin bound iron (NTBI) appears in the plasma consisting of circulating iron not bound to transferrin, ferritin or heme. Labile plasma iron (LPI) is a fraction of NTBI which is redox-active and available for chelation. LPI can permeate cells and generate free radicals, which are thought to be the major cause of tissue damage in transfusion iron overload.

LPI values have also been evaluated in different chelation regimes. In long-term chelated TM patients, 24 hour LPI is well controlled during long-term therapy with DFX or with daily sequential combination of DFP and DFO. During monotherapy with DFO infusions, levels increase after discontinuing the infusion. During standard DFP therapy, levels fluctuate during the day and increase overnight (Daar, Pathare *et al.* 2009; Porter, El-Alfy *et al.* 2016).

Measurement of transferrin saturation (TSAT) is a routine biochemical test, and may be useful in assessing mild untreated iron overload. Measurements may be unreliable when chelators are present in the plasma, and are not informative in detecting changes when there is severe iron overload and fully saturated transferrin (Porter, El-Alfy *et al.* 2016).

Various assays have been described which measure different components of NTBI. One reported method for LPI uses a fluorescent probe which measures redox-active iron, and the chelatable form is calculated as the proportion which is removed in the presence of excess DFO (Esposito, Breuer *et al.* 2003). Comparisons of methodologies have confirmed correlations with TSAT, but demonstrate significant differences in absolute values measured for LPI or NTBI (de Swart, Hendriks *et al.* 2016).

In TM patients, LPI is detected once TSAT increases above 70% (Cabantchik, Breuer *et al.* 2005). One study has suggested that TSAT>90% can be used to predict LPI appearance in chelation-naïve TM children and this may be of value in deciding when to start chelation (Danjou, Cabantchik *et al.* 2014). A reduction in TSAT may also be an indication that chelation can be reduced or temporarily discontinued in patients whose SF and LIC values are below recommended limits, but there are no clinical trials evaluating this proposal.

Liver iron concentration (LIC)

Liver biopsy

Liver tissue obtained directly using a needle or intra-operative wedge biopsy can be analysed chemically for iron content. Histological examination of liver tissue also gives useful information about hepatic inflammation, fibrosis and cirrhosis. Liver biopsy was previously recommended as the most reliable means of assessing iron loading in children in order to decide on when to start DFO chelation (Olivieri and Brittenham 1997). However, biopsy LIC is invasive, and results show

poor reproducibility, particularly if the biopsy is small or cirrhotic. The co-efficient of variation has been estimated at about 19% in non-diseased, and 40% in fibrotic, livers (Kreeftenberg, Koopman *et al.* 1984; Villeneuve, Bilodeau *et al.* 1996; Emond, Bronner *et al.* 1999).

MRI methodologies

Magnetic resonance imaging (MRI) can exploit the paramagnetic properties of iron to obtain a quantitative measurement of concentration in body tissues. MR scanning is non-invasive, allows averaging of LIC over a large volume of liver tissue, and is suitable for sequential assessment. All MRI-based methods require calibration against LIC measured by chemical analysis of liver tissue and are subject to variability, which may be increased with higher degrees of iron loading and hepatic fibrosis. Additional factors, such as hepatic fat content, may also play a role. This variability is probably less than for LIC determined from biopsy.

Spin-echo (R2) and gradient echo (R2*) methods have been developed, refined and evaluated in various clinical settings over the past 15 years and both are now considered suitable for routine clinical use provided they are done using a standardised and validated protocol.

R2 LIC (Ferriscan™)

St Pierre and colleagues have developed an R2 scanning protocol and demonstrated a robust calibration curve of R2 against biopsy LIC, applicable to different iron loading conditions, patients on different chelation regimes, and to young children. The method has been commercialised under the trade name Ferriscan®, and electronic transfer of MR data to a centralised processing centre allows LIC to be calculated and reported in a standardised manner (St Pierre, Clark *et al.* 2005; St Pierre, El-Beshlawy *et al.* 2014), www.resonancehealth.com.

R2* LIC

The Royal Brompton group in the UK demonstrated a logarithmic relationship between R2* and LIC on liver biopsy as a proof of concept for development of myocardial iron estimation (Anderson, Holden *et al.* 2001). The technical details of the original methodology have been significantly improved by several groups, and re-calibrated against biopsy liver iron resulting in a more reliable estimation of LIC over the range of clinical values. These groups have produced different calibration curve compared to the original method (Wood, Enriquez *et al.* 2005; Hankins, McCarville *et al.* 2009; Garbowski, Carpenter *et al.* 2014). At present a consensus has not been reached on the standardisation of R2* methodology for routine clinical use.

One recent study compared a modification of R2* LIC with R2 (Ferriscan®) (Garbowski, Carpenter *et al.* 2014). Although both methods showed a good linear relationship between LIC and MR parameter, the agreement of results between the two methods was inadequate over the range of clinically relevant values. This suggests that R2 and R2* have different sensitivities to different forms of storage iron in the liver, and that the methods cannot be used interchangeably.

Optimal levels of LIC

Determining the optimal range of LIC requires a balance between avoidance of iron toxicity and prevention of chelator-induced toxicity. Although normal LIC is 0.2-1.8 mg/g dry weight (dw), maintaining levels within the normal range may increase the risk of chelator toxicity, and the desired LIC range for a regularly transfused TM patient should probably be higher (Olivieri and Brittenham 1997). Clinical observations in genetic haemochromatosis suggest that levels between 3-7 mg/g dw - the range seen in heterozygotes - should not result in hepatic or endocrine toxicity (Olivieri and Brittenham 1997). Levels above 15 mg/g dw in thalassaemics on DFO have been associated with an increased risk of morbidity and mortality from iron overload (Brittenham, Griffith *et al.* 1994; Telfer, Prestcott *et al.* 2000).

Cardiac iron

In iron loaded TM patients, myocardial tissue iron concentrations are usually less than in the liver. Assessment of cardiac iron overload by gradient-echo R2* MRI was initially developed at the Royal Brompton Hospital (Anderson, Holden *et al.* 2001). These sequences are particularly sensitive to magnetic properties of tissue iron, and are acquired over a short time span, so that motion artifacts from myocardial contraction can be minimised. The relationship between myocardial iron concentration (mg/g dry weight) and T2* was derived in a study of 12 post

mortem or explanted hearts from patients with iron overload. T2* is expressed in milliseconds: the higher the reading, the lower the cardiac iron.

Cardiac T2* has been shown to be reproducible on different scanners, and made widely available for clinical use (Westwood, Anderson *et al.* 2003). An international panel recently recommended that myocardial T2* is assessed on 1.5 Tesla CMR, using single breath hold multi-echo sequence with image acquisition from the full-thickness short axis view of the intraventricular septum. Clinically validated software should be used for image analysis. More detailed technical aspects of myocardial iron assessment by T2* have been reviewed in the same document (Pennell, Udelson *et al.* 2013).

Cardiac MRI is an excellent tool for measurement of ventricular size and performance. It has shown that normal left ventricular ejection fraction (LVEF) in TM patients is higher than in non - thalassaemic controls (Westwood, Anderson *et al.* 2007). LV impairment becomes increasingly likely when T2* falls below 20 milliseconds (ms) (Anderson, Holden *et al.* 2001; Tanner, Galanello *et al.* 2006). Nearly all patients with clinical evidence of heart failure have a very low T2* (<10 ms) (Westwood, Wonke *et al.* 2005; Tanner, Galanello *et al.* 2006; Kirk, Roughton *et al.* 2009). A study of clinical outcomes in 600 UK TM patients has shown a strong association between myocardial T2* and development of heart failure (HF) and cardiac arrhythmias. Patients with a cardiac T2* <6 ms had a 50% likelihood of developing HF within 12 months if no change in iron chelation treatment was instituted. A normal cardiac T2* has a very high predictive value for exclusion of HF for 12 months (Kirk, Roughton *et al.* 2009), but does not rule out previous cardiac damage and arrhythmia risk as it will not reflect historical iron deposition and consequent fibrosis.

A consistent finding is a poor correlation between myocardial T2* and SF or LIC. This may be due to the kinetics of myocardial iron loading and unloading. Loading is relatively slow and may be dependent on liver status, so that cardiac iron only begins to accumulate once the liver is heavily loaded. Similarly, liver iron is removed more rapidly than cardiac iron during chelation therapy (Noetzli, Carson *et al.* 2008). Myocardial iron loading is less common in childhood, although it has been detected in children in the age range 6-10 years (Wood, Origa *et al.* 2008; Borgna-Pignatti, Meloni *et al.* 2014), leading authors to recommend myocardial T2* scanning starting as early as possible when a scan can be undertaken without sedation.

A grading scheme for assessing myocardial iron and guiding changes in chelation therapy is presented in Table 10.1 (Kirk, Roughton *et al.* 2009).

Table 10.1: A grading scheme for assessing myocardial iron and guiding changes in chelation therapy

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

Assessment of iron overload in other organs

Since endocrine damage is an important clinical consequence of transfusion iron overload, MR might be of value in assessing changes in endocrine tissue iron loading and identifying patients at risk of future endocrine deficiency.

Wood and co-workers have made careful studies of the pancreas and pituitary gland in TM patients, using R2* sequences (Noetzli, Papudesi *et al.* 2009; Noetzli, Panigrahy *et al.* 2012). They found that pancreatic iron overload is an indicator of future myocardial iron loading, and a risk factor for onset of diabetes and glucose intolerance. Pituitary iron overload in the presence of a normal sized pituitary gland is an indication of potentially reversible pituitary iron overload. Once the pituitary gland is shrunken, damage is unlikely to be reversible. Some specialist centres are using pancreatic T2*, taken at the same time as liver, to reduce the frequency of cardiac MRI, and using pituitary MRI to help guide therapy in young people when the gland seems especially susceptible to the iron. The results require further validation, and the methodology needs to be

standardised before MRI assessment of iron overload in endocrine tissue is recommended for routine clinical use.

Iron chelating drugs

There are three chelating drugs which can be used for treatment of iron overload in TM: desferrioxamine (Desferal®, DFO); deferiprone (Ferriprox®, DFP) and deferasirox (Exjade®, DFX). Current licensing indications in the UK are presented in Table 10.2.

Table 10.2: Current UK licensing indications for iron chelating drugs (See Summary of Product Characteristics of the respective drugs)

	DFO	DFP	DFX
Children age 2 – 6	First line	Insufficient information	Second line if DFO contra- indicated or inadequate
Children age > 6 and adults	First line	Second line: If DFO not tolerated or ineffective	First line
Route	s.c/i.m or i.v injection	Oral, tablet or liquid	Oral, dispersed tablet
Dosage	20-60 mg/kg 3-7 times per week. Children's dose up to 30 mg/kg	75-100 mg/kg/day	10-40 mg/kg/day
Contra-indications	Hyper-sensitivity	Previous agranulocytosis Pregnancy – teratogenic risk	Hyper-sensitivity Estimated creatinine clearance < 60ml/min Pregnancy

Desferrioxamine (DFO)

Iron chelation therapy with subcutaneous DFO infusions given 5-6 days per week over 8-12 hours and rigorously maintained has been the accepted chelation regime in TM for over 30 years and there is a wealth of long-term clinical data describing its benefits and adverse effects (Olivieri and Brittenham 1997).

Efficacy

Evidence for the efficacy of DFO will not be reviewed again here in detail. Long term treatment is associated with improved survival, mainly through reduction of cardiac mortality (Brittenham, Griffith *et al.* 1994; Olivieri, Nathan *et al.* 1994; Borgna-Pignatti, Rugolotto *et al.* 2004). DFO reduces hepatic iron(Brittenham, Griffith *et al.* 1994), stabilises or improves hepatic fibrosis(Barry, Flynn *et al.* 1974; Aldouri, Wonke *et al.* 1987) and also protects against endocrine complications(Borgna-Pignatti, Rugolotto *et al.* 2004; De Sanctis, Roos *et al.* 2006).

Some patients who are apparently adhering well with subcutaneous DFO and have low body iron stores as assessed by sequential SF can still develop cardiac dysfunction due to myocardial iron (Tanner, Galanello *et al.* 2006; Tanner, Galanello *et al.* 2008). Furthermore, endocrine complications are still observed in patients who have been chelated with DFO from an early age (De Sanctis 2002; Borgna-Pignatti, Rugolotto *et al.* 2004; Cunningham, Macklin *et al.* 2004; De Sanctis, Eleftheriou *et al.* 2004; De Sanctis, Roos *et al.* 2006). This probably reflects earlier periods of poor adherence or, in older patients, delayed start of DFO in the period prior to 1980, when it became accepted as standard therapy. Inadequate control of NTBI in the DFO-free period between infusions is likely to increase the risk of iron toxicity.

When tissue damage is already present, intensification with continuous intravenous DFO can reverse cardiac dysfunction (Davis and Porter 2000; Anderson, Westwood *et al.* 2004), but there is no evidence that endocrine dysfunction, once established, can be reversed by DFO monotherapy.

Infusion/delivery systems

Disposable elastomeric pre-filled infusers are usually preferred to battery operated infuser pumps in older children and adults. These are light and noiseless, and facilitate subcutaneous chelation during daytime activities. For most patients, this translates to better acceptability,

adherence and efficacy. They are prepared in a sterile pharmacy facility, and often delivered to the patient's home, to optimise convenience. A battery operated infuser pump (e.g. Cronos®) is recommended for young children up to the age of 5; use of disposable infusers in this age range is not recommended because the infusion volume is excessive (at least 20ml). Small gauge 'thumb-tack' type subcutaneous needles (e.g. Thalaset®) are recommended as they are easier to use and less painful than traditional 'butterfly needles'.

Vitamin C

Oral vitamin C has been shown to enhance mobilisation of iron and to increase the efficacy of chelation with DFO. Children and adults chelating with DFO should take ascorbic acid, either as a regular daily dose, or prior to each infusion. The recommended dose is 200mg (adults) or 100 mg for children.

There is a potential risk of increasing toxic iron levels and precipitating cardiac toxicity in patients who are heavily iron loaded and at risk of cardiomyopathy. Ascorbic acid should not be used in the early stages of intensive chelation therapy for patients with cardiac failure or with myocardial T2* <10 msec.

There is currently no evidence that ascorbic acid enhances chelation efficacy with DFX or DFP.

Adherence

Adherence to DFO therapy has been a major challenge facing thalassaemic patients and those involved in their care. Patient surveys have consistently shown that regular subcutaneous infusions of DFO have a major negative impact on quality of life (Pakbaz, Fischer *et al.* 2005; Telfer, Constantinidou *et al.* 2005; Pakbaz, Treadwell *et al.* 2010; Trachtenberg, Mednick *et al.* 2012).

Adherence is enhanced in childhood when the parents understand the rationale for the therapy, and feel confident in setting up the DFO infusions safely and efficiently. Additionally, long-term adherence is improved if the child takes responsibility for the infusions at an early age. It is important to offer practical support, and psychological support in identifying and addressing problems which may impede adherence.

Adverse effects

The commonest side effects are pain, swelling and itching at infusion sites. These symptoms usually subside within 12 hours of the infusion, but can persist longer, with significant impact on quality of life and reduced adherence to the prescribed regime.

Abnormalities of bone growth such as vertebral dysplasia leading to disproportionate short trunk, pseudo-rickets and genu valgum have been described in pre-pubertal children treated with relatively large doses of DFO (>40mg/kg) and are more likely to occur in childhood when iron stores are low (De Virgiliis, Congia *et al.* 1988). High-tone sensorineural hearing loss is a serious adverse effect of DFO which can be anticipated by calculating average daily dose of DFO/serum Ferritin >0.025 (e.g. higher risk, at ferritin 1000 µg/l, if receiving more than average of 25 mg DFO/kg/day) (Porter, Jaswon *et al.* 1989). Early identification of DFO toxicity, with annual checks of pure tone audiometry, and sitting and standing heights during childhood, are essential for prevention of irreversible damage (Bronspiegel-Weintrob, Olivieri *et al.* 1990; Olivieri and Brittenham 1997).

Yersinia infection, presenting with fever, diarrhoea and abdominal pains, is facilitated by iron loading and DFO therapy (Lesic, Foulon *et al.* 2002). Severe and occasionally fatal Klebsiella infection has also been associated with DFO (Li, Shing *et al.* 2001; Chung, Ha *et al.* 2003; Chan, Chan *et al.* 2009). Patients developing high fever or signs of infection should be instructed to stop DFO chelation and seek medical advice as soon as possible

Deferiprone (DFP)

Deferiprone is orally active and chelates iron in a 3:1 drug: iron complex. The affinity for iron is relatively low compared to DFO and DFX. DFP is a small, non-charged molecule, and crosses the cell membrane readily, suggesting suitability as an intracellular chelator. It has a relatively short plasma half-life and consequently t.d.s. or even q.d.s. dosing is needed to optimise drug levels

over the 24 hour period. Drug and iron complexes are predominantly excreted in the urine, giving the urine a red colour.

Current licensed indications are given in Table 10.2. There is experience using DFP in young children as first line chelation (Aydinok, Nisli *et al.* 1999; Lucas, Perera *et al.* 2000; Lucas, Perera *et al.* 2002; Gomber, Saxena *et al.* 2004; Bartakke, Bavdekar *et al.* 2005; El-Alfy, Sari *et al.* 2010; Makis, Chaliasos *et al.* 2013; Botzenhardt, Sing *et al.* 2015; Songdej, Sirachainan *et al.* 2015). Recently, a liquid preparation has been evaluated in young children and appears to be well tolerated and effective (El-Alfy, Sari *et al.* 2010).

Efficacy

There is substantial published clinical experience with use of DFP (Cohen, Galanello *et al.* 2000, Ceci, Baiardi *et al.* 2002), and unpublished clinical experience in large centres where some patients have been effectively chelated with DFP monotherapy for many years. Randomised controlled studies comparing DFO with DFP have shown similar efficacy over 6 to 12 months in controlling SF and LIC (Maggio, D'Amico *et al.* 2002; Pennell, Berdoukas *et al.* 2006; Fisher, Brunskill *et al.* 2013). Liver iron, however, may not be adequately controlled over the longer term with DFP monotherapy at 75mg/kg/day (Hoffbrand, F *et al.* 1998; Olivieri, Brittenham *et al.* 1998; Tondury, Zimmermann *et al.* 1998; Hoffbrand, Cohen *et al.* 2003).

A consensus view, based on published trials and clinical experience, is that DFP therapy produces a reliable and rapid reduction in myocardial iron loading compared with other chelating drugs. Ventricular function assessed by cardiac MRI (left and right ventricular ejection fraction) also increases more consistently, and there is a reduced risk of clinical cardiac events such as arrhythmia, cardiac failure and cardiac death (Anderson, Wonke *et al.* 2002; Piga, Gaglioti *et al.* 2003; Pepe, Lombardi *et al.* 2006; Pepe, Meloni *et al.* 2011; Pennell, Udelson *et al.* 2013).

Adverse effects

Adverse effects include agranulocytosis, neutropenia, and arthropathy – the latter in 4-50% (the higher rates reported in series from the Indian sub-continent). Gastro-intestinal disturbance, intermittent elevation in ALT, zinc deficiency, and increased appetite are often reported (Hoffbrand, F *et al.* 1998; Cohen, Galanello *et al.* 2000; Ceci, Baiardi *et al.* 2002; Maggio, D'Amico *et al.* 2002; Naithani, Chandra *et al.* 2005; Fisher, Brunskill *et al.* 2013). Some patients have to discontinue DFP as a result of these side effects. Arthropathy is usually reversible and in some cases, DFP can be re-introduced once symptoms have subsided.

Agranulocytosis (absolute neutrophil count of < 0.5 x10^9/l), is a severe and potentially fatal adverse effect of DFP. In pooled data from clinical trials, agranulocytosis occurred in 1.5% of patients, at a median of 162 days after starting therapy. There was no significant association of agranulocytosis with DFP dose or with splenectomy status. Episodes were more common in children, but this was not statistically significant. Episodes were rapid in onset, and not generally pre-empted in clinical trials where weekly monitoring of FBC had been undertaken. There was a high risk of recurrence of agranulocytosis with rechallenge. Similar observations were made in post-marketing surveillance. (Tricta F *et al.*, submitted for publication, 2016). No genetic predisposing factors for DFP-associated agranulocytosis have been identified.

Neutropenia (neutrophil count in the range 0.5 – 1.5 x10^9/l) was observed in 6.7% of patients in pooled data from clinical trials. Episodes were more common in splenectomised patients, and were usually self-limiting, but could be recurrent and lead into agranulocytosis. In one paediatric trial 100 children were treated with a liquid formulation of DFP over 6 months. Six children with mild neutropenia (1 – 1.5 × 10^9/l) were managed by continuing therapy and monitoring with daily blood counts. Four resolved, one had a further episode of neutropenia and another child developed agranulocytosis after two episodes of mild neutropenia (El-Alfy, Sari *et al.* 2010).

Acceptability and quality of life

Adherence to chelation therapy is generally improved in patients switched from DFO to DFP (Olivieri, Brittenham *et al.* 1998; Telfer, Constantinidou *et al.* 2005), and those who find DFO infusions intolerable may have better long- term control of iron stores with DFP.

Deferasirox (DFX)

DFX is an orally active chelating agent, which chelates iron in a 2:1 drug: iron complex. The affinity for iron is intermediate between DFP and DFO. DFX is neutrally charged and lipophilic and crosses cell membranes readily. The chelator: iron complex is positively charged and this may impede egress from the cell. It has a long plasma half-life and once daily dosing usually produces adequate drug levels over the whole 24 hour period. Drug and iron complexes are predominantly excreted in the faeces (Vlachodimitropoulou Koumoutsea, Garbowski *et al.* 2015).

Efficacy

DFX has undergone a rigorous process of drug development to assess efficacy and safety. Trials have included patients with TM (Nisbet-Brown, Olivieri *et al.* 2003; Cappellini, Cohen *et al.* 2006; Galanello, Piga *et al.* 2006; Piga, Galanello *et al.* 2006), and other transfusion-dependent conditions. In the pivotal Phase III trial, DFX was compared with DFO in 596 TM patients. 50% of subjects were under the age of 16 years, and the trial included chelation-naïve children as young as 2 years. Over 12 months, DFX at doses of 20 or 30 mg/kg/day was comparable in efficacy to DFO in controlling LIC and SF. At doses of 30mg/kg, neutral or negative iron balance was achieved in 82-96%, and at 20mg/kg in 47-75% of patients depending on transfusion intensity (Cappellini, Cohen *et al.* 2006; Cohen, Glimm *et al.* 2008). In a 4 year non-controlled extension study, SF levels continued to fall and LIC improved significantly. There was also evidence of normal growth and pubertal development in adolescents (Cappellini, Bejaoui *et al.* 2011).

Subsequent non-randomised trials have confirmed that DFX can produce a significant reduction in SF and LIC, but with variability in response between patients. Higher doses (usually >25mg/kg) are required to reduce transfusion iron overload in patients with higher intensity of transfusion, or with higher levels of iron overload at baseline. 3 monthly dosage adjustments, within the range 10 – 40 mg/kg/day, based on trends in SF, are recommended in order to optimise chelation efficacy and minimise adverse effects (Taher, El-Beshlawy *et al.* 2009; Cappellini, Porter *et al.* 2010). Reduction of iron stores in heavily iron loaded patients may take several years of regular DFX therapy. About 80% of patients who respond to DFX chelation with a decline in SF have a corresponding decline in LIC. Conversely, clinically useful reductions in LIC have been seen in about 50% of patients with no significant reduction in SF.

The efficacy of DFX in removing myocardial iron and improving left ventricular function has also been evaluated. Preliminary reports suggested an improvement in T2* but not in ejection fraction in patients with mild to moderate myocardial iron loading (Pennell, Porter *et al.* 2010; Pennell, Carpenter *et al.* 2011; Pennell, Porter *et al.* 2011; Pennell, Porter *et al.* 2012). The Cordelia trial compared DFX at 40mg/kg/day (a relatively high dose) with DFO at 50-60mg/kg 5-7 days per week in 197 randomised subjects. Patients had myocardial iron loading (T2* 6-20 milliseconds) but no signs of cardiac dysfunction. DFX and DFO therapy resulted in a similar improvement of about 4 ms in T2* over 24 months. There was no change in LVEF in either group. The conclusion of the trial was that DFX is non-inferior to DFO in improving myocardial T2* (Pennell, Porter *et al.* 2014; Pennell, Porter *et al.* 2015)

Adverse effects

These include self-limiting skin rash (10.8%), gastro-intestinal symptoms (15.2%) and less frequently drug induced hepatitis, hepatic failure, gastrointestinal ulceration, gastrointestinal haemorrhage, renal tubular damage, lens opacities and sensorineural hearing loss (Exjade SPC 2013). A mild dose-dependent increase in serum creatinine is common. This generally occurs during the first 4-8 weeks of therapy or after dose increase. In the phase III study, dose reduction was necessary in 13% of patients on DFX because of persisting changes, and the serum creatinine returned to baseline level in 25% of these (Cappellini, Cohen *et al.* 2006). The remainder continued to show mild increases, but still within the normal range for creatinine. In the extension study, increase in serum creatinine was observed in 11%, and was more prevalent in the first year of study than in the subsequent 4 years. These increases were more common in patients on higher doses (25-35 mg/kg/day), and were usually reversible on lowering the dose. There was no evidence of progression in renal abnormalities (Cappellini, Bejaoui *et al.* 2011).

Gastrointestinal intolerance due to symptoms of abdominal pain, diarrhoea or nausea is common (up to 26%) and requires dose reduction or occasionally discontinuation. GI intolerance is more common during the first year of therapy, and in patients on higher doses of DFX. Elevated transaminase (ALT) is also common, but generally in the range 2 – 5 × upper limit of normal. The causes and consequences of transient elevations in ALT during DFX therapy need further clarification. The manufacturers recommend that if there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, DFX should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

Upper gastrointestinal ulceration (sometimes multiple) and haemorrhage have been reported in patients on DFX. The manufacturers recommend that physicians and patients are aware of this complication, and know to initiate additional evaluation and treatment if a serious gastrointestinal adverse reaction is suspected. Physicians should be cautious in prescribing substances that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, at the same time as DFX. It should also be used with caution in patients receiving anticoagulants and in patients with platelet counts below 50,000/mm^3 (50×10^9/l).

Acquired Fanconi's syndrome (proximal renal tubulopathy) is an important but rare adverse effect reported particularly in children and adolescents, some of whom were well chelated with low SF. The biochemical features include renal impairment, and acidosis with hypokalaemia, hypophosphataemia, glycosuria and proteinuria. It is expected to resolve with discontinuation of DFX.

Acceptability and quality of life

Prospective evaluation of patient-reported outcomes in the Phase III study showed that patients preferred DFX over DFO. A large majority on DFX found the once daily oral therapy convenient and were willing to continue with it (Cappellini, Bejaoui et al. 2007).

Combination regimes

Combining iron chelating drugs in tailor-made regimes was first proposed by Wonke et al. (Wonke, Wright et al. 1998) as a means of improving adherence and efficacy of chelation in patients with severe iron overload who had previously used DFO or DFP monotherapy. The concept of combination chelation therapy has developed to encompass a wide range of drug combinations and dosing regimes, and the lack of agreed standard terminology has led to confusion in comparing results in terms of efficacy, safety and acceptability.

Combinations include simultaneous daily administration of drugs, sequential therapy where oral drug is given every day of the week together with a variable frequency of overnight DFO infusions, and alternating therapy regimes where different drugs are given on alternate days. Simultaneous or sequential therapy might allow a chelator which rapidly crosses cell membranes to access intracellular pools, and after leaving the cells to donate iron to another chelating drug with higher avidity for iron. This process can result in enhanced efficiency of excretion of chelator-iron complexes from all body iron pools. Evidence for this 'shuttle' hypothesis has come from in vitro studies (Evans, Kayyali et al. 2010; Vlachodimitropoulou Koumoutsea, Garbowski et al. 2015) which confirm synergistic chelation of intracellular iron, by combinations of DFO/DFP, DFO/DFX and DFP/DFX.

Iron balance studies in TM patients have also demonstrated that combinations of drugs given simultaneously enhance iron excretion. For both DFO/DFP and DFO/DFX combinations, iron removal was more than the sum of the excretion with individual drugs in some patients, supporting the concept of a shuttling mechanism. Chelation was generally more effective with the DFO/DFP combination than with DFO/DFX, and with the latter combination, not all patients were in negative iron balance (Galanello, Agus et al. 2010; Grady, Galanello et al. 2013).

Combined DFO and DFP

At present, DFO and DFP is the combination most widely studied and used in clinical practice. Clinical trials have included non-controlled pilot studies, and randomised comparative studies. These have generally been small, conducted over one year (too short for adequate assessment of

long-term effects), have used variants of daily sequential therapy with DFP given every day at a dose of 75 – 100mg/kg and DFO infusions varying in frequency from 2 – 7 nights per week, or alternate day therapy.

A prospective randomised trial in patients with abnormal cardiac T2* has shown a significant improvement in cardiac iron loading and LVEF in patients on combination therapy compared to DFO monotherapy, with a difference of 3% change in ejection fraction over one year (Tanner, Galanello *et al.* 2007). There is also good evidence that intensive combination therapy with daily DFP and subcutaneous DFO 5 – 7 days per week, overnight or with initial continuous infusion at 40-60mg/kg is effective for reversing cardiac failure (Wu, Chang *et al.* 2004; Porcu, Landis *et al.* 2007; Tanner, Galanello *et al.* 2008). It is generally thought that endocrine complications, once established, are irreversible, but intensive combination chelation therapy has shown improvements in patients with impaired glucose tolerance (Farmaki, Angelopoulos *et al.* 2006). There have also been reports of improved long-term outcomes and survival in cohorts of patients switched from single agent regimes (mostly DFO) to combination therapy (Telfer, Coen *et al.* 2006; Telfer, Warburton *et al.* 2009; Lai, Grady *et al.* 2010).

In summary, the combination of DFO and DFP given as a daily sequential or simultaneous regime is a potent chelation modality, which can enhance urinary iron excretion and produce significant negative iron balance. SF and LIC can be controlled in patients who have become severely iron overloaded, and myocardial iron is generally depleted at a quicker rate than with a single agent (Pennell, Udelson *et al.* 2013). Long-term therapy may reverse cardiac disease and enhance survival in TM patients. The combined use of DFO and DFP on alternate days is less effective, but may be of benefit for some patients who have difficulty in adhering to standard therapy because of intolerance of individual drugs.

There is currently no consensus about initial dosing regimes and monitoring of therapy. Although negative iron balance is usually achievable if DFO is given at least two times per week together with DFP (Galanello, Agus *et al.* 2010), doses of DFP and DFO and frequency of DFO infusions may need to be higher if iron loading is severe. Dosage reductions are necessary in order to avoid chelator toxicity as iron levels drop, and it is often possible to discontinue DFO altogether whilst continuing DFP monotherapy once serum ferritin and liver iron level are consistently in the low-risk range.

Adverse effects with combination therapy are common and the precautions concerning monotherapy with DFO and DFP should be applied with a high level of vigilance.

Combination of DFX with DFO

Currently there is limited data on clinical use of DFO and DFX combination (Lal, Porter *et al.* 2013; Cassinerio, Orofino *et al.* 2014; Aydinok, Kattamis *et al.* 2015). The Hyperiron study (Aydinok, Kattamis *et al.* 2015) was a prospective non-randomised single-arm study of the combination DFX (20-40 mg/kg/day) and DFO (40mg/kg over at least 8 hrs 5 times per week) in patients with significant myocardial iron loading (T2* 5-10 msec) but normal ventricular function, and with evidence of severe hepatic iron loading. 36 of 60 (60%) patients completed 24 months in the study. T2* increased from mean 7.2 to 9.5 msec and LIC reduced from 33.4 to 12.8 mg/g dw. Adverse events led to discontinuation in 8% and dose reduction in 42%.

Combination of DFX and DFP

The in vitro synergistic effect of DFX and DFP in removal of intracellular iron is more pronounced than with other combinations (Vlachodimitropoulou Koumoutsea, Garbowski *et al.* 2015), but clinical experience with this combination remains limited (Balocco, Carrara *et al.* 2010; Berdoukas, Carson *et al.* 2010; Voskaridou, Christoulas *et al.* 2011). A randomised trial in 96 children at two Egyptian centres compared DFO (40mg/kg overnight infusion 6 per week) + DFP (75 mg/kg/day in two divided doses per day) with DFX (30mg/kg/day, evening dose) + DFP (75 mg/kg in two divided doses per day) (Elalfy, Adly *et al.* 2015). There were significant improvements in both groups in SF, LIC and myocardial T2* at 6 months and 1 year. The difference between the two groups was only significant for myocardial T2* with DFX/DFP combination resulting in an increased rate of change. Quality of life improved in both arms, but patient satisfaction was higher for the DFX/DFP combination. There were no significant side effects leading to discontinuation of chelation regimes and no deaths during the study.

The results indicate that other combinations may have an important role in controlling high iron burden in selected patients, but cannot yet be recommended for routine therapy. These regimes should be further evaluated in controlled clinical trials. Decisions about initiation of treatment, monitoring and changing of doses should be made by the specialist centre. Outside of clinical trials, funding would need to be agreed on an individual basis with specialist commissioners.

Adherence to chelation therapy

The most common reason for inadequate control is poor adherence to the prescribed regime – and this problem has continued in the current era of oral iron chelation therapy. In all cases, a careful exploration of problems with adherence and motivation is needed, leading to formulating an individualised strategy to enhance adherence. This may involve further education about the importance long-term control of iron stores to prevent future morbidity and mortality, psychological support, increased supervision by carers or health care staff, peer support, and a radical change in life style.

Comparison of chelators: Systemic reviews and meta-analyses of iron chelation drugs and strategies in thalassaemia

There have been three Cochrane review updates published since the last edition of the *Standards* (Fisher, Brunskill *et al.* 2013; Meerpohl, Schell *et al.* 2014). The authors of one of these reviews comment that most of the randomised controlled trials were small and conducted over too short a time period to provide data on important clinical outcomes. There were significant variations in the patients studied in different trials, and methodological differences in assessing end points relating to iron overload and clinical outcomes, so that meta-analysis of data was not possible. The authors concluded that DFO, DFP and DFX can all produce significant reductions in iron stores in transfusion-dependent, iron-overloaded TM patients. Long term trials were recommended in order to compare chelator efficacy in terms of significant clinical end-points.

NHS England has developed a clinical commissioning policy proposal for the treatment of iron overload in patients with chronic inherited anaemias. The policy proposes that monotherapy with each of DFO, DFP and DFX and combination of DFO and DFP should be routinely commissioned for patients. MRI should be available for monitoring. Oversight of iron chelation should be undertaken by experienced clinicians at a Specialist Centre, and decisions should take into account the clinical circumstances together with the views of the patients and carers. This policy is under consideration by the Clinical Priority Action Group (CPAG) and a decision is expected in summer 2016.

Guidelines for control of iron overload with iron chelating drugs

Initiation of chelation therapy

The long-standing recommendation to start chelation once SF reaches 1000 µg/l (on at least two readings), after 10-12 transfusions or after significant liver iron loading, was designed to avoid chelator toxicity in children starting therapy too early (TIF Guidelines, 3rd Edition 2014; UKTS Guidelines 2nd Edition 2008; Olivieri and Brittenham 1997). One recent study has investigated the progressive saturation of serum transferrin with iron, and appearance of LPI in TM children not yet started on chelation. The authors suggested that chelation could be started when TSAT>90% and more than 1000g red cells transfused (Danjou, Cabantchik *et al.* 2014).

There are no randomised prospective data comparing initiation of therapy with different chelation agents. DFO has been used for many years as initial chelation therapy and there is substantial clinical experience with its use in children age >2. There is study evidence for the safety and efficacy of DFX in young children, including those who are chelation-naïve, and DFX would be a good choice for initiation were it not for the limitations specified in its current EU licensing agreement. There are limited data on use of DFP in young children, and DFP is not currently recommended as a first line iron chelation drug.

Monitoring of chelation therapy

Table 10.3: Current recommendations for toxicity monitoring, from the respective SPCs

	DFO	DFP (or combination with DFO)	DFX
Neutrophil count	Not required	Weekly during therapy	Not required
Creatinine	Not required	Not required	Twice before start, then weekly during first month after initiation and change of dose. Thereafter monthly
ALT	Monthly	Monthly	Twice before start, then 2 weekly for first month after initiation of therapy. Thereafter monthly
Urinalysis	Not required	Not required	Twice before start, then weekly during first month after initiation and change of dose. Thereafter monthly
Pure tone audiometry	Annual	6-12 monthly for combination DFO and DFP, not if used as single agent	Annual
Ophthalmology	Annual	6-12 monthly for combination DFO and DFP, not if used as single agent	Annual

The chelation regime should be reviewed every 3 months, and decisions regarding dose adjustment should take into account:

- Problems with adherence as reported by the patient
- Clinical evidence of adverse effects
- Biochemical and haematological evidence of toxicity, although results of monitoring tests should be checked more often in case of substantial derangements
- Trend in SF
- The annual monitoring tests for tissue iron (LIC and cardiac iron concentration by MRI)
- Past history of iron-related tissue damage including liver, endocrine and heart disease
- For children and adolescents, additional monitoring of height centile, height velocity, and symptoms such as joint pains, stiffness or swelling.

Modification of iron chelation therapy to optimise control of iron overload.

All licensed chelators can be effective in maintaining iron balance and reducing iron stores in overloaded patients. However, in practice there is variability in individual response to each chelator, and differing susceptibility and tolerance to their adverse effects.

There are particular clinical situations in which a decision may need to be made about changing chelation. In most cases these are not specifically addressed in randomised controlled trials. Although DFO is still regarded as first line chelation, a flexible approach should be taken to ensure that a chelation regime can be identified which achieves the desired chelation goals and is acceptable to the patient.

With regard to management of myocardial iron overload there are well conducted clinical trials, summarised above. These studies are generally consistent in showing an increased rate of myocardial iron clearance and a more reliable increase in LVEF with DFP at the higher dose range compared to DFO given as a standard s.c. infusion. DFX at higher dose range is non-inferior to DFO but does not consistently bring about an improvement in LVEF.

Myocardial iron appears to clear more quickly with continuous i.v. DFO (Anderson, Westwood *et al.* 2004) or DFO/DFP combination (Tanner, Galanello *et al.* 2007) compared to DFX regimes. This may result from differing chelator efficacy, but could also relate to the degree of iron loading in

the heart and liver at baseline. It has been shown that cardiac iron decreases only after liver iron is controlled, and it is noteworthy that patients in the DFX trials had higher LIC than in the DFP trials. Despite these reservations it is advisable for patients with the severest degrees of myocardial iron loading to be chelated with continuous intravenous DFO or DFO/DFP combination. DFX monotherapy (at a dose around 40mg/kg/day) should only be used in patients unwilling or unable to sustain treatment with continuous DFO or DFO/DFP combination. In all patients careful review of compliance and trends in SF, and echocardiographic parameters should be undertaken regularly to ensure that the patient continues to engage with treatment.

Adjustments to chelation regime with acceptable iron stores (SF consistently 500 – 1500 µg/l, LIC 3 – 7 mg/g dw, myocardial T2* > 20 ms)

There is no indication to switch chelation regime, but for patients who have maintained acceptable iron stores with DFO monotherapy, a switch to DFX can be considered if adherence to DFO infusions is difficult.

Adjustments to chelation regime with increasing or high total body iron stores and no cardiac iron (SF > 1500 µg/l, LIC > 7 mg/g dw, myocardial T2* > 20 ms)

The aim of chelation therapy in this group is to bring SF and LIC down to acceptable levels. Options would be as follows:

Patient on DFO:

- Optimise adherence
- Optimise DFO dosage and infusion regime by:
  - Increasing the frequency of infusions to 6 or 7 times per week
  - Increasing the duration of infusion to at least 12 hours
  - Increasing DFO dose to 50 mg/kg per infusion, if an adult.
- Consider switching to either DFX or to DFP/DFO combination.

Patient on DFP or combined DFP/DFO:

- Consider switching to DFX.
- Increase DFP dosage up to 100 mg/kg/day and/or increase frequency and dosage of DFO.

Patient on DFX:

- Bear in mind that it may take several years for SF and LIC to reach target levels in those with severe body iron burden. Higher doses of DFX above 30 mg/kg/day should be considered and should be continued provided there is a trend to decreasing SF and LIC.
- Consider switching to either DFO or DFO/DFP combination. In exceptional circumstances where other options are not possible, DFX/DFO combination can also be considered. The latter has been shown to produce a rapid decrease in liver iron stores
- DFX should be continued provided there is a trend to decreasing SF and LIC. Dose should be increased every 3 months within the licensed range (20-40mg/kg/day) in increments of 5 mg/kg.

Adjustments to chelation regime with moderately increased cardiac iron and satisfactory body iron stores (SF consistently 500 – 1500 µg/l, LIC < 7 mg/g dw, myocardial iron 10 – 20 ms)

- Consider switching to DFP 75 – 100 mg/kg/day seven days per week. The dose of DFP should be escalated depending on response as determined by myocardial T2*.

Adjustments to chelation regime with moderately increased myocardial and high body iron stores (SF consistently > 1500 µg/l, and/or LIC > 7 mg/g dw, myocardial iron Cardiac T2* 10 – 20 ms)

Three options can be considered:

1. Daily combination of DFO 40 – 50mg/kg, (initially at least 4-5 infusions per week) plus DFP 75-100mg/kg/day seven days per week. The dose of DFP should be determined by the cardiac T2* value.

2. DFX at maximal dosage (35-40 mg/kg/day)
3. Intensive DFO chelation at 50-60mg/kg 6-7 days per week with optimal adherence. Continuous subcutaneous or continuous i.v. DFO infusion through an indwelling venous device would be options.

Adjustments to chelation regime with severe myocardial iron loading (Myocardial T2* < 10 ms) not clinically in HF

If iron stores are low (SF < 1000 µg/l, LIC < 7 mg/g dw), DFP monotherapy should be considered first line therapy. The dose should be escalated to 100 mg/kg/day.

If iron stores are high (SF > 1000 µg/l, LIC > 7 mg/g dw), DFO/DFP combination is recommended. DFP should be given at 85-100 mg/kg/day and combined with DFO infusions (40 – 60mg/kg/day), either continuous i.v., continuous s.c., or intermittent s.c. infusions over 12 hours 5 – 7 times per week depending on iron levels.

If DFP therapy is not tolerated, the alternative options are continuous i.v. DFO (40-60mg/kg/day, 7 days per week) or high dose DFX (30-40 mg/kg/day) with careful monitoring for adverse effects. Chelator doses should be adjusted based on SF and LIC for avoiding chelator toxicity.

Adjustments to chelation regime with severe myocardial iron loading (Myocardial T2* < 10 ms), clinically in HF

DFO at a dose 50-60 mg/kg should be started immediately via a peripheral line and given as a continuous 24 hour i.v. infusion. A long-term intravenous line should be inserted to facilitate long-term therapy. Simultaneous DFP (75-100mg/kg/day) should be combined with the DFO infusions as soon as possible.

Adjustments to chelation regime – dose decreases with low iron stores

The risk of chelator toxicity is likely to be higher when body iron stores are either low (SF persistently < 1000 µg/dl and/or DFO mg/kg to serum ferritin ratio > 0.025, or when LIC is < 3 mg/g dw) or when SF is decreasing rapidly. The association of chelator toxicity and low iron stores is less clear in the case of DFP and DFX but the same precautions should nevertheless be taken, particularly in SF < 500 µg/L). DFP is probably the least toxic chelator in this scenario.

Chelator dose should be reduced and may need to be maintained in a very low range (e.g. DFO 10 – 20mg/kg per infusion 5 per week; DFX 5 – 10mg/kg/day, DFP 50 – 75 mg/kg/day) in these patients. Licensing of DFX recommends considering an interruption of chelation when SF is <500. This may not be the best strategy in regularly transfused patients as they will continue to load iron at a rate of 0.3 – 0.5 mg/kg/day. An alternative approach is to continue chelation at very low dosage (e.g. DFX 5 – 10 mg/kg/day) with monthly monitoring of adverse symptoms, increment in SF, creatinine, ALT and urinalysis.

• Chelator dose should be reduced if there is a rapid decline in SF (> 500 over a three month period), and SF is persistently < 1000 µg/dl, and when LIC is <3 mg/g dw, cardiac T2* is > 20ms.

• DFO dose per infusion should be reduced rather than the frequency of infusion.

• Conversion from DFO to oral chelation should be considered if SF is consistently in the range 500 – 750 µg/l or LIC < 3 mg/g dw.

Iron chelation in special circumstances

Pregnancy

There are reports of serious adverse outcomes during pregnancy, including heart failure and dysrhythmias. This is unsurprising since cardiac workload increases significantly, and cardio-protective iron chelation therapy is often discontinued during the nine months of pregnancy to avoid toxicity to the fetus. Women who are planning to become pregnant should undergo a period of intensive chelation to reduce SF, LIC and myocardial iron to optimal levels before attempting to become pregnant.

Evidence from case reports suggests that the risk of DFO toxicity may be low when used during the later stages of pregnancy (Singer and Vichinsky 1999), however in the case of spontaneous pregnancy, all chelator drugs should be discontinued as soon as the pregnancy is diagnosed. The

standard advice for DFO to be withheld throughout pregnancy can be reviewed in cases of high iron loading where the risk of cardiac complications is judged to be high. DFO can be considered from 20 weeks gestation. Some centres recommend continuous i.v. DFO, 20 mg/kg/24 hours during labour to reduce the possible risk of dysrythmia or cardiac failure during and after childbirth.

For DFX, potential reproductive toxicity has been investigated in rats and rabbits. DFX was not teratogenic, but caused increased frequency of skeletal variations and stillborn pups in rats at high doses. There were no other effects on fertility or reproduction (Exjade™ SPC). There have been several case reports of successful pregnancies without evidence of fetal toxicity in women taking DFX during the early stages of pregnancy. The potential risk for humans is unknown, and as a precaution, it is recommended that Exjade™ is not used during pregnancy unless clearly necessary.

DFP is contraindicated in pregnancy (Ferriprox™ Summary of Product Characteristics). This is based on absence of adequate data from the use of deferiprone in pregnant women and studies in animals showing reproductive toxicity. Women of childbearing potential must be advised to avoid pregnancy while taking DFP, to take contraceptive measures and must be advised to immediately stop taking deferiprone if they become pregnant or plan to become pregnant.

A common practical approach for planned or assisted pregnancy is to stop oral chelators three months before likely conception, continuing with desferrioxamine until the time of ovulation.

Renal impairment

Managing iron overload in patients with renal impairment or renal failure is challenging, and there are relatively few published data to guide recommendations. There are potential problems with all three licensed chelators.

DFO is not reported to be nephrotoxic, but should be used with caution in patients with renal impairment because the kidneys are one of the routes for excretion of DFO metabolites and DFO: iron complexes. Although DFO is used to chelate aluminium in haemodialysis patients, the dosage recommended is only 5 mg/kg. When given at iron chelation dosing level (40 mg/kg) plasma drug levels are significantly increased, suggesting that DFO dosage in patients with renal failure should be reduced in order to avoid toxicity (Desferrioxamine SPC).

There are no data available on the use of DFP in patients with renal impairment. DFP is not reported to be nephrotoxic but should be used with caution in patients with renal failure because free drug, DFP metabolites and DFP: iron complexes are excreted predominantly via the kidneys (Ferriprox™ SPC).

DFX is potentially nephrotoxic and is contraindicated in patients with estimated creatinine clearance < 60 ml/min. For patients with end stage kidney disease on renal replacement therapy, DFX could potentially have a role, since the kidney is not the predominant site of drug metabolism or elimination. In one study of non-thalassaemic patients undergoing haemodialysis treated with intravenous iron, a dose of 10 mg/kg was not sufficient to achieve a plasma concentration in the therapeutic range, while 15 mg/kg maintained plasma concentration well above that expected for this dose (40 – 50 mmol/l). Although adverse clinical events were not reported, these observations suggest the possibility of unpredictable toxicity with therapeutic dosing (Maker, Siva *et al.* 2013).

In practice, the chelation regime in these patients needs to be formulated on an individual basis, taking into account the degree of iron loading and likely risk of morbidity and mortality from iron overload in the short to medium term. Decisions on treatment should be made in consultation with the patient's renal specialist. Goals of optimal chelation will be difficult to achieve, as there is an increased risk of chelator toxicity with dose escalation. Monitoring for auditory, ophthalmological and other toxicities should be done more frequently, perhaps every 3 months.

For patients with reduced creatinine clearance below 60ml/min, not yet on renal replacement therapy, prolonged infusions of low dose DFO (e.g. 10 mg/kg over 12 hours 6-7 per week) may be helpful in reducing the risk of toxicity from toxic iron, and could be combined with low dose

DFP (50 – 75 mg/kg/day in three or four divided doses), although there is no published data to support the safety and efficacy of this approach.

For patients with end stage renal failure on renal replacement therapy, it is reasonable to use DFX, at a low therapeutic dose (20 – 25 mg/kg). For patients on haemodialysis, DFO 5 mg/kg once a week administered during the last hour of a dialysis as a slow intravenous infusion, to reduce loss of free active substance in the dialysate, may be used.

Requirements

Monitoring of transfusion iron overload

◆ The age of starting regular transfusions and iron chelation therapy should be documented for each patient.

◆ An annual record of blood usage (ml/kg pure red cells) and daily iron loading (mg/kg/day) should be maintained for each patient.

◆ SF should be measured 1 – 3 monthly, depending on which chelator the patient is receiving.

◆ LIC and myocardial iron should be monitored regularly in patients from age 7 or younger if able to tolerate MRI scanning without sedation.

◆ Liver iron concentration LIC should be assessed using a validated and standardised MR technique. R2 (Ferriscan®) is preferable to R2* because the methodology is more robustly standardised and has been licensed for use in routine clinical practice. MRI LIC methods should not be used interchangeably. In particular, sequential MRI LIC estimations in an individual patient should be done with the same methodology.

◆ Myocardial iron should be assessed by T2* Cardiac MRI using a validated protocol and validated software.

Initiation of iron chelation

◆ Iron chelation therapy should be started once all of the following criteria have been met:
  – 10 – 12 transfusions
  – Serum ferritin >1000µg/l on two readings
  – Age > 2

◆ For children transfused from a very young age, consideration might be given to starting earlier than this, if the serum transferrin saturation exceeds 90%, and/or when 1000 g of pure red cells have been transfused.

◆ Children < 6 years old should initially be offered sub-cutaneous DFO infusions. If there is failure to comply to DFO or the patient is intolerant, then DFX should be started as soon as possible to prevent worsening iron loading.

DFO

◆ Parents should be taught how to set up the infusions. This requires initial instruction and repeated checking of competence.

◆ DFO dose in children should normally fall within the range of 20 – 30mg/kg/infusion. For children the dose should not exceed 40mg/kg/infusion.

◆ Subcutaneous infusions of DFO should be given over 8 – 12 hours.

◆ Monitoring for DFO adverse effects should include:
  – 3 monthly height and weight (children and adolescents)
  – Annual sitting and standing height (children and adolescents)
  – Annual ophthalmology (Age > 5)
  – Annual pure tone audiometry (Age > 5)
  – Radiological investigation of any bony symptoms.

◆ DFO 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 and Klebsiella, and seek medical attention as soon as possible if they have symptoms or signs of severe infection.

DFP

◆ A protocol for management of the risk of agranulocytosis should be agreed prior to initiating treatment.

◆ The risk of neutropenia and agranulocytosis should be explained to the patient/carer prior to initiating therapy and re-iterated at follow-up visits. This should be supported by written information.

◆ DFP should not be initiated if the patient is neutropenic (baseline absolute neutrophil count (ANC) is less than 1.5×10^9/l)

◆ During treatment, if the neutrophil count falls to $0.5\text{-}1.0 \times 10^9$/l, DFP should be stopped immediately, together with all other medicinal products with a potential to cause neutropenia, and full blood counts repeated daily until acceptable neutrophil recovery.

◆ For neutrophil counts in the range $1.1 – 1.5 \times 10^9$/l, it may be reasonable to continue deferiprone with daily monitoring of FBC.

◆ In the case of agranulocytosis (neutrophil count $<0.5 \times 10^9$/l), consider admitting the patient to hospital. Daily injections of GSF should be started immediately and continue until two consecutive counts >1.5 x109/l. Clinical evidence of infection or fever >38 °C should be managed with broad-spectrum antibiotics using a standard neutropenic sepsis protocol.

◆ After a single, short-lived episode of neutropenia, rechallenge may be considered with careful monitoring of blood counts. After an episode of agranulocytosis, re-challenge is contraindicated.

DFX

◆ Monitoring for adverse effects, including blood tests for assessment of creatinine, liver function tests and urinalysis must be undertaken according to the current licensed recommendations for DFX.

Combination chelation therapy

◆ Combination chelation therapy with DFO and DFP should be considered when iron overload is not well controlled with single agent therapy. Daily sequential therapy is likely to be more effective in producing a negative iron balance and should be used in preference to alternate day therapy.

◆ There is insufficient evidence at present to recommend combinations of DFO with DFX or DFP with DFX. These combinations should only be used under exceptional circumstances.

◆ Once chelation goals have been obtained with combination therapy, single drug chelation therapy should be resumed.

Changing chelator regimen

◆ The regimen should be reviewed every 3 months. The decision to adjust doses or agents should take into account the following:

– Transfusion iron loading

– Past history of iron-related tissue damage including liver, endocrine and heart disease.

– Trend in SF, LIC and myocardial T2*

– Problems with adherence as reported by the patient

– Clinical evidence of adverse effects, including biochemical and haematological toxicity

◆ Specific recommendations for suitable regimen change for patients with different levels of serum ferritin, and varying iron levels in the myocardium and liver, are detailed above.

Special indications

Severe myocardial iron loading (Myocardial T2* < 10 ms) in a patient clinically in HF

◆ DFO at a dose 50 – 60 mg/kg should be started immediately via a peripheral line and given as a continuous 24 hour i.v. infusion.

◆ A long-term intravenous line should be inserted to facilitate long-term therapy.

◆ Simultaneous DFP (75 – 100 mg/kg/day) should be combined with the DFO infusions as soon as possible.

Pregnancy

◆ Women planning to become pregnant should undergo a thorough assessment of their current transfusion status, cardiac and liver iron loading and chelation regime.

◆ A risk assessment for maternal health during pregnancy and delivery should be made by the specialist treatment team together with an obstetrician with special interest and previous experience of managing pregnancies in thalassaemia.

◆ Women who are planning to become pregnant should undergo a period of intensive chelation to reduce SF, LIC and myocardial iron to optimal levels before attempting to become pregnant.

◆ Oral chelator drugs should be stopped three months before anticipated conception.

◆ Standard advice for DFO to be withheld throughout pregnancy can be reviewed in cases of high iron loading where the risk of cardiac complications is judged to be high. DFO can be considered in the second and third trimesters. On the basis of current evidence, DFX and DFP should not be used during pregnancy.

Renal impairment

◆ DFX should not be used if creatinine clearance < 60 ml/min but can be considered in patients with end stage kidney disease on renal replacement therapy. Low dose desferrioxamine given during the last hour of dialysis is an alternative.

◆ DFO or DFP can be used in patients with renal impairment (creatinine clearance < 60ml/min) but chelator doses should be kept as low as possible, and monitoring for toxicity should be intensified, with clinical, haematological and biochemical assessment every month, and audiology and ophthalmology checks every 3-6 months.

Recommendations

Monitoring of transfusion iron overload

- The target SF level is between 500 and 1000 µg/l. It is recognised that SF may not reflect total body iron levels or organ specific levels in some patients, and SF should not be assessed independently of LIC and myocardial iron.

- LIC of 3-7 mg/g dw is an acceptable therapeutic goal in TM patients. It is recommended that levels are kept towards the lower part of this range.

- The frequency of LIC assessment should be guided by LIC and rate of change in LIC.
  - Stable levels in the range 3-7 mg/g dw: One to two yearly
  - Levels >7 mg/g dw: yearly
  - Levels falling rapidly or <3 mg/g dw: 6 -12 monthly

- The frequency of cardiac MR scan should be guided by myocardial iron level:
  - Stable T2* > 20 milliseconds: two yearly
  - T2* 10-20 milliseconds: yearly
  - T2* < 10 milliseconds: 6 monthly

Other measures of iron overload

- Measurement of NTBI and LPI are yet to be validated and standardised for clinical use. LPI and NTBI cannot currently be recommended for routine assessment of iron overload and chelation therapy.

- MRI scanning to assess iron overload in endocrine tissue may provide additional information to guide treatment decisions but is not validated or standardised for routine clinical use at present.

Practical recommendations for DFO infusions

- Subcutaneous infusions of DFO should be given over 8-12 hours. The longer the duration of infusion, the better chelation efficacy.

- For infants and young children commencing infusions, a run-in period of one to three months is recommended, where the frequency is increased from 2 up to 5 or 6 per week.

- DFO should be administered after reconstitution in water. The solution for infusion should not be more concentrated than 10% (i.e. 250 mg in at least 2.5 ml, 500mg in at least 5 ml, 1g in at least 10 ml)

Subcutaneous needle insertion

- The abdominal wall is generally the most suitable site for subcutaneous infusion, and can be divided into four quadrants around the umbilicus to allow for rotation of sites.

- Additional sites include the thighs and upper arms, and these will be required if 5 or more infusions are to be given each week.

Administration device

- A battery operated infuser pump (e.g. Cronos®) is recommended for young children up to the age of 5. Use of disposable infusers in this age range is not recommended because the infusion volume is excessive (at least 20mls).

- For older children and adults, disposable elastomeric pumps are recommended. These should be produced under sterile conditions in a dedicated pharmacy.

- Arrangements should be made for batches to be delivered to the patient's home every 1-2 weeks. Alternatively, supplies can be collected from the clinic or hospital, depending on local arrangements.

Training in administration of DFO infusions

- Parents should be taught how to reconstitute the infusion, draw up the solution into a syringe, attach to infusion pump, insert subcutaneous needle and fix to pump, remove needle and dispose of used items safely.
- This will require initial instruction and repeated checking of competence.
- Instruction in different formats (written, verbal and using video resources) should be offered.
- Periodic home visits are recommended to ensure adequate technique and to trouble-shoot any persisting practical issue with administration of the infusion.
- Older children and adults should be encouraged to take responsibility for administering the infusions themselves.

Managing local adverse effects of DFO infusions

The following actions are recommended:

- Arrange home visit or hospital appointment for examination of several examples of skin reactions and for review of DFO infusion technique.
- Consider alternative sites of infusion.
- Decrease the concentration of DFO in infusion fluid.
- Increase the duration of infusion.
- Addition of a small dose of hydrocortisone with the infusion.
- If these measures do not help to resolve the problem, consider switching to an alternative chelation agent.

11: Referral for Blood and Marrow Transplantation

"I had a bone marrow transplant when I was little, I was too young to remember it. Obviously I'm happy to have been cured, but I ended up getting divorced because I couldn't get pregnant. It devastated me because we really loved each other but his family persuaded him to divorce me."

"We want a cure for everyone, but one that includes the older generation too!"

Aims

The families of children with thalassaemia will be fully informed of the possibility of blood and marrow transplantation (BMT) as a curative option, so that they can make an informed choice about this intervention for their child.

Outcomes for children undergoing transplantation will be optimised.

As techniques for reduced intensity conditioning regimens and alternative, haploidentical donors are refined, this option should become more available for adults also.

Standards

■ The families of all children with thalassaemia should have the opportunity to discuss the option of BMT with the team at a transplant centre with experience in undertaking the procedure for this indication, whether or not there is currently a matched sibling donor.

■ They will be fully informed about all the potential risks and benefits of the procedure, in the immediate, middle and long term.

■ For those with an appropriate donor who choose to proceed with transplant, it must be undertaken at a centre with specific experience and expertise of managing thalassaemia transplants.

Background

Bone marrow transplantation is at present the only proven treatment modality that can establish long-term normal haemopoiesis avoiding the need for transfusions and chelation treatment and there is now long-term outcome data supporting its efficacy (Baronciani, Angelucci *et al.* 2016). Hence, the provision of related transplantation for those patients and families to whom the risks and benefits are acceptable and who seek a permanent cure has become an accepted standard of care (indications published online at bsbmt.org/indications-table/). However, the main constraint in offering this has been the limited availability of donors (Kollman, Abella *et al.* 2004) and the risks undertaken when considering alternative donor transplantation. Since the publication of the last edition of the standards, there have been considerable advances in reducing toxicity with fludarabine-based conditioning regimens rather than the conventional

combination of alkylating agents (Bernardo, Zecca *et al.* 2008) and in the development of effective and safe protocols for unrelated and haploidentical transplantation (Anurathapan, Hongeng *et al.* 2016). These are now accepted clinical options for the management of children and young people with thalassaemia in the UK.

Discussion with the family must stress the usually excellent outcomes for children and adults managed conventionally with transfusion and chelation, now that monitoring for iron overload is more accurate and chelation choices are wider. For the majority of patients, there is now no expected impact on overall survival with BMT (Telfer, Coen *et al.* 2006) and the decision-making process has shifted to avoiding medium to long-term end organ damage and morbidity, and improving quality of life.

The establishment of normal haemopoiesis, and cessation of regular transfusion, allows for effective approaches to reduce iron load and reverse significant iron damage and avoid long-term organ dysfunction (Angelucci, Muretto *et al.* 1998; Mariotti, Angelucci *et al.* 1998). Quality of life studies demonstrate great improvements for patients following BMT and long-term superiority of outcomes, particularly in relation to role limitation, bodily pain and social functioning (La Nasa, Caocci *et al.* 2013; Javanbakht, Keshtkaran *et al.* 2015). These benefits can be over-ridden by chronic graft versus host disease, and conditioning regimens and strategies to prevent graft versus host disease after transplantation in haemoglobinopathies need to address this (Caocci, Efficace *et al.* 2011).

The benefits of transplantation need to be carefully balanced with the risks and difficulties of the procedure, which do not preclude the benefits but need to be carefully and appropriately explained to the patient and family so that they make an informed decision whether to proceed. The main limitations of transplantation include the following:

- The length and intensity of treatment.
  BMT requires an initial period of hospitalisation in isolation of around four to six weeks followed by a period of immunosuppression requiring weekly specialised monitoring for approximately six months during which the patient cannot attend nursery or school, or use public transport and may face frequent readmissions to hospital to manage complications. This has significant implications for family life, including practical aspect of family arrangements, financial considerations, parents' employment, and effects on siblings.

- Transplant related mortality.
  All forms of transplantation carry an upfront mortality risk, even if very low, in order to achieve a long-term cure.

- Long-term effects of transplantation.
  These are caused by the conditioning regimens and the ability of the new bone marrow to recognise the recipient patient as 'other', and react against them 'graft versus host disease' or GVHD. The use of fludarabine, less toxic alkylating agents, drug exposure monitoring and serotherapy have made significant advances in limiting this. Chronic graft versus host disease has been identified as the main factor impacting on quality of life long-term, though with current approaches the risk is very low (< 5%). Infertility in particular remains a significant problem. Oocyte vitrification, sperm cryopreservation and ovarian/testicular tissue cryopreservation approaches have been developed to address this.

Optimal outcomes in transplantation are obtained by ensuring the patient enters the procedure with low iron load, achieved by good chelation therapy. The worse outcomes seen in studies in older age are often surrogate markers for inadequate chelation status at transplantation. It is the experience of transplant centres that patients who have had significant difficulties with chelation, or to whom more intensive chelation has been unacceptable, will be willing to undertake a period of intensive treatment to reverse their situation – provided it is for a limited period – in order to allow them to undertake a curative treatment. Hence, early evaluation by the transplant centre is recommended.

Collection of cord blood at the birth of a new sibling should be offered if possible, although funding is not standard. Cord as the sole source of stem cells has a higher risk of rejection in thalassaemia and unstable long-term mixed chimerism can have a significant impact on the outcomes of transplantation and add significantly to the complexity and length of treatment.

However, cord stem cells can make an important contribution to achieving an adequate stem cell dose to enable a combined cord and bone marrow transplant, avoiding the need for a second bone marrow harvest from a smaller sibling donor. In the majority of cases of transfusion-dependent thalassaemia the transplant can be delayed until the new sibling can donate sufficient bone marrow to allow a combined transplant (Soni, Boulad *et al.* 2014). The case for collection of cord blood cells is strengthened if there has been prenatal diagnosis ruling out a haemoglobinopathy, with the same DNA used to confirm that the new pregnancy is matched for the potential recipient.

Adult bone marrow transplantation is indicated because of the patients' experience of the impact of the disease on quality of life and this is often because of the development of end-organ damage. Adult BMT has been limited by the poor outcomes at this stage with conventional approaches, and the limited availability of donors. Recent limited advances in the reduction of intensity and alternative donors make this an area for development.

A small number of adult patients have been treated with gene therapy, achieving transfusion independence (Negre, Eggimann *et al.* 2016). The efficiency of this approach is likely to improve, and trials will become available. At this stage gene therapy requires the use of conditioning chemotherapy with significant impact on fertility, though it avoids the complication of graft versus host disease, and is likely to be of lower intensity than conventional transplantation. The nature of the therapy makes it likely that trials will be conducted by transplant centres and hence the cellular and gene therapy approach to establishment of normal haematopoiesis should be unified.

Although cellular and gene therapies require a significant upfront investment, the cost effectiveness of these forms of therapies is well established (Ho, Lin *et al.* 2006; Leelahavarong, Chaikledkaew *et al.* 2010).

Requirements

◆ Referral to a transplant centre for discussion about blood and marrow transplantation should be offered to parents when the child is 1 – 2 years of age. This is regardless of the availability of a matched sibling donor as subsequent children born to the parents may prove to be an HLA match and alternative donor transplantation could be considered.

◆ It is especially important to discuss with families the major risks of transplantation including transplant related mortality and infertility. Fertility cryopreservation should be considered for all patients.

◆ The child should be included in the discussions in an age appropriate manner and this requires adequate provision of play specialists, psychology and clinical nurse specialists experienced in the procedure for thalassaemia.

◆ There is a systematic 'work up' of the child pre-transplant, including assessment of renal and hepatic function, echocardiogram, lung function, dental assessment, and most important evaluation of iron load and optimisation of chelation pre-transplantation.

◆ The evaluation of iron load and end-organ damage must include MR liver iron quantitation, also T2* of the heart if possible, under sedation if required in young children. A liver biopsy for the assessment of fibrosis is usually undertaken (Ishak staging).

◆ Post-transplant follow up in the early months is at the transplant centre, with regular communication to the referring team.

◆ In order to achieve the full benefits of a transplant, the patient's iron load needs to be re-evaluated post-transplantation and interventions undertaken to normalise it. This involves as a minimum measurement of ferritin and MR liver iron quantitation. Usually iron load has increased due to the transfusion requirements of transplantation on top of the existing load at transplantation. Depending of the stability of the graft and venous access reduction of the iron load is achieved either with venesections or chelation for a few months. It is usual to evaluate this around 6 months post-transplantation. The aim should be to normalise the iron load (ferritin ≤ 300 µg/l and MR liver iron quantitation showing < 3 mg/g dw).

◆ Patients who have had a transplant should be followed up in a long-term effects clinic for transplanted patients. During follow up, pubertal development and fertility function should be assessed, and discussed with the patient and family, and genetic counselling offered.

◆ Families should be aware that the child, when s/he grows up, needs to be advised that their partner needs early testing for thalassaemia or other haemoglobin disorders. The transplanted individual will still pass on the thalassaemic mutation to their offspring despite a successful transplant, so there would be a risk of significant haemoglobin disorder in their children if the partner was a carrier for thalassaemia, sickle cell, or other relevant variants.

Recommendations

• If the mother of a child with thalassaemia becomes pregnant, prenatal diagnosis should be offered and if accepted HLA typing of the fetus can be undertaken. Cord blood stem cell harvesting should be offered to all families whether or not prenatal diagnosis has been undertaken.

• The referring team can often support on-going transplant care, for example by arranging venesections to continue reducing iron load once healthy haematopoiesis is established.

12: Growth, Development and Endocrine Function

"I haven't grown like my brothers and I also look a lot younger than them. It has made me very depressed."

"I'm small and look like a child that's why I haven't had a relationship."

"During my young adult life I was basically a child aged 18! No facial hair, no adult male features, I looked like a kid – I feared rejection so stayed away from girls."

Note: This chapter should be read in conjunction with the following chapters, with which there is some inevitable overlap:

- 14: Fertility and Management of Pregnancy
- 18: Management of Impaired Glucose Tolerance and Diabetes Mellitus
- 19: Management of Bone Problems

Aims

To preserve endocrine function allowing completion of normal puberty, optimal height, and achievement of peak bone mass.

To maintain this function throughout adulthood and to maintain normal fertility and good bone mineral density, reducing the incidence of bone thinning and its attendant complications.

To screen for, detect and treat endocrine disturbance promptly and effectively.

Standards

- Iron loading should be kept to a minimum, by careful monitoring and the use of effective chelation treatment, to reduce the risks of endocrine damage.

- Paediatric and adult specialists in bone metabolism and endocrinology, with interest and expertise in managing the particular complications encountered, should be involved in the care of children and adults with thalassaemia, ideally in a joint clinic setting.

- Children should have growth and development monitored regularly from diagnosis until they have achieved full sexual maturity and final adult height. Any change in expected growth and development should be identified, investigated and treated promptly.

- Where paediatric endocrine input has been necessary then careful transition plans should be made at completion of puberty and linear growth. Ideally such transition should take place in a combined clinic. A detailed clinical summary and discussion should take place to ensure there is no disruption to treatment at this critical stage of adolescence.

- Adults and children should be routinely assessed, at least annually, for evidence of disturbance of the hypothalamo-pituitary axis, for calcium and bone homeostasis, and thyroid function.

Background

Endocrine deficiencies are common, potentially avoidable complications in thalassaemia. The commonest complication has been hypogonadotrophic hypogonadism alongside short stature and delayed puberty in children (De Sanctis 2002). Iron toxicity is the most common cause of these disorders, and can be responsible for pituitary damage even in well-chelated individuals. However, it remains important to consider other factors which may be contributory, for example the effects of desferrioxamine on bone although this is rare now with moderated doses in growing children.

Once endocrine damage had occurred, it was generally thought to be irreversible, although there is some evidence that with the intensive chelation regimens used to reverse cardiac iron loading there can be reversal of endocrine failure (Farmaki *et al.* 2010).

Growth delay may become apparent around the age of 10, and probably relates to the sensitivity of the pituitary gland to iron toxicity at a young age when total body iron burden is still relatively modest. Children who are well treated from early childhood can usually avoid this complication. However, a growth hormone stimulation test should be undertaken and supplementary GH treatment given if deficient. For any child on desferrioxamine chelation whose growth is faltering, it should be ensured they are not receiving too high a dose. 20 – 30 mg/kg/day is usually appropriate, and the dose should not exceed 40 mg/kg/day.

Growth hormone deficiency and resistance in adults is recognised as being relatively common, but there is currently no evidence to support supplementing growth hormone in adults.

Delayed puberty is defined as a lack of breast development in girls by the age of 13, and a lack of testicular development in boys by the age of 14. While primary gonadal failure is recognised in iron overload pituitary, gonadotrophin failure – hypogonadotrophic hypogonadism – is more common. Deficiency should be treated with oestrogen/testosterone particularly remembering that under-replacement will contribute to bone thinning.

The timing of hormone replacement therapy is controversial. Patients with delayed puberty may still have substantial growth potential, and excessive gonadal hormone administration may cause premature epiphyseal fusion. Guidelines exist for managing this problem, but individual children need to be assessed, treated and monitored by the specialist paediatric endocrinology team (Cappellini *et al.* 2000).

In boys, where there is delayed puberty and an absence of testicular development, there is a case to be made for inducing puberty with gonadotrophins which would allow seminiferous tubule development and may increase the chances of future fertility.

With the numerous medications taken, many men prefer the option of depot testosterone, e.g. Nebido, which can be given 3-4 monthly when attending for transfusion, over daily topical preparations but either are suitable.

For women with hypogonadotrophic hypogonadism and primary or secondary amenorrhoea, oestrogen replacement is recommended. A combined oral contraceptive preparation is recommended when contraception is also required, otherwise a "post-menopausal" replacement regime is used is also suitable. The aim should be to restore a normal menstrual cycle with 3-5 days of bleeding using the lowest dose of oestrogen required. It is reasonable to try a low dose combined preparation for 3-6 months in the first instance and if insufficient bleeding is occurring, step up to a high dose preparation. If amenorrhoea persists, further investigations will be required to assess the endometrial lining and it may be that a tailor made regime is required. Where a satisfactory cycle is produced but side effects occur, a switch to a preparation with an equivalent dose of oestrogen but a different progestogen may help.

In adolescence and adulthood, further endocrine complications may evolve. These include the development of further pituitary failure in addition to secondary gonadal failure and GH deficiency, development of secondary hypothyroidism and secondary adrenal failure, especially when iron chelation is poor. Primary hypothyroidism, primary hypoparathyroidism and primary adrenal failure may also occur with an incidence also linked to poor iron chelation (Chirico *et al.* 2015)

A high index of suspicion for secondary hypothyroidism should be maintained, particularly in the context of poor iron chelation and the presence of other iron overload complications and should be suspected if there are hypothyroid symptoms, a low or low normal free thyroxine with a normal TSH, or a fall in free thyroxine with time.

If primary hypoparathyroidism is diagnosed, activated vitamin D will be required (alphacalcidol/calcitriol). This is seen as a complication of severe or long-standing iron overload and is not uncommon in the older patients. The aim of treatment is to place the corrected calcium at the lower limit of the normal range to avoid complications of hypercalciuria and subsequent nephrocalcinosis.

Both primary and secondary adrenal failure are recognised complications which are probably underestimated and should be considered in unwell patients. An annual morning cortisol allows any trending decline to be noted and any low or low normal values to be carefully considered in the clinical context. However a normal cortisol when well does not exclude partial adrenal insufficiency when unwell. The literature describing adrenal insufficiency is contradictory due to the difficulty assessing the hyothalamo-pituitary-adrenal axis but the threshold for considering hydrocortisone supplementation should be low, when a person is very unwell, or having surgery or another significant intervention (Poomthavorn *et al.*, Elsedfy *et al.*, Scacchi *et al.*).

The development of any of the above endocrine disturbances can lead to significant symptoms, adverse effects on cardiac function and a significant impact on bone development, limiting the attainment and maintenance of peak bone mineral density if not promptly and adequately treated.

These disorders require precise diagnosis, and appropriate endocrine replacement therapy. For a full overview, see also the international network on endocrine complications in thalassemia (I-CET) position statement and guidelines (DeSanctis *et al.*, 2013).

Requirements

◆ Regular assessments of growth, including weight and height (standing and sitting), should be recorded every six months from diagnosis until final adult height is attained, with referral to paediatric endocrinologist if there is any concern. Data should be charted and height velocity calculated to ensure any change is detected promptly.

◆ Puberty should be systematically assessed annually from the age of 10, with referral to a paediatric endocrinologist if there is any suspicion of delay (no pubertal changes in girls by age 13 and boys by age 14) or arrested puberty (puberty starts but then does not proceed). Progress should be documented using Tanner staging.

◆ Assessment of bone age is useful, by plain hand and wrist XR every 1-2 years until epiphyses fuse, if there are concerns about pubertal delay or a fall in height velocity.

◆ Evidence of faltering growth, with declining centiles for height and height velocity, is often apparent around the age 8-12. This should be investigated thoroughly with consideration given to desferrioxamine toxicity, and growth hormone deficiency. A growth hormone stimulation test should be administered, and if positive, growth hormone therapy instituted.

◆ Delayed puberty should be fully investigated. Adolescents with evidence of hypogonadism should be treated with hormone replacement therapy, under guidance from the paediatric endocrinologist.

◆ Oral glucose tolerance test should be undertaken yearly from puberty, or from aged 10 if there is a family history of diabetes mellitus. Details of the test and results interpretation are included in chapter 18: Management of Impaired Glucose Tolerance and Diabetes Mellitus .

◆ T4 and TSH measurement should be checked annually from age 12, or if any symptoms of hypothyroidism develop in between times, and hypothyroidism should be treated promptly with regular checks as to the adequacy of replacement thyroxine dose.

◆ Calcium, phosphate and alkaline phosphatase levels should be monitored at least 6 monthly from aged 12, with measurement of parathyroid hormone if the calcium level is low.

◆ Vitamin D should be checked at least annually from age 2 at the latest, and supplemented as necessary (chapter 19).

◆ A morning cortisol should be checked annually.

◆ An annual clinical assessment of gonadal function should take place throughout adulthood, with a careful menstrual history and direct questioning for impotence in men.

– For women with a normal menstrual history, no testing is required.

– If amenorrhoea or oligomenorrhoea develop, careful history and testing will be required to identify the cause. A low LH/FSH and oestradiol may be indicative of developing hypogonadotrophic hypogonadism but could also be due to other causes and further testing is recommended before initiating oestrogen replacement. Involvement of the specialist endocrinologist is necessary if menstrual disturbance persists.

– For men, a morning testosterone should be checked annually. A low level should be repeated together with LH/FSH and SHBG and correlation with symptoms.

– Deficiency should be treated with oestrogen/testosterone particularly remembering that under-replacement will contribute to bone thinning.

Recommendations

• Appropriate investigations, replacement therapy, and planned management of problems are best achieved by joint consultation between the endocrinologist, and the thalassaemia clinician, optimally in joint clinics but if these are not in place then with meticulous communication between the two specialist teams, the GP, and the patient/the patient's parents.

13: Transition from Paediatric to Adult Services

*"Talking to the doctor and worrying about my blood levels has
 always been my mum's job."*

*"I'm the oldest of 3 brothers but because I have thalassaemia
 I'm the baby of the family."*

Aims

To prepare and support young people's health, educational and psychosocial needs when moving from paediatric to adult services by:

- a flexible but planned process to equip the young person within the adult healthcare system
- education and support of the young person to foster independence, and by ensuring informed self-management and
- ongoing engagement with adult health services to optimise health outcomes and wellbeing.

Standards

■ Support and education will be given to the young person and their parents or carers over time to nurture independent, informed young people who can take responsibility for their health and choices.

■ Each young person requires a named/key worker for transition and the transition process should commence by 13 years of age.

■ Adult and paediatric teams will work collaboratively with the young person and their parents or carers to provide a timely and smooth hand-over. Primary, secondary and tertiary health care providers and community teams should be involved in the process, and in the young person's ongoing care.

■ Any anxieties that the young person and their parent(s) or carer(s) may have, arising from the change from paediatric to adult health providers, will be addressed.

■ Psychosocial stresses that may negatively impact on adherence with their transfusion regime, medication and/or and self-care will be identified and managed.

■ Close monitoring of thalassaemia treatment should continue over the transition period, with particular attention to monitoring of iron stores and adherence to iron chelation therapy.

Background

Transition is defined as the "purposeful, planned process that addresses the medical, psychosocial, educational and vocational needs of adolescents and young adults with chronic medical and physical conditions as they move from child-centred to adult orientated healthcare systems." (Blum 1993). Moving over to adult services, unless managed carefully, can be a high risk time for non-engagement with services, and non-adherence with therapy.

The process, although flexible, needs to be standardised to incorporate the following:

- preparation of the young person and their family through education, support and communication about thalassaemia, its management and potential complications,

- communication with both the young person and their parents or carers together and independently to gather their views, concerns and aspirations and to address these,
- introductions to and familiarisation with adult staff and facilities,
- transfer to the adult team, and
- ongoing education, support and communication with the young person within the adult services.

Transition occurs at a time when there are a number of other physical, biological, developmental and psychosocial changes due to adolescence occurring in the young person's life. As far as possible all efforts must be made to ensure that there is engagement with the young person and their family throughout the process, and that the process proceeds at a rate that is appropriate for the needs and maturity of the young person. Although the family is usually the main source of support to young people, especially for those with long term conditions, it is important to acknowledge the wishes and expectations of both the young person and their parents, which may differ, and to offer peer support too. Cultural sensitivities should also be taken into account.

In addition to the usual young person's concerns regarding independence, self-image, peer acceptance, emotional and sexual maturation, career, family and employment prospects, the young person with thalassaemia also has to manage their health needs: transfusion, chelation, and multiple hospital attendances, and possible complications of the condition such as iron overload, delayed puberty due to hypogonadotrophic hypogonadism and/or bone thinning (Yacobovich and Tamary 2014).

Growing up with thalassaemia, and particularly leaving familiar paediatric health care providers, can have a major psychological effect on young people, causing feelings of apprehension, anxiety and abandonment, unless well managed (Musallam 2008; Bryant 2011). These feelings can have a negative impact on subsequent engagement with adult healthcare professionals, treatment adherence and hospital attendance. Thus the transition process requires time, commitment and resources from professionals to provide support and to achieve best outcomes. Transition for all young people with long-term conditions to adult services has been highlighted in the UK as an area requiring improvement (DoH 2006; DoH 2011; CQC 2014). Recently published NICE guidance recommends involvement of health and social care managers and commissioners in the development and delivery of transition pathways (NICE 2016).

Teenagers and young adults are at risk of complications of iron overload. This is because the toxic effects of progressive iron accumulation often present clinically in this age range, and because adherence to iron chelation therapy is often compromised when young people begin to take over responsibility for self treatment from their parents. The other social and psychological challenges which young people face tend to be prioritised over attention to their long-term health. Ensuring that transfusion iron loading remains within an acceptable range also presents an important challenge to the thalassaemia care team, who need to find ways of supporting the young person to continue with effective chelation.

Requirements

◆ Transition planning should take account of the young person's maturity and may start from 12 years onwards. However it should commence by school year 9 (13 to 14 years of age) at the latest.

◆ A named worker to support the young person and their parent(s) or carer(s) is required. The worker may be their specialist nurse, a youth worker or their paediatrician who will provide support, education and continuity until the young person is settled and confident within the adult services.

◆ Transition should be a dynamic, interactive process involving the young person and their family, with the transfer of care presented in a positive manner rather than an inevitable, undesirable event. All efforts must be made to listen to and address any concerns raised by the young person and/or their family.

◆ A transition plan should be created with input from the young person and their parents or carers that describes the transition process and its purpose, and introduces the key worker for transition who should be well known to the young person and their family or carers.

◆ An assessment of the young person's understanding of their condition, potential complications and their medication should be undertaken, and also an assessment of their confidence/maturity and their readiness to move to adult services.

◆ The young person should be given the opportunity – and encouraged – to speak with clinicians in the absence of their parents, if they so choose.

◆ In addition to explaining and providing information about their condition, the key worker should also be able to signpost young people to voluntary, charity and community sector services who can provide support and information about thalassaemia, such as the UK Thalassaemia Society, and other services that provide information about careers, finance, relationships, emotional and sexual health. The named worker can also help the young person to understand the roles and responsibilities of the primary, community, secondary adult and paediatric tertiary health services, and how to navigate the different services.

◆ Information about the adult service, facilities, contacts and resources should be provided. The young person with their key worker should be introduced to the adult team, through a joint appointment with both adult and paediatric teams in either the paediatric or adult setting, or through transition clinics which are held jointly by the paediatric and adult teams if these are available (CQC 2014). Introductions to other team members such as the staff of the day unit or ward where the young person will receive blood transfusions and a clinical psychologist, if attached to the team, are also valuable.

◆ Specialist haemoglobinopathy centres will have a transition guideline and information about transition in place (WMQRS QS 2014) which should be shared with their local hospitals and other centres within the network. If the young person with thalassaemia is transfused at a local clinic or LHT, it is important that robust links are made in the same way so that blood transfusions can continue seamlessly when moving from paediatric to adult services.

◆ Peer support is invaluable during the transition process. Opportunities to meet with other young people with thalassaemia should be provided, through facilitated support groups at the centre if patient numbers and geography allow.

◆ Psychosocial support through individual or group meetings is also valuable in promoting confidence, well-being, communication skills and healthy independence.

◆ Summary information regarding the young person's health including any complications, medication and test results should be prepared and discussed with the young person, to form the basis of a transfer summary for the adult team. The young person should also receive a copy of the transfer summary.

◆ The transition plan should be reviewed annually to assess progress in terms of understanding of their condition, ability to communicate with professionals, maturity and readiness for transfer.

◆ Transfer to adult services should occur when the young person is adequately prepared and ready to leave paediatrics; however paediatric services are often contractually unable to provide ongoing care beyond 16 years of age. Flexibility is encouraged where possible.

◆ The named worker should attend the adult clinic with the young person for the first appointment if possible, and continue to support the young person for a defined period following transfer of their care to adult services. A minimum of 6 months is recommended

◆ All efforts should be made to make the young person feel comfortable and welcomed into the adult services, both in the outpatient setting and on the unit where they will be receiving blood transfusions.

◆ An adult equivalent named worker who may be a specialist nurse, youth worker or a haematologist will continue the transition process providing support and education through other significant "transitions" such as moving on to college, university or the workplace. As they reach adulthood, the young person may leave the family home, so will require advice and support on independent living such as managing financial affairs, student life, housing, and relationships whilst still attending for blood transfusions, managing their regular medications, and attending outpatient appointments.

◆ Delivery of thalassaemia care, including convenient and flexible access to transfusions, monitoring of iron stores, adjustment of chelation therapy taking into account adverse effects, efficacy and tolerability, and evaluation of treatment adherence, must be sustained and organised to ensure continuity during the transition pathway.

◆ It is particularly important for services to audit clinical outcomes in young people and make changes to improve services where deficiencies are detected.

Recommendations

• Throughout transition the young person should be treated in age-appropriate facilities, and where possible, be seen in outpatients and attend day care settings with other similar aged patients.

• The concept of transition to adult services and allocation of a key worker, preferably a clinical nurse specialist – should be introduced early to allow adequate preparation, adjustment, education and readiness to move onto adult services. Guidance, support, openness and information sharing with the young person and their parents or carers are key.

• Information provided about transition, thalassaemia and other aspects of adolescence and adulthood should be age-appropriate and be delivered in a convenient format for the young person such as written materials, email, text messaging, and/or signposting to useful websites and apps, such as "ThaliMe" produced by the Thalassaemia International Federation.

• Routine involvement with psychology during adolescence, and especially during transition, familiarises the young person and their family with the service, and then can provide professional support to the young person if they struggle with the challenges associated with both adolescence and living with thalassaemia.

• Following transfer to adult services, transition input from the adult provider should continue until at least 18 years of age. The attendance of the young person should be closely monitored, as this can be a high risk time for non-engagement with services, and non-adherence with therapy, with potentially detrimental consequences. Thus all efforts should be made to identify and overcome any barriers to a successful transition.

14: Fertility and Management of Pregnancy

"I had no luck with fertility treatment, I think it was left too late before treatment started. Thals need to be monitored and treatment introduced early in life if they are not developing normally."

"I'm worried about being able to conceive and I lack confidence about meeting a partner. I am especially worried about not being able to fulfil "his" needs of having children."

"The only thing missing from my life is having a baby, but I'm working on it!"

Aims

Optimum iron chelation from infancy will reduce the likelihood of infertility, and this is a primary aim for the younger patient.

To allow for discussion about fertility, and potential pregnancy, with appropriately experienced specialists at a time the patient wishes.

To maximise the chances for people who have thalassaemia to have children, if they wish.

To ensure that pregnancy in women with thalassaemia is managed so as to optimise outcomes for both mother and baby.

Standards

■ Each Specialist Centre will identify a paediatric endocrinologist with experience in the management of thalassaemia.

■ Pubertal development, growth, and endocrine function will be closely monitored in boys and girls with thalassaemia, and prompt referral made if there is any suspicion of problems.

■ Women contemplating pregnancy will be assessed for possible risks to themselves and their babies and this evaluation up-dated as needed.

■ At any time when the patient wishes she/he should be referred to a fertility/endocrine/assisted conception clinic with experience of thalassemia patients, to allow discussion about treatment options; culturally appropriate advocacy will inform these discussions.

■ Women will be jointly managed during pregnancy and delivery by a 'maternal medicine' obstetrician experienced with haemoglobin disorders, and by their haematologist.

Background

Many people with thalassaemia who are well managed from childhood remain naturally fertile; however, many older patients will be subfertile (58% of those below 30 years, 68% of those between 30 and 40 and 75% of those above 40 years of age) (Ang *et al.* 2014), and need specialist evaluation and, where appropriate, fertility induction treatment.

The pituitary and hypothalamus are very sensitive to iron damage, and hypogonadotrophic hypogonadism was a frequent complication which has fallen in incidence in recent years with better chelation therapy (Belhoul *et al.* 2013) . Diabetes and hypothyroidism can also impair fertility. Building a family is a key concern for many patients and their extended families, and they greatly value discussion with a specialist who is able to explain realistically the options and likelihood of success, minimising unrealistic expectations and consequent psychological and emotional problems.

Patients who have undergone bone marrow transplantation for thalassaemia will commonly be infertile. Although they may be 'cured' from the condition clinically, it is essential for them to understand that they still have, and will pass to any children, their thalassaemic globin genes. Partner testing and counselling, in regard to the risk of haemoglobin disorders in the children, is essential before fertility treatment is undertaken.

For all patients, if induction of ovulation or spermatogenesis is necessary, it must be undertaken by fertility experts experienced in managing people with thalassaemia (Kyei-Mensah *et al.* 2014)

Increased risks to a woman with thalassaemia in pregnancy principally relate to:

- cardiac problems (cardiomyopathy and arrhythmias), given the 40% increase in cardiac workload during pregnancy,
- the risk of accelerating cardiac dysfunction, pre-existing diabetic retinopathy or nephropathy (Jensen, Tuck and Wonke 1995)
- worsening osteoporosis: both pregnancy and lactation will exacerbate this problem, and crush fractures of the vertebrae are possible at this time.
- the appearance of new sequelae of haemosiderosis after delivery, since iron chelation is usually halted for the duration of the pregnancy, as well as any period of fertility treatment leading up to it.

For the baby, issues include:

- the possibility of having a major haemoglobin disorder, depending on the globin genotype of the other parent
- if the mother has diabetes, there is a four-old increased risk of fetal anomaly and three-fold increase in perinatal mortality (Excellence 2008)
- if ovulation induction results in a multiple pregnancy, there is increased risk of premature delivery, growth restriction, and disability in the infants.

Careful assessment of the woman considering pregnancy should be undertaken, ensuring that her cardiac iron status and function are sufficiently good to manage the extra demands of pregnancy, and that other possible complications are detected and optimally managed. A full review of her medication is necessary, ensuring she remains on necessary medications including penicillin if she has undergone splenectomy, thyroxine if needed, medications to ensure glycaemic control, and vitamin D supplements if there is any deficiency. Vitamin D is needed for fetal bone development and to avoid neonatal rickets, as well as for the woman herself. Any potentially teratogenic medications must be discontinued, including ACE-inhibitors, bisphosphonates, and oral chelator agents.

Specialist fertility care for women should minimise the risks of ovarian hyper-stimulation and multiple pregnancy. Although patients may consider this a "welcome complication", there are significant obstetric complications associated with multiple pregnancy which are further heightened by the potential multiple endocrine and other co-morbidities in some women with the thalassaemia.

In hypogonadal patients, clomiphene is of no value. Gonadotrophins should be administered subcutaneously, and ovarian response monitored with serum oestradiol and / or by follicular tracking with transvaginal ultrasounds. Human Menopausal Gonadotrophin ovulation regimes are well tolerated and will produce a mono-follicular response with careful monitoring. Typical doses are 75mg HMG daily.

Serial follicular tracking ultrasounds commence on day 14 after starting the injections and are repeated as indicated, typically weekly, until follicular development greater than 10 mm is observed in either ovary, at which point more frequent scanning is initiated. Once a dominant

follicle is noted (18 mm in diameter or greater) an injection of hCG (5000 iu) is given to trigger ovulation and the couple advised to have sexual intercourse within 36 hours.

If there are additional factors that contribute to infertility including male factor, tubal factor or stage 3-4 endometriosis, or if the patient does not conceive despite satisfactory ovarian stimulation with gonadotrophin treatment, assisted reproductive technologies including In Vitro Fertilisation (IVF) are likely to be considered.

During pregnancy, the woman should be closely supervised by her obstetrician, cardiologist and haematologist (Kyei-Mensah *et al.* 2014) with prompt communication between them after any clinical appointment. Transfusion requirements are likely to increase. Iron chelation is usually withheld throughout pregnancy, however desferrioxamine is known to have low toxicity in the second and third trimesters (Singer and Vichinsky 1999) and in women with significant cardiac iron overload, continued chelation with low dose desferrioxamine during later pregnancy can be considered. Penicillin should continue in those who have undergone splenectomy. Women should be reviewed by a cardiologist at 28 weeks gestation to assess cardiac function and help advise on plan for delivery.

The mode of delivery should be discussed in advance, taking account of any cardiac problems, and possible bone problems affecting the pelvis and suitability for vaginal delivery. Women with reduced stature are particularly likely to need delivery by caesarean section, since fetal growth is usually normal and cephalo-pelvic disproportion is therefore common.

Desferrioxamine at a dose of 2g over 24 hours by continuous i.v. or s.c. infusion, can be started from the time of arrival to deliver the baby, to minimise the risk of cardiac decompensation or dysrrythmia during the peri-partum period. Women who have had operative delivery, or who are splenectomised, are at increased risk of venous thromboembolism and should receive prophylaxis for up to 6 weeks post partum.

Women should be encouraged to resume iron chelation as soon as possible after they deliver a baby. Breast feeding is encouraged and desferrioxamine can be used safely during this period. Deferiprone and deferasirox should not be recommended until after breastfeeding ceases. For women with hypogonadotrophic hypogonadism, who required ovulation induction to achieve pregnancy, resuming oestrogen replacement therapy should also wait for this time. Prolonged breast feeding adds to the risk of worsening bone thinning, and calcium and vitamin D supplements, as well as other measures such as weight bearing exercise, should be continued. Bisphosphonates are contraindicated during breast feeding.

Male infertility

Men with thalassaemia who have completed puberty naturally are expected to be fertile and should not need assisted conception. Pregnancy should nonetheless be planned, as deferiprone and deferasirox should be stopped for three months prior to planned pregnancy. Patients should at that point switch onto desferrioxamine infusions, and should remain on these for a period of 3 months prior to attempted conception.

Although most hypogonadal women can successfully conceive, the situation is more complex for men with hypogonadotrophic hypogonadism and if at all possible the aim should be that male patients pass through puberty naturally (De Sanctis *et al.* 2013). In male patients who completed puberty spontaneously and hypogonadothrophic hypogonadism develops later, HCG at 1500 units twice weekly may be sufficient to generate sufficient intra-testicular testosterone levels to allow spermatogenesis. Where puberty was not completed spontaneously, both FSH and LH will be required, and some limited evidence suggests priming with FSH first may result in better outcomes (Anawalt 2013). However, spermatogenesis induction takes time; often around 12-24 months. It is difficult treatment, and may not result in successful sperm production despite good testosterone levels. A number of patients will progress to testicular biopsy and intracytoplasmic sperm injection treatment if the biopsy shows viable sperm (De Sanctis *et al.* 1988).

Hypogonadal males who need spermatogenesis induction should be referred to a specialist reproductive endocrinology clinic with experience in the management of men with thalassaemia (Bajoria and Chatterjee 2011). For optimal spermatogenesis, their iron burden and any pre-existing diabetes should be well managed with a fructosamine target of below 300 µmol/l. They

can continue on their existing chelation regimes until they get an adequate sperm count, at which point oral chelation should stop and patients should switch to desferrioxamine, with a plan to continue on this for a three month 'wash-out' period prior to conception.

Requirements

◆ If there is any clinical or biochemical evidence of delayed puberty, referral to a specialist paediatric endocrinologist will be made promptly for appropriate management.

◆ At a time of their choosing, patients with thalassaemia who are wishing to conceive will be referred to an endocrine/andrology clinic (men) or assisted conception clinic (women) with specific experience in managing people with thalassaemia. Both the thalassaemia patient and their partner will need to complete fertility investigations.

◆ A woman must be fully pre-assessed as to her fitness for pregnancy before conception, spontaneous or assisted. This needs to be by an obstetrician experienced in the area, and there needs to be a discussion about possible risks. These assessments should be up-dated no more than 12 months before conception (Kyei-Mensah *et al.* 2014).

  – A cardiology review including myocardial iron quantification by T2*, ejection fraction assessment, and an assessment for arrythymias if there is a history of palpitations.

  – Assessment for diabetes by a glucose tolerance test in non diabetic patients and assessment of fructosamine for effectiveness of diabetic control in known diabetics. A target pre-conception fructosamine of < 300 nmol/l is desirable for optimal outcomes.

  – Thyroid function should be normal before pregnancy, with or without thyroxine replacement.

  – Patients who have been splenectomised need to be up to date with immunisations including pneumococcus, and all women should be fully hepatitis B virus immune.

  – Bone density assessment, with treatment to improve this prior to pregnancy, if required.

  – Women who are alloimmunised should be assessed for risk of risk of haemolytic disease of the fetus and newborn, including red cell phenotype/genotype of the father.

◆ Medication review is required in a woman pre- and during pregnancy

  – Folic acid 5 mg/day should be started 3 months prior to conception.

  – Prophylactic penicillin V 250 mg twice daily should continue if splenectomised.

  – Oral iron chelation drugs should be stopped 12 weeks prior to any planned fertility treatment or attempting natural conception.

  – Desferrioxamine can be continued up to the day of ovulation for assisted conception or as soon as a period is missed and pregnancy test is positive in natural conception.

  – Most other medication should cease – particularly bisphosphonates and ACE inhibitors.

  – If ACE inhibitors are required to improve arrhythmia, or intensive iron chelation necessary to reduce cardiac iron, conception should be postponed until these can be safely stopped or converted to alternative drugs that are safe in pregnancy.

  – Vitamin D levels should be optimal pre conception and during pregnancy.

  – Women with thalassaemia who have undergone splenectomy and / or have a platelet count greater than 600 x 10^9/l should commence or continue taking low-dose aspirin (75 mg/day) and they should be offered low-molecular-weight heparin thromboprophylaxis (Kyei-Mensah *et al.* 2014)

  – Women with thalassaemia who are not already using prophylactic low-molecular-weight heparin should be advised to use it during antenatal hospital admissions.

◆ General pre-pregnancy issues need to be considered, as for any other woman, including rubella immune status, HIV, hepatitis C, smoking cessation/limitation of alcohol intake.

◆ Fertility treatment must be at a centre experienced in managing women with thalassaemia, and clinical care during times of fertility treatment will be jointly between the endocrine / assisted fertility clinicians and the specialist haematologist.

◆ Management of women in pregnancy and during delivery will be by an obstetrician with experience of women with thalassaemia, jointly with the specialist haematologist.

◆ Women should be reviewed by the specialist cardiologist at 28 weeks gestation to assess cardiac function and help advise on plan for delivery

◆ Mode of delivery will be discussed and planned in advance, taking account of any cardiac concerns and possible cephalo-pelvic disproportion.

◆ If there has been operative delivery, or the woman has had splenectomy, is a smoker, or has any additional risk factors, VTE prophylaxis with low molecular weight heparin should be given for up to 6 weeks post partum.

◆ There should be an early review by the specialist haematologist, ideally before the woman leaves hospital, to discuss which medications – usually including desferrioxamine iron chelation – can be restarted immediately, and which need to be with-held until after breast feeding stops.

◆ Although optimally managed men with thalassaemia may be spontaneously fertile, there should be planning for pregnancy as they need to stop oral iron chelators at least 3 months before conception, switching to desferrioxamine for that period. Other complications such as diabetes mellitus and hypothyroidism should be optimally managed before attempted conception.

◆ Men who have hypogonadotrophic hypogonadism need to be referred to a specialist reproductive endocrinology clinic with experience in the management of men with thalassaemia. There should be realistic discussion about the likelihood of spermatogenesis induction, as treatment is long and may not be successful.

◆ Patients who have undergone successful bone marrow transplantation for thalassaemia will still pass on thalassaemic globin genes to their children, so partner testing and counselling is required before any fertility treatment starts.

Recommendations

• Early referral for discussion of fertility issues should be offered, even if not specifically requested, as some patients may hesitate to bring up the subject.

• Partner testing for anyone with thalassaemia should be early, and discussion of whether the person has a partner with whom they might possibly want children should form part of, at least, each annual review. If the partner carries thalassaemia or a variant haemoglobin such as sickle cell, they should be counselled together about the risk of their baby having a major haemoglobin disorder and offered pre-natal diagnosis or pre-implantation genetic diagnosis. In discussing pre-natal diagnosis, the issue of incidental chromosomal disorders or other genetic conditions should also be considered. This may be particularly relevant if the couple are related.

• Couples may be infertile for reasons unrelated to thalassaemia, and a range of investigations may be necessary to establish the nature of the problem. Treatment will depend on the findings of these investigations and the couple should be assessed comprehensively, not focusing only on thalassaemia and treatment sequelae. Prior to starting treatment, it is essential that a normal semen analysis, and tubal patency, have been confirmed. Assumptions should never be made, as overlooking simple tests can cause unnecessary delay in starting definitive treatment.

• Starting desferrioxamine by i.v. or s.c. infusion, at a dose of 2 g over 24 hours, should be considered when the woman arrives in hospital to deliver the baby, to minimise the risk of cardiac decompensation or dysrrythmia during the peri-partum period.

• The patient and the haematologist need to be vigilant for the development of any new iron-related complications after the period when she has been off regular iron chelation, and a full reassessment of cardiac and endocrine status undertaken as soon as possible after delivery.

15: Acute Clinical Presentation

"Even if you're in hospital for another reason you still want to see your haematologist, because that's the doctor who knows you best."

Aims

To ensure that patients who become acutely unwell are managed promptly and effectively by clinical staff who are aware of the range of thalassaemia complications.

To optimise outcomes for patients who become acutely ill.

Standards

■ Specialist Haemoglobinopathy Centre teams will offer education about thalassaemia-specific acute presentations to patients and health professionals across the network, including Emergency Department and Primary Care colleagues, with details of how to access specialist advice.

■ Specialist haemoglobinopathy teams will make clear to their patients and to acute medical services at the local and specialist hospitals how they can be contacted for urgent clinical advice.

■ Patients presenting with acute clinical problems will be assessed with consideration given to the range of thalassaemia-specific complications they might develop.

■ If staff with appropriate knowledge and experience are not available on site, there must be urgent consultation with the specialist centre, and referral on after stabilisation where necessary.

■ Appropriate management should be instituted as quickly as possible.

Background

The majority of medical management of thalassaemia takes place in the outpatient clinic and day unit. However, patients occasionally present acutely and when they do so they may be seriously ill. They need prompt assessment and management, and will often need admission to hospital. Staff and patients need to be aware of thalassaemia-related health risks. Patients should have access to their health record, and be aware of their diagnoses, and relevant test results. One requirement of Specialist Haemoglobinopathy Centre teams is to educate staff in ED, acute assessment units and primary care to allow cascading of knowledge, means of accessing specialist advice and recognising the role of the 'expert patient'.

Acute presentations may be of a general medical or surgical nature, coincident with the diagnosis of thalassaemia, but there are also specific clinical presentations which occur more frequently in thalassaemia and can result in rapid clinical deterioration with associated morbidity and mortality if not recognised and treated promptly. A history of severe iron overload poor compliance with chelation therapy is obviously a risk factor for iron overload-related complications, especially cardiac failure and arrhythmia, but other factors also play a role.

Some examples of acute presentations in thalassaemia are:

• Cardiac failure, cardiac arrhythmias

• Sepsis – including post splenectomy, different profile of organisms

• Venous thromboembolism – including line related, atypical site, unprovoked

- Osteoporotic fracture
- Spinal cord compression after vertebral fracture or from extramedullary haematopoiesis
- Endocrine dysfunction – including diabetes, thyroid, calcium, adrenal
- Gallstones
- Renal stones
- Acute on chronic liver decompensation – cirrhosis, concurrent viral hepatitis.

Most primary and secondary care teams have limited experience of thalassaemia and as acute presentations are relatively rare, it is often recommended that contact with the specialist centre is made on every occasion to discuss the issues.

The questions to cover in assessing acutely ill thalassaemia patient are listed in Table 15.1. The use of these in conjunction with local trust policies (e.g. antibiotic policies, Sepsis Six, transfusion policies, VTE assessments) should facilitate early diagnosis and relevant care.

Table 15.1: Key Questions

Key Questions	Consider	Remember
• What is the transfusion history?	• Is the patient on a regular transfusion programme, intermittently transfused or not transfused? • When was the last transfusion? • Are the symptoms compatible with a transfusion reaction?	• Baseline Hb/pre transfusion Hb • Alloantibodies • Transfusion reactions including: delayed transfusion reaction, hyperhaemolysis syndrome, transfusion transmitted bacterial infection, transfusion-transmitted acute lung injury, fluid overload, anaphylactic reactions.
• Is there an indwelling venous device – e.g. PICC, Portacath, Hickman line?	• Sepsis – local or systemic? • Venous thromboembolism?	• Check when line last accessed • Any anticoagulation – is this therapeutic?
• Any features of sepsis? • Note: Sepsis Six; consider as immunocompromised	• Does the patient have an indwelling line? • Has the patient undergone splenectomy, and if so, has appropriate post-splenectomy infection prophylaxis been continued? • Is the patient chelating with deferiprone, and if so, has neutrophil count been checked to exclude agranulocytosis? • Is the patient chelating with desferrioxamine and if so, are the clinical features compatible with Yersinia or Klebsiella sepsis? Also consider gallstones, CNS sepsis, UTI, endocarditis	• Klebsiella and Yersinia sepsis more common in iron loaded patient, may include meningitis, cerebral abscess, UTI. • Yersinia enterocolitica may mimic appendicitis. • Malaria if relevant travel
• Has the patient undergone splenectomy?	• Sepsis • VTE	• Pneumococcal, meningococcal and haemophilus infections risk • Local antibiotic resistance patterns. • Risk of VTE – especially in non-transfusion-dependent thalassaemia

Key Questions	Consider	Remember
• What drugs are used for iron chelation?	• Drug side effects	• Deferiprone: neutropenia and agranulocytosis • Deferasirox: renal and liver toxicity, upper gastrointestinal ulceration and haemorrhage, acquired Fanconi's syndrome (acute renal tubular damage). • Desferrioxamine: Sepsis with Yersinia, Klebsiella, mucormycosis. • See Chapter 10: Monitoring and Management of Iron Load and product SPC for full range of possible adverse effects.
• What is the degree of iron overload – is this patient at risk of cardiac iron? • What history of palpitations?	• Trends in ferritins • Recent MRI results - cardiac T2*, liver iron • Cardiac drugs - ACE inhibitor, amiodarone, digoxin	• 89% patients in cardiac failure seen when Cardiac T2* < 10ms • Those with previous cardiac iron may still develop arrhythmias. • T wave abnormalities are common in thalassaemia patients and non specific. • Other symptoms and signs should be used to support a diagnosis of ischemic cardiac complications.
• What history of liver disease?	• Recent LIC measurements, viral hepatitis, B or C	• Liver disease may be advanced if the patient also has hepatitis, or a history of poor iron chelation over a prolonged period or alcohol excess.
• Is the patient diabetic? What is their control like?	• Hypo-/hyperglycaemia?	• Review fructosamine to consider control. If this is not available the $HbA1_c$ can be used but this is diluted with blood transfusion and may mask poor control.
• Is there any other endocrine complication, treated or undiagnosed?	• Hypocalcaemia, hypothyroidism, hypoparathyroidism, adrenal insufficiency, undiagnosed diabetes	• May impair cardiac function/rhythm • Adrenal function presentation may be subacute, only manifesting at times of acute illness
• Could thalassaemia explain acute pain?	• Wide range of complications including gallstones, renal stones, fracture, pancreatitis, PE.	• Use wider history to focus on underlying cause

Table 15.2. Acute symptoms and important pathologies to consider

Key Questions	Consider	Remember
• Acute breathlessness?	• Assess for pneumonia, CCF, PE, sepsis, acidosis, severe anaemia	• BP may be low normally in these patients – check previous records
• Acute abdominal pain?	• Gallstones, biliary tract sepsis • Renal stones (hypercalciuria) • Hepatic congestion from CCF? • Yersinia infection • NTDT post splenectomy – VTE? • Portal vein thrombosis, mesenteric infarction	• Review medical pathologies prior to any surgical intervention • Pancreatitis ± gallstones • NB: Measure splenomegaly – compare to baseline, consider splenic infarcts
• Acute back pain?	• On treatment for osteoporosis? • Recent DXA results - risk osteoporotic fracture?	• Confirm any history of trauma • Assess for spinal cord compression – e.g. weakness, paraesthesia, bladder control.
	• At risk of extramedullary haemopoeisis? e.g. NTDT, undertransfused although can occur in any patient	• Urgent MRI spine should be undertaken if suspected
• Acute neurological presentation?	• Any features of sepsis consider specific infections above. • Leg weakness, bladder or bowel dysfunction • Extramedullary haematopoiesis with spinal cord compression	• Imaging, blood and CSF cultures where indicated • Urgent MRI spine if any possibility
• Acute anaemia?	• Baseline Hb, transfusion history? • Any intercurrent illness, fevers, diet issues?	• Parvovirus (and if considered possible, any other family members with thalassaemia should have review/Hb check) • Folate deficiency

Examples of specific acute presentations (see also relevant complications chapters)

Cardiac

Patients with cardiac iron (highest risk when MRI T2* < 10 ms) can present acutely with cardiac arrhythmias (e.g. atrial fibrillation, ventricular dysrhythmias, heart block) and heart failure. They can present in ways that are not typical e.g. reduced appetite/early satiety, abdominal pain with hepatic congestion, and at ages when health professionals unfamiliar with thalassaemia may not expect to see such cases. Those with previous cardiac iron may still present years later with arrhythmias, typically atrial. Without a comprehensive assessment the severity of a patient's presentation or risk may be underestimated. The ECG and echo changes may be non-specific or subtle, the left ventricular ejection fraction can appear to be preserved, but it should be remembered that well thalassaemia patients have ejections fractions of 63 – 75%. Findings should be used in conjunction with the clinical history and MRI results. Concurrent infection can be a precipitant as can other factors e.g. hypocalcaemia, hypothyroidism, uncontrolled diabetes, pulmonary embolus. Pericarditis may be a less common presentation.

Management should include discussion with a cardiologist experienced in managing thalassaemia, and care given in an appropriate setting e.g. HDU/ITU or coronary care unit. There must be discussion with the Specialist Centre, and consideration of transfer when clinically stable. Blood pressure support should be targeted to clinical measures of renal and cerebral perfusion, and care with diuresis is needed to avoid precipitating pre renal acute kidney injury. Intensification of chelation should be started immediately, usually with combination

desferrioxamine (50 – 60 mg/kg/day, continuous intravenous infusion) and oral deferiprone (75-100 mg/kg in three divided doses).

Sepsis

Patients presenting with features of acute sepsis should be assessed fully, and managed as potentially immuno-compromised with 'sepsis 6' interventions, including taking blood cultures – peripherally and from any indwelling line - and starting on appropriate antibiotics, in line with local patterns of resistance and hospital antibiotic policies, within an hour of presentation. These should cover any identified relevant risk e.g. line related infection, features of focal risk e.g. Klebsiella, Yersinia, malaria. Some thalassaemia patients particularly those with severe iron overload can present with non-specific symptoms and no fever or a low grade fever only, and it is important to monitor these patients very carefully as often a rising white cell count and CRP may be the only indication of sepsis.

VTE

Some patients should be on therapeutic anticoagulation, e.g. those with indwelling lines, and should have compliance reviewed at presentation, although thrombi can occur even if the patient is anticoagulated.

For others there is an increased risk of VTE particularly in NTDT following splenectomy, so with any clinical presentation suspicious of DVT, PE or unusual site e.g. portal vein thrombosis, therapeutic anticoagulation should be considered while arranging diagnostic tests.

Acute back pain/spinal cord compression

Osteopenia and osteoporosis are seen commonly in thalassaemia, frequently of multi-factorial aetiologies, usually defined by DXA scanning. Minor trauma may lead to fracture and a low threshold for imaging is recommended.

Extramedullary haematopoeisis, typically paraspinal, can be seen especially in under transfused thalassaemia major or NTDT patients. This can present with acute neurological symptoms, back pain, referred pain, bladder or bowel dysfunction, spinal cord compression. Urgent investigation with MRI is required and urgent discussion with the specialist centre recommended. Transfusion, with or without hydroxycarbamide, can lead to rapid resolution of symptoms and is preferred to radiotherapy for most patients except where there is spinal cord compression. Rarely, surgical decompression may be necessary (Taher *et al.* 2010).

Endocrine

Diabetes mellitus is a common complication seen in thalassaemia, increased in those with a first degree relative with type II diabetes. Acute and chronic complications of diabetes e.g. hyperglycaemia, hypoglycaemia, nephropathy may be seen. Although glucose tolerance tests form part of the regular monitoring for complications, patients may present with previously undiagnosed diabetes.

Calcium metabolism abnormalities may be seen – hypocalcaemia, hypocalcaemia tetany – and review of vitamin D, bone profile, PTH, ABG and renal losses is required. Resistant chronic hypocalcaemia may impair cardiac function and input from the Specialist Centre's endocrine and renal teams should be considered.

Thyroid abnormalities are seen, with iron overload related hypothyroidism typically presenting with insidious symptoms or identified through routine monitoring tests. Less commonly a patient may present after taking inappropriate doses of levothyroxine e.g. poor compliance or self-medicating with higher doses than advised.

Gallstones and renal stones

Both are seen more frequently in thalassaemia and standard assessments should be initiated. Renal stones are a particular problem in older patients, with an incidence of around 10%. If the patient is symptomatic or has an unexpected decline in renal function, with or without symptoms, a renal tract ultrasound to look for hydronephrosis should be undertaken as a matter of urgency. If hydronephrosis is found, it should be managed as a matter of urgency with urology and interventional radiology input.

Any surgical interventions should be planned with the Specialist Centre, with detailed consideration of all thalassaemia related issues as described in chapter 16: Management of Surgery .

Liver

Transfused patients are at risk of transfusion transmitted infection. If a patient presents with jaundice, possibilities also include haemolytic transfusion reaction, or gallstone obstruction. The history and symptoms and signs, as well as laboratory investigations including alkaline phosphatase, γGT, direct antiglobulin test, reticulocytes, blood film and red cell antibody screen, should help differentiate between the two. Some patients with thalassaemia have advanced liver disease, typically related to iron overload, with or without transfusion transmitted infections. There may be features of cirrhosis, and such patients are at risk of acute hepatic decompensation and variceal bleeds. Details of the care plan should be urgently confirmed and input from the liver team experienced in thalassaemia sought. If a patient is accepted for liver transplant, Hepatitis E negative blood products should be given. Urgent transfer to the regional liver unit should be discussed with the Specialist Centre.

Anaemia

Review of the transfusion history is important in distinguishing between those with TDT or NTDT. Rarely, patients on a regular programme present for urgent transfusion away from their local centre if they have missed their regular appointments. In any patient with recent transfusion a delayed transfusion reaction must be considered with acute unexplained anaemia, although this would usually be accompanied by jaundice. Any intercurrent illness such as parvovirus may disproportionately affect the anaemia in thalassaemia.

In patients with NTDT, worsening anaemia may be due to sepsis, pregnancy, folate deficiency, G6PD deficiency, and if the presentation is not to the patient's usual centre their baseline haematology results should be sought, and the presentation discussed with the Specialist team as transfusion may or may not be necessary.

Bone marrow transplant patients.

Any acute presentation in a patient who has undergone allogeneic bone marrow transplantation should be discussed immediately with the transplant centre. Complications can include sepsis, graft versus host disease, veno-occlusive disease, steroid induced diabetes, metabolic disturbances.

Requirements

◆ Acute and Emergency health care staff should be aware of the diagnosis when a patient with thalassaemia (TDT, NTDT) presents with any acute illness.

◆ Health professionals assessing patients should consider if thalassaemia could explain the presentation.

◆ The patient should be discussed with the Specialist Haemoglobinopathy Centre team as soon as possible and transfer to the centre should be considered once the patient is stabilised.

Recommendations

- Following acute admission all patients should be referred for follow up in the Specialist Centre after discharge.
- Information for follow up should be shared with the patient to add to hand held records and minimise delays.
- Any adverse events arising from acute presentations should be reviewed at local morbidity and mortality meetings, and at the next network educational meeting, with teaching planned around the case.
- Serious acute complications should be entered on the National Haemoglobinopathy Registry.

16: Management of Surgery

*"I always seem to be picking up infections, I have had surgery
for liver abscesses and kidney stones."*

Aims

To optimise outcomes for the patient with thalassaemia requiring surgery, and to minimise associated risks.

To plan elective surgical procedures in a timely manner to allow optimisation of thalassaemia-related health of the patient at the time of surgery

To ensure close working between surgical, anaesthetic and paediatric/haematology teams around the time of any elective or urgent surgery.

To ensure the risk of perioperative complications related to thalassaemia are considered by all the clinical teams involved, and by the patient/parent giving consent

Standards

■ Patients should be carefully assessed pre operatively with specific reference to complications relating to thalassaemia including cardiac, thrombotic, endocrine and metabolic disturbances.

■ There should be close liaison between the surgical, anaesthetic, and paediatric/haematology teams in planning surgery, and shared care arrangements should be agreed prior to a surgical admission.

■ Patients undergoing urgent surgery should always be discussed with the SHC team, during preparations for theatre.

■ Patients should have been given adequate information regarding thalassaemia-specific and other issues related to surgery to allow informed consent.

Background

General

Surgical procedures are more frequently needed in people with thalassaemia. All patients should have a clear understanding of the indication for, benefits of and risks involved with surgery. There must be a clear management plan taking into account pre- and peri-operative transfusion requirements, thromboprophylaxis, and management of any endocrine disorders.

Patients who are on long term transfusions (TDT) and those with non-transfusion-dependent thalassaemia (NTDT) may have significant medical issues, often related to iron overload, which can affect the outcomes of surgery. Surgery should be planned in collaboration between the specialist surgical team, the specialist centre and the local centre. The nature of surgery, including emergency or elective, should be considered in the context of the patient's thalassaemia, to assess the balance of risks versus benefits. A comprehensive assessment should be undertaken to identify medical and surgical issues relevant for patient care.

A preoperative assessment should include transfusion history, baseline haemoglobin, an assessment of current iron loading and of iron chelation therapy, current and previous complications relating to iron overload, particularly regarding the potential risk of precipitating or worsening cardiac, endocrine, metabolic and liver dysfunction. An assessment of thrombotic risk is important, taking into account splenectomy status, previous history of thrombosis, and presence of indwelling intravenous lines.

Transfusion

Blood transfusion for the TDT patient should be planned around elective surgery, to allow surgery to be undertaken with optimal Hb level (100 – 120 g/l). Special blood requirements should be communicated well in advance to the surgical unit's transfusion laboratory. This applies to patients with TDT and NTDT. For emergency surgery any transfusion support should be considered in line with the patient's clinical condition and local transfusion policy, after discussion with the SHC team.

In considering transfusion for the NTDT patient, the risks/benefits of elective pre-operative transfusion should be assessed with the SHC. Pre-operative preparation with one or more transfusions may be considered for specific procedures, particularly if the patient is splenectomised and has a high nucleated red cell count. In these patients there is some evidence to suggest that a period of hypertransfusion prior to a surgical procedure may reduce the thrombotic risk (Chen *et al.* 1996; Musallam *et al.* 2013; Taher *et al.* 2006).

Endocrine

Control of any existing endocrine complications, for example diabetes mellitus, should be optimised. Other endocrine complications should be tested for, if no recent routine monitoring results are available. Thyroid function and serum calcium levels should be normalised. Many patients with TDT have subclinical adrenocortical deficiency which may manifest clinically during surgery. If possible, assessment and endocrinology advice should be sought about appropriate steroid replacement therapy to cover the surgical procedure. In the case of emergency surgery where no recent normal results are available, deficiency should be presumed and replacement therapy with hydrocortisone given peri-operatively.

Cardiac and liver

Where possible cardiac and liver iron should be optimised pre-operatively to reduce the risks of perioperative complications. For patients with evidence of severe cardiac and/or liver iron loading and current or previous history of organ dysfunction, specialist advice should be sought about optimal peri-operative support. For urgent surgery in such patients, continuous intravenous desferrioxamine at 50 – 60 mg/kg should be considered during the perioperative period. In all cases, anaesthetic and surgical teams should maintain careful fluid and electrolyte balance, and monitor for cardiac arrhythmias.

Specific considerations.

Yersinia infection

Iron loaded patients chelated with desferrioxamine may present with acute abdominal symptoms which suggest acute appendicitis, due to Yersinia enterocolitica infection. This infection should be treated with appropriate antibiotics and does not require surgery.

Splenectomy

Splenectomy is less commonly required in those with TDT who have been transfused appropriately since early childhood. However it is sometimes still indicated for hypersplenism and for those with splenomegaly and high transfusion requirements, of more than 200 – 220 ml red cells/kg/year (Rebulla and Modell 1991). Laparoscopic splenectomy can be considered as an alternative to an open procedure.

The spleen is often enlarged in NTDT but routine splenectomy is not recommended and any anticipated benefit has to be balanced against possible long-term risks of sepsis, thrombosis, pulmonary hypertension and enhanced iron loading. Before a decision on splenectomy, it may be helpful to consider a period of hypertransfusion as this may reduce spleen size.

Splenectomy may be appropriate in people with NTDT who run a low haemoglobin and are returning to low-resource countries where reliable safe blood transfusion services and adequate chelation may not be available.

Discussion with the patient should cover the generic risks of surgery and the special risks of post-splenectomy infection and thrombosis. For each individual a plan for peri-operative thrombo-

prophylaxis should be discussed and decision documented prior to the procedure. There is an increased risk of thrombotic complications in the peri-operative period, partly related to the increase in platelet count and in prothrombotic thalassaemic red cells post-splenectomy (Mannu *et al.* 1995). Peri-operative thrombo-prophylaxis should be initiated routinely and extended thrombo-prophylaxis considered until the patient is back to normal mobility, or up to 4 weeks post operatively. In addition, for those with a persistent thrombocytosis above 500×10^9/l, long term aspirin should be considered (Taher *et al.* 2014). In the post-operative period it is recommended that the haemoglobin is kept above 100 g/l to reduce the presence of abnormal red cell fragments which increase the thrombotic risk (Chen *et al.* 1996)

Vaccinations for prevention of infection in the asplenic patient should be completed before elective surgery. Current vaccination guidance is provided in 'The Green Book, immunisation against infections disease' (Public Health England 2014b).

Lifelong prophylactic antibiotics (oral penicillins or macrolides) should be offered to reduce the risk of severe pneumococcal infection. For children this should be given regularly. For adults, antibiotics can be taken on a regular twice daily basis, but many do not adhere to this and accepted practice is to ensure that they have a supply on hand to take – at a treatment dose: penicillin V 500 mg four times a day, amoxycillin 500 mg three times a day, or erythromcycin 500 mg twice a day if penicillin allergic – at the first hint of infection, sore throat, fever. It is important that patients fully understand why this is necessary, and how and when to take antibiotics (Davies *et al.* 2011). If the usual oral antibiotics are not improving symptoms within 24 hours, of if fever exceeds 38 °C, patients should present to the Emergency Department. Hand-held letters explaining this need will help them to get appropriate attention if they need to present in this way.

Patients must be given appropriate written or electronic information and offered a 'post splenectomy card' to alert health professionals to the risk of overwhelming infection. They may wish to buy an alert bracelet or pendant. Patients should be educated as to the potential risks of overseas travel, particularly with regard to malaria and unusual infections, e.g. those resulting from animal bites. Patients' records must be clearly labelled to indicate the underlying risk of infection. Vaccination status and re-vaccination recommendations must be clearly documented.

Patients developing infection, despite the above measures, must be given systemic antibiotics and admitted urgently to hospital. Empirical antibiotics should be based on local antibiotic guidelines and/or microbiology advice for patients with non-functional spleen.

Cholecystectomy

Gallstones are frequently identified in patients with thalassaemia (TDT and NTDT). Cholecystectomy is recommended if there is a history of complications related to gallstones such as biliary colic, cholecysitis, cholangitis, gallstone-related pancreatitis or biliary obstruction due to passage of stones. In general surgery is not recommended for asymptomatic gallstones. The laparoscopic approach is suitable if surgically indicated.

Orthopaedic Surgery

Severe arthritis or fracture associated with osteoporosis may be indications for elective or urgent surgery, including large joint replacement.

Requirements

◆ All patients undergoing planned surgery should have a clear management plan drawn up by the surgical, anaesthetic and Specialist Haemoglobinopathy Centre teams documenting their fitness for surgery for the patient with regard to cardiac, endocrine, hepatic and metabolic factors, and the timing of surgery should be planned and agreed.

◆ All patients should have an individualised risk assessment for thrombosis and be appropriately managed to reduce the risk.

◆ It is preferable for surgery to be undertaken at the Specialist Haemoglobinopathy Centre. If there is a particular reason for the surgery to be done at an alternative hospital, there should

be clear communication with the specialist team at all stages of planning and undertaking surgery.

◆ If there appears to be an acute surgical problem, medical pathologies that could explain the presentation must be excluded prior to surgery

◆ Urgent surgical interventions should be undertaken without undue delay, but always after discussion with the Specialist Centre team, even if out of hours, to help reduce the risk of adverse outcomes

◆ Blood transfusion support should be planned with the SHC.

◆ All patients undergoing splenectomy must be given relevant health education about avoiding/managing infections, and must have recommended antibiotic supply and vaccinations.

Recommendations

• All staff involved in the care of the patient should have access to recent correspondence, problem lists, care plans, current medication and investigation results before the procedure is undertaken, even if this is required urgently.

• Patients with cardiac iron overload should be reviewed by the named cardiologist at the SHC and have a clear management plan for care during any planned elective procedure, and this should be explicitly agreed between all involved clinical teams.

• Patients should give informed consent for surgery, after clear discussion of potential risks and benefits, both general and thalassaemia-specific.

• Long term risks of surgical procedures such as infection and thrombosis should be detailed, and explained at the time of consent.

• Information at discharge should be shared with the patient, SHC and primary care.

• Outcomes of surgery, and any adverse events, should be reviewed with the SHC team at network meetings, or more urgently if necessary, for the purposes of learning and to make any changes to clinical pathways.

Section C: Prevention and Management of Complications

17: Management of the Cardiovascular System

"I ended up having iron overload in heart which caused atrial fibrillation causing more tiredness and making me unable to work"

"I would like to see a cardiologist regularly, at least annually to set my mind at rest"

"Due to heart problems caused by thalassaemia my life has slowed down and there are days when I can't go out of the house."

Aims

To guide clinicians and thalassaemia patients on strategies to prevent cardiovascular complications arising through their thalassaemia or through the consequences of medical interventions used to treat it, especially blood transfusion.

To guide clinicians and thalassaemia patients on the use of appropriate monitoring to detect cardiovascular complications prior to the development of symptoms, or damage to the heart and circulatory system.

To illustrate the limitations of current clinical approaches in preventing every manifestation of cardiovascular dysfunction in this group of individuals.

To promote awareness of other risk factors that may impact on cardiovascular health, such as diabetes and poor life style habits, including smoking and sedentary living.

Standards

■ Every patient must have access to a cardiology service with experience in the management of cardiac consequences of thalassaemia.

■ Children should be referred for their first cardiac evaluation, including clinical assessment, ECG, echocardiogram and MR T2* between the ages of 7 – 10 years.

■ Cardiology assessments thereafter should be at intervals guided by symptoms, adequacy of chelation and findings of previous assessments.

■ A high risk time for development of cardiac problems is 16 – 25 years of age, and during this period assessments should be undertaken at least yearly.

■ Patients with myocardial iron and left ventricular (LV) impairment with new-onset symptoms must be discussed with the SHC team, and reviewed urgently for consideration of inpatient intensive chelation.

■ Patients must be considered for anticoagulation if they have indwelling venous lines, or atrial fibrillation, including paroxysmal AF.

Background

Pathophysiology of the heart and circulation in thalassaemia

The heart and circulation will be affected in a number of ways by the consequences of the ineffective erythropoiesis that characterises the thalassaemia genotype, depending on the severity of the β-globin gene mutation, the co-inheritance of other genetic modulators, and the type and intensity of treatment, particularly blood transfusion.

Chronic anaemia and the cardiovascular system

Despite regular blood transfusions the thalassaemia patient has a degree of chronic anaemia, which can be severe in those individuals not receiving regular transfusion, mainly those with NTDT. This leads to a hyperdynamic circulation, with low peripheral resistance, vasodilatation, a low blood pressure and cardiac chamber dilatation. These are appropriate physiological responses in the healthy person with thalassaemia. Parameters of cardiac size on chest X-ray, echocardiography and MRI scanning are larger than for an age-matched population. Measures of cardiac function demonstrate higher values than for an aged matched non-anaemic population. An increased resting heart rate in these patients is not universal. Many have relatively low heart rates, presumably on the basis of autonomic function changes, which are not well characterised.

Cardiac departments unused to interpreting data from this group of patients may imply disease where there is none (an "enlarged heart") and conversely, more worryingly, may report "normal" values, particularly for the left ventricular ejection fraction (LVEF), where in fact values < 60% may represent dysfunction in this group of patients. It is now generally accepted that a lower limit for EF in thalassaemia major patients, using MRI scanning, is approximately 63% (Pennell, Udelson *et al.* 2013). Left ventricular (LV) end diastolic dimensions on echo, and LV volumes and LV mass by cardiac MRI or echo, are all increased in healthy thalassaemia major patients, although precise normal ranges are not available. Cardiac parameters should also be related to body size in this group of patients, many of whom are of smaller habitus than their peers.

It is increasingly apparent that some of the age-related changes in cardiac function in this population may be the effect of chronic anaemia. There is an increased incidence of ventricular diastolic dysfunction in the older transfused TM population, which may progress to features of heart failure with normal EF (the so called HFpEF). Increased size/volume of the atria are commonly encountered, attributable in part to the changes in LV compliance, which may have their origin in LV remodelling and myocardial fibrosis.

The increased shear forces associated with anaemia and a hyperdynamic circulation may account for remodelling of the arterial vessel walls, particularly in the large, compliance arteries. This may lead to abnormal vascular dynamics, which in turn exacerbates a tendency to develop LV diastolic dysfunction (Cheung, Chan *et al.* 2002).

Anaemia may account for some of the symptoms encountered in the TM population. The symptoms are non-specific, consisting primarily of exercise limitation and breathlessness, but may cause confusion because of their similarity to the clinical presentation of cardiac failure.

Blood Transfusion

Blood transfusion is essential for people with thalassaemia major, but inevitably leads to iron overload. Chelation therapy is required to deal with excess iron accumulation and is lifesaving in the context of tissue, and in particular cardiac, iron load (Modell *et al.* 2008).

With regular transfusion from infancy, it is possible to detect iron in the heart from as early as 6 years of age (Wood, Origa *et al.* 2008). Maintaining a good haemoglobin by transfusion will, however, mitigate against the physiological consequences of anaemia discussed above. It is unclear whether all of the adaptations and features, such as aortic compliance and LV diastolic function, can be prevented, nor is it known what the optimal transfusion regimen might be to achieve this goal.

Myocardial accumulation of iron through blood transfusion occurs once transferrin is fully saturated and is closely linked to the levels of NTBI in the blood. The heart has a significant

buffering capacity for iron, but when this is exceeded the risk is of brisk deterioration in myocyte contractile function leading to the clinical manifestation of cardiac failure (HF). This is systolic heart failure (HFrEF) and carries a high mortality if intensive, continuous iron chelation is not instituted urgently (Pennell, Udelson *et al.* 2013).

It is uncommon for blood transfusion to cause volume overload problems for TM patients, but in those with poor LVEF and in the older age groups, with restrictive ventricular physiology, slower transfusion rates, limited volume blood products and more frequent, smaller transfusions may be helpful. Occasionally loop diuretics (furosemide or bumetanide) may be given at the time of transfusion, but the potentially serious consequence of volume contraction needs to be avoided by careful clinical assessment.

Thalassaemia associated endocrinopathy

Diabetes

Diabetes is common as a consequence of pancreatic β-cell dysfunction secondary to iron overload. The classical association between diabetes and an increased prevalence of arteriosclerotic cardiovascular disease is not a feature in this population. However, there is a high prevalence (> 70%) of diabetes amongst older TM patients (> 40 yr), who develop atrial fibrillation. Whether this is a non-specific association, due to a more severe phenotype or to a specific role for diabetes, is unclear. However, when considering the possibility of AF in an older TM patient the co-existence of diabetes should increase suspicion.

Thyroid and gonadotrophin deficiency

The frequent co-existence of these endocrinopathies has not been examined independently as factors in the development of cardiovascular complications.

Adrenal insufficiency

Adrenal dysfunction may be a particular problem when managing severely ill TM patients. In the context of acute illness and severe heart failure, consideration should be made to providing adrenal support, even before formal proof of insufficiency is available.

Lifestyle

Smoking

It is not clear whether there are any specific interactions between smoking and the development of cardiovascular complications in the TM population but it is very unlikely that they are immune to the general deleterious effect of smoking on health. All patients should be given strong recommendations to stop smoking and appropriate support "to quit" should be offered.

Sedentary lifestyle

People with thalassaemia may have challenges in maintaining a healthy degree of physical exercise, due to associated bone and joint complications. Nevertheless they should be encouraged to maintain regular exercise within their capacity. In particular, reassurance needs to be provided that cardiovascular status is likely to be improved in the long term by a healthy active lifestyle.

Diet and Lipids

In this group of patients, often affected by hypotension, generic advice given to the general population regarding the limitation of salt intake may not be appropriate. The risk of arteriosclerosis also appears to be low in TM patients, so extreme diets, including low fat, need to be discouraged and a more holistic approach undertaken.

By the same token, although it appears reasonable to offer prospective primary prevention therapy in the situation of abnormal lipid metabolism, there is no data to support this approach, particularly as people with thalassaemia appear to have an unexpectedly low incidence of arteriosclerotic heart disease. Efforts to encourage lifelong compliance with chelation and diabetic control should probably take precedence.

Cardiovascular Investigations

Clinical history and examination

The insidious development of cardiac dysfunction can be difficult to detect, as symptoms are frequently non-specific. Exercise limitation, breathlessness, exhaustion are all symptoms frequently associated with anaemia. Changes in status are generally the key and mandate investigation. Chest pain and palpitations are relatively common, and may not always relate to clinically significant pathology, cardiac dysfunction or iron overload, but require investigation.

There are no thalassaemia-specific cardiovascular features to be found on examination. However, it is common to encounter a low normal blood pressure, frequently with systolic BP < 100 mmHg and anaemia-associated, usually innocent, systolic murmurs at the base of the heart. Of particular importance is the appearance of changes in signs, particularly the development of indicators of cardiac failure or pulmonary hypertension. Clinical examination, including recording of pulse, blood pressure, oxygen saturation by pulse oximetry, and cardiovascular findings should be recorded at least at every annual review visit.

ECG and ambulatory recording

A standard 12 lead ECG commonly shows non-specific abnormalities particularly of repolarisation (non-specific T-wave changes), but these are of unclear significance if long-standing. They are more common in patients with a history of severe iron overload, but are not a reliable indicator of current cardiovascular iron status. An early baseline ECG is important, to enable changes across time to be identified. The frequency of surveillance ECGs is dependent on individual circumstances, but a minimum of once every 2 years for completely stable, non-iron overloaded TM patients is useful to detect subtle but uncommon developments, such as conduction disturbance, QT prolongation, ventricular hypertrophy or RV overload. Annual ECGs, at least, should be obtained for those with iron overload, an abnormal baseline ECG and any patient with in-dwelling central venous catheters.

As intermittent arrhythmias will frequently be missed on a standard ECG, ambulatory recordings need to be considered. The standard 24hr Holter monitor will miss many intermittent and potentially important abnormalities of rhythm and conduction. Longer term monitoring, using Holter recorders, newer patient activated recorders, adhesive patch ECGs and implantable loop recorders (ILR) need to be considered in individual cases. There is no clear indication at this time to embark on prospective arrhythmia surveillance in asymptomatic TM patients, with the exception of those who have suffered a neurological, or other possible embolic event, where silent atrial fibrillation must be excluded.

Echocardiography

Echocardiography is the most practical means of regular long-term monitoring of ventricular size and function, and can be used for annual or more frequent follow up for myocardial iron toxicity, and in experienced hands can even identify patients at risk. Some cardiovascular complications, such as intra-cardiac thrombus may be detectable on echocardiography but undetectable by other imaging modalities, such as MRI scanning. Echocardiography remains the best method of detecting pulmonary hypertension and diastolic ventricular dysfunction, or restrictive physiology.

The most frequently used parameter of ventricular function is the ejection fraction (EF) although this parameter alone cannot fully describe cardiac function. Echo EF has a coefficient of variation (CV) of 7% at best and is probably closer to 10% in general cardiology services. MRI values are better, probably closer to 5% (Grothues *et al.* 2002) and this lower CV is also associated with more contemporary echo techniques, including 3D volume analysis. More sophisticated measures of cardiac function, such as Tissue Doppler Imaging (TDI) and global longitudinal strain (GLS) have demonstrated their usefulness in TM and other cardiomyopathies, achieving greater sensitivity and specificity, particularly for detecting minor changes in function. It is particularly important to identify these early changes in this patient group, so that appropriate chelation treatment can be discussed.

Table 17.1: Parameters for an adequate echocardiogram in TM population

(E = essential, D = desirable)

Parameter	Comment	E/D
Chamber dimensions	LV end-diastolic and end systolic; LA diameter or area; RV size	E
Ventricular systolic function; radial	SF; EF by Teicholz and by biplane analysis, modified Simpson's; not "visual estimate"	E
Ventricular diastolic function	E/E' plus other parameters	D
Tricuspid jet Vmax	To detect pulmonary hypertension; preferable to calculated PAsp: <2.5 m/s is normal; > 3.0 m/s is abnormal. No TR jet in many cases, generally means normal R heart pressures.	E
Ventricular function, longitudinal	TAPSE, LV and RV; better by Tissue Doppler (TDI) Sa parameters	D
Strain imaging	Global longitudinal strain (GLS); likely to supplant EF for surveillance	D
3D Volume analysis	3D volumes and derived EF improve accuracy of surveillance; will supplant current methodology	D

Cardiac MRI

The introduction of MRI for the detection of cardiac iron has transformed the management of patients with thalassaemia major. Prior to 2000, serum ferritin or liver biopsies were used to measure iron overload but these are inaccurate and do not always accurately reflect cardiac iron; the primary source of mortality. Over a decade of investigation, the T2* Cardiovascular Magnetic Resonance (CMR) technique was developed allowing an accurate non-invasive assessment of cardiac and liver iron burden (Anderson *et al.* 2001). T2* is one of the three fundamental tissue signal MRI rate constants. T2* measurements are derived from a single mid-ventricular short-axis slice. It is a robust, reliable method and has been validated histologically. Cardiac iron levels are inversely related to myocardial T2* values. Values of 20 ms or higher indicate absence of clinically important iron overload, lowest risk; 10 – 19 ms indicate mild to moderate cardiac iron, low risk of heart failure; < 10 ms: severe iron overload with substantial risk of immediate cardiac complications: heart failure risk rising from 14 – 30% within 1 year if 6 – 9 ms, and 50% risk of heart failure within 1 year if < 6 ms (Kirk *et al.*, 2009)

All patients receiving regular transfusions should have a quantitative tissue iron load assessment, by CMR scanning at the earliest possible opportunity, which for most TM patients is likely to be between 7 to 10 years. Repeat scanning every year in the most vulnerable danger period, as their care moves from the paediatric services to adult medicine is to be encouraged, with at least CMR, ECG and echocardiography. Thereafter the interval of surveillance should not exceed 2 years for well chelated individuals able to take their treatment but should be more frequent in patients having difficulties with treatment, or with abnormal baseline results, or suggestive cardiac symptoms. Investigations at less than 6-monthly intervals are unlikely to detect meaningful changes, the rate of iron removal being relatively slow in the heart.

Appropriate CMR scanning intervals are:

- T2* > 20 milliseconds – every 2 years
- T2* 10 – 20 milliseconds – yearly
- T2* < 10 milliseconds – 6 monthly

In non-iron loaded patients a search must be made for alternative causes of ventricular function impairment. Echocardiography is more readily available for serial and frequent assessment of dimensions and function, with CMR being utilised more sparingly to confirm associated iron load changes.

Clear communication with patients regarding CMR scans should clarify that scans are free from ionising radiation and repeated scanning poses no health risk. Patients sometimes find the MR scanner claustrophobic, and the nature of the machine should be explained to them before their appointment. If a patient has a pacemaker or other implanted device, confirmation that it has MRI compatible components will be required.

Nuclear Medicine

Nuclear studies were used before the introduction of the T2* technique. Early left ventricular dysfunction could be detected using radionuclide cineangiography (MUGA scanning) during exercise in patients with thalassaemia. Nuclear medicine however requires the use of radioactive isotopes and this modality is no longer recommended for routine investigation.

Blood biomarkers

Brain natruiretic peptide (BNP) is a serum biomarker for the presence of cardiac failure. It has not been shown to be helpful in the routine surveillance of the TM population, nor does it appear to give early warning of ventricular involvement or cardiac iron overload (Pennell, Udelson *et al.* 2013). In individual cases of established heart failure, measurement of BNP can help guide volaemic status and it may be useful in differentiating breathlessness due to pulmonary problems versus that due to cardiac failure.

Management of cardiovascular complications

Arrhythmia

A variety of arrhythmias have been described complicating thalassaemia. These are mostly tachycardias, but in inadequately chelated patients, bradycardia and heart block may be seen. The heart block will usually, but not always, respond to removal of myocardial iron. Pacemakers are rarely required, but if symptomatic bradycardia or heart block do not improve despite intensive chelation, the use of MRI compatible pacemakers is justified.

Acute arrhythmia

Ventricular tachycardia (VT) is a grave indicator of heart dysfunction, as in any form of cardiomyopathy, requiring urgent and expert assessment. It is almost uniquely a feature of severe myocardial iron overload in the TM population and usually responds intensification of chelation.

VT is a medical emergency requiring admission to hospital and severe cardiac decompensation or non-responsive VT mandates the use of DC cardioversion to restore sinus rhythm as quickly as possible. Intra-venous continuous chelation with desferrioxamine (DFO) 50 – 60 mg/kg/ day should be started as soon as possible, with the early addition of oral treatment with deferiprone (DFP) 100 mg/kg/day in divided doses. Other therapies are dependent upon the response to chelation, but would include beta-blockers and amiodarone as well as normalisation of electrolyte disturbance, particularly potassium and magnesium.

Consideration of device therapy, ICD, after the initial event, should be delayed until the response to chelation has been fully assessed. It will usually prevent further MRI scanning, a potentially serious problem for TM patients. Unlike virtually all other cardiomyopathies faced by cardiologists and EP physicians, VT in this group of patients can be considered a toxic manifestation of iron and its removal associated with minimal risk of further VT, unless there is evidence of irreparable damage to ventricular function.

Atrial fibrillation (AF) may be the precipitating event that causes acute cardiac decompensation in severely iron-overloaded hearts. Under these circumstances, treatment should follow the principles outlined above for VT. Early consideration of DC cardioversion is advised.

Chronic and late appearing arrhythmia

Atrial arrhythmias, including atrial fibrillation (AF) do not always indicate severe cardiac iron toxicity and are increasingly evident in older cohorts of thalassaemia patients, even though they may have successfully chelated down their cardiac iron level decades previously.

Atrial fibrillation may carry a higher risk of stroke than in age-matched non-thalassaemic individuals. This is especially true for those who have undergone splenectomy and for those with diabetes. All TM patients describing anything other than very infrequent, transient arrhythmia or palpitations need prolonged ECG monitoring for diagnosis and detection. Cardiac MR imaging, if not on recent record, should be repeated to establish if cardiac iron is present, in which case a suitable intensive chelation regimen should be started promptly. Medical management of arrhythmias is similar to non-thalassaemia patients. Beta-blockers and class I anti-arrhythmics appear to be safe and effective. Anti-coagulation (vitamin K antagonists, such as warfarin, or the newer Direct Oral Anti-Coagulants, such as dabigatran, apixaban or rivaroxaban) should be strongly considered for patients with a significant burden of AF. The standard CHADS-Vasc scoring system for stroke risk in AF should not be applied to TM patients.

Ablation treatment for arrhythmia have been successfully used; it is very effective and often curative for atrial tachycardias (AT, atrial flutter), but less reliably successful for atrial fibrillation (AF). Nevertheless these techniques offer promise for severely symptomatic patients, particularly as these patients' ability to tolerate adequate doses of beta-blockers or other anti-arrhythmic therapy may be limited by systemic hypotension.

Heart Failure (HF)

Acute, decompensated HF

The development of acute heart failure complicating thalassaemia is now thankfully rare, but still has a high immediate mortality risk, approaching 50%. This emphasises the importance of avoiding this complication by adherence to regular chelation, guided by CMR T2* measurements. Patients with a T2* <6 ms have a > 50% risk of developing heart failure within 12 months (Kirk *et al.* 2009).

However, even with acute severe decompensated heart failure, restoration of completely normal ventricular function is possible with the intensive continuous chelation as described above for acute VT. The potential for complete reversibility of heart failure in TM may not be appreciated by clinicians who are not familiar with the management of these patients. Improvements in ventricular function assessed by echo or CMR precede demonstrable improvements in iron content measured by T2*.

In addition to intravenous DFO (50 – 60 mg/kg/day) with oral DFP (≤100 mg/kg/day), grade IV heart failure patients should receive adrenocorticoid therapy, thiamine and electrolytes to maintain high normal values of serum K+ and Mg++. All efforts should be made to support the circulation, but care must be taken to ensure that intensivists are aware of the particular haemodynamic features of this patient group. Inotropic support must be used cautiously in these patients, who often improve on much lower central systemic blood pressures than seen in non-thalassaemia heart failure patients. Support should be continued long enough to allow adequate removal of the toxic iron accumulation, which may take days or weeks in some circumstances, particularly if renal function is impaired. Scrupulous attention to diabetic control and rapid treatment of associated arrhythmia is essential.

As soon as practicable, the introduction of conventional heart failure medication, including ACE inhibitors or angiotensin receptor blockers with beta-blockers and aldosterone receptor blockers should be considered, (Pennell, Udelson *et al.* 2013), although conventional doses may not be tolerable because of low blood pressure. Although in non-thalassaemia heart failure these medications are prescribed for long term use, the length of time of exposure for the TM sub-group is not established. People are usually advised to avoid alcohol for at least a few months after an episode of acute heart failure.

Chronic heart failure

Although recovery of function with adequate chelation is the expected outcome of treatment of HF in TM, a number of patients have long term impaired ventricular function. In some this may be due to a coincidental dilated cardiomyopathy, unrelated to iron overload, or follow a viral myocarditis. Rarer diseases need to be excluded in any atypical presentations or inadequate responses to conventional approaches with chelation and HF medication. Valve disease is approached conventionally and successful heart surgery has been undertaken in TM patients.

A more insidious condition, of diastolic heart failure, is increasingly seen in older patients with TM. This does not seem to be immediately associated with iron overload, but may be more common in individuals with a past history of heart failure. Sometimes termed heart failure with preserved ejection fraction (HFpEF), the features are of normal or mildly reduced EF, increased ventricular filling pressures, dilated atria and an increased propensity to AF. Symptoms are similar to heart failure with reduced ejection fraction (HFrEF), but the implications for prognosis are probably less severe, at least in the medium term. Features of congestion, with peripheral or pulmonary oedema, and the development of pulmonary hypertension in the long term are potential consequences of HFpEF, for which there is no specific therapy. Diuretics have a role, for symptom control, but must be used with caution. Despite the lack of evidence of efficacy most cardiologists also treat HFpEF with conventional HF treatments.

Occasionally surveillance reveals progressive change in ventricular function, often not accompanied by symptoms. Under these circumstances CMR assessment for T2* (iron overload) should be undertaken as soon as possible and initiation of intensive chelation therapy begun. Consideration needs to be made whether conventional heart failure medication, such as beta-blockers, ACE inhibitors or angiotensin receptor blockers and aldosterone antagonists, should also be introduced at this stage; there is little to argue against this approach, which can be reviewed in subsequent clinic visits once improvement in cardiac function is achieved.

Pulmonary hypertension (PHT)

This is uncommon in thalassaemia major, but is a particular feature of untransfused patients. It is believed that intra-vascular haemolysis plays a major part in the development of pulmonary vascular endothelial dysfunction. Thus the emphasis in treatment has been to transfuse TI patients intensively if PHT is diagnosed. However, chronic pulmonary thrombo-embolism may contribute, so consideration should also be given to life-long anticoagulation. Once established, PHT carries a poor prognosis, with the development of right ventricular (RV) dilatation followed by RV dysfunction and failure, for which there are no adequate treatments available.

There is some experience to support the use of phospho-diesterase 5 inhibitors (sildenafil, tadalafil) in the treatment of PHT. Individual patients should be referred to national pulmonary hypertension centres to be considered for more complex therapies, such as endothelin antagonists or phosphodiesterase inhibitors.

Iatrogenic pulmonary hypertension has been observed in patients with indwelling central venous catheters (IVC), due to undetected chronic pulmonary thromboembolism. There are instances of successful use of surgical pulmonary thromboembolectomy to treat these patients, but this high risk surgical intervention must be avoided if possible. This experience has led to the recommendation for full anti-coagulation of all patients fitted with IVC devices, usually with vitamin K antagonists.

Management of the cardiovascular system in pregnancy

Fitness to consider pregnancy

Fertility is commonly reduced in patients with thalassaemia due to iron loading in the anterior pituitary gland, and will often require assisted reproductive methods to successfully conceive. Thalassaemia poses an increased risk to both mother and fetus, and the risk of cardiac complications ranges from 1% to 15% (Pennell, Udelson *et al.* 2013).

The RCOG recommend review by a cardiologist with expertise in thalassaemia during the planning stages (Royal College of Obstetricians & Gynaecologists 2014). A thorough assessment is required to determine the cardiac status prior to embarking on pregnancy and this must include ECG, transthoracic echocardiogram for assessment of longitudinal and radial function, and valvular assessment, and cardiovascular MRI for cardiac iron quantification.

It is recommended cardiac T2* values should be above 20ms, indicating no significant iron loading and left ventricular function should be normal (EF > 65%). Reduced LV function is a relative contraindication to pregnancy. T2* values <10ms indicate severe myocardial iron and patients should be advised to avoid pregnancy, at least until a period of intensive chelation has improved cardiac iron, due to the risk of developing overt heart failure.

Surveillance/Antenatal care

Pregnant patients with thalassaemia must receive specialist cardiac assessment and should undergo assessment of cardiac function with transthoracic echocardiography. Iron loading should be assessed by CMR scanning, which is safe from 20 weeks gestation if it was not undertaken pre-conceptually. Women with T2* values < 20 ms are at risk of decompensation and therefore require regular clinical assessment. In the event of unplanned pregnancy, an iron overloaded patient must have immediate and regular cardiovascular investigation including echocardiography, and chelation therapy with low-dose subcutaneous desferroxamine (20 mg/kg/day) for 4-5 days per week can be considered starting from 20 weeks.

Management of labour

Timing of labour is dependent on co-morbidities identified throughout the antenatal period. Patients with cardiac iron off chelator medication have high serum concentrations of non-transferrin bound iron which may cause free radical damage and arrhythmias during labour, and some centres recommend that peripartum chelation therapy with low dose desferrioxamine is started.

Fitness for non-cardiac surgery and other medical procedures

Sudden cardiac decompensation is possible in individuals with severely iron overloaded hearts (T2* < 10 ms) when faced by increased haemodynamic demands, even if the pre-morbid ventricular function appears to be normal. Those individuals with impaired function previously documented need to have their condition optimised with conventional anti-failure medication, accepting there are no prospective studies in this area. The surgical and anaesthetic teams need to be aware of the baseline haemodynamic status, as low blood pressure may be the patient's normal, and of the potential restrictive ventricular issues likely to be encountered in the older patient. Careful fluid management and optimisation of haemoglobin are required before any intervention. The potential for increased risk of thrombotic events means that anti-VTE prophylaxis should be given if there is no contra-indication.

Organisational issues

Local haemoglobinopathy centre cardiologists are unlikely to have a significant experience in managing the various cardiovascular issues affecting this group of complex patients. All patients should routinely be seen and assessed at a Cardiology Clinic with a special interest and expertise in the management of cardiac iron overload, and the other complications described here.

Protocols for CMR scanning to obtain T2* values are in the public domain, but MRI unit directors need to accept the necessity of validation, if the scans are to be undertaken locally and not only at specialist tertiary imaging centres, (Pennell, Udelson *et al.* 2013).

Requirements

◆ Clinical examination, including recording of pulse, blood pressure, oxygen saturation by pulse oximetry, and cardiovascular findings should be recorded at least at every annual review visit.

◆ Referral to a cardiology service with specific experience in the management of cardiac consequences of thalassaemia should first be made when the child is 7 – 10 years of age.

◆ Assessments should be undertaken as follows:

– Uncomplicated, well chelated patient on stable therapy and without symptoms or abnormalities on previous testing – see Table 17.2

Table 17.2: Assessment schedule for uncomplicated, well chelated patient on stable therapy and without symptoms or abnormalities on previous testing

Assessment	First	Surveillance interval	Comment	E/D
Clinical cardiology visit and exam	7 – 10 yr	2 yr Annual 2 yr	If no symptoms or abnormalities Between risk ages 16 to 25 yr After age 25	E D E
ECG		As above	At each visit	E
ECHO	7- 10 yr	As above	At each visit	D
MRI	7- 10 yr	2 yr if > 20 ms on last assessment		E

– Poorly chelated patient, without heart failure or impaired LV function, AND patients recovered from an episode of acute heart failure AND those with impaired LV but no symptoms – see Table 17.3

Table 17.3: Assessment schedule for poorly chelated patient, without heart failure or impaired LV function, AND patients recovered from an episode of acute heart failure AND those with impaired LV but no symptoms.

Assessment	Surveillance interval	Comment	E/D
Clinical cardiology visit and exam	Immediate, then 3 to 6 monthly	Dependent on severity of T2*; 3 monthly if < 6 ms	E
ECG	At each visit		E
ECHO	6 monthly		E
MRI	6 monthly if T2* < 10 ms Yearly if T2* < 20 ms	Unlikely to be helpful to repeat MRI at less than 6 month intervals	E

◆ Particular vigilance is required before and during pregnancy – see Table 17.4

Table 17.4: Assessment schedule during pregnancy

Assessment	First visit	Surveillance	Comment	E/D
Clinical cardiology visit and exam	When planning pregnancy	Pre-conception At ~ 12/40 gestation At 28/40 gestation 3 months post delivery	If abnormalities on testing, or significant symptoms, may need more intensive monitoring	E D D
ECG		First visit		D
ECHO		Every visit		E
MRI		Pre-conception and post-delivery visits		E

◆ Echocardiographic assessment must be undertaken and reported by an operator experienced in cardiac assessments in thalassaemia. A minimum data set, detailed in table 17.1, should be recorded each time.

◆ Findings of any cardiac iron on T2*, or impairment of cardiac function, or new arrhythmia should lead to an early review of the patient's chelation regimen, to ensure it is optimised in regard to reducing myocardial iron (see chapter 10: Monitoring and Management of Iron Load).

◆ Patients with ventricular arrhythmias or clinical cardiac failure must be admitted to hospital, and started on continuous intravenous desferrioxamine 50-60 mg/kg/day, with oral

deferiprone 100 mg/kg /day in three divided doses being introduced as soon as possible, in the absence of any contraindications.

◆ Patients with ventricular arrhythmias or clinical heart failure must be managed in liaison with the SHC, and preferably transferred for in-patient management there.

◆ Patients found to have pulmonary hypertension must be managed in conjunction with the most convenient national pulmonary hypertension service team.

◆ Patients who have an in-dwelling venous device should be fully anti-coagulated.

◆ Patients with atrial fibrillation, including paroxysmal, must receive anti-coagulation therapy.

◆ Patients who have suffered a neurological, or other possible embolic event must be investigated for silent or paroxysmal atrial fibrillation.

Recommendations

• Lifestyle factors likely to affect cardiovascular health should be explored, and patient strongly advised to undertake physical exercise, and not to smoke cigarettes.

• Co-morbidities such as diabetes mellitus and hypothyroidism should be optimally managed so as not to contribute to cardiovascular morbidity.

• Repetition of T2* measurements within 6 months of a previous measurement is not recommended.

• A T2* > 20ms and EF > 65% is recommended prior to embarking on pregnancy.

18: Management of Impaired Glucose Tolerance and Diabetes Mellitus

"I am being treated for diabetes but I would like to see a specialist doctor."

"We need better focus on preventative medicine rather than fixing once broken e.g. osteoporosis & diabetes."

Aims

To optimise quality of life and prevent diabetes complications and premature death by:

• encouraging meticulous adherence to iron chelation medication to lower the risk of developing diabetes, as well as other complications, and possibly to improve or normalise glucose metabolism if impaired.

• early diagnosis of impaired glucose regulation and diabetes.

• preventing the progression of impaired glucose regulation to diabetes.

• optimising glycaemic control and other cardiovascular risk factors.

• early detection and treatment of diabetic complications.

• supporting patient self-management.

Standards

■ A paediatric and adult consultant diabetologist should be identified for each Specialist Haemoglobinopathy Centre.

■ Patients should be checked annually for impaired glucose regulation and diabetes from puberty, or from age of 10 years if there is a family history of diabetes.

■ Patients with diabetes should have a full annual diabetes review, including glycaemic control, cardiovascular risk factors, diabetic complications and sexual health.

■ Patients with diabetes should have access to a clinical health psychologist with experience in diabetes management.

Background

Impaired glucose regulation and diabetes mellitus are common and significant complications of thalassaemia. In adult patients attending a UK thalassaemia service, around 20% have impaired glucose regulation and up to 41% have diabetes (Ang *et al.* 2014). The main aetiological factor is transfusional iron overload which damages pancreatic β-cells, reducing insulin secretion. The other key factors for some patients are insulin resistance secondary to liver disease, and hepatitis C virus infection affecting glucose metabolism (Mowla *et al.* 2004). Risk factors for diabetes also include poor compliance with chelation therapy or advanced age at onset of chelation (Gamberini *et al.* 2004), increasing patient age, average serum ferritin over 10 years > 1250 μg/l, and myocardial T2 < 20 ms (Ang *et al.* 2014). In addition, with the global pandemic of diabetes, patients can develop type 1 or type 2 diabetes independently of their thalassaemia.

Impaired glucose regulation and diabetes must be detected early to allow prompt treatment of hyperglycaemia and intensification of iron chelation therapy. Very intensive combined chelation can improve or normalise glucose metabolism in patients with impaired glucose regulation or non-insulin dependent diabetes, mainly through marked increase of insulin secretion (Farmaki *et al.* 2006, Farmaki *et al.* 2010). Intensive chelation can prevent progression to frank diabetes.

Screening is with the oral glucose tolerance test, OGTT, which includes measurement of fasting plasma glucose (FPG) and plasma glucose 2 hours after oral ingestion of 75 gram glucose. According to the recommendations of the World Health Organisation (WHO/IDF 2006), results are interpreted as following:

> A. Fasting Plasma Glucose:
>> i. FPG ≤ 6.0 mmol/l = Normal
>> ii. FPG 6.1 – 6.9 mmol/l = Impaired Fasting Glycaemia (IFG)
>> iii. FPG ≥ 7.0 mmol/l = Diabetes
> B. 2 Hour Plasma Glucose:
>> i. 2-hour plasma glucose < 7.8 mmol/l = Normal
>> ii. 2-hour plasma glucose 7.8 – 11.0 mmol/l = Impaired Glucose Tolerance (IGT)
>> iii. 2-hour plasma glucose ≥ 11.1 mmol/l = Diabetes.

If diabetes develops, a critical aim of care must be prevention, early detection and management of diabetic complications, including macrovascular complications (cardiovascular disease, cerebrovascular disease, peripheral vascular disease) and microvascular complications (diabetic retinopathy, nephropathy, neuropathy and erectile dysfunction). These complications can cause major patient morbidity and mortality and account in general for 80% of direct patient care costs in the UK. In patients with thalassaemia and diabetes, the prevalence of diabetic nephropathy is 13 – 55% (Tzoulis *et al.* 2014; Loebstein *et al.* 1998) and of diabetic retinopathy 13-26% (Tzoulis *et al.* 2014; Incorvaia *et al.* 1998). Macrovascular disease is uncommon, but is expected to increase as the life expectancy of patients with thalassaemia rises. Further, diabetes significantly increases the risk for cardiac complications, heart failure, hyperkinetic arrhythmias and myocardial fibrosis in patients with thalassaemia (Pepe *et al.* 2013).

Living with diabetes and thalassaemia can have a major psychological effect, with feelings of treatment burden, being different, dependence, damage, anxiety and impact on daily life. Healthcare professionals need to be able to support their patients to manage their diabetes and enable patients to apply self-management skills to lead a full and rich life.

Requirements

◆ All non-diabetic patients should be screened with Oral Glucose Tolerance Test (OGTT) and fructosamine annually from puberty or from the age of 10 years if there is a family history of diabetes.

◆ In patients with impaired glucose regulation (IFG/IGT) or non-insulin treated diabetes, iron chelation therapy should be intensified, with consideration given to using combination chelation regimens, aiming to normalise the iron load as judged by cardiac and hepatic magnetic resonance imaging.

◆ Patients with evidence of diabetes must be referred to the nominated consultant diabetologist in each Specialist Centre for further evaluation and treatment guidance, and their management kept under regular review by the specialist diabetes team. This is essential to provide adequate care for complex patients.

◆ Overall glycaemic control should be monitored using fructosamine levels. Fructosamine is a circulating glycated protein which measures overall glucose control in the previous 2 – 3 weeks. Normal ranges vary in different laboratories but are generally around 205 – 285 µmol/l. $HbA1_c$ or glycated haemoglobin should be avoided in thalassaemia as it is unreliable after transfusion. Patients with impaired glucose regulation (IFG/IGT) should have fructosamine measured every 6 months to identify trends in glycaemic control, aiming to keep their fructosamine levels ≤ 325 µmol/l. Patients diagnosed with diabetes should have fructosamine measured every 3 months.

◆ Any patient with symptoms of hyperglycaemia (e.g. thirst, polyuria, polydipsia, candida infections) should have urgent measurement of random plasma glucose and fructosamine. If random plasma glucose ≥ 11.1 mmol/l, which is diagnostic of diabetes, then blood or urinary ketones should be measured to exclude diabetic ketoacidosis.

◆ Patients with diabetes who are acutely unwell and who are hyperglycaemic (plasma glucose > 12 mmol/l) should have blood or urinary ketones measured to exclude diabetic ketoacidosis.

◆ Patients with diabetes should test capillary blood glucose at home in order to monitor glycaemic control and identify hypoglycaemia or severe hyperglycaemia. The frequency of monitoring depends mainly on their treatment, with increased frequency needed especially in patients on insulin.

◆ Patients with mild to moderate hyperglycaemia should be treated with antidiabetic drugs. The choice of agent should be individualised and depends on the balance of impaired insulin secretion versus insulin resistance and on the patient's co-morbidities. There is very limited data on the efficacy and safety of antidiabetic drugs in patients with thalassaemia. Metformin is the first line drug of choice except in patients with significant chronic kidney disease (eGFR < 30 ml/min), acute heart failure or acute respiratory failure. The choice of second line agent must be personalised. There are currently 5 classes of antidiabetic drugs, some of which are associated with weight loss and low rates of hypoglycaemia.

◆ Patients with severe hyperglycaemia or worsening glycaemia on multiple oral antidiabetic drugs, should be treated with insulin. Severely insulin deficient patients should be considered for a multiple daily injection (MDI) or a basal-bolus insulin regimen, which contains slow-acting basal background insulin administered usually once a day and rapid-acting insulin taken with each meal.

◆ Patients must have further diabetes specialist input in specific situations requiring excellent glycaemic control, including pre-conception, pregnancy and surgery.

◆ Patients with diabetes must be regularly assessed, at least once a year, for other endocrinopathies, as they are at high risk of hypogonadism, hypothyroidism, hypoparathyroidism and bone thinning.

Recommendations

• Patients with impaired glucose regulation or diabetes should be encouraged to undertake 150 minute of moderate-intensity activity per week which accelerates the heart rate (such as brisk walking). This can be taken in 10 minute bouts (NICE 2012).

• Overweight patients with impaired glucose regulation or diabetes should be encouraged and supported to make lifestyle changes in diet and exercise, aiming to lose 5 – 10% of weight per year to reach a body mass index (BMI) < 25 kg/m^2 or <23 kg/m^2 if of South Asian or Chinese descent (NICE 2012).

• Healthcare professionals should help patients to assess their diet and encourage them to increase consumption of foods high in fibre (e.g. vegetables, fruit) as well as avoid food high in saturated fat.

- The nominated consultant diabetologist and their team must work in close partnership with the haematology team to enable integrated care, optimally in joint clinics.

- Patients with diabetes should have a planned programme of recommended checks each year that includes the 9 Key Care Processes: measurement of glycaemic control (fructosamine); serum cholesterol; serum creatinine and eGFR; urinary albumin excretion (urinary albumin/protein-to-creatinine ratio); smoking status review; weight; blood pressure; diabetic foot examination; diabetic retinal screening. This should be part of personalised care planning that enables patients and their healthcare professionals to jointly agree actions for managing their diabetes, and to meet their individual needs.

- Patients with diabetes should be managed according to treatment targets and recommendations for type 1 and type 2 diabetes given by the National Institute for Health and Care Excellence (NICE) and available on their website. This should include targets for blood pressure and cholesterol.

- Patients with diabetes should be invited to attend structured education in diabetes self-management. For patients on MDI insulin regimens, this should include training in carbohydrate counting and insulin dose adjusting.

- Healthcare professional must be aware of the psychological impact of having both diabetes and thalassaemia. They should offer patients counselling by a clinical health psychologist with experience in working with patients with diabetes.

19: Management of Bone Problems

The bone pain is the worst thing about having thalassaemia. It makes me feel older than I am which depresses me."

"Thalassaemia has affected my height I am very short and look young for my age."

"I just tripped over the kerb and managed to break my arm and leg on the same side; ended up in hospital for weeks."

Aims

To prevent the variety of bone diseases which can occur in thalassaemia.

In those with bone thinning, to monitor and provide effective treatment to lessen associated morbidity, fractures, and reduced quality of life.

Standards

■ Transfusion therapy will be initiated in time to prevent irreversible deformities associated with bone marrow expansion.

■ Doses of desferrioxamine will be kept in the range to minimise the risk of bone toxicity or reduce height velocity. Any bone changes possibly related to deferrioxamine toxicity should be suspected and investigated in children with bone/joint pain or short stature.

■ Management of the maturing skeleton should focus on achieving peak bone mass.

■ All patients should have vitamin D measured with supplements given if needed.

■ All patients should be advised of the need for adequate dietary calcium for healthy bones.

■ All patients should be advised on lifestyle changes that promote achieving peak bone mass and maintaining bone mineral density, BMD: smoking cessation, avoiding excessive alcohol consumption and undertaking weight bearing exercise.

■ Diagnosis of hypogonadism and other endocrinopathies should be prompt, and appropriate hormone replacement therapy given.

■ Adult patients should be monitored for low bone mass/osteoporosis.

■ Bisphosphonates and other bone specific agents should be considered in patients with deteriorating BMD/osteoporosis confirmed on DXA bone mineral density scanning, particularly if there have been fractures.

■ Osteoporosis treatments should be regularly reviewed.

■ If there is chronic severe bone pain, not amenable to corrective treatment, a patient should be managed together with a specialist pain team.

Background

Bone disease is an important cause of morbidity in thalassaemia patients with problems related to inadequate transfusion, desferrioxamine use, failure to reach peak bone mass and progressive bone thinning in adults.

Characteristic bone disease is seen with inadequate transfusion causing deformities of the skull and face. Dental and sinus complications should be managed by early referral to a specialist dental service (see chapter 21: Management of Dental Problems). These problems are related to marrow expansion and can be prevented by adequate blood transfusion regimes; they should rarely now occur in the optimally transfused patient, although those with NTDT remain at risk.

Desferrioxamine-associated bone lesions in children include cartilaginous dysplasia of the long bones and spine, giving rise to shortening of the trunk and a 'pseudorickets' appearance. These changes can be prevented by using relatively low doses of desferrioxamine (15-35 mg/kg) in young children (Olivieri and Brittenham 1997) and since treating physicians became aware of this are rare in younger patients. It remains to be seen whether newer chelating agents will have any adverse effect on growing bones; to date they do not appear to.

Low bone mineral density (BMD) is seen in a high proportion of patients with thalassaemia. Bone density is measured by Dual-Energy X-ray Absorptiometry (DXA) scanning. The pathology of this low bone mass is complex and not fully understood, but includes delayed sexual maturity, parathyroid gland dysfunction and hypogonadism. There are high reported rates of fracture (Vogiatzi 2006) however the relationship between BMD and fracture risk is not fully understood. Low bone mass in thalassaemia patients has been shown to be related to raised levels of bone turnover markers and increased rates of bone resorption (Voskaridou, Kyrtsonis, *et al.* 2001).

Low bone mass is also present in children under 10 (Vogiatzi 2004), however there are technical issues with performing DXA scans on children as these need to be adjusted for bone size and also for pubertal stage. There is no evidence for the treatment of low bone mass in children with thalassaemia, therefore there is little rationale for performing DXA scanning on patients until they reach pubertal maturity. Management of bone disease in children should focus on lifestyle measures such as calcium intake and weight bearing exercise as well as ensuring adequate levels of serum vitamin D. Peak bone mass is only achieved when an individual is in their late 20s so the focus should remain on maximising the opportunities to achieve this peak.

In the absence of supplementation vitamin D deficiency is very common in thalassaemia. Vitamin D is essential for calcium homeostasis and mineralisation of the skeleton and Vitamin D levels directly correlate to bone mineral density. 25OH vitamin D assays are now widely available and supplementation is possible with a variety of supplements available, both prescribed and over the counter. Vitamin D3 should be the replacement of choice by an oral route (NOS guidance 2013). In the absence of research evidence, expert opinion is to target a vitamin D level of 80 nmol/l, somewhat above the traditional 'normal range' of 50 nmol/l. Maintenance therapy is likely to be required.

Loading regimens for treatment of deficiency up to a total of approximately 300,000 IU given either as weekly or daily split doses. The exact regimen will depend on the local availability of vitamin D preparations but will include:

- 50,000 IU capsules, one given weekly for 6 weeks (300,000 IU)
- 20,000 IU capsules, two given weekly for 7 weeks (280,000 IU)
- 800 IU capsules, five a day given for 10 weeks (280,000 IU).

Supplements should be taken with food to aid absorption. Calcium/vitamin D combinations should not be used as sources of vitamin D for the above regimens, given the resulting high dosing of calcium.

Maintenance regimens may be considered with doses equivalent to 800 to 2000 IU daily (occasionally up to 4,000 IU daily), given either daily or intermittently at a higher equivalent dose. Where available high dose weekly supplementation such as 10,000unit capsules may help compliance.

Total daily calcium intake should be 700 – 1000mg/day (in diet or supplements) from aged 11 upwards, and for younger children 1 – 3 years: 350 mg, 4 – 6 years: 450 mg, 7 – 10 years: 550 mg.

Where dietary calcium is deemed to be inadequate or borderline, calcium supplementation should be considered. Advice should be given around the timing of these tablets to minimise the possibility of them reducing absorption of other medications (such as thyroxine)

The following treatment approaches have been demonstrated not to work well, or to lead to toxicity, and are therefore not recommended:

- annual depot vitamin D therapy either by intramuscular injection or orally
- use of activated vitamin D preparations (calcitriol and alfacalcidol). These agents should only be considered if there is proven hypoparathyroidism secondary to iron overload.

Where oral compliance remains very poor, consideration of an IM vitamin D regime given with transfusion visits could be given such as 300,000 iu 3 monthly, but this often produces inferior levels of vitamin D due to variable absoprtion.

Vitamin D levels should be monitored 3-6 months after loading doses are complete, and should be intermittently monitored depending on levels and compliance with therapy.

Bone mineral density assessments should be undertaken regularly, usually by DXA scanning, from completion of puberty.

Bisphosphonates are potent inhibitors of bone resorption and short term studies have shown increases in BMD, reductions in bone turnover and reductions in bone pain. Regimes used include daily oral alendronate (Morabito 2002), monthly IV pamidronate (1 mg/kg) with HRT (Chatterjee 2012) and without HRT (Voskaridou 2003), and IV Zoledronate 4mg 6 monthly (Voskaridou 2006).

No thalassaemia studies have shown fracture reductions with bisphosphonates. There are significant concerns about long term bisphosphonate use. Osteonecrosis of the jaw is a condition of exposed necrotic bone in the maxillofacial region, not healing after 6-8 weeks. In patients treated with high dose bisphosphonates for malignancy at similar doses to some of those used in the thalassaemia studies, the reported incidence is 1.4% with 3 years of treatment. In patients treated with oral bisphosphonates for post-menopausal osteoporosis rates of 1:10,000 are quoted. Rare cases have been seen in patients with thalassaemia treated with IV bisphosphonates (Chatterjee *et al.* 2014).

There have been reported cases of atypical femoral fractures seen with bisphosphonate use. These are fractures along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. A specific case definition of these fractures has been described (ASBMR task force report 2013), and some probable cases have been seen in patients with thalassaemia (personal communication).

Due to these rare, but significant side-effects long-term bisphosphonate therapy should not be advised without reassessment of fracture risk and if possible an opinion from a specialist in osteoporosis (rheumatology, endocrinology, care of the elderly medicine depending on local provision). Current practice would suggest first ensuring adequate vitamin D levels, and supplementing testosterone/oestrogen for a period of at least two years, before starting a bisphosphonate for osteoporosis in this group. If it is decided to start treatment, this should be reviewed after a maximum of 5 years of oral bisphosphonates or 3 years of IV treatment and consideration of a "drug holiday" (National Osteoporosis Guidelines Group 2016) The drug adheres strongly to hydroxyapatite and remains in bones for long periods, so fracture protection is maintained during interruptions in treatment. Caution should be taken in giving bisphosphonates to women of childbearing age. The bone half-life of these drugs is years and the impact on a developing foetus is not known.

Denosumab (anti-RANKL monoclonal antibody) has been shown to increase BMD and reduce bone turnover in patients with thalassaemia major within 1 year of treatment (Yassin 2014). If this is considered it is advisable that treatment is supervised with a clinician with an interest in osteoporosis and experience of this drug.

Persisting pain, especially in the bones and joints, is a common complaint. A North American questionnaire based study identified that pain was a significant symptom in more than 50% of adults with thalassaemia over the age of 35 years, and affects patients with both TDT and NTDT. The commonest sites of pain are the low back, followed by the mid back, legs and head. (Haines

et al. 2013). Pain of this sort contributes to a reduction in quality of life (Sohota *et al.* 2010). Pain may be localised or of a more generalized nature. In many cases, a causative factor can be identified, such as osteoporotic fractures of the spine, extra medullary haematopoietic masses causing nerve root compression or entrapment, disc disease, or arthritic changes in the large joints. These findings may be amenable to treatment with resolution of pain symptoms. Chronic pain not amenable to corrective treatment requires management by a specialised team with careful choice of analgesic drugs (preferably avoiding long-term use of strong opioids), and use of non-pharmacological and cognitive methods. A description of these is beyond the scope of the Standards. There are many resources to assist patients and health care professionals in formulating a management plan (Opioids for Persistent Pain, British Pain Society 2010; Pain Tool-kit booklet 2012).

Requirements

◆ Children with thalassaemia major should receive optimal transfusion to prevent excessive bone expansion

◆ The recommended desferrioxamine dose in childhood should not be exceeded

◆ Regular assessment of standing and sitting height should be undertaken in children with thalassaemia, until full height is achieved .

◆ Hormone replacement therapy should be initiated after assessment by a paediatric endocrinologist if hypogonadism is diagnosed. Other endocrine derangements should be sought and corrected

◆ Vitamin D levels should be measured regularly from age 2, and replacement with oral supplements should be advised if insufficient until an optimal level, ~ 80 nmol/l, is achieved.

◆ Bone mineral density should be measured by dual-energy x-ray absorptiometry (DXA) of the spine and hip. A suitable screening regime should start at completion of puberty and occur on a 2-3 yearly basis. Ongoing frequency of scanning should be determined by results and therapy, but expert opinion suggests that minimal interval between scans should be 18 months.

◆ Bisphosphonates and other bone active drugs should be considered in patients with a low BMD for age (z-score < -2.0 if pre-menopausal or under 50, t-score < -2.5 if post-menopausal or over 50), if there are fragility fractures and/or falling BMD despite adequate vitamin D levels, and hormone supplementation if there is hypogonadism. Bisphosphonate treatment should be reviewed after a maximum of 5 years for oral agents and 3 years for IV agents, and it is recommended after these intervals to consider a pause in treatment for a period of 2-3 years, a bisphosphonate 'holiday'.

◆ Bisphosphonates should be stopped if there is suspicion of atypical femoral fractures or osteonecrosis of the jaw.

◆ Chronic pain from causes not amenable to corrective treatment requires management by a specialised pain team with careful choice of analgesic drugs (preferably avoiding long-term use of strong opioids), and use of non-pharmacological and cognitive methods

Recommendations

• In children and adolescents who are treated with desferrioxamine and who suffer bone or joint pains, radiological investigations to rule out treatment-related bone disease should be requested.

• Dietary calcium should be assessed and advice given to achieve adequate calcium levels for age.

• Children and adults should be encouraged to undertake regular weight-bearing exercise, and high alcohol intake and cigarette smoking strongly discouraged.

20: Management of Liver Problems

"All those years of battling thalassaemia only to end up with liver cancer is the ultimate irony."

"I would like to see a liver specialist who understands thalassaemia."

Aims

To preserve liver function and avoid liver damage related to iron toxicity, viral hepatitis and adverse effects of therapy including iron chelation therapy.

To investigate and treat liver abnormalities promptly.

Standards

■ Liver function tests should be monitored at regular monthly intervals.

■ Liver iron levels should be maintained within safe limits to avoid hepatic damage, using the range of available chelation options and taking steps to encourage adherence to treatment.

■ Adjustments to chelation and other treatment should be made promptly if abnormalities of liver function are detected on routine monitoring tests.

■ Vaccination against hepatitis A and B virus infection should be ensured.

■ Liver disease should be managed jointly with a designated specialist hepatologist.

■ Management of chronic hepatitis C virus infection should include histological assessment of fibrosis on biopsy and/or non-invasive techniques.

■ Antiviral therapy aimed at sustained viral clearance should be planned and managed in collaboration with a designated specialist hepatologist.

■ Patients with established cirrhosis should have regular surveillance checks for hepatocellular cancer.

Background

Liver disease is common in patients with TDT and NTDT. Several contributory factors may co-exist, including hepatic toxicity due to iron loading of the liver parenchyma, viral hepatitis, biliary disease, and drug toxicity. The spectrum of clinical presentations includes acute and chronic hepatitis, obstructive jaundice, cholangitis, portal hypertension, hepatic insufficiency and hepatocellular carcinoma. It is important to recognise that liver fibrosis may occur in patients with normal liver function tests and so should be assessed in patients at risk of liver disease.

Viral infections and liver disease

A study of predominantly adult patients with thalassaemia in North America showed cirrhotic change in 10.3%, and hepatitis C virus (HCV) positivity in 14.2% (Cunningham, Macklin, Neufeld, Cohen, and Thalassemia Clinical Research 2004). In the UK, approximately 20% of adults are HCV positive. The rate is higher in patients who were treated outside of the UK (for instance in Italy, Egypt, South Asia). Most affected patients were infected prior to introduction of blood donor screening for HCV.

Hepatocellular carcinoma (HCC) is increasingly reported, particularly in older patients (mean age 48 years). Risk factors include high iron levels and chronic viral hepatitis, but HCC is not restricted to those with chronic viral hepatitis, and is well recognised in those with NTDT. HCC was not a common cause of death in survival studies published over the past 20 years, however it is now becoming a more important cause of mortality (Borgna-Pignatti *et al.* 2014). Previous guidance was that surveillance by scan and measurement of alpha fetoprotein should be at least once a year, but this is now revised to 6 monthly as the tumours can be fast growing.

Treatment of hepatitis C virus infection previously required lengthy periods on unpleasant medication including interferons and ribavirin, but has been revolutionised by the introduction of highly effective directly acting oral antiviral agents that can clear infection in the majority of patients with very few side effects (NICE TA363, TA364 and TA365). In some cases ribavirin can now be avoided, but it is still indicated for the treatment of patients with established cirrhosis. Ribavirin provokes haemolysis, and transfusion requirements are substantially increased during combination treatment, thus chelation needs to be intensified during and after completion of therapy. There is no consensus about use of deferiprone or deferasirox during antiviral therapy. In one trial, some of the patients used deferiprone during therapy, though assessment of neutropenia becomes more problematic, since both deferiprone and interferon may cause a decrease in neutrophil count (Telfer *et al.* 1997).

Hepatitis B infection is now rare among UK thalassaemia patients, as a result of exclusion of high risk donors, screening of units before transfusion, and hepatitis B vaccination for recipients. Patients who are infected with hepatitis B should be reviewed at a specialist liver unit where a decision can be made about antiviral therapy. These patients remain at high risk of complications such as cirrhosis and hepatomas and need to be on long term surveillance programmes.

It is now recommended for patients to be immunised against hepatitis A. Although this is very rarely transmitted by blood transfusion, the rationale is that many patients with thalassaemia will have a degree of liver inflammation or damage from iron or previous hepatitis B or C, and the extra insult of an acute hepatitis, however it is contracted, is to be avoided if possible. A second dose 6 – 12 months after the first confers immunity for up to 20 years.

Iron overload and chelation therapy

There is evidence from post-BMT children that liver iron concentration and hepatitis C infection act synergistically to accelerate progression of hepatic fibrosis and that, in the absence of hepatitis C infection, fibrosis is only observed in those with a high liver iron concentration (> 16mg/g dw of liver tissue). However, this observation was made over five years of follow-up in young patients, and progression to fibrosis may be more rapid in adult patients (Angelucci *et al.* 2002). In general, liver iron levels should be kept low irrespective of concurrent viral hepatitis, and it is advisable to maintain levels in the lower part of the range of 3 – 7 mg/g dw.

MRI assessment of liver iron concentration enables monitoring of liver iron levels without the need for serial biopsies and is considered less subject to variability than analysis of liver biopsy samples (Anderson *et al.* 2001; St Pierre *et al.* 2005; Wood *et al.* 2005). Non-invasive assessment of liver fibrosis using Fibroscan® may be helpful in assessing liver disease in thalassaemia, but further validation is required. Liver biopsy remains the only modality able to provide a histopathological diagnosis, but non-invasive tests of liver fibrosis should be considered for assessment of liver fibrosis if histological examination of the liver parenchyma is not essential. Biopsy should be reserved for the investigation of complex liver pathology and for the staging of liver fibrosis when clinical signs and non-invasive assessment are in conflict or equivocal.

Elevations of transaminase levels are relatively common in patients receiving deferiprone, particularly in patients with HCV infection, but these changes are usually mild and non-progressive, and rarely of sufficient severity to discontinue treatment (Ceci *et al.* 2002; Cohen, Galanello, Piga, De Sanctis and Tricta 2003). One small study of hepatic histology showed progression of hepatic fibrosis in 5 out of 14 patients treated with deferiprone for a median of 2.3 years (Olivieri *et al.* 1998). Four of these five patients were infected with hepatitis C. Subsequent studies were unable to confirm an association between treatment with deferiprone and progression to liver fibrosis, and later publications suggest that the fibrosis was more related to hepatic iron loading in the presence of hepatitis C infection (Maggio *et al.* 2002; Tondury, Zimmermann, Nielsen and Hirt 1998; Wanless *et al.* 2002).

Elevated serum transaminase levels are common in patients treated with deferasirox but the association with drug therapy is not always clear. In the Phase III one year study and 5 year follow-up, approximately 1% of patients had confirmed elevations of ALT > 10 × upper limit of normal (Cappellini *et al.* 2011) and drug-induced liver damage is an infrequent but important adverse reaction reported in association with deferasirox therapy (Cappellini *et al.* 2006). There is histological evidence that liver fibrosis scores improve in patients on deferasirox even in the absence of changes in the liver iron (Deugnier *et al.* 2011). Liver function tests should be checked at baseline in duplicate, two weekly for the first month or after increasing dose, and thereafter monthly. If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, the medication should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious re-initiation of treatment at a lower dose followed by gradual dose escalation may be considered.

Lifestyle and other factors

Iron overload alone in the absence of hepatitis infections or chelation drugs results in raised transaminase levels (Angelucci *et al.* 2000; Jensen, Jensen, Christensen, Nielsen and Ellegaard 2003) and this should be taken into account when monitoring iron chelation side effects.

Patients with thalassemia are still susceptible to liver disease from non-transfusion, non-infective and non-drug related causes. Underlying liver problems are worsened by the impact of excess alcohol use. Patients should be advised to use alcohol within the national gender based guidelines limits and to avoid binge drinking.

Non-Alcoholic Fatty Liver Disease (NAFLD) is common in both adults and children ("EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease" 2016). NAFLD can result in iron overload in non thalassaemic patients and this is known as dysmetabolic iron overload. NAFLD results in liver damage due to non-alcoholic steatohepatitis. Patients with thalassaemia who may be at risk of this complication as a consequence of obesity should be given life style advice and referred to dieticians and hepatologists for appropriate advice.

Requirements

◆ A hepatologist should be designated for each thalassaemia Specialist Centre.

◆ Liver function tests and serum ferritin should be monitored at least every 3 months in patients on desferrioxamine and monthly in patients receiving oral chelation drugs.

◆ Liver iron level should be maintained between 3 – 7 mg/g dw, aiming towards the lower end of the range. Assessments of liver iron should be by MRI (R2 or T2*) rather than liver biopsy.

◆ Serological tests to monitor for viral hepatitis (anti–HCV, HBsAg, anti HB core ab) should be done every year. Adequate protection from hepatitis B virus should be ensured by a full course of vaccination initiated before the first transfusion or as soon as possible after it, and then by serial monitoring of anti-HBs ab titre and 'booster' vaccination as needed. Hepatitis A immunisation, a second dose 6 – 12 months after the first, should also be offered.

◆ Patients with active hepatitis C infection (HCV RNA positive) or chronic active hepatitis B should be referred to the designated hepatologist for further virological studies (genotype, quantitation of viral load), assessment of liver fibrosis and decisions about management. Anti-viral therapy is recommended in all patients with HCV viraemia.

◆ Patients with unexplained abnormalities of liver function tests should have a detailed drug and alcohol history, and be investigated promptly.

◆ Patients with a history of excess alcohol use should be supported with regular advice on safe consumption and carefully monitored for development of alcoholic liver disease.

◆ Patients with established cirrhosis should be reviewed regularly, by the designated hepatologist. Surveillance for hepatocellular carcinoma (measurement of alpha fetoprotein, liver ultrasound or cross-sectional abdominal imaging by MRI or CT) should be done every 6 months. Surveillance for oesophageal varices should be undertaken at the time of diagnosis of cirrhosis and every 2-3 years thereafter. If varices are detected they should be treated by a specialist hepatologist.

Recommendations

• Patients should be given regular information about avoidance of liver disease, and on how to recognise clinical signs of liver disease. This could be part of the role of the specialist nurse.

• Patients with deranged liver function tests and evidence to suggest Non Alcoholic Steatohepatitis or NAFLD should be given appropriate lifestyle and dietary advice management by a specialist with an interest in NAFDL.

21: Management of Dental Problems

"My local dentist is scared to treat me because I have thalassaemia and my hospital has no specialist service so where does that leave me?"

Aims

To improve awareness of the potential dental and orofacial manifestations of thalassaemia.

To ensure the appropriate pathways of dental care are in place, including prevention and the timely management of dental infections.

To outline the dental implications in relation to the use of bisphosphonates in patients with thalassaemia.

Standards

- Adequate red cell transfusion in children with thalassaemia should be sufficient to prevent the development of marrow overgrowth and facial bone changes, and some of the associated dental problems.

- All patients should access regular dental care to prevent oral infection and manage the potential orofacial features of thalassaemia.

- Patients presenting with acute dental infections/abscesses should receive urgent dental care and antimicrobial therapy as required.

- Close liaison with the haematology team is required to determine the potential complications when delivering invasive dental treatment, and to put measures in place to reduce risk.

- All patients should ideally have a comprehensive dental assessment with their local dentist prior to the commencement of bisphosphonate therapy to ensure that they are as dentally fit as feasible.

Background

In the United Kingdom, as the prevalence of thalassaemia is patchy, many dentists may not have experience in treating a patient with the condition. This can impact on access to dental care and lead to problems with oral health for people with thalassaemia. It is well recognised that oral health has an important role in general health and well-being of individuals, and impacts significantly on the quality of life (Public Health England 2014c). Improving the knowledge of the dental and oral manifestations of thalassaemia is key to removing these barriers.

Patients with thalassaemia should be encouraged to register with their local primary care general dental services at an early age so that preventative regimes can be put in place and regular care provided. Occasionally, patients may have multiple associated medical co-morbidities which increase risk and require special adaptations to be put in place. In these cases, regular care within specialised services such as paediatric dentistry services or primary care based Special Care Dentistry services may be more appropriate.

Hospital based Special Care Dentistry services also exist but are limited. They provide care for the most complex patients, particularly those who may require surgical intervention or dental extractions. They do not usually provide continuing care; on completion of treatment patients

are discharged to the primary dental services for regular review. Occasionally referral to hospital based Oral Surgery/Maxillofacial Surgery services may be required.

Oro-Facial Manifestations of Thalassaemia

Many orofacial features have been described in thalassaemia, the extent of the changes depends on the severity of the anaemia, the patient's age, the duration of the clinical symptoms, and the timing of blood transfusion especially when transfusion is started late or is less intensive than recommended. In addition to thalassaemia major patients, non-transfusion-dependent patients are at risk.

Facial bones

Bone marrow hyperplasia may result in malformation/enlargement of the facial bones, including the maxilla and mandible. This is usually more significant in the upper jaw, resulting in a characteristic appearance with prominent high cheekbones and relatively smaller lower facial bones.

Bone marrow overgrowth may also result in a reduction in the size of the maxillary sinuses and nasal obstruction

Where there is misalignment of teeth due to maxillary expansion, orthodontic treatment or cosmetic dentistry may be required to correct alignment. Orthodontic treatment can be more complex due to the hypercellular nature of the bone, short roots, and changes in dental arch parameters. Where teeth have been lost, the dimension of the dental arch can slowly expand making dentures feel tight and uncomfortable, causing ulceration.

Teeth

Changes in the jaw dimension may also result in spacing of the upper teeth and rotation or forward drift of the upper front teeth. Delayed dental development / eruption may occur. The colour of the permanent teeth can be dark in patients with thalassaemia because of progressive iron accumulation within the tooth tissue as it is forming.

Where there is misalignment of teeth due to maxillary expansion, orthodontic treatment or cosmetic dentistry may be required to correct alignment but dentists need to be aware that the result, as with dentures, may not be stable and requires close review.

Although it has been suggested these patients may also have an increased risk of dental caries the evidence is not conclusive and there may be geographical variability in terms of access to dental care, which may impact on the findings.

Soft tissues of the mouth

Oral ulceration and burning tongue may be present secondary to chronic anaemia. Iron deposition in the parotid glands can result in painful facial swelling but is rare.

Necrotising stomatitis, possibly linked to agranulocytosis due to deferiprone, has also been described (Tewari *et al.* 2009).

Radiographic appearance of the facial bone and teeth

The maxillary sinuses may be reduced in size. Thinness of the cortical bone, absence of the inferior dental canal and a 'chicken wire' appearance of the lower jaw are often observed (Hazza'a and Al-Jamal 2006). The roots of the teeth may be short and slender with the lamina dura (bundle bone around the tooth) appearing faint/attenuated.

Co-morbidities that may impact on dental care

Individuals with thalassaemia may have multiple secondary effects of their disorder. These can impact on the delivery of dental care:

Chronic anaemia

Dental care should be adapted to their tolerance of the planned procedure on the day of treatment.

Infections

Iron overload and splenectomy both increase the risk of infection (Wang *et al.* 2003). Multiple immune abnormalities (Vento *et al.* 2006), defective neutrophil and macrophage chemotaxis, and increased oral Candida albicans colonisation (Hazza *et al.* 2010) have been noted in patients with thalassaemia. Certain organisms are particularly common causes of dental infection in thalassaemia major; for example Klebsiella dental infections can act as a source of generalised septicaemia (Sarma 2007), which can be serious or fatal if not managed quickly.

Recurrent transfusions

Prior to screening of blood products, people with thalassaemia were at increased risk of infection with hepatitis viruses and human immunodeficiency virus. Appropriate cross-infection protocols should be in place when providing care. In the case of associated hepatic disease / liver cirrhosis, caution must be used when prescribing medication.

Iron overload and consequent deposition in tissues

Iron accumulation in cardiac, endocrine and hepatic tissues is well documented for patients with thalassemia major. Insulin dependent diabetes mellitus and cardiac iron overload are common. Patients may be receiving anti-dysrrhythmics and occasionally anticoagulation if they have intermittent atrial fibrillation or indwelling intravenous devices.

Although many patients are asymptomatic despite cardiac iron overload, cardiac symptoms or complications may develop when they are anxious or undergoing a stressful dental procedure. Dentists need to be aware of the degree of cardiac involvement in an individual patient and implement appropriate precautions.

Bisphosphonates (BPs) and osteonecrosis of the jaw (ONJ)

Bisphosphonates have been commonly used in thalassaemia patients for bone thinning, and cases of ONJ have recently been reported (Chatterjee *et al.* 2014). ONJ is characterised by trans-mucosal exposure of necrotic bone often triggered by surgical trauma such as dental extractions. The incidence of ONJ is higher with more potent intravenous BPs, ranging between 2% and 28%, with the majority of studies suggesting an incidence of 5-8% (< 10%). These studies however are in patients with different underlying conditions, predominantly myeloma or other malignancies. Incidence is time-dependent and dose-dependent, with the time to onset ranging from 4 to 120 months. The incidence of ONJ associated with oral BP is lower and is generally accepted to be less than 1% (Fedele *et al.* 2009). Incidence is again time-dependent and dose-dependent, with the time to onset ranging from 3 to 10 years.

There is currently no clear evidence for the efficacy of any intervention to manage ONJ; in the case of non-vital teeth/dental abscesses, root canal treatment should be considered to try and stabilise the infection, although where this is not possible, dental extractions are unavoidable.

There is no evidence supporting the discontinuation of bisphosphonates temporarily as the drugs persist in the skeletal tissues for years. There is also no conclusive evidence supporting the use of antibiotics or topical antiseptic prophylaxis in reducing the risk of ONJ (Fedele *et al.* 2009).

Depression

Lifelong adherence to a complicated medical regimen can potentially impact on the emotional functioning of patients with thalassaemia. This can impact on patient motivation and ability to accept dental intervention (Mednick *et al.* 2010).

Requirements

◆ Dental care should be delivered as a coordinated team approach, ensuring close liaison with the paediatrician or haematologist. This will help to identify and manage the risk factors associated with thalassaemia and the potential associated co-morbidities. The appropriate setting for any given dental treatment, namely primary or secondary (hospital-based) care can then be determined.

◆ Where dental infection is present, it should be managed early and aggressively.

◆ Patients, especially those who have had the spleen removed, are at increased risk of infection following any dental procedures associated with bacteraemia, including extractions or scaling. but oral co-amoxiclav, a dose before the procedure and continuing at 625 mg three times daily for 48 hours after, is usually given.

◆ If sedation or GA is planned, close liaison with the haematology team is required – this will allow transfusion to be arranged and the haemoglobin to be optimised. Inhalation sedation is preferable to intravenous sedation but may not be sufficient to enable the delivery of a longer/more complex treatment, particularly when the patient is very anxious.

◆ Anaesthetists should also be made aware of any additional cardiac, liver and/or renal complications.

◆ All patients should have a comprehensive dental assessment with their local dentist prior to starting bisphosphonate therapy to ensure that they are as dentally fit as feasible. To minimise the risk of osteonecrosis of the jaw, emphasis is on reduction of mucosal trauma and avoiding dental extraction where possible. Preventive dental advice should be given, emphasising the importance of reporting any symptoms such as loose teeth, pain, or swelling, as soon as possible.

Recommendations

• For all patients with thalassaemia receiving regular transfusions, invasive dental care should be delivered as soon as possible after a planned transfusion, as the patient's haemoglobin will be optimal.

• Individuals with thalassaemia should have access to early, regular and preventive dental care. This will help reduce the impact of any associated oral features and allow dental development to be monitored. This should include preventive oral care, including fluoride application / prescription, fissure sealants, and dietary advice.

• Comprehensive oral assessment age 12-13 will enable planning for/prevention of difficulties from overcrowding/misplaced teeth

• Although there is a theoretical risk associated with local anaesthetic containing adrenaline (may lead to impairment of local circulation), this is used routinely for patients with thalassaemia without reported problems.

• If maxillofacial surgery is planned for managing severe facial deformity associated with bone marrow expansion due to thalassaemia, careful consideration should be given to the medical and surgical risks, including the risk of more extensive bleeding from the hyper-vascular bone. (Park 2012)

• If a patient has spontaneous or chronic bone exposure, referral to an oral surgery/oral and maxillofacial surgery specialist should be considered. When a patient is already on bisphosphonates and a dental extraction is unavoidable, straightforward extractions can be undertaken in primary care, although a second opinion can be sought when necessary. Surgical extractions should be undertaken by a specialist in oral surgery/maxillofacial surgeon. All patients should be advised of the risk of osteonecrosis of the bone pre-operatively and closely monitored post-operatively.

22: Patients Previously Treated Outside the UK

"People born in the UK take the medical system for granted, they don't know how it feels to choose between buying food and going to hospital."

"We left a very comfortable life behind us for the sake of our 2 children who have thalassaemia. When I arrived in the UK I had never cooked a meal or cleaned my own house. My children are young adults now; but all the children we used to know from the hospital back home are dead."

Aims

To ensure that patients starting, or returning, to use thalassaemia services in the UK can be assessed thoroughly at the outset, and start receiving care without delay.

To ensure that patients and their families have a proper understanding of the condition and any complications.

To address any unidentified or unmanaged problems.

To ensure the person and family is introduced and integrated into local continuing care arrangements.

Standards

■ Children and adults who have been receiving treatment outside the UK will be seen, as soon as possible after they arrive, at an established Specialist Haemoglobinopathy Centre for a thorough assessment.

■ Transfusion treatment will be re-started without delay.

■ Any complications which may have developed will be detected and discussed with the individual and family and management plans put in place.

Background

Thalassaemia services in many countries are of the highest quality and it is unlikely that a patient previously managed in, for example, Italy will have undetected problems.

However, in some lower resource countries blood supplies may be erratic, screening of donor units may not be complete, or iron chelation may be unaffordable. It is possible therefore that the patient may have problems or complications of which they are unaware and/or which are untreated. Optimising transfusion and chelation treatment regimens, and actively managing any complications which have not been recognised to date, are likely to improve well-being and reduce morbidity and mortality.

Patients who have recently arrived in the UK may present to A&E with anaemia or infection, may be referred by their GP or may make contact through the local support organisation or another patient. It is necessary to make an early appointment, to establish in the first instance when their next transfusion is due, and to start to make an overall assessment of their condition and its

treatment. They may arrive with a full understanding about their condition, and plentiful documentation about their management to date, or they may have very little or none.

Their initial assessment will include a full medical history covering:

- age at diagnosis
- age at first transfusion
- transfusion history including transfusion reactions
- chelation treatment, current and previous, including frequency, doses, route and any chelator intolerances or complications
- any co-incident diagnoses
- any other current medication
- developmental history including puberty if of relevant age
- surgical procedures, in particular splenectomy
- complications from iron overload including cardiac failure, dysrhythmia and endocrinopathies: diabetes, hypothyroidism, hypoparathyroidism or hypogonadism
- history of bone problems such as fractures and treatment for osteoporosis.

The results of any investigations they are aware of should be explored – including haematology, biochemistry, virology, and any recent MR iron quantitation of the heart/liver, and where the tests were done.

A family history is important for general clinical assessment, and will help elucidate whether other family members should be screened for thalassaemia.

Patients should have a full medical examination, recording height (sitting and standing), weight, presence of thalassaemic facies or dental problems, signs of cardiac failure, the presence of an enlarged liver or spleen, surgical scars, stigmata of chronic liver disease, stage of pubertal development and any clinical signs suggesting endocrinopathy.

Requirements

◆ Any newly arriving patient should be offered an early review with the team at the most convenient specialist Centre, with appropriate translation services available if needed. This will include a full discussion of their condition from the time of diagnosis, and previous and current treatment regimens, together with the results of any investigations of which they are aware, and a comprehensive medical examination.

◆ Baseline investigations should be discussed with the patient and with their consent the assessments listed in Table 22.1 undertaken.

◆ An early review visit should be planned to discuss the results of these investigations and any necessary treatment changes.

◆ If hepatitis B non-immune, vaccination should be recommended and started as soon as possible.

◆ It should be decided, and carefully discussed with the patient and family, what the recommended arrangements for continuing care will be: either at the local clinic with review visits at the Specialist Centre, or wholly at the Specialist Centre depending on proximity.

◆ The family should be introduced to their key contact(s), and contact numbers exchanged.

Recommendations

◆ The patient/family should be given written information about the services, and how to make contact as needed, in or out of hours.

◆ A 'first clinic visit checklist' should be completed.

◆ As soon as possible they should be taken to visit the transfusion unit which they will be attending, and meet the staff there. If possible they should be put in touch with some other patients and families.

◆ They should be given contact details for any local support groups or organisations and for the UK Thalassaemia Society.

Table 22.1: Baseline investigations and assessments

Immediate investigations	FBC, blood film, haemoglobin HPLC (although may not be informative if recently transfused; family study may help)
	Serum or plasma ferritin assay
	Blood group and antibody screen. Red cell genotyping, offered through the NHSBT.
	Hepatitis B and C serology to include Hep B surface antibody titre.
	HIV serology preceded by pre-test counselling.
	Full renal, liver, bone, sex hormone profiles, TFTs, random glucose, fructosamine if diabetic, PTH, vitamin D level, G6PD level.
	Globin genotyping (α and β globin genotype, -158 $^G\gamma$ *Xmn*1 C$\rightarrow$T polymorphism). Parental samples may be informative.
Semi urgent investigations	Glucose tolerance test if not established diabetes mellitus
	Abdominal and pelvic ultrasound to assess for gallstones, liver fibrosis or cirrhosis, spleen size and renal tract pathology (renal stones) and uterine/ovarian tissue in females
	Cardiac T2*
	Liver iron quantification using T2* or R2
	DXA scan
Other specialist assessments and clinical reviews	Audiology
	Ophthalmology
	Cardiac review
	If diabetic, specialist diabetic clinic
	If impaired glucose tolerance, dietician and diabetes nurse review
	If other endocrinopathies, endocrine clinic
	If hepatitis B antigen or C antibody positive, hepatology clinic
	Patient and family members should be offered genetic counselling, as appropriate

23: Prevention Using Prenatal Diagnosis and Preimplanation Genetic Diagnosis

"We knew we were both carriers when we got married so there was always that risk. With my first baby I refused PND and he was born with thalassaemia. I don't think I could cope with more than one child with thalassaemia so I chose PND with my other pregnancies."

Aims

To ensure that all couples at risk for having children with a thalassaemia disorder - including β thalassaemia major, β thalassaemia intermedia, haemoglobin E/β thalassaemia, α zero thalassaemia hydrops fetalis or severe haemoglobin H disease – are enabled to make informed choices concerning their reproductive options, through specialist genetic counselling.

To support couples to have healthy families.

Standards

■ All couples at risk of having children with a thalassaemia disorder should be referred to specialist genetic counselling as soon as the risk is recognised.

■ Counselling is provided by a genetic specialist with specific experience in both prenatal diagnosis and preimplantation genetic diagnosis for haemoglobin disorders.

■ DNA analysis is provided for all at risk couples.

■ All at risk couples are informed of prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD) as options to achieve a healthy family.

■ A couple at risk of having a child with a thalassaemia disorder should be offered PGD if the female partner is under 40 years of age at the time of treatment, and there is no living unaffected child from the current relationship.

■ If the woman has a thalassaemia disorder, her treating haematologist should be involved in the management plan prior to PGD.

Background

Prenatal diagnosis

Prenatal diagnosis (PND) using chorionic villus sampling (CVS) is available to all at risk couples from 11 weeks gestation onwards. PND, undertaken by experienced operators, carries a risk of miscarriage of 0.5% (Jauniaux and Petrou 2013). If a woman presents in later pregnancy, and the placenta is not accessible for CVS then amniocentesis may be carried out instead.

DNA testing should be offered to both partners (ideally before any pregnancy) to identify the precise mutations they carry. The woman should be encouraged to self-refer for counselling for

prenatal diagnosis as soon as a pregnancy is confirmed, so that CVS, if chosen, can be planned by the 11th week of pregnancy.

If prenatal diagnosis shows an affected fetus, the woman should be offered termination of pregnancy. If this is her choice, termination should take place as a matter of urgency and preferably within five days of the woman receiving the result, so she has the option of an early surgical termination of pregnancy.

If prenatal diagnosis shows an unaffected fetus, and the couple already have a child with thalassaemia, fetal HLA typing should also be performed. If the fetus and the affected child are HLA-compatible, cord blood cells should be collected at birth, and stored for possible transplant to the affected child in the future.

Preimplantation genetic diagnosis (PGD)

PGD is the only way for an at risk couple to ensure a fetus is unaffected, while avoiding the risk of an invasive procedure and the risk of termination of pregnancy associated with conventional prenatal diagnosis. It may be acceptable to some couples who would not accept a termination of pregnancy on religious or other grounds. It allows the diagnosis of single gene disorders such as thalassaemia, or of chromosomal abnormalities, or HLA typing, in IVF embryos before they are transferred to the woman's uterus.

PGD is used by fertile or infertile couples at high risk of transmitting a genetic condition to their children, and there is now excellent evidence that it is safe and accurate. Ever since it was introduced in 1990 (Handyside *et al.* 1990; Verlinsky *et al.* 1990) the number of indications for PGD has increased steadily, as has the number of couples requesting PGD. It is estimated that over 16,000 children have now been born using PGD.

However PGD is a long and complex process that combines in-vitro fertilisation (IVF) techniques with DNA testing. The pregnancy rate for a young woman is approximately is 29% (1 in 3) per embryo transfer with an average of 1.9 embryos transferred (Harper *et al.* 2012). Seven main steps are involved

1. The couple has a 'genetic work up' to determine the best method for embryo testing.
2. The woman undergoes controlled ovarian stimulation. This results in multi-follicular growth and suppression of ovulation.
3. Transvaginal egg collection. Approximately 36 hours before the egg collection, a 'one-off' injection of hCG is given, when three or more follicles measure greater than 18mm. Under sedation the ovarian follicles are aspirated under transvaginal ultrasound control via a needle passed through the vaginal wall. Eggs are identified within the follicular aspirate.
4. A sperm sample is provided by the man. The eggs are fertilised using intra cytoplasmic sperm injection (ICSI), to prevent paternal contamination from excess sperm lodged in the zona pellucida (Harton *et al.* 2011). Only mature eggs can be injected by ICSI.
5. Eggs using polar body biopsy (rarely used) or more commonly embryos are biopsied at day 3 (blastomere biopsy) or at 5-6 days (trophectoderm biopsy) after fertilisation. The trophectoderm-biopsied embryos are cryopreserved to provide sufficient time for the genetic analysis.
6. Embryos that do not have a thalassaemia gene disorder are identified by DNA testing of the embryonic cells or polar body.
7. One or two unaffected embryos are transferred into the woman's uterus, either in the stimulated cycle or a subsequent cycle if embryos are frozen. Embryos can remain in storage for up to 10 years (HFEA). The chance of successful thaw is not affected by the duration of storage. Current HFEA guidelines allow transfer of a maximum of two embryos in women less than 40 years of age.

A pregnancy test is carried out 14-16 days after embryo transfer.

The likelihood of becoming pregnant is strongly linked to the age of the woman being treated. On average a woman aged 18-34 years of age is more likely to conceive than an older woman.

Misdiagnosis after PGD is complex and difficult to identify: however there is agreement on an overall misdiagnosis rate of 0.14-0.27% after embryo transfer (Harper *et al.* 2012; De Rycke 2015). All women who become pregnant following PGD should be offered prenatal diagnosis by CVS.

A cycle may need to be cancelled due to under-stimulation of the ovaries, or over-stimulation which may lead to ovarian hyperstimulation syndrome. On occasion, there may be no suitable embryos to transfer as some may not have fertilised, some may have not survived the biopsy procedure, or all embryos may be affected.

Couples should avoid unprotected intercourse before the procedure and afterwards until the outcome of the procedure is known, to avoid the risk of a natural conception and the risk of an undiagnosed affected child.

The treating haematologist should be involved in the management plan with the IVF team. If the woman has a thalassaemia disorder then the haematologist should review the suitability of the woman to undergo IVF treatment, including a review of the chelation regime, when iron chelation treatment and other medication should stop prior to the procedure, optimal transfusion therapy during treatment, a cardiology review, liver assessment and requirement for thromboprophylaxis during treatment.

Access to PGD

PGD is available at several centres in the UK as a private service.

At present PGD is available on the NHS only to couples who meet the criteria in Table 23.1. Such couples are entitled to receive three complete cycles.

If couples choose to have PGD and fall within the criteria for PGD funding, or are prepared to pay privately, they should be referred for PGD.

Table 23.1: Access criteria for PGD on the National Health Service (NHS)

Access criterion	Position for thalassaemia disorders
The couple is at risk of having a child with a serious genetic condition	Fulfilled
The risk of conceiving a pregnancy affected by a serious genetic condition should be 10% or more	Fulfilled
The couple have been referred to the PGD provider by an NHS clinical genetics service	This requirement can cause delay because most clinical genetics services have limited experience with haemoglobin disorders, and so may refer patients back to specialist haemoglobinopathy centres for counselling. The problem can be overcome by conducting joint clinics.
The couple have received genetic counselling from a clinical geneticist or a registered genetic counsellor	
The female partner is under 40 years of age at the time of treatment	
There is no living unaffected child from the current relationship	
The female partner has a body mass index (BMI) of more than 19 and less than 30 (but can be referred if she undertakes to lose weight)	
Both partners are non-smokers or undertake to stop smoking.	
The Human Fertilisation and Embryology Authority (HFEA) has licensed the indication for PGD	Yes
The test is included in the list of UKGTN approved tests, or suitable for inclusion	Licence is already in place for β thalassaemia, α thalassaemia and HbE/β thalassaemia
The couple must not be seeking PGD primarily because they are infertile	It is recognised that individuals with thalassaemia disorders may have to be treated for infertility

It is possible to HLA-test unaffected embryos for compatibility with an existing affected child. However HLA testing is not included in the NHS criteria for PGD funding. It requires a specific application to NHS England, including evidence from the treating paediatric haematologist and the PGD centre. The process may be long-drawn-out and the application may not be successful.

Which couples should be referred for PGD?

- At risk couples who wish to avoid the risk of having an affected child, but would not consider termination of an affected pregnancy.
- Couples undergoing fertility assessments: couples who have been referred for IVF, or if the male partner has been referred for intra-cytoplasmic sperm injection (ICSI) may be suitable candidates for PGD.
- Couples where one partner has a thalassaemia disorder (or has had a successful bone marrow transplant for thalassaemia) and the other is a healthy carrier. These couples are at 50% risk of having an affected child, in every pregnancy.
- Couples at risk for more than one diagnosable genetic disorder. The chance of being at risk for two disorders is highest for couples who are close blood relatives. One in ten related couples at risk for thalassaemia is also at risk for another recessive disorder (for example, risk of thalassaemia plus risk of cystic fibrosis, phenylketonuria, maple syrup urine disease etc.). Such couples have a 43.75% risk of having a child with one disorder and a 6.25% risk of a child with two disorders.

Counselling for related couples at risk for thalassaemia should include a basic family history designed to identify other possible genetic disorders in the extended family. If any potential disorder is identified the couple should be referred to a clinical genetic service for expert assessment of additional risk, including DNA testing when this is feasible.

Both partners need to stop smoking as smoking has been shown to reduce the chances of conceiving. Cutting down on alcohol consumption to less than two units per week is recommended for men as excessive alcohol consumption can decrease sperm production and reduce motility. Women who hope to conceive should stop alcohol consumption.

Evidence base

The European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium has been collecting data from international PGD centres since 1997. Yearly data collections are published from approximately 60 centres worldwide offering PGD. This data collection is an extremely valuable resource for monitoring accuracy, reliability, effectiveness and safety of PGD. For more technical details about PGD, readers are referred to Dahdouh EM *et al.* (2015) and Konstandinides *et al.* (2015).

A summary of the first ten years of international data collection (1997-2007) showed that 17% of 27,000 cycles that reached oocyte retrieval were for risk of single gene disorders. The commonest indication was for haemoglobin disorders: 530 PGD cycles were for beta thalassaemia and sickle cell disorders, and 170 cycles for beta thalassaemia and HLA selection. The overall pregnancy rate was 23% per oocyte retrieval and 29% per embryo transfer (Harper *et al.* 2012). However the proportion of successful embryo diagnoses is rising (De Rycke *et al.* 2015), as is the proportion of successful pregnancies. The rate of referral for PGD is steadily increasing (Harper *et al.* 2012) and there is continuous improvement in available DNA diagnostic techniques (Lathi *et al.* 2012; Thornhill *et al.* 2015; Konstandinides *et al.* 2015) and there has been improved pregnancy rates of up to 63% of live birth per embryo transfer with trophectoderm biopsy, vitrification of blastocysts and transfer in a subsequent normal cycle (Lathi *et al.* 2012).

The Human Fertilisation and Embryology Authority (HFEA) lists UK clinics and their success rates. In 2013, 18 clinics performed 533 cycles in 422 patients at risk for single gene or chromosomal disorders. These resulted in 137 births and 149 babies, giving an overall pregnancy rate per cycle started of 25.7%. (HFEA 2013).

Currently the Centre of Reproductive and Genetic Health (CRGH) in London, where a significant number of PGD cases for single gene disorders are done, has the best success rates among UK

centres (see data on HFEA website www.hfea.gov.uk/preimplantation-genetic-diagnosis.html). For couples undergoing ICSI, there is a 61% clinical pregnancy rate per embryo transfer for women under 35 years of age, and 58% for women 35-37 years of age. However for PGD patients, the clinical pregnancy rate for single gene disorders is now reported to be 70% (personal communication CRGH). Approximately 5-10% of pregnancies achieved in this way will result in a spontaneous miscarriage.

Requirements

◆ All at risk couples should be referred to a genetic specialist or genetic counsellor, with expertise in the genetic aspects of the haemoglobin disorders and prevention, to ensure the couple fully understand the risk of having an affected child and the benefits and limitations of available options for preimplantation genetic diagnosis and prenatal diagnosis.

◆ DNA studies should be carried out on both partners.

◆ The couple should be referred for PGD if they choose, and they fulfil the criteria in Table 23.1 or elect to pay for private treatment.

◆ Couples opting for PND should be given the contact details of the PND centre so they can self-refer as soon as a pregnancy is recognised, or the genetic counsellor should refer immediately on their behalf.

◆ If the woman chooses to terminate an affected pregnancy following PND, this should be carried out as soon as possible and preferably within five days of the woman receiving the results.

Recommendations

Couples seeking PGD should be advised that:

• A cycle may need to be cancelled due to under-stimulation of the ovaries, or over-stimulation which may lead to ovarian hyperstimulation syndrome, or that there may be no suitable embryos to transfer as some may not have fertilised, some may have not survived the biopsy procedure, or all embryos may be affected.

• They should avoid unprotected intercourse before the procedure and afterwards until the outcome of the procedure is known, to avoid the risk of an undiagnosed affected child.

• All women who become pregnant following PGD should be offered prenatal diagnosis to confirm the results of PGD because the techniques used for PGD have technical limitations including the possibility of a misdiagnosis.

Section D: Non-Transfusion-Dependent Thalassaemias

24: Management of Non-Transfusion-Dependent Thalassaemias

"People think thal intermedia is just a less severe type of thal major, but it has its own problems, especially as you get older."

Introduction

This section addresses issues covered by preceding chapters as they apply to NTDT. Where the same standards and key interventions apply, they are not repeated; where there are differences, these are highlighted.

There have been developments in understanding the natural history and pathophysiology of NTDT since the last edition of the *Standards* (Musallam *et al.* 2011; Taher *et al.* 2010). Most of these derive from observations in the Middle East and some European centres, and may not be fully applicable to patients from other ethnic backgrounds, with different genotypes. For instance, cases of Haemoglobin E/β thalassaemia (EBT), a form of NTDT seen in people from Bangladesh and SE Asia, were not included in many of these studies.

Aims

To maintain good health, normal growth and development, and a good quality of life during childhood, adolescence, and adulthood in people with NTDT, avoiding unnecessary treatment with regular transfusions in those with milder clinical features, but intervening with appropriate transfusion as needed.

To monitor regularly and systematically for early signs of morbidity due to chronic anaemia, iron overload and other consequences of untransfused thalassaemia.

Standards

■ A comprehensive DNA diagnosis (β globin mutations, α globin genotype, *Xmn*1 C→T polymorphism) should be undertaken as soon as the diagnosis of thalassaemia has been established.

■ Parents, carers, and patients should be counselled at diagnosis, and as often as needed thereafter, about the likely course of the condition and therapeutic options available.

■ During the first 3-5 years of life, children with thalassaemia should be monitored carefully and systematically for evidence of thalassaemic features which may require regular transfusion therapy. Older children, adolescents and adults with a diagnosis of NTDT should continue to be monitored regularly, for consideration of indications for transfusion, and for iron loading, pulmonary hypertension, and extramedullary haematopoietic masses in particular.

■ Complications of NTDT should be identified at an early stage and treated promptly.

Background

Definition

NTDT encompasses the spectrum of clinically significant thalassaemia syndromes which do not require regular transfusions in early childhood to sustain acceptable health, growth and development. The definition includes a broad range of phenotypes and genotypes, and can be subdivided into those who have never been transfused and those who require occasional transfusions. This has not been formally defined, but may be up to 6 transfusions per year (Taher *et al.* 2011; Weatherall 2012). The pathophysiology and severity of iron overload in these two groups will differ, and in general iron overload and the need for chelation is likely to be increased in the latter group.

Genetics

NTDT 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 the inheritance of a genetic determinant of enhanced fetal haemoglobin production, can also alleviate the severity of the thalassaemia. An important effect of these additional factors is to reduce the intracellular damage due to free α chains within the developing erythroblast. The clinical phenotype can usually be predicted from knowledge of the β globin, α globin and *Xmn*1 polymorphism analysis (Table 24.1) but sometimes the clinical phenotype is not as predicted from genetic analysis. The α thalassaemia syndrome Haemoglobin H disease (HbH) has a relatively variable phenotype and is usually mild, although in a few cases may be severe enough to require regular transfusions.

Table 24.1: Genetic determinants of non-transfusion-dependent thalassaemia

Homozygote (or compound heterozygote) for mild β-mutation (such as IVS1-6 T>C, Codon 9 C>T)	
Homozygote for severe β mutation but persistence of Hb F due to:	Homozygote for *Xmn*1 polymorphism
	HPFH
	Other factors increasing HbF
Co-inheritance of β thalassaemia (heterozygote) and a thalassaemia-like Hb variant (these may result in a major or intermedia phenotype)	Hb E/β thalassaemia
	Hb Lepore β thalassaemia
Co-inheritance of α thalassaemia mutations (homozygous α$^+$ or heterozygous α^0) with homozygous β thalassaemia resulting in decreased globin chain imbalance	
Co-inheritance of extra α gene(s) with heterozygous β thalassaemia resulting in increased globin chain imbalance	
Inheritance of a 'dominant thalassaemia' mutation (hyperunstable β globin variant)	

Clinical phenotypes

Moderate/severe

This includes up to 10% of patients with homozygous β thalassaemia, the majority of those with EBT and a very small proportion of those with HbH. 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 osteoporosis and will gradually accumulate iron, particularly in the liver, due to increased gastro-intestinal iron absorption. The majority in this group end up requiring regular transfusions (Taher *et al.* 2015; Taher *et al.* 2014).

Mild

This group includes a small proportion of patients with homozygous β thalassaemia (usually predictable from genotype), some patients with EBT, and the large majority of patients with HbH. It is important to identify this very mild group and to provide information tailored to their

condition. Long-term complications including pulmonary hypertension, hypersplenism, gall stones, endocrinopathies, osteoporosis, chronic ankle ulceration, thromboembolic disease and iron overload can occur, but usually not before the age of 30.

Specific clinical considerations

Transfusion

Considerations to be taken into account in deciding whether to start a child on regular transfusion include the following:

- Episodes of acute anaemia may be related to intercurrent infection and are not necessarily an indication for long-term transfusion.
- Parvovirus B19 and other viral or atypical infections are common causes of acute resolving anaemia. The haemoglobin level returns to baseline once the infection resolves.
- It is important to remember that acute haemolysis may also be exacerbated by G6PD-deficiency, and that folate deficiency may occur; patients with NTDT should be prescribed folic acid supplements.
- Transfusion initiated for delayed growth and pubertal development in NTDT should be reviewed once growth is complete.
- Older patients may become increasingly symptomatic with anaemia and regular and transfusion programme may be indicated.
- Since red cell allo-immunisation is common in NTDT with incidence varying between 4 – 37% (Taher *et al.* 2015), phenotype matched units for transfusion is mandatory.

Splenectomy

Splenectomy should be considered for patients with:
- hypersplenism resulting in clinically important leucopenia, thrombocytopenia, bleeding or symptomatic anaemia;
- massive splenomegaly with clinical symptoms.

Previously splenectomy was recommended in order to increase haemoglobin level and avoid regular transfusion. However, it is increasingly clear that splenectomy does not provide a permanent alternative to transfusion in these patients, and probably increases the risk of long-term complications such as thromboembolic disease and pulmonary hypertension. Avoidance of transfusion is no longer a standard indication for splenectomy in the UK, where blood is readily available and safe, and several options for iron chelation exist.

Managing iron overload

Recent data has shown that iron overload complications are associated with considerable morbidity in patients with NTDT and that this is under recognised. The serum ferritin is unreliable in NTDT, and underestimates the degree of liver iron loading. Iron -related cardiomyopathy is rare in NTDT but endocrinopathies are encountered (Taher *et al.* 2014; Taher *et al.* 012). Patients should be offered liver iron monitoring by either T2* or R2 (Ferriscan) to assess the degree of iron burden.

Liver iron concentration (LIC)

The relationship between LIC and total body iron which has been established in TM is not applicable to NTDT, and the mechanism of iron deposition differs. Therefore, LIC values in NTDT should be interpreted with caution. Liver iron increases by an average of 0.35 mg/g dw per year in NTDT patients. Some studies have shown an association between age and LI, but others have not been able to demonstrate this (Taher *et al.* 2012; Pakbaz *et al.* 2007; Taher *et al.* 2008; Origa *et al.* 2008).

Serum ferritin

Although levels of SF correlate with LIC in NTDT, potentially toxic LIC levels are associated with lower SF levels than in TM, and the range of values of SF used to predict morbidity and mortality in TM may not be directly applicable NTDT. In one study, the authors found elevated LIC levels in

patients with SF levels below 1000 µg/l, a level generally considered safe in TM (Taher *et al.* 2012; Pakbaz *et al.* 2007; Taher *et al.* 2008; Origa *et al.* 2008).

Myocardial iron

In cross-sectional studies using myocardial T2* MRI, non-transfused or rarely transfused NTDT do not appear to have measurable cardiac iron loading. There is insufficient published data to assess the long-term risk of cardiac iron loading beyond the age of 40. Furthermore, for patients who switch to regular transfusions, there is a risk of cardiac iron accumulation as for TM (Taher *et al.* 2010; Taher *et al.* 2009).

Non-transferrin bound iron (NTBI)

Detectable NTBI has been reported in one study, associated with the frequency of previous transfusions (12). This may relate to increased uptake and mobilisation of iron which is thought to relate to low hepcidin levels in NTDT. Thus, NTBI may be apparent before serum transferrin is fully saturated, in contrast to TM, where NTBI is detected when erythropoiesis is suppressed, hepcidin levels normal, and transferrin fully saturated. It is not yet clear how NTBI levels correlate with clinical outcomes in NTDT and whether NTBI levels can be used clinically to decide on initiation and adjustment of chelation therapy.

Iron chelation in NTDT

There have been a number of small uncontrolled trials of chelation therapy with DFO (Cossu *et al.* 1981), and DFP (Olivieri *et al.* 1992; Rodrat *et al.* 2012; Limenta *et al.* 2011), which have demonstrated that these agents can chelate iron in NTDT patients with an acceptable short-term safety profile. An initial pilot trial (Voskaridou *et al.* 2010) and a more recent placebo controlled trial (Taher *et al.* 2013) have shown that DFX is safe, effective and acceptable for reducing LIC and SF at doses of 5, 10 and 20 mg/kg. The lower limit of LIC for inclusion was 5 mg/g/dw. There have been no studies which compare different levels of liver iron at which to start chelation therapy, and no studies which demonstrate a beneficial effect of chelation on morbidities in NTDT.

Pulmonary hypertension (PHT)

PHT is prevalent in untransfused adults (30%), particularly those who have been splenectomised, and causes significant morbidity and mortality (Musallam *et al.* 2011; Taher *et al.*2010; Taher *et al.* 2011; Teawtrakul *et al.* 2014; Teawtrakul *et al.* 2015). Autopsy studies show pulmonary vascular occlusion with thrombus, presumably a result of hypercoagulability, increased platelet count and activation. Nitric oxide depletion through scavenging by free plasma haemoglobin may also play a role in promoting pulmonary vascular changes.

Echocardiography is a useful screening test, particularly if done sequentially. If there is a suspicion of PHT on the basis of clinical symptoms and signs, and/or findings on echocardiography, referral should be made to a specialised unit for assessment and consideration of right heart catheterisation to confirm the diagnosis.

Patients with PHT should be managed jointly with a national specialist PHT unit. Treatment options include hypertransfusion and hydroxyurea. Anticoagulant therapy may be beneficial in some cases. Decisions about specific therapy for PHT including sildenafil and endothelin antagonists should be guided by the PHT specialist centre.

Extramedullary haematopoiesis

Asymptomatic paravertebral masses are observed in 15% - 20% of patients. Symptoms can be subtle, for example a feeling of incomplete bowel emptying can indicate a pre-sacral mass, and spinal cord compression may be present in individuals who complain of minor symptoms of weakness or discomfort in a knee joint. A full neurological examination should be undertaken if there is any suspicion, with consideration of MR scanning of the spine. Masses causing spinal cord compression, root compression, or pressure symptoms in other anatomical sites require urgent management. The optimal treatment modality is not established but radiotherapy can induce rapid resolution of pressure effects. Good results, although generally slower in onset, have been described with hypertransfusion and hydroxycarbamide.

Asymptomatic masses may require therapy depending on their position (e.g. if impinging on the spinal cord), but if not threatening vital structures, for example lying in the paravertebral gutters in the thorax, may simply be monitored.

Low bone mineral density (BMD)

Low BMD is very common in NTDT. One cross sectional study found Z score <-2 in 67% of adult patients, a similar prevalence to TM. Low BMD affects the spine and femora and results in a significant increased risk of fractures (Vogiatzi *et al.* 2009). The prevalence of osteoporosis increases with age, and is reported in 30% of patients aged 32 or more (Taher *et al.* 2010). The high prevalence is probably a result of expanded ineffective erythroid marrow combined with reduced growth, deficiency of endocrine function and high rate of bone turnover. Bone mineral density should be assessed every 5 years. There is very little data on different treatment options for osteoporosis in NTDT. Recommendations for treatment in TM apply, and in addition, osteoporosis with fractures may be an indication for regular transfusion in a patient with NTDT, as this may reduce the rate of loss of bone mass by suppressing ineffective erythropoiesis in the spine, femora and other affected bones.

Role of hydroxycarbamide

Hydroxycarbamide is a cytotoxic agent which can suppress intra- and extramedullary erythropoietic activity and enhance fetal haemoglobin production. The potential clinical benefits include alleviation of symptoms of anaemia, reduction in clinical jaundice, relief of bone pain, reduction in bone marrow and spleen enlargement and regression of extramedullary masses. Transfusion requirements may be reduced.

In general, the clinical experience and results published in case series show that the response is variable. Better results have been reported for specific genotypes, notably those who are homozygous for the *Xmn*1 polymorphism (Karimi, *et al.* 2010; Karimi *et al.* 2009; Bradai *et al.* 2007). Some patients are particularly sensitive to bone marrow suppression and become leucopenic with relatively modest doses, and too high a dose may suppress erythropoiesis rather than enhance haemoglobin levels.

Stem cell transplantation (SCT)

Since many patients with moderate/severe phenotype of NTDT have relatively poor quality of life, and many will eventually require transfusions and chelation therapy, SCT should not be ruled out. The decision whether or not to pursue this option is especially difficult given the established risks of the procedure, the improving outlook for those managed with transfusions and chelation therapy, and the difficulty in predicting the long-term consequences of NTDT in a young child. The discussion requires careful counselling, accurate and consistent information, and good communication between the family, the Transplant Centre and thalassaemia team.

Requirements

General

◆ The organisation of services for NTDT should be similar to TM. Input from the Specialist Haemoglobinopathy Centre is especially important as the conditions are relatively rare and the optimal management is often finely balanced and patient-specific.

◆ Patients should receive regular folic acid supplementation.

◆ Patients should be reviewed at least annually at the Specialist Centre.

Transfusion

◆ After transfusion for an episode of acute anaemia, the patient should be observed carefully for several months to determine steady-state symptoms and haemoglobin level.

◆ The decision for regular transfusions should be made in collaboration with the Specialist Centre. 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.

◆ Red cell units transfused must be matched for ABO, Rhesus antigens (C/c,D,E/e) and Kell.

Monitoring of iron load and chelation therapy

◆ LIC is the most important parameter for assessing iron overload in NTDT and should be assessed using R2 or T2* MRI. Assessments should start from age 10, and repeated every 2-5 years.

◆ SF should be measured at least once per year, and correlated with LIC. Increasing SF levels (particularly > 800μg/l) should prompt a repeat LIC assessment.

◆ Myocardial T2* should be considered for assessment of myocardial iron loading in older patients and those who require more frequent transfusions (3-6 per year).

◆ Iron chelation is recommended in older children and adults whose LIC is more than 5 mg/g/d.w.

◆ DFX is recommended as first line chelation, with the goal of reducing LIC and maintaining within the range 3-7 mg/g d.w. The starting dose should be 10 mg/kg/day and dose adjusted within the range 5-20 mg/kg/day on the basis of monthly SF and periodic LIC. DFX should be discontinued when LIC <3 mg/g dw or SF < 300 μg/l. (Exjade Summary of Product Characteristics)

◆ DFO or DFP can be considered for chelation in patients who are unable to tolerate or have adverse effect with DFX.

Splenectomy

◆ Careful consideration should be given to the risks/benefits of splenectomy. The decision must be made with the team at a Specialist Haemoglobinopathy Centre.

◆ Patients with NTDT should be transfused for several months prior to splenectomy to reduce spleen size, suppress marrow activity, and reduce the numbers of circulating, prothrombotic thalassaemic red cells.

Growth and pubertal development

◆ Growth and pubertal development should be monitored regularly from the age of 10, and referral to the designated endocrinologist made if abnormalities are documented.

◆ A period of regular transfusion should be offered during adolescence if growth spurt and/or pubertal development are delayed.

Pulmonary hypertension

◆ NTDT patients should have regular echocardiography from age 15. If there is clinical or echocardiographic evidence to suggest significant PHT, they require assessment and consideration of right heart catheterisation to confirm the diagnosis and plan management.

◆ Treatment of PHT should be co-ordinated in close collaboration between the local centre, Specialist Centre and PHT centre. Regular transfusion is normally recommended for these patients.

Extramedullary haematopoietic masses

◆ Suspected extramedullary haematopoietic masses should be investigated promptly, particularly if causing pressure effects. Radiotherapy can be considered if there is urgent need to alleviate pressure effects. Hypertransfusion and/or hydroxycarbamide may be appropriate therapy if there are mild or moderate clinical consequences.

Other treatments

◆ The treatment goals should be discussed and agreed between the patient, carer and Specialist Centre haematologist before initiating hydroxycarbamide therapy. The patient should be made fully aware of possible adverse effects of the drug, and supplied with written information. It should be started at a dose of 10-15 mg/kg/day, and the full blood count monitored regularly and systematically. It is unlikely that patients will tolerate doses in excess of 20 – 25 mg/kg/day.

◆ Referral to a centre with experience of transplanting for thalassaemia should be offered to families, for detailed discussion of transplant as an option.

Recommendations

• Suggestions for regular monitoring tests, which differ in some respects from those for TM, are given in Table 24.2.

Table 24.2: Regular monitoring test for non-transfusion-dependent thalassaemia

	Frequency	Age at start
Clinical examination to include: • Height • Weight • Spleen size • Liver size • Assessment of facial bone deformity and dental state	3 monthly, but according to severity of clinical syndrome, can be less frequent if mild	from birth or time of diagnosis
Pubertal development	6 monthly	Age 10
Cardiac assessment including echocardiogram	moderate severity : 1 – 2 yearly, mild phenotype: 5 yearly.	Age 15
Blood tests FBC Liver function, renal function, urate Ferritin	3 monthly, but according to severity of clinical syndrome, can be less frequent if mild	from birth or time of diagnosis
Formal assessment of liver iron concentration by MRI	2 – 5 yearly or more frequently if abnormal	Age 10
Cardiac iron assessment by MR T2*	2 – 5 yearly depending on previous results	Age 20 + or earlier if needing > 3 transfusions per year
DXA bone density	5 yearly	Age 15

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Appendices

Appendix A: Summary Guide to Routine Investigations

Establishing the diagnosis

A diagnosis of thalassaemia should be anticipated from antenatal screening of the parents and established by prenatal diagnosis where requested. Otherwise, it may be suggested by the results of the newborn screening programme. Occasionally the diagnosis will not be made at these early stages, and the diagnosis is suggested by clinical presentation as the child becomes ill. Testing to confirm a diagnosis should include:

- Full blood count and blood film examination
- Haemoglobin analysis by electrophoresis, high performance liquid chromatography (HPLC) or equivalent
- β and α globin genotyping, and *Xmn*1 C→T polymorphism
- Family studies may be informative, if parental results are not available through antenatal screening.

Before a first transfusion

Specialty	Investigations
Haematology	Serial Hb measurements G6PD screen + assay if low
Transfusion	Full red cell extended phenotype and genotype (C, c, D, E, e, K, k, Jka, Jkb, Fya, Fyb, Kpa, Kpb, MNS, Lewis)
Biochemistry	LFT and baseline ferritin assay
Microbiology	Hepatitis B surface antigen Hepatitis C antibody HIV antibody

Monitoring tests during iron chelation

	Desferrioxamine, DFO	Deferiprone, DFO (or combination with DFO)	Deferasirox, DFX
Ferritin	1-3 monthly	1 -3 monthly	Monthly
Neutrophil count	not required	Manufacturers recommend weekly during therapy	not required
Creatinine	not required	not required	Twice before start, then weekly during first month after initiation and change of dose. Thereafter monthly.
ALT	not required	not required	Twice before start, then 2 weekly for first month after initiation of therapy. Thereafter monthly.
Urinalysis	not required	not required	Twice before start, then weekly during first month after initiation and change of dose. Thereafter monthly.
Pure tone audiometry	Annually aged > 5 years	6-12 monthly for combination DFO and DFP, not if used as single agent	Before starting therapy and annually
Ophthalmology	Annually aged > 5 years	6-12 monthly for combination DFO and DFP, not if used as single agent	Before starting therapy and annually

Tissue iron levels should be monitored by MR techniques:

For liver iron concentration – starting from age 7 – 10 or as soon as able to tolerate procedure without sedation, and then repeated at intervals depending on previous result:

- Stable levels in the range 3 – 7 mg/g dw: 1 – 2 yearly
- Levels > 7 mg/g dw: yearly
- Levels falling rapidly or < 3 mg/g dw: 6 – 12 monthly.

For cardiac iron levels – starting from age 7 – 10 or as soon as able to tolerate procedure without sedation, and then repeated at intervals depending on previous result:

- Stable T2* > 20 milliseconds: two yearly
- T2* 10-20 milliseconds: yearly
- T2* < 10 milliseconds: 6 monthly

Note: see also cardiovascular assessments, below.

Growth, development and endocrine function

Measurement	Frequency
Assessments of weight and height – sitting and standing	6 monthly from diagnosis until final adult height.
Assessment of puberty, using Tanner staging	Yearly from age 10 years
Plain X ray of wrist to check for epiphyseal fusion	1-2 yearly from age 10 if concern about fall in height velocity or pubertal progression
Growth hormone stimulation test	If declining growth velocity from age 8
Oral glucose tolerance test	Yearly from puberty, or from age 10 years if family history of diabetes mellitus
Full annual diabetes review, including glycaemic control, cardiovascular risk factors, diabetic complications and sexual health	Yearly if a diagnosis of diabetes is established
Thyroid function test	Yearly from age 12, or if any suggestive symptoms of thyroid deficiency between times
Calcium, phosphate, alkaline phosphatase levels Parathyroid hormone level	6 monthly from age 12 If calcium level is low
Vitamin D level	At least every year from age 2
Morning cortisol level	Yearly from age 14
LH/FSH and oestradiol	If menstrual disturbance develops
Morning testosterone level	Yearly from age 14
LH/FSH and sex hormone binding globulin level	In men if morning testosterone level is low

Assessments for fitness for pregnancy.

- Cardiology review including echocardiogram and T2* cardiac magnetic resonance scan
- Glucose tolerance test to exclude diabetes
- In known diabetic, fructosamine level, as indicator of glycaemic control, aiming at < 300 nmol/l
- Thyroid function
- Hepatitis B serology – ensure fully immune
- Check up to date with other immunisations for example pneumococcal vaccine if spleen removed
- Bone density by DXA scanning

Acute clinical presentations.

Please refer to the full tables guiding diagnostic considerations in chapter 15: Acute Clinical Presentation .

Cardiovascular assessments

Uncomplicated, well chelated patient on stable therapy and without symptoms or abnormalities on previous testing

Assessment	First visit	Surveillance interval	Comment
Clinical cardiology visit and examination	7 – 10yr	2 yr Annual 2 yr	If no symptoms/abnormalities Between risk ages 16 to 25 yr After age 25
ECG		As above	At each visit
ECHO	7- 10yr	As above	At each visit
MRI	7- 10 yr	2 yr if > 20 ms on last assessment 1 yr if < 20 ms on last assessment	

Poorly chelated patient, without heart failure or impaired LV function, AND patients recovered from an episode of acute heart failure AND those with impaired LV but no symptoms.

Assessment	Surveillance interval	Comment
Clinical cardiology visit and examination	Immediate, then 3 to 6 monthly	Dependent on severity of T2*; 3 monthly if <6 ms
ECG	At each visit	
ECHO	6 monthly	
MRI	6 monthly if T2* < 10 ms Yearly if T2* < 20 ms	Unlikely to be helpful to repeat MRI at less than 6 month intervals

Before and during pregnancy

Assessment	First visit	Surveillance	Comment
Clinical cardiology visit and exam	When planning pregnancy	Pre-conception At ~ 12/40 gestation At 28/40 gestation 3 months post delivery	If abnormalities on testing, or significant symptoms, may need more intensive monitoring
ECG		First visit	
ECHO		Every visit	
MRI		Pre-conception and post-delivery visits	

Bone mineral density

- Vitamin D level at least every year from age 2
- Calcium, phosphate, alkaline phosphatase levels 6 monthly from age 12 years
- Parathyroid hormone level if calcium level is low
- DXA scan every 2 – 3 years from puberty

Monitoring for liver disease

- Liver function tests monthly
- Hepatitis serology testing: hepatitis B (Hep B surface antigen, Hep B surface antibody level, Hep B core antibody) and hepatitis C (HCV antibody) yearly
- If established cirrhosis, surveillance for hepatocellular carcinoma: alpha fetoprotein measurement, and liver ultrasound or cross sectional abdominal imaging (MR or CT) every 6 months.
- MR quantitation of liver iron using a standardised and validated technique:
  - Stable levels in the range 3-7 mg/g dw: one to two yearly
  - Levels > 7 mg/g dw: yearly
  - Levels falling rapidly or <3 mg/g dw: 6 -12 monthly

Patients returning to/arriving in UK who have been treated elsewhere

Immediate investigations	• FBC, blood film, haemoglobin HPLC (although may not be informative if recently transfused; family study may help) • Serum or plasma ferritin assay • Blood group and antibody screen. • Red cell genotyping, offered through the NHSBT. • Hepatitis B and C serology to include Hep B surface antibody titre. • HIV serology preceded by pre-test counselling. • Full renal, liver, bone, sex hormone profiles, TFTs, random glucose, fructosamine if diabetic, PTH, vitamin D level, G6PD level. • Globin genotyping (α and β globin genotype, -158 $^G\gamma$ Xmn1 C→T polymorphism). • Parental samples may be informative.
Semi urgent investigations	• Glucose tolerance test if not established diabetes mellitus • Abdominal and pelvic ultrasound to assess for gallstones, liver fibrosis or cirrhosis, spleen size and renal tract pathology (renal stones) and uterine/ovarian tissue in females • Cardiac T2* • Liver iron quantification using T2* or R2 • DXA scan
Other specialist assessments and clinical reviews	• Audiology baseline • Ophthalmology baseline • Cardiac review • If diabetic - specialist diabetic clinic • Abnormal GTT- dietician and diabetes nurse review • If other endocrinopathies, endocrine clinic • If hepatitis B antigen or C antibody positive, hepatology clinic • Patient and family members should be offered genetic counselling, as appropriate

Non-transfusion-dependent thalassaemia

	Frequency	Age at start
Clinical examination to include: • Height • Weight • Spleen size • Liver size • Assessment of facial bone deformity and dental state	3 monthly, but according to severity of clinical syndrome, can be less frequent if mild	from birth or time of diagnosis
Pubertal development	6 monthly	Age 10
Cardiac assessment including echocardiogram	moderate severity : 1 – 2 yearly, mild phenotype: 5 yearly.	Age 15
Blood tests FBC Liver function, renal function, urate Ferritin	3 monthly, but according to severity of clinical syndrome, can be less frequent if mild	from birth or time of diagnosis
Formal assessment of liver iron concentration by MRI	2 – 5 yearly or more frequently if abnormal	Age 10
Cardiac iron assessment by MR T2*	2 – 5 yearly depending on previous results	Age 20 + or earlier if needing > 3 transfusions per year
DXA bone density	5 yearly	Age 15

Appendix B: Glossary

ablation
removal or destruction of tissue, usually by surgery but in some cases by chemicals or medicines

adherence
the extent to which a person is able to take medication exactly as prescribed

adrenal
small gland above the kidney which makes adrenaline and other hormones

aetiology
cause

agranulocytosis
absence or very low levels of granulocytes (neutrophils), the white blood cells which fight off bacterial and fungal infections

aldosterone
hormone which regulates salt balance, blood volume and blood pressure

albumin
the major protein found in blood plasma

alkylating agents
drugs used for chemotherapy and sometimes used in conditioning for bone marrow transplantation

alpha fetoprotein
a chemical marker which can be measured in the blood. Its level is raised in, for example, liver cancer and in some circumstances during pregnancy.

alpha globin
one of the two proteins required to make adult type haemoglobin, the other being β globin.

amenorrhoea
absence of menstrual periods

amniocentesis
withdrawal of some of the amniotic fluid surrounding an unborn foetus to diagnose congenital abnormalities

anaemia
low blood level, specifically low level of haemoglobin (the red oxygen carrying pigment inside the red blood cells).

angiotensin
hormone controlling arterial blood pressure

anomaly
abnormality, usually of development

antenatal
literally "before birth", meaning during pregnancy.

antibiotic
medication to treat bacterial infections

antibody
protein the body's immune system makes in response to infection, to fight it off. Antibodies can be artificially provoked by immunisation/vaccination to try to prevent infection. Additionally, antibodies can form against other 'unfamiliar' proteins, for example after blood transfusion, against some of the proteins on the surface of the transfused red cells.

anticoagulation
the prevention or hindering of coagulation of the blood by an anticoagulant drug – includes Warfarin and heparin and newer 'direct oral anticoagulant' drugs (DOACs).

appendix/appendicitis/appendicectomy
small elongated projection at the beginning of the large bowel, which has no useful function in humans. It can become inflamed causing pain and fever (appendicitis) and may need to be removed (appendicectomy)

arteriosclerosis
disease of the arterial blood vessels marked by thickening, hardening and loss of elasticity in the aterial walls.

arthritis
painful inflammation and swelling in joints

arthropathy
pain in the joints

atrial fibrillation
heart arrhythmia marked by very fast contractions of the heart muscle of the atria, or smaller upper chambers of the heart, causing an irregular, rapid heartbeat

audiology
clinical speciality of managing hearing.

audiometry
measurement of hearing

autonomic

not subject to voluntary control

autosomal recessive

a gene which can be passed on to offspring by a mother or a father, and which if inherited with a "normal" equivalent gene from the other parent, gives rise to no health problems (a healthy carrier). In order to develop a clinical condition, it needs to be inherited from both parents.

bacteraemia

infection in which bacterial organisms circulate in the blood

bart's hydrops fetalis

an unusual condition, which usually causes a late miscarriage or stillborn baby, caused by the foetus inheriting no functioning alpha globin genes from either parent. Alpha globin is one of the two proteins required to make adult type haemoglobin, the other being β globin

beta globin

one of the two proteins required to make adult type haemoglobin, the other being alpha globin

biliary tract

the tube system leading from the liver into the small bowel, and carrying bile. This has the dual purpose of aiding digestion and carrying waste products such as bilirubin formed when haemoglobin is broken down in the liver. The gall bladder is a small storage pouch for bile between the liver and bowel.

biopsy

a small sample of tissue removed for microscopic or other examination, in order to aid diagnosis or guide treatment.

bisphosphonates

a group of drugs which help put calcium back into the bones.

bone marrow transplant

a major medical procedure in which the patient's bone marrow, usually because of a condition such as thalassaemia or leukaemia, is replaced by bone marrow from a healthy donor of the same or very closely matched tissue type.

bone resorption

a normal process in which bones are being continually eaten away at their surface. It goes along with new bone formation, and the result of the two is called bone remodelling

bradycardia

slow resting heart rate

butyrate

a naturally occurring fatty acid chemical which has been shown to increase production of foetal or baby type haemoglobin in certain circumstances

capillary

the smallest blood vessels in the circulatory system

carcinoma

the most common type of cancer or tumour.

cardiac arrhythmia

disturbance of the normal, regular heart rhythm.

cardiac decompensation

failure of the heart's pumping mechanism to work strongly enough.

cardiologist

doctor specialising in cardiology.

cardiology

clinical speciality of managing heart disorders.

cardiomyopathy

problem in the heart muscle, weakening the pumping action.

cardiovascular

relating to the heart and blood vessels/circulation

cartilaginous dysplasia

abnormality of the developing cartilage, the smooth material at bone ends causing joints to move smoothly

chemotaxis

movement by a cell or organism towards or away from a chemical stimulus

chelation

removal of excess iron from the body, using a specific medication called a chelator.

chimerism/mixed chimerism

a situation following bone marrow transplant in which the patient's own bone marrow remains functional alongside the donor bone marrow.

chlamydia

a micro-organism sometimes found in the cervix, which can cause fertility problems

cholangitis

inflammation of the bile ducts

cholecystitis

inflammation of the gall bladder.

cholecystectomy

surgical removal of the gall bladder.

cholelithiasis

stones in the gall bladder or biliary tract.

chorionic villus sampling

procedure, usually undertaken at 11 or 12 weeks of pregnancy, to remove a small piece of the placenta in order to test for a condition which may affect the fetus.

cirrhosis

a liver disease which can be caused by a range of problems, in which the liver is scarred with areas of functioning liver tissue trapped between scar tissue bands

colic

spasms of pain caused when a hollow organ is blocked, for example, the bowel or tubes of the biliary tract

creatinine

a chemical waste product produced by muscle metabolism; levels in blood are used to measure kidney function as the kidneys clear it when they are working properly

ct scan

computerised tomography imaging technique which interprets multiple X-ray images to visualise internal anatomy

cystic fibrosis

an autosomal recessive condition, in which the affected individual has chronic cough, repeated lung infections and difficulty with digestion

deferasirox

an iron chelating drug which is active when taken by mouth. Its original name was ICL670 and it is licensed under the name Exjade.

deferiprone

an iron chelating drug which is active when taken by mouth. Its original name was L1, and it is licensed under the name Ferriprox.

densitrometry (bone)

measurement of bone density or strength of the bones.

desferrioxamine

the first available iron chelating medication which is still the most commonly used. It is licensed under the name Desferal. It is not active when taken by mouth.

diabetes mellitus

a condition in which the body is unable to process carbohydrates and sugars properly.

diabetes Type 2

a type of diabetes which is usually of later onset, and which frequently responds to diet or tablets rather than needing insulin.

diagnostic imaging

a general term for any sort of X-ray or scan used to aid diagnosis

diaphysis

the shaft part of a long bone

disc disease

problems affecting the soft tissue discs which sit between the spinal bones and aid spinal movement.

diuretic

a medication which increases the kidneys' output of salt and water, causing an increase in urine output.

dysplasia

an abnormality of development

dysrhythmia

disturbance in the heart's normal, regular rhythm.

echocardiography

an ultrasound scan of the heart in which the movement of the heart muscle and heart valves can be visualised.

electrocardiogram (ECG)

a tracing representing the heart's electrical action

electrophoresis

a laboratory technique in which different proteins in solution are separated, by passing a weak electric current through the solution.

embolism

obstruction of a blood vessel by a mass (usually a blood clot)

endocrine

relating to hormones

endocrinologist

a medical specialist in conditions causing hormone disturbance

endocrinopathy

a condition affecting the hormone producing glands

enzyme

a protein chemical which speeds up metabolic processes in the cells of the body. The level of certain enzymes can be measured and may give a guide to the condition of the organ producing them (for example, liver enzymes).

epiphyseal fusion

epiphyses are the ends of the growing bones. When a person is reaching maturity, the epiphyses fuse or lock together with the main part of the bone in certain areas, after which no more growth can occur.

erythroid

relating to red cell production

erythroid marrow hyperplasia

overgrowth of the bone marrow caused by increased red cell production.

erythropoiesis

the process of red cell formation.

erythropoietin

the hormone produced by the kidneys which drives red cell production.

fallopian tube

the tube which connects the ovary to the body of the uterus or womb.

ferritin

a soluble transport form of iron, which can be measured in the blood and used as an indication of the total amount of iron in the body.

fetus (also spelt foetus)

the unborn baby.

fludarabine

a chemotherapy drug also used in conditioning regimens prior to stem cell transplant

folic acid

a vitamin of the B group which is required for red cell formation. It is found in green leafy vegetables and nuts.

fracture

breakage (of a bone).

free radical

unstable atom or molecule which is highly reactive and can cause cell damage

fructosamine

a protein used to assess long term glucose control in diabetes

fulminant

full-blown or obvious.

G6PD deficiency

low levels of a chemical called glucose 6 phosphate dehydrogenase, found in the red cells, which is used by the red cells to resist damage by certain chemicals. Deficiency is an inherited condition, usually causing few problems but which can lead to red cell breakdown, especially if a person takes certain medications which should therefore be avoided.

gall bladder

is a small storage pouch for bile, positioned on the biliary duct or tube between the liver and bowel

gall stone

a lump of hard material developing in the biliary system or gall bladder

gene

an inherited instruction which determines one or a number of functions which occur in the chemical machinery of the cell. The gene consists of a stretch of DNA containing unique coding sequence which is eventually translated into a protein. This sequence is copied as the cell divides

genetic

relating to one or more genes

geneticist

scientist or doctor who has a specialist interest in conditions caused by genetic problems

genotype

a particular type or combination of genetic changes

genu valgum

tendency to have "knock knees".

Gestation

the period from conception to birth

globin

the protein parts of the haemoglobin molecule.

glucose intolerance

a mild form of inability of the body to handle glucose and sugars optimally, not as severe as diabetes mellitus.

gonadal

relating to the organs of reproduction; ovaries in women and testes in men.

gonadotrophin

hormones produced by the pituitary gland in the brain that stimulate the ovaries and testicles

graft rejection

a situation where, after a transplant (for example, of bone marrow), the immune system of the person receiving the transplant reacts against it and tends to destroy it.

graft versus host disease (GVHD)

a condition following a transplant in which the functioning immune cells in the transplanted tissue react against and damage tissues of the person receiving the transplant.

gram negative/gram positive organism

bacteria which either do (positive) or do not (negative) stain with a reagent called Gram's stain, used by laboratories to differentiate organisms viewed under the microscope.

growth hormone deficiency

a shortage of a hormone produced by the pituitary gland which is chiefly responsible for controlling growth.

haematocrit

percentage of the blood which is taken up by the blood cells as opposed to the fluid plasma.

haematology

the clinical speciality relating to blood disorders.

haematologist

medical specialist managing blood disorders.

haematopoiesis

the process of blood cell formation, which usually takes place within the bone marrow. 'Extra-medullary haematopoiesis' describes the situation in which the tissue performing this function extends outside the bone margins

haemochromatosis

a condition where the body gradually loads up with too much iron. The term usually refers to the hereditary sort, where too much iron is absorbed from the diet, rather than to the condition resulting from repeated blood transfusions.

haemodynamic

relating to blood circulation

haemoglobin

the red, oxygen-carrying pigment which circulates in the red blood cells. From infancy onwards the majority type is adult-type or Haemoglobin A, and it is the beta globin protein part of this which cannot be made adequately in thalassaemia major.

haemoglobin H disease

a condition resulting from inheritance of only one functioning alpha globin gene, of the usual four. It is usually quite a mild anaemia with not many clinical problems.

haemoglobinopathy

a general term which covers all the inherited medical conditions which are due to abnormal or under-produced haemoglobin proteins.

haemolysis

premature red cell breakdown

haemolytic

resulting from premature red cell breakdown.

haploidentical stem cell transplant

transplant from a "half matched" related donor, e.g. mother or father

hepatic

relating to the liver.

hepatitis

inflammation of the liver.

hepatologist

medical specialist in liver disorders.

hepatomegaly

liver enlargement.

hepatosplenomegaly

liver and spleen enlargement.

heptaocellular carcinoma

cancer of the liver cells.

Heterozygote

an individual who inherits one type of a gene from one parent, and another type from the other. Relating to haemoglobin disorders it most usually describes inheritance of a normal gene from one parent together with a thalassaemic or sickle gene from the other - the healthy carrier state.

high performance liquid chromatography (HPLC)

an automated, rapid and accurate way of separating different protein bands in a solution, for example, different sub-types of haemoglobin from a blood sample.

histology

the appearance of tissue examined under a microscope.

histopathology

the clinical speciality of analysing tissue specimens for abnormality.

HIV

the 'human immunodeficiency virus', which causes AIDS.

HLA (human leucocyte antigen)

describes a set of proteins on the white blood cells. Commonly referred to as "tissue type".

homeostasis

self-regulating biological processes which maintain normal chemical levels, temperature etc in the body

homozygote

a person who inherits the same gene type from both parents, for example, beta thalassaemia major (beta thalassaemia gene from both parents) or haemoglobin SS sickle cell anaemia (sickle cell gene from both parents).

hormone replacement therapy

usually used to describe oestrogen hormones given to women after the menopause, but can also relate to the replacement of any hormone which is lacking because of underactivity of the endocrine glands.

HPFH (hereditary persistence of fetal haemoglobin)

continued production of fetal or baby type haemoglobin into adult life. This is an inherited feature.

hydroxyurea (also known as hydroxycarbomide)

a medication used for many years for bone marrow over-activity syndromes, but more recently found to be of use in sickle cell anaemia and to some extent in thalassaemia.

hyperdynamic

very active, quick, usually applied to blood circulation

hyperglycaemia

elevated blood sugar.

hyperkinetic

hyperactive, fast-paced or excessive movement

hyperplasia

abnormal increase in volume of new normal tissue cells

hypersplenism

overactive spleen, often also enlarged, resulting in lowered blood counts.

hypertension

high blood pressure.

hypertransfusion

a transfusion regimen when a person is transfused up to even higher levels than normally needed to keep well, for a particular therapeutic purpose, for example before surgery or to reduce bone marrow growing outside the bone edges, as pre-transfusion haemoglobin levels of 110 – 120 g/l (rather than the usual 90 g/l) can suppress bone marrow activity and production of the person's own blood cells more effectively.

hypocalcaemia
　low calcium level in the blood.

hypogonadism
　failure of the normal activities of the testes in men, or ovaries in women.

hypogonadotrophic hypogonadism
　hypogonadism resulting from underproduction of gonadotrophin hormones which are produced by a small gland inside the brain, and which normally drive ovarian/testicular function.

hypoparathyroidism
　underactivity of the parathyroid glands which control body calcium levels.

hypothalamus
　a small gland situated deep in the brain which, with the pituitary gland adjacent to it, controls many of the hormone producing glands.

hypothyroidism
　underactivity of the thyroid gland, which controls the body's activity levels.

iatrogenic
　symptoms induced unintentionally by medical treatment

inotropic
　affecting muscle contraction, especially heart muscle, making the heart pump more strongly

intermedia
　when relating to thalassaemia, describes the condition in which, although a person inherits a thalassaemic gene from both parents, he/she can make enough haemoglobin to get along without always needing regular blood transfusions.

intrauterine
　inside the uterus or womb.

jaundice
　a symptom of liver disease in which the skin and whites of the eyes are discoloured yellow (due to excess bile pigments in the blood)

ketones
　acidic chemicals produced by the body when fat instead of glucose is burned for energy, which can happen in diabetes or starvation

Klebsiella
　a gram-negative bacteria which can cause serious infections

laparoscopy
　a procedure for looking and/or operating inside the abdomen through small, keyhole incisions.

laparotomy
　an operation to open up the abdomen, using ordinary 'open' surgery

leukaemia
　cancer of white blood cells.

left ventricular ejection fraction (LVEF)
　the percentage of blood present in the left ventricle that is effectively pumped forward at each heart beat to supply the peripheral circulation

lipids
　organic fats and fatty acids

macrophage
　large white blood cell which ingests foreign particles/bacteria

malocclusion (dental)
　the teeth do not meet properly when the jaws close

maxillofacial
　relating to the jaws and face

meningitis
　inflammation, usually by infection, of the meninges or brain coverings.

menopause
　the time, in women, at which the ovaries stop producing eggs and the periods cease

metabolism
　the body's chemical processes or activities.

monotherapy
　single drug treatment.

morbidity
　illness.

mortality
　death.

MRI (magnetic resonance imaging)
　a scanning technique which gives clear pictures and no exposure to X-rays

MUGA
　'multigated acquisition' scan, which uses injection of a radio-isotope to show up the heart muscle and measure its function

myeloma
　a cancer of the antibody -producing cells within the bone marrow

myocardial
　relating to the muscular tissue of the heart

necrosis
　tissue death

neonate
　newborn

nephropathy
　kidney problem

neutropenia
　abnormally low level of neutrophils (white cells) in the blood

obstetrics
　the medical speciality of caring for pregnant women and their unborn children, until after delivery.

oedema
abnormal accumulation of fluid in body tissues, causing swelling

oesophagus
the gullet connecting the mouth and stomach, down which the food is swallowed.

oesophagoscopy
a procedure to look down into the gullet.

ophthalmology
the clinical speciality of managing eye disease.

orthopaedics
the clinical speciality of managing bone and joint problems, particularly by surgery.

osteomalacia
bone weakness, usually resulting from lack of vitamin D or calcium

osteonecrosis
destruction of bone tissue

osteopenia
a mild degree of bone thinning.

osteoporosis
A more severe degree of bone thinning which can cause pain and increased risk of fracture.

ovary
the organ in females which produces eggs.

ovulation
egg production

oximetry
a method of determining the amount of oxygen in the blood

paediatrics
the clinical speciality of caring for illness in children

palpitations
sensation of irregular, hard or rapid heartbeat

pamidronate
a medication (one of the bisphosphonates) which can help put calcium back into bones).

pancreas
large gland behind the stomach which secretes insulin and other hormones

parathyroid
the glands which control calcium levels in the blood and bones, by producing parathyroid hormone

parenchyma
the essential/functional elements of an organ

pathogenic
causing illness.

pathology
the study of disease processes, and of diseased tissues or organs

pathophysiology
the study of structural and functional changes in tissue and organs that lead to disease

pericarditis
inflammation of the fibrous sac which surrounds the heart.

perinatal
around the time of birth.

peri-operative
around the time of an operation.

perioral
around the mouth.

peripheral
towards the edges, in medicine usually used to describe towards the hands and feet.

phenotype
describes the structure or appearances resulting from different gene makeup, or genotype.

phlebotomy
blood removal.

physiology
the study of normal body processes.

physiotherapy
the speciality of trying to improve joint and muscle function and mobility, often by massage, exercise etc.

pituitary
a small gland deep inside the brain, which, with the hypothalamus which lies next to it, controls most of the body's hormone producing glands.

pneumococcus
a type of bacteria (also known as streptococcus pneumoniae) which in most people causes tonsillitis, but in people whose spleen is absent or not working can get into the bloodstream and cause very serious infections.

polydipsia
excessive thirst and fluid intake

polymorphism
(literally "many forms") usually describing the possibility of different forms which can occur at a single gene site

polyuria
excessive excretion of urine

portal hypertension
increased blood pressure in the circulation of the liver

prenatal diagnosis
diagnosis on a baby before birth.

prognosis
outlook or expected outcome.

prophylaxis
treatment given to try to prevent a problem, rather than waiting until it develops and then treating it.

pulmonary

relating to the lungs

pulmonary hypertension

increase of blood pressure in the blood vessels of the lung

R2/R2*

a magnetic property of tissues which increases with raised iron content and can be measured by magnetic resonance imaging (MRI)

radiology

the clinical speciality of interpreting X-rays and other diagnostic images.

radiotherapy

the clinical speciality of giving treatment with radiation.

renal

relating to the kidneys.

retina

the membrane at the back of the eye which senses light and sends messages to the brain, where they are interpreted into vision.

retinopathy

disease or problem affecting the retina.

rheumatology

the clinical speciality of managing joint disease (with medicine, not surgery).

rickets

a condition which arises when the bones are softened by lack of vitamin D or calcium (osteomalacia), and which can cause deformity in developing bones

rubella

virus infection more commonly known as 'German measles'.

sensorineural

usually used to describe a form of deafness due to damage to the auditory or hearing nerves.

sepsis

infection, usually bacterial.

septicaemia

infection in the blood.

serum

the clear fluid remaining when blood has been allowed to clot and the clot removed.

serology

testing of serum.

sickle cell disorders

a group of inherited conditions in which altered structure of haemoglobin can give rise to anaemia, sudden severe pain 'crises' and a range of other health problems

sinuses

air spaces within the bones of the face

sinusitis

inflammation, usually caused by infection, in the sinuses

spermatogenesis

formation of sperm by the testes

spleen

large organ lying under the lower ribs on the left, which helps in fighting infection and removes old or damaged cells from the blood

splenectomy

removal of the spleen

splenomegaly

enlarged spleen

staphylococcus epidermidis

a type of bacterium which can infect tubes or 'lines' put through the skin into the veins so that medication can be administered through them

steatohepatitis

fatty liver

stem cells

the earliest, most primitive cells in the body which can mature into almost any of the tissues

stomatitis

inflammation of the mouth

sub-clinical

not apparent as not causing symptoms, or signs on examination

subcutaneous

under the skin

synergy/synergistic

working together

T2/T2*

a magnetic property of tissues which falls with increased iron content

teratogen

an agent that can disrupt the development of a fetus; i.e. which causes birth defects

tetany

muscle spasm caused by low calcium level in the blood

thromboprophylaxis

medication given to try to prevent blood clots forming in the blood vessels

thrombosis

blood clot forming in the blood vessels

thyroid

the gland which produces thyroxine hormone, which controls the body's activity levels

transaminases

liver enzymes

transferrin

a plasma protein that combines with and transports iron

UKCCSG

United Kingdom Children's Cancer Study Group

ultrasound

a type of scan using high frequency sound waves

vaccination

injection to provoke an immune response to an infection, and therefore protect against it

varices

enlarged vein containing blood at higher pressure than usual

vascular

to do with the blood vessels (intravascular - inside a blood vessel)

vasodilatation

widening of blood vessels due to relaxation of the muscle in the vessel walls, allowing a greater volume of blood to flow

ventricles

when relating to the heart, indicates the main pumping chambers

vertebra(e)

bone(s) in the back or spine

paravertebral

around the vertebral bones

vertebral dysplasia

abnormality in development of the vertebrae

Yersinia (enterocolitica)

bacterial organism which can cause infection in the bowel, giving severe pain and fever which can mimic appendicitis. It infects particularly people who have high iron levels and are on iron chelation.