2023

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

4th Edition

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Production

This publication is a joint effort by the United Kingdom Thalassemia Society and the UK Forum for Haemoglobin Disorders. The writers and editors generously volunteered their time and expertise, without any monetary compensation or benefits. It is important to note that no financial or other support was obtained from the pharmaceutical industry for the creation of these standards. The UK Thalassemia Society solely covered all the expenses related to their production and publication.

Clinical disclaimer

Whilst the information presented in this document is based on available evidence and the knowledge and perspectives of its authors, including the UK Thalassemia Society and the UK Forum on Haemoglobin Disorders, it is important to note that they cannot be held liable for any clinical issues that may arise in individual patients who are treated according to the content of this document.

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Forewords

BAMBOS CHARALAMBOUS MP
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October 2023

Standards of clinical care for treating people with Thalassaemia

The standards of clinical care for treating adults and children with thalassaemia brought forth by the UK Thalassaemia Society, represent a significant step towards improving the quality of care and support for individuals living with thalassaemia. These guidelines will undoubtedly assist healthcare professionals in adopting standardised practices, leading to enhanced patient outcomes and an improved quality of life for patients living with thalassaemia and their families.

As the Chair of the All-Party Parliamentary Group for Thalassaemia, I commend the UK Thalassaemia Society and the authors for their relentless dedication and applaud their efforts in creating this comprehensive resource. It is my hope that these guidelines will inspire collaboration, education, and ultimately raise the standards of care of thalassaemia throughout the United Kingdom.

Together, let us strive for a society where individuals affected by thalassaemia can lead fulfilling lives, access quality and consistent care no matter where they live in the United Kingdom.

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4 October 2023

4th Edition of the Standards for the Clinical Care of Children and Adults living with Thalassaemia
Foreword by Professor Baba Inusa, Chair, National Haemoglobinopathy Panel

I am proud to be able to comment on this great work led by the UK Thalassaemia Society and in particular the energy by Roanna is exceptional, thanks Romaine for putting up a great team. The fourth edition of the standards for the Clinical Care of Children and Adults living with Thalassaemia in the UK is so named because of jurisdiction but I know that this resource will be used across the world.

As Chair of the National Haemoglobinopathy Panel, I am honoured to work closely with you and the team that put this comprehensive document together. The table of contents is well put together to enable users to navigate their way efficiently through. The introduction in itself is an educational material about the first description of thalassaemia and an attempt to demystify the diagnosis, the management and the prospect of future therapy. The reader would also understand the justification for the 4th edition when they go through the "what is different in this edition". There are a number of service developments that have taken place, and this has contributed to better coordination of services and the increase in communication between specialists across the country. The establishment of the All-Party Parliamentary Group (APPG) for thalassaemia in 2019 and the active involvement of the Member of Parliament in your work has been a great achievement.

Chapter 2 describes the "Organisation of Services" which includes the establishment of the networks of care with the designation of the four haemoglobinopathy coordination centres (HCC) for thalassaemia in England, the designation of Specialist Haemoglobinopathy treatment centres (SHT) and the overarching role of the National Haemoglobinopathy Panel (NHP) for complex cases and high-cost therapies including bone marrow transplantation. Your description of the different roles and responsibilities of the network arrangements is excellent, well done. I think the need to share information across different centres must be encouraged and the role of the NHP is provide the platform to do this. It is worth noting that engagement between the different levels needs to be supported by patients and their families and we are indebted to the contribution of the UKTS.

Chapter 3: Annual Review
This is a useful manual and guide for clinicians in specialist and local treatment centres. It is almost prescriptive and useful tool for all levels of experience. It provides guidance for clinicians and also a tool for patients to understand why these assessments are necessary.

Subsequent chapters in section B provides detailed standards of care for the different presentations and complications in thalassaemia. Each chapter ends with a summary recommendation, useful references and additional reading which the authors are encouraged to do.

I recommend this excellent material for your reading and adoption for improvement in the care of your patients

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30th August 2023

There is no doubt that care for thalassaemia has improved over recent years but, relative to other subspecialist areas of haematology, it remains neglected from the perspective of investment in staff, facilities and research. The UK Thalassaemia Society has worked tirelessly to change this, and the updated guidelines provided in this document serve as a foundation for good care.

Working with patients living with thalassaemia is a privilege, there are few areas of practice which offer the unique opportunity for doctors and patients to grow older together. As a consequence, the nature of the patient doctor relationship is different from other areas of haematology. Thus, caring for patients with the inherited haemoglobinopathies has been a professional high point and I believe this aspect of haematology is rightly becoming a more popular area in which to sub-specialise.

The inclusion of new chapters in this edition of the guidelines, such as adherence, quality of life, and social issues, is a significant and valuable addition. These topics reflect the comprehensive approach needed to provide holistic care for individuals with thalassaemia. By addressing not only medical aspects but also the broader impact of the condition on patients' lives, these guidelines help healthcare providers offer better support and guidance to patients and their families, ultimately improving the overall care experience.

By highlighting the importance of adherence to treatment regimens, they emphasize the need for patients to actively participate in their own care. Furthermore, focusing on quality of life and social issues recognizes the broader impact of thalassaemia beyond its medical implications. The guideline authors should be congratulated on the high quality and thoughtful nature of this document which will help those involved with thalassaemia understand the nature of good holistic care.

BSH supports these guidelines and will continue working with UKTS and clinicians to improve care and implement the standards into practice throughout the UK.

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On behalf of the UK Forum on Haemoglobin Disorders I am delighted to support the development of the 4th Edition of the Standards for the Care of Thalassaemia Syndromes. These clinical standards are utilised by health care provides throughout the UK and abroad and define the core standards to be achieved to maximise clinical outcomes.

The UKTS has a long-standing collaborative partnership with the UKFHD, and development of the revised standards will help provide a benchmarking framework for the peer review programme led by the UKFHD.

Provision of clinical care of thalassaemia patients has improved markedly over the last decade with MRI assessments becoming standard of care along with clear improvements in multidisciplinary working between and within centres. The establishment of the National Haemoglobinopathy Panel (NHP), the Haemoglobinopathy Coordinating Centres (HCC) and the specialist haemoglobinopathy teams (SHT) helping support the delivery of care in local haematology centres means that patients have specialist oversight into their clinical care from local, regional, and national experts.

The framework will help improve clinical outcomes for patients and ensure best practice is available everywhere.

Alongside this data from the National Haemoglobinopathy Registry (NHR) will allow centres (SHT and HCC) to review and audit outcomes.

The clinical reference group has supported the development of the revised iron chelation policy, and this means that patients now have access to all the chelation options.

There are still many challenges ahead, but an immense amount of work has been undertaken to ensure and support provisional of optimal care nationally. These revised standards will ensure there are clear recommendations for all centres and teams nationally.

Dr Farrukh Shah

Chair UKFHD
Chair NHR

Message from the Chair

I am delighted to introduce to you the long-awaited Standards for the Clinical Care of Children and Adults Living With Thalassaemia in the UK (4th Edition), produced by the UK Thalassaemia Society. As the Chair of the Society, it is my privilege to present this comprehensive and invaluable resource to the medical community.

Thalassaemia, a group of inherited blood disorders, poses a significant challenge to patients, families and healthcare professionals worldwide. Despite the undeniable progress achieved through improved chelation, care networks and peer reviews, individuals living with thalassemia in the UK still face social stigma, discrimination and, in some cases, inadequate access to specialised care. As a patient society, we see it as our responsibility to address the medical and social barriers hindering the fulfilment of goals for individuals living with thalassaemia.

In light of this, our Society has worked tirelessly to develop these guidelines, aiming to enhance the care and management of individuals living with thalassaemia throughout the United Kingdom.

These guidelines represent the culmination of extensive research, collaboration and expertise from a multidisciplinary team of renowned specialists in the field of thalassaemia. Their dedication and commitment to improving patient outcomes have resulted in a document that encompasses the most up-to-date evidence-based recommendations.

The 4th edition covers a wide range of topics, including diagnosis, treatment, monitoring, new therapies and psychosocial support. They provide clear and concise guidance on various aspects of patient care, ensuring that healthcare professionals can deliver optimal treatment and support for patients with thalassaemia in a consistent manner.

We have also taken great care to include practical recommendations for the management of complications associated with thalassaemia, such as iron overload, transfusion-related complications and the use of chelation therapy. These guidelines will serve as a valuable resource for healthcare professionals at all levels, from trainees to seasoned practitioners.

Furthermore, we believe that these guidelines will facilitate collaboration and knowledge-sharing among healthcare providers, ultimately contributing to the improvement of thalassaemia care globally. Our hope is that they will serve as a foundation for further research and advancements in the field.

I would like to express my deepest gratitude to all the authors who generously volunteered their time and expertise to contribute to this project. A special thank you goes to Dr Shivan Pancham and Dr Farrukh Shah, the editors, who dedicated most of their free time over the past year and a half to this endeavour. Their unwavering commitment and expertise have made this achievement possible. I would also like to express my appreciation to Roanna Maharaj, our Vice Chair, without whom this book would not have come to fruition.

I encourage all healthcare professionals involved in the care of patients with thalassaemia to familiarise themselves with the Standards for the Clinical Care of Children and Adults Living With Thalassaemia in the UK. By implementing these recommendations into our practice, we can collectively enhance the quality of care of, and make a positive impact on, the lives of those affected by this challenging condition.

To my fellow 'patients', I encourage you to utilise this publication, educate yourselves about your condition and don't hesitate to ask questions. It is extremely important that you take an active role in your treatment journey! Together with the medical community we have established the clinical standards of care and now it's time for us to join forces and ensure these standards are upheld throughout the United Kingdom.

Thank you for your ongoing support and dedication to the thalassaemia community.

With very best wishes,

Gabriel Theophanous

Chair, UK Thalassaemia Society

Context and Aims of the 4th Edition

The United Kingdom Thalassaemia Society (UKTS) has been actively involved in the development and dissemination of thalassaemia care clinical practice recommendations and related documents for more than 45 years. The UKTS *Standards for the Clinical Care of Children and Adults Living With Thalassaemia in the UK*, referred to as the *Standards of Care*, is viewed as an important resource for healthcare professionals who look after individuals living with thalassaemia.

About the publication

This publication aims to provide comprehensive guidance on diagnosing and managing thalassaemia, with a focus on monitoring the condition, managing symptoms, and preventing or delaying the onset of common secondary conditions. By following these recommendations, healthcare professionals can enhance the quality of life of individuals living with thalassaemia. The publication emphasises the importance of a multidisciplinary approach to provide integrated care and address the heterogeneous needs of the patient population.

Background

Thalassaemia is a complex, chronic congenital condition characterised by abnormal production of haemoglobin (Hb). It is primarily caused by mutations in the genes that control the production of either the alpha- or beta-globin chains of Hb. These mutations lead to reduced or absent production of one or both globin chains, resulting in ineffective erythropoiesis and subsequent severe anaemia.

Thalassaemia is believed to have been known about in ancient times and present in various parts of the world, especially among the populations of the Mediterranean regions and Southeast Asia. Ancient Greek authors attributed the first recorded description of thalassaemia to Hippocrates (Zaino, 1964). The condition has also been diagnosed in well-preserved in Egyptian mummies, ancient Sardinian and Sicilian populations, Native Americans (Incas, Peruvians), Indians of Columbia, Mexican Aztecs, Mayas of Yucatan and the remains of a population in central Thailand dating back 4000 years (Sanna, 2006)

Thalassaemia is prevalent in populations with a history of malaria, as the genetic mutation that causes thalassaemia also provides some resistance to malaria. This selective advantage has led to a higher frequency of thalassaemia carriers in areas where malaria has been endemic because they have had a survival advantage over individuals without the mutation. Consequently, over time, the high carrier rates in these populations have led to higher incidence of thalassaemia cases.

Since the early 1920s, the genetic evolution of thalassaemia among Mediterranean populations has been extensively studied, providing valuable insights into its history, prevalence and distribution in different regions of the world.

In 1927, the American paediatrician Thomas Cooley first described a severe form of thalassaemia now known as beta thalassaemia major. Cooley published a report on a group of five children with a form of severe anaemia and splenomegaly. His work was crucial in identifying and understanding the clinical and genetic aspects of thalassaemia, and his observations and research paved the way for advancements in treatment.

The clinical management of thalassaemia has long been of paediatric dominance. In the 1960s and 1970s, when its pathogenesis was poorly understood and blood transfusions and iron-chelating agents were scarce, few patients entered adulthood. Though this is no longer the case in the UK, with most patients living into early adulthood, premature deaths still occur due to iron overload-related illnesses, infection and substandard care.

The prevalence of thalassaemia varies across different regions in the UK. Data published in May 2021 from a review by the National Haemoglobinopathy Registry (NHR) indicate that there were 924 people living with beta thalassaemia major in the UK, 275 people living with beta thalassaemia intermedia, 123 people living with beta thalassaemia/HbE disease, and 285 people living with HbH disease. Each year, there are around 20–30 new births with a moderate-to-severe form of thalassaemia in the UK.

UKTS Survey (2021–2022)

In 2021, the UKTS surveyed its members via an online questionnaire to investigate the incidence of secondary conditions and the impact on their quality of life. Of 106 respondents, 97% of patients reported having acquired more than one secondary condition, 63% of patients reported having five or more secondary conditions, and 32% of patients reported having 10 or more secondary conditions. Chronic bone and joint pain, which was previously underreported in publications and undertreated, were experienced by 83.3% of patients and reported in children as young as 3 years of age.

Worryingly, the survey also highlighted the significant disparity between life expectancy and the early onset of secondary conditions among individuals from various ethnic groups.

When asked about their quality of life, 86.4% of respondents reported thalassaemia as having a moderate-to-severe impact on their overall quality of life. Respondents also reported thalassaemia having a significant emotional and social impact on patients and their families. Overall, 78.2% of patients reported feelings of anxiety, depression and fear

due to their condition, and reported experiencing stigma and discrimination during several periods of their lives. Additionally, adult patients and parents/carers expressed concern, stress and anxiety about managing their/their child's complex medical needs, and navigating the national health services, education and employment. The average time that a patient with transfusion-dependent thalassaemia (TDT) with **no incidence of secondary conditions or emergencies** may spend visiting hospital for routine 3 weekly transfusions and iron monitoring is 64 days, whilst they spend 365 days receiving iron chelation medication administered up to four times per day.

Not only does this impair the family's overall quality of life, but it can also negatively impact the financial status of the household regarding the need for time off work for transfusions, clinic reviews, diagnosis/monitoring investigations, leave for acute illnesses, etc.

Improving thalassaemia care

Many individuals living with thalassaemia surpass their own life expectancy expectations and achieve some of their lifelong dreams as a result of being extremely well managed and supported.

This has partly resulted from the understanding that the clinical spectrum of thalassaemia is wider than originally believed, and from greater diagnostic consideration of complications presenting in adolescence and adulthood. However, there is no doubt that outstanding achievements in increasing survival predominantly stem from improvements in services and care.

The establishment of haemoglobinopathy specialist centres and multidisciplinary teams, the creation of large epidemiological data sets, and the emphasis on early diagnosis and treatment, together with important new therapies that originate from dynamic preclinical and clinical research, have all been instrumental in the improvement in standards of care.

However, it is important to note that despite the best efforts of clinicians, the standards of thalassaemia care are variable throughout the UK due to a combination of factors that include small patient numbers, lack of funding and prioritisation of services, and institutional racism.

The findings of the *2020 Peer Review for Children and Adults living with Haemoglobin Disorders* revealed that there is an uneven distribution of patients with thalassaemia across the UK. Other than the Northwest of England, the West Midlands and some regions of London (where the majority of patients reside), most centres that specialise in treating patients with haemoglobinopathy have only a few patients living with thalassaemia (fewer than 15 patients), and a much larger number of patients with sickle

cell disease. As a result, there are only a limited number of centres that can be considered to be providing true specialist care for thalassaemia.

Further work is needed to achieve the original aim of the 1st Edition of the UK Thalassaemia Society *Standards of Care* (2005); that every patient, regardless of location, should have access to optimal, specialist management guidance and supervision, as well as local routine care.

Progress made since the 3rd Edition

There have been a number of significant developments since the 3rd Edition of the *Standards of Care* was published in 2016. In 2019, an All-Party Parliamentary Group for Thalassaemia was established to raise awareness of and advocate for improved policies, and to provide a platform for discussion and collaboration among parliamentarians, policy makers, healthcare professionals and families affected by thalassaemia. The chair of the All-Party Parliamentary Group for Thalassaemia since its inauguration has been Bambos Charalambous MP with secretariat duties provided by the UKTS.

A revised NHR was launched in 2020, with the aim of informing commissioning and healthcare planning by collecting information regarding the numbers of affected people looked after at various centres, and recording aspects of their clinical care and outcomes. Additionally, in 2020, the National Haemoglobinopathy Panel (NHP) was launched along with four haemoglobinopathy coordinating centres (HCCs) for thalassaemia (North of England; the Midlands; London and Southeast; and London, South Central and Southwest.

A Clinical Reference Group (CRG) for haemoglobinopathies – which includes clinicians, commissioners, public health experts and service users – has continued the work under the auspices of the National Programme of Care for Blood and Infection to advise National Health Service (NHS) England on how these specialist services can best be commissioned and provided. The CRG prepared the Service Specifications *Specialised Services for Haemoglobinopathy Care (All Ages)* and, in 2021, developed a clinical commissioning policy proposal for the treatment of iron overload in patients with chronic inherited anaemias, including the thalassaemias. As well as the use of monotherapy or combination routes already approved as per the 3rd Edition of the UKTS Clinical Standards for the Clinical Care (2016) of Children and Adults with Thalassaemia, the policy proposes that combination of the oral chelators deferiprone and deferasirox should be routinely commissioned for patients on the basis of clinical need and patient choice. The NHSE service specification (NHSE 2019) indicates that consistent magnetic resonance imaging (MRI) scan programmes to quantify tissue iron levels should be available nationally for monitoring, that oversight of iron chelation and annual reviews should be undertaken by experienced clinicians in a Specialist Haemoglobinopathy Team

(SHT) or an HCC, and that decisions should consider holistic circumstances together with the views of patients and carers. More recently the policy for allogeneic haematopoietic stem cell transplantation (HSCT) for adult patients with transfusion dependent thalassaemia has been approved by NHSE (November 2023) and will be an option for patients who have matched siblings but were not transplanted as children.

In England, there is a dedicated NHS Sickle Cell and Thalassaemia Screening Programme (NHS SCTSP) that aims to identify carriers of thalassaemia, sickle cell or other haemoglobin variants. The screening programme targets pregnant women, the biological father and newborn babies.

Although the UK National Screening Committee recommends screening newborns through the newborn blood spot test (heel-prick test) for some haemoglobinopathies, such as sickle cell disease, it does not recommend screening for thalassaemia. This is because thalassaemia may not be detected at an early age due to the presence of fetal haemoglobin (HbF), although the most serious form of thalassaemia may still be detected and should be reported.

Work to address the complex issues surrounding the late detection of at-risk couples is ongoing. Births of babies affected by clinically significant thalassaemias have remained consistent at between 20 and 30 affected births per annum (Public Health England 2018).

In 2018, the UKTS and the Sickle Cell Society (SCS) were awarded a 5-year contract commissioned by the NHSSCTSP that aimed to improve screening services for thalassaemia and sickle cell disorders in the UK. Some of the projects included sharing resources and expertise, joint awareness campaigns, collaborative evaluation and data sharing, training and capacity building, and advocacy and policy development.

The Societies have made significant achievements in improving screening services for thalassaemia and sickle cell disease in the UK. One of the primary goals of the collaborative project was to address the challenges highlighted in the NHSSCTSP's trends and performance data. The Societies have been successful in supporting the NHSSCTSP to achieve this goal by providing direct support to users of the NHSSCTSP and ensuring that service provision addresses user needs and preferences, reducing inequalities.

One of the most significant achievements of the collaborative project is the development of new resources and tools to support screening services. The UKTS and the SCS has worked with the NHSSCTSP to create a variety of resources, including patient information leaflets, awareness-raising materials, educational resources (the *It's In Our Genes* Report, based on the experiences of service users and launched in 2022) and e-learning resources (currently under revision, expected to relaunch 2024) for healthcare

professionals. These resources have helped to increase awareness of thalassaemia and sickle cell disease, and have improved the quality of care provided to patients.

The Societies have also provided education and awareness-raising sessions for communities at high risk of sickle cell disease and thalassaemia. These sessions have helped to increase the uptake of screening services and improve the early detection of these conditions.

In addition, the Societies have played an essential role in advocating for the rights of families with thalassaemia and sickle cell disease. The collaboration has helped the NHSSCTSP to ensure that screening services are accessible and equitable for all individuals, regardless of their background or socioeconomic status.

The UK Forum for Haemoglobin Disorders, working with the formerly known West Midlands Quality Review Service (WMQRS) developed a comprehensive set of Quality Requirements drawn from the 1st edition of the *Standards of Care*; these have been used to introduce a system of 'peer reviews' to assess service provision across networks for care. Since 2008, four peer reviews have taken place: the WMQRS Review of Services for Haemoglobin Disorders for Children 2010–2011, the WMQRS Review of Services for Haemoglobin Disorders for Adults 2012–2013, the WMQRS Review of Services for Haemoglobin Disorders for Children and Adults 2014–2016, and the WMQRS Review of Services for Haemoglobin Disorders for Children and Adults 2019–2020. The resulting reports highlighted a number of issues, of which the most worrying is the lack of resources in terms of experienced specialist medical, nursing and allied healthcare staff. Patients with Hb disorders have highly complex conditions and cannot be successfully managed without a holistic, individually tailored treatment regimen supervised by skilled and experienced clinicians. Networks for care and annual reviews by expert clinicians should have eliminated most of the inequalities in care that existed before the publication of the first *Standards of Care* in 2005. There is no doubt that improvements have been made; the majority of patients surveyed report that they receive their essential monitoring tests regularly, including heart and liver MRI scans and dual-energy X-ray absorptiometry (DXA) scans (UKTS national survey, 2021), and this is to be welcomed; however, there are still areas that do not seem to be adequately covered by the network system and there are patients who have never had an appointment with an expert clinician.

The NHP is a panel of experts in the field of haemoglobinopathies appointed by the NHS in the UK. The panel is responsible for providing guidance and recommendations on the screening, diagnosis and management of haemoglobinopathies, including thalassaemia and sickle cell disorders. The panel consists of healthcare professionals with expertise in various disciplines relevant to haemoglobinopathies, such as haematology, genetics, laboratory medicine and primary care. Their collective knowledge and experience help to

inform national policies and guidelines for the screening and management of these conditions.

The NHP collaborates closely with national patient organisations, such as the UKTS and the SCS, to ensure a coordinated approach in addressing the needs of individuals affected by haemoglobinopathies. Working together, they develop and implement screening programmes, raise awareness, provide support and advocate for policy changes.

The recommendations and guidelines provided by the NHP are used by healthcare professionals across the country to ensure standardised and evidence-based approaches to the screening, diagnosis and management of haemoglobinopathies. These guidelines help to improve the quality of care and outcomes for individuals with thalassaemia and sickle cell disorders in the UK.

In 2022, the UKTS was invited to join the UK Rare Disease Framework Panel to raise awareness about thalassaemia, highlight the specific needs of individuals affected by the condition and advocate for equitable access to healthcare services, research funding and support networks. The UKTS was included to help shape the national strategy for rare diseases, ensuring that thalassaemia received appropriate attention and resources within the broader rare disease landscape.

In 2023, NHS Blood and Transplant (NHSBT) commissioned by NHS England will offer blood group genotyping to all individuals living with TDT and sickle cell anaemia in England. This new initiative will help to ensure that individuals living with TDT receive blood transfusions that are safer, more effective and better matched to their needs, to reduce the risk of transfusion reactions and other complications. It is a revolutionary step in the right direction towards improving the quality of life of those living with thalassaemia in England. No decision has been made with regards to Wales, Scotland and Northern Ireland.

Standards of care

The UKTS *Standards of Care* are intended to provide clinicians, researchers, policy makers and other interested individuals with the components of thalassaemia care, general treatment goals and tools to evaluate the quality of care. The recommendations in the *Standards of Care* are not intended to preclude clinical judgement and must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities and other patient factors.

The recommendations in the *Standards of Care* include screening, diagnostic and therapeutic actions that are known or believed to favourably affect the health outcomes of individuals living with thalassaemia.

As indicated, the recommendations encompass care for youths (children between birth and age 11 years, and adolescents aged 12–18 years) and older adults (aged 50 years and older).

The UKTS strives to improve and update the *Standards of Care* to ensure that clinicians and policy makers can continue to rely on it as the most authoritative source for current thalassaemia care guidelines.

Aims and scope of these *Standards of Care*

In this publication, we have again outlined a model of care with defined standards for the delivery of care for individuals living with thalassaemia. We have addressed predominantly the needs of those who live with TDT and, in a separate section, those living with non-transfusion-dependent thalassaemia (NTDT). This publication is not intended to offer full clinical guidelines as these are well covered in other available published guidance. Our key focus is on the way in which services are structured and delivered.

In this 4th edition, we have ordered the main chapters in line with a pathway for a person living with thalassaemia, from birth into older adulthood. This works well in parts, but is to some extent artificial as many potential complications span the age ranges to varying degrees.

What is new in the 4th edition?

There are several changes and updates throughout these guidelines, but the principal ones are: **Chapter 7: Disease-Modifying Therapies** (including survival and late effects following allogeneic HSCT in thalassaemia and gene therapies); **Chapter 8: Growth, Development and Endocrine Functions**; **Chapter 9: Reproductive Health Across the Lifespan** (including menopause); and **Chapter 20: Optimising Venous Access**. There is also a new section dedicated to psychosocial wellbeing (Section E, which includes chapters on general psychology, adherence, holistic care and quality of life, and Social Welfare.

Appreciating the central role of the UKTS in planning and implementing changes, as in previous editions, we have included a number of relevant quotations at the start of each section, mainly derived from the 2021 national survey of adult patients organised by the

UKTS (*Incidence of Secondary Conditions, 2021)*. We hope that these enliven the text, as well as giving insight into how patients experience their condition and prioritise the issues they face.

Who is it for?

- Healthcare professionals
- Adults with thalassaemia, and their families and carers
- Policy makers
- Commissioners

Levels of evidence

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

Requirements: things that providers must do to ensure safe and adequate care, where omission could lead to poor clinical outcomes.

Recommendations: things that would be beneficial and that providers should try to do, but that would be unlikely to have an important impact on clinical outcomes.

Conclusion

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

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Summary of Standards of Care

SECTION A: Thalassaemia Services

Chapter 1: Organisation of Thalassaemia Services

- All Trusts treating patients with thalassaemia are expected to be part of a network.
- This network will consist of Local Haemoglobinopathy Teams, Specialist Haemoglobinopathy Teams and Haemoglobinopathy Coordinating Centres. There should be clear pathways between these centres.
- All patients with thalassaemia should have access to a Specialist Haemoglobinopathy Team. The role of the Specialist Haemoglobinopathy Team includes:
    - Agreeing and monitoring compliance with network care pathways and treatment protocols (elective and emergency) for its caseload of patients.
    - Supporting the provision of coordinated expert care and advice within the network. This will include the provision of 24/7 emergency advice for other clinical teams within the hospital and with other local hospitals.
    - Supporting the local provision of routine, non-complex care and ensuring that all patients have an annual review.

- The Haemoglobinopathy Coordinating Centre provides a coordinated leadership function, supporting Specialist Haemoglobinopathy Teams in the delivery of clinical care. This includes provision of a network multidisciplinary team meeting for the discussion of complex cases.

- The National Haemoglobinopathy Panel will work alongside the Clinical Reference Group, Haemoglobinopathy Coordinating Centres, Specialist Haemoglobinopathy Teams and other key bodies in thalassaemia care. It will provide all Specialist Haemoglobinopathy Teams and Haemoglobinopathy Coordinating Centres with access to national expert clinical opinion with regard to the treatment of complex cases, and will drive the delivery of a nationally consistent approach to care.

- Patients with thalassaemia may receive their regular management including transfusion therapy at either the Specialist Haemoglobinopathy Team, if this is their local centre, or via a Local Haemoglobinopathy Team if they live further away from the Specialist Haemoglobinopathy Team.

- Decisions about commencing transfusion and chelation therapy, and overview of the efficacy of these therapies, should be overseen by the Specialist Haemoglobinopathy Team.

