



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

2005

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Foreword

from the UK Thalassaemia Society

I am delighted to introduce the first *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK*.

Part of our work at UKTS involves travelling around the country to meet patients and families. From these meetings and from many telephone calls to our office, it is abundantly clear to us that there is wide disparity in the quality of treatment available to thalassaemics. We have been made aware of many sad situations where patients are being failed by the system. In our major treatment centres however, it is commonplace to see adult thalassaemics leading very full lives, with careers and children of their own. In the 21st century it is unacceptable that, with our healthcare system, thalassaemics are still dying prematurely and suffering from preventable disabilities.

At our first national conference for thalassaemia doctors in 2002, it became apparent that many of the leading haematologists shared our views. Together we decided that something must be done, and this document is the beginning of that process. We hope that, as well as providing guidance for clinicians, it will inform and empower patients and families to seek, and if necessary demand, the best treatment and therefore the best quality of life available to them.

The UKTS thanks the Writing Group, and in particular Dr Anne Yardumian and Dr Paul Telfer, for the many hours of dedicated work which have gone into preparing this document. We hope that readers will find it useful and will not hesitate to contact the Society at any time if we can help.

With best wishes,



Michael Michael
President, UK Thalassaemia Society



from the Department of Health



We welcome this publication which sets out clear standards for the delivery of care to patients with thalassaemia.

The document builds on the considerable expertise of the UK Thalassaemia Society and has not only involved patients closely in the process of developing the standards, but also encourages patients and empowers them to manage many aspects of their condition. This is very much in keeping with a patient-centred NHS.

For the first time, performance indicators are provided to enable the monitoring, on a national basis, of treatments available and outcomes. Feedback of this information to clinicians should lead to ongoing improvements in treatment and outcome, and is an essential part of Clinical Governance.

We are sure that this document will be also be an invaluable source of information to commissioners when developing future services for patients.



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Summary of Standards

Section A: Organisation of thalassaemia services

Standard: thalassaemia as a long term condition

- Families will be offered comprehensive education about the condition and their role in care will be emphasised.
- Families will be carefully trained to deliver home chelation and other treatment, and supervise the child's care generally, and will receive continued support in doing so
- Unnecessary hospital admissions will be minimised by adequate monitoring, management of chelation, and early identification and treatment of any complications.
- Each care network will systematically record and exchange information relating to clinical events and results of monitoring investigations. This should cover concerns expressed by the patient and family, information from specialist clinic visits and any clinical management decisions.
- Patients and families should be fully involved in all care decisions, and be able to follow their progress closely, receiving copies of clinical letters and/or recording important information in a hand-held record.
- Families should have access to networks for peer support
- One 'Key Contact' health professional must be designated for each individual patient/family.
- A national register of patients needs to be maintained.

Standard: a network for care

- All areas will be served by a clinical network incorporating local thalassaemia Clinics and one or more specialised thalassaemia Centres. In regions where sickle cell disorders are also prevalent, the Centres are likely to have additional commitments to these patients.
- Local procedures must be agreed to ensure that all patients have access to the specialist Centre, either for their regular care if living nearby, or for annual reviews and specific consultations if living more distantly.
- The network will need to be adequately commissioned, funded and staffed, with clear systems for information sharing, clinical governance, accountability and staff development.

Section B: Core Management Standards

Standard: 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 genotype.
- The child must be monitored closely to determine the likely clinical course.
- The family should be informed fully and sensitively from the outset, 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.

Standard: Decision to start regular transfusions

- 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 sufficient clinical evidence of severe anaemia, failure to thrive, and/or thalassaemic bone deformity.

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

Standard: Red cell transfusions

- Haemoglobin levels should be maintained above 9.5-10g/dl.
- Cannulation will be undertaken by an experienced nurse or doctor.
- Pre-arranged transfusions should be started promptly.
- Good transfusion practice must be observed
- Transfusions will be given on each occasion in a designated area with suitable facilities, experienced regular named nurses and familiar supervising medical team.

Standard: Iron load, monitoring and treatment

- Every transfusion-dependent child will start to receive iron chelation therapy with subcutaneous desferrioxamine infusions in time to prevent iron-related toxicity.
- Parents and patients should be made fully aware of the reasons for chelation therapy, and trained to administer it at home. They should be kept informed of developments with new chelator drugs and modes of delivery of chelators.
- Transfusion iron loading, body iron stores, adherence to chelation and evidence of chelator-related toxicity must be monitored carefully and systematically. Complications should be managed by optimising chelation therapy according to a local protocol agreed between the local thalassaemia Clinic and specialist Centre.
- All patients and families should have access to support in the practical and psychological challenges that arise from the demands of daily chelation therapy.
- Problems with adherence will be carefully identified and addressed.

Standard: Psycho-social issues

- The psycho-social needs of patients growing up with thalassaemia must be considered alongside every aspect of their clinical care. This is a key role for all professionals managing the child, to be considered in each communication with the child and family.
- Core staffing of specialist thalassaemia Centres should include a Clinical Psychologist.

Standard: Acute clinical presentation in the treated patient.

- Individual presenting to their primary care professionals, or a hospital A&E Department or clinic, with new symptoms and/or signs will be rapidly assessed by staff aware of the various acute complications which can occur in this condition.
- If staff with appropriate knowledge and experience are not available, there must be urgent consultation with members of the specialist team on site or at the Centre, and referral on after stabilisation, as necessary.
- Appropriate management should be instituted as quickly as possible.
- GPs of patients with thalassaemia should be aware of the range of acute complications they can encounter.

Standard: Referral for consideration of bone marrow transplant

- All families who have a child with a serious thalassaemia syndrome will be offered the opportunity to discuss bone marrow transplant as a treatment option at an early stage, usually around the age of 12 – 18 months.
- Referral does not depend upon the family having an available donor at the time, and discussions may inform the family's subsequent decisions on family size.
- The discussion must be with a transplant team with specific experience in transplanting for thalassaemia.

Standard: Surgery including splenectomy

- Surgical procedures requiring general anaesthetic should be undertaken at, or after consultation with, the thalassaemia specialist Centre.
- Patients should be carefully assessed pre-operatively with special reference to cardiac, endocrine and metabolic disturbances which may require correction. A designated paediatric or adult anaesthetist should be involved in managing the patient.

Standard: Transition from paediatric care and management of adults

- Transfer from paediatric to adult care must be planned in advance for each individual, and timed to take into account his or her level of physical and psychological development.
- The young person will be familiar with the staff and facilities of the adult clinic prior to transfer.
- In adults, active vigilance is required for development of clinical complications, so that appropriate management can be instituted.

Section C: Prevention and management of complications

Standard: Cardiac complications

- A paediatric and an adult Cardiologist with responsibility for care of thalassaemics must be designated for each thalassaemia specialist Centre.
- All patients will have a cardiological assessment at least once per year from age 10.
- Symptoms or signs suggestive of cardiac disturbance should be investigated and managed urgently.
- Local protocols for monitoring and treatment will be developed based on best current practice.

Standard: Endocrine complications

- A paediatric and an adult Endocrinologist will be designated for each specialist Centre.
- Children should be monitored regularly and systematically for growth and development, from diagnosis up until the time when they have achieved full sexual maturity and final adult height.
- Deviations from expected pattern should be investigated and managed promptly. Children who are found to be growth hormone deficient should receive replacement therapy.
- Patients from age 10 should be checked annually for biochemical evidence of glucose intolerance, and from age 12 for hypothyroidism and hypoparathyroidism, and deficiencies treated appropriately.

Standard: Liver complications

- Liver function tests will be monitored regularly.
- Liver iron levels should be maintained within safe limits to avoid progressive hepatic damage.
- Efforts to avoid viral liver disease must be made, ensuring transfusion with appropriately screened blood and full vaccination against hepatitis B infection.
- Liver disease will be managed in collaboration with a designated specialist Hepatologist.
- Hepatitis C infection should be staged and treated vigorously to obtain sustained viral clearance whenever possible.

Standard: Bone complications.

- Transfusion therapy will be initiated in time to prevent irreversible deformities associated with bone marrow expansion.
- Bone changes related to desferrioxamine toxicity should be suspected and investigated in children with bone/joint pain or short stature.

- All patients should be encouraged to exercise and maintain a diet rich in calcium and vitamin D.
- Hormone replacement therapy should be given to those with hypogonadism.
- Teenage and adult patients will be monitored for osteoporosis.
- Established osteoporosis in adults should be treated with bisphosphonates.

Standard: Fertility, and management of pregnancy.

- Pubertal development and endocrine function will be closely monitored and prompt referral to the designated Endocrinologist made if there is any suspicion of problems.
- At any time when the patient wishes she/he should be referred to a fertility clinic with experience of thalassaemia patients, to allow discussion about treatment options. Culturally appropriate advocacy in these discussions is imperative.
- Women contemplating pregnancy will be assessed for possible risks to themselves and their babies.
- Women should be jointly managed during pregnancy by a 'high-risk' obstetrician experienced with thalassaemia, and by their haematologist.

Section D: Specialist Review

Standard: Annual review at Specialist Thalassaemia Centre.

- Every person with thalassaemia will have the opportunity for their care and condition to be reviewed at least annually, at a thalassaemia Centre, with a team of health care professionals who have particular experience in the field.
- This should allow for broad discussion of treatment options, including any new information which has become available, and an individual treatment plan for the next 12 months will be confirmed.
- People in families affected by thalassaemia should be able to meet and gain support from other affected families at the Centre.

Standard: Review of patients previously treated outside the UK

- Children and adults who have been receiving treatment outside the UK will, on arrival, be seen promptly at an established Centre and thoroughly assessed.
- Any complications which may have developed will be detected and discussed with the individual and family and management plans made accordingly.

Section E: Management of thalassaemia intermedia

Standard:

- A comprehensive DNA diagnosis (β globin mutations, α globin genotype, *Xmn1* polymorphism) should be undertaken as soon as the diagnosis of thalassaemia has been established. Detailed consideration will be given to clinical and laboratory findings in order to reach a decision about transfusion and other treatment needs.
- 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 suspected of having thalassaemia intermedia should be monitored carefully and systematically for evidence of thalassaemic features which may require regular transfusion therapy
- Children, adolescents and adults with this condition should be monitored carefully and regularly, in conjunction with the specialist Centre
- Complications of thalassaemia intermedia should be minimised by anticipation, early detection, and intervention with appropriate therapy.

Introduction

1

Context: The Aim of this Document

1.1 Thalassaemia in the UK

Modern treatment of thalassaemia can be considered a success story. Children are surviving to adult life in good health, are able to lead essentially normal lives and have families of their own (Weatherall and Clegg 2001). Unfortunately, this outcome is not universal in the UK. Adults and adolescents are still dying, most commonly from heart failure, and children often develop complications such as growth failure and hypogonadism due to endocrine damage. These complications are directly related to transfusion iron overload, and the ability to adhere to iron chelation therapy (Modell and Berdoukas 1984, Olivieri et al 1994, Brittenham et al 1994). Outcomes are far better in some specialist centres than in the UK as a whole (Modell et al 2000, Porter and Davis 2002). This suggests that some aspects of care can be unsatisfactory in smaller, less specialised clinics. The majority of thalassaemic patients in the UK are managed in clinics of less than 10 patients (Modell et al 2001) reflecting the patchy geographic distribution of patients. Difficulty in accessing optimal, patient-centred services can be a factor in reduced patient adherence to recommended treatment, leading in some cases to early death.

1.2 Opportunities to make a change in thalassaemia care

There is an opportunity to improve this situation, the impetus deriving from several sources. The UK Thalassaemia Society has recognised the problem and demanded action. The Government's NHS plan published in July 2000 envisaged investments and reforms to transform the NHS into a patient-centred service. The plan included a commitment to a linked antenatal and neonatal sickle cell and thalassaemia screening programme¹, which is currently in the process

of implementation. This will identify the majority of neonates affected with thalassaemia throughout the country. There is a commitment within the programme to deliver a universally high standard of care to the identified children, whether they are affected with sickle cell disease or thalassaemia.

Concurrently, *The New NHS*² and *A First Class Service – quality in the New NHS*³ introduced a range of measures to drive up quality and decrease variations in services, including the programme of National Service Frameworks (NSFs). These set national standards, define service models for their target patient group, put in place strategies to support implementation and establish performance milestones against which progress can be measured. The NSFs and other related NHS initiatives have direct relevance to the care of children and adults with thalassaemia. The *National Service Framework for Children*⁴ although not yet complete, impacts on the hospital care of young thalassaemics, and the NSF for people with long term conditions is expected later in 2005. The Department of Health document *Supporting people with long term conditions – an NHS social care model to support local innovation and integration*⁵ has recently been published. Issues of inequality in access to health care are important since people with thalassaemia originate from ethnic minority populations⁶. In parallel, there has been a broad re-evaluation of how best to manage long-term or chronic health problems, with focus on patient choice and involvement in their services. The National Service Frameworks emphasise the importance of user

1. www.kcl-phls.org.uk/haemscreening/
2. www.archive.official-documents.co.uk/document/doh/newnhs/newnhs.htm
3. www.dh.gov.uk/publications
4. www.dh.gov.uk/nsf/children/
5. www.dh.gov.uk/assetRoot/04/09/98/68/04099868.pdf
6. www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/HealthInequalities

involvement, and The Expert Patient Programme¹ is intended to empower patients with chronic conditions to manage aspects of their condition which are traditionally poorly addressed within conventional services. Recommendations and themes from these initiatives are reflected in our proposed standards for thalassaemia care.

1.3 Aims and scope of these Standards

In this document we have 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 who are not transfusion dependent (thalassaemia intermedia, section E). It is not intended to offer full clinical guidelines as these are well covered by the Thalassaemia International Federation's *Clinical Management for Thalassaemia* (Cappellini et al, April 2000), to which readers looking for more detailed clinical guidance are advised to refer. Where a subject is not well covered in other publications, more details are included, for example presentation of the acutely ill patient (section B.11) and the management of patients starting treatment in the UK who have previously been treated elsewhere (section C.20). Overall our central focus has been on the way in which services are structured and delivered.

Performance Indicators are provided for monitoring and evaluation of services, enabling individual hospitals to measure their current provision and the effectiveness of the care they give. These have been kept quite brief, acknowledging that to include demanding and detailed indicators initially would be likely to overwhelm. They may later form part of a central reporting mechanism regarding the levels of service provision. They are intended also to provide a framework for commissioning authorities, to help them to ensure that the services they are supporting provide appropriate quality care.

A similar review of the provision of sickle cell services is underway. Publication of a parallel set of standards for the management of sickle

cell disorders is expected in the next few months.

Appreciating the central role of patients in planning and implementing changes, we have included at the start of each section, a number of relevant quotations, derived largely from focus groups and questionnaires organised by the UK Thalassaemia Society. We hope that these enliven the text, as well as giving insight into problems as seen from the patients' perspective.

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, it is likely that some of it may be of interest or value to patients and their families, and a Glossary is included (Appendix E) to try to facilitate understanding of what may be unfamiliar terms.

1.4 Levels of evidence

Wherever possible, we have established a base in published research for proposals made. It will be clear that although there is a wealth of clinical experience and understanding of outcomes based on it, there is a lack of prospective, randomised, double-blinded trials to inform these guidelines. This is perhaps not surprising in a condition which is relatively rare in affluent countries, and does not attract large amounts of 'drug company money'. The conditions are most prevalent in low-resource countries where research funding is too often lacking. We have therefore had to rely largely on published retrospective analysis of clinical data and non-randomised, non-controlled interventions, expert opinion, and the views of patients and families.

Where this is the case, there is sometimes a range of opinion about what constitutes optimal care. In clinical decision making, there is frequently a tension between the need to wait for formal evidence - based on randomised controlled double-blind prospective studies - to support an intervention before offering it, and the imperative to offer patients what is judged to be best for them even before such evidence becomes available. This is especially the case if delaying might deprive them of a potentially valuable investigation or therapy in the meantime. There has, for instance, been

1. www.expertpatients.nhs.uk/

debate among professionals as well as patients about the use of the newer options for iron chelation. This situation is changing, and we expect more formal scientific data to emerge in the near future concerning, for example, the results of randomized studies comparing desferrioxamine and various deferiprone regimes for managing cardiac problems, and the oral iron chelator ICL 670 whose Phase III trials have recently been completed.

To reflect the current situation, we have adopted a simplified form of grading evidence, which essentially recognises three Grades: A, B and C (Petrie et al 1995, Appendix D). The 'Key Interventions' are all graded, but as the great majority are Grade C, only for those which are *other than* Grade C is this specifically indicated.

1.5 New editions of the Standards

We propose that a committee is established to review relevant new developments and publications and to adapt the standards in the light of them. In the first instance it is expected they will need to be updated after two years (2007). Suggested additions or amendments for consideration in future editions are invited, via the UKTS Office.

1.6 Conclusion

In conclusion, we hope that this document will contribute towards uniformly excellent care becoming available to patients throughout the country.

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The following individuals contributed directly to the writing process.

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2

Thalassaemia: clinical features and treatment

2.1 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 beta 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 α globin chains, damages red cell precursors in the bone marrow. This results in ineffective erythropoiesis, severe anaemia and compensatory erythroid marrow hyperplasia.

2.2 Classification

The thalassaemias can be broadly categorised clinically as:

- β thalassaemia major (BTM) 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) 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 to start.

The compound heterozygous states of β thalassaemia with a thalassaemic haemoglobin

variant (Including HbE, Lepore, Knossos) or an alternative thalassaemic mutation (e.g. $\delta\beta$ thalassaemia) often result in a thalassaemia intermedia phenotype, but can cause thalassaemia major.

- Alpha (α) thalassaemia major and haemoglobin H disease arise as a result of deletion of three or four of the four α globin genes or from non-deletional mutations which inactivate the gene. If all 4 α globin genes are affected, the result is typically intrauterine anaemia and usually the early stillbirth of a hydropic infant (Bart's Hydrops fetalis) as α globin chains are required to form fetal haemoglobin. The next most severe form of α thalassaemia, when 3 of 4 α genes are affected, is often clinically mild. This condition, known as Haemoglobin H disease, is usually a mild condition with features typical of a chronic haemolytic anaemia, although a few individuals develop more severe problems, including transfusion dependency.

These standards apply to transfusion dependent patients and those with thalassaemia intermedia (section E).

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 β thalassaemia major. Separate guidelines are necessary for the antenatal management of this condition.

2.3 Haemoglobinopathy screening

Population and antenatal screening to identify carriers of β thalassaemia is technically easy and cheap. 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 Mediterranean countries (e.g. Cyprus, Italy, and Greece) but delivery has been inconsistent across the UK (Modell et al 1997). Systematic screening of pregnant women in England is part of a national policy for linked antenatal and newborn screening for thalassaemia and sickle cell disease, currently being implemented¹.

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.

2.4 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 β thalassaemia major die from heart failure or infection before the age of five.

2.5 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 develop cardiac problems and die 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 of 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 has been 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 hypogonadotropic hypogonadism may also be prevented (Olivieri 1997).

2.6 Adherence to treatment

The main problem with iron chelation therapy is 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 10-12 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 a large, well organised thalassaemia Centre, physical and psychological problems with adherence can be addressed methodically, and excellent survival can be expected in younger patients (Porter and Davis 2002). In the UK as a whole, survival has not improved to the extent hoped 30 years ago when desferrioxamine became available, and this is probably due to the problems thalassaemic patients experience in tolerating regular self-administered infusions (Modell et al 2000).

1. www.kcl-phs.org.uk/haemscreening

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 life experience, but also the way in which that care is delivered.

Patients often feel that provision of patient-centred services is one of the most important factors, and that clinics should take particular care to minimise disruption to education, employment and family life, allowing them 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

Thalassaemia as a long-term condition

3.1 Aims

Families affected by thalassaemia will be educated and supported to manage and monitor all feasible aspects of their own condition, improving their health and quality of life. As expert patients they will be able to work in partnership with professionals to optimise their care. Effective communication between patients and families, and their primary and secondary health care teams, is key to the successful management of this long-term condition.

3.2 Standards

- Families will be offered comprehensive education about the condition and their role in care will be emphasised.
- Families will be carefully trained to deliver home chelation and other treatment, and supervise the child's care generally, and will receive continued support in doing so
- Unnecessary hospital admissions will be minimised by adequate monitoring, management of chelation, and early identification and treatment of any complications.
- Each care network will systematically record and exchange information relating to clinical events and results of monitoring investigations. This should cover concerns expressed by the patient and family, information from specialist clinic visits and any clinical management decisions.
- Patients and families should be fully involved in all care decisions, and be able to follow their progress closely, receiving copies of clinical letters and/or recording important information in a hand-held record.
- Families should have access to networks for peer support
- One 'Key Contact' health professional must be designated for each individual patient/family.

- A national register of patients needs to be maintained.

3.3 Rationale

Recent health service focus on the management of chronic health problems, 'Supporting people with long term conditions' (DoH 2005) with its emphasis on supported self-care and pre-emptive interventions, has considerable resonance for those involved with thalassaemia. While hospital care is inevitable for transfusions and complex clinical and diagnostic interventions, most routine care in the form of administering iron chelation and other treatment, and other forms of support, are undertaken by the family at home. Patients and families who understand fully their condition, are involved in every care decision, and are guided and supported in their self-care become truly expert patients, and their management and quality of life can be optimised.

Support should be offered by the hospital team, making itself readily available for contact, by outreach personnel going into the home to train and support families, and by primary health care teams being fully aware of the condition and its implications and potential problems.

Communication will be a key element in efficient functioning of the care network. When a patient is being treated by multiple agencies it is vital that relevant information is shared to avoid omission or duplication and to optimise treatment. This is more challenging but particularly important where there are communication or language difficulties. Patient-held records can be an effective way of transmitting essential clinical information between health care workers in different clinics, and also provide an

opportunity for the patient to gain a better understanding and become more involved in their own care and monitoring. A hand-held 'filofax' file is available from the UK Thalassaemia Society.

A named 'key contact' health professional, with whom the family will become familiar and comfortable, is essential to enable them to ask questions or express concerns whenever they wish, without having to wait for the next formal appointment.

The need to identify those affected, and ensure appropriate levels of care, as well as detecting trends in clinical problems, will be best served by maintaining a national register of patients. The UK Thalassaemia Society has previously funded a national register, which generated much very useful information, and it is hoped that funding will be identified to continue this valuable resource. Individual patient consent to be included is necessary.

3.4 Key Interventions

3.4.1 As soon as a diagnosis of thalassaemia is established, the family will be offered opportunities to discuss the condition and its implications, and the way in which they will be centrally involved in the care of their child. Written information should back up these discussions.

3.4.2 When desferrioxamine chelation treatment is to be started, families will be taught how to administer this in the home,

and guided and supervised until they are confident and comfortable undertaking it independently. This is best achieved by a specialist nurse repeatedly visiting the family at home.

3.4.3 The patient's primary care team should be offered information about the condition and advised about possible acute presentations and their significance. Clinics should consider sending sections of this document, for example section B.10 (acute clinical presentation in the treated patient) to their patients' general practices. The GP and primary care team are likely to become involved also in supporting the child and family to manage their condition.

3.4.4 Flow Charts for investigations, treatment changes and significant events (suggested formats are provided in Appendix A) should be maintained in the Clinic records, duplicated in the patient-held record if used, and sent to specialist Centre in time for the Annual Review visit (see later).

3.4.5 Letters should be exchanged between the Clinic and Centre, with copies to the GP, at least every 6 months, after each formal annual review visit and whenever there are changes in the patient's clinical condition or treatment plan

3.4.6 When a national register is re-established, Clinics should discuss entry onto it with their patients, and request consent.

A network for care

“There is a problem of being treated at a regional hospital where they very rarely see a thalassaemia patient and awareness is almost non-existent. One does feel isolated. It would be good if at least one doctor could take an interest in my condition!”

“My doctor is not a specialist in thalassaemia treatment and I sometimes feel he should know more.”

“My doctor could do more for me by ensuring he has contact with specialist units and consultants to compare treatments. He could be better informed.”

4.1 Aim

To provide a uniformly high standard of care, delivered by, or in collaboration with, a specialist thalassaemia multi-disciplinary team, while ensuring that patients receive their regular treatment conveniently and close to home.

There will be an emphasis on prevention of complications and early detection and management to reduce morbidity.

4.2 Standards

- All areas will be served by a clinical network incorporating local thalassaemia Clinics and one or more specialised thalassaemia Centres. In regions where sickle cell disorders are also prevalent, the Centres are likely to have additional commitments to these patients.
- Local procedures must be agreed to ensure that all patients have access to the specialist Centre, either for their regular care if living nearby, or for annual reviews and specific consultations if living more distantly.
- The network will need to be adequately commissioned, funded and staffed, with clear systems for information sharing, clinical governance, accountability and staff development.

4.3 Rationale

In areas where there are many patients, a Centre for thalassaemia care, with a specialist team and comprehensive services, is likely to be established already. However, where there are only a small number of patients attending

a local hospital, such specialist care is unlikely to be available. Excellent results for thalassaemia treatment have been reported from some large Centres in the UK (Porter and Davis 2002) but the majority of patients are not managed in such centres (Modell et al 2001) and survival in the UK as a whole has not improved to the extent expected (Modell et al 2000). For many years, some patients have travelled to distant centres of excellence from choice, on an ‘ad hoc’ basis. Formally linking all smaller Clinics with larger specialist Centres in a clinical network, and recommending shared care with individual patient review at the Centre at least once a year, should bring optimal specialist input to the care of all patients. At the same time, it will drive up quality and efficiency through consolidating teams for the most specialised procedures in tertiary Centres (Children’s NSF, Department of Health 2003). Clinical networks involving local clinics and specialised centres have a long and successful track record in managing childhood leukaemia and other childhood cancers, and have been successfully developed for management of other chronic conditions in childhood such as Cystic Fibrosis (Cystic Fibrosis Trust 2001).

4.4 Key Features

4.4.1 General Considerations

In many areas, an effective local health network has built up around patients and families with thalassaemia, with care delivered within the family, and by primary care, outreach services and local hospitals. Issues of

supporting the individual and family in self-care, are covered in the previous section.

This section outlines a proposed formal network of hospital providers, which can provide comprehensive care to appropriately high and specified standards: near the patient's home for frequent and routine care, and if necessary more distantly for highly specialised services and for regular expert clinical review.

Local Thalassaemia Clinics will offer regular treatment and monitoring, taking into account the specific needs and quality of life of the individual. Treatment should be given to children, adolescents and adults in such a way as to minimise the disturbance to normal everyday activities, such as schooling and work.

Specialist Centres will undertake the above role for their local population, but will have a larger team of experienced and specialised staff, under the leadership of a Paediatrician or Haematologist with a specialist interest in the field of thalassaemia. These arrangements will apply to sickle cell disease if the specialist Centre is designated for this role as well. Staff at the Centre will provide expert advice and guidance, and offer clinical consultations and specialist monitoring services which are not available to the patient locally. They will need access to more resources to fulfil their extended role.

As a guide, it is expected that a specialist Centre will manage at least 20 patients on a regular basis. This will allow staff to be sufficiently experienced also to undertake additional review of, and to offer advice to, patients coming at least annually from local Clinics. It is recognised that in many places, there may be fewer children or adults, but more than 20 in total. Where this is the case, staff can gain and maintain sufficient experience if the clinics are held by Paediatric and Haematology teams working together. This has additional benefits for families in terms of continuity of care and familiarity with staff when the time is reached for transfer from paediatrics to adult services.

Clinics where fewer patients receive their regular care should link with the nearest specialist Centre for all services they are unable to provide to the required levels.

In order to prevent patients travelling undue distances, in one or two geographical areas where a Centre has not naturally emerged, it may be necessary for one to be identified, and services there developed and staff recruited or trained specifically to undertake these roles.

4.4.2 Role of the local Clinic

The extent of services offered by local Clinics will vary, but it is expected that, as a minimum, they will be able to:

- provide regular transfusions and prescriptions for chelation and any other necessary therapy
- monitor growth, and general health and wellbeing
- organise some, or all of the regular assessment tests
- offer support to the patient and family.

4.4.3 Role of the specialist Centre.

A thalassaemia Centre (in addition to the above) should:

- offer consultation at specific key 'milestones' (at diagnosis, at initiation of regular transfusion, at initiation of regular chelation therapy, annual review, at transfer to adult clinic)
- lead discussions around complex management issues (alterations to chelation regime, problems with adherence to chelation, consideration of splenectomy and other major surgery, management of endocrine, bone/joint, cardiac, liver complications and fertility treatment, possible bone marrow transplantation, complex psychosocial issues)
- offer education and training for staff at local Clinics and the Centre
- audit performance and outcomes
- be involved in clinical research studies to further refine clinical care decisions

4.4.4 Staffing

Staffing recommendations are shown in Table 1. Key staff include one or more designated thalassaemia specialist doctors in each Centre, and a designated clinician in each local thalassaemia Clinic. In both Clinics and Centres, a 'Key Contact' (usually a nurse specialist) is required to help patients and families navigate their way around the system and support them in accessing the different services available. Both Clinics and Centres will have nursing staff working in an identified

treatment area who can cannulate and supervise transfusions. Staff will need the time, as well as the expertise, to undertake the care of these children. Precise staff numbers will depend on the number of patients being managed.

4.4.5 Facilities

Suitable facilities should be designated for out-patient consultation, phlebotomy and transfusions. Services should be offered at times to suit the families, and out of hours

provision should always be made for routine aspects of care. The out-patient consultation area, particularly in the Centre, should enable individual members of the multi-disciplinary team to conduct in-depth consultations with patients and families. Children's out-patient and treatment areas should be separate from the general in-patient ward, and designed with the needs of the child and family in mind, providing play therapy and facilities for education and school work supervision by a hospital teacher (Children's NSF 2003).

Table 1: Staffing recommendations

	Local Clinic	Specialist Centre	
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		✓	
Designated Paediatrician and / or Haematologist (depending on age spread of patients)	✓		
Named deputy for each	✓	✓	
Middle grade cover (SpR/Staff Grade) available out of hours	✓	✓	
Staff to cover the roles of:	1) Lead nurse for thalassaemia service: training, liaison, audit	✓	
	2) Regular nurse(s) in ward area who can cannulate and start/supervise transfusions on day care unit, and also during evenings, overnight and weekends	✓	✓
	3) Specialist nurse outreaching into community (responsible for home visits, teaching parents to set up desferrioxamine pump etc)		✓
	4) Key contact – could be any of above	✓	✓
	5) Identified deputy for key contact	✓	✓
Clinical psychologist with special interest, for paediatrics; Clinical psychologist for adults where available, Health psychologist if not.		✓	
Access to named Psychologist	✓		
Appropriate laboratory support (transfusion and other), diagnostic imaging	✓	✓	
Access to translation services	✓	✓	
Access to dental team		✓	
Access to Social Worker	✓	✓	
Access to Dietician	✓	✓	
Administrative support sufficient to ensure proper communication between patient and family/ clinic/centre/ GP	✓	✓	
Access to designated paediatric and adult Cardiologist		✓	
Access to designated paediatric and adult Endocrinologist		✓	
Access to designated paediatric and adult Hepatologist		✓	
Designated paediatric and adult Anaesthetist – to liaise between medical and anaesthetic/surgery teams		✓	
Access to designated contact in Genetics services		✓	
Access to fertility services and support from designated Obstetrician		✓	
Link with bone marrow transplant service		✓	

Section B

Core Management Standards

5

Initial management of the newly diagnosed infant

5.1 Aims

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

To ensure a good level of understanding and to minimise distress by communicating information and advice in a way which is appropriate to the culture and language of the family.

5.2 Standard

- 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 genotype.
- The child must be monitored closely to determine the likely clinical course.
- The family should be informed fully and sensitively from the outset, 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.

5.3 Rationale

Learning that their infant has a serious blood condition inevitably comes as a shock to the parents. It is expected that most parents will be aware of the risk of having an affected child through 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.

Infants born to at-risk couples should have a blood sample (cord or baby blood) tested in the neonatal period, and DNA diagnosis undertaken if there is concern about the results.

If the antenatal programme has not identified a couple to be at risk, so that the baby has not been specifically tested at birth, the National Newborn Screening Programme will now enable later diagnosis of most with homozygous β thalassaemia. In these cases parents can be made aware of the diagnosis during the first three months of life, before the infant develops severe anaemia. Some children may be diagnosed at a later stage, either because the condition was not diagnosed on newborn screening, or because they were not born in England. 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.

Parents will need to understand that it is not possible to predict the severity of the condition or the need for transfusions and chelation therapy from the outset, and 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 *Xmn1* C-> T polymorphism) (Ho et al 1998).

5.4 Key interventions

5.4.1 The diagnosis should be anticipated from antenatal screening, and established by prenatal diagnosis where requested or by neonatal testing at birth. If not, affected infants may be identified through the Newborn Screening programme. The baby and parents should be seen as soon as possible and preferably within two weeks. There should be no delay in referral because the child remains clinically well: important information is given, discussions take place and investigations should be instigated at this stage. If the diagnosis has not been made at these stages, and the presentation is a clinical one, then assessment may be urgent, within one to two days.

5.4.2 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. It is important to stress the initially unpredictable clinical course for any individual child, and the range of possible needs should be covered in discussion. The nurse can then accompany the family to the first hospital consultation soon after.

5.4.3 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)
- Genetic analysis for β thalassaemia mutations, α thalassaemia genotype and *Xmn1* C->T polymorphism

Family studies may be informative

The parents should also be tested if results are not available from prior screening

5.4.4 The initial clinic visit will usually be to the unit where most of the care will be provided, most often the local Clinic. Staff seeing the family may want to discuss details of the case with the Centre beforehand, and to set up an opportunity for the family to be seen at the Centre soon after (see below). 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. The arrangements for care should be discussed - wholly at the Centre if they live near, or based at the local Clinic if more convenient - and the plan for regular, at least annual, review at the Centre with additional contact whenever required should be explained.

5.4.5 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.

5.4.6 Appropriate written information should be made available¹. The family should additionally be given the contact details for the UK Thalassaemia Society and any local branches/support organisations.

5.4.7 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; it must not be forgotten or eclipsed by clinical concerns about the child. 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.

5.4.8 The parents should meet and exchange contact details with their local Key Contact staff member.

5.4.9 Arrangements should be made for the child and parents to visit the most convenient Specialist Centre as soon as possible (within six weeks), and before a red cell transfusion is given, unless transfusion is clinically urgent.

1. Suitable materials are available (without charge) from the APoGI – Accessible Publishing of Genetic Information – website at <http://www.chime.ucl.ac.uk/APoGI/>

5.4.10 After the visit a written summary, covering the discussion and follow up arrangements, should be exchanged between

local Clinic and Centre, and copies sent to the GP and the family.

Decision to start regular transfusions

6.1 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 (thalassaemia intermedia).

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.

6.2 Standard

- 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 sufficient clinical evidence of severe anaemia, failure to thrive, and/or thalassaemic bone deformity.
- Infants and children with a thalassaemia intermedia phenotype will be identified clinically and not subjected to regular transfusion inappropriately.

6.3 Rationale

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

(Loukopoulos D, Thalassaemia International Federation Conference, Palermo, October 2003)

The decision about when to start red cell transfusions in a child with homozygous 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 plainly

failing to thrive. A decision to treat cannot be made on haemoglobin level alone. 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 a clinician with specific experience in this area, after detailed evaluation of each child.

A decision to commence transfusion should be based on the presence of anaemia (usually below 7 g/dl) *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, evidence of bony expansion, 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, the decision to start regular transfusions should not be delayed until after the 3rd year, as the risk of developing multiple red cell antibodies increases, with subsequent difficulty in finding suitable units for transfusion.

Where transfusion is started 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 section 21).

6.4 Key interventions

6.4.1 After diagnosis, infants will be monitored regularly in the local Clinic and/or Centre. From the age of 4 months, these visits should be at least monthly, until the clinical phenotype is established.

6.4.2 Monitoring will include history of feeding difficulties, infections, ill health, developmental delay. Examination will include an assessment of bone expansion (including head circumference), growth curves, hepatosplenomegaly. Haemoglobin level should be checked at least monthly. (See chart for infant monitoring, Appendix A1)

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

6.4.4 Before the first transfusion, the investigations in Table 2 should be carried out. It is assumed that DNA studies have already been undertaken previously, at diagnosis, see B.5.4.3

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

Table 2: Investigations prior to first transfusion

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

Red cell transfusion

“When I go on the ward seeing the same nurses who know me is very reassuring.”

“The best thing about my hospital is that the environment is friendly and relaxed.”

“Staff should be well trained in cannulation and should realise that our veins are precious to us!”

“There is only one person at my hospital who can cannulate me and I dread him not being there.”

“Everything is great now I go to a special unit but when I had treatment on the wards it was a nightmare.”

“I sometimes have to wait 4 hours for my transfusion which is boring and frustrating.”

“Please open the unit on evenings/weekends!”

“I would like to have my transfusions at home.”

7.1 Aims

To ensure that children are transfused to an acceptable level to promote growth and well being.

To prevent complications of under-transfusion.

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

7.2 Standard

- Haemoglobin levels should be maintained above 9.5-10g/dl.
- Cannulation will be undertaken by an experienced nurse or doctor.
- Pre-arranged transfusions should be started promptly.
- Good transfusion practice must be observed
- Transfusions will be given on each occasion in a designated area with suitable facilities, experienced regular named nurses and familiar supervising medical team.

7.3 Rationale

Blood transfusions, given regularly every 2-4 weeks, enable normal growth and development in childhood. A haemoglobin level maintained above 9.5-10g/dl is

sufficient to inhibit bone marrow expansion and minimize transfusion iron loading (Cazzola et al 1995). The risks associated with regular transfusion include acute transfusion reactions, allo-immunisation to red cell antigens, transmission of viral infection and, in the long-term, iron overload. Serious reactions due to misidentification can be minimized by meticulous attention to protocol in transfusion practice (BCSH Guideline 1999, BCSH Guideline 2004). Viral infections from blood are now very uncommon in the UK; however, there is always a small risk of infection from units donated during the ‘window-period’ of infectivity: between contracting the infection and developing the detectable antibody, or from blood-borne pathogens not currently tested for by the Blood Services.

Provision of red cell units for transfusion dependent patients requires some special considerations. Efforts must be taken to minimise the likelihood of antibody production (alloimmunisation) in these patients. Alloimmunisation to red cells may delay the provision of blood and exposes the patients to the small additional risk of a haemolytic transfusion reaction. Transfusion red cells whose blood group profile or phenotype is matched to that of the recipient, in particular the Rh (D, C, c, E, e) and Kell (K) blood group antigens can substantially reduce

the likelihood of alloimmunisation. The patient's full phenotype should be determined before transfusions are given (see B.6.4.4). The selection of red cell units which have as large a volume of red cells as possible, and are not near the end of their shelf-life, may reduce the frequency of transfusion.

For the patient and the family, the organization and efficiency of administering transfusions has a major effect on quality of life. The process includes attending for a blood sample for pre-transfusion testing, usually two to three days before the transfusion, (BCSH Guideline 2004), and then attending for the transfusion, which usually takes 4-6 hours. For blood administration, an intravenous cannula must be inserted, and this can be difficult and traumatic, particularly if the veins are hard to find. Cannulation done inexpertly increases anxiety and distress, and can damage veins, so that future access is more difficult. It is imperative to preserve the veins carefully, since the patient is dependent on life-long venous access.

Where families are able to fit in regular hospital attendances conveniently around their other activities, quality of life and motivation to adhere to treatment is enhanced. A small number of families have, at their request, been trained to supervise transfusions at home and this has continued for 8 years without any problems. This has proved very popular and convenient for those who have chosen to undertake it (Madgwick and Yardumian 1999).

7.4 Key interventions

7.4.1 The patient should be reviewed prior to each transfusion by a specialist nurse or doctor, to determine pre-transfusion haemoglobin level, to ensure that the planned transfusion is appropriate, and to discuss any problems. In the early months of treatment,

the child and family should ideally be seen by the designated Paediatrician/Haematologist at every visit. Subsequently there should be a review with the designated clinician at least every 3 months in addition to the formal Annual Review visit at the specialist Centre.

7.4.2 Pre-transfusion haemoglobin level should be between 9.5 - 10 g/dl (**GRADE B**); transfusion interval is usually between 3 and 4 weeks.

7.4.3 Red cell units which are matched for Rh (D, C, c, E, e) and Kell (K) blood group antigens should be selected.

7.4.4 Large volume units should be chosen, preferably greater than 300 mls (for adults and children when one or more full unit is required), and wherever possible units should be less than 2 weeks old.

7.4.5 Transfusions should be given in a familiar clinical area by regular staff who are experienced in setting up and supervising transfusions. Nursing staff should be trained to site the iv cannula and set the transfusion up independently. No more than 3 attempts to site a cannula should be made by any one individual.

7.4.6 Facilities for out of hours provision are a key requirement, and become increasingly important for children of school age and beyond.

7.4.7 There should be a written transfusion policy, specifying 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. Adherence to the policy should be audited.

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

Iron load - Monitoring and Treatment

“The worst thing about my treatment is the [desferrioxamine] injections which are very painful. An alternative treatment would be fantastic.”

“I wish our hospital could provide me with ... (thumb-tack type) needles as many other patients find they make taking the desferrioxamine easier.”

“The home-delivered infusion pumps are fantastic!”

“The thing I would like to change about my treatment is coming off my pump and going onto an oral chelator. I have been using the pump since I was 9 years old, now I am 36...”

“I would rather have tablets than the pump; if there was one thing I could change about my treatment it would be not having to do the pump every night.”

“The most helpful thing my doctor does for me is find new forms of chelation therapy”

“I would love to have combination treatment but don't know if it is appropriate for me”

8.1 Aims

To monitor body iron stores accurately, minimize body iron accumulation in both transfusion-dependent and transfusion-independent patients, and prevent tissue damage and organ dysfunction.

In those already iron loaded, to reduce body iron load to safe levels as quickly as possible to prevent further organ damage.

To identify adverse side effects due to chelator toxicity and manage them promptly.

8.2 Standard

- Every transfusion-dependent child will start to receive iron chelation therapy with subcutaneous desferrioxamine infusions in time to prevent iron-related toxicity.
- Parents and patients should be made fully aware of the reasons for chelation therapy, and trained to administer it at home. They should be kept informed of developments with new chelator drugs and modes of delivery of chelators.
- Transfusion iron loading, body iron stores, adherence to chelation and evidence of chelator-related toxicity must be monitored carefully and systematically. Complications should be managed by

optimising chelation therapy according to a local protocol agreed between the local thalassaemia Clinic and specialist Centre.

- All patients and families should have access to support in the practical and psychological challenges that arise from the demands of daily chelation therapy.
- Problems with adherence will be carefully identified and addressed.

8.3 Rationale

Iron overload in thalassaemia major, if untreated, is usually fatal in the 2nd or 3rd decade of life. The majority of deaths occur because of iron related cardiomyopathy, presenting as cardiac arrhythmias and cardiac decompensation (Section B.14). Iron toxicity also causes hypothalamic and pituitary damage resulting in hypogonadotrophic hypogonadism, and less commonly growth hormone deficiency. These can result in short stature, delayed or absent puberty, and infertility. Other endocrine problems include glucose intolerance, diabetes mellitus, hypothyroidism, and hypoparathyroidism (Olivieri et al 1997) (Section B.15). Liver damage is a further complication (Section B.16). Iron chelation therapy with subcutaneous desferrioxamine infusions given 5-6 nights per week over 8-12 hours and

rigorously maintained, can prevent most of these complications (Olivieri et al 1994, Brittenham et al 1994). When tissue damage is already present, intensification of desferrioxamine treatment can reverse organ dysfunction. For instance, continuous intravenous desferrioxamine, given for several months or even years can reverse iron-induced cardiomyopathy (Davis and Porter 2000; Anderson 2004). However, the majority of endocrine complications, once established, are irreversible.

Adherence to chelation therapy is the major challenge now facing thalassaemic patients, their families and their carers. Adherence is enhanced in childhood when the parents understand the rationale for the therapy, and feel confident in setting up the desferrioxamine infusions safely and efficiently. Additionally, it is beneficial for long-term adherence if the child takes responsibility for the infusions at an early age. It is important to offer practical support to enhance adherence wherever possible. Disposable desferrioxamine infusers (Fielding and Wonke 1992; Araujo et al 1996), and fine 'thumb-tack' type sub-cutaneous needles can help. It is vital to offer psychological support in identifying and addressing problems faced by the patient and the family which may impede adherence.

The dose of desferrioxamine must be adjusted carefully in order to maximize efficacy, while avoiding adverse side effects. 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 desferrioxamine (>40mg/kg) and are more likely to occur when iron stores are low (De Virgilis et al 1988). High-tone sensorineural hearing loss is also seen under these conditions, and can be predicted by calculating average daily dose of desferrioxamine/serum Ferritin >0.025 [e.g. higher risk, at ferritin 1000 µg/l, if receiving more than average of 25 mg desferrioxamine/kg/day] (Porter et al 1989). Early identification of desferrioxamine toxicity, with annual checks of pure tone audiometry, and sitting and standing heights during childhood, have been recommended in recent expert guidelines (Cappellini et al 2000). Yersinia infection, which may present with

fever, diarrhoea and abdominal pains, is much commoner in iron loaded patients receiving desferrioxamine (Lesic et al 2002) and must be watched for.

Monitoring of iron stores is essential in order to make correct clinical decisions regarding chelation therapy. Issues include: when to start chelation, the indications for changing from the standard subcutaneous desferrioxamine regimen, and at what point to consider introducing alternative chelating agents. The assessment of body iron stores requires knowledge of the transfusion history, chelation and adherence history, and an assessment of iron related tissue damage (cardiomyopathy, endocrinopathies, liver damage etc). This assessment is supplemented by serial serum ferritin measurements. Although an imperfect tool, as it is an acute phase reactant and therefore quite frequently falsely elevated, persistently high levels (>2500µg/l) are associated with an increased risk of cardiac disease and death (Olivieri et al 1994), and a level of around 1000-1500 µg/l is generally recommended (Cappellini et al 2000). However, even where ferritin measurements are consistently low, cardiac problems can develop.

Direct measurement of liver iron, following needle or intra-operative wedge biopsy, provides an accurate measure of body iron stores (Angelucci et al 2000), however the method is invasive, iron deposition is patchy, and results show poor reproducibility, particularly if the biopsy is small or cirrhosis is present. Various MRI-based techniques are being developed and it is hoped that one or more of these will enable an accurate, non-invasive estimate of organ-specific iron loading. The T2* parameter appears to be sensitive to cardiac iron loading and may enable early detection of patients at risk from heart disease (Anderson et al 2001, and see Section 13). In this study, cardiac iron estimated by MRI did not correlate with liver biopsy iron level. A recently published R2 technique shows a high degree of sensitivity and specificity over a wide range of liver iron concentrations; it has received a CE mark for use in Europe (St Pierre et al 2005). It should be possible for these techniques to be used in many hospitals possessing an up-to date 1.5-T MRI scanner.

The oral iron chelating agent deferiprone, formerly known as L1, is now licensed in the

European Union, for adults and children over the age of 6 (although with 'limited data' concerning its use in children between the ages of 6 and 10) as a second line chelating agent in those who are intolerant of desferrioxamine, or where desferrioxamine therapy is inadequate. There is now substantial clinical experience with its use (Ceci et al 2002, Cohen et al 2000; Hoffbrand and Cohen 2003), and a randomised, controlled study has been published in which deferiprone was comparable with desferrioxamine as single chelator therapy over a period of one year (Maggio et al 2002). Long term studies show that liver iron is not adequately controlled by deferiprone monotherapy in a significant proportion of patients (Hoffbrand et al 1998, Olivieri et al 1998, Tondury et al 1998). On the other hand, there is also evidence that deferiprone may remove myocardial iron more effectively than desferrioxamine (Anderson et al 2002), and that patients taking deferiprone may have a survival benefit compared to those on desferrioxamine (Piga et al 2003). Deferiprone is easier to take, and in practice, adherence to therapy is much improved in those who have difficulties with desferrioxamine (Olivieri et al 1998). Those who find desferrioxamine infusions intolerable may have better long-term control of iron stores with deferiprone. Current practice in some Centres is to use deferiprone alone or in combination with desferrioxamine in patients with cardiac failure, or judged to be at high risk of cardiac problems because of iron overload. These judgements are usually made taking into account cardiac T2* MRI findings (See Section 13). The use of deferiprone in this setting is widely practiced, although opinion remains divided on the appropriate use of these regimes.

Adverse effects of deferiprone include agranulocytosis in 0.5-1%, arthropathy in 4-50% (the higher rates reported in series from the Indian sub-continent), nausea, and intermittent increases in transaminase levels. The reported finding that deferiprone was associated with increased liver fibrosis (Olivieri et al 1998) was not subsequently confirmed (Wanless et al 2000, Tondury et al 1998, Maggio et al 2002).

There is considerable interest, and increasing clinical experience, in the use of 'combination' chelation therapy with deferiprone and

desferrioxamine, simultaneously or sequentially. Wonke et al (1998) showed, in a small group of patients not adequately chelated with desferrioxamine alone, that this was feasible. Many centres have several years of experience with this approach, and are reporting beneficial results in reduction of serum ferritin (Wonke et al 1998, Balveer et al 2000, Mourad et al 2003), improvement in cardiac function (Wu et al 2004) and better adherence. Limited data are available on the effect on liver iron; benefit was found in one study (Aydinok et al 1999) but no benefit in another (Balveer et al 2000). However there are not yet many peer-reviewed publications on combination therapy. At least one prospective controlled study is currently underway. It is expected that additional information will become available within the next 12 months, which will be helpful in making recommendations on the optimal dosing schedule, and long-term side effect profile. In the interim, careful monitoring of patients on combined treatment is essential.

A new oral iron chelator, currently referred to as ICL670, has recently been developed and trialled (Nisbet-Brown et al 2003). It is taken at a once daily dosage, and chelated iron is excreted predominantly in the faeces. It is relatively free of side effects, though gastrointestinal disturbances, skin rashes and, at high doses, nephrotoxicity have been reported. Phase III studies, in which ICL670 was compared with desferrioxamine at standard dosage over the course of one year, were recently completed and will soon be reported. At doses of 20 and 30 mg/kg/day, liver iron levels in the two groups were controlled equally effectively. An application for drug registration has been sent.

Iron chelation therapy is currently an active area of clinical research. It is likely that important information will be published over the next twelve months which will significantly change the recommendations for optimal chelation for those with well controlled iron stores, and those at high risk of cardiac disease. In particular, our recommendations will need to be reviewed in the light of data from (1) prospective studies comparing cardiac T2* MRI outcomes in patients treated with deferiprone, desferrioxamine and with combinations of the two, (2) long-term survival studies in patients treated with deferiprone compared

with desferrioxamine, (3) the registration of the new oral iron chelator ICL670.

8.4 Key interventions

8.4.1 Children with transfusion-dependent thalassaemia should be started on subcutaneous desferrioxamine infusions after receiving 10-12 transfusions, or when the serum ferritin level is consistently greater than 1000 µg/l. The starting frequency should be 1-2 nights per week and increased over the first year of therapy to the standard dose in childhood of 20-40mg/kg over 10-12 hours on 5-6 nights per week (GRADE B).

8.4.2 The clinic doctor should be assisted by nurse specialist(s) and preferably a clinical psychologist in managing chelation therapy and ensuring adherence with chelation. All of those involved in the multi-disciplinary team should have an up-to-date knowledge of chelation therapy, and keep abreast of new developments.

8.4.3 Parents (and thalassaemic children when they reach an appropriate age) should be given a thorough explanation of the reason for chelation therapy, backed up with written information, and explanations need to be periodically repeated. They should be fully informed of the types of chelator drugs in use and in development, the routes of administration, and the justification for the particular regime being recommended.

8.4.4 Parents and patients should be carefully taught how to administer subcutaneous desferrioxamine infusions. The training and performance should be clearly documented in the patient's records. Their technique should be assessed regularly. Children should be encouraged to participate in setting up and administering the desferrioxamine infusions at an early age.

8.4.5 Means of facilitating the delivery of desferrioxamine ('thalaset' or other thumb-tack type needles; disposable, pre-filled infuser devices) improve adherence to therapy, and should be offered wherever possible (GRADE B).

8.4.6 Adherence to the chelation regime should be monitored and recorded at each transfusion visit, at the three monthly clinic visit and at the annual Thalassaemia Specialist Clinic Visit. Use of a treatment diary should be encouraged.

8.4.7 Psychosocial problems impacting on adherence to chelation should be sought at clinic visits, during the transfusion visit, and may be brought by the family to any members of the multi-disciplinary team (for example: play specialist, hospital school teacher, community nurse specialist, child psychologist, social worker). Problems identified in this way should be addressed from a multi-disciplinary approach, and a plan of management agreed upon with involvement of the child and parents/carers.

8.4.8 Iron stores, clinical evidence of tissue toxicity due to iron, and chelator-induced toxicity should be assessed regularly. Suggested monitoring tests are summarised in Appendix B (GRADE B).

8.4.9 If complications are detected which require an adjustment to the chelation regime, a clear management plan should be discussed and agreed between the patient and family, the local Clinic and the thalassaemia Centre, and clearly documented. This should be a central part of the three monthly local Clinic visits and the annual specialist Centre review visit.

8.4.10 Deferiprone therapy, and combination chelation therapy with desferrioxamine and deferiprone, should be restricted to patients who have evidence of high iron stores, and who are judged to be at high risk of iron-related tissue damage, after attempts have been made to optimise adherence with desferrioxamine. This treatment should be initiated only after consultation with the designated clinician in the specialist thalassaemia Centre (GRADE B).

8.4.11 Where there is continuing concern about the ability or intention of a patient to adhere to standard desferrioxamine therapy despite application of the above methods, patients should be offered alternative chelation options. Currently, these would comprise either continuous intravenous desferrioxamine via a central venous access device (Fielding and Wonke 1992), continuous subcutaneous desferrioxamine (Araujo et al 1996) or the oral chelating drug deferiprone, alone or in combination with desferrioxamine (GRADE B).

8.4.12 Deferiprone, either alone or in combination with desferrioxamine should be given according to a standard written protocol, agreed locally in the network. This

should specify the indications, dosing schedule, monitoring tests and management of side effects which might be encountered.

8.4.13 Patients should be monitored carefully for side effects of deferiprone, with frequent blood counts (weekly counts are recommended) to detect early signs of agranulocytosis. Patients should be aware of the side effects of deferiprone, and should understand that if they develop fever or symptoms of infection, they should stop the

medication and immediately attend for a blood count. They should carry a treatment card indicating they take deferiprone, contact details of their treating doctor, and what action should be taken if they seek medical advice after becoming unwell (**GRADE B**).

8.4.14 Physicians in thalassaemia Clinics and Centres should make every effort to update themselves regularly on evidence as it emerges concerning different chelation options.

9

Psycho-social issues

The most helpful thing my doctor does for me is...

"... listens to what I say and is honest with me"

"... explains everything well"

"... allows me to take decisions about my treatment"

"... gives me hope and fights for me"

"A psychologist or counsellor should be part of the regular team so that we feel comfortable to go and see them on their own should the need arise."

"All staff should attempt to make patients feel as normal as possible. Be truthful. Be realistic. But, above all, be hopeful and positive about the future. Talk in practical terms about when the person will be studying, working, having homes and families of their own"

9.1 Aims

To minimise the negative impact of thalassaemia on the emotional well-being of patients.

To promote the patient's capacity for social and psychological adaptation to the condition.

9.2 Standard

- The psycho-social needs of patients growing up with thalassaemia must be considered alongside every aspect of their clinical care. This is a key role for all professionals managing the child, to be considered in each communication with the child and family.
- Core staffing of specialist thalassaemia Centres should include a Clinical Psychologist.

9.3 Rationale

It is recognised that growing up with a chronic medical condition presents significant challenges to children in accomplishing developmental tasks (Eiser 1993). Provision of psycho-social care to children should be therefore be proactive rather than reactive. It is known that a number of psychosocial factors influence patient adherence. Particular difficulties with adherence can emerge at adolescence and may require specific attention (Kyngas, et al 2000). Clinicians may

also have to consider possible cultural influences on adherence, particularly where social roles are impeded by a treatment regime (Joshi 1998).

Many patients acknowledge that the way in which their regular doctors and nurses approach them, and the messages and expectations they convey in every clinical interaction, are centrally important to the way in which they think about themselves and their illness. The psychosocial wellbeing of the individual is a concern for the whole team.

9.4 Key interventions

9.4.1 Equitable access to psychology services. Patients should have the opportunity to self-refer to the psychologist. Where there are several people with thalassaemia in the same family, patients should not be required to use the same psychologist. It may also be inappropriate for parents and child to be seen by the same psychologist (particularly in the case of adolescents).

All staff working in the area should have access to training in working cross-culturally and with interpreters. They should be aware of the variety of cultural influences on health beliefs (Helman 2002).

9.4.2 Providing information. Information should be given in a variety of formats, including verbal and written. Information may need to be provided in alternative format in the family's first language; this is not yet

available for many. Information given verbally should be documented. Information should be given to children and young people at repeated points during the course of the condition, at an age appropriate level. It may also have to be given at repeated points to adult patients: particularly in the light of changes in treatment or course of the condition.

9.4.3 Child development. Regular multi-disciplinary reviews of all children, should take place, to include the Clinical Psychologist, and social worker if appropriate. Reviews should take place at defined 'milestones', and after important medical or social events

Reviews should include consideration of all aspects of the child's psychological and social development, including relationships with parents, peers and siblings, schooling issues, self esteem, identity, coping skills as well as attitude towards growing up with thalassaemia. Outcome of reviews should be documented. Where psychological or developmental problems are suspected, children/parents should be referred to clinical psychology for assessment and treatment as appropriate. Where serious psychological difficulty or psychiatric disturbance is identified, referral to specialist (tertiary) child or adult mental health services should be considered.

9.4.4 Adherence to medical regime and self-management. Information should be given to parents/patients on the options for treatment including the relative benefits or disadvantages of each option. This should include information on potential consequences of non-adherence to agreed medical treatment. Patients should be involved in decisions about treatment regimes

(e.g. frequency/days off). Prescribed treatments should take into account, as far as possible, the social constraints imposed by treatment, and should incorporate some flexibility to accommodate these. All changes in treatment should be discussed with the parents/patients, and the reasons for changes made clear. Parents/patients should be involved in monitoring their progress (e.g. ferritin levels) and understanding may be enhanced if results are entered into a hand-held record. They should have the opportunity to discuss difficulties with adherence in confidence with a psychologist.

9.4.5 Supporting patients in adapting to loss and mobilising coping. Staff should be trained and supported in breaking bad news. The patient's support networks should be included where appropriate. Staff breaking bad news should remain aware of the significant impact of this on patients, and should be prepared for the range of emotional responses that may accompany this, for example anger, denial, distress. Staff should be prepared to offer support in both accepting losses associated with the bad news and in fostering realistic hope. Giving false promises should be avoided. Where appropriate, referral to the psychologist should be considered. Staff should remain alert to the possibility of depression in response to bad news, and the impact of this on motivation to adhere to medical regimes.

9.4.6 Child protection. Issues of child protection may arise in regard to a family's management of the child and his or her condition. If this is a possibility, staff should promptly seek guidance by referring to their local child protection policy or guidelines, and discussing with the lead Paediatrician for child protection.

10

Acute clinical presentation in the treated patient

10.1 Aims

To ensure that patients with thalassaemia who become acutely ill have rapid assessment and treatment, bearing in mind the range of serious complications with which they can present.

To optimise outcome after onset of a new clinical problem.

10.2 Standard

- Individual presenting to their primary care professionals, or a hospital A&E Department or clinic, with new symptoms and/or signs will be rapidly assessed by staff aware of the various acute complications which can occur in this condition.
- If staff with appropriate knowledge and experience are not available, there must be urgent consultation with members of the specialist team on site or at the Centre, and referral on after stabilisation, as necessary.
- Appropriate management should be instituted as quickly as possible.
- GPs of patients with thalassaemia should be aware of the range of acute complications they can encounter.

10.3 Rationale

Most of the management of people with thalassaemia can take place in out-patients clinics and day care. Occasionally, however, patients present unexpectedly to their GP, clinic, or the A&E Department of their usual or any other hospital. When they do so they may be seriously ill and need prompt assessment and management, often requiring hospital admission. Assessment can be facilitated by patients carrying health records listing their diagnoses, recognised complications and recent investigation results.

While acute problems can include the same range of pathology as for any other individual, other clinical presentations occur more frequently or are of greater risk in this group and should be particularly watched for.

Awareness of these, some of which are not common in a general population, will allow prompt intervention which may help towards successful outcome. General Practitioners and smaller hospital Clinics, with fewer thalassaemia patients, should contact the nearest specialist Centre if there is any concern about a patient with thalassaemia who presents acutely, or in whom the diagnosis is potentially serious or not immediately obvious.

10.4 Key interventions

Front line staff should be aware of the following possible presentations and their management.

10.4.1 Fever and infection. Splenectomised patients should have had appropriate extra immunisation against pneumococcus, and have available oral penicillin V (BCSH guidelines, Davies et al 2002). Bacterial infection is a major source of morbidity and mortality, with deaths from infection outnumbering those from iron overload for the first time in the years 2000 - 2004 (data from the UK Thalassaemia Register). Despite splenectomy, and perhaps because of successful pneumococcal prophylaxis, a majority of bacteraemias are now with gram negative organisms: Klebsiella, E Coli, sometimes salmonella species (Li et al 2001; Wanachiwanawin W 2000; Ghosh et al 2000; UK Thalassaemia Register circular 2004). Presentation is with high fever, and sometimes associated circulatory collapse, there may be evidence of pneumonia, biliary tract infection, meningitis or cerebral abscess. A high index of suspicion, and prompt treatment with broad spectrum antibiotics such as intravenous gentamicin and piptazobactam before waiting for results of blood cultures, may reduce an otherwise high mortality risk. Where individuals have central venous catheters there is added risk of gram positive organisms, particularly Staphylococcus epidermidis; in such cases vancomycin or teicoplanin should be considered.

Yersinia enterocolitica causes infection in this patient group far in excess of others, as it thrives in high iron conditions (Cherchi et al 1995). It can cause localised infection in the tonsil or bowel, or can cause septicaemia. There is usually high fever and abdominal pain, sometimes vomiting and diarrhoea. It can be mistaken for appendicitis or other acute surgical abdomen. The organism can be cultured from blood or stool specimens. If it is suspected, all chelation treatment should be stopped until the infection is treated, or – if not confirmed – until abdominal symptoms resolve. Treatment for *Yersinia* is usually with ciprofloxacin - usually intravenously at first; Septrin and augmentin are also reported to be effective. Antibiotic treatment should be commenced on clinical suspicion of *Yersinia* infection, in a chelated patient with fever and abdominal pain, pending a diagnosis.

Uncommonly, other specific transfusion transmitted infections such as hepatitis B (although not likely in vaccinated individuals), hepatitis C or rarely HIV cause the patient to present acutely and should be borne in mind.

10.4.2 Abdominal pain and/or jaundice may be caused by infection, but cholelithiasis is common and biliary colic or obstruction, with or without infection, should also be considered.

10.4.3 Cardiac problems. Sudden onset of dysrhythmias or decompensation of ventricular function with fulminant heart failure can cause acute presentation. The latter can present atypically, e.g. with abdominal swelling and pain from hepatic enlargement and ascites. Clinical assessment, ECG, CXR, and echocardiogram, should allow a diagnosis. Treatment will include diuretics and ACE inhibitors +/- inotropes, and intensive iron chelation (see section B.14). These problems can be critical. Advice of the designated Centre Cardiologist should be sought urgently. Even if symptoms, such as palpitations or breathlessness, have resolved, hospital admission should be encouraged for urgent cardiological review as there may be a life threatening intermittent dysrhythmia.

10.4.4 Endocrine problems should have been recognised by routine clinic screening and treated before becoming symptomatic, but occasionally cause acute presentations. Diabetic patients may present with hypo- or

hyperglycaemia. Unrecognised hypothyroidism is a rare problem in a well-monitored patient. More likely is an acute presentation of hypoparathyroidism, with perioral or peripheral tingling or numbness or tetany.

10.4.5 Those who have hepatitis due to viral infection, usually complicated by iron overload, may rarely present with decompensated liver failure and hepatic coma.

10.4.6 For most presentations, desferrioxamine treatment should be continued. The exception is suspected *Yersinia Enterocolitica* infection, where it must be stopped and not restarted until the infection is fully resolved.

10.4.7 When acutely unwell, patients may not tolerate any degree of anaemia and should be transfused to a haemoglobin of >12 g/dl. Transfusion should be preceded by contact with the laboratory usually responsible for issuing units for the individual, in order to check for any specific requirements such as need for antigen negative blood in cases where there has been a previously identified antibody, which may no longer be detectable.

10.4.8 Recommended assessment for the acutely presenting patient should include the following (those starred * depending on clinical presentation):

- FBC, group and antibody screen, direct antiglobulin test, U+E, LFT, Calcium and Phosphate, Glucose, thyroid function.
- Blood cultures, urine culture, culture of stool*, CSF*
- ECG
- CXR*
- Echocardiogram*
- Ultrasound of abdomen*

10.4.9 Accident and emergency staff must contact the patient's own usual specialist team (Paediatrics and/or Haematology) - whether at the same or a different hospital - as soon as possible. This is facilitated where the patient carries some health records including key contact numbers. Even if the patient is not admitted, a copy of the A&E note should be sent to that team as soon as possible to alert them to the problem, and allow appropriate prompt follow-up.

11

Referral for consideration of Bone Marrow Transplantation

11.1 Aims

To ensure that children and families can make properly informed choices about bone marrow transplantation as a treatment option for them.

11.2 Standard

- All families who have a child with a serious thalassaemia syndrome will be offered the opportunity to discuss bone marrow transplant as a treatment option at an early stage, usually around the age of 12 – 18 months.
- Referral does not depend upon the family having an available donor at the time, and discussions may inform the family's subsequent decisions on family size.
- The discussion must be with a transplant team with specific experience in transplanting for thalassaemia.

11.3 Rationale

Bone Marrow Transplantation (BMT) from HLA identical family donors is an established alternative treatment option for children with thalassaemia, and the only one which can result in cure. Results in recent years have improved with advances in supportive care and better understanding of the risks of graft rejection and graft versus host disease.

Several factors impact on the outcomes, including the adequacy of earlier chelation therapy, and the presence of liver disease as reflected by presence of hepatomegaly, and fibrosis on liver biopsy (Lucarelli and Clift 1999). Liver disease significantly worsens outcome. In a patient with no adverse risk factors (Lucarelli Class I) probability of survival and disease free survival are 93% and 91% respectively, with a transplant related mortality of 7%. If all three risk factors are present (Lucarelli Class III) survival and disease free survival fall to 79% and 58% respectively with a 10% risk of death during the procedure. The risk of transplant is least between 18 months - 3 years of age. UK

results are broadly in keeping with this data (Lawson et al 2003). The monitoring of uptake and success of this therapy can most easily be achieved by analysis of the existing UKCCSG BMT database; all UK transplant units provide detailed data which is regularly analysed and updated.

It is possible to tissue-type on a chorionic villus sample (CVS), and some children have been transplanted from an unaffected, matched sibling donor typed on a sample taken for prenatal diagnosis.

Umbilical cord cells from a younger sibling can act as a source of stem cells for transplantation. The results of using cord cells alone as a source of stem cells were initially variable, with slower engraftment and higher rejection risks, but there are increasing numbers of successful transplants reported (Locatelli F et al 2003), and there is reduced risk of graft versus host disease compared to bone marrow or peripheral blood stem cell transplants. Unrelated umbilical cord haematopoietic cell transplants have also proved feasible (Tan et al 2004).

11.4 Key interventions

11.4.1 Bone marrow transplants, using marrow or cord stem cells, should be performed only in centres specifically experienced in transplants for thalassaemia.

11.4.2 Referral to such a centre should be encouraged for families of all children with thalassaemia major around the age of 12 – 18 months. It is paramount in all discussions of this treatment option to stress the usually excellent results of conventional transfusion and chelation therapy.

11.4.3 If the mother of a child with thalassaemia becomes pregnant, referral to the specialist transplant centre should be made for discussion of possible cord blood stem cell harvesting as a source for donor material for the affected child. If not already tested, the HLA type of the affected child should be established.

11.4.4 If she is undergoing pre-natal diagnosis for thalassaemia, fetal HLA typing can be undertaken on the same sample. As long as the fetus does not also have homozygous β thalassaemia, cord cells should then be harvested if matched, and stored for potential transplant later.

11.4.5 In the absence of CVS typing, in a family with an affected child all potential sibling donor cord material should be collected using the existing National Blood Authority service, tissue-typed and stored if matched.

11.4.6 Follow up after transplant of the patient should be agreed between the bone

marrow transplant centre and referring unit. Issues such as the presence of mixed chimerism and post transplant iron removal need special consideration. Most transplant centres have the facility for long-term post-transplant follow up of patients, when routine haematology care is no longer required, to monitor fertility, endocrine, cardiac and pulmonary complications.

11.4.7 It is important for transplanted individuals to be counselled that, when trying to conceive, they will pass a thalassaemic β gene to their children, and partner testing for haemoglobin disorder is essential.

12

Surgery, including splenectomy

12.1 Aim

To ensure that surgical procedures are undertaken with minimal risk to the patient.

12.2 Standard

- Surgical procedures requiring general anaesthetic should be undertaken at, or after consultation with, the thalassaemia specialist Centre.
- Patients should be carefully assessed pre-operatively with special reference to cardiac, endocrine and metabolic disturbances which may require correction. A designated paediatric or adult anaesthetist should be involved in managing the patient.

12.3 Rationale

Surgical procedures are often needed in thalassaemic patients. Splenectomy was often performed in the past in thalassaemia major patients with hypersplenism or with high blood requirements. Transfusion requirements could be significantly decreased by splenectomy if requirements were more than 200-220 ml red cells/kg/year assuming haematocrit of packed cells 75% (Rebulla and Modell 1991). This equates to 250-275 ml/kg/year of SAG-M, Buffy Coat Depleted Red Cells with a haematocrit of about 60%, currently supplied by the UK Blood Transfusion Service. However, splenectomy is less commonly required nowadays in thalassaemia major children who have been transfused appropriately since early childhood. The risks of splenectomy include post-splenectomy sepsis, and guidelines exist for infection prophylaxis (Davies et al, BCSH guidelines 2002). Thrombocytosis and thrombotic complications can occur post-operatively, particularly in thalassaemia intermedia patients who are not regularly transfused.

Symptomatic gallstone disease is relatively common in thalassaemia major and intermedia, and cholecystectomy can often be done laparoscopically. Another common

procedure in adult patients is hip replacement, which may be required for severe arthritis or fracture.

Acute presentations may include appendicitis, cholecystitis and fractures, particularly of the hip. *Yersinia enterocolitica* infection can mimic acute appendicitis, and it is extremely important to consider this diagnosis before undertaking unnecessary appendicectomy.

Any patient undergoing laparotomy should be considered for intra-operative open wedge biopsy of the liver. It is important not to miss this opportunity to stage liver disease and to assess body iron stores safely. Patients with thalassaemia major and intermedia are at increased risk of thrombosis, therefore peri-operative thromboprophylaxis should generally be given to cover major procedures.

12.4 Key interventions

12.4.1 An anaesthetist with special responsibility for thalassaemic patients children, and another for adults should be identified at each thalassaemia specialist Centre.

12.4.2 Planned surgical procedures should be managed through collaboration between the local Clinic, the specialist Centre, the surgeon undertaking the procedure and the designated Anaesthetist.

12.4.3 Preparation for planned procedures should generally include a period of optimal chelation therapy, and a detailed cardiac assessment. Patients should also have a dental check. Endocrine or metabolic disturbance should be excluded or corrected, with particular attention to management of hypocalcaemia, diabetes, and hypothyroidism.

12.4.4 A plan for peri-operative thromboprophylaxis should be discussed and decisions documented prior to the procedure.

12.4.5 Surgery in thalassaemia major patients should be undertaken with optimal haemoglobin level (10-12 g/dl). In patients with thalassaemia intermedia, consideration should be given to a period of regular

transfusion of several months before and after certain types of surgery, for example joint replacement, in order to suppress bone marrow and extra-medullary haematopoietic activity.

12.4.6 For all patients, the annual total volume (ml) of transfused red cells required should be recorded, to enable calculation of the average ml/kg received during the year. If high (see above) then splenectomy should be considered and discussed (**GRADE B**).

12.4.7 Patients undergoing splenectomy should be informed about the risks of post-splenectomy sepsis and should receive the following vaccinations several weeks prior to the procedure (if not previously vaccinated): pneumococcal vaccine, HiB conjugate

vaccine, Meningitis C conjugate vaccine.

Pneumococcal vaccination requires lifelong booster doses. Asplenic patients should be advised to take long-term antibiotic prophylaxis, as per BCSH Guidelines (Davies et al 2002), and should carry a 'splenectomy card' if locally used. Thromboprophylaxis should be considered for those with persistently elevated platelet counts (**GRADE B**).

12.4.8 Patients undergoing laparotomy for any reason may benefit from the additional procedures of open liver biopsy (for chemical iron estimation and histopathology), and cholecystectomy. Ultrasound examination should be done pre-operatively to identify gall stone disease.

13

Transition from paediatric care and management of adults

13.1 Aims

To ensure continuity of care and minimise disruption and anxiety as a child makes the necessary transfer from paediatric to adult services.

To identify and address psychosocial problems, and declining adherence to iron chelation and other therapy which may develop during adolescence and early adult life.

To ensure that optimal clinical care continues throughout adult life.

13.2 Standard

- Transfer from paediatric to adult care must be planned in advance for each individual, and timed to take into account his or her level of physical and psychological development.
- The young person will be familiar with the staff and facilities of the adult clinic prior to transfer.
- In adults, active vigilance is required for development of clinical complications, so that appropriate management can be instituted.

13.3 Rationale

The transfer of young people from child to adult services requires special attention, as described in the Children's NDSF. Evidence shows that it is generally poorly handled and that this increases the risk of deteriorating adherence to regular treatment (Anionwu and Atkin 2001). There is some evidence in chronic conditions that properly planned transition programmes result in better disease control and improved patient satisfaction.

The risks are especially high in young people with thalassaemia. Adolescents begin to challenge the need to continue the painful and disruptive routine of desferrioxamine infusions imposed on them by parents, doctors and nurses, and stop adhering as an expression of independence or rebellion.

They may become more aware of the physical changes caused by thalassaemia and its treatment, and may be distressed at failure of pubertal development. Change of treatment routines at this vulnerable time needs to be sensitively handled.

Iron-related and other transfusion-related complications become increasingly common into adult life, especially if earlier management has not always been optimal. The emphasis of care increasingly focuses on early detection and treatment of emerging complications.

13.4 Key interventions

13.4.1 Transition should be planned well in advance of actual hand over of care with a written transition care plan developed in collaboration between adult and children's services.

13.4.2 Timing of transfer should be based on a flexible approach that takes developmental readiness into account, and links to other social transitions such as leaving school. It should also be based on the assessment of patient's knowledge of thalassaemia and treatment, and take into account concerns that the young person or family may have about the move to taking on adult responsibilities.

13.4.3 It is very important for the teenager and family to be taken by a familiar staff member, preferably their paediatric key contact, to visit the adult outpatient and day treatment areas, and introduced to the team there, before the first time they attend.

13.4.4 Preferably, some key staff will be involved in managing both children and adults. If the designated Haematologist works in both the children's and adult clinic, this will greatly enhance continuity. Otherwise, where practicable the Paediatrician should make arrangements to be in the clinic with the Haematologist on the first one or two occasions, and/or other key contacts from paediatrics should attend.

13.4.5 The administrative handling of the transfer should be planned in advance, to include transfer of medical, social care and other relevant records, and provision of summaries, including a patient's handheld summary if used locally. In particular, the first appointments in the adult clinic and treatment area should be organised such that the

individual is immediately made to feel welcomed and included.

13.4.6 In caring for adults, additional attention needs to be focussed on early detection and management of systemic complications. These are the subject of Section C.

Section C

Prevention and Management of Complications

14

Cardiac complications

14.1 Aims

To minimise cardiac morbidity and mortality by optimal iron chelation from childhood and regular monitoring for cardiac dysfunction.

To institute effective treatment according to best current practice.

14.2 Standard

- A paediatric and an adult Cardiologist with responsibility for care of thalassaemics must be designated for each thalassaemia specialist Centre.
- All patients will have a cardiological assessment at least once per year from age 10.
- Symptoms or signs suggestive of cardiac disturbance should be investigated and managed urgently.
- Local protocols for monitoring and treatment will be developed based on best current practice.

14.3 Rationale

Cardiac disease remains the commonest cause of death in thalassaemia (Zurlo et al 1989, Borgna-Pignatti et al 2004). Effective iron chelation with desferrioxamine can reduce the risk of cardiac disease and improve survival (Modell and Berdoukas 1984; Olivieri et al 1994, Brittenham et al 1994). Patients who are poorly compliant with desferrioxamine and whose serum ferritin levels are generally above 2500 µg/l are more likely to develop cardiac problems, but ferritin level is not a sufficiently sensitive predictor of sub-clinical cardiac disease. Cardiac arrhythmias, cardiac failure and sudden death can occur abruptly in a previously well patient, and this outcome is not restricted to those with ferritin levels

above 2500 µg/l. Deaths from cardiac disease can occur before the age of 15, but have been most commonly seen in the age range 15-30 in patients born between 1960 and 1980 (Borgna-Pignatti et al 2004)

Various techniques have been used to detect pre-symptomatic cardiac disease. These include echocardiography with tissue Doppler imaging (TDI) (Vogel et al 2003), MUGA scanning (Porter et al 2004), and more recently cardiac T2* MRI. This latter technique is currently being evaluated as a tool for quantitating cardiac iron loading and assessing myocardial function. Cardiac T2* levels less than 20 milliseconds correlate with left ventricular dysfunction (Anderson et al 2001), and the majority of patients with symptomatic heart disease have T2* levels below 8 milliseconds (Pennell D, personal communication). In patients treated with intensive desferrioxamine regimes, sequential improvements in ventricular function are paralleled by increasing cardiac T2* values (Anderson et al 2004). Biopsy and autopsy studies are currently underway in order to make a direct calibration of cardiac iron level with Cardiac T2* values. The reproducibility of this technique has been excellent in the centre where the methodology was developed (Anderson et al 2001), and it seems likely that it is reproducible between different scanners in different centres, provided that identical software and set-up are used, so that regional centres will soon be able to offer scans locally. Results of these scans are already being used in some clinics for making treatment decisions, and some clinicians have commented that patients can be better motivated to adhere to chelation therapy by direct visualization of their own T2* scans.

It is likely that a combination of methods will be advantageous in risk stratifying individuals. MRI T2* should ideally be performed in every patient during their teenage years as this is when the risk of cardiac disease begins to increase. Detailed functional assessment by digital echocardiography (or MUGA where readily available) can be used for annual or biannual follow up. ECG and Holter ECG are valuable to investigate specific symptoms, but are poor as screening tools for risk. The ideal timing of investigation and repetition frequency is yet to be firmly established, though MRI every 2-5 years for high T2* patients and 6 monthly to yearly for low T2* groups with 6 monthly to yearly echocardiography could be justified.

Patients presenting with heart failure require specialist cardiac management, together with urgent intensification of chelation therapy. The prognosis in patients with symptomatic heart failure is usually considered to be poor, but good results have been achieved using continuous intravenous desferrioxamine delivered via an in-dwelling intravenous line (Davis and Porter 2000, Anderson 2004). There is evidence that deferiprone may remove myocardial iron more effectively than desferrioxamine (Anderson et al 2002), and that patients taking deferiprone may have a survival benefit compared to those on desferrioxamine (Piga et al 2003).

Two treatment approaches have been used in patients with, or at significant risk of, heart disease. The conventional approach, supported by several reports in the literature, is to deliver continuous iv desferrioxamine at about 50mg/kg/day through a central venous access device (Davis and Porter 2000). Alternatively, some are now using deferiprone therapy at 75mg/kg per day together with desferrioxamine 30-50 mg/kg over 12-14 hours 2-6 times per week. The desferrioxamine dose should be higher and treatment more frequent if there is evidence of high total body iron load, with serum ferritin >1500 µg/l and liver iron concentration >7mg/g dry weight (chemical analysis or MRI estimate). The decision to use deferiprone is usually based on clinical features, an assessment of the patient's ability to comply with intensified desferrioxamine compared with an oral agent, and cardiac MRI findings. Deferiprone might be particularly appropriate in patients with a low T2* level

(<8milliseconds). These decisions should be taken by the Centre Physician in conjunction with the Cardiologist.

Further clinical studies are required to clarify the natural history, risk factors, optimal monitoring and treatment of thalassaemia-related heart disease. Prospective randomised studies are currently underway to study the role of cardiac MRI, the relative efficacy of desferrioxamine and deferiprone in chelating myocardial iron, and the optimal chelation strategy for patients with cardiac dysfunction. This is a rapidly evolving area and recommendations are likely to be refined in the next two or three years.

14.4 Key interventions

14.4.1 A designated paediatric and adult cardiologist should be identified for each thalassaemia specialist Centre. Cardiac monitoring for children under the age of 15 should be supervised by a paediatric cardiologist, and transfer to adult cardiac care should be carefully co-ordinated.

14.4.2 Local and national protocols for monitoring cardiac function and treating cardiac complications should be developed based on best available evidence.

14.4.3 Every patient should have a clinical examination of the cardiovascular system at least 6 monthly. They should also have a formal Cardiology assessment, to include cardiac imaging and functional assessment, every year from age 10, or more frequently if chelation adherence has been erratic or there are high iron levels.

14.4.4 Any symptoms or signs suggestive of cardiac disease should be addressed immediately. Urgent referral to the Centre Cardiologist should be made, and if cardiac disease is thought likely, chelation therapy should be intensified. The findings, implications for prognosis, and treatment plan must be discussed in detail with the patient and the family. Adherence will only be successful if the patient has been fully involved in any decisions reached. Support from the psychologist may be helpful in exploring treatment adherence issues.

14.4.5 In the absence of prospective, randomised data, it is difficult to provide recommendations for those with cardiac disease, and/or abnormal cardiac MRI

findings. We suggest that patients with clinical evidence of heart failure and/or, arrhythmias (where no other cause is found), or suspected to have substantial myocardial iron loading (cardiac T2* <8 milliseconds), should be offered the options of intensified chelation either with continuous iv desferrioxamine given at 50mg/kg/day via a port-a-cath (Grade B) or alternatively with deferiprone at 75mg/kg/day together with desferrioxamine 30-50mg/kg over at least 10 hours 2-5 days per week. These patients should be monitored frequently by the designated Cardiologist, and the MRI scan repeated after 6 months of therapy. If the cardiac T2* is between 8 and

20 milliseconds, and there are abnormalities of systolic or diastolic function on MRI and/or echocardiograph, chelation therapy should be intensified or modified. Options would include increasing the dose frequency and duration of desferrioxamine infusions, switching to deferiprone monotherapy (if total body iron stores are low), or a combination chelation therapy regime as detailed above. If cardiac T2* is between 8 and 20 milliseconds and cardiac function is normal as assessed by MRI and echocardiograph, intervention is not necessary. MRI and echocardiography should be repeated in 6-12 months.

Endocrine complications

15.1 Aims

To ensure optimal growth, normal pubertal development and fertility.

To prevent thalassaemia-related diabetes, thyroid and parathyroid disturbance.

To detect and treat endocrine disturbance promptly and effectively.

15.2 Standard

- A paediatric and an adult Endocrinologist will be designated for each specialist Centre.
- Children should be monitored regularly and systematically for growth and development, from diagnosis up until the time when they have achieved full sexual maturity and final adult height.
- Deviations from expected pattern should be investigated and managed promptly. Children who are found to be growth hormone deficient should receive replacement therapy.
- Patients from age 10 should be checked annually for biochemical evidence of glucose intolerance, and from age 12 for hypothyroidism and hypoparathyroidism, and deficiencies treated appropriately.

15.3 Rationale

Endocrine deficiencies are common, potentially avoidable complications in thalassaemia. The commonest complications reported in a large Italian clinic are secondary amenorrhoea (50%), hypogonadotropic hypogonadism (43%) and short stature (34%) (De Sanctis 2002). Iron toxicity is the most likely cause of these disorders, and may be responsible for pituitary damage even in well-chelated patients. However, it is important to consider other factors which may be contributing to a complex aetiology. For instance, desferrioxamine toxicity has been shown to cause vertebral dysplasia and truncal shortening in children given inappropriately high doses (De Virgili et al 1988).

Once endocrine failure is established, it is generally irreversible. Short stature becomes 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. It is not clear whether children who are well treated from early childhood can avoid this complication (De Sanctis 2002). However, there is good evidence that iron chelation therapy with desferrioxamine, when begun before the age of 10, significantly enhances the probability of attaining normal sexual development (Bronspiegel-Weintrop et al 1990). There can be considerable problems assessing growth and growth velocity in some ethnic groups, because of the lack of standardised normal data relating to individual groups.

Delayed puberty and hypogonadism are the most common endocrinological findings in iron overload. Delayed puberty is defined as the complete lack of pubertal development in girls by the age of 13, and in boys by the age of 14. Hypogonadism is defined in girls by the absence of breast development by the age of 16, and in boys by the absence of testicular enlargement (<4ml) by the age of 16 (De Sanctis 1995). 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 cases need to be assessed, treated and monitored by a specialist Endocrinologist (Cappellini et al 2000).

In adolescence and adulthood, further endocrine complications may be seen. The most common complications reported in an Italian clinic were diabetes mellitus (18.8%), hypothyroidism (9%) and hypoparathyroidism (5%) (De Sanctis et al 2002).

These disorders require precise diagnosis, and appropriate endocrine replacement therapy. Investigations and management in this complex and specialised area must be

undertaken by an Endocrinologist with a special interest in thalassaemic problems.

15.4 Key interventions

15.4.1 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.

15.4.2 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).

15.4.3 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.

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

15.4.5 Delayed puberty should be fully investigated. Adolescents with evidence of hypogonadism should be treated with hormone replacement therapy, usually by 16 years, under guidance from the paediatric Endocrinologist.

15.4.6 Surveillance needs to continue into adult life too for patients who have no pubertal problems in their teens, in case of secondary gonadal failure, impotence or infertility.

15.4.7 Glucose intolerance should be watched for, with random glucose levels every 3-6 months, and oral glucose tolerance tests annually from puberty or from age 10 if there is a positive family history. Calcium and phosphate levels should be checked every 3-6 months from age 12 and parathyroid hormone levels measured if low. Thyroid function should be assessed at least annually from age 12. Endocrine deficiencies should be treated with standard therapy.

15.4.8 Patients with diabetes should be managed according to standard recommendations for Type 2 Diabetes (Diabetes NSF) and in conjunction with a specialist diabetes clinic. Patients with impaired glucose tolerance (Fasting glucose <7mmol/l, 140 min glucose 7-11.5 mmol/l) should be monitored for diabetic complications, receive advice concerning diet and exercise, and should intensify chelation. The role of oral hypoglycaemic agents in these patients is unclear.

Liver complications

16.1 Aims

To preserve liver function, and avoid liver disease related to viral hepatitis and iron toxicity.

To investigate liver abnormalities promptly, and offer effective treatment for disorders such as viral hepatitis

16.2 Standard

- Liver function tests will be monitored regularly.
- Liver iron levels should be maintained within safe limits to avoid progressive hepatic damage.
- Efforts to avoid viral liver disease must be made, ensuring transfusion with appropriately screened blood and full vaccination against hepatitis B infection.
- Liver disease will be managed in collaboration with a designated specialist Hepatologist.
- Hepatitis C infection should be staged and treated vigorously to obtain sustained viral clearance whenever possible.

16.3 Rationale

Liver disease is a common problem in thalassaemia major. The common aetiologies include viral hepatitis, hepatic toxicity due to iron loading of the liver parenchyma, biliary disease due to gallstones, and drug toxicity. The spectrum of pathological changes includes raised liver enzymes, histological changes on biopsy (including hepatitis and hepatic fibrosis), cirrhosis, and hepatocellular carcinoma. Liver disease was reported as the second commonest cause of death in Italian patients over the age of 15 (Zurlo et al 1989). However, it should be noted that viral hepatitis is more prevalent in Italian than in UK thalassaemics, and liver disease is not such a significant cause of mortality in the UK. A recent study of predominantly adult thalassaemics in North America showed cirrhotic change in 10.3%, and hepatitis C RNA positivity in 14.2% (Cunningham et al 2004).

There is evidence from post-BMT children that liver iron concentration and hepatitis C infection (antibody positivity) have a synergistic effect on 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 ($>16\text{mg/g}$ dry weight 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). Hepatocellular carcinoma has been described predominantly in older patients (mean age 45 yrs) with hepatitis C infection (Borgna-Pignatti et al 2004) and is likely to become more common in the UK as people with thalassaemia grow older.

Oral chelation therapy with deferiprone has been associated with hepatic toxicity. Mild elevations of transaminase levels are relatively common in patients receiving deferiprone, particularly if they are also hepatitis C antibody positive, but these are usually non-progressive, and rarely of sufficient severity to discontinue treatment (Ceci et al 2002; Cohen et al 2000). 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 progressive fibrosis observed was more related to hepatic iron loading and hepatitis C infection (Wanless et al 2002, Maggio et al 2002; Tondury et al 1998).

Small studies of treatment for hepatitis C infection in thalassaemia with interferon- α monotherapy (Donoghue et al 1993, Di Marco et al 1997), and combination therapy with interferon- α and ribavirin (Telfer et al 1997), suggest that sustained viral clearance can be achieved in about 40% of patients. Cirrhotic patients can benefit from this treatment. Side effects are frequent, and in

thalassaemic patients, it is especially important to monitor for interferon-induced thyroid disease, and drug-induced psychological reactions. Ribavirin induces haemolysis, and combination anti-viral therapy is expected to increase transfusion requirements. General guidelines for treating hepatitis C infection (e.g. Recommendations from the National Institutes of Health consensus development conference statement: management of hepatitis C: 2002) should be consulted.

It has not yet been established how best to assess liver iron concentration, nor what level of liver iron should be considered 'safe'. Chemical analysis of liver biopsy tissue has been regarded as the gold standard. However, this may give an inaccurate assessment if cirrhosis is present, or if the biopsy size is small (<1 g dry weight). Furthermore, there is variability in iron concentration throughout the liver, particularly in heavily iron overloaded cirrhotic livers, and the coefficient of variation for the analysis is high. Evidence is now becoming available that MRI-based techniques, such as the R2 measurement, show close agreement with direct chemical analysis of needle-biopsy specimens (St Pierre et al 2005).

One study of liver iron levels and hepatic fibrosis in post-transplant children demonstrated that progressive fibrosis did not occur provided the iron concentration was <16mg/g dry weight, and there was no evidence of hepatitis C infection (Angelucci et al 2000). This may be too high a level for adults who are continuing to accumulate iron through regular transfusions. A level not exceeding 7mg/g dry weight has been suggested by analogy with genetic haemochromatosis. Fibrosis is not seen in haemochromatosis heterozygotes, whose levels do not exceed this (Olivieri et al 1997). However, it is not clear whether these levels can be extrapolated to patients with thalassaemia receiving iron chelation, in whom iron is in dynamic change depending on the amount of continued iron loading, and the intake of iron chelating agents.

16.4 Key interventions

16.4.1 A Hepatologist should be designated for each thalassaemia specialist Centre.

16.4.2 Liver function tests and serum ferritin should be monitored every 3 months, and hepatitis virology every year. Adequate protection from hepatitis B virus should be ensured by a full course of vaccination in infancy, where possible before the first transfusion, and then by annual checking of anti-Hep BsAb titre (or as recommended by local virology laboratory on the basis of existing antibody titre).

16.4.3 If liver iron can be measured, either by direct chemical analysis, or by a MRI- based method, liver iron level should be maintained below 7mg/g dry weight (**GRADE B**). This includes patients who have undergone bone marrow transplantation.

16.4.4 Patients with active hepatitis C infection (HCV RNA positive) should be referred to the designated Hepatologist. HCV genotype must be established and, generally, a liver biopsy should be undertaken in order to stage liver disease. Effective anti-viral therapy should be considered even if liver disease is relatively mild, in view of the interaction between hepatic iron loading and hepatitis C infection (**GRADE B**).

16.4.5 Unexplained abnormalities of liver function tests should be investigated promptly. Liver biopsy may be necessary in order to obtain histopathological diagnosis and chemical analysis of liver iron content.

16.4.6 Patients with established cirrhosis should be reviewed regularly, at least annually, by the designated Hepatologist. Surveillance for hepatocellular carcinoma (alpha fetoprotein, liver ultrasound or abdominal CT) is necessary, at least once each year, together with oesophagoscopy to examine for varices. Liver iron levels should be kept as low as possible in these patients, and anti-viral treatment should be considered if infected with hepatitis C.

Bone problems

17.1 Aims

To prevent the variety of bone disorders associated with thalassaemia.

In those with established bone disease, to provide effective treatment and monitoring.

17.2 Standard

- Transfusion therapy will be initiated in time to prevent irreversible deformities associated with bone marrow expansion.
- Bone changes related to desferrioxamine toxicity should be suspected and investigated in children with bone/joint pain or short stature.
- All patients should be encouraged to exercise and maintain a diet rich in calcium and vitamin D.
- Hormone replacement therapy should be given to those with hypogonadism.
- Teenage and adult patients will be monitored for osteoporosis.
- Established osteoporosis in adults should be treated with bisphosphonates.

17.3 Rationale

Inadequately transfused thalassaemics develop characteristic deformities of the skull and face. They are susceptible to fractures following minor trauma, and often develop dental deformities, dental malocclusion, and recurrent sinusitis due to inadequate drainage. These problems are related to erythroid marrow expansion and are preventable by adequate blood transfusion regimes (Weatherall 2001). Asian children in the UK are particularly susceptible to vitamin D deficiency and rickets. Desferrioxamine-associated bone lesions in children include cartilaginous dysplasia of the long bones and spine, giving rise to shortening of the trunk and a 'pseudo-rickets' appearance. These changes can be prevented by using relatively low doses of desferrioxamine (15-35mg/kg) in young children. (Olivieri and Brittenham 1997)

Bone density scans in adolescents and adults with transfusion dependent thalassaemia

show very high rates of osteoporosis and osteopenia (Jensen et al 1998). Low bone mass is also present in children below the age of 10 (Vogiatzi et al 2004). Patients with low bone density are at increased risk of fracture, but it is still unclear how the fracture risk relates to the bone density as assessed by Z score, and whether bone fragility is as closely related to DEXA-scan findings as in post-menopausal women. Diminished bone density is seen in well chelated and well-transfused patients (Jensen et al 1998). There is evidence of increased bone resorption relative to formation (Voskaridou et al 2001). Risk factors include hypogonadism and diabetes (Anapilotou et al 1995; Jensen et al 1998). Plain X-ray of the hand and wrist can give useful information about sub-clinical bone disease, as well as an assessment of bone age in younger patients.

Adults may develop severe back pain with dire effects on quality of life. This may not be simply due to osteoporosis, and such symptoms have been observed in patients with milder degrees of bone loss, and in the absence of crush fractures. Other contributory factors may include disc disease, possibly related to long-term desferrioxamine toxicity, or extramedullary haematopoietic masses in people with thalassaemia major who have been undertransfused, or those with thalassaemia intermedia. These patients need careful evaluation, usually with MR imaging of the spine, and specialist input may be needed from an orthopaedic surgeon, rheumatologist, physiotherapist, and chronic pain specialist.

In general, patients should be given advice about increasing calcium and vitamin D intake in the diet, undertaking plenty of exercise and avoiding smoking and excessive alcohol consumption. Hormone replacement therapy is associated with less bone mineral loss (Anapilotou et al 1995). Treatment of established osteoporosis with bisphosphonate therapy has been effective, and reduces bone pain, and should be considered in adults, before major complications occur or severe pain develops

(Voskaridou et al 2003; Morabito et al 2002). Intravenous pamidronate given at 30-60 mg monthly is a convenient means of administration as it can be given on the same day as the transfusion. It is unclear how long such therapy should continue, or at what level the treatment can be stopped.

Bisphosphonates should probably not be given to children and adolescents, since they may interfere with bone growth.

17.4 Key interventions

17.4.1 Children with thalassaemia major should receive optimal transfusion to prevent excessive bone expansion (GRADE B).

17.4.2 Dietary intake should be assessed and advice given to maintain an adequate intake of calcium and Vitamin D.

17.4.3 Children and adults should be encouraged to exercise regularly.

17.4.4 The recommended desferrioxamine dose in childhood should not be exceeded (GRADE B).

17.4.5 Regular assessment of sitting height, and in the case of bone or joint pains, radiological investigations should be undertaken to rule out desferrioxamine-related bone disease (GRADE B).

17.4.6 Hormone replacement therapy should be initiated after discussion with the Centre paediatric Endocrinologist, usually by the age of 16 if hypogonadism is present, and other endocrine derangements have been sought and corrected (GRADE B).

17.4.7 Bone mineral density in the hip and spine should be measured every 18 – 24 months, more frequently if there is concern, by dual energy x-ray absorptiometry (DEXA) in all patients over 10 years of age.

17.4.8 Established osteoporosis (Z score < -2.5 in either hip or spine) should be managed with advice about diet, exercise, hormone replacement therapy, and bisphosphonate therapy in those over 16 years of age (Grade B).

17.4.9 Patients with severe back pain should be carefully evaluated with MRI scanning. They should be referred promptly for orthopaedic advice and pain management.

Fertility, and management of pregnancy

“I want to ask my doctor about the possibility of having children but my mum gets upset if I talk about it because she thinks it will be too risky for me. I would like to know how many women with thalassaemia have had babies.”

18.1 Aims

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

To optimise 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.

18.2 Standard

- Pubertal development and endocrine function will be closely monitored and prompt referral to the designated Endocrinologist made if there is any suspicion of problems.
- At any time when the patient wishes she/he should be referred to a fertility clinic with experience of thalassaemia patients, to allow discussion about treatment options. Culturally appropriate advocacy in these discussions is imperative.
- Women contemplating pregnancy will be assessed for possible risks to themselves and their babies.
- Women should be jointly managed during pregnancy by a ‘high-risk’ obstetrician experienced with thalassaemia, and by their haematologist.

18.3 Rationale

The pituitary and hypothalamus are very sensitive to iron damage, and hypogonadotropic hypogonadism is a frequent complication. Diabetes and hypothyroidism can also impair fertility. Building a family is a key concern for patients and their parents, and they greatly value discussion with a specialist who is able to explain realistically the options and likelihood

of success, so minimising unrealistic expectations and consequent psycho-emotional problems. Induction of ovulation or spermatogenesis may be necessary, and must be undertaken by those with experience in managing patients with thalassaemia (Skordis et al 1990).

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

- cardiac problems, given the 40% increase in cardiac workload, and
- the risk of accelerating cardiac dysfunction, pre-existing diabetic retinopathy or nephropathy (Jensen et al 1995).
- worsening osteoporosis

For the baby, issues include

- the possibility of its having a major haemoglobin disorder
- a four-fold increased risk of fetal anomaly and three-fold increase in perinatal mortality if the mother has diabetes
- an increased risk of chromosomal non-dysjunction, probably related to maternal iron overload
- a substantially increased risk of premature delivery, growth restriction, and disability if ovulation induction results in multiple births. Specialist fertility care should minimise the risks of multiple pregnancy and ovarian hyperstimulation.

18.4 Key interventions

18.4.1 Iron chelation should be optimised from childhood, to reduce the risks of infertility.

18.4.2 Where there is clinical or biochemical evidence of pubertal delay or hormone disturbance, management by the designated Endocrinologist is required.

18.4.3 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. This should be to to a clinic experienced in treating patients with thalassaemia so that an informed and realistic discussion can take place. Input from other members of the multidisciplinary team may be helpful in this regard.

18.4.4 It is imperative that the couple is given the opportunity to discuss the risk of having a child with thalassaemia or other major haemoglobin disorder, for example sickle cell disease if the partner carries sickle cell trait. The partner must be offered a test and, if he or she carries thalassaemia or a variant haemoglobin, they should be counselled together about their options, and pre-natal diagnosis arranged if they wish. In discussing pre-natal diagnosis, the issue of chromosomal disorders should also be considered.

18.4.5 Careful pre-assessment of a woman with thalassaemia considering pregnancy is required, by an obstetrician experienced in the area, with proper discussion about possible risks (Protonotariou and Tolis 2000). A cardiology assessment with a view to assessing her fitness for pregnancy is recommended, including echocardiogram and consideration of MRI quantitation of cardiac iron where available.

18.4.6 General pre-pregnancy issues need to be considered, as for any other woman:

- folic acid supplements
- red cell antibodies
- rubella immune status
- HIV
- hepatitis C
- smoking/alcohol.

18.4.7 It should be remembered that couples may be infertile for reasons unrelated to thalassaemia, and a range of investigations may be necessary to establish the nature of the problem.

18.4.8 Induction of ovulation or spermatogenesis may be required for patients who have hypogonadism, and treatment in a centre with experience of such patients will minimise the risk of hyperstimulation syndromes and multiple births.

18.4.9 During pregnancy, the woman should be closely supervised by her obstetrician, cardiologist and haematologist (Tuck et al 1998). Transfusion requirements are likely to increase, and most medication should cease - particularly bisphosphonates and ACE inhibitors. It is usually advised that desferrioxamine should be withheld throughout pregnancy, although there are reports (Singer and Vichinsky 1999) that its toxicity in the second and third trimesters may be very low and that, in women who need iron chelation in pregnancy, continuing it could be considered. Folic acid is important in the pre- and early pregnancy period and penicillin should continue in those splenectomised. Calcium and vitamin D supplements are advisable if bone density was already reduced prior to the pregnancy

18.4.10 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.

18.4.11 The woman should be encouraged to resume her iron chelation as soon as she feels able to, after the delivery. If she is breastfeeding, desferrioxamine can be used. Deferiprone should not be recommended until after breastfeeding ceases.

Section D

Specialist Review

19

Annual Review at Specialist Thalassaemia Centre

“I would like my doctor to ensure he has contact with specialist units and consultants to compare treatments, and to be better informed”

“I am not sure if my treatment is up-to-date”

“I would like to have regular cardiology appointments and bone density scans. I would like to have combination [desferrioxamine + deferiprone chelation] treatment but don't know if I should ask about this.”

“I think the doctor could give me more information about the latest developments in treatment, also I would like to be sure that all the routine tests are being carried out correctly.”

“My doctor does not really help me a lot. This is a problem of being treated at a hospital that very rarely sees a thal patient.”

19.1 Aim

To provide all children and adults with thalassaemia, regardless of where they live, access to a full range of specialist professionals and services at least yearly and more often if necessary, to ensure that their care is optimal.

19.2 Standard

- Every person with thalassaemia will have the opportunity for their care and condition to be reviewed at least annually, at a thalassaemia Centre, with a team of health care professionals who have particular experience in the field.
- This should allow for broad discussion of treatment options, including any new information which has become available, and an individual treatment plan for the next 12 months will be confirmed.
- People in families affected by thalassaemia should be able to meet and gain support from other affected families at the Centre.

19.3 Rationale

Patients with these complex multi-system disorders require input from a range of specialist health professionals and access to a number of investigations not available everywhere. Linking smaller Clinics with larger specialist Centres, and individual case review there at least once a year, will offer all patients optimal specialist care regardless of where they live. The annual review is intended to be a detailed assessment of every aspect of the patient's treatment and condition to assess progress and identify areas where treatment could be improved.

19.4 Key interventions

19.4.1 The patient and family will usually visit the Centre for a pre-booked appointment. For some larger Clinics, a local agreement may be made for a Paediatrician and/or Haematologist from the Centre, often with a specialist nurse, to hold an outreach clinic there.

19.4.2 Communication of results between Clinic and Centre will be key to the

effectiveness of these visits. To be effective, information on the individual patient's progress, growth charts, and results of monitoring tests undertaken in the preceding year, will need to be available for the review visit. Copies of completed monitoring charts (as in Appendix A), with copies of letters from any specialist clinics attended, will give the necessary information. It will be a matter for local discussion, and will depend on availability of the different investigations, which are undertaken at the local Clinic or at the Centre. If to be done at the Centre, this should require the minimum possible number of hospital visits. Where logistically possible, investigations should be combined with the annual review visit.

19.4.3 Where test results become abnormal between annual reviews, Clinics are encouraged to discuss them with the Centre to decide on the need to refer/start additional treatment.

19.4.4 At the visit, the consultation will be with the designated Paediatrician or Haematologist. Assessment will be made of progress in general and a review made of the patient's and family's knowledge of the condition. Any questions the family has about the child's condition, or treatment options, should be addressed. If possible the clinical psychologist can also be present, as part of the clinical team, and can pick up any problems identified at the same or a separate consultation.

19.4.5 There will be detailed review of current iron chelation regimen, adherence to it, and consideration of whether it can be improved in terms of tolerability and efficacy.

19.4.6 It will be ensured that prophylaxis against infection for splenectomised patients is appropriate (penicillin and vaccinations).

19.4.7 Weight, and sitting and standing height will be recorded and growth charts reviewed, and clinical examination will be undertaken

with particular reference to heart, liver, spleen, pubertal status in relevant age group and any features of endocrine dysfunction.

19.4.8 It will be checked that the individual is attending the appropriate specialist clinics for his/her age and clinical status (cardiac, endocrine) and if not, referrals made.

19.4.9 For patients with a positive hepatitis C antibody test, an extra review together with the designated Hepatologist should be included or arranged, if the individual is not already under active regular follow up/treatment at an appropriate hepatology clinic.

19.4.10 The issue of possible bone marrow transplantation should be raised, and consideration given to referral to a transplant centre (see section 19). 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.

19.4.11 Discussion about the family's plans for further pregnancies should be considered at intervals, with reference to their choice regarding pre-implantation genetic diagnosis, pre-natal diagnosis and testing/storage of cord blood.

19.4.12 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 families at the Centre.

19.4.13 After the visit the consultant should write a report including any problems highlighted and management changes suggested, with copies to the referring hospital, the GP and the patient/family. The patient's hand-held record, if used, can be completed at the end of the annual review visit.

Review of patients previously treated outside the UK

20.1 Aims

To ensure that patients starting or returning to use thalassaemia services in the UK can be assessed thoroughly at the outset.

To ensure proper understanding of their condition and any complications.

To have any problems addressed, and be integrated into local continuing care arrangements.

20.2 Standard

- Children and adults who have been receiving treatment outside the UK will, on arrival, be seen promptly at an established Centre and thoroughly assessed.
- Any complications which may have developed will be detected and discussed with the individual and family and management plans made accordingly.

20.3 Rationale

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. Starting on an improved transfusion/chelation treatment regimen, and appropriate management of any complications which have not been recognised to date is likely to improve well-being and reduce morbidity and mortality.

20.4 Key interventions

20.4.1 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. They should be offered an early review with the designated

Paediatrician/Haematologist and nurse specialist in a convenient specialist Centre, with appropriate translation services available if needed.

20.4.2 A full medical history should be recorded including age at diagnosis, age at first transfusion, transfusion history including transfusion reactions, chelation history - frequency, doses, route; developmental history including puberty if relevant age, surgical procedures (in particular splenectomy), any identified endocrine problems, and all current medication.

20.4.3 A family history is important for general clinical assessment, and will help elucidate whether other family members should be screened for thalassaemia. A 'family tree' should be completed if possible, indicating which members have already been tested for thalassaemia.

20.4.4 Enquiry about social circumstances will help to decide if referral to social services might be helpful.

20.4.5 Patients should receive a full medical examination, recording height, weight, presence of thalassaemic facies or dental problems, the presence of an enlarged liver or spleen, stigmata of chronic liver disease, signs of cardiac failure, leg ulcers; stage of pubertal development and suggestion of any endocrinopathies.

20.4.6 Baseline investigations should be discussed with the patient and with their consent the assessments listed in Table 3 undertaken.

20.4.7 An early review visit should be planned to discuss the results of these investigations and any necessary treatment changes.

20.4.8 If hepatitis B non-immune, vaccination should be recommended, and started if accepted.

20.4.9 It should be decided, and carefully explained to the patient and family, what the recommended arrangements for continuing care will be: either at the local Clinic with

review visits at the Centre, or wholly at the Centre depending on proximity.

Table 3: 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
	ABO and full red cell phenotype and antibody screen. [If recently transfused, DNA studies for red cell antigens, via Reference Laboratory of National Blood Service]
	Hepatitis B & C serology to include Hep B surface antibody titre.
	HIV serology preceded by pre-test counselling.
	Full renal, liver, bone, sex hormone profiles, random glucose, TFTs, fructosamine if diabetic.
	Sample to Regional Transfusion Centre to define molecular variants (α and β globin genotype, -158 $G_{\gamma}Xmn1$ C>T polymorphism). Parental samples may be informative.
Other specialist assessments	Audiology if using desferrioxamine
	Retinal screening
	Bone densitometry
	Cardiac review
	Psychology review
	If diabetic, specialist diabetic clinic
	If other endocrinopathies, endocrine clinic
	If hepatitis B antigen or C antibody positive, hepatology clinic
Genetic counselling, once diagnosis defined	

20.4.10 The family should be introduced to their key contact, and contact numbers exchanged.

20.4.11 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.

20.4.12 They should be given contact details for any local support groups or organisations and for the UK Thalassaemia Society.

Section E

Thalassaemia Intermedia

21

Management of thalassaemia intermedia, including haemoglobin E/ β thalassaemia

Introduction

This section, while conforming to the format of previous chapters in summarising aims and standards, followed by rationale and key interventions, differs in that it takes a broader overview of the condition, and then looks in turn at the issues covered by preceding chapters as they apply to intermedia, compared to transfusion-dependent thalassaemia.

Where the same standards and key interventions apply, they are not repeated here; where there are differences these are highlighted. Some additional issues which particularly apply to these conditions are covered.

21.1 Aims

To maintain good health, normal growth and development, and a good quality of life throughout childhood, adolescence, and adulthood in people with thalassaemia intermedia, avoiding unnecessary treatment with regular transfusions in those with milder clinical features, but intervening with appropriate transfusion therapy if it becomes necessary.

To monitor regularly and systematically for early signs of morbidity due to chronic anaemia, iron overload and other consequences of untransfused thalassaemia.

21.2 Standards

- A comprehensive DNA diagnosis (β globin mutations, α globin genotype, *Xmn1* polymorphism) should be undertaken as soon as the diagnosis of thalassaemia has been established. Detailed consideration will be given to

clinical and laboratory findings in order to reach a decision about transfusion and other treatment needs.

- 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 suspected of having thalassaemia intermedia should be monitored carefully and systematically for evidence of thalassaemic features which may require regular transfusion therapy
- Children, adolescents and adults with this condition should be monitored carefully and regularly, in conjunction with the specialist Centre
- Complications of thalassaemia intermedia should be minimised by anticipation, early detection, and intervention with appropriate therapy.

21.3 Rationale

Definition

The term thalassaemia intermedia is used to categorise patients with thalassaemia who do not have an absolute requirement for regular transfusions in order to survive during the first 3-5 years of life. It includes a wide spectrum of severity, from patients who only just manage without transfusions during childhood, to those who are virtually asymptomatic, and have no more problems than thalassaemia carriers during childhood.

Genetics

Thalassaemia intermedia can be the result of inheritance of milder β globin gene mutations, allowing sufficient β globin chain production for some adult haemoglobin

production. Additional genetic factors, such as co-inheritance of α thalassaemia, or 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 *Xmn1* polymorphism analysis (Table 4) but sometimes the clinical phenotype is not as predicted from genetic analysis.

Moderate/severe thalassaemia intermedia

This includes 7-10% of patients with β thalassaemia, the majority of those with Haemoglobin E/ β thalassaemia and a very small proportion of those with haemoglobin H disease (α thalassaemia intermedia). At the severe end are patients who can only just

manage without transfusions, but who have severe anaemia, reduced exercise tolerance, mild to moderate bone changes, hypersplenism, poor growth during childhood, and a delay in pubertal development. They are likely to develop gallstones, extramedullary haematopoietic masses, and gradually accumulate iron, particularly in the liver, due to increased gastro-intestinal iron absorption.

Mild thalassaemia intermedia

This group includes a small proportion of patients with homozygous β thalassaemia (usually predictable from genotype), some patients with haemoglobin E/beta thalassaemia, and the large majority of patients with haemoglobin H disease. It is important to identify this very mild group and to provide information tailored to their condition. Long-term complications can include hypersplenism, gall bladder disease, and chronic ankle ulceration.

Table 4: Genetic determinants of thalassaemia intermedia

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

Specific clinical considerations

The key issue of deciding whether to start a child on regular transfusion is covered in section B.6. Acute anaemic episodes occur in children with thalassaemia intermedia and are not necessarily an indication for long-term transfusion. Such episodes may be caused by parvovirus infection, but are more commonly associated with other viral or atypical infections, and acute haemolysis may also be exacerbated by G6PD-deficiency. Relative folate deficiency may occur and folic acid supplements are recommended (Cappellini 2000). Red cell allo-immunization is more

frequent in thalassaemia intermedia (Spanos et al 1990), so providing phenotype matched units is mandatory.

Bone marrow expansion may cause malformation of facial bones, difficulty hearing or chewing and increased sinus infections. Bone pain and pathological fracture of long bones may occur.

Untransfused patients tend to develop hepatic iron overload as a result of increased gut iron absorption. However, it is easier to achieve negative iron balance in thalassaemia intermedia, because the rate of iron loading

from the gut is much less than from regular transfusions. The serum ferritin is unreliable in thalassaemia intermedia, and tends to underestimate the degree of liver iron loading. Iron-related cardiomyopathy is unusual in children and young adults.

Particular psychosocial issues have been identified in thalassaemia intermedia patients and their families, particularly around the areas of uncertainty and anxiety about the condition, and chronic ill health (Ratip et al 1995).

Standard treatment for these patients has been splenectomy, if the spleen is large, and avoidance of regular transfusion. Doctors and patients may try to avoid transfusion dependence because of the increased burden of treatment with regular transfusions and iron chelation, the increased risk of death associated with thalassaemia major as a result of iron overload, and/or unwillingness to accept the diagnosis of thalassaemia. However, with current advances in chelation therapy and improved survival seen in thalassaemia major, and the enhanced quality of life which may accompany conversion to regular transfusions, the standard approach to treatment of thalassaemia intermedia may need to be reconsidered. Indications for splenectomy include massive splenomegaly and hypersplenism. Many patients with lesser degrees of splenomegaly do benefit, with an improvement in haemoglobin level and a reduction in ineffective erythropoiesis so that transfusion dependence is delayed or averted. Removing the spleen can also improve growth velocity and pubertal development. However, the benefit is not always dramatic, and many will still eventually require regular transfusion (Fiorelli et al 1988). This variability is also seen in Haemoglobin E/beta thalassaemia (Hathirat et al 1989). Risks of splenectomy in thalassaemia intermedia include a marked thrombocytosis, post-splenectomy sepsis (Pinna 1988), thrombotic events, pulmonary hypertension, and possibly enhanced iron deposition in the liver. The risk of thrombosis, already increased in thalassaemia intermedia (Borna-Pignatti 1998) is further increased after splenectomy (Cappellini 2000).

Pulmonary hypertension is increasingly being recognised in untransfused adults, particularly those who have been splenectomised, and can lead to right heart failure (Aessopos et al 1995,

Aessopos et al 2001). The aetiology is unclear. There is evidence from autopsy for recurrent pulmonary vascular occlusion with thrombi (Sonakul et al 1988). Hypercoagulability, thrombocytosis and increased platelet activation may be involved, and nitric oxide depletion through scavenging by free plasma haemoglobin may also play a role, as in sickle cell disease (Reiter et al 2002). Optimal management for this complication is not yet established. Aspirin therapy reduces hypoxaemia in the majority of cases (Fucharoen et al 1981). Regular transfusion is likely to be beneficial. The role of hydroxyurea, phosphodiesterase inhibitors or nitric oxide donors/analogues need further investigation.

Children and adolescents with thalassaemia intermedia are less likely than those with thalassaemia major to have short stature due to growth hormone deficiency, hypogonadism due to gonadotrophin deficiency, and other iron-related endocrinopathies.

Short stature and delayed puberty are more commonly due to chronic anaemia, hypersplenism and energy deficit due to hypermetabolism. Bone age is often significantly delayed.

Asymptomatic paravertebral masses are commonly observed on routine chest X-rays, and chest or abdominal scans. Masses causing spinal cord compression, root compression, or pressure symptoms in other anatomical sites require urgent management (Dore 1992). The optimal treatment modality is not established. Radiotherapy can induce rapid resolution of pressure effects (Issaragrisil et al 1981). Good results, although generally slower in onset, have been described with hypertransfusion and hydroxyurea (Saxon et al 1998).

An additional therapeutic option for patients with thalassaemia is hydroxyurea (also known as hydroxycarbamide). This is a cytotoxic agent which can suppress erythropoietic activity and enhance fetal haemoglobin production. The potential clinical benefits include alleviation of symptoms of anaemia, reduction in clinical jaundice because of decreased haemolysis, relief of bone pain, reduction in bone marrow and spleen enlargement and regression of extramedullary masses. In general, the clinical experience and

results published in case series have been disappointing, although response is variable. Encouraging results have been reported for specific genotypes, notably those with haemoglobin E/beta thalassaemia (Fucharoen et al 1996), Haemoglobin Lepore, and in some Middle Eastern patients (Bradai et al 2003, Alebouyeh et al 2004, Yavarian et al 2004). Better results are also expected in patients who are homozygous for the *Xmn1* polymorphism, which confers enhanced fetal haemoglobin production (Alebouyeh et al 2004). Some patients are particularly sensitive to bone marrow suppression and become leucopenic with relatively modest doses. In addition, too high a dose may suppress erythropoiesis rather than enhance haemoglobin levels.

Since many patients with moderate/severe thalassaemia intermedia have relatively poor quality of life, and many will eventually require transfusions and chelation therapy, allogeneic bone marrow transplant 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 thalassaemia intermedia in a young child. The discussion requires careful counselling, accurate and consistent information, and good communication between the Transplant Centre, local Clinic and specialist Centre.

21.4 Key interventions

21.4.1 Organization of services for thalassaemia intermedia: the same considerations broadly apply to thalassaemia intermedia as for thalassaemia major, although since intermedia is relatively rare, and presents difficult management problems which cannot be easily protocolised, input from the Centre is especially important.

21.4.2 Patients should receive regular folic acid supplementation.

21.4.3 After transfusion for an episode of acute anaemia, for example after infection, the patient should be observed carefully for several months to determine steady-state symptomatology and haemoglobin level.

21.4.4 The decision for regular transfusions should be made at, or in collaboration with, the Centre. Indications for long-term transfusions include symptomatic anaemia, growth failure, delayed puberty, bone problems (facial deformities, recurrent fractures, premature epiphyseal fusion), symptomatic extramedullary haematopoietic masses, chronic ankle ulceration.

21.4.5 The rationale for transfusion should be carefully discussed with the patient and/or parents and family, perhaps over the course of several clinic visits. This will entail accepting the reality of a chronic condition in an older child, and preparing for the problems associated with regular transfusion.

21.4.6 Red cell units transfused must be phenotype compatible, at least for ABO, Rhesus (CDE) and Kell.

21.4.7 Assessment of iron stores should take into account the severity of the anaemia, number of transfusions received, and clinical evidence of iron-related toxicity (heart, liver and endocrine disease).

21.4.8 As the serum ferritin is unreliable in thalassaemia intermedia, additional measure of iron stores should be undertaken every 5 years. A single liver biopsy to assess iron load and histology should be considered; more regular assessments are appropriately undertaken using a non-invasive technique such as MRI (see section B.8).

21.4.9 Chelation regimes for untransfused children and young adults can be less intense than in thalassaemia major. The choice of chelator drugs is as for thalassaemia major.

21.4.10 Careful consideration should be given to the risks/benefits of splenectomy in these patients. The decision must be made after consultation with the Centre, and requires careful counselling and discussion.

21.4.11 Patients with thalassaemia intermedia should be transfused for several months prior to splenectomy to reduce spleen size, suppress marrow activity, and reduce the numbers of circulating, pro-thrombotic thalassaemic red cells.

21.4.12 Prior to the procedure, an abdominal ultrasound scan should be done to detect gall stones. If present, a cholecystectomy should also be considered. A wedge liver biopsy should be taken at the time of laparotomy, for

histological assessment and analysis of liver iron content.

21.4.13 Chronic anaemia with enlargement of the heart and increased cardiac output may eventually lead to cardiac decompensation, and a regular transfusion programme should obviously be started before patients with thalassaemia intermedia reach this stage. Regular cardiac monitoring is therefore important.

21.4.14 Thalassaemia intermedia patients should have regular echocardiography from age 15. The ideal echocardiography protocols to detect pulmonary hypertension in this setting are not yet established. In situations where echocardiography proves inconclusive, further investigation with cardiac MRI and right heart catheter studies should be considered to confirm the diagnosis.

21.4.15 If pulmonary hypertension is found, treatment with regular transfusion should be strongly considered. Support should be given to clinical trials in these areas.

21.4.16 Growth and pubertal development should be monitored regularly from the age of 10, and referral to the designated endocrinologist made if abnormalities are documented.

21.4.17 A period of regular transfusion during the years of puberty should be considered.

21.4.18 Symptoms due to extra-medullary haematopoietic masses should be carefully watched for, investigated, and treated. Radiotherapy can be considered if there is urgent need to reduce the mass; hypertransfusion and hydroxyurea act more slowly.

21.4.19 Hydroxyurea therapy for this indication, or in an attempt to improve the patient's clinical state, should be instituted only after careful definition of the expected benefits. The decision should be made by the Centre physician. 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 frequently, initially every week. The dose should not exceed 20-25 mg/kg/day

21.4.20 Referral to a bone marrow transplant centre, with specific experience of transplanting for thalassaemia, should be offered to families, for detailed discussion of transplant as an option.

21.4.21 Patients with moderate/severe thalassaemia intermedia should be reviewed at least annually at the specialist Centre.

21.4.22 Suggestions for regular monitoring tests, (which differ in some respects from those for thalassaemia major) are given in Table 5.

Table 5: Suggested monitoring for moderate/severe thalassaemia intermedia patients, after age 3

	Frequency	Age at start
Clinical examination	3 monthly	Age 3
Height		
Weight		
Spleen size		
Liver size		
Assessment of facial bone deformity and dental state		
Pubertal development	6 monthly	Age 10
Cardiac assessment	5 yearly, or more frequently if abnormal	Age 15
Blood tests	3 monthly	Age 3
FBC		
Liver function, renal function, urate		
Ferritin		
Bone age (X-ray wrist)	Annual	Age 12
DEXA bone density	5 yearly	Age 15
ECHO, including assessment for pulmonary hypertension (Tricuspid jet velocity should be quoted)	5 yearly, or more frequently if abnormal	Age 15
Formal assessment of body iron stores/MRI if available (see 21.4.8)	5 yearly or more frequently if abnormal	Age 15

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Appendix A

Suggested Formats for Monitoring Flowcharts

Notes

- To be used in conjunction with standard “centile charts” for monitoring height and weight, and head circumference in infants.
- For children up to the age of 3 years, A1 and A3 should be used.
- For patients over 3 years of age. A2, 3 and 4 should be used.
- Each is intended to be used for a 12 month period (year stated at top), starting new sheets each January.
- Electronic or hard copy versions of these tables formatted for actual clinical use and suitable for printing or photocopying can be requested from the UK Thalassaemia Society free of charge.

A1 Monitoring chart for children up to 3 years of age

Patient Name:	(or attach sticky ID label)
Date of birth:	
Unit number:	
NHS number:	
Year:	

Date	Height cm	Weight kg	Head circum- ference	Hb level g/dl	Ferritin ng/ml	Liver function tests [#]	Spleen size cm	Transfusion (ml)/date	Comments

[#] record 'n'(normal) or include abnormal results

Total ml transfused this year:	
/ mid-year wt (kg):	
= Red cell transfusions - ml/kg for this year:	

Date	Vaccinations given:

A2 Transfusion Record and 3 monthly monitoring

Patient Name:	(or attach sticky ID label)
Date of birth:	
Unit number:	
NHS number:	
Year:	

Date	Pre-Tx Hb g/dl	Mls transfused	Ferritin* ng/ml	LFT*#	Glucose* mmol/l	Calcium* µmol/l	Comments

* usually 3 monthly
 # record 'n' (normal) or include abnormal results

Total ml transfused this year:	
/ mid-year wt (kg):	
= Red cell transfusions - ml/kg for this year:	

Any transfusion reactions	
Date	Reaction type

A3 Chelation Record

Patient Name:	(or attach sticky ID label)
Date of birth:	
Unit number:	
NHS number:	
Year:	

Regimen	Date	Desferrioxamine				Other chelator			Comments
		Dose	Route	Frequency	Delivery device	Name	Dose	Frequency	
Usual regimen (start of year)									
Change in regimen:									

A4 Yearly Monitoring Summary (from age 3)

Patient Name:	(or attach sticky ID label)
Date of birth:	
Unit number:	
NHS number:	
Year:	

Start at age (yrs)	Investigation/ measurement	Date of investigation	Undertaken at		Result	✓	Comments
			Clinic	Centre			
3	Growth				Height progressing along satisfactory centile		
					Growth velocity unsatisfactory		
3	Physical examination				Bone changes		
					Splenomegaly		
					Hepatomegaly		
3	Average Hb (pre-transfusion)				<9.5 g/dl		
					9.5-10.5 g/dl		
					>10.5 g/dl		
3	Average serum Ferritin				<1000		
					1000-2500		
					>2500		
3	Liver function tests (over last 12 months)				Transaminases >2x upper limit of normal on one or more occasions		
					Transaminases consistently <2x upper limit normal		
3	Virology (within last 12 months)				HbsAg+ve		
					Anti-Hbs protective		
					HCV RNA +ve		
					Anti-HIV+ve		
10	Glucose tolerance test (within last 12 months)				Normal		
					Impaired glucose tolerance		
					Diabetes		
12	Calcium levels (over last 12 months)				Normocalcaemic on treatment		
					Normocalcaemic not on treatment		
					Hypocalcaemia on one or more occasions		
12	Thyroid function tests (over last 12 months)				Euthyroid off treatment		
					Euthyroid on treatment		
					Hypothyroid on one or more occasions		
10	Cardiac review (within last 12 months)				Normal		
					Cardiac arrhythmia		
					Cardiac failure		
10	Endocrine review (within last 12 months)				Growth Hormone deficient		
					Normal puberty		
					Delayed puberty*		
					Hypogonadism* (* see definitions, section B.15)		
10	Audiometry (within last 12 months)				Normal		
					Hearing loss		
10	Ophthalmology (within last 12 months)				Normal		
					Abnormal		
10	Liver iron (within last 12 months, biopsy or MRI estimation)				<7mg/g dry wt		
					7-15mg/g dry wt		
					>15mg/g dry wt		
10	Cardiac T2* MRI (within last 12 months)				T2*>20ms		
					T2* 8-20 ms		
					T2*<8 ms		
10	DEXA bone scan (within last 12 months)				Normal		
					Osteopenia		
					Osteoporosis		

Key Clinical Events

Date	Event	Yes/No	Comment / detail.
	Yersinia		
	Other Sepsis		
	Fracture		
	Heart failure		
	Dysrhythmia		
	Splenectomy		
	Cholecystectomy		
	Other operation		
	Bone marrow transplantation		
	Death		
	Other		

Vaccinations given:

Hepatitis B vaccine	Date last given:	Hep BsAb level * (date) :
Pneumococcal vaccine (if spleen out)	Date last given:	
HiB vaccine	Date given:	
Meningococcal vaccine	Date given:	

Appendix B

Summary guide to routine investigations and management

It will be a matter for local discussion which of the monitoring tests is undertaken at the local Clinic in advance of, or at the Centre during, the Annual Review visit. Communication of results between Clinic and Centre will be key to the effectiveness of these visits.

Where test results become abnormal between annual reviews, clinics are encouraged to discuss results with the Centre to decide on need to refer/start additional treatment.

For initial investigations on the newly diagnosed infant or child, please refer to Sections 5 and 6.

B1 Growth and development

B1.1 Record parental heights at first visit

B1.2 Height (standing and sitting) and weight at least 6 monthly, plotted on appropriate growth and velocity charts

B1.3 Puberty staging, yearly from 10 years

B1.4 Enquire regularly about onset of menstruation in girls, and thereafter ask intermittently to check that periods are continuing spontaneously

B1.5 If growth velocity falling, or no pubertal development by 13 in girls, 14 in boys, or arrested puberty, refer to paediatric Endocrinologist at Centre

B1.6 Any hormone replacement therapy recommended by the Endocrinologist should be continued and monitored.

B2 Iron levels

B2.1 Ferritin 3-monthly

B2.2 Consider quantitative check (liver biopsy or MRI-based method)

B3 Liver function

B3.1 Liver function tests 3-monthly

B3.2 Ultrasound for gallstones if obstructive picture

B3.3 Viral hepatitis – see below

B4 Cardiac function

B4.1 Clinical examination of the cardiovascular system at least 6 monthly

B4.2 Specialist cardiac function assessment annually from age 10

B4.3 Urgent referral to Centre Cardiologist if any suspicion of cardiac symptoms of signs between regular assessments.

B5 Endocrine function

B5.1 Glucose metabolism

B5.1.1 Random blood glucose every 3-6 months and oral glucose tolerance test if elevated

B5.1.2 Oral GTT routinely annually from puberty - or from 10 years if positive family history

B5.1.3 Dietetic input for impaired glucose tolerance

B5.1.4 Diabetes team review if indicated

B5.2 Thyroid

B5.2.1 Annual TFTs - T4/FreeT4 and TSH from 12 or on clinical suspicion

B5.2.2 Refer to paediatric Endocrinologist and thyroxine replacement if indicated

B5.2.3 Check response to treatment and adjust dose if required 3 monthly initially or as advised by local specialist

B5.3 Parathyroid

B5.3.1 3-6 monthly calcium and phosphate measurements from age 12

B5.3.2 Measure Parathyroid Hormone if calcium low

B5.3.3 Treatment with oral vitamin D or analogue and calcium, usually in conjunction with Endocrinologist

B5.3.4 Monitor efficacy of treatment with calcium and phosphate levels 3 monthly

B6 Chelator toxicity

B6.1 Audiometry yearly from 10 years if receiving desferrioxamine.

B6.2 Ophthalmology yearly from 10 years if receiving desferrioxamine.

B6.3 Frequent full blood count if receiving deferiprone.

B6.4 Assess zinc levels every three months and supplement if low.

B7 Osteopenia/osteoporosis

B7.1 Advice re calcium-rich diet, importance of exercise, avoid smoking

B7.2 Bone densitometry (DEXA scanning) every 18 – 24 months, or annually if there is concern, from age 10 years

B7.3 Replacement of any hormone deficiencies

B7.4 For patients over the age of 16 consider treatment with bisphosphonates if osteopenic or osteoporotic

B8 Viral screening

B8.1 Hepatitis C serology annually

B8.2 Hepatitis B surface antibody titre, at intervals recommended by local virology laboratory on the basis of existing antibody titre

B8.3 Boost hepatitis B vaccination when hepatitis B surface antibody level falls to level advised by microbiology lab

B8.4 HIV testing, with pre-test counselling, if transfused abroad, or if requested by patient or family, or if clinical concerns

B9 Consideration of splenectomy and infection prophylaxis after splenectomy

B9.1 Review of red cell use and splenic size to consider splenectomy

B9.2 If splenectomy planned, pneumococcal immunisation and check HiB and meningococcal vaccine have been given

B9.3 Advise and repeat prescribe penicillin prophylaxis

B9.4 Offer travel precautions as for other splenectomised patients

B9.5 Issue 'splenectomy card' if locally used

B9.6 Consider aspirin 75 mg daily for persistent thrombocytosis after splenectomy [$>750 \times 10^9/l$], although aspirin is avoided in children (<16 years).

B10 Referral for consideration of Bone Marrow Transplantation

B10.1 All families who have a child with transfusion dependent beta thalassaemia major should be offered the opportunity to discuss bone marrow transplant as a treatment option at an early stage, regardless of there being an available donor at the time.

Appendix C

Performance Indicators

Monitoring Services - delivery and effectiveness tool for audit of local services against standards

It is recommended that, in the first instance, these are used locally by all Clinics and potential Centres, and by health care commissioners. They may help to identify gaps in service, against expected standards. It is recognised that some Clinics will not have readily available all the data to complete these, but it is expected that all will want to start collecting data.

Fair Access to and Effective Delivery of Healthcare

Local Thalassaemia Clinic

Clinic Size

	Number of patients
Paediatric (<16 years) thalassaemia patients managed at Clinic	
+ Adult (16 years and over) thalassaemia patients managed at Clinic	
= Total number of thalassaemia patients managed at Clinic:	

Staffing

(numbers/WTE not specified, as depends on numbers treated)		Fully met	Working towards	Not met	Comments [expected date]
Designated Paediatrician/Haematologist					
Named deputy					
Middle grade cover (Specialist Registrar or Staff Grade doctor) out of hours					
Staff to cover roles of	Regular staff on day-care area to cannulate, start and supervise transfusions				
	Key contact for patients and families				
	Deputy for Key contact				
Haematology, biochemistry, microbiology and appropriate blood bank laboratory facilities, diagnostic imaging					
Access to named psychologist					
Access to	dietician				
	social worker				
	language interpreters				
	sufficient A&C support to ensure proper communication between family/Clinic/Centre/GP plus the child/family				

Thalassaemia Specialist Centre

Clinic Size

	Number of patients
Paediatric (<16 years) thalassaemia patients managed	
+ Adult (16 years and over) thalassaemia patients managed	
= Total number of thalassaemia patients managed:	

Staffing

(numbers/WTE not specified, as depends on numbers treated)		Fully met	Working towards	Not met	Comments [expected date]
Designated lead consultant Paediatrician/Haematologist for whom thalassaemia is a major interest and responsibility					
Named deputy					
Middle grade cover (Specialist Registrar or Staff Grade doctor) out of hours					
Staff to cover the roles of	Lead nurse - training, audit, liaison				
	Regular nursing staff on day-care area to cannulate, start and supervise transfusions				
	Nurse specialist/counsellor outreaching into community (teach to use pumps etc)				
	Key contact for patients and families				
	Deputy for Key contact				
Clinical psychologist for children with special interest					
Clinical or health psychologist for adults					
Haematology, biochemistry, microbiology and appropriate blood bank laboratory facilities					
Access to	Dietician				
	Social worker				
	Language interpreters				
	Dental team				
	Sufficient A&C support to ensure proper communication between family/Clinic/Centre/ GP plus the child/family				
	Designated paediatric and adult Cardiologist				
	Designated paediatric and adult Endocrinologist				
	Designated paediatric and adult Hepatologist				
	Designated paediatric and adult Anaesthetist - liaison with medical and surgical teams				
	Designated contact in Genetics services				
	Fertility services and support from designated Obstetrician				
	Link with bone marrow transplant service				

Clinic and Centre Services

	Fully met	Working towards	Not met	Comments [expected date]
Times patients can access phlebotomy include at least 2 hours before 9 am or after 5 pm at least once a week				
Transfusions given in specified, regular treatment area				
Transfusion can be offered out of hours (after 5 pm or at weekend)				
Transfusion area has regular nursing staff who can cannulate				
All patients have a ferritin level recorded in the last 3/12				
All patients offered choice of thumb-tack type needles as alternative to butterfly needles for infusions of desferrioxamine				
All patients with high ferritin [> 2500 ng/ml] and/or difficulty adhering to standard desferrioxamine pump treatment offered pre-filled balloon type infusers				
Patients with ferritin > 2500 ng/ml, or cardiac impairment or desferrioxamine sensitivity have been offered escalated or alternative chelation, as per local protocol				
Patients receiving desferrioxamine have had audiogram within last 12 months				
Patients receiving desferrioxamine have had ophthalmology check within last 12 months				
All patients receiving deferiprone are monitored according to locally agreed written protocol				
All patients receiving deferiprone are issued 'adverse effect' warning cards				
All patients are monitored according to schedule in Appendix B				
Hepatitis B and C serology checked if LFT's abnormal				
All patients referred to Hepatologist if Hepatitis B or C positive				
Patients with osteopenia or osteoporosis considered for regular biphosphonates				
Immunisations	All patients have had Hepatitis B immunisations			
	Pneumococcal, HiB and meningococcal vaccines up to date if splenectomised			
Appropriate infection prophylaxis post-splenectomy				
All patients/families have considered/discussed/been referred to centre for full information about bone marrow transplantation				
All patients have had multi-disciplinary team review at Clinic or Centre (where they receive routine care) at relevant points				
All patients/families have had full specialist review at Centre within the last 12 months.				

Health Outcomes of Care

The following tables are intended, for local use initially, to help Clinics and Centres to audit the progress of patients under their care.

Clinic Size

	Number of patients
Paediatric (<16 years) thalassaemia patients managed	
+ Adult (16 years and over) thalassaemia patients managed	
= Total number of thalassaemia patients managed:	

Investigation/ measurement	Result	Number of patients	% patients	Comments
Growth	Height progressing along satisfactory centile			
	Growth velocity unsatisfactory			
Physical examination	Bone changes			
	Splenomegaly			
	Hepatomegaly			
Average Hb (pre-transfusion)	<9.5 g/dl			
	9.5-10.5 g/dl			
	>10.5 g/dl			
Average serum Ferritin	<1000			
	1000-2500			
	>2500			
Liver function tests (over last 12 months)	Transaminase >2x upper limit of normal on one or more occasions			
	Transaminase consistently <2x upper limit normal			
Virology (within last 12 months)	HbsAg+ve			
	Anti-Hbs protective			
	HCV RNA +ve			
	Anti-HIV+ve			
Glucose tolerance test (within last 12 months)	Normal			
	Impaired glucose tolerance			
	Diabetes			
Calcium levels (over last 12 months)	Normocalcaemic on treatment			
	Normocalcaemic not on treatment			
	Hypocalcaemia on one or more occasions			
Thyroid function tests (over last 12 months)	Euthyroid off treatment			
	Euthyroid on treatment			
	Hypothyroid on one or more occasions			
Cardiac review (within last 12 months)	Normal			
	Cardiac arrhythmia			
	Cardiac failure			
Endocrine review (within last 12 months)	Growth Hormone deficient			
	Normal puberty			
	Delayed puberty*			
	Hypogonadism* (* see definitions, section B.15)			

Audiometry (within last 12 months)	Normal			
	Hearing loss			
Ophthalmology (within last 12 months)	Normal			
	Abnormal			
Liver iron (within last 12 months, biopsy or MRI estimation)	<7mg/g dry wt			
	7-15mg/g dry wt			
	>15mg/g dry wt			
Cardiac T2* MRI (within last 12 months)	T2*>20ms			
	T2* 8-20 ms			
	T2*<8 ms			
DEXA bone scan (within last 12 months)	Normal			
	Osteopenia			
	Osteoporosis			

Key Clinical Events

Event	Number of patients	% of patients	Comment / detail
Yersinia			
Other Sepsis			
Fracture			
Heart failure			
Dysrhythmia			
Splenectomy			
Cholecystectomy			
Other operation			
Bone marrow transplantation			
Death			
Other			

Appendix D

Levels of Evidence

Grading of recommendations

Grade Type of recommendation (based on AHCPR 1992)

A (levels I a, I b)

Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation

B (levels I a, I b, III)

Requires availability of well conducted clinical studies but no randomized clinical trials on the topic of the recommendation

C (Level IV)

Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable formal studies.

Appendix E

Glossary

adherence

the extent to which a person is able to take medication exactly as prescribed.

aetiology

cause.

agranulocytosis

absence or very low levels of granulocytes (neutrophils), the white blood cells which fight off bacterial and fungal infections.

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 beta globin.

amenorrhoea

absence of menstrual periods

anaemia

low blood level, specifically low level of haemoglobin (the red oxygen carrying pigment inside the red blood cells).

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.

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).

arthritis

painful inflammation and swelling in joints.

arthropathy

pain in the joints.

audiology

clinical speciality of managing hearing.

audiometry

measurement of hearing.

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 beta 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.

biphosphonates

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

butyrate

a naturally occurring fatty acid chemical which has been shown to increase production of foetal or baby type haemoglobin in certain circumstances.

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.

cartilaginous dysplasia

abnormality of the developing cartilage, the smooth material at bone ends causing joints to move smoothly.

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(?)

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

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

deferiprone

an iron chelating drug which is active when taken by mouth. Its original name was L1, and is licensed under the name Ferriprox.

densitometry (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 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.

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.

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.

electrophoresis

a laboratory technique in which different proteins in solution are separated, by passing a weak electric current through the solution.

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.

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).

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".

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.

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.

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.

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 nor-

mal 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”.

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.

hyperglycaemia

elevated blood sugar.

hypersplenism

overactive spleen, often also enlarged, resulting in lowered blood counts.

hypertension

high blood pressure.

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.

ICL670

the name of a recently developed iron chelating tablet, which is likely to be licensed soon.

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.

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.

malocclusion (dental)

the teeth do not meet properly when the jaws close.

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

necrosis

tissue death

neonate

newborn.

nephropathy

kidney problem.

obstetrics

the medical speciality of caring for pregnant women and their unborn children, until after delivery.

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.

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.

paediatrics

the clinical speciality of caring for illness in children.

pamidronate

a medication (one of the biphosphonates) which can help put calcium back into bones).

parathyroid

the glands which control calcium levels in the blood and bones, by producing parathyroid hormone.

pathogenic

causing illness.

pathology

the study of disease processes, and of diseased tissues or organs

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.

polymorphism

(literally "many forms") usually describing the possibility of different forms which can occur at a single gene site.

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.

R2/R2*

a magnetic property of tissues which increases with raised iron content

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

stem cells

the earliest, most primitive cells in the body which can mature into almost any of the tissues

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

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

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)

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. It infects particularly people who have high iron levels and are on iron chelation.