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

Chapter 2: Annual Reviews

- Every person with thalassaemia will have the opportunity for their care and condition to be reviewed at least annually with a team of healthcare professionals who have experience in caring for thalassaemia disorders. This can take place during a visit to the Specialist Centre or at an outreach clinic where members of the Specialist Haemoglobinopathy Team visit the local centre at which the person receives their routine care.
- The assessment should cover all aspects of care, including educational and lifestyle factors that may affect health or influence adherence to treatment.
- Discussion of treatment options should include any new information that has become available, and an individual treatment plan for the next 12 months will be agreed.
- A copy of the annual review consultation, including the care plan, will be copied to the patient or, for children, their parents as well as health professionals involved in their care.
- Data should be entered into the annual review screens of the National Haemoglobinopathy Registry.
- People in families affected by thalassaemia should be able to meet and gain support from other affected families at the Specialist Centre or in the community.

SECTION B: Core Management Standards

Chapter 3: Standard Features and Treatment

- The mainstay of treatment for most patients with severe clinical phenotypes of thalassaemia remains a regular blood transfusion programme. Transfusions are typically delivered every 2–4 weeks, aiming to maintain haemoglobin levels high enough to support normal activity and prevent ongoing ineffective erythropoiesis, with its associated complications. Typically, the haemoglobin level should be

maintained above 95 g/L, but higher pretransfusion targets may be required in some individuals.

- Despite their necessity, each blood transfusion brings with it the delivery of excess iron to the body, which can accumulate in, and cause toxic damage to, vital organs: most notably, the heart, liver, and endocrine glands. Therefore, alongside regular transfusions, the other cornerstone of treatment is the prevention and management of iron overload and its consequences. This involves the use of iron chelation treatment which helps to bind and eliminate excess iron from the body and should usually be started after 10–12 transfusions or when serum ferritin is persistently >1000 µg/L. Ongoing management must take place.

- For a minority of patients, allogeneic haematopoietic stem cell transplantation (donor bone marrow transplant) may be curative. This option should be explored as a matter of course for younger children with transfusion-dependent thalassaemia who have a matched sibling donor.

- Providing services which are flexible and individualised, to maximise benefit and minimise disruption to patients' lives, must be the aim, and will help patients to adhere to sometimes onerous treatment and monitoring regimens.

- Recognition and support with the psychological, emotional, and social impacts of living with thalassaemia and the burdens of treatment it brings, are also key to delivering care in a way which meets the needs of patients and their families.

Chapter 4: Initial management of the newly diagnosed infant

- Confirmation of the diagnosis of a child with a serious thalassaemia syndrome will be timely and accurate.
- Laboratory investigations will include determination of globin genotype, Xmn1 polymorphism status, glucose-6-phosphate dehydrogenase status and red blood cell genotype/phenotype.
- The child will be monitored at least monthly to determine the likely clinical course.
- The family will be informed fully and sensitively from the outset once the diagnosis is confirmed, by appropriately experienced professionals, with the use of a culturally appropriate health advocate if necessary, and with the opportunity for full discussion.
- Suitable written information will be given to the family.

- A management plan tailored to the individual child will be agreed and implemented.
- The family will meet their 'key contact(s)' within the clinical team and be given contact numbers.
- The family will be informed about the National Haemoglobinopathy Registry with registration to include Local Haemoglobinopathy Team/Specialist Haemoglobinopathy Team and Haemoglobinopathy Coordinating Centre details.
- The family will be given the contact details for the United Kingdom Thalassaemia Society and any local support group(s).

Chapter 5: Red Blood Cell Transfusion

- At diagnosis all patients should have a group and screen with at a minimum: A, B, O, Rh (DCcEe), and Kell tested. Furthermore, extended red cell typing should be performed, in preference using genotyping (essential if transfused within last 3/12) with variant analysis (where available).
- Patients should receive ABO and Rh (DCcEe) and Kell compatible blood that is negative for antigens to clinically relevant antibodies.
- There should be a valid group and antibody screen available prior to transfusion being administered.
- Prior to the first blood transfusion at each hospital site, a full transfusion history should be taken and communicated to the Blood Transfusion laboratory, who can communicate with other hospitals where the patient has been transfused as well as the Blood Service so that the appropriate flags are placed on the transfusion laboratory information system.
- Hospitals in England should permit the sharing of the NHS Blood and Transplant (NHSBT) results on their patients with other hospitals.
- A Group and Screen validity of 1 week can be considered for those with thalassaemia on regular transfusion whether they have allo-antibodies or not.
- People with transfusion dependent thalassaemia (TDT) should be transfused every 3 to 4 weeks, to maintain the pretransfusion haemoglobin level 95-105 g/l. The pretransfusion haemoglobin level may be increased in those in whom it is deemed insufficient or in those who are symptomatic e.g., presence of significant extramedullary haematopoiesis.
- People with thalassaemia who are not yet transfusion dependent may need a one-off transfusion to treat a temporarily worsened anaemia e.g., during an episode of infection.

- For those who are small (<40kg) then a more accurate measure should be employed in calculating volume of blood to be transfused. A common formula is (desired – actual Hb (g/l)) x weight (kg) x 0.3 = ml to be transfused (assuming the haematocrit of the unit is 0.58 (Davies et al)) where the desired haemoglobin is usually set at 135g/l.
- British Society for Haematology guidance states that adults can be transfused at a rate of a unit over 90 minutes in adults (Robinson et al., 2018). Though, a faster protocol is used at several thalassaemia centres in England in adults >45kg, free of cardiac disease and receiving up to 3 units of mean volume of 260ml can be administered at the rate of one unit per hour (Sinclair, Trompeter & Al-Khafeji, 2013).
- Valid consent for blood transfusion should be obtained and documented in the patient's clinical record by the healthcare professional. There should be a modified form of consent for long term multi-transfused patients, details of which should be explicit in an organisation's consent policy.(https://www.transfusionguidelines.org/transfusion-practice/consent-for-blood-transfusion/guidance-for-healthcare-practitioners-involved-in-this-role#:~:text=The%20SaBTO%202020%20updated%20guidance,transfusion%20of%20a%20blood%20component).
- Certain transfusion reactions as well as near misses must be reported to SHOT/MHRA as per national guidance.

Chapter 6: Iron Overload and Management

- A protocol for iron chelation therapy in children and adults should be shared between the Specialist Haemoglobinopathy Team and local hospital teams within the clinical network, and reviewed at regular intervals. This should be based on current published evidence, expert opinion and national guidance.
- Decisions about initiating and changing chelation therapy should be made by the haemoglobinopathy specialist, taking into account the preferences of the patient and carers, and the views of other involved healthcare workers.
- Patients and carers should be informed about the benefits and possible adverse effects of each chelation option, and offered information in formats appropriate to their age and language and literacy level, with health advocacy as needed. The decision process should be recorded in the patient’s records.
- Patients and carers should be supported to adhere to chelation therapy using an multidisciplinary team approach including clinic doctors, nurse specialists and clinical psychologists, and play therapists for children. Peer support should be encouraged.

- Adherence should be monitored regularly, and problems carefully identified and addressed in a non-judgemental manner.
- Cultural competence is important in addressing adherence where patients and clinical teams are from different ethnic backgrounds. Having an understanding of a patient's social and cultural upbringing and behaviours plays an important role, together with an multidisciplinary team approach to support adherence in chelation.
- All patients should have access to cardiac magnetic resonance imaging for the assessment of myocardial iron overload and cardiac function, and to liver magnetic resonance imaging for the assessment of liver iron concentration. The magnetic resonance imaging methodology should be standardised and validated.
- Patients should be carefully monitored for side effects of iron chelation therapy, and treatment interrupted or reduced promptly to avoid serious toxicity.
- The outcomes of chelation therapy within local clinics and the clinical haemoglobinopathy network should be audited regularly.

Chapter 7: Disease-Modifying Therapies

Part A: Haematopoietic Stem Cell Transplant

- The families of all children with thalassaemia should have the opportunity to discuss the option of haematopoietic stem cell transplantation with the team at a transplant centre with experience in undertaking the procedure for this indication, whether or not there is currently a matched donor.
- Adults with thalassaemia should have the opportunity to discuss the option of haematopoietic stem cell transplantation with the team at a transplant centre with experience in undertaking the procedure for this indication, whether or not there is currently a matched sibling donor.
- They will be fully informed about all the potential risks and benefits of the procedure, in the immediate, middle and long term.
- For those with an appropriate donor who choose to proceed with transplantation, it must be undertaken at a centre with specific experience and expertise of managing thalassaemia transplants.
- Post-endocrinopathy care is essential, please see **Chapter 8: Growth, Development and Endocrine Function** for management.
- Psychological and social support for adults, children and their families should be provided to aid them on their transplant journey.

Part B: Cellular Therapies (Gene Therapies)

- Once gene therapies become available for the treatment of patients with transfusion-dependent thalassaemia in the UK, all eligible patients (or their parents/carers) will have the opportunity to discuss this treatment option. This will include a full discussion of risks and benefits associated with the procedure.

Chapter 8: Growth, Development and Endocrine Function

- Transfusion therapy should be initiated in time to prevent irreversible deformities associated with bone marrow expansion.
- Iron loading should be kept to a minimum, by careful monitoring and the use of effective chelation treatment, to reduce the risks of endocrine damage.
- Doses of desferrioxamine should be kept within a range that will minimise the risk of bone toxicity, phosphate wasting or reduced height velocity. Any bone changes possibly related to desferrioxamine toxicity should be suspected and investigated in children with bone/joint pain, bone biochemical abnormalities or short stature.
- Paediatric specialists in bone metabolism and endocrinology, with interest and expertise in managing the complications encountered, should be involved in the care of children with thalassaemia, ideally in a joint clinic setting.
- Children should have their growth and development monitored regularly from diagnosis until they have achieved full sexual maturity and final adult height. Any change in expected growth and development should be identified, investigated and treated promptly.
- Management of the maturing skeleton should focus on achieving peak bone mass.
- All patients should have their vitamin D level measured with supplements given if needed.
- All patients should be advised of the need for adequate dietary calcium for healthy bones.
- All patients should be advised to undertake weight-bearing exercise that promotes the achievement of peak bone mass and the maintenance of bone mineral density.
- Where paediatric endocrine input has been necessary then careful transition plans should be made at completion of puberty and linear growth. Ideally such transition should take place in a combined clinic. A detailed clinical summary and discussion should take place to ensure there is no disruption to treatment at this critical stage of adolescence.

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

Chapter 9: Reproductive Health Across the Lifespan

- In women with thalassaemia aged ≥45 years presenting with menopausal symptoms, the diagnosis of perimenopause or menopause should be considered based on their symptoms.
- Women with thalassaemia presenting with menopausal symptoms should be made aware of resources available for guidance, and should be offered treatment (lifestyle, non-hormonal interventions, and hormone replacement therapy) after information and support to help them make an informed decision about their management.
- Women with thalassaemia having treatment for menopausal symptoms should ideally have a review 3–4 months after starting treatment and should continue to be reviewed at least annually after that.
- Duration of treatments such as hormone replacement therapy should be individualised. No arbitrary limits should be placed on the dose of hormone replacement therapy, duration of usage or age of women having treatment.
- Women with thalassaemia aged <40 years presenting with premature ovarian insufficiency or early menopause (women aged 40–45 years) should be advised to take hormone replacement therapy and to continue to do so until at least the natural age of the menopause.
- Each Specialist Centre will identify a paediatric endocrinologist with experience in the management of thalassaemia.
- Pubertal development, growth, and endocrine function will be closely monitored in girls with thalassaemia, and prompt referral made if there is any suspicion of problems.
- At any time when the patient wishes they should be referred to a fertility/endocrine/assisted conception clinic with experience of thalassemia patients, to allow discussion about treatment options; culturally appropriate advocacy will inform these discussions.

Chapter 10: Reproductive Informed Choice – Prenatal Diagnosis and Preimplantation Genetic Testing

- Patients contemplating pregnancy will be assessed for possible risks to themselves and their babies; this evaluation should be updated as needed.

- At any time when the patient wishes they should be referred to a fertility / endocrine clinician with experience of thalassemia patients, to allow discussion about treatment options; culturally appropriate advocacy will inform these discussions.

- Patients contemplating Preimplantation Genetic Diagnosis (PGT should be referred to a genetics specialist to allow discussion and an onward referral for PGT if appropriate.

- Pregnant patients will be jointly managed during pregnancy and delivery by a ‘maternal medicine’ obstetrician experienced with haemoglobin disorders and by their haematologist.

Chapter 11: Management of Pregnancy

- Patients contemplating pregnancy will be assessed for possible risks to themselves and their babies; this evaluation should be updated as needed.
- At any time the patient wishes, they should be referred to a fertility/endocrine/assisted conception clinic with experience of thalassemia patients, to allow discussion about treatment options; culturally appropriate advocacy will inform these discussions.
- Pregnant patients will be jointly managed during pregnancy and delivery by a ‘maternal medicine’ obstetrician experienced with haemoglobin disorders and by their haematologist.

Chapter 12: Transition From Paediatric to Adult Services

- Young people should be supported to take responsibility for their health needs and choices. Education should be given to the young person and their parents or carers over time, to nurture and empower independence.

- Each young person requires a named/key worker for transition. The transition process should commence by age 12–14 years; this is dependent on development stages.
- Adult and paediatric teams will work collaboratively with the young person and their parents or carers to provide a timely and smooth handover. Primary, secondary and tertiary healthcare providers and community teams should be involved in the process, and in the young person's ongoing care.
- Any anxieties that the young person and their parent(s) or carer(s) may have, arising from the change from paediatric to adult health services, should be addressed.
- Psychosocial stresses that may negatively impact on adherence with their transfusion regimen, medication and/or self-care should be identified and managed.
- Close monitoring of thalassaemia treatment should continue over the transition period, with particular attention to the monitoring of iron stores and adherence to iron chelation therapy.
- Use of a recognised health transition framework, such as 'Ready Steady Go Hello', may be utilised to support the transition pathway protocols.
- A structured approach should be used to support the young person and their family to facilitate their transition journey in a gradual way.

Chapter 13: Acute Clinical Presentations of the Unwell Patient

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

- To enable timely escalation and transfer, where appropriate, for specialist management.

- To optimise outcomes for patients who become acutely ill.

Chapter 14: Management of Surgery

- All patients listed for elective surgery should undergo an assessment of risk related to the planned procedure, taking their underlying thalassaemia and comorbidities into consideration. Any discussions should involve patients/parents in shared

decision-making and make specific reference to cardiac, thrombotic, endocrine and metabolic disturbances.

- All patients undergoing major surgery should undergo a review by an anaesthetist with a specialist interest in perioperative assessment and optimisation.
- Patients undergoing urgent surgery should be discussed with the Specialist Haemoglobinopathy Team and escalated to the thalassaemia Haemoglobinopathy Coordinating Centres as required.
- Patients listed for planned surgical procedures can be referred to the thalassaemia Haemoglobinopathy Coordinating Centre multidisciplinary team for preoperative discussion if deemed to be high risk or to require specific input. All splenectomy cases should be discussed and referred to the National Haemoglobinopathy Panel in line with referral guidelines.
- Patients should be given access to all relevant information regarding thalassaemia-specific and anticipated issues related to surgery to allow for informed consent.

SECTION C: Prevention and Management of Complications

Chapter 15: Management of the Cardiovascular System

- Every patient must have access to a cardiology service with experience in the management of cardiac consequences of thalassaemia.
- Children should be referred for their first cardiac evaluation – including clinical assessment, electrocardiogram, echocardiogram and cardiovascular magnetic resonance imaging T2* – between the ages of 6 and 8 years, dependent on their ability to do breath holds for the scan.
- Cardiology assessments thereafter should be at intervals guided by symptoms, adequacy of chelation and the findings of previous assessments.
- A high-risk time for the development of cardiac problems is 16–25 years of age, and during this period assessments should be undertaken at least yearly.
- Patients with myocardial iron and left ventricular impairment with new-onset symptoms must be discussed with the Specialist Haemoglobinopathy Team, and reviewed urgently for consideration of inpatient intensive chelation.
- Patients must be considered for anticoagulation if they have indwelling venous lines or atrial fibrillation, including paroxysmal atrial fibrillation.

Chapter 16: Management of Impaired Glucose Tolerance and Diabetes Mellitus

- A paediatric and adult consultant diabetologist should be identified for each Specialist Haemoglobinopathy Team.
- Patients should be checked annually for impaired glucose regulation and diabetes from puberty, or from the age of 10 years if there is a family history of diabetes.
- Patients with diabetes should have a full annual diabetes review, including glycaemic control, cardiovascular risk factors and diabetic complications.
- Patients with diabetes should have access to a clinical health psychologist with experience in diabetes management.

Chapter 17: Management of Bone Complications

- Transfusion therapy should be initiated in time to prevent irreversible deformities associated with bone marrow expansion.
- Doses of desferrioxamine should be kept within a range to minimise the risk of bone toxicity or reduce height velocity. Any bone changes possibly related to desferrioxamine toxicity should be suspected and investigated in children with bone/joint pain or short stature.
- Management of the maturing skeleton should focus on achieving peak bone mass.
- All patients should have vitamin D measured with supplements given if needed.
- All patients should be advised of the need for adequate dietary calcium for healthy bones.
- All patients should be advised on lifestyle changes that promote the achievement of peak bone mass and the maintenance of bone marrow density: smoking cessation, avoiding excessive alcohol consumption and undertaking weight-bearing exercise.
- Diagnosis of hypogonadism and other endocrinopathies should be prompt, and appropriate hormone replacement therapy given.
- Adult patients should be monitored for low bone mass/osteoporosis.

- Bisphosphonates and other bone specific agents should be considered in patients with deteriorating bone marrow density/osteoporosis confirmed on dual-energy x-ray absorptiometry bone marrow density scan, particularly if there have been fractures.
- Osteoporosis treatments should be reviewed regularly.

Chapter 18: Managing Dental Complications

- Red blood cell transfusion in children with thalassaemia should be sufficient to prevent the development of marrow overgrowth and facial bone changes, and some of the associated dental problems.
- All patients should access regular dental care to prevent oral infection and manage the potential orofacial features of thalassaemia.
- Patients presenting with acute dental infections/abscesses should receive urgent dental care and antimicrobial therapy as required.
- Close liaison with the haematology team is required to determine the potential complications when delivering invasive dental treatment, and to put measures in place to reduce risk.
- All patients should ideally have a comprehensive dental assessment with their local dentist prior to the commencement of medication associated with the risk of medication-related osteonecrosis of the jaw to ensure that they are as dentally fit as feasible.

Chapter 19: Miscellaneous Complications in Thalassaemia

Part A: Gallstones

- When gallstones are symptomatic and require surgical intervention, cholecystectomy should be done via the laparoscopic route as this is associated with fewer postoperative complications and a shorter hospital stay.

Part B: Leg Ulcers

- Patients with leg ulcers should be assessed by a multidisciplinary team familiar with the management of leg ulcers in patients with haemoglobinopathies.
- Standard principles apply such as good wound hygiene, compression therapy if appropriate, and managing complications such as pain and infections.

- Patients should be offered lifestyle advice to promote ulcer healing and reduce the risk of recurrence such as regular walking, avoiding leg trauma and the use of frequent emollients.

- Hypertransfusion regimens are frequently used to improve anaemia although there are no data on the optimal pretransfusion target haemoglobin. Maintaining pretransfusion haemoglobin levels >105 g/L may be useful in some patients in addition to standard leg ulcer care.

- Referral to specialist dermatology and plastic surgical teams for skin grafting may be needed in severe cases.

Part C: Liver

- Liver function tests should be monitored at regular monthly intervals.
- Liver iron levels should be maintained within safe limits to avoid hepatic damage, using the range of available chelation options, and taking steps to encourage adherence to treatment.
- Adjustments to chelation and other treatment should be made promptly if abnormalities of liver function are detected on routine monitoring tests.
- Vaccination against hepatitis A virus and hepatitis B virus infection should be ensured.
- Liver disease should be managed jointly with a designated specialist hepatologist.
- Management of chronic hepatitis C virus infection should include histological assessment of fibrosis on biopsy and/or non-invasive techniques.
- Antiviral therapy aimed at sustained viral clearance should be planned and managed in collaboration with a designated specialist hepatologist.
- Patients with established cirrhosis should have regular surveillance checks for hepatocellular cancer.
- Patients presenting with deranged renal function and/or renal colic should be assessed for renal stones, with appropriate referral for specialist care as required.
- Weight loss, abdominal pain and diarrhoeas with or without steatorrhea should prompt investigation for pancreatic exocrine deficiency and/or other gastrointestinal complications.

Part D: Ophthalmological Manifestations in Thalassaemia

- All patients with thalassaemia who describe changes to vision or other ophthalmology symptoms should be reviewed by an ophthalmology team; assessments should include electrodiagnostic tests.

- All patients who are on continuous intravenous desferrioxamine infusion should have a baseline assessment and then have close ophthalmologic monitoring, as prompt drug discontinuation might potentially arrest the retinal damage.

- Patients on high doses of desferrioxamine should have regular measurement of serum ferritin level and the therapeutic index of desferrioxamine should be maintained below 0.025.

- Patients treated with deferasirox should have a baseline ophthalmological evaluation and further assessment if new visual symptoms occur.

Part E: Pancreatic Exocrine Insufficiency

- Patients presenting with weight loss and abdominal pain should have a detailed history and examination followed by a faecal elastase test.
- Patients should be referred for specialist gastroenterology input if faecal elastase is low.
- Patients should be encouraged to stop smoking and reduce/limit alcohol.

Part F: Renal Complications

- Renal function should be assessed monthly for patients on deferasirox.
- In the presence of unexplained electrolyte abnormalities and or glycosuria/microalbuminuria, consider renal Fanconi syndrome.
- Input from a renal specialist team should be obtained if renal function does not improve following dose reduction or omission of iron chelation.

Part G: Urological Complications

- Individuals with thalassaemia can develop urological complications such as renal stones.

- Presentation can be varied from asymptomatic to development of acute kidney injury and hydronephrosis from a stone causing obstruction. This may first be identified with unexplained renal impairment on biochemistry done as part of routine monitoring. It is important to ask about renal/loin/groin pain and check for haematuria.

- Renal impairment can be assumed to be due to iron chelation if a patient is using deferasirox, and if renal function does not improve after a week of withdrawal of deferasirox an urgent scan should be considered to look for renal stones, especially if there are symptoms suggestive of a renal stones.

- Patients presenting with symptoms suggestive of renal stones should be referred to specialist urology for management of renal stones.

- Patients may develop recurrent urinary tract infections as renal stones can harbour bacteria and a low threshold used for use of prophylactic antibiotics.

Chapter 20: Optimising Venous Access

- Peripherally inserted venous cannulas are suitable for periods of therapy lasting fewer than 5 days. The goal is to use the smallest gauge cannula in the largest vein available in a position suitable for the patient.
- Consider central venous access devices when peripheral access becomes difficult or for longer-term therapy with intravenous desferrioxamine.
- Adult patients with central venous access devices should be considered for thromboprophylaxis for the duration of the use of the central venous access device, unless there is a contraindication or unacceptable risk of bleeding.

Chapter 21: Review of Patients Previously Treated Outside the UK

- Children and adults who have been receiving treatment outside the UK will be seen, as soon as possible after they arrive, at an established Specialist Haemoglobinopathy Team for a thorough assessment.
- Transfusion treatment will be restarted without delay.

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

SECTION D: Non-Transfusion-Dependent Thalassaemia

Chapter 22: Non-Transfusion-Dependent Thalassaemia

- A comprehensive DNA diagnosis (beta-globin mutations, alpha-globin genotype, Xmn1 C→T polymorphism) should be undertaken as soon as the diagnosis of thalassaemia has been established.
- Parents, carers and patients should be counselled at diagnosis, and as often as needed thereafter, about the likely course of the condition and the therapeutic options available.
- During the first 3–5 years of life, children with thalassaemia should be monitored carefully and systematically for evidence of thalassaemia features that may require regular transfusion therapy. Older children, adolescents and adults with a diagnosis of non-transfusion-dependent thalassaemia should continue to be monitored regularly, for consideration of indications for transfusion, and for iron loading, pulmonary hypertension and extramedullary haematopoietic masses in particular.
- Complications of non-transfusion-dependent thalassaemia should be identified at an early stage and treated promptly.

Chapter 23: Psychosocial Needs Requirements

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

- Consideration of the family context and developmental/life stage of the person with thalassaemia is key to ensure that care and treatment recommendations are individually tailored to and appropriate for each patient.
- Psychosocial support, alongside specialist psychological care, should be provided as a standard part of thalassaemia clinical care, in both paediatric and adult services.

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

Chapter 24: Adherence

- Care teams should regularly discuss adherence with patients and families.

- Care teams should consider how they are able to best facilitate conversations around adherence with patients and families so that these can be continued in future appointments. This will include how they communicate with each other within the multidisciplinary team.

- Conversations around adherence should be collaborative and non-judgemental.

Chapter 25: Holistic Care and Quality of Life

- To optimise the quality of life of people with thalassaemia through both self-care and medical intervention.
- To support clinical teams in managing older patients with thalassaemia in acute settings.
- To recognise the need to review the goals of care of patients' management plans when appropriate.
- To give patients who are deteriorating and may be approaching the last year of their life the opportunities to discuss their wishes for their future care.
- To involve and support patients and their loved ones in developing an individualised plan of care that meets their needs.

Chapter 26: Social Welfare

- To ensure all individuals living with thalassaemia and their families have access to equitable specialised thalassaemia care and support services irrespective of where they reside in the UK.

- To assess the diverse lifespan-specific challenges families may face and recommend suitable adjustments or services that may help to improve quality of life.

- To signpost families and other healthcare professionals to the types of financial welfare services available in the UK

- To provide an insight into completing Personal Independence Payment applications for healthcare professionals

SECTION A: Thalassaemia Services

Chapter 1: Organisation of Thalassaemia Services

Networks for care and commissioning

Aims

To reduce morbidity and mortality, and to improve the experience of all haemoglobinopathy patients by reducing inequalities and improving timely access to high-quality, expert care.

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

To optimise care for all patients, wherever they live, by giving them access to specialist multidisciplinary care whilst ensuring that regular treatment is given as conveniently as possible, close to the patient's home.

To ensure good communication between patients and their families and the various agencies involved in their welfare, including the Haemoglobinopathy Coordinating Centre (HCC), Specialist Haemoglobinopathy Team (SHT), Local Haemoglobinopathy Team (LHT), primary care and, where relevant, social services and education.

Standards

- All English Trusts treating patients with thalassaemia are expected to be part of a network.
- This network will consist of LHTs, SHTs and HCCs. There should be clear pathways between these centres.
- All patients with thalassaemia should have access to an SHT. The role of the SHT includes:
    - Agreeing and monitoring compliance with network care pathways and treatment protocols (elective and emergency) for its caseload of patients.
    - Supporting the provision of coordinated expert care and advice within the network. This will include the provision of 24/7 emergency advice for other clinical teams within the hospital and with other local hospitals.
    - Supporting the local provision of routine, non-complex care and ensuring that all patients have an annual review.

- The HCC provides a coordinated leadership function, supporting SHTs in the delivery of clinical care. This includes provision of a network multidisciplinary team (MDT) meeting for the discussion of complex cases.

- The National Haemoglobinopathy Panel (NHP) will work alongside the Clinical Reference Group (CRG), HCCs, SHTs and other key bodies in thalassaemia care. It will provide all SHTs and HCCs with access to national expert clinical opinion with regard to the treatment of complex cases, and will drive the delivery of a nationally consistent approach to care.

- Patients with thalassaemia may receive their regular management including transfusion therapy at either the SHT, if this is their local centre, or via an LHT if they live further away from the SHT.

- Decisions about commencing transfusion and chelation therapy, and overview of the efficacy of these therapies, should be overseen by the SHT.

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

Background

Hospital care is inevitable for the majority of patients with thalassaemia, for transfusions, for often complex clinical and diagnostic assessments and their interpretation, and for decisions about chelation and other necessary medications. Ensuring that routine hospital care can be accessed locally at times to suit the patient and family, whilst meeting the need for every patient to have access to skilled specialist healthcare professionals – with particular interest, experience and knowledge of the condition – has led to the development of care networks. These networks were initially set up informally using a ‘hub and spoke’ model, but more formal arrangements have now been embedded.

Commissioning is the process of assessing needs, planning and prioritising, purchasing and monitoring health services, to get the best health outcomes using an evidence-based approach where possible. Specialist services are designated as those that are low volume and high cost, or that are very complicated to deliver. CRGs bring together groups of clinicians, commissioners, public health experts, patients and carers to advise National Health Service (NHS) England on the best ways for it to provide specialist services. The CRG for haemoglobinopathies covers thalassaemia, sickle cell disease and other rare

anaemias. CRGs lead on the development of clinical commissioning policies, Service Specifications and quality dashboards. They also provide advice on innovation, conduct horizon scanning, advise on service reviews, identify areas of unexplained clinical variation, and guide work to reduce variation and deliver value. CRGs, through their Patient and Public Voice members, also help to ensure that any changes to the commissioning of specialist services are co-produced with patients and the public.

Hospital services for children and adults with thalassaemia, sickle cell disease and other inherited anaemias have been commissioned by NHS England as specialist services since April 2014 (Specialised Services National Definition set no 38). The networks were initially set up with sites self-designated as LHTs and SHTs. NHS England, working with the CRG, produced an updated and formally agreed network system in 2019, and NHS standard contract Service Specifications were published in July 2019 (NHSE 2019).

These Service Specifications describe the Clinical Networks and state that all English Trusts treating patients with haemoglobinopathies are expected to be part of a network. The LHT refers to any hospital Trust caring for patients with haemoglobinopathies. All LHTs are linked to an SHT that has responsibility for providing specialist haemoglobinopathy care for a specific geographical area. Overseeing the work of one or more SHTs are the HCCs, which have a more strategic role in leadership for education, research and auditing. Working alongside the HCCs and SHTs is the NHP. This is a new and innovative structure that provides, for the first time, national oversight for haemoglobinopathy care in the UK. The NHP has a dual role; it runs a national multidisciplinary meeting that coordinates discussion of complex clinical cases by national experts, and it supports the HCCs and highlights any issues that may need policy input to NHS England and the CRG. More information is available on the NHP website (https://www.nationalhaempanel-nhs.net).

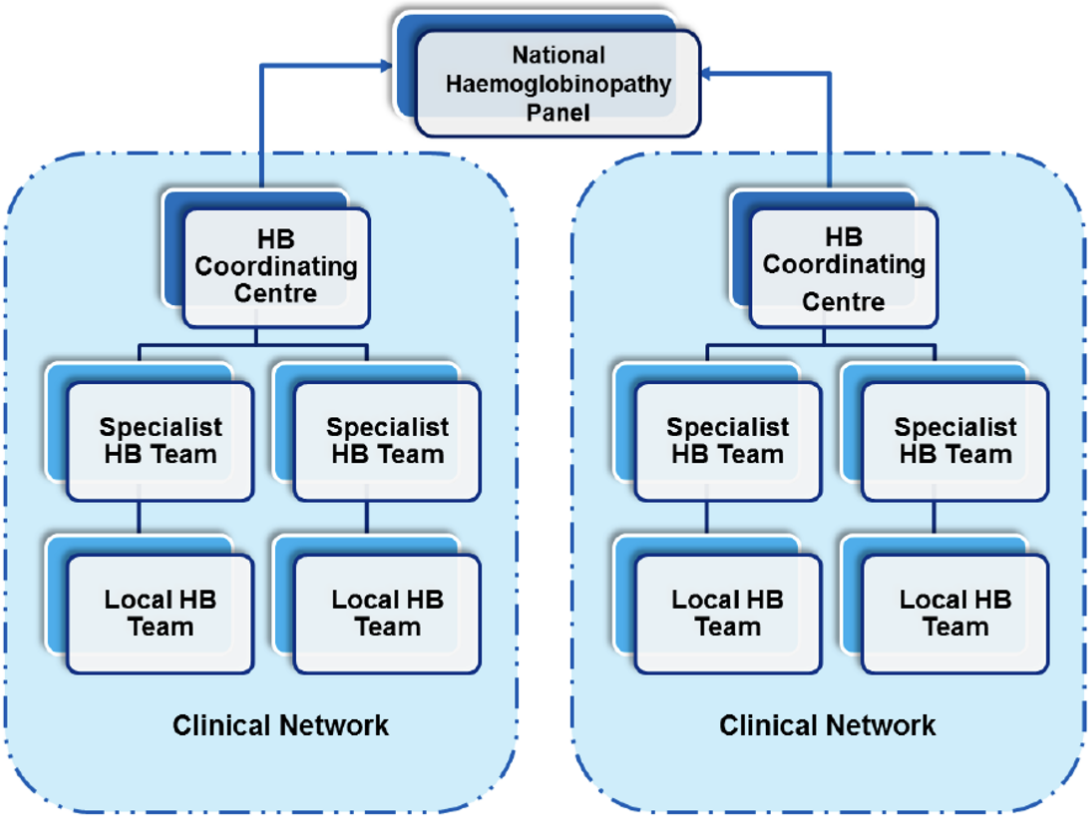

Figure 1.1: Displaying Service Specification Source: HCC Service Specification, (NHSE 2019, pg. 2)

A formal procurement process for the NHP and HCCs, and a provider selection exercise for the SHTs, was completed in October 2019 (NHSE 2019).

There are 25 SHTs in England that cover thalassaemia, sickle cell disease and rare inherited anaemias: 13 in London, 4 in the Midlands and East, 5 in North England and 3 in South England.

There are 4 HCCs for thalassaemia (also covering rare inherited anaemias).

- North: Manchester University Hospital NHS Foundation Trust.
- The Midlands: Sandwell and West Birmingham Hospitals NHS Trust, subcontracting to Birmingham Women's and Children's Hospital.
- London and Southeast: Barts Health NHS Trust.

- London, South Central and Southwest: University College London Hospitals NHS Foundation Trust in collaboration with Imperial College Healthcare NHS Trust, St George's University Hospitals NHS Foundation Trust and London North Central and West University Hospitals Healthcare NHS Trust.

The establishment of these services has led to marked advances in network developments although progress has been slowed by the impact of the coronavirus disease 2019 (COVID-19) pandemic. All thalassaemia HCCs now have Network Managers, and regular business and regional multidisciplinary meetings. There has been a marked increase in the provision of regional educational updates and improvement in communication about ongoing research.

The Service Specifications define the standards of care expected from organisations funded by NHS England to provide specialist care and are linked to quality indicators. Results from the quality indicators are reviewed by NHS England Regional Commissioners and the CRG to determine the impact of the process so far, and whether modification of the Service Specifications is required.

A mapping exercise carried out by the National Haemoglobinopathy Registry (NHR) in 2022 has confirmed which LHTs are linked to which SHTs and HCCs, and it is now possible to map the pathways from every patient in each LHT to ensure that every patient has a clear pathway for access to specialist care.

Responsibilities of SHTs, HCCs and the NHP

Full details can be accessed here:

- https://www.england.nhs.uk/wp-content/uploads/2019/07/Specialist-Haemoglobinopathy-Teams-Service-Specification.pdf
- https://www.england.nhs.uk/wp-content/uploads/2019/07/Haemoglobinopathy-Coordinating-Centres-Service-Specification.pdf

Table 1.1: Responsibilities of SHTs, HCCs and the NHP

SHTs	HCCs	NHP
To agree and monitor compliance with network care pathways and treatment protocols (elective and emergency) for its caseload of patients. To support the provision of coordinated expert care and advice within the network. This will include the provision of 24/7 emergency advice for other clinical teams within the hospital and with other local hospitals. To support the provision of routine, non-complex care for its local provision and ensure that all patients have an annual review. To work with the HCC to produce a training and education plan for all healthcare staff involved in the delivery of thalassaemia care in the network. To ensure that all patients in the network are registered on the NHR.	The HCC provides a coordinated leadership function, supporting SHTs in the delivery of clinical care. <u>This includes:</u> - Support of local providers to register all consenting patients on the NHR. - Organisation of at least two meetings per year for all healthcare staff involved in the delivery of thalassaemia care within the network. - Ensuring that local and national protocols and pathways are in place. - Provision of a regional MDT meeting for the management of very complex cases. - Support training and development in the network and lead on research.	To work alongside the CRG, HCCs, SHTs and other key bodies in thalassaemia care. To provide SHTs and HCCs with access to national expert clinical opinion with regard to the treatment of complex cases. To drive the delivery of a nationally consistent approach to care by working with HCCs and SHTs. To support the introduction of commissioned innovative therapies by acting as a national panel to consider individual patients most able to benefit from them, and to enable patients to have access to these therapies, irrespective of where they live.

Requirements

Patient care should be delivered as close to the patient's home as possible, facilitated by the use of protocols, pathways and access to specialist expertise either at the SHT or HCC/NHP level.

- LHTs will offer pretransfusion compatibility testing, and organise and deliver routine transfusions once the need for them is established by the SHT.

- The LHT team will provide regular prescriptions for medications as agreed with the SHT, check the child/adult before each transfusion in the clinic or day-care setting, organise some (if not all) of the routine assessment checks, 'troubleshoot' any symptoms or problems, and offer support to the patient and family.

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

- There should be clear exchange of information between LHTs and SHTs. Clinic letters and investigation results must, throughout the care pathway, be exchanged between the LHT, SHT and primary care team, with the patient/family copied in to all correspondence.

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

- Adequate numbers of sufficiently trained staff must be available at each point of care across the pathway. At the SHTs, robust arrangements must be in place to provide expert consultant advice at all times. Hospitals with single-handed consultants should consider new appointments, and all should consider the need to make formal arrangements with other centres to cover out-of-hours periods when the haemoglobinopathy consultant is not on call, and for times when they are on leave or otherwise absent.

- Transition arrangements need to be considered at both the Local Haemoglobinopathy Centre for regular care, and the Specialist Haemoglobinopathy Centre (SHC) for specialist reviews.

Quality assessment of thalassaemia services

Aims

The aim of having a Quality Assessment Programme for haemoglobinopathy centres is to improve services nationally for all individuals living with thalassaemia or other haemoglobin (Hb) disorders, and for their families. This programme involves setting clear Quality Standards that services are expected to meet, and a peer review programme to measure their performance against these standards.

The Quality Standards should be used to guide those setting up, providing, overseeing and commissioning services because they provide an objective picture of what a good service should offer. They also describe the criteria against which services are measured when undergoing peer reviews. Peer reviews involve visits by a specialist team to other centres in order to assess the local services and networks of care, and to offer constructive guidance to the teams involved. Peer review schemes provide an external assessment of quality, measured against the Quality Standards, and have taken place at least every 5 years since the development of the Quality Assessment Programme. Finally, the findings from peer reviews are intended to be used to inform local and national policies, governance and commissioning decisions in relation to thalassaemia care.

Background

Quality standards

Thalassaemia services have come a long way over the past two decades. There has been a shift from care delivered by interested but isolated clinicians with national guidelines for clinical care, to networks of care across the UK and the publication of *Standards of Care* guidelines by the United Kingdom Thalassaemia Society (UKTS). This brings with it the opportunity to ensure that all patients, wherever they live, have equity of access to specialist care, and that these services are delivering a standard of care that lives up to these national guidelines. It became necessary to set expectations for each level of service – whether an LHT, SHT or HCC – to ensure that the activities delivered by each are meeting these requirements.

The development of specific Quality Standards for haemoglobinopathy services began in 2006 for children's services, and Quality Standards for adult services followed shortly after, in 2010. Initially, they were developed jointly by the UK Forum on Haemoglobin Disorders, the UKTS, the Sickle Cell Society (SCS) and the NHS Sickle Cell and Thalassaemia Screening Programme (NHSSCTSP), working with the West Midlands

Quality Review Service. The ongoing Quality Assessment Programme is now led and managed by the UK Forum on Haemoglobin Disorders. Their Quality Standards Steering Group is composed of multiple specialist healthcare professionals from medical, nursing and psychology backgrounds, and includes leads from patient groups including the UKTS.

The *Standards of Care* have evolved over time to reflect changes to the setup of specialist care provision, new evidence and changes to clinical practice. The previous version (Version 4) of the Quality Standards was used for the 2019–2020 review programme, which included self-assessments from the majority of centres (64 services) and also peer review visits to 10 adults' and 15 children's services.

The most recent version of the UK Forum for Haemoglobin Disorders *Quality Standards for Health Services for People with Haemoglobin Disorders: Version 5 (UKFHD 2021),* builds on all previous versions and incorporates learning from earlier peer review exercises. Particular updates in this version relate to the more recent establishment of the NHP, which is now a core component of haemoglobinopathy care nationally, and there has also been standardisation of the patient experience survey that centres should distribute at least annually, allowing more valid comparison of performance measures between centres. There is also more focus on outcomes, with recommendations for data collection and analysis relating to clinical outcomes and patient experiences. The current version of the Quality Standards will be used as the basis for the upcoming peer review visits from 2023 - 2024.

Peer reviews

Peer review programmes for adults' and children's care were initially conducted separately, but more recently there has been a focus on joint assessment of services, and this is reflected in the joint Quality Standards. Peer review teams consist of doctors, nurses and psychologists specialising in haemoglobinopathy care, patient and carer representatives, and service managers from other centres, all trained in conducting the peer review process.

Peer reviews are informed initially by documentation including self-assessments provided by the centres. The peer review team also visits centres to examine the facilities and services available, interviews staff and patients, and assesses the service against the Quality Standards that the service is expected to meet. Meetings with patients and families during the peer review visit, as well as consideration of results from regular patient experience surveys, are particularly valuable in gaining insight into the everyday functioning of a service and the experiences of those it is designed to support.

A visit report is produced, which is considered by the peer review team, and reviewed by the Steering Group. Reports are then shared with the service provider and are made available to commissioners and regulatory bodies. These reports are expected to inform local service changes and development, and national policies for the management and commissioning of thalassaemia care.

Overview of the *Quality Standards for health services for people with haemoglobin disorders (Version 5)*

In addition to the *Standards of Care* guidelines for thalassaemia and sickle cell disease, and other relevant clinical guidelines, these Quality Standards consider policies and recommendations from national bodies including NHS England, the National Institute for Health Research, the Care Quality Commission and the British Standards Institute. The Standards cover the following areas and provide guidance regarding what should be available to service users and/or families, as well as information on how a service will be assessed against the relevant metric.

1. **Information for patients and families:** Written information should be available to patients and, for children's services, also to families. This information should cover details of the local service, contact arrangements and what to do in an emergency. Information about the Hb disorders themselves, and an individual's management plan, should also be available. Relevant information should also be shared with the primary care team.

2. **Patient and family feedback and involvement:** The importance of feedback from patients – and for children and young people also from their families – is emphasised, as well as the necessity of patient and family input into decisions regarding service organisation and improvement.

3. **Specialist staffing and support services:** A number of Quality Standards provide guidance on the requisite multidisciplinary constituents of a good specialist team, including medical and nursing staff, psychology, administrative staff and other specialist support services as required. Specialist laboratory and other services, such as genetic counselling and critical care provision, are also considered. The availability of safe care within normal working hours and the management of emergencies out of hours is covered.
4. **Clinical care guidelines and protocols:** Requirements for clinical guidelines to be readily available at each level of service are specified. They should be used to support the education and training of staff, and to ensure that safe and comprehensive care is delivered to all patients. They cover a range of areas including routine monitoring, long-term treatment, and the management of acute and chronic complications.

5. **Service organisation:** This section of the Quality Standards covers the structure and running of services at each site and within networks of care. Consideration of multidisciplinary discussion of patients and the availability of expert advice for local centres when required are all included. Liaison with NHS Blood and Transplant (NHSBT) and with the Antenatal and Neonatal Screening Programmes is covered.

6. **Outcomes:** Audits of the patient pathway for regularly transfused patients, and of patients admitted to inappropriate settings, are now required. An annual, standardised patient experience survey should also be conducted, and the results used to inform improvements required to services. Mechanisms for reviews of incidents, 'near misses' and patient complaints will be assessed.

7. **Additional standards relating to children and young people:** There are also standards specific to children and young people's services. These include the need to have fail-safe arrangements to ensure that newborns diagnosed with thalassaemia are seen by specialist teams in a timely manner, the provision of a school or college care plan, and a focus on ensuring that the transition process from children's to adults' services is as smooth and supported as possible.

Some of these standards are applicable only to SHTs, although many will also apply to LHTs, and it is made clear throughout where there is a distinction. Whether standards relate to adults' or children's services is also specified. There are also additional standards that should be met by the HCCs, which are set up to oversee and support care within their region. These relate to oversight of the regional services and ensuring that there is provision in place for both in- and out-of-hours expert haemoglobinopathy advice where required.

Conclusion

In summary, the Haemoglobinopathy Quality Assessment Programme seeks to ensure that a consistently good standard of specialised care and support is available to all patients and families living with thalassaemia throughout the UK. This is with the aim of ensuring that individuals living with thalassaemia have the best quality of life, and the fewest complications and inconveniences possible, so that their haemoglobin disorder does not limit their ability to pursue their own goals and priorities in life.

Recommendations

- Commissioners should monitor the quality of care provided by HCCs, SHTs and LHTs by reviewing their annual data outputs.

- NHS England should ensure that there is support for an ongoing peer review programme.

The National Haemoglobinopathy Registry

The NHR was developed in 2009, initially as a means of identifying centres treating large numbers of patients with sickle cell disease and thalassaemia. The NHR initially only collected annual review data for patients but was redeveloped in 2020–2021. The new NHR now collects data on patients living with sickle cell disease, alpha and beta transfusion-dependent and non-transfusion-dependent thalassaemia (TDT and NTDT, respectively) and rarer thalassaemias, membranopathies and enzymopathies that are transfusion-dependant or considered severe, and rarer inherited anaemias. It is a secure registry, held on the NHS servers on a level 3 network similar to all NHS Hospital data. Each patient's record is based on their NHS number and therefore only one record should exist per patient.

A larger set of patient outcomes are collected, including results of critical investigations (MRI assessments), complications, comorbidities, surgical interventions, transfusion requirements, RBC antibodies and treatment with novel therapies. The annual review includes data to support SSQD data collection and patients access to novel therapeutics. Reports are provided to the SHTs monthly for serious comorbidity events, as well as compliance with annual review.

SHTs and LHTs are expected to record key aspects of care for patients on the NHR, including annual reviews, transfusion requirements, MRI scan assessments and novel therapies as they enter funding pathways. The more comprehensive a patient's record on the NHR the more information is available for clinical teams that may see the patient when they present to a centre that is not their usual one. This helps to ensure that the team managing the patient is aware of any historical complications.

The registry is commissioned by NHS England, and the current provider of the registry is Medical Data and Solutions Services Ltd (MDSAS). NHS England are also the data controllers of the registry and ensure that any data held by the registry are only used in line with ethical and data regulation laws.

Data linkage has been developed with NHSBT to allow RBC antibody data to transfer into NHR patient records. Transfusion and RBC antibody records are added to the patient records from all centres where the patient may have been transfused and from NHSBT, hence providing a single place for RBC antibody data from multiple sources.

As the purpose of the NHR is to support the direct care of patients, the registry does not require consent and all patients should have a record on the NHR. If the patient requests erasure from the NHR they will still have key records held on the NHR but in a non-identifiable format (removal of their NHS number and issuance of a unique identifier number to prevent the duplication of records). In the event of an erasure being requested, RBC antibody records will not be recorded and will not provide a safety net for the patient requesting erasure.

Roles and responsibilities of the NHR

The primary purpose of the NHR is to support direct patient care and treatment (as part of the patient's pathway of care) by ensuring accurate record keeping, using good-quality data relating to patients, their treatment and their outcomes. The data collected in the registry are used by medical staff and provide clinical information to aid decision-making, in partnership with patients, regarding their treatment and care. The NHR publishes an annual report every year on the data held in the registry. The NHR has a Steering Committee that oversees all the work of and data held on the NHR.

Research using data on the NHR can be undertaken provided a formal process is followed. This includes completion of a data request that is reviewed by the NHR data committee, which includes the Patient Voice representatives. Once approved by the Data Analysis and Research Group, it is then reviewed by NHS England registry leads and signed off subject to NHS England data governance processes. More detailed and non-anonymised data requests require an additional process with ethical submissions via the Integrated Research Application System or section 251 process, which has to be undertaken and completed by the organisation/team wanting the data, and only once the Data Analysis and Research Group and NHS England have approved the research project.

Membership of the NHR (under review)

- NHS England: the commissioners of specialist services including haemoglobinopathy services, and the data controller and funding organisation for the NHR. The lead for the registries and the lead CRG commissioner attend the Steering Committee meetings.
- NHP representative.
- Newborn screening registry lead.
- HCC representatives (×10).

- NHSBT representative.
- Patient Voice representatives (×4–5: thalassaemia, sickle cell disease and rare anaemias).
- Data Managers' Group representatives (×2).
- Chair of NHR appointed by NHS England on a 3 yearly cycle.

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Chapter 2

Annual Reviews

Aims

To ensure that all children and adults will have a comprehensive annual assessment by specialist healthcare professionals, or more often, if necessary, to optimise their care, and so that they are fully informed about their condition, are kept up to date about any possible treatment changes and have a clear management plan for the year ahead.

Standards

- Every person with thalassaemia will have the opportunity for their care and condition to be reviewed at least annually with a team of healthcare professionals who have experience in caring for thalassaemia disorders. This can take place during a visit to the Specialist Centre or at an outreach clinic where members of the SHT visit the local centre at which the person receives their routine care.
- The assessment should cover all aspects of care, including educational and lifestyle factors that may affect health or influence adherence to treatment.
- Discussion of treatment options should include any new information that has become available, and an individual treatment plan for the next 12 months will be agreed.
- A copy of the annual review consultation, including the care plan, will be copied to the patient or, for children, their parents as well as health professionals involved in their care.
- Data should be entered into the annual review screens of the NHR.
- People in families affected by thalassaemia should be able to meet and gain support from other affected families at the SHC or in the community.

Background

Patients with complex, multisystem disorders like thalassaemia require input from a range of specialist health professionals and access to investigations that may not be available everywhere. An individual case review by an SHT/nominated professional at least once per year will offer all patients access to optimal specialist care regardless of where they live. The annual review is intended to be a comprehensive assessment of every aspect

of the patient's treatment and condition, to assess progress and identify any areas where treatment could be improved. HCCs should ensure that networks have effective arrangements for all patients to have an annual review by appropriately trained staff.

A pro forma should be considered for the annual review visit to ensure thorough and consistent care, and to facilitate data collection. The annual review should be shared with the patient, their general practitioner (GP) and the local hospital team. An example of an annual review proforma is provided in Appendix 1.

Requirements

- The patient and family will usually visit the SHT for a pre-booked appointment. In some areas, a local agreement may be made for a paediatrician and/or haematologist from the SHT, often with a specialist nurse, to hold an outreach clinic. In areas where the designated SHT does not have specific thalassaemia expertise, arrangements will be made to link with another SHC with the appropriate experience.
- The SHT should agree with the patient's LHT which investigations can be performed there, and the results, together with information on clinical progress and treatment, should be available at the time of the annual review.
- At the visit, the consultation will be with the designated paediatrician or haematologist. Access to other SHT members (such as specialist nurses or clinical psychologists) should be provided, ideally at the same visit or, if not possible, at a separate consultation.
- Assessment will be made of progress in general and a review conducted of the patient's and family's knowledge of the condition. The patient and their family should have the opportunity to ask questions.

The review should include:

- Assessment of any new or ongoing symptoms.
- Adverse events over the preceding 12 months.
- Assessment of growth and development: weight, sitting and standing height, and a review of growth charts (children).
- Review of transfusions:
    - For patients who are transfusion-dependent this should include pretransfusion Hb levels
    - For patients who are non-transfusion-dependent this should be a review of any transfusions given
    - Change in transfusion requirements

        - Transfusion complications such as transfusion reactions, alloantibodies and blood-borne viruses
        - Emergence of splenomegaly.
    - Assessment of iron overload:
        - Rate of iron loading
        - Serum ferritin (SF) trends
        - Review of cardiac and liver MRI measurements of iron loading.
    - Assessment of iron chelation:
        - Review of current chelation
        - Review of adherence (crucial)
        - Complications of chelation and screening for toxicities.
    - Assessment and review of complications:
        - Endocrine dysfunction:
            - Assessment of growth
            - Growth hormone (GH) deficiency
            - Assessment of pubertal development and secondary sexual characteristics
            - Hypogonadism
            - Hypothyroidism
            - Hypoparathyroidism
            - Impaired glucose tolerance (IGT) and diabetes, with a review of the patient's family history of diabetes.
        - Cardiac assessment: investigations to include an echocardiogram; patients with previous/current cardiac iron may need assessment for dysrhythmias if there are symptoms
        - Chronic liver disease: consider screening for cirrhosis for patients with previous severe liver iron overload and for hepatocellular carcinoma in at-risk patients with ultrasound and alpha fetoprotein
        - Pancreatic insufficiency
        - Bone health and checks for bone density
        - Gallstones
        - Leg ulceration
        - Thrombosis
        - Pseudoxanthoma
        - Chronic pain.
    - Review of therapies: review of adherence is crucial, complications of therapy for example diabetic control.
    - Review of venous access:

    - adequacy of peripheral veins
    - If venous access devices, review complications and conduct risk assessment to determine whether anticoagulation is required.
- Review of immunisation status and prophylaxis against infection:
    - Hepatitis B
    - coronavirus disease 2019 (COVID-19)
    - Post-splenectomy vaccines
    - Ensure primary vaccination schedule completed.
- Referral for specific investigations and, if appropriate, review in joint clinics.
- Discussion about contraception, fertility, pregnancy and (where appropriate) genetic information, and partner screening.
- Ensuring the patient has a named contact within the service
- Attendance at the appropriate specialist clinics (e.g., cardiac, endocrine, hepatology etc.) for his/her age and clinical status; if not, a referral should be made.
- Documentation of clinical observations including oxygen saturations and clinical examination with particular reference to the heart, liver, spleen and pubertal status in relevant age groups.
- The issue of possible bone marrow transplantation should be raised, and consideration given to referral to a transplant centre (see **Chapter 9: Reproductive Health Across the Lifespan**); once a discussion has taken place this should be noted and it is not necessary to repeat it at each visit, unless the family wishes to revisit the question or new circumstances have arisen, e.g., pregnancy or birth of another sibling.
- Review of emerging therapies available and available clinical trials.
- Follow up plans with specialist teams (e.g., diabetes, liver, cardiac and endocrine clinics).
- Referral for MDT discussion with SHT/HCC/ NHP.
- Education around the condition and lifestyle factors that may affect health:
    - Holistic needs assessment
    - Support for work or education
    - Welfare concerns.
- Assessment of emotional and psychosocial wellbeing with referral onto psychology teams if required.
- Referral for community or voluntary sector support if required.
- After the visit, the clinician should write a summary including any problems highlighted and recommended changes to management;

copies should be sent to the referring hospital, the patient's GP and the patient/family.

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

Recommendations

- Any specialist investigations should be planned so as to require the minimum possible number of hospital visits and, where logistically possible, should be combined with the annual review visit.
- It should be ensured that the patient/family has access to relevant written informational material. They should know how to access the UK Thalassaemia Society and be put in touch with any local support group or organisation. Ideally, they should be able to meet other patients/families at the centre.
- The annual review visit is also an opportunity to discuss with parents of an affected child their plans for further pregnancies with reference to their choice regarding prenatal diagnosis (PND), preimplantation genetic testing (PGT) and testing/storage of cord blood.
- The patient's hand-held record, if used, can be completed at the end of the annual review visit.
- Following the visit, data should be submitted to the NHR.

SECTION B: Core Management Standards

Chapter 3

Standard Features and Treatment

Pathophysiology and geographical distribution

Haemoglobinopathies are inherited abnormalities of haemoglobin and the thalassaemias are caused by reduced or absent globin production. Normal adult haemoglobin (HbA) is composed of alpha- and beta-globin chains with associated haem groups, and abnormalities of the alpha- or beta-globin genes can lead to alpha or beta thalassaemia, respectively, due to a lack of adequate HbA production.

Beta thalassaemia is usually caused by mutations of the beta-globin genes and is inherited in an autosomal recessive manner (although rare autosomal dominant mutations exist). These lead to reduced beta-globin chain production, leaving an excess of free alpha chains that damage early RBC precursors in the bone marrow, resulting in dyserythropoiesis and severe anaemia. The inheritance of alpha thalassaemia is more complex, as healthy individuals have four alpha-globin genes (two on each copy of chromosome 16). Alpha thalassaemia is usually caused by the deletion rather than the mutation of these genes, with individuals usually only clinically affected if at least three out of the four genes have been lost.

Sometimes there is compound heterozygosity (combined inheritance) with a thalassaemia (i.e., haemoglobin produced at lower-than-normal quantities) or an unstable Hb variant, such as HbE or Hb Lepore (beta-globin abnormalities), or Hb Constant Spring (abnormal alpha-globin). Beta thalassaemia may also be coinherited with mutations of other genes that sit near the beta-globin gene on the same chromosome, for example in delta-beta thalassaemia. The wide variations in genetic changes that lead to thalassaemia are reflected in the variable degrees of clinical features observed in affected individuals.

Thalassaemia is estimated to affect 1:2000 conceptions globally, and predominantly affects people whose family origins are from South Asia, Southeast Asia, the Mediterranean or the Middle East, although people who are of African or European origin may also be affected (Modell and Darlison, 2008).

Classification

Thalassaemias are classified based on their clinical phenotype as TDTs or NTDTs. However, there is a spectrum of severity and there is not always a clear distinction between these classifications.

TDT indicates that an individual is entirely dependent on regular, lifelong RBC transfusions for survival, from very early in life. Most people with TDT in the UK have beta thalassaemia, caused by homozygous or compound heterozygous inheritance of beta thalassaemia mutations of varying severity, sometimes inherited with thalassaemic variant Hbs (e.g., HbE). People affected by NTDT, on the other hand, may not always require regular transfusions. However, the need for regular or intermittent transfusions may develop later in childhood or in adulthood, due to a failure to thrive or other complications of thalassaemia.

Haemoglobin H disease (HbH) is one example of a condition that usually presents as NTDT and is caused by the loss of three out of the four alpha-globin genes in an individual. Features are usually those of a mild to moderate haemolytic anaemia, although regular transfusions may be required in a minority of individuals (Chui et al., 2003). However, if all four alpha-globin genes are lost then a fetus cannot produce the early form of Hb that is necessary for in utero life, fetal Hb (HbF). This results in hydrops fetalis and is almost always incompatible with survival.

Haemoglobinopathy screening

Antenatal screening for the risk that a baby may be severely affected by thalassaemia takes place routinely through the NHSSCTSP. If a woman is identified as a potential carrier of beta thalassaemia or a high-risk type of alpha thalassaemia, screening of the biological father is offered. If he is also a carrier of the same type of thalassaemia or cannot be tested, the pregnant woman will be offered counselling and the option to undergo prenatal testing of the fetus, to allow her to make informed choices regarding whether to continue with the pregnancy. Such prenatal screening and diagnosis must always be managed in a manner sensitive to the individual's needs and beliefs. There is also routine screening of all newborn babies (with the 'Guthrie' or 'heel-prick' test). Although not specifically introduced to pick up babies affected by thalassaemia, this screening test can detect the majority of cases of severe beta thalassaemia, allowing early referral to specialised teams for further assessment.

In addition, screening for thalassaemia carriage may be appropriate at other time points for individuals. Examples include premarital screening, where results may be taken into

account in the process of considering a marriage partner, or preconceptual screening to allow couples to be counselled regarding the risk of having an affected child and alternative reproductive options if both are carriers of thalassaemia. More detailed consideration of prenatal screening and diagnosis is contained in **Chapter 10: Reproductive Informed Choice – Prenatal Diagnosis and Preimplantation Genetic Testing**.

Symptoms of untreated thalassaemia

The clinical presentation of untreated thalassaemia varies greatly depending primarily on the extent of the inherited defects in the affected globin genes, as well as coinherited changes in other globin genes, which in some cases may ameliorate the clinical phenotype. Regardless of the genetic mutation involved, the clinical features are invariably driven by:

- decreased Hb production due to ineffective haematopoiesis
- reduced RBC survival (chronic haemolysis) due to the accumulation of excess unaffected globin chains that precipitate and damage erythrocytes (Rachmilewitz and Gardina, 2011)
- the expansion of haematopoietic tissues in an attempt to compensate.

For beta thalassaemia, these processes only begin, and symptoms start to manifest, following the physiological switch from the gamma chains in HbF to the beta chains in HbA, typically from around 4–6 months of age.

The clinical features resulting from these abnormal processes in patients with untreated thalassemia that are described below primarily relate to patients with TDT who are not transfused, or who are undertransfused, but may also be seen in those with NTDT, in which case they may indicate the need to commence or increase transfusions.

- Progressive anaemia that can present as failure to thrive, poor feeding, irritability, jaundice (due to haemolysis) and reduced activity in infants; left untreated, this can ultimately lead to cardiopulmonary failure and death.
- Bone marrow expansion leading to dysmorphic facies, other bony deformities and osteoporosis.
- Extramedullary haematopoiesis including hepatosplenomegaly, and abnormal haematopoietic tissues developing at other sites such as paraspinal regions.
- Pulmonary hypertension (PHT) due to nitric oxide (NO) depletion and endothelial damage secondary to chronic haemolysis.
- A hypercoagulable state is increasingly recognised, particularly in patients with NTDT after the second decade of life, with increased risk of deep venous thrombosis, pulmonary embolism and cerebral thrombosis. This is thought to be

driven in part by exposure of negatively charged phospholipids on RBCs, enhanced platelet and endothelial cell activation, a drop in protein C and protein S levels, and the depletion of NO (Vasilopoulou et al., 2022).

- Increased compensatory intestinal iron absorption leading to iron overload even without blood transfusions.

Standard treatment

The mainstay of treatment for most patients with severe clinical phenotypes of thalassaemia remains a regular blood transfusion programme. Transfusions are typically delivered every 2–4 weeks and aim to maintain high-enough Hb levels to support normal activity and prevent ongoing ineffective erythropoiesis, with its associated complications. Typically, Hb should be maintained above 95 g/L, but higher pretransfusion targets may be required in some individuals. The clinical severity of thalassaemia cannot be predicted with complete certainty from a genotype in early life; hence, careful assessment and monitoring of clinical features and laboratory results remain the most important factors in deciding if, or when, to start regular transfusions. Further detail on starting and managing a regular transfusion regimen is found in **Chapter 5: Red Blood Cell Transfusion**.

Despite their necessity, each blood transfusion brings with it the delivery of excess iron into the body that can accumulate in, and cause toxic damage to, vital organs, most notably the heart, liver and endocrine glands. Therefore, alongside regular transfusions, the other cornerstone of treatment is the prevention and management of iron overload and its consequences. This involves the use of iron chelation treatment, which helps to bind and eliminate excess iron from the body and should usually be started after 10–12 transfusions or when SF is persistently >1000 µg/L (Shah et al., 2022). Ongoing monitoring for complications associated with iron overload must also take place, and joint working with other relevant specialties is key. It should also be noted that whilst iron overload is primarily driven by regular transfusion therapy in patients with TDT (on average at a rate of 0.3–0.5 mg/kg/day), those with NTDT can also experience a degree of iron loading from increased gastrointestinal absorption, although it is estimated to be at a 40-fold slower average rate of 0.01 mg/kg/day (Cohen et al., 2012).

There are three iron chelation treatments currently available in the UK. The first, and most long standing, is desferrioxamine (DFO). This is delivered subcutaneously by slow infusion pump, usually over 8–12 hours, 5–7 nights per week, or less commonly can also be given by intravenous infusion. Oral medication options are deferasirox (DFX), which can be taken once per day, or deferiprone (DFP), which is usually given three times per day. Although most patients are managed with a single chelation medication, combination therapy should be considered if monotherapy inadequately controls iron levels or where side effects are associated with using higher doses of a single agent. All three

combinations of dual chelation therapy are now licensed. The efficacy and side-effect profiles of each of these treatments differ, and further detailed discussion of iron chelation can be found in **Chapter 6: Iron Overload and Management**.

For a minority of patients, allogeneic haematopoietic stem cell transplantation (HSCT; donor bone marrow transplant) may be curative. This option should be explored as a matter of course for younger children with TDT who have a matched sibling donor (see **Chapter 7: Disease-Modifying Therapies**). However, for most people, careful management of lifelong transfusion and iron chelation treatments will be required. General principles for the optimal management of long-term health conditions must be applied. These include the importance of delivering holistic, patient-centred care that supports patients in meeting their personal goals and responsibilities. Providing services that are flexible and individualised, to maximise benefit and minimise disruption to patients' lives, must be the aim, and will help patients to adhere to sometimes onerous treatment and monitoring regimens. Recognition of and support with the psychological, emotional and social impacts of living with thalassaemia, and the burdens of treatment it brings, are also key to delivering care in a way that meets the needs of patients and their families.

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Chapter 4

Initial Management of the Newly Diagnosed Infant

Aims

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

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

To ensure appropriate safety netting with clarity of the roles of local and specialist services.

Standards

- Confirmation of the diagnosis of a child with a serious thalassaemia syndrome will be timely and accurate.
- Laboratory investigations will include determination of the beta and alpha globin genotype, Xmn1 polymorphism status, glucose-6-phosphate dehydrogenase (G6PD) status and RBC genotype/phenotype.
- The child will be monitored at least monthly to determine the likely clinical course.
- The family will be informed fully and sensitively from the outset once the diagnosis is confirmed, by appropriately experienced professionals, with the use of a culturally appropriate health advocate if necessary, and with the opportunity for full discussion.
- Suitable written information will be given to the family.
- A management plan tailored to the individual child will be agreed and implemented.
- The family will meet their ‘key contact(s)’ within the clinical team and be given contact numbers.

- The family will be informed about the NHR with registration to include LHT/SHT and HCC details.
- The family will be given the contact details for the UKTS and any local support group(s).

Background

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

If the risk was not identified during the pregnancy, affected infants may be identified through the newborn screening programme. This involves a screening test, and not all cases of thalassaemia will be identified. If the test shows 'HbF only', follow-up is necessary and diagnostic confirmatory tests should be performed. If undiagnosed in the neonatal period, the child may present with failure to thrive, poor feeding and other non-specific symptoms of anaemia, and may have an enlarged spleen and liver. Depending on the level of Hb at this time, initial RBC transfusion may be urgently required. Infants identified through the neonatal screening pathway should be referred for entry into the care pathway without delay and seen within 90 days.

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

The fact that there is a 'greyscale' of transfusion dependency should be explained, and parents should understand that it is usually not possible to predict the severity of the condition, or the need for transfusions, from the outset. Children need to be monitored carefully for signs of poor growth, failure to thrive, recurrent infections, 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 the beta-globin genotype, alpha-globin genotype and a determinant of persistent HbF production (the Xmn1 C→T polymorphism).

Requirements

- The diagnosis should be anticipated from antenatal screening and established by PND where requested. If not, affected infants may be identified through the newborn screening programme. The baby and parents should be seen to discuss the provisional results as soon as possible, and preferably within 14 days. The parents must be given the provisional diagnosis by a knowledgeable professional, often a specialist nurse, who can start to explain the condition and offer some written information, as well as give them contact numbers for any urgent concerns or questions.
- Confirmatory testing will be required to establish the diagnosis. Confirmatory testing should be organised following referral to the outpatient clinic, usually with a consultant paediatrician, paediatric haematologist or haematologist with experience of looking after children with the condition. This will be with the LHT and, at the earliest opportunity, a multidisciplinary consultation should be organised with the SHT.

If a diagnosis has not been made at these stages, and the presentation is a clinical one, then assessment and treatment may be more urgent. Confirmatory haematological and DNA diagnosis should be established by the following tests:

- Full blood count (FBC), reticulocyte count and blood film examination.
- Hb analysis by capillary electrophoresis or high-performance liquid chromatography (HPLC), beta- and alpha-globin genotyping, and Xmn1 C→T polymorphism analysis.
- Family studies may be informative, and the parents should also be tested if results are not available from prior screening.
- Additional baseline investigations should be organised (these investigations can be requested through the regional genomics laboratory):
    - G6PD screen
    - RBC phenotype/genotype.
- Once the diagnosis has been established, the child should be initiated on oral folic acid and will require monthly monitoring in the outpatient clinic.
- The outpatient visits should be conducted as multidisciplinary consultations to introduce the family to the wider team, to include the consultant, acute and community specialist nursing teams, a psychologist, play therapist and a dietician. This should be followed up by an early clinic appointment.
- It should be emphasised that the clinical phenotype cannot be predicted accurately in the early stages, and that the child will be monitored carefully for clinical signs indicative of the need to commence transfusion, when that might be and the implications of this.

- The importance of the family as central carers should be emphasised.

The arrangements for care should be discussed. This may involve shared care with the SHT and LHT, with a plan for regular (at least biannual) review at the SHT with additional contact whenever required.

- Appropriate written information should be made available. The family should additionally be given the contact details for the UKTS and any local support groups.
- The parents should meet and exchange contact details with their key contact staff member(s) at the LHT and SHT, and the team psychologist, and offered support.
- After the visit, a written summary covering the discussion and follow-up arrangements should be exchanged between the LHT and SHT, and copies sent to the family and their GP.

Recommendations

- Infants identified through the neonatal screening pathway should be referred for entry into the care pathway without delay and seen within 90 days.
- Laboratory investigations to support diagnosis should include genomics.
- Families should have an early introduction to the MDT to support their understanding of diagnosis and management.
- Services should have clear pathways and guidelines for network-based shared-care management to ensure regular clinical review for the monitoring of progress to determine the phenotype.
- Antenatal and neonatal screening services should be linked to support families with an ‘at-risk pregnancy’.
- For newborns 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, they may be the best person to make this contact. The nurse can then accompany the family to the first hospital consultation soon after.
- There should be no delay in referral following suspected diagnosis because the child remains clinically well; important information should be given, discussions should take place and investigations to confirm the diagnosis should be instigated at this stage.
- Referrals should be made electronically using the newborn outcomes solution/NHR portal.
- 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 what was discussed during the consultation.

- 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 their own questions and discuss their own issues. The initial meeting is likely to be dominated by the family's need to understand the nature and implications of the child's newly diagnosed condition. Genetic counselling, with regard to options for future pregnancies, can be mentioned but it is better to arrange a further meeting to address this issue, although this should not be long delayed. At the genetic counselling meeting there should also be a discussion of the implications of possible carriers including siblings and other family members, who should be offered testing.
- During the early clinic visits, treatment options for the child in future should be discussed including the different options for iron chelation and the availability of stem cell transplantation (SCT). They should be made aware of clinical trials and novel therapies. Families should be made aware of the need for frequent monitoring of growth, development, and blood test results.
- Monthly monitoring should detail feeding, growth, development, the frequency/ severity of infections, measurement of height and weight, clinical assessment of facial bone changes and measurement of liver/spleen size.
- Where possible, the family should be given the opportunity to meet with other families who have children with thalassaemia.

Chapter 5

Red Blood Cell Transfusion

"I'm grateful for the liquid ruby that keeps us all alive."

"Life for me changed when I started having transfusion reactions, the thing that I needed most to keep me alive and well became a nemesis that was undiagnosed for far too long."

This chapter will address important considerations relating to transfusion therapy in patients with thalassaemia. It will draw on the following British Society for Haematology Guidelines:

1. Guidelines for pretransfusion compatibility procedures in blood transfusion.
2. The administration of blood components.

Aims

The aim of blood transfusion in thalassaemia is to deliver a safe and effective transfusion regimen whilst minimising the burden of transfusion therapy on everyday life.

An effective transfusion regimen will result in:

- good growth and development
- good energy levels
- sufficient suppression of intra- and extramedullary haematopoiesis.

A safe transfusion regimen will

- use a product that is collected, tested, selected, issued and administered adherent to established quality and safety regulations and guidance
- be administered by staff trained in blood transfusion
- involve informed patient consent
- be delivered in an environment with appropriate governance and haemovigilance structures in place.

Background

Pretransfusion testing and selection of units for transfusion

Pretransfusion testing

The development of RBC antibodies following transfusion is frequently seen in those with Hb disorders, with those with thalassaemia in the UK having an incidence rate of 22% (Trompeter, Estcourt et al., 2020). Processes have been put in place to mitigate this risk (namely the selection of A-, B-, O-, Rh (DCcEe) and K-compatible units); however, alloimmunisation still occurs (British Committee for Standards in Haematology, 2013). Although it has been argued that the degree of routine RBC matching should be extended in this cohort (Compernolle et al., 2018), the incidence of new alloimmunisation is relatively low in England (Trompeter et al., 2015) and the feasibility of such an approach is beyond the capability of the current infrastructure (Trompeter, Massey et al., 2020); however, a research strategy is underway to develop processes to develop this (www.haemmatch.org and www.bgc.io). Blood should be selected that is compatible with any known clinically significant RBC antibodies (British Committee for Standards in Haematology, 2013).

The knowledge of a patient's RBC antigen profile is important. A, B, O, Rh (DCcEe) and K grouping information should be available prior to transfusion because blood should be selected that is compatible with these antigens. For the other RBC antigens, it is preferable that groupings are known because, if alloimmunisation develops or there is a transfusion reaction, this knowledge will facilitate understanding of the process that is occurring and inform the choice of appropriate units for further transfusion. Practically, people should undergone A, B, O, Rh (DCcEe) and K grouping and an antibody screen (can be done locally), with more extended RBC typing performed at the Blood Service. In England, extended RBC antigen typing is performed by NHSBT and there is also a facility for genotyping that includes variants. This is particularly advantageous as genotyping with this particular panel can reveal RBC variants that are not detected via phenotyping or routine genotyping. The other advantage of genotyping in general is that it can be done post-transfusion. This is important as there are two groups in particular that may already be receiving regular transfusions that have never had their full RBC antigen profiles determined: older patients for whom this was not available prior to them starting transfusions, and those who have come from abroad, particularly if from low- and middle-income countries where this testing is often not offered and/or available. In the devolved territories of the UK, there are different blood services and different provisions, although there are relationships between these services that can be leveraged for patient need.

Unless there is an emergency, blood banks currently reconfirm the ABO and D groups and perform a screen for new antibodies before a transfusion. An indirect antiglobulin test (IAT) crossmatch is performed in order to select compatible units. Where patients are not pregnant and have no history of alloimmunisation, electronic issue may be used in place of IAT crossmatch, provided that guidelines surrounding electronic issue are met (British Committee for Standards in Haematology, 2013; Anon, 2005; Medicines and Healthcare products Regulatory Agency, 2010).. This is only appropriate in blood banks that adhere to strict regulations regarding computer systems, sample labelling and other critical issues (British Committee for Standards in Haematology, 2013). Using either approach, new clinically significant antibodies must be identified so that blood lacking the corresponding antigen(s) is selected. Further guidance on blood transfusion administration can be found here in Robinson et al. (2018).

A complete and detailed record of antigen typing, current and historical RBC antibodies, and transfusion reactions should be maintained for each patient, and should be readily available if the patient is transfused at a different centre. Although, regrettably, there is currently no single transfusion record system for patients in the UK, there are various things that can be done to mitigate the risk of a patient with an antibody that is no longer detectable arriving at a new hospital, having a negative antibody screen and then being transfused with antigen-positive blood that will react with their previously detectable antibody and having a transfusion reaction.

These include:

- The patient being aware of any antibodies they may have had (ever).
- The information regarding antibodies being given to the patient on an antibody card.
- The information regarding antibodies being recorded on the NHR.
- The information regarding antibodies being recorded on the patient's key record.
- The laboratory being informed that:
    - the patient has thalassaemia
    - where else they have been transfused
    - which antibodies they have developed.
- The laboratory can then:
    - consult the NHS Blood and Transplant Service, and any aforementioned hospitals for any transfusion history
    - update the patient's records, flagging any specific requirements.
- All hospitals should sign a waiver that lets the results of the tests that have been performed by their blood services be available to other hospitals.

The length of time between sample acquisition, antibody screen and the transfusion of blood for regularly transfused patients is usually 72 hours but a 1 week interval has been deemed safe in centres with full Rh and Kell antigen matching for patients who are regularly transfused, whether they have had pre-existing antibodies or not (Trompeter et al., 2015).

Age of blood

Over the recent decades, improvements have been made in the way blood is processed, stored and issued. In addition, more stringent processes have been adopted to improve the quality of the RBC units, such as rules about the cold chain, the types of anticoagulants used in the units and how they are prepared. As such, the quality and the safety of the blood products have improved significantly over the years. Age restrictions have therefore been removed for blood required for patients with haemoglobinopathies, including patients with thalassaemia in the UK.

Criteria for initiating transfusion therapy

The decision to initiate a long-term transfusion regimen should be based on a definitive diagnosis of TDT. This diagnosis should consider the molecular defect, the severity of anaemia based on repeated measurements, the level of ineffective erythropoiesis, and clinical criteria such as failure to thrive or significant symptoms or bone changes (see Table 5.1). It must be established that the severity of anaemia is not transient and linked to issues such as infection; in such cases, a one-off transfusion may be sufficient.

The initiation of regular transfusion therapy for severe thalassaemia genotypes usually occurs in the first 2 years of life, and is usually due to severe anaemia or significant anaemia with accompanying symptoms, such as not being able to feed or failure to thrive. Some patients with milder forms of thalassaemia who only need sporadic transfusions in the first two decades of life may later need regular transfusions because of a falling Hb level or the development of serious complications.

Table 5.1: Criteria for starting transfusion in thalassaemia

Investigative criteria	
Confirmed diagnosis of thalassaemia	
PLUS at least one of these laboratory or clinical criteria:	
Laboratory criteria	**Clinical criteria (irrespective of Hb level)**
• Hb <70 g/L on 2 occasions, >2 weeks apart (excluding all other contributory causes such as infections)	• Significant symptoms of anaemia • Poor growth/failure to thrive • Complications from excessive intramedullary haematopoiesis such as pathological fractures and facial changes • Clinically significant extramedullary haematopoiesis

Transfusion thresholds and frequency

The recommended treatment for TDT is lifelong regular blood transfusions, usually administered every 3–4 weeks, to maintain a pretransfusion Hb level of 95–105 g/L. This transfusion regimen promotes normal growth, allows normal physical activities, adequately suppresses bone marrow activity in most patients and minimises transfusional iron accumulation (Cazzola et al., 1995, 1997). A higher target pretransfusion Hb level of 110–120 g/L may be appropriate for patients with heart disease, clinically significant extramedullary haematopoiesis or other medical conditions, and for those patients who do not achieve adequate suppression of bone marrow activity at the lower Hb level. Sometimes back pain occurs prior to blood transfusion and may respond to a higher pretransfusion Hb level. Although shorter intervals between transfusions may reduce overall blood requirements, the choice of interval must consider other factors such as the patient's school or work schedule, and other lifestyle issues.

The schedule outlined above has been shown to minimise iron loading, whilst suppressing bone marrow expansion in Italian patients with thalassaemia major (TM) (Cazzola et al., 1995, 1997).

Volume to be transfused and transfusion interval

The right regimen is one in which the haematological targets are met and the clinical aims of the transfusion regimen are achieved. In reality, most patients are transfused at 3–4 weekly intervals, and for adults the number of units is usually 2–3 units of packed RBCs. Units of blood provided by NHSBT and the other UK blood services have strict manufacturing criteria and the volume of a unit of blood should not significantly impact the rise in Hb that is expected. To prevent transfusion delay, in the day-care unit, patients will often have a threshold below which the transfusion can take place without additional medical consideration according to local processes; an example might be 'if Hb ≤100 g/L give 2 units, if Hb <95 g/L give 2 units and discuss with medical team to bring back patient at a shorted interval for their next transfusion, if Hb >110 g/L delay by one week'.

For patients of a smaller size and children, the volume of blood needs to be more accurately calculated to avoid over transfusion and transfusion associated circulatory overload.

To achieve pretransfusion Hb of 95–105 g/L, it is often usual to aim for a post-transfusion Hb level of 130–150g/L. This overall approach to transfusion has been shown to promote normal growth, allow normal physical activities, adequately suppress bone marrow activity and minimise transfusional iron accumulation in most patients (Cazzola et al., 1997). A standard unit should provide a 10g/l rise in Hb for a person weighing 75kg. For children or for others who may need a specific volume, the following calculation in Table 5.2 is generally used (Davies et al., 2007).

Table 5.2: Calculation for volume of blood for children and others in need of specific volumes

(Desired – actual Hb (g/L)) × weight (kg) × 0.3 = mL to be transfused assuming the haematocrit of the unit is 0.58 **Example:** Patient's Hb is 95 g/L, desired post-transfusion Hb is 135 g/L, patient weight is 20 kg: **(135 – 95) × 20 × 0.3 = 240 mL: order one unit and prescribe 240 mL of blood**

Large changes in Hb are not desirable because this can change the blood viscosity markedly and result in complications. It is common in paediatric transfusions (often in malignancy) to transfuse 15–20 mL/kg per episode, but it is important to check that this is not going to exceed the desired post-transfusion target.

To limit donor exposure, a certain number of units (e.g., 1 or 2 units) rather than a particular volume of blood is ordered. For example, if in the calculation in a child results in a recommendation to prescribe 280 mL, then prescribe 1 unit; there may only be 260 mL in the bag but it is not worth opening another bag for such a small amount of blood. Younger children may require a fraction of a unit to avoid under- or over-transfusion.

Post-transfusion Hb can be measured when evaluating the effects of changes in the transfusion regimen, the degree of hypersplenism or unexplained changes in response to transfusion, but this is not usually needed and is not commonly performed. Although erythrocytapheresis, or automated RBC exchange, has been shown to reduce net RBCs infused and, thus, the rate of transfusional iron loading in sickle cell disorder (Friedman et al., 2003; Berdoukas et al., 1986), its use in thalassaemia-setting audits has not shown similar benefits (Wall and Bolster, 2019). Lastly, financial constraints and additional blood use issues with such a procedure, in addition to logistical issues regarding the need for suitable venous access.

Rate of transfusion

The rate of transfusion has not been subjected to a prospective study and will depend on the component issued. Since universal leucodepletion began in 1999 to reduce systemic reactions, RBC units are of smaller volume than previous whole blood units.

British Society for Haematology Guidelines state that, for adults, units of blood (here packed RBCs of a mean volume of 260 mL) can be infused over 90 minutes (Robinson et al., 2018); however, the clinical state of the patient needs to be ascertained to see whether this is suitable. An study in two London thalassaemia centres suggests that in very carefully selected adults (weight >45 kg, free of cardiac disease and receiving up to 3 units of mean volume of 260 mL) can be administered at a rate of 1 unit/hour (Sinclair et al., 2013). A more cautious approach to rate of transfusion should be taken with smaller patients, particularly children and patients with cardiac failure or very low initial haemoglobin levels.

Calculating the transfusional iron loading rate

International guidelines regarding the keeping of transfusion records are now incorporated into British law. Historically, additional records were kept for patients with

thalassaemia. These included the volume or weight of the administered units, the haematocrit of the units or the average haematocrit of units with similar anticoagulant-preservative solutions, and the patient's weight. With this information, it was possible to calculate the annual blood requirements as volume of transfused blood or pure RBCs (haematocrit 100%) per kilogram of body weight. The latter (pure RBCs per kg of body weight) when multiplied by 1.08, the estimated amount of iron per millilitre of RBCs (see **Chapter 6: Iron Overload and Management**), yields an approximate value for the amount of transfusional iron that the patient receives per kilogram of body weight in 1 year.

Table 5.3 shows a detailed example of how the daily rate of iron loading (mg/kg/day) is calculated. Nowadays, this level of calculation is not often done as the predominant predictor of iron control is the correct use of chelation therapy, although it may be useful in situations where there has been a change in blood requirement, development of hypersplenism or where access to accurate MRI measurements of iron loading is poor.

Table 5.3: Calculation of annual blood requirements and transfusional iron loading

Patient weight (60 kg)	Annual blood requirement/kg	Annual transfusion iron loading	Daily transfusion iron loading
Transfusion regimen: 2 units (average 260 mL/unit) every 3 weeks = 17.3 transfusion episodes per year Haematopoietic cell transplantation of packed RBCs = 0.58	= volume of blood per transfusion episode × number of transfusions per year/weight (kg) = 520 × 17.3/60 = 150 mL/kg/year	= mL/kg/year × the amount of iron per mL of packed RBCs (1.08) = 150 × 1.08 = 162 mg Fe/kg/year	= annual transfusion iron loading/365 = 0.44 mg/Fe/kg/day

Consent for transfusion

It is a general legal and ethical principle that valid consent should be obtained from a patient before they are treated.

In October 2020, the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) published a report titled *Patient Consent for Blood Transfusion* (Advisory Committee on the Safety of Blood, Tissues and Organs, 2020). This report updated SaBTO's 2011 recommendations to NHS Trusts on patient consent for a blood transfusion, following stakeholder consultation in June 2020.

The report includes the following recommendations:

- Valid consent for blood transfusion should be obtained and documented in the patient's clinical record by the healthcare professional.
- Patients who have been given a blood transfusion, and who were not able to give informed and valid consent prior to the transfusion, are informed of the transfusion prior to discharge, and provided with relevant paper or electronic information.
- There should be a modified form of consent for long-term multitransfused patients, details of which should be explicit in an organisation's consent policy.
- The UK blood transfusion networks are working towards producing new resources for patients and staff to assist the consent process.

Useful links

https://www.nhsbt.nhs.uk/what-we-do/clinical-and-research/blood-group-genotyping/

https://hospital.blood.co.uk/diagnostic-services/red-cell-immunohaematology/

NHSBT Patient Information Leaflets

LearnBloodTransfusion (includes a specific Consent for Blood Transfusion module)

www.learnbloodtransfusion.org.uk

BCSH Blood Administration Guidelines (plus Consent for blood transfusion addendum)

http://b-s-h.org.uk/guidelines/guidelines/administration-of-blood-components

http://b-s-h.org.uk/media/13489/bcsh-blood-admin-addendum-august-2012.pdf

General Medical Council Consent Guidance

www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/decision-making-and-consent

Department of Health Reference Guide to Consent for Examination or Treatment

Adverse reactions

Blood transfusion exposes the patient to a variety of risks and adverse events, and these are covered comprehensively in the Serious Hazards of Transfusion (SHOT) yearly reports that are frequently accompanied by a chapter on haemoglobinopathies (Narayan et al., 2021). This chapter will not go into detail regarding transfusion complications, as this information is well described elsewhere. Guidance regarding the investigation and management of acute transfusion reactions can be found here (Tinegate et al., 2012). If a reaction does take place, it is important that it is discussed with the patient as part of the duty of candour, but also so that they are fully informed (e.g., if they have formed an antibody).

Non-haemolytic febrile transfusion reactions used to be commonplace, but their incidence has been dramatically reduced by universal leucodepletion (conducted in the UK since 1999), which sharply reduces cytokine accumulation and leukocyte alloimmunisation. Since fever may accompany a haemolytic transfusion reaction or the administration of a unit with bacterial contamination, such other causes should always be considered in a patient who develops fever during the administration of RBCs.

Allergic reactions are usually due to plasma proteins and range from mild to severe. Milder reactions include urticaria, itching and flushing, and they are generally mediated by immunoglobulin (IgE). More severe reactions (such as stridor, bronchospasm, hypotension or other symptoms of anaphylaxis) may occur, especially in patients with IgA deficiency and anti-IgA antibodies. Allergic reactions have been reported in patients who receive units of blood from donors who have been exposed to something that the patient is allergic to (e.g., a donor eating strawberries and then donating blood to someone who is allergic to them).

Occasional mild allergic reactions often can be prevented using antihistamines or corticosteroids before transfusion. Recurrent allergic reactions can be markedly reduced by washing the RBCs to remove the plasma. Patients with severe IgA deficiency and severe allergic reactions may require blood from IgA-deficient donors.

Acute haemolytic reactions, usually caused by ABO incompatibility, most commonly arise as a result of patient misidentification, either at the bedside or in the laboratory; hence, a rigorous process of patient identification must be adhered to, however well the patient is known to the hospital. Such reactions begin within minutes or sometimes hours of initiating a transfusion, and are characterised by the abrupt onset of fever, chills, lower back pain, a sense of impending death, dyspnoea, haemoglobinuria and shock, and are frequently life-threatening.

The risk of receiving the wrong blood is greater for a patient with thalassaemia who travels to another centre, or who is admitted to a hospital that is not familiar with their case and medical history as the correct blood matching may not be informed.

Alloimmunisation, as described above, is a common complication of transfusion therapy, occurring in as many as 22% of patients with thalassaemia (Trompeter, S., Estcourt, L., et al. (2020)). Alloimmunisation is more common in children who begin transfusion therapy after 1–3 years of age than in those who begin transfusion therapy earlier. This may reflect the fact that such patients are often transfused in an emergency (i.e., often not at the hospital where they are known to have thalassaemia and are therefore inadequately matched) or when immune activated (i.e., when they are unwell). Some evidence also suggests that new alloantibodies develop more frequently after splenectomy (Thompson et al., 2011). The use of partially extended antigen-matched donor blood (A, B, O, Rh (DCcEe) and K) is effective in reducing the rate of alloimmunisation considerably, but not completely.

Delayed transfusion reactions due to alloimmunisation usually occur 5–14 days after transfusion and are characterised by unexpected levels of anaemia, haemoglobinuria, malaise and jaundice. These reactions may be due to an alloantibody that was not detectable at the time of transfusion or to the development of a new antibody. The former cause is preventable if a full transfusion history is sought and conveyed to the laboratory (see section above and British Committee for Standards in Haematology, 2013).

Transfusion-associated graft versus host disease (GvHD) is caused by viable lymphocytes in donor RBC units. It is a rare but often fatal complication of transfusion in people with poor T-cell function. In thalassaemia, this is usually relevant if the patient has entered or is entering the HSCT pathway, at which point their transfusions should routinely be irradiated.

Transfusion-associated circulatory overload (TACO) may occur in the presence of recognised or unrecognised cardiac dysfunction, or when the rate of transfusion is inappropriately fast. Signs and symptoms include dyspnoea and tachycardia, and chest radiographs show the classic findings of pulmonary oedema. Treatment focuses on volume reduction and cardiac support, as required.

Transfusion-transmitted infections (TTIs) – including viruses, bacteria and parasites – are a risk in blood transfusion and the recent ‘Blood Enquiry’ in the UK is very clear evidence of the tragic consequences of viral transmission through blood products. SaBTO issues guidance to the blood services around the safety of blood products and mitigating actions that the blood services should employ to ensure the safety of the products that they supply. Nevertheless, even though the residual risk of transmission of clinically significant pathogens – human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C

virus (HCV) and syphilis – through blood transfusion has been reduced to minimal levels, problems continue to exist or emerge because:

- Laboratory tests may fail to identify viruses during the window period or because of imperfect sensitivity
- The clinical significance of newly identified infectious agents is not always clear and donors are not screened for these agents
- There is an absence of widely accepted or routinely used tests for certain bacterial, viral and other pathogens (e.g., Yersinia enterocolitica, hepatitis A, toxoplasmosis, malaria and babesiosis).

Although the standard of care to prevent TTIs is questionnaire use and sample screening, there is growing interest in the use of pathogen inactivation/reduction technologies. These have enjoyed greater development in platelet and plasma products, and there are ongoing studies of the use of such technologies for RBC products.

Recommendations

- At diagnosis all patients should have a group and screen with at a minimum: A, B, O, Rh (DCcEe), and Kell tested. Furthermore, extended red cell typing should be performed, in preference using genotyping (essential if transfused within last 3/12) with variant analysis (where available).
- Patients should receive ABO and Rh (DCcEe) and Kell compatible blood that is negative for antigens to clinically relevant antibodies.
- There should be a valid group and antibody screen available prior to transfusion being administered.
- Prior to the first blood transfusion at each hospital site, a full transfusion history should be taken and communicated to the Blood Transfusion laboratory, who can communicate with other hospitals where the patient has been transfused as well as the Blood Service so that the appropriate flags are placed on the transfusion laboratory information system.
- Hospitals in England should permit the sharing of the NHS Blood and Transplant (NHSBT) results on their patients with other hospitals.
- A Group and Screen validity of 1 week can be considered for those with thalassaemia on regular transfusion whether they have allo-antibodies or not.
- People with transfusion dependent thalassaemia (TDT) should be transfused every 3 to 4 weeks, to maintain the pretransfusion haemoglobin level 95-105 g/l. The pretransfusion haemoglobin level may be increased in those in whom it is deemed insufficient or in those who are symptomatic e.g., presence of significant extramedullary haematopoiesis.

- People with thalassaemia who are not yet transfusion dependent may need a one-off transfusion to treat a temporarily worsened anaemia e.g., during an episode of infection.
- For those who are small (<40kg) then a more accurate measure should be employed in calculating volume of blood to be transfused. A common formula is (desired – actual Hb (g/l)) x weight (kg) x 0.3 = ml to be transfused (assuming the haematocrit of the unit is 0.58 (Davies et al)) where the desired haemoglobin is usually set at 135g/l.
- British Society for Haematology guidance states that adults can be transfused at a rate of a unit over 90 minutes in adults (Robinson et al., 2018). Though, a faster protocol is used at several thalassaemia centres in England in adults >45kg, free of cardiac disease and receiving up to 3 units of mean volume of 260ml can be administered at the rate of one unit per hour (Sinclair, Trompeter & Al-Khafeji, 2013).
- Valid consent for blood transfusion should be obtained and documented in the patient's clinical record by the healthcare professional. As part of the consent process, patients should be aware of the potential adverse effects of blood transfusion and be informed if any of these should occur.There should be a modified form of consent for long term multi-transfused patients, details of which should be explicit in an organisation's consent policy.(https://www.transfusionguidelines.org/transfusion-practice/consent-for-blood-transfusion/guidance-for-healthcare-practitioners-involved-in-this-role#:~:text=The%20SaBTO%202020%20updated%20guidance,transfusion%20of%20a%20blood%20component).
- Guidance regarding adverse events should be followed with close liaison with the transfusion laboratory and the Blood Service as required.

- Certain transfusion reactions as well as near misses must be reported to SHOT/MHRA as per national guidance.
- A blood group and antibody screen sample should be taken prior to each transfusion, and blood may be issued via electronic issues providing the standard electronic issue requirements are met.
- The volume of blood for adult transfusions is usually 2–3 units of packed red blood cells per transfusion episode.
- Do not break into an additional unit for a very small amount of blood as this is wasteful and increases donor exposure, without any appreciable benefit to the patient.
- It is not usually necessary to calculate iron loading in thalassaemia as this has been superseded by other methods such as MRI evaluation of iron overload.

- Exceptions may include when there has been a change in blood requirement or the development of hypersplenism.

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Chapter 6

Iron Overload and Management

"It is sometimes really difficult to stay on top of all my medication because of life but what choice do we have."

"Oral tablets have changed my life but I still take the pump a few times a week."

"The worst part of having thalassaemia is iron overload and having to take these medications."

Aims

To understand the importance of monitoring in thalassemia syndromes. This includes patients living with TDT and NTDT, both of whom can develop iron overload.

To understand that robust monitoring of body iron stores minimises iron accumulation, and prevents tissue damage and organ dysfunction resulting from transfusional iron overload.

To recognise that for those patients who have accumulated iron, early intensification with iron chelation to reduce body iron load will minimise the toxic effects of intracellular and extracellular iron on organ function.

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

To recognise when to consider intensification and combination iron chelation.

Standards

- A protocol for iron chelation therapy in children and adults should be shared between the SHC and local hospital teams within the clinical network, and

reviewed at regular intervals. This should be based on current published evidence, expert opinion and national specialist commissioning guidance.

- Decisions about initiating and changing chelation therapy should be made by the haemoglobinopathy specialist, taking into account the preferences of the patient and carers, and the views of other involved healthcare workers.
- Patients and carers should be informed about the benefits and possible adverse effects of each chelation option, and offered information in formats appropriate to their age and language and literacy level, with health advocacy as needed. The decision process should be recorded in the patient's records.
- Patients and carers should be supported to adhere to chelation therapy using an MDT approach including clinic doctors, nurse specialists and clinical psychologists, and play therapists for children. Peer support should be encouraged.
- Adherence should be monitored regularly, and problems carefully identified and addressed in a non-judgemental manner.
- Cultural competence is important in addressing adherence where patients and clinical teams are from different ethnic backgrounds. Having an understanding of a patient's social and cultural upbringing and behaviours plays an important role, together with an MDT approach to support adherence in chelation.
- All patients should have access to cardiac MRI (CMR) for the assessment of myocardial iron overload and cardiac function, and to liver MRI for the assessment of liver iron concentration (LIC). The MRI methodology should be standardised and validated.
- Patients should be carefully monitored for side effects of iron chelation therapy, and treatment interrupted or reduced promptly to avoid serious toxicity.
- The outcomes of chelation therapy within local clinics and the clinical haemoglobinopathy network should be audited regularly.

Background

Introduction to and complications from iron overload

Diagnosis, monitoring and effective treatment of iron overload are crucial for patients with thalassaemia. Iron overload is responsible for increased morbidity and mortality in thalassemia patients.

Most complications of iron overload can be prevented or reversed before irreversible damage and dysfunction occurs. This is well established for cardiac disease (Farmaki et al., 2010; Anderson et al., 2004; Tanner et al., 2008).

Clinically significant iron overload can occur early in young children with ineffective erythropoiesis, such as in TDT. Iron overload in TM is usually fatal in the second or third decade of life if not treated. Toxic effects are attributed to non-transferrin-bound iron (NTBI) in the plasma and toxic unbound iron in intracellular compartments. These accumulate when the normal physiological mechanisms that sequester iron are overwhelmed (Cabantchik et al., 2005).

In patients with TDT, myocardial iron overload is more likely when transfusion iron loading rates significantly exceed iron utilisation by the bone marrow (Garbowski et al., 2017). The majority of deaths, even when effective iron chelation therapy is available, are due to iron-related cardiomyopathy presenting as cardiac arrhythmias and cardiac failure (Borgna-Pignatti et al., 2004).

Complications in patients with NTDT are typically delayed due to slower gastrointestinal iron absorption rates, resulting in lower toxicity of iron species. LIC can be a surrogate marker for the risk of other endocrine complications including osteoporosis, thrombosis and PHT. Patients with NTDT with iron overload are also at increased risk of developing renal dysfunction and glomerular dysfunction (Musallam et al., 2012). In the absence of transfusion myocardial iron overload is rare, even with a high LIC.

For more information on the diagnosis and management of complications related to iron overload, please refer to the relevant chapters.

Monitoring of iron overload

Monitoring for iron overload is important in identifying existing complications, and for quantifying the risk of and therefore preventing future complications from developing.

Functional parameters of end-organ damage have been the mainstay of monitoring iron overload (Table 6.1). However, the quantification of iron overload allows organ-specific measurement of iron in the heart, liver, pancreas and pituitary, and may identify high-risk patients before end-organ damage occurs.

SF is important in quantifying the overall risk of complications and is most useful for detecting long-term trends. Patients should be reviewed regularly to assess adherence to treatment and to enable trends in iron burden to be monitored using both functional assessment of end-organ damage and quantitative assessments of iron overload.

Rate of iron loading from transfusion

Estimating current iron stores helps informed clinical decisions to be made regarding chelation therapy. To do this accurately, it is necessary to know the patient's transfusion history, age at which chelation was started, and past and present prescribed chelation therapy. It is important to ascertain the pattern of adherence to therapy and whether there have been periods of poor or absent chelation.

Average daily transfusional iron loading (expressed as mg/kg/day) can be calculated assuming that 1 mL of pure RBCs contains 1.08 mg of iron. The ROIL in mg/kg/day can be calculated from the number of units given over a measured time period. Patients with an average ROIL (0.3–0.5 mg/kg/day) will require average doses, where as those with a ROIL <0.2 mg/kg/day or >0.5 mg/kg/day will require dose adjustment accordingly (Cohen et al., 2008). The recommendation is that a period of 6–12 months is used to calculate the ROIL.

Table 6.1: Calculation of the ROIL

ROIL (mg/kg/day) (adult)	**ROIL (mg/kg/day) (paediatric)**
= units of blood transfused × 200 Weight × days over which the blood was administered	= mL of blood transfused × 1.08 Weight × days over which the blood was administered

Serum ferritin

SF broadly correlates with total body iron loading. Values up to about 3000 µg/L reflect macrophage iron, whereas levels >3000 µg/L also reflect hepatocyte damage (Brittenham et al., 1993).

Ferritin is an acute-phase protein and levels are elevated during intercurrent infections, chronic inflammatory conditions and chronic viral hepatitis, which can lead to an overestimate of the degree of iron loading. Conversely, low levels may give false reassurance in cases of vitamin C deficiency. SF is also affected by individual chelation

drugs (Ang et al., 2017. In patients with NTDT, SF levels may result in underestimation of the degree of iron overload (Origa et al., 2007).

Long-term control of ferritin with DFO therapy has historically been shown to have prognostic significance (Olivieri et al., 1994), and maintenance of SF levels <2500 µg/L is associated with a lower risk of cardiac disease and death in patients on DFO monotherapy (Brittenham et al., 1994; Gabutti and Piga, 1996; Borgna-Pignatti et al., 2004; Davis et al., 2004). Maintenance of SF <1000 µg/L may be associated with additional advantages in patients with TDT (Borgna-Pignatti et al., 2004; Farmaki et al. 2010, 2011).

Any SF trend can be used as a guide to modify chelation dosing, but should take into account the patient's liver iron burden and the type of chelation regimen being used. Where possible, patients should have SF-based goals that are specific for them based on the patient's normal SF level when the iron burden is well controlled. Cardiac iron does not correlate with SF and a low SF level does not exclude the presence or confirm the clearance of cardiac iron (Tanner et al., 2008).

Other serum markers of iron overload

Iron is transported in the plasma predominantly bound to transferrin. Regular transfusion progressively overwhelms the normal body storage and transport mechanisms. As a result, transferrin quite quickly becomes fully saturated and NTBI appears in the plasma consisting of circulating iron not bound to transferrin, ferritin or haem. Labile plasma iron (LPI) is a fraction of NTBI that is redox-active and available for chelation. LPI can permeate cells and generate free radicals, which are thought to be the major cause of tissue damage in transfusional iron overload. Regular or prolonged periods of uncontrolled NTBI/LPI can cause myocardial iron to develop even when the LIC may not be >15 mg/g dry weight (dw).

Liver iron concentration

Liver biopsy

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

biopsy is small or cirrhotic. The coefficient of variation has been estimated at about 19% in non-diseased and 40% in fibrotic livers (Kreeftenberg et al., 1984; Villeneuve et al., 1996; Emond et al., 1999).

MRI methodologies

MRI can exploit the paramagnetic properties of iron to obtain quantitative measurements of iron concentrations in body tissues. MRI scanning is non-invasive, allows averaging of LIC over a large volume of liver tissue and is suitable for sequential assessment. All MRI-based methods require calibration against LICs measured by chemical analysis of liver tissue and are subject to variability, which may be increased by higher degrees of iron loading, hepatic fibrosis and hepatic fat content.

LIC values, where possible, should be assessed using the same methodology (T2*, R2 or R2*) sequentially for the patient as the values for LIC do not concur across different techniques for data acquisition and analysis. There may also be considerable intercentre variability, even if the same methodology is being used to acquire the data (Garbowski, et al., 2014). Both T2* and R2 methods are approved as per NHS England policy, but a method with validated quality control should be used in preference where possible.

Patients who are transfusion-dependent should routinely have tailored MRI assessments of LIC with the frequency dependent on the severity of their iron burden, the intensity of chelation and the concordance with iron chelation therapy (Cappellini, Cohen et al. 2014).

Optimal concentrations of liver iron

Determining the optimal range of LIC requires a balance between the avoidance of iron toxicity and the prevention of chelator-induced toxicity. Although a normal LIC is 0.2–1.8 mg/g dw, maintaining levels within the normal range may increase the risk of chelator toxicity. Long-term LICs >7 mg/g dw have been associated with increased risk of fibrosis, which can progress to cirrhosis (Deugnier et al., 2011; Maira et al., 2017). LICs >15 mg/g dw are associated with increased risk of myocardial iron overload (Jensen et al., 2003; Wood et al., 2010). Where possible, the LIC should be maintained <7 mg/g dw and ideally <5 mg/g dw.

Cardiac iron

In iron-loaded patients with TM, myocardial tissue iron concentrations increase with the severity of the liver iron burden and the duration during which a high level of liver iron is maintained. In addition, myocardial iron loading can occur due to frequent episodes of

uncontrolled NTBI/LPI due to short but frequent episodes of no chelation, even in patients with well-controlled SF trends and LICs on annual scans. This is most likely to be seen in patients on DFO who follow regimens such as 2–3 week breaks in chelation and 2–3 weeks of intensive chelation.

Please refer to **Chapter 15: Management of the Cardiovascular System**.

Assessment of iron overload in other organs

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

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

Table 6.2: Monitoring for complications of transfusional iron overload[1]

	Routine test	Frequency	Notes	Quality and grade
Iron load and distribution	SF MRI cardiac T2* and LVEF (baseline by age 8 years and thereafter)	Every 1–3 months 2-yearly Annually	>20 msec 10–20 msec	1C 1C 1B

		6-monthly	<10 msec	1B
	Routine test	**Frequency**	**Notes**	**Quality and grade**
Iron load and distribution	Liver R2 (Ferriscan) or T2* (baseline by age 8 years and thereafter)	Done concurrentl y with cardiac T2*	Liver iron quantification using T2* must be assessed using the same calculation and cross-validated for results to be comparable	1B
		1–2-yearly	1.8–7 mg/g dw	1C
		Annually	7–15 mg/g dw	1C
		6–12-monthly	>15 mg/g dw	1C
Endocrine	Height/weight	Every 6 months	Until adult height	1B
	Pubertal status	Annually	From age 10 years	1B
	OGTT	Annually	From puberty	1C
			From age 10 years if family history of diabetes	1B
	Routine test	**Frequency**	**Notes**	**Quality and grade**

Endocrine	Thyroid function	Annually	Patients with diabetes and those on HRT 3–6-monthly	1B
	Morning cortisol	Annually		1B
	Gonadal function	Annually		1B
Bone	Vitamin D	Annually	From age 2 years	1C
	Bone density scan	2-yearly	From puberty	1B
Cardiac	Good chelation Cardiology review	2-yearly/ annually	From age 16 years	1C
	Electrocardiograph	Annually		1C
	Echocardiogram	Annually		1B
	MRI cardiac T2* and LVEF	See above	As per iron load and distribution recommendation	1B
	Routine test	**Frequency**	**Notes**	**Quality and grade**
	Poor chelation	3–6-monthly	Baseline when poor chelation identified as per cardiologist recommendations	2C
	Cardiology review	3–6-monthly		2C
	Electrocardiogram	6-monthly		1B
	Echocardiogram			
	MRI cardiac and LVEF	6–12-monthly	As per iron load and distribution recommendation	1B

Liver	Liver function tests	Monthly		2C
	Anti-HCV, hepatitis B surface antigen, anti-hepatitis B core antibody	Annually		1C
	Ultrasound	6-monthly	In patients with cirrhosis	1B
	Liver iron assessment	6 months to 2 years	As per iron load and distribution recommendation	1B
Other useful tests	Soluble transferrin receptors	Annually	Low levels relative to transfusional loading may indicate high cardiac risk	2C
	Audiology/ophthalmology			

[1]British Society for Haematology guideline for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias 2021. LVEF, left ventricular ejection fraction; OGTT, oral glucose tolerance test.

Treatment of iron overload

Licensed chelating drugs and formulations

There are three iron chelating drugs that can be used for the treatment of iron overload in thalassemia syndromes: Desferrioxamine (DFO); Deferiprone (DFP); Deferasirox (DFX) . Iron chelating drugs act:

- to bind iron and to excrete the iron-chelate complex at a rate equal to or greater than the iron accumulation rate
- to decrease free radical-mediated tissue damage whilst the process is taking place.

Desferrioxamine

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

Efficacy

Long-term treatment is associated with improved survival, mainly through the reduction of cardiac mortality (Brittenham et al., 1994; Olivieri et al., 1994; Borgna-Pignatti et al., 2004). DFO reduces hepatic iron (Brittenham et al., 1994), stabilises or improves hepatic fibrosis (Barry et al., 1974; Aldouri et al., 1987) and also protects against endocrine complications (Borgna-Pignatti et al., 2004; De Sanctis et al., 2006).

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

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

Infusion/delivery systems

Disposable elastomeric pre-filled infusers are usually preferred over battery-operated infuser pumps in older children and adults. These are light and noiseless, and facilitate subcutaneous chelation during daytime activities. For most patients, this translates into better acceptability, adherence and efficacy. They are prepared in a sterile pharmacy facility and are often delivered to the patient's home to optimise convenience. A battery-

operated infuser pump (e.g., Cronos®) is recommended for young children up to the age of 5 years; use of disposable infusers in this age range is not recommended because the infusion volume is excessive (≥20 mL). Small-gauge 'thumb-tack'-type subcutaneous needles (e.g., Thalaset®) are recommended as they are easier to use and less painful than traditional 'butterfly needles'.

Ascorbic acid

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

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

Adherence

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

Adherence is enhanced in childhood when the parents understand the rationale for the therapy, and feel confident in setting up the DFO infusions safely and efficiently. Additionally, long-term adherence is improved if the child takes responsibility for the infusions at an early age. It is important to offer practical and psychological support in identifying and addressing problems. **To read more on how to target adherence issues, please read Chapter 24: Adherence**.

Adverse effects

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

Abnormalities of bone growth – such as vertebral dysplasia leading to disproportionate short trunk, pseudo-rickets and genu valgum – have been described in prepubertal

children treated with relatively large doses of DFO (>40 mg/kg) and are more likely to occur in childhood when iron stores are low (De Virgiliis et al., 1988). High-tone sensorineural hearing loss is a serious adverse effect of DFO, which can be anticipated if the average daily dose of DFO/SF is calculated to be >0.025 (e.g., higher risk, at SF 1000 µg/L, if receiving on average >25 mg DFO/kg/day) (Porter et al., 1989). Early identification of DFO toxicity, with annual checks of pure tone audiometry, and sitting and standing heights during childhood, are essential for the prevention of irreversible damage (Bronspiegel-Weintrob et al., 1990; Olivieri and Brittenham, 1997).

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

Deferiprone

DFP is orally active and chelates iron in a 3:1 drug–iron complex. It has a relatively short plasma half-life and consequently three or even four times-daily dosing is needed to optimise drug levels over a 24-hour period. Drug and iron complexes are predominantly excreted in the urine, giving the urine a red colour. It is available in liquid and tablet formulations.

Efficacy

There is substantial published clinical experience about the use of DFP (Cohen et al., 2000; Ceci et al., 2002), and unpublished clinical experience in large centres where some patients have been effectively chelated with DFP monotherapy for many years. Randomised controlled studies comparing DFO with DFP have shown similar efficacy over 6–12 months in controlling SF and LIC (Maggio et al., 2002; Pennell et al., 2006; Fisher et al., 2013). However, LIC may not be adequately controlled over the longer term with DFP monotherapy at 75 mg/kg/day (Hoffbrand et al., 1998, 2003; Olivieri et al., 1998; Tondury et al., 1998). In paediatric patients, DFP has been shown to be effective and safe in inducing control of iron overload during 12 months of treatment (Maggio et al., 2020).

A consensus view, based on published trials and clinical experience, is that DFP therapy produces a reliable and rapid reduction of myocardial iron loading compared with other chelating drugs. Ventricular function assessed by CMR (right and left ventricular [LV] ejection fraction [LVEF]) also increases more consistently, and there is a reduced risk of

clinical cardiac events such as arrhythmia, cardiac failure and cardiac death (Anderson et al., 2002; Piga et al., 2003; Pepe et al., 2006, 2011).

Adverse effects

Adverse effects include agranulocytosis, neutropenia and arthropathy, the latter in 4–50% of cases (the higher rates reported in series from the Indian subcontinent). Gastrointestinal disturbance, intermittent elevation in alanine aminotransferase (ALT), zinc deficiency and increased appetite are often reported (Hoffbrand et al., 1998; Cohen et al., 2000; Ceci et al., 2002; Maggio et al., 2002; Naithani et al., 2005; Fisher et al., 2013). Some patients have to discontinue DFP as a result of these side effects. Arthropathy is usually reversible and, in some cases, DFP can be reintroduced once symptoms have subsided.

Agranulocytosis (an absolute neutrophil count of 0.5×10^9/L) is a severe and potentially fatal adverse effect of DFP. In pooled data from clinical trials, agranulocytosis occurred in 1.5% of patients at a median of 162 days after starting therapy. There was no significant association of agranulocytosis with DFP dose or with splenectomy status. Episodes were more common in children, but this was not statistically significant. Episodes were rapid in onset and were not generally pre-empted in clinical trials where weekly monitoring of FBCs had been undertaken. There was a high risk of recurrence of agranulocytosis with rechallenge. Similar observations were made in post-marketing surveillance (Tricta et al., 2016). No genetic predisposing factors for DFP-associated agranulocytosis have been identified.

Neutropenia (neutrophil count in the range $0.5–1.5 \times 10^9$/L) was observed in 6.7% of patients in pooled data from clinical trials. Episodes were more common in splenectomised patients and were usually self-limiting, but could be recurrent and lead into agranulocytosis (Elalfy et al., 2010).

Adherence

Adherence to chelation therapy is generally improved in patients switched from DFO to DFP (Olivieri et al., 1998; Telfer et al., 2005). However, patients may struggle with the three times-daily regimen and therefore forget midday doses due to school- or work-related issues. It is important to specifically discuss the patient's daily routine for medication usage, to understand the frequency of missed doses. In addition, initiation of therapy can be associated with gastrointestinal symptoms, and slowly increasing to the desired dose may reduce the frequency and severity of gastrointestinal side effects. **To read more on how to target adherence issues, please read Chapter 24: Adherence**.

Deferasirox

DFX is an orally active chelating agent, which chelates iron in a 2:1 drug–iron complex. It has a long plasma half-life and once-daily dosing usually produces adequate drug levels over the whole 24-hour period. Drug and iron complexes are predominantly excreted in the faeces (Vlachodimitropoulou Koumoutsea et al., 2015).

Efficacy

The original formulation was a dispersible tablet (DFX-D), but DFX is now available as a film-coated tablet (DFX-FCT).

Clinical trials and long-term follow-up have confirmed that DFX can produce a significant reduction in SF and LIC. Doses need to be adjusted according to the ROIL. Three-monthly dosage adjustments based on trends in SF are recommended in order to optimise chelation efficacy and minimise adverse effects (Taher et al., 2009; Cappellini et al., 2010). Reduction of iron stores in heavily iron-loaded patients may take several years of regular DFX therapy. Around 80% of patients who respond to DFX chelation with a decline in SF have a corresponding decline in LIC. Conversely, clinically useful reductions in LIC have been seen in about 50% of patients with no significant reduction in SF.

DFX is non-inferior to DFO in improving myocardial T2* (Pennell et al., 2014, 2015).

Adverse effects

These include self-limiting skin rash (10.8%), gastrointestinal symptoms (26%) and, less frequently, drug-induced hepatitis, hepatic failure, gastrointestinal ulceration, gastrointestinal haemorrhage, renal tubular damage, lens opacities and sensorineural hearing loss (Deferasirox Summary of Product Characteristics [SPC] 2013).

A mild dose-dependent increase in serum creatinine is common. These increases are more common in patients on higher doses in relation to the iron burden, and are usually reversible on lowering the dose. There is evidence of progression of renal abnormalities (Cappellini et al., 2011).

Gastrointestinal intolerance due to symptoms of abdominal pain, diarrhoea or nausea is common (up to 10–26%), and requires dose reduction or, occasionally, discontinuation. The DFX-FCT tablet causes fewer problems with diarrhoea and nausea.

Upper gastrointestinal ulceration (sometimes multiple) and haemorrhage have been reported in patients on DFX. The manufacturers recommend that physicians and patients be aware of this complication, and know to initiate additional evaluation and treatment if a serious gastrointestinal adverse reaction is suspected. DFX also be used with caution in patients receiving anticoagulants and in patients with platelet counts <50,000/mm^3 (50 × 10^9/L).

Transaminitis can be seen with DFX and is generally 3–5 times the upper limit of normal. If a person's transaminase level is >5 times the upper limit of normal the recommendation is to stop DFX and wait for it to normalise. When reinitiating, start at 7 mg/kg/day and increase the dose stepwise over several weeks. Mild transaminitis generally will not require dose reduction.

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

Adherence

Generally, once-daily treatment is easier to adhere to; however, it is equally easily forgotten. It is important to ask patients about their daily routine for chelation and how often they miss doses in a week or month. Managing side effects and alleviating them by adjusting the timing of treatment, and understanding their relationship with meals, can help improve compliance. **To read more on how to target adherence issues, please read Chapter 24: Adherence**.

Initiation of chelation therapy

The longstanding recommendation to start chelation once SF reaches 1000 µg/L (on at least two readings), after 10–12 transfusions or after significant liver iron loading, was designed to avoid chelator toxicity in children starting therapy too early with Desferrioxamine (TIF Guidelines, 4th Edition 2021; UKTS Guidelines 3rd Edition, 2016; Olivieri and Brittenham, 1997).

There are no randomised prospective data comparing the initiation of therapy with different chelating agents. DFO has been used for many years as initial chelation therapy and there is substantial clinical experience with its use in children aged over 2 years. There is study evidence for the safety and efficacy of DFX in young children, including

those who are chelation-naïve, and DFX would be a good choice for initiation were it not for the limitations specified in its current European Union licensing agreement. There are limited data on the use of DFP in young children, and DFP is not currently recommended as a first-line iron chelation drug.

In children under the age of 2 years, as per SPC recommendations, chelation should be initiated with DFO with appropriate support provided to parents to support and develop confidence in administering treatment.

Once the child is over the age of 2 years, a discussion should be had with the family about switching to oral chelation with DFX-FCT (DFX SPC).

Table 6.3: Initiation of iron chelation over a person's lifespan

Age	Ferritin threshold	Chelation option 1	Alternative options	Contraindications and cautions
<2 years	SF >1000 µg/L or 100 mL/kg blood transfused	DFO 20–40 mg/kg/day 3–5 Nights/week 8–12 hours subcutaneous infusion	DFX-FCT 7–21 mg/kg/day Unlicensed indication	DFO Avoid dose >40 mg/kg/day

Age	Ferritin threshold	Chelation: option 1	Alternative options	Contraindications and cautions
>2 years and <6 years		DFO 20–40 mg/kg/day 5 days/week 8–12 hours subcutaneous infusion OR DFX-FCT 7–28 mg/kg/day	Switch to alternative regimen if on DFO then DCX-FCT OR if on DFX-FCT switch to DFO	<u>DFO</u> Avoid dose >40 mg/kg/day in children Monitor closely in renal impairment and reduce dose/frequency of administration <u>DFX</u> Monitor closely if creatinine clearance <60 mL/minute and consider dose reduction Avoid if creatinine clearance <30 mL/minute Avoid in severe hepatic impairment <u>DFP</u> Avoid if history of recurrent neutropenia Avoid if hypersensitivity to the active substance

Age	Ferritin threshold	Chelation option 1	Alternative options	Contraindications and cautions
Adults		DFX-FCT 14–28 mg/kg/day once daily	DFO 40–60 mg/kg/day 8–24 hours subcutaneous infusion or DFP 75–100 mg/kg/day	
Second-line therapy for patients failing to respond to monotherapy regimens				
Adults and children	-	Any of the combinations below based on patient prior tolerability and compliance DFO + DFP Initiate at appropriate dose of DFO for age and cardiac iron burden; DFP to start at 50 mg/kg/day, then dose increases based on side effects and severity of iron overload DFX + DFO	As above for individual agents Aim for optimised doses for each agent Check compliance to therapy and document	

		Initiate at appropriate dose of DFO for age and 14 mg/kg/day of DFX; dose escalation of DFX at regular intervals based on side effects and tolerability DFX + DFP Add in to the existing oral regimen and start the new oral agent at its standard initial dose (14 mg/kg/day DFX or 75 mg/kg/day DFP); consider a twice-daily regimen of both agents if needed to support compliance	

Chelation monitoring

This can be partly undertaken with specialist nurses. Dose adjustments should be made if there are derangements in the neutrophil count (DFP), liver function tests or renal function (DFX). An assessment of SF should be undertaken as a minimum every 3 months. Monitoring of chelation is a continuous process because it assesses safety as well as the efficacy of therapy, and should not be confined to clinic visits only.

Treatment intensification and optimisation of iron

This is required when the LIC has increased to concentrations where liver damage may develop (>7 mg/g dw) or when myocardial iron has accumulated to abnormal levels (T2*<20 msec). Emergency intensification is required when there is evidence of cardiac decompensation (LVEF <56%) or there is a high risk of this occurring (T2* <8 msec).

If iron burden is not well controlled, as measured by MRI quantification, then an assessment of the ROIL along with the dose of iron chelation and adherence to therapy should be undertaken. In some patients, although the SF level is high, the LIC will be in a safe range, in which case the SF level should be used only as a trend in the context of the previous LIC, otherwise there is a risk of overchelation with all the attendant side effects.

In a stepwise fashion, the dose of chelation should first be optimised (if the patient is fully compliant with the prescribed regimen). If the patient is not able to comply with the correct dose then the dose/drug regimen should be adjusted to support adherence, which may include changing the time of medication administration or switching to a combination regimen to help improve adherence (e.g., reducing DFO frequency and adding in DFP or DFX as a combination schedule).

It is important that the regimen that is used is tailored for the patient to fit it in with their challenges (school/work/family) as well as to reduce the risk of side effects. No patient will be on one regimen throughout their life, and tailoring therapy to achieve good adherence and iron control is the ultimate goal of therapy.

Table 6.4: Intensification of iron chelation for patients with cardiac iron overload

Cardiac T2*	Ejection fraction	Intensification therapy
8–20 msec	**Normal**	**On DFO:** Intensify DFO dose and/or frequency Switch from subcutaneous to intravenous administration Consider adding in one of the following: • DFP 75–100 mg/kg/day • DFX-FCT 14–28 mg/kg/day

		On DFX: Intensify dose to 21–28 mg/kg/day; if no improvement or patient compliance suboptimal consider following options, adding in one of the following: • DFO (40–60 mg/kg/day, 5–7 days/week) • DFP 75–100 mg/kg/day Or consider switching to: Monotherapy with DFP at 75–100 mg/kg/day if LIC is <5 mg/g dw
		On DFP: Optimise dose to maximum 100 mg/kg/day Consider adding in one of the following: • DFO (40–60 mg/kg/day), 5–7 days/week • DFX 14–20 mg/kg/day, 7 days/week
<8 msec	**Normal**	**First-line** DFO 50–60 mg/kg/day and DFP 75–100 mg/kg/day; preference must be given to intravenous regimens If unable to tolerate above regimen, then consider one of the following with preference given to an intravenous regimen: • DFO (50–60 mg/kg/day) + DFX (21–28 mg/kg/day)

		• DFO (50–60 mg/kg/day) + DFP (75–100 mg/kg/day)
<20 msec	**Abnormal: outside the normal values** **Acute heart failure** **Cardiac arrhythmia**	Intravenous DFO infusion (24 hours, 50–60 mg/kg/day) **Add in** DFP 75 mg/kg/day once stable cardiovascular status (provided no previous complications such as agranulocytosis) or, if unable to tolerate DFP due to side effects, consider adding in DFX 14–28 mg/kg day

Combination regimens

The term 'combination therapy' is used to describe the various ways in which chelators can be combined (true combination or sequentially). Whilst combinations are not recommended as first-line therapy they can be useful:

1. to increase overall exposure to iron chelation when monotherapy at licensed doses is insufficient
2. when dose-dependent toxicity limits monotherapy
3. when compliance with monotherapy at the required frequency is inadequate
4. when simultaneous combination has the potential to synergistically increase cellular iron removal rates.

Specialist advice should be obtained from the HCCs prior to commencing combination therapy.

The concept of combination chelation therapy has developed to encompass a wide range of drug combinations and dosing regimens, and the lack of agreed standard terminology has led to confusion in comparing results in terms of efficacy, safety and

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

Combination of desferrioxamine with deferiprone

DFO with DFP is the combination most widely studied and used in clinical practice. There is also good evidence that intensive combination therapy with daily DFP and subcutaneous DFO 5–7 days/week, overnight or with initial continuous infusion at 40–60 mg/kg, is effective for reversing cardiac failure (Wu et al., 2004; Porcu et al., 2007; Tanner et al., 2008). It is generally thought that endocrine complications, once established, are irreversible, but intensive combination chelation therapy has shown improvements in patients with IGT (Farmaki et al., 2006). There have also been reports of improved long-term outcomes and survival in cohorts of patients switched from single-agent regimens (mostly DFO) to combination therapy (Telfer et al., 2006, 2009; Lai et al., 2010).

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

There is currently no consensus about initial dosing regimens and monitoring of therapy. Although negative iron balance is usually achievable if DFO is given at least two times per week together with DFP (Galanello et al., 2010), doses of DFP and DFO, and the frequency of DFO infusions, may need to be increased if iron loading is severe.

Combination of deferasirox with desferrioxamine

Combinations of DFO and DFX are also effective and well tolerated (Lal et al., 2013; Cassinerio et al., 2014; Aydinok et al., 2015; Eghbali et al., 2019). The Hyperiron study (Aydinok et al., 2015) was a prospective, non-randomised, single-arm study of DFX (20–40 mg/kg/day) combined with DFO (40 mg/kg over at least 8 hours, 5 times per week) in patients with significant myocardial iron loading (T2* 5–10 msec) but normal ventricular function, and with evidence of severe hepatic iron loading. Thirty-six out of 60 patients (60%) completed 24 months on the study. T2* increased from a mean of 7.2 to 9.5 msec, and mean LIC reduced from 33.4 to 12.8 mg/g dw. This study showed significant reductions in SF and LIC of 44% and 52%, respectively, with a 33% increase in T2* value. The degree of improvement in myocardial T2* was greatest in those with baseline LIC <30 mg/g dw.

Combination of deferasirox with deferiprone

The in vitro synergistic effect of DFX and DFP in removing intracellular iron is more pronounced than with other combinations (Vlachodimitropoulou Koumoutsea et al., 2015), and clinical experience with this combination is increasing (Balocco et al., 2010; Berdoukas et al., 2010; Voskaridou et al., 2011). In a randomised trial, 96 children at two centres in Egypt compared DFO (40 mg/kg overnight infusion 6 times per week) combined with DFP (75 mg/kg/day in two divided doses per day) with DFX (30 mg/kg/day, evening dose) combined with DFP (75 mg/kg in two divided doses per day) (Elalfy et al., 2015). There were significant improvements in both groups in SF, LIC and myocardial T2* at 6 months and 1 year. The difference between the two groups was significant for myocardial T2*, with the DFX/DFP combination resulting in a significant improvement in cardiac T2*. Quality of life improved in both arms, but patient satisfaction was higher for the DFX/DFP combination. It may be a useful combination for those patients with myocardial iron and a mild to moderate LIC where other options have failed, or in patients where the side effects of one chelator make it difficult to optimise iron burden.

Many patients previously on DFO/DFP combination regimens have switched over to DFX/DFP regimens following the same schedule (7 days/week DFP) and 2–3 days of DFX.

Adherence to chelation therapy

The most common reason for inadequate iron control is poor adherence to the prescribed regimen, and this problem has continued in the current era of oral iron chelation therapy; adherence issues are not unique to thalassemia. A report published by the World Health Organization (WHO) in 2003 stated that adherence for chronic diseases was only 50% in

higher-income countries. In all cases, a non-judgemental approach with careful exploration of problems leading to the formulation of an individualised strategy is needed. The language used matters in addressing compliance in this group of patients because the patients are trying their best and need support. This may involve further education about the importance of long-term control of iron stores to prevent future morbidity and mortality, psychological support, having cultural competence, increased supervision by carers or healthcare staff, peer support and a radical change in lifestyle. **To read more on how to target adherence issues, please read Chapter 24: Adherence**.

Table 6.5: Monitoring for complications of iron chelation

	DFX	**DFP**	**DFO**
Prior to starting	Duplicate, creatinine, ALT, urinalysis	FBC, creatinine, ALT	FBC, creatinine, ALT
Month 1	Weekly creatinine and urinalysis Fortnightly ALT	Weekly neutrophils	
Month 2 onwards			
ALT	Monthly	Monthly	Monthly
Creatinine	Monthly	Monthly	Monthly
Urinalysis	Monthly		
Neutrophil		Weekly for 12 months then 2–4-weekly	

Audiometry	Baseline assessment from the age of 5 years or when symptoms are present	6–12-monthly if used in combination only	Annual (age >5 years)
Ophthalmology	Baseline assessment from the age of 5 years or when symptoms are present	6–12-monthly if used in combination only	Annually (age >5 years)
Growth			Height every 3 months
Other	Transfusional ROIL		6-monthly to annually sitting/standing height
		Zinc level	Zinc level
			Transfusional ROIL
			Calculate therapeutic index*

*Therapeutic index. Mean daily dose (mg/kg)/SF (µg/L). Aim to keep <0.025 at all times.

Additional considerations

Pregnancy

Historically, there have been reports of serious adverse outcomes during pregnancy, including heart failure and dysrhythmias. This is unsurprising because cardiac workload increases significantly, and cardioprotective iron chelation therapy is discontinued during the 9 months of pregnancy to avoid toxicity to the fetus. Women who are planning to become pregnant should undergo a period of intensive chelation to reduce SF, LIC and myocardial iron to optimal levels before attempting to become pregnant.

Evidence from case reports suggests that the risk of DFO toxicity may be low when used during the later stages of pregnancy (Singer and Vichinsky, 1999); however, in the case of spontaneous pregnancy, all chelator drugs should be discontinued as soon as the pregnancy is confirmed. The standard advice for DFO to be withheld throughout pregnancy can be reviewed in cases of high iron loading where the risk of cardiac complications is judged to be high. DFO can be considered from 20 weeks gestation in patients with cardiac iron overload or severe liver iron overload.

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

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

A common practical approach for planned or assisted pregnancy is to stop oral chelators 3 months before likely conception, continuing with DFO until the time of ovulation. Women planning to become pregnant should undergo a thorough assessment of their current transfusion status, cardiac and liver iron loading, and chelation regimen.
Please refer to **Chapter 11: Management of Pregnancy**, the Royal College of Obstetricians and Gynaecologists (RCOG) green-top guideline 66 and BCSH guidelines on the management of pregnancy in thalassaemia syndromes for more details.

Renal impairment

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

DFO is not reported to be nephrotoxic, but should be used with caution in patients with renal impairment because the kidneys are one of the routes of excretion of DFO metabolites and DFO–iron complexes. Although DFO is used to chelate aluminium in patients undergoing haemodialysis, the dosage recommended is only 5 mg/kg. When given at an iron chelation dosing level (40 mg/kg), plasma drug levels are significantly

increased, suggesting that DFO dosage in patients with renal failure should be reduced in order to avoid toxicity (DFO SPC).

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

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

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

For patients with reduced creatinine clearance <60 mL/min, not yet on renal replacement therapy, prolonged infusions of low-dose DFO (e.g., 10 mg/kg over 12 hours, 6–7 days/week) may be helpful in reducing the risk of toxicity from iron, and could be combined with low-dose DFP (50–75 mg/kg/day in three or four divided doses), although there are no published data to support the safety and efficacy of this approach.

For patients with end-stage renal failure on renal replacement therapy, it is reasonable to use DFX at a low therapeutic dose (7–14 mg/kg/day), DFO 5–10 mg/kg the day before dialysis given over 12–24 hours subcutaneously or intravenously, or DFP 50–75 mg/kg/day dependant on patient preference.

Liver failure

Liver fibrosis and cirrhosis are increasingly encountered in older patients with longstanding iron overload. Anecdotal experience using DFO in sickle cell disease has led to improved liver function, even in patients with hepatic disease. DFO may benefit

liver function by rapidly scavenging free radicals as well as more slowly decreasing storage iron. DFX has been shown to stabilise or reverse liver fibrosis in iron overload but is contraindicated in patients with severe hepatic impairment (Child–Pugh class C), and should be used with caution where patients are Child–Pugh class B (Deugnier et al., 2011). All three chelators can be considered in patients with raised transaminase levels and Child–Pugh class A hepatic impairment.

Recommendations

- Patients should have their transfusional iron loading per year calculated annually.
- SF should be measured at 1–3-month intervals to identify trends.
- MRI assessment:

a. Initial MRI of the heart and liver to assess iron burden should be undertaken in transfused patients who have never had assessment, and in children as soon as they are able to lie in a scanner without sedation (generally before the age of 8 years).
b. MRI of heart and liver for iron overload can be undertaken with sedation if there is clinical evidence to suggest severe iron overload in very young children who are not able to undergo MRI assessment without sedation.
c. Surveillance MRI for assessment of cardiac/liver iron should be performed at regular intervals on transfused adults and children. The frequency is described in Table 6.2.
4. Cardiac assessments:
a. LVEF should be assessed annually either by echocardiography or by MRI from age 8 years in patients receiving top-up transfusions.
b. Patients presenting with palpitations should be assessed for cardiac arrhythmias.
5. Liver assessments:
a. Patients over the age of 40 years should be assessed for liver fibrosis.
b. Patients who have had severe liver iron overload, previous HCV infection or fibrosis should be screened every 6 months for hepatocellular carcinoma with ultrasound.
6. NTDT:
a. Patients with non-transfused NTDT should have liver MRI assessment if their SF level is >800 µg/L at baseline.
b. Patients with NTDT with previous iron overload or who are receiving iron chelation therapy should have regular liver MRI assessment as SF levels are unreliable.
7. Poor compliance with chelation therapy should prompt earlier scans if needed.
8. Initiation of chelation:
a. Patients with TDT should be commenced on iron chelation therapy after 10–12 transfusions or when the SF level is >1000 µg/L on two occasions.
b. Patients with NTDT should be offered iron chelation therapy if their SF level is >800 µg/L or their LIC is >5 mg/g dw.

c. Children aged <6 years should be initially offered subcutaneous DFO infusions. If there is failure to comply with DFO then DFX should be started as soon as possible to prevent worsening iron overload.
d. Patients aged >6 years starting on DFP must be informed of the risk of agranulocytosis and monitoring requirements.
9. Iron chelation therapy:
a. The starting dose of monotherapy should be guided by the ROIL for DFO and DFX.
b. DFO 50–60 mg/kg 5 days/week or DFX-FCT at 21 mg/kg/day (DFX-D 30 mg/kg) will achieve negative iron balance in most patients with an average ROIL (0.3–0.5 mg/kg/day).
c. Patients on DFP monotherapy should have doses adjusted up to a maximum of 100 mg/kg/day in three divided doses if the SF level is not reducing, provided the patient is fully compliant with administration.
d. Iron chelation therapy should be reviewed every 3 months to review efficacy, and to assess for complications and compliance with treatment.
e. Combination therapy should be considered when iron overload is not controlled with monotherapy.
f. Patients who fail to achieve negative iron balance despite adherence to optimal doses of monotherapy, or patients who develop dose-limiting toxicities, should be considered for combination therapy.
g. Patients on iron chelation therapy should be monitored for concordance and side effects of treatment.
h. The selection of iron chelation therapy should be determined by the site and severity of iron overload, together with history of compliance and prior toxicity and patient choice.
10. Patients with renal failure:
a. Low-dose DFO and/or DFP can be used in patients with chronic kidney disease prior to dialysis.
b. Once dialysis is initiated, any of the chelators may be used at low doses with close monitoring for toxicity.

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Chapter 7

Disease-Modifying Therapies

"As a parent, I will always feel guilty for passing thalassaemia on to my child seeing that he has to go through every day. Seeing him suffer and knowing I can't fix it, is the hardest part. I would do anything to be able to cure him and give him a chance of life without hospitals like his brother."

This chapter will be divided into two sections. Part A will address HSCT whilst Part B will cover cellular therapies.

Part A: Haematopoietic Stem Cell Transplantation

Aims

The families of children with thalassaemia will be fully informed about the possibility of HSCT as a curative option, so that they can make an informed choice about this intervention for their child.

Adults with thalassaemia will be fully informed about the possibility of sibling donor HSCT as a curative option, so that they can make an informed choice about this intervention.

Outcomes for children and adults undergoing transplantation will be optimised.

As outcomes improve for unrelated donor transplants, and as techniques for reduced-intensity conditioning regimens and alternative donor transplants (including haploidentical SCT) are refined, this option may also become available for adults.

Standards

- The families of all children with thalassaemia should have the opportunity to discuss the option of HSCT with the team at a transplant centre with experience

in undertaking the procedure for this indication, whether or not there is currently a matched donor.

- Adults with thalassaemia should have the opportunity to discuss the option of HSCT with the team at a transplant centre with experience in undertaking the procedure for this indication, whether or not there is currently a matched sibling donor.
- They will be fully informed about all the potential risks and benefits of the procedure, in the immediate, middle and long term.
- For those with an appropriate donor who choose to proceed with transplantation, it must be undertaken at a centre with specific experience and expertise of managing thalassaemia transplants.
- Post-endocrinopathy care is essential, please see **Chapter 8: Growth, Development and Endocrine Function** for management.
- Psychological and social support for adults, children and their families should be provided to aid them on their transplant journey.

Background

Considerations

At present, HSCT is the only proven treatment modality that can establish long-term normal haemopoiesis, avoiding the need for transfusions and chelation treatment, and there are now long-term outcome data supporting its efficacy (Baronciani et al., 2016). Hence, the provision of related transplantation for those patients and families to whom the risks and benefits are acceptable and who seek a permanent cure has become an accepted standard of care (British Society of Blood and Marrow Transplantation, 2012). However, the main constraint in offering this has been the limited availability of matched donors (Kollman et al., 2004) and the risks undertaken when considering matched unrelated and alternative donor transplantation. Over the last decade, fludarabine-based conditioning regimens have become standard with a reduction in toxicity compared to previous regimens. (Bernardo et al., 2008). Since the publication of the last edition of the *Standards of Care*, it has become clear that the outcomes for children receiving matched related donor transplants are now equivalent to those receiving matched related transplants. This largely reflects improvements in high-resolution tissue typing as well as in supportive care. Consequently, matched unrelated transplants are now considered to be a standard of care option for children and young people with thalassaemia in the UK (Li, 2019). There is ongoing work to develop effective and safe protocols for haploidentical transplantation (Anurathapan et al., 2016), which is an accepted clinical option for the management of children and young people with thalassaemia in the UK, typically in those

with complications of thalassaemia (British Society of Blood and Marrow Transplantation, 2012).

Adult SCT is indicated on the basis of the patients' experience of the impact of the disease on their quality of life and this is often because of the development of end-organ damage. Adult SCT has been limited by the poor outcomes at this stage following conventional approaches and the limited availability of donors. Data relating to adult patients transplanted after 1997 demonstrate modest improvements in results (overall survival 67%; transplant-related mortality 27%). The less favourable results that have been observed in adult patients treated with myeloablative conditioning likely relate to the advanced stage of their disease.

More recently, with advances in chelation treatments and monitoring strategies, young adult patients have sustained low iron burdens and the risk of organ damage has been reduced. Therefore, with improvements in supportive care, transplant conditioning regimens and strategies to prevent graft rejection and GvHD, allogeneic HSCT is an increasingly feasible option for adults who have who have well-controlled iron, lack significant iron-related morbidities, have good performance status and are likely to benefit from cure.

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

The establishment of normal haematopoiesis, and cessation of regular transfusion, allows for effective approaches to reduce iron load, reverse significant iron damage and avoid long-term organ dysfunction (Angelucci et al., 1998; Mariotti et al., 1998). Quality of life studies have demonstrated great improvements for patients following SCT and long-term superiority of outcomes, particularly in relation to role limitation, bodily pain and social functioning (La Nasa et al., 2013; Javanbakht et al., 2015). These benefits need to be balanced against the risk of long-term effects, especially chronic GvHD. Strategies to prevent GvHD as well as effective GvHD treatment for patients with haemoglobinopathies are constantly developing to address this (Caocci et al., 2016).

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

1. The length and intensity of treatment. SCT requires an initial period of hospitalisation in isolation of around 6–8 weeks followed by a period of immunosuppression requiring specialised monitoring every 1–2 weeks for approximately 6 months, during which time the patient cannot attend nursery or school, or use public transport. During this time they need frequent readmissions to hospital to manage complications. This has significant implications for family life, including practical aspects of family arrangements, financial considerations, employment implications for parents and effects on siblings.
2. All forms of transplantation carry an upfront risk of transplant-related mortality, even if very low, in order to achieve a long-term cure.
3. Long-term effects of transplantation are caused by the conditioning regimens and the ability of the new immune system to recognise the recipient patient as 'other' and react against them. The use of fludarabine, less-toxic alkylating agents, drug exposure monitoring and serotherapy have been significant advances in limiting this. Infertility remains a particularly significant problem. Oocyte vitrification, sperm cryopreservation and ovarian/testicular tissue cryopreservation approaches have been developed to address this, and are offered as a standard of care to all those undergoing to SCT. Chronic GvHD has been identified as the main factor impacting quality of life long-term, although with current approaches the risk is very low (<5%).

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

The collection of cord blood at the birth of a new sibling should be offered if possible, although funding is not standard across the country and is the subject of a current review. Cord blood, as the sole source of stem cells, has a higher risk of rejection in patients with thalassaemia and of unstable long-term mixed chimerism, which can have a significant impact on the outcomes of transplantation and add significantly to the complexity and length of treatment. However, cord stem cells can make an important contribution to achieving an adequate stem cell dose to enable a combined cord and bone marrow transplant, avoiding the need for a second bone marrow harvest from a smaller sibling donor. In the majority of patients with TDT, the transplant can be delayed until the new sibling can donate sufficient bone marrow to allow a combined transplant. The case is strengthened if there has been prenatal diagnosis ruling out a haemoglobinopathy. In

theory, this permits the same DNA to be used to determine whether the new pregnancy is matched for the potential recipient, although this is rarely done in practice.

A small number of adult patients have been treated with gene therapy, achieving transfusion independence (Negre et al., 2016). The efficiency of this approach is likely to improve, and trial results will become available. At this stage, gene therapy requires the use of conditioning chemotherapy with significant impacts on fertility, although it avoids the complication of alloreactivity and is likely to be of lower intensity than conventional transplantation. Advances have been made in reducing the risks of insertional mutagenesis. The nature of the therapy makes it likely that trials will be conducted by transplant centres and hence the cellular and gene therapy approach to establish normal haematopoiesis should be unified.

Whilst cellular and gene therapies require a significant upfront investment, the cost-effectiveness of these forms of therapies is well established (Ho et al., 2006; Leelahavrong et al., 2010).

Survival and late effects

Patients with beta thalassemia experience severe anaemia, iron overload and multiple complications that affect their quality of life and wellbeing. Allogeneic HSCT from a human leukocyte antigen (HLA)-matched sibling donor, performed in childhood, has been the gold standard for patients with thalassaemia for decades. Unfortunately, siblings are available only for the minority of patients. Fully matched unrelated donors have been the second choice for cure, with equal results as far as overall survival is concerned, but with the accompanying cost of frequent and serious complications (Tauchmanovà et al., 2003).

Allogenic HSCT represents an important chance of treatment in thalassemia, including for adult patients, and can be ethically recommended to patients with an available matched donor, either sibling or unrelated. The survival rate of transplanted patients is similar to that of those who are conventionally treated, and the vast majority of long-term HSCT survivors are cured of thalassemia (Caocci et al., 2017).

Lowering of the incidence of transplant-related mortality due to acute GvHD remains an unmet need. The 30-year survival rate of ex-thalassemia patients after HSCT is similar to that expected for chelation and patients with TDT, with the vast majority of HSCT survivors cured of thalassemia.

HSCT represents the only effective approach for the cure of TM, offering high rates of success, particularly in the paediatric setting. Over the past few decades, several new

approaches have reduced the toxicity of conditioning regimens and decreased the incidence of GvHD, improving patients' post-transplant health-related quality of life.

A recent retrospective study from the European Bone Marrow Transplantation Registry reported 10-year probability of overall survival and thalassemia-free survival to be 88% and 81%, respectively in a cohort of 1493 patients transplanted in 127 centres worldwide. Most transplant procedures were performed in paediatric patients from a sibling (Lucarelli et al., 1993; Bernado et al., 2012; Mathews et al., 2013; La Nasa et al., 2013).

Patients with TM should be offered transplantation before they develop end-organ damage and iron overload-related complications, the earlier the better (Mohamed et al., 2017).

The advantages of SCT over chronic transfusion–chelation therapy are many, including a high cure rate following recent advances in transplant engineering, patient selection and conditioning regimens, lower cost and better cost-effectiveness, and better impact on quality of life for both patients and families (Javanbakht et al., 2015).

In a study involving over 134 patients transplanted in the period 1984–2012 in 21 centres in France, with a median follow-up of 12 years, 107 patients were alive and well 2 years after HSCT, although 2 subsequently died from chronic GvHD and 6 were later lost to follow-up (Angelucci et al., 2018).

Late effects after HSCT are influenced by recipient age at transplantation, disease status, pre-existing comorbidities, the transplant method and conditioning regimen, donor source, HLA compatibility, post-transplant complications and immune reconstitution (Shenoy et al., 2018). Endocrine complications after SCT can be classified as in Table 7.1. These complications are mainly related to the conditioning regimen, which requires powerful chemotherapy for total body irradiation (myeloablation) or immunosuppression (non-myeloablation). Moreover, hormone replacement therapy (HRT) can modulate the cardiovascular or tumoural risk of patients (Daikeler et al., 2011, Danner-Koptik et al., 2013; Vantyghem et al., 2014).

Table 7.1: Endocrine complications after HSCT

	Endocrine complications after HSCT
Endocrine deficiencies	Particularly gonadotropic and somatotropic failure influencing growth, puberty, bone and fertility
Autoimmune diseases	Dysthyroidism
Secondary tumours	Risk is 24-fold higher compared with the general population, involving either endocrine glands (thyroid carcinoma) or dependent on oestrogen and progestin (breast cancer, meningioma)
Metabolic complications	Steroid-induced diabetes, associated increased cardiovascular risk and reduced bone density

Ovarian failure in HSCT recipients is likely to be caused principally by myeloablative treatments, but the condition of gonadal and androgen insufficiency can be worsened by altered immunomodulation in allogeneic setting (Tauchmanovà et al., 2003).

One study has evaluated the impact of a busulfan- and treosulfan-based conditioning regimens on clinical outcomes in transplanted patients. Treosulfan was introduced recently to replace busulfan in conditioning regimens, in view of its favourable toxicity profile in the reduction of the risk of life-threatening complications and in increasing the number of patients successfully cured (Caocci et al., 2017). Another study has shown that, in addition to mild extramedullary toxicity, the combination of treosulfan/thiotepa/fludarabine is an effective myeloablative regimen for allogeneic unrelated donor HSCT, and is suitable in adult patients with poor performance status and organ dysfunctions (Bernado et al., 2012).

Requirements

- Referral to a transplant centre for discussion about SCT should be offered to parents when the child is 1–2 years of age. This is regardless of the availability of a matched donor, as subsequent children born to the parents may prove to be an HLA match and volunteer donors are continually added to the registry.
- Adults with thalassaemia who have a matched sibling donor, and fulfil the eligibility criteria, should be referred to a transplant centre for discussion about SCT

- It is especially important to discuss with families the major risks of transplantation, including transplant-related mortality and infertility. Fertility cryopreservation should be considered for all patients.
- The child should be included in the discussions in an age-appropriate manner and this requires adequate provision of play specialists, and psychology and clinical nurse specialists experienced in the procedure for thalassaemia.
- There is a systematic 'workup' of the child pre-transplant, including assessment of renal and hepatic function, echocardiogram, lung function, dental assessment and, most importantly, evaluation of iron load and optimisation of chelation pre-transplantation.
- The evaluation of iron load and end-organ damage must include assessment of iron overload, ideally with Ferriscan and, if possible, T2*MR liver/cardiac iron quantitation. Sedation may be required in young children. The target LIC before SCT is <7 mg/g dw. A liver biopsy for the assessment of fibrosis may be considered if there are specific concerns arising from these assessments and usually after a period of more intensified chelation to allow Ishak staging.
- In order to reduce the risk of graft failure, pre-transplant immunosuppression is given as 8–12 weeks of hydroxycarbamide 30 mg/kg with monitoring for cytopenia alongside hypertransfusion to keep the Hb level >120 g/L, with a target Hb of 15 g/L. In cases where there is a further increase in the risk of graft failure (use of a mismatched unrelated or haploidentical donor, or in those having a second transplant), pre-transplant immunosuppression should be escalated to include cycles of fludarabine and dexamethasone with or without cyclophosphamide.
- Post-transplant follow-up in the early months is at the transplant centre, with regular communication with the referring team.
- In order to achieve the full benefits of a transplant, the patient's iron load needs to be re-evaluated post-transplantation and interventions undertaken to normalise it. This involves, as a minimum, SF level measurement and MR liver iron quantitation. Usually, iron load increases due to the transfusion requirements of transplantation on top of the existing load at transplantation. Depending on the stability of the graft and venous access, reduction of the iron load is achieved either with venesections or chelation for a few months. It is usual to evaluate this around 6 months post-transplantation. The aim should be to normalise the iron load (SF ≤300 µg/L and MR liver iron quantitation showing <3 mg/g dw).
- Patients who have had a transplant should be followed up in a long-term effects clinic for transplanted patients. During follow-up, pubertal development and fertility function should be assessed, discussed with the patient and family, and genetic counselling offered (see **Chapter 8: Growth, Development and**

Endocrine Function and **Chapter 10: Reproductive Health Across the Lifespan**).

- Adults with thalassaemia (and families of transplanted children with thalassaemia should be aware that children, when they grow up) need to be advised that their partner needs early testing for thalassaemia or other Hb disorders. The transplanted individual will still pass on the thalassaemia mutation to their offspring despite a successful transplant, so there would be a risk of significant Hb disorders in their children if the partner was a carrier for thalassaemia, sickle cell disease or other relevant variants.
- Evaluate height, weight and body mass index (BMI) at 6 months and then yearly. Monitor every 6 months if growth velocity plateaus so intervention can be planned as needed. Assess hormone levels for short stature (insulin-like growth factor-1 [IGF-1] and insulin-like growth factor binding protein 3 [IGF-BP3]), and bone age if within growth period by age. Refer patients with growth retardation to an endocrinologist to discuss GH treatment.
- Thyroid function tests (thyroid-stimulating hormone [TSH], free thyroxine [FT4]) at 6 months, 1 year, then annually through 5 years. Refer patients with abnormal thyroid tests to endocrinologist for treatment.
- Consider fasting glucose and oral glucose tolerance test (OGTT) at 1-year follow-up if there is significant iron overload or patient has been given steroid therapy for immunosuppression.
- We advise yearly physical examination, tracking of Tanner progression, and measurement of gonadal hormones and gonadotropin levels when age-appropriate. Test total and free testosterone, luteinising hormone (LH) and follicle-stimulating hormone (FSH) in males ≥11 years of age, yearly for 2 years, then as clinically indicated if puberty delayed.
- Consider age-appropriate sperm analysis in male patients. Check LH, FSH, anti-Mullerian hormone and oestradiol levels in female patients ≥11 years of age, at 1 and 2 years post-HSCT, then as clinically indicated if puberty is delayed. Refer patients with evidence of pubertal delay, low testosterone levels, or females with primary or secondary amenorrhea to and endocrinologist, gynaecologist or andrologist for hormonal treatment.
- Counsel regarding genetic transmission of disease.
- Conduct vitamin D (25-OH) level and bone mineral density (BMD) evaluation for all patients at 1 year after HSCT, and subsequently as indicated. Patients with osteopenia and/or osteoporosis should receive vitamin D and calcium supplementation.
- Consider MRI of the joints to evaluate for avascular necrosis in symptomatic patients on steroid therapy (chronic GvHD). Consider referral to endocrinology services for patients with osteoporosis.

Recommendations

- If the mother of a child with thalassaemia becomes pregnant, PND should be offered and, if accepted, HLA typing of the fetus can be undertaken. Cord blood stem cell harvesting should be offered to all families, whether or not PND has been undertaken.
- The referring team can often support ongoing transplant care, for example by arranging venesections to continue reducing iron load once healthy haematopoiesis is established.
- Patients with TM should be offered transplantation before they develop end-organ damage and iron overload-related complications, the earlier the better.
- Low-toxicity conditioning regimens should be considered for suitable candidates to reduce the risk of long-term complications in patients with thalassaemia with poor performance status and organ dysfunctions.
- Refer patients with evidence of pubertal delay, low testosterone levels, or females with primary or secondary amenorrhea after HSCT to an endocrinologist, gynaecologist or andrologist for hormonal treatment.
- It is important to counsel regarding genetic transmission of disease.

Part B: Cellular Therapies (Gene Therapies)

"I don't have a donor for the bone marrow transplant so until gene therapy is offered there is no cure for me and other people with thalassaemia. People don't understand just how much thalassaemia affects us and how different our lives are compared to people my age without thalassaemia. It really affects every part of my life including my relationships and work. I don't even have the energy to do the basic things far less to even go out like people my own age. I just want to be free and be cured."

Standards

- Once gene therapies become available for the treatment of patients with TDT in the UK, all eligible patients (or their parents/carers) will have the opportunity to discuss this treatment option. This will include a full discussion of risks and benefits associated with the procedure.

Background

Long-term cure of thalassaemia depends on either the replacement of, or modification to, a patient's haematopoietic stem cells (HSCs). This can be achieved by a donor SCT, although this curative option is limited by low availability of suitably matched donors and also carries risks of serious complications related to the donor nature of the stem cells, including GvHD or graft rejection.

More recently, novel therapies have been developed that modify the DNA of a patient's own (autologous) HSCs without the need for a donor transplant. The aim of these changes can be to correct the causative mutation, to supply a new copy of a healthy gene or to induce compensatory changes in the genome that counteract the effects of the thalassaemia abnormality. Correction of a patient's HSCs with gene therapy presents an alternative, potentially curative, approach to treatment. Use of autologous HSCs avoids the need for a matched donor, and removes the risks associated with immunological cross-reactivity that are seen in donor transplants. Therefore, these approaches offer some advantages over the donor SCT procedure.

Types of gene therapy

There are two main types of gene therapy for the treatment of thalassaemia. The first involves delivery of a new, healthy gene to the cell using a modified viral vector (usually a self-inactivating lentiviral vector), and is known as ‘gene addition therapy’.

A second approach to gene therapy is with the use of genome editing technology. Genome editing involves creating a targeted DNA break or alteration using guided nucleases. A number of different constructs can be used to deliver this, including transcription-activator-like effector nucleases, zinc finger nucleases and – most recently and arguably most successfully – CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9) compounds.

Where a double-stranded DNA break is created in HSCs, this is usually repaired by an error-prone mechanism termed non-homologous end joining (NHEJ), resulting in the incorporation of different insertions and deletions (also known as indels) at the site that disrupt the normal reading and function of the gene, reducing its function and effectively ‘knocking out’ the gene. An alternative mechanism for cellular repair, homology-directed repair (HDR), can be harnessed to add – or ‘knock in’ – new genetic material. For HDR to take place, a new copy of the desired genetic sequence must be introduced alongside the targeted nuclease, and can be used as a template for DNA repair. However, the HDR repair mechanism is relatively inactive in HSCs, and therefore treatment methods relying on HDR are not yet as advanced as those using the NHEJ gene-knockout approach. Base editing and prime editing technologies are also now in development, which allow targeted modifications of DNA without requiring the creation of a double-stranded break.

Most current clinical trials follow a similar protocol in delivering gene therapy to patients with TDT are summarised below:

1. Administration of mobilisation agents granulocyte colony stimulating factor ± plerixafor to the patient, followed by collection of their peripheral blood stem cells by apheresis in 1–2 sessions.
2. Ex vivo modification of the HSCs in the laboratory, followed by delivery back to the patient after quality control testing to make sure that the gene therapy process has been successful.
3. Prior to reinfusion of the modified stem cells, patients receive conditioning chemotherapy, usually with a myeloablative busulphan protocol (often with dosing guided by pharmacokinetic monitoring).
4. Patients remain in hospital until there is engraftment of neutrophils and platelets.
5. Ongoing monitoring, with RBC transfusions stopped in patients who maintain satisfactory Hb levels following treatment.

Gene addition therapy

Gene addition therapy for the treatment of beta TDT usually involves introducing a healthy copy of a beta-globin gene (*HBB*) into recipient HSCs, leading to the production of HbA. This gene can be either a normal copy of *HBB* or a modified one, such as by introduction of the T87Q mutation that results in HbA^{T87Q} production.

Bluebird Bio have successfully developed a gene addition therapy product: Betibeglogene Autotemcel (or Beti-cel). This is made by transducing a patient's HSCs with the LentiGlobin® BB305 lentiviral vector encoding the modified beta-globin (*βA-T87Q*) gene. Initial clinical trials of Beti-cel were the phase 1–2 HGB-204 (NCT01745120) and HGB-205 (NCT02151526) studies, in which 12/13 patients with a non-$beta^0$/$beta^0$ genotype were able to stop RBC transfusions after treatment, but with a more moderate response in patients with a homozygous $beta^0$/$beta^0$ or $beta^0$/$beta^0$-like (i.e., IVS1-110 mutation) genotype. In their phase 3 HGB-207 trial (Northstar-2, NCT02906202), only patients with a non-$beta^0$/$beta^0$ genotype were enrolled including, for the first time, children aged <12 years. Transfusion independence occurred in 20 out of 22 patients after treatment. A further phase 3 trial, HBG-212 (Northstar-3, NCT03207009), has been set up to investigate whether refinements to the LentiGlobin® product will improve treatment outcomes for patients with a $beta^0$/$beta^0$ genotype, and early results are more promising. Adverse events in all LentiGlobin® trials were consistent with side effects of the busulphan conditioning regimen used, without additional complications observed to be resulting from the Beti-cel infusion itself.

Beti-cel received US Food and Drug Administration (FDA) approval in August 2022, where it is now available under the brand name Zynteglo® for the treatment of beta TDT in the United States of America (USA). However, related to the high financial cost of their product, Bluebird Bio have reported that they were unable to reach funding agreements with any European governments and are not currently pursuing the availability of their product within European markets, including the UK.

Further clinical trials are underway investigating alternative lentiviral vector products encoding the T87Q beta-globin gene, whilst in others an unmodified beta-globin gene is used, such as the GLOBE lentiviral vector used in the TIGET-BTHAL trial (NCT02453477).

Gene therapy approaches for the treatment of alpha thalassaemia are not yet as advanced, but one currently registered clinical trial (NCT05757245) is investigating a lentiviral vector encoding a healthy alpha-globin gene. Although results have not yet been reported, such studies may offer the prospect of amelioration or cure in the future for individuals with a severe alpha thalassaemia phenotype as well.

One potential drawback specific to gene addition treatments is that new genetic material integrates into the genome in a semi-random manner, conferring at least a theoretical risk of insertional mutagenesis and possibly increased risk of future malignancy. Modern viral vector constructs have significantly reduced this risk in comparison with early gene therapy trials in other conditions, and no cases of cancer were reported in any of the LentiGlobin® trials or others to date, but the inability to target which area of the genome will be disrupted is one disadvantage of the gene addition methods compared with more precise genome editing therapies.

Genome editing

The most successful genome editing treatments for TDT to date rely on the NHEJ pathway to disrupt areas of the genome responsible for the natural Hb switch away from HbF production, and thereby reinduce HbF production. These treatments aim to recapitulate the naturally occurring genetic variants causing hereditary persistence of fetal haemoglobin (HPFH), which have long been known to reduce the severity of beta thalassaemia when coinherited. Promising results have been reported by targeting either the erythroid enhancer region of *BCL11A* on chromosome 2, or the gamma-globin (*HBG*) promotor regions on chromosome 11. By either reducing production of the transcription factor BCL11A, or by disrupting its binding site in the *HBG* promotor regions, the physiological switch away from gamma-globin – and therefore HbF – production can be effectively reversed.

The current leader in the field is Exagamglogene autotemcel (Exa-cel, also termed CTX001), developed by Vertex and CRISPR Therapeutics. CRISPR/Cas9 editing is used to target the erythroid enhancer region of *BCL11A* within autologous peripheral blood stem cells, resulting in effective reinduction of HbF production. In their THAL-111 clinical trial (NCT03655678), 48 patients aged 12–35 years with beta TDT were treated, including those with a $beta^0/beta^0$ genotype. The majority of patients were able to stop RBC transfusions after treatment, with significantly reduced transfusion requirements in others. Stable levels of edited cells were found in the blood and bone marrow at the last follow-up appointment >3 years after treatment, all supportive of a long-lasting effect of treatment. Improved quality of life assessed by a number of different measures was also demonstrated.

The majority of adverse events in this trial were related to busulphan conditioning. Two patients had serious side effects thought to be related to the Exa-cel treatment itself, but all serious adverse effects resolved, with no deaths or malignancies reported. A further trial investigating the safety and efficacy of CTX001 treatment in paediatric patients aged 2–11 years (NCT05356195) is now underway.

In the UK, Exa-cel has been conditionally approved by the Medicines and Healthcare products Regulatory Agency for patients over the age of 12 years with beta TDT. This product is currently undergoing an assessment process by NICE to determine whether or not Exa-cel will be funded for patients with TDT, with a decision expected in 2024.

The FDA is similarly considering approval of this treatment in the USA. Therefore, at the time of writing, the question of accessibility to this treatment in the future remains unanswered. It is also unclear what the eligibility criteria would be, if approved.

There are a number of other genome editing products in development. Sangamo Therapeutics and Sanofi are using an alternative genome editing platform, zinc finger nucleases, to also target the *BCL11A* gene in a clinical trial (NCT03432364), with trial recruitment now closed and results awaited. A number of clinical trials are investigating CRISPR/Cas9 editing at the *HBG* promotor with a similar aim of increasing HbF production, including the RUBY trial of gene editing product EDIT-301, currently recruiting across multiple sites in the USA (NCT05444894). Two clinical trials employing base editing at the *HBG* promotor loci are ongoing, but no results are currently available (NCT06065189, NCT06024876). Other genome editing strategies that are not yet at such an advanced stage of clinical testing include editing at the alpha-globin locus to downregulate alpha-globin expression and thereby rebalance the alpha/beta imbalance causing dyserythropoiesis, or the use of HDR-directed approaches to introduce healthy copies of the beta- or gamma-globin genes into prespecified loci.

Challenges and limitations

At the time of writing, Zynteglo® gene addition therapy from Bluebird Bio in the USA is the only available gene therapy treatment for TDT, with no gene therapy treatment available in the UK outside clinical trials. Even in the USA where this treatment is FDA-approved, the cost and funding arrangements make this treatment option inaccessible for most patients who may benefit from it. It is anticipated that costs of other gene therapy treatments will also be high, and this may be a key limiting factor in making these promising treatments accessible to patients. It is important that when assessing the cost-effectiveness of gene therapies, regulatory and funding bodies take into account the suboptimal outcomes that many patients with TDT continue to experience with standard care. The true lifetime economic costs of TDT when patients are not offered curative treatment must also be considered. These costs include not just the provision of transfusion and chelation therapies, but costs associated with managing the multiorgan complications of thalassaemia and iron overload; time lost and outcomes compromised in education, employment or caring responsibilities.

A further limitation to the general applicability of gene therapy treatments is toxicity associated with the chemotherapy conditioning regimen used, which in the majority of

clinical trials has involved myeloablative doses of busulphan. This carries risks such as acute organ toxicities, including the risk of veno-occlusive disease, infertility and an increased long-term risk of secondary malignancy. As a result of such risks, clinical trial entry for gene therapies has been restricted to fitter, generally younger patients, as those with pre-existing organ dysfunction would be at greater risk of complications. Uncontrolled iron overload also often excludes clinical trial entry, as this again increases the risks of treatment.

All gene therapy treatments for TDT are relatively new developments and, as such, there is currently a shortage of long-term data on safety and efficacy. Most of the large clinical trials are now enrolling patients into long-term follow-up studies, such as CLIMB-131 (NCT04208529) for patients treated with CTX-001, and LTF-303 (NCT02633943) for participants in the Bluebird Bio LentiGlobin® trials; therefore, this information will be reported in time.

Finally, almost all gene therapy approaches being investigated in clinical trials are for the treatment of beta TDT. There is a lack of data on their use in patients with NTDT, and only one trial registered relates to alpha thalassaemia, indicating the need for further research into genetic therapies for these conditions.

Requirements

- Patients being worked up for gene therapy should have the same considerations and optimisation of health as described in Section A for transplantation.

Recommendations

- The option of potentially curative therapy should be discussed with patients when/if they become available; with counselling about benefits and risks, including the need for long-term follow-up.

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Chapter 8

Growth, Development and Endocrine Function

"I look so much younger than my friends and haven't had a period yet and I'm 16. This makes me feel like I'm not normal".

"My friends are growing facial hair and I still look like a child. I'll never find anyone to be in a relationship with."

"The bone pain is the worst thing about having thalassaemia. Nobody seems to know what to do about it or know anything that could help."

Please read this chapter together with Chapters 9, 10 and 11, with which there is some inevitable overlap.

Aims

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

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

To maintain endocrine function throughout adulthood to maintain normal fertility and to reduce the incidence of endocrine complications, including low BMD.

To preserve or restore fertility and reproductive hormones.

To optimise adult bone health, assess fracture risk and prevent fragility fractures.

Standards

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

- Iron loading should be kept to a minimum, by careful monitoring and the use of effective chelation treatment, to reduce the risks of endocrine damage.
- Doses of DFO should be kept within a range that will minimise the risk of bone toxicity, phosphate wasting or reduced height velocity. Any bone changes possibly related to DFO toxicity should be suspected and investigated in children with bone/joint pain, bone biochemical abnormalities or short stature.
- Paediatric specialists in bone metabolism and endocrinology, with interest and expertise in managing the complications encountered, should be involved in the care of children with thalassaemia, ideally in a joint clinic setting.
- Children should have their growth and development monitored regularly from diagnosis until they have achieved full sexual maturity and final adult height. Any change in expected growth and development should be identified, investigated and treated promptly.
- Management of the maturing skeleton should focus on achieving peak bone mass.
- All patients should have their vitamin D level measured with supplements given if needed.
- All patients should be advised of the need for adequate dietary calcium for healthy bones.
- All patients should be advised to undertake weight-bearing exercise that promotes the achievement of peak bone mass and the maintenance of BMD.
- Where paediatric endocrine input has been necessary then careful transition plans should be made at completion of puberty and linear growth. Ideally such transition should take place in a combined clinic. A detailed clinical summary and discussion should take place to ensure there is no disruption to treatment at this critical stage of adolescence.
- Children should be routinely assessed, at least annually, for evidence of disturbance of the hypothalamo–pituitary axis, for calcium and bone homeostasis, and thyroid function.
- Adults and children should be routinely assessed, at least annually, for evidence of disturbance of the hypothalamo–pituitary–gonadal axis, thyroid function, and for calcium and bone homeostasis.

Background

Over the years, advances in treatment have improved the survival of patients with thalassaemia. However, endocrine complications (Figure 8.1) – including growth failure, hypogonadism, hypothyroidism, glycaemic disorders, hypoparathyroidism and adrenal insufficiency (AI) – are common (Mahmoud et al., 2021; Casale et al., 2022; Jobanputra

et al., 2020). The prevalence of these endocrine complications in both children and adults with thalassaemia has been well established (Figure 8.2) (De Sanctis et al., 2004). Of note, approximately 1 in 4 children with thalassaemia under the age of 12 years have an endocrine complication (Mahmoud et al., 2021). The commonest complication in children is hypogonadotropic hypogonadism (HH) alongside short stature (De Sanctis et al., 2004; Sharma et al., 2016*).*

Iron toxicity is the most common cause of endocrine disorders in people with thalassaemia and can be responsible for pituitary damage, even in well-chelated individuals (Cappellini et al., 2014; Taher et al., 2013; Gao et al., 2009). Nonetheless, it remains important to consider other factors that may be contributory (for example the effects of DFO on bone, although this is rare now with moderated doses administered to growing children).

Figure 8.1: A synopsis of the various endocrinopathies in thalassaemia

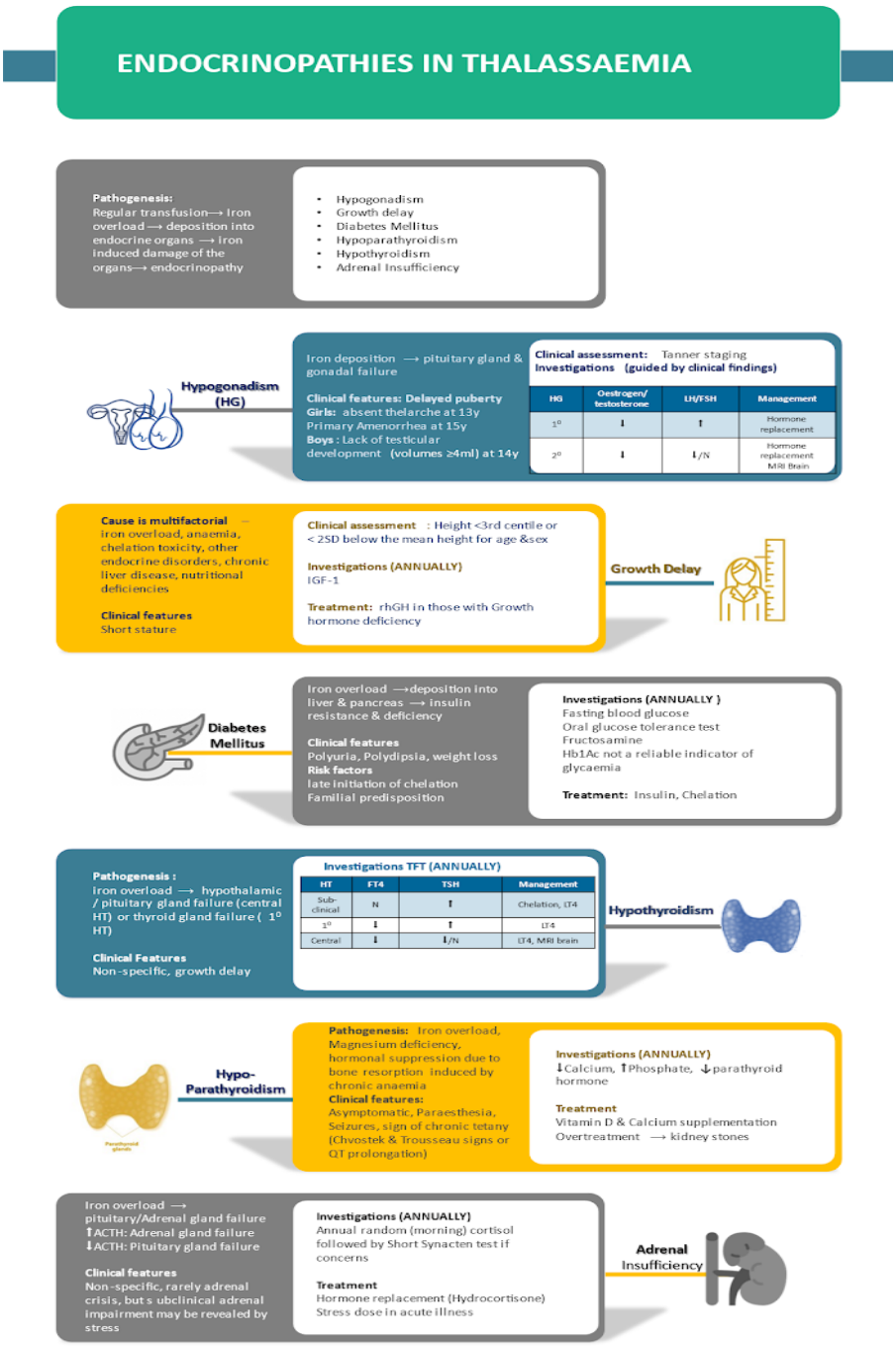


FIGURE 1: ENDOCRINE DISORDERS IN THALASSAEMIA

LH/FSH: luteinising hormone
FSH: Follicle stimulating hormone
rhGH: Recombinant human GH
SD: Standard deviation
IGF-1:Insulinlike growth factor 1
TFT: Thyroid function test
LT4: Levothyroxine
FT4: Thyroxine
TSH: Thyroid stimulating hormone
ACTH: Adrenocorticotropic hormone
HT: Hypothyroidism
HG: Hypogonadism
MRI: Magnetic Resonance Imaging
ml: milliliter
Y: years
N: Normal
↑: Increased
↓ : Decreased

Figure 8.2: Endocrine complications in thalassaemia

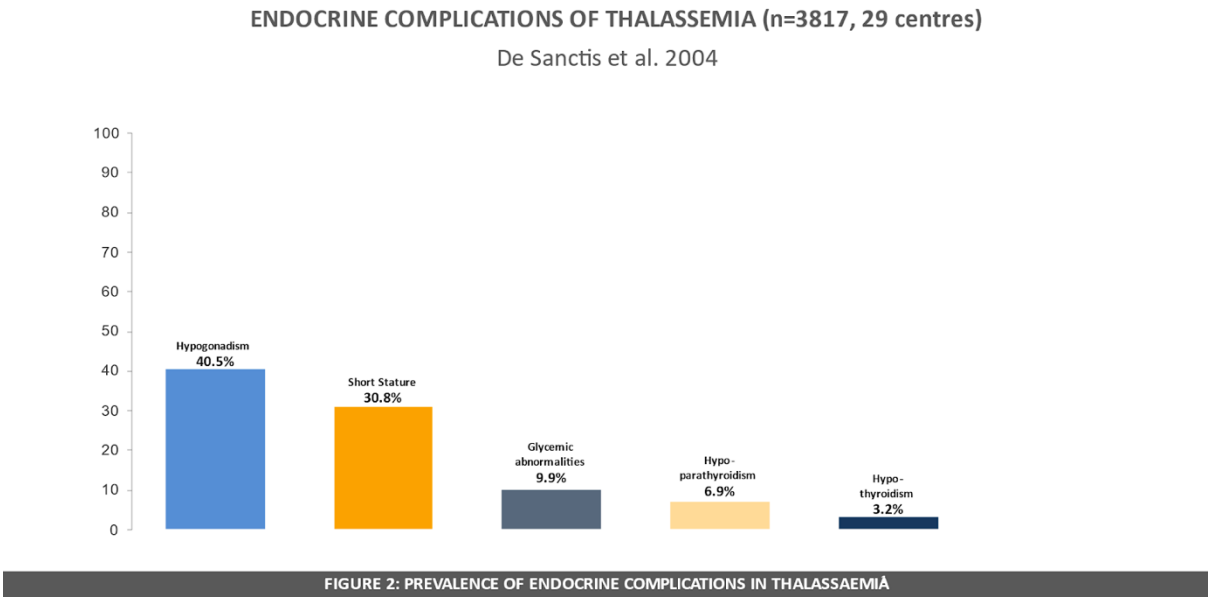
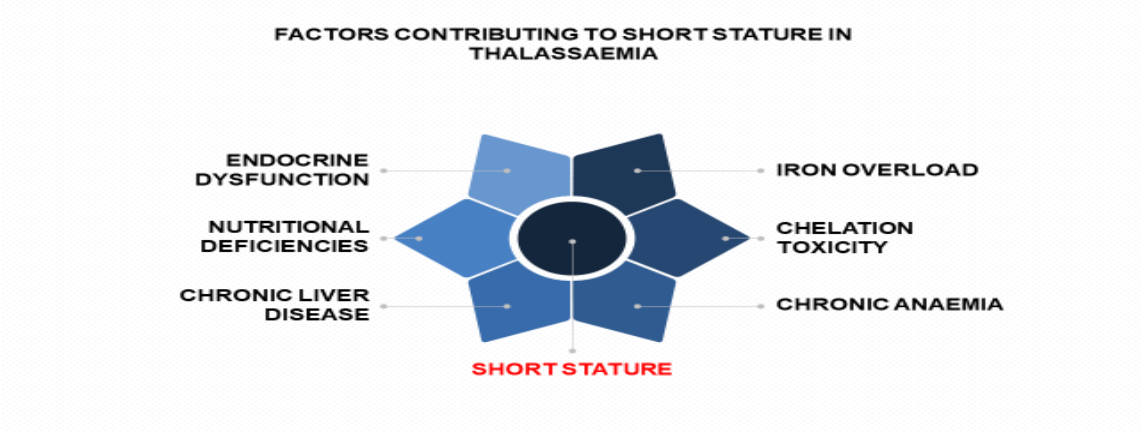


FIGURE 2: PREVALENCE OF ENDOCRINE COMPLICATIONS IN THALASSAEMIÅ

Short stature/growth impairment

Poor growth with short stature may be encountered in children and adolescents with thalassaemia. Failure to recognise this at an early stage leads to long-term psychological impacts in adulthood. The pathogenesis is complex and multifactorial (De Santis, 2002*).*

Figure 8.3: Factors contributing to short stature in thalassaemia



Short stature in children and needs careful assessment in order to ensure patients reach a normal adult height. Regular monitoring of height (sitting and standing) and plotting on age-appropriate centile charts is important to identify impaired growth early and allow timely intervention.

Anaemia

Children may encounter growth delay at various time points and different causes may be identified. Initially, delayed growth may be primarily driven by anaemia and correction of the Hb level and keeping it >100 g/L prior to transfusion may correct the patient's growth, with a rapid return to the previous centile. In patients with NTDT, careful assessment of growth is important and may signal a need to initiate transfusion to support the attainment of puberty and normal height (Taher et al., 2013). In patients with TDT, where growth has slowed along with a drop in centiles, then the pretransfusion Hb level should be adjusted to ensure that anaemia is not driving the impaired growth.

Chelation toxicity

For any child on DFO chelation whose growth is faltering, assessment of sitting and standing height should be undertaken, and DFO doses should be adjusted to avoid doses >40 mg/kg/day. This can occur at any age during childhood and should be assessed at 6-month intervals as a minimal standard if the child is chelated with DFO. There are no reports of patients having chelation toxicity impacting on growth as a result of DFP or DFX treatment.

Nutritional factors

Poor nutritional status will impact on a child's growth and, if growth is poor, a detailed history of nutritional status and assessment should be undertaken. Referral to dieticians and support in healthy eating is essential to support good growth.

Endocrine disorders impacting growth

The pituitary gonadotrophs are incredibly vulnerable to oxidative stress caused by iron deposition in the hypothalamus and pituitary gland (Low LC 2005*)*. GH deficiency may occur in children but is less frequently seen in comparison with hypogonadism (De Sanctis, 2002). Thyroid status should be assessed in children with impaired growth and managed appropriately.

Growth hormone deficiency

The reported prevalence of GH deficiency or IGF-1 deficiency, or both, in adults with thalassaemia varies from 8% to 44 % (Soliman et al., 2013). Children who are well treated from early childhood can usually avoid these complications. However, a GH stimulation test should be undertaken and supplementary GH treatment given if deficient. Treatment with recombinant human GH (rhGH) is recommended when GH deficiency is established (NICE, 2010). Therapeutic response with rhGH administration in patients with GH deficiency may be suboptimal. Concurrent hypogonadism should be ruled out in this situation and the patient may require treatment of GH deficiency followed by treatment of hypogonadism to achieve a good response. Treatment with rhGH for 1 year seems to be effective in increasing growth velocity without causing adverse effects on bone maturation, glucose tolerance, serum lipids and blood pressure (Wu et al., 2003; Cavallo et al., 2005).

In adults, GH deficiency has been associated with an adverse lipid profile, increased cardiovascular and cerebrovascular events, and decreased BMD, muscle strength, exercise capacity, cognitive function and quality of life (de Boer et al., 1995; Rosén and Bengtsson, 1990). GH deficiency and resistance in adults is recognised as being relatively common, but there is currently no evidence to support supplementing GH in adults.

RhGH is administered via subcutaneous injection at bedtime (Arcasoy et al., 1999; Wu et al., 2003). Bedtime dosing is designed to mimic the metabolic effects of GH secretion in normal individuals as closely as possible (Takeda et al., 2010).

Hypogonadism

Thalassemia-induced hypogonadism is primarily due to iron overload in the gonads or in the pituitary gland resulting in primary gonadal failure or gonadotrophin failure, respectively. Whilst the former is recognised, the latter (also called HH) is more common (Kyriakou and Skordis, 2009).

Hypogonadism presents as delayed or incomplete puberty in adolescents with thalassaemia (Kyriakou and Skordis, 2009). Delayed puberty is defined as a lack of breast development in girls by the age of 13 years or primary amenorrhoea by age 15 years, and as a lack of testicular development (volumes ≥4 mL) in boys by the age of 14 years (Palmert et al., 2012). Tanner staging should be performed from the age of 10 years to assess pubertal development at 6-monthly intervals.

As with any chronic illness, self-limiting delayed puberty should also be considered in adolescents with thalassaemia. Review with further investigation by a paediatric endocrinologist is advised.

The timing of HRT is complex, considering growth as well as pubertal parameters. Patients with delayed puberty may still have substantial growth potential, and excessive gonadal hormone administration may cause premature epiphyseal fusion. Therefore, assessment and monitoring by a specialist paediatric endocrinology team is advised.

Table 8.1: Tanner staging in girls

Tanner stage in girls	Breasts	Pubic hair	Growth	Other
1	Elevation of papilla only	Villus hair only	2–2.4 inches per year	Adrenarche and ovarian growth
2	Breast but under the areola enlargement	Sparse hair along the labia	2.8–3.2 inches per year	Clitoral enlargement, labia pigmentation, growth of uterus
3	Breast tissue grows but has no contour or separation	Sparse hair curled pigmented covers the pubis	3.2 inches per year	Axillary, acne
4	Projection of areola and papilla, secondary mound information	Adult hair, does not spread to thigh	2.8 inches per year	Menarche and development of menses
5	Adult-type contour, projection of papilla only	Adult hair, spreads to medial thigh	Cessation of linear growth	Adult genitalia

Table 8.2: Tanner staging in boys

Tanner stage in boys	Breasts	Pubic hair	Growth	Other
1	Testes <2.5 cm	Villus hair only	2.0–2.4 inches per year	Adrenarche
2	Testes 2.5–3.2 cm Thinning and reddening of the scrotum	Sparse hair of penis base	2.0–2.4 inches per year	Decrease in body fat
3	Testes 3.3–4.0cm Increase of penis length	Thicker curly hair spreads to the pubis	2.8–3.2 inches per year	Gynaecomastia, voice break, increased muscle mass
4	Testes 4.1–4.5 cm Penis growth, darkening of scrotum	Adult hair, does not spread to the thighs	4.0 inches per year	Axillary hair, voice change, acne
5	Testes >2.5 cm Adult genitalia	Adult hair, spreads to the medial thigh	Deceleration of cessation of linear growth	Facial hair, increased muscle mass

Deficiency should be treated with oestrogen/testosterone as per British Society of Paediatrics and Endocrinology (BSPED) guidance (Matthews et al., 2016; Chinoy et al., 2018), remembering that under-replacement will contribute to suboptimal bone density.

Induction of puberty

In boys and men

Boys with TDT will be managed along the same lines as boys with constitutional delay in growth and puberty (CDGP). Testosterone treatment in boys with CDGP is usually started around 13–14 years of age. Low doses should be used to avoid premature epiphyseal

maturation and reduce the risk of suppressing the endogenous hypothalamic–pituitary–testicular axis. A one-off course 3–6 months long is usually given, with review 1–2 months after; if there has been no increase in testicular volume, a further 3–6-month course of testosterone can be given. In general, boys with thalassaemia need low-dose supplementation for around 12 months. Once pubertal development is underway, regular (3–6-monthly) assessment of Tanner stage should continue to ensure puberty completes. Occasionally, pubertal arrest can occur when testosterone is stopped, in which case low-dose induction should continue until puberty is completed. At this point treatment can be stopped, and assessment at 6 months after stopping treatment should be undertaken to see if endogenous testosterone production has started. If there is no evidence of this and testicular volumes remain low, then adult treatment doses of HRT should be started (Chinoy et al., 2018).

Table 8.3: Induction schedule (BSPED guideline on testosterone supplementation in infancy and adolescence)

Route	Intramuscular (option 1)	Transdermal (second line)	Oral (second line)
Preparation	Testosterone entantate, testosterone propionate (Sustenon 250®)	2% metered-dose gel (Tostran®; 10 mg/metered application)	Testosterone undecanoate (restandol® tesocaps)
Dose	50–100 mg	10–20 mg	40 mg
Frequency	Monthly	Daily	Daily
Duration	3–6 months	3–6 months	3–6 months

In men who have epiphyseal closure and who have not undergone puberty, testosterone replacement is indicated to complete pubertal development and to treat or prevent symptoms of testosterone deficiency (low libido and erectile dysfunction), and preserve health (prevent osteoporosis, maintain muscle mass and vitality).

A regimen comprising stepwise incremental doses of testosterone gel via calibrated dispenser would appear to offer the best possibility of achieving physiological simulation of male puberty. However, in a study involving older apubertal men, the majority chose a less physiological, but much simpler, regimen of 4-monthly intramuscular depot injections of testosterone undecanoate 1 g, leading to full pubertal development after around 1 year (Dunkel and Quinton, 2014).

Table 8.4: Testosterone preparations used for induction of puberty in males in permanent hypogonadism (Dinkel and Quinton, 2014)

Drug and formulation	Puberty induction	Side effects/cautions
Testosterone enanthate, and propionate: testosterone enanthate has a longer duration of effect than testosterone propionate, intramuscularly	50 mg/month increasing by 50 mg at 6–12-monthly intervals; after reaching 100–150 mg/month decrease interval to every 2 weeks; adult dose 200 mg every 2 weeks	All intramuscular preparations: local side effects (pain, erythema, inflammatory reaction and sterile abscess); priapism can occur
Testosterone undecanoate, intramuscularly	Adult dose 1000 mg every 10–14 weeks	Rare: paroxysms of coughing and dyspnoea post-injection, ascribed to lipid embolisation from vehicle
Testosterone gel, transdermal preparation	Can be started when around 50% adult dose with intramuscular testosterone has been achieved; adult dose 50–80 mg daily	Local irritation; after applying, avoid close skin contact with others
Aromatase inhibitors		Not recommended for this indication

In girls

Girls with TDT will be managed along the same lines as girls with CDGP (Chinoy et al., 2018; Matthews et al., 2016). Management of pubertal induction should occur with the guidance and oversight of a paediatric endocrinology specialist with expertise in this area.

Breast development and adolescent growth spurts are achieved by aiming to mimic the pubertal process in normal girls, both in tempo and magnitude. The use of low-dose

oestrogen at the start of pubertal induction, increasing in small amounts and monitoring clinical response (by reviewing linear growth rate and breast staging), will help optimise this.

Use of high doses of oestrogen early in puberty or rapid escalation of doses may result in a reduced final height along with poor breast development (normal nipple development but poor supporting breast tissue). There are concerns that non-physiological supplementation may also affect uterine growth and development, and bone mass accrual. The ideal age for commencing pubertal induction is around 11–12 years (although some girls may actually present much later).

Table 8.5: Suggested oestrogen therapies for pubertal induction

Timing from start of induction (months)	25 µg 17β-oestradiol matrix patch (e.g., Evorel® 25)**	17β-oestradiol (Oestradiol valerate 1-mg tablets)	Ethinyloestradiol (2-µg tablets)	Ethinyloestradiol (10-µg tablets)
0	¼ patch for 3–4 days, no patch 3–4 days	0.5 (½ tablet) alternate days	2 µg daily	5 µg (½ tablet) alternate days
6	¼ patch all week (changing every 3–4 days)	0.5 (½ tablet) alternate days	4 µg daily	5 µg (½ tablet) alternate days
12	½ patch for 3–4 days, ¼ patch for 3–4 days	0.5 (½ tablet) daily	6 µg daily	5 µg (½ tablet) daily
18	½ patch all week (changing every 3–4 days)	0.5 mg and 1 mg alternate days	8 µg daily	5 µg and 10 µg alternate days
24*	1 patch all week (changing every 3–4 days)	1 mg (1 tablet) daily	10 µg daily	10 µg daily
30*	Adult COCP or HRT	Adult COCP or HRT	Adult COCP or HRT	Adult COCP or HRT

*Progestogens should be introduced only after a suitable duration of unopposed oestrogen (usually 2–3 years) or if more than one episode of significant breakthrough bleeding occurs. **50-µg 17β-oestradiol matrix patches (e.g., Evorel® 50) can also be used but cut to one-half the size of the 25-µg patches. COCP, combined oral contraceptive pill. Matthews et al., 2016.

Progestogens should only be introduced after 2–3 years of unopposed oestrogen replacement, or if more than one episode of significant breakthrough bleeding occurs. Introducing a progestogen early on in therapy may compromise uterine growth and development. Utrogestan® is a natural micronised progesterone that can be given orally (200 mg once daily) and gives good cycle control without significant side effects. Alternatively, medroxyprogesterone acetate 5–10 mg once daily for 12 days may also be used if required.

When puberty induction is completed, it is advised to stop therapy for 6 months to assess if spontaneous menstruation occurs and oestradiol levels are maintained. If normal menstruation does not start independently then HRT should be commenced. The aim should be to restore a normal menstrual cycle with 3–5 days of monthly bleeding.

Hypogonadism in adults

Hypogonadism is common in thalassaemia, with prevalence ranging from 20–36% in published studies from large centres. In most cases it relates to HH due to iron overload, as pituitary gonadotrophs are particularly sensitive to iron (De Sanctis et al., 2004; Belhoul et al., 2012; Chirico et al., 2015.

In men

Diagnosis

Diagnosis is established in men with symptoms or signs of hypogonadism, with unequivocally and consistently low serum testosterone levels combined with low or non-elevated levels of gonadotropins (LH and FSH). Testosterone levels exhibit diurnal variation and may be suppressed by food intake or glucose. Therefore, testosterone deficiency should only be confirmed with a morning (08:00–09:00 ideally) fasted sample. Men with thalassaemia who have low or falling BMD should be evaluated for hypogonadism.

Serum testosterone measures total testosterone levels. However, many men with thalassaemia have elevated sex hormone binding globulin (SHBG) levels due to liver disease. This binds testosterone resulting in a low levels of free testosterone that is biologically active. In men with high SHBG, free testosterone can be calculated using total

testosterone, SHBG and albumin concentration. Several online calculators exist (including http://www.issam.ch/freetesto.htm)

The suggested cutoff for considering a diagnosis of hypogonadism is total testosterone <11 nmol/L or free testosterone <0.22 nmol/L, but may vary considerably according to local assays. In practice, testosterone levels are often much lower and the diagnosis is obvious.

Testosterone replacement

Hypogonadism before the initiation or completion of puberty is discussed elsewhere. In men who acquire HH post pubertally, testosterone replacement is indicated to treat or prevent symptoms of testosterone deficiency (low libido and erectile dysfunction), and preserve health (prevent osteoporosis, maintain muscle mass and vitality).

Testosterone replacement has a suppressive effect on spermatogenesis and should not be used in men who are actively trying to reproduce. Refer to the British Society for Haematology Guidelines on *Management of Conception and Pregnancy in Thalassaemia Syndromes* (Shah et al., 2023). Testosterone replacement can be used for men who have a future need for reproduction. Spermatogenesis is discussed elsewhere.

In the UK, the two main modes of testosterone replacement are topical or intramuscular injection. Topical (transdermal) testosterone gels should be applied daily. The most common side effects (affect more than 1 user in 10) are skin reactions at the site of application, such as a burning or prickling sensation, dryness, rash, redness or itchiness. It is important that men wash their hands thoroughly after the application of testosterone to avoid its accidental transfer to others, such as female partners or children. The main advantage of topical testosterone is the ease of dose adjustment as many formulations come in metered-dose applications. Intramuscular testosterone preparations include Sustanon 250 mg/1 mL solution (containing four types of testosterone esters) and Nebido (testosterone undecanoate) 1000 mg/4 mL solution. Sustanon contains peanut oil so should not be used to treat anyone with a peanut or soy allergy. In the non-thalassaemia population, Sustanon is generally administered at 3-weekly intervals and Nebido at 12-weekly intervals after an initial loading dose. There are no clearly established dosing intervals for men with thalassaemia and the recommendation is to maintain trough testosterone levels (immediately prior to a subsequent dose of intramuscular testosterone) in the lower-end-of-normal range. For men with elevated SHBG, free testosterone levels should be used instead of total testosterone for treatment monitoring. Many men with thalassaemia choose Nebido as the preferred intramuscular preparation as administration can often be timed to coincide with blood transfusions. Prostate-specific antigen should be monitored annually in men aged >40 years on testosterone replacement.

Given the lack of an observed 'andropause' in unaffected men and the huge degree of overlap between the adverse consequences of untreated hypogonadism and those of normal male ageing (sarcopaenia, osteopaenia, etc.), there is no plausible upper age limit beyond which pubertal induction should not generally be undertaken.

In women

HH is diagnosed in females when they develop amenorrhea, either after successful pubertal induction or sometime after having successfully completed puberty. FSH, LH and oestradiol levels should be assessed, and the patient started on HRT to maintain menstruation and bone health (Matthews et al., 2017).

There are a number of options for HRT, including oral 17β-oestradiol, transdermal 17β-oestradiol, the combined oral contraceptive pill (COCP) and equine conjugated oestrogens. The COCP is readily available and cost-effective, and is more acceptable socially in younger women. However, it can give rise to obesity and hypertension, and is linked to adverse metabolic profiles.

Females with HH can successfully conceive with ovulation induction or in vitro fertilisation (IVF). HRT should be continued until the normal age of female menopause, but an assessment of bone health/osteoporosis and other factors should be taken at that time, and extension of time on HRT may be considered for the management of these issues.

Other endocrine abnormalities in thalassaemia

In adolescence and adulthood, further endocrine complications – including primary hypothyroidism, primary hypoparathyroidism and primary adrenal failure – may evolve, especially when iron chelation is poor (Belhoul et al., 2012; Chirico et al., 2015).

Hypothyroidism

"I was overly tired, sluggish, not sleeping properly and really suffered from low mood and I thought It was just me until my doctors realised this was affected and started me on thyroxine which fixed everything"

According to recent studies (Upadya et al., 2018; Dixit et al., 2022) the prevalence of hypothyroidism ranges between 4.8% and 16% in people with thalassaemia. A lower

prevalence rate correlates with good chelation therapy, but not SF levels or splenectomy status of patients (Seow et al., 2021).

Hypothyroidism develops as a result of iron deposition in the thyroid gland (primary hypothyroidism) or iron toxicity to the hypothalamic–pituitary axis (central hypothyroidism) (De Sanctis, 2002; Skordis, 2011; Carsote et al., 2022).

A meta-analysis identified that the overall prevalence of hypothyroidism in patients with beta thalassaemia over the last 5 years was higher among patients with TDT when compared with patients with NTDT. In addition, this meta-analysis found a significant association of high SF levels with hypothyroidism. These findings highlight the importance of prevention measurements, timely diagnosis and the management of iron overload in patients with beta thalassemia (Haghpanah S., et al., 2021).

Secondary (central) hypothyroidism should be suspected, particularly in the context of poor iron chelation and the presence of other pituitary iron overload complications, if hypothyroid symptoms are associated with low FT4, normal or low TSH, or a fall in FT4 with time with inappropriately normal TSH.

In the general population, secondary hypothyroidism is about 1000-fold rarer than primary hypothyroidism (Haghpanah S., et al., 2021). In contrast with primary hypothyroidism, FT4 with low/normal TSH levels are the biochemical hallmarks of overt forms of secondary hypothyroidism, whilst the milder defects, characterised by FT4 levels still within the normal range, could remain undiagnosed (Persani, 2012).

Table 8.6: Prevalence of hypothyroidism in people with TM

Country/city	Indonesia	ndi a	Malaysia	Greece	Pakistan	Iran	Pulau Pinang
Hypothyroidism	26.8%	5.6%	16.5%	16.5%	25.7%	14.6%	21.6%
Primary/overt	1.7%	0%	3.7%	4%	1.4%	1.5%	2%
Subclinical	25.1%	10 %	13.4%	12.5%	24.3%	10.8%	5.9%
Secondary/central	0%	5.6 %	1.2%	0%	0%	2.3%	13.7%

Tan et al., 2019; Zervas et al., 2002; Malik et al., 2010; Eshraji et al., 2011.

Table 8.7: Diagnosis of hypothyroidism

	TSH	FT4	Tri-iodothyronine
Primary/overt hypothyroidism	High	Low	Low
Subclinical	High	Normal	Normal
Secondary/central	Low or normal	Low	Low

As the symptoms of hypothyroidism can often be non-specific, a high index of suspicion should be maintained in patients. Annual biochemical monitoring of thyroid function, and FT4 and TSH levels starting at 10 years of age is advised. Treatment is with levothyroxine, with the dose adjusted based on thyroid function monitoring.

In cases of secondary hypothyroidism, assessment of the cortisol axis is required before commencing treatment with levothyroxine, to avoid precipitating adrenal crises in undiagnosed cortisol deficiency.

Hypoparathyroidism

Hypoparathyroidism is an uncommon endocrine complication of thalassaemia that presents in the adolescent or older years (Mahmoud et al., 2021). It is characterised by hypocalcaemia, hyperphosphatemia, and reduced or inappropriately normal parathyroid hormone (PTH; in the context of hypocalcaemia) (Brandi et al., 2016)

The main cause of hypoparathyroidism in people with thalassaemia is the deposition of iron in the parathyroid glands. Many of the symptoms of hypoparathyroidism may be ascribed to hypocalcaemia and can be mild (tingling sensation, carpopedal spasm and muscle cramps) or severe (seizures and long QT syndrome). Further, hypocalcaemic tetany may be revealed by Chvostek's sign and Trousseau's sign (Jesus and Landry, 2012; Méneret et al., 2013).

If primary hypoparathyroidism is diagnosed (hypocalcaemia with low or inappropriately normal PTH), the standard treatment is vitamin D or vitamin D analogues (alphacalcidol/calcitriol), and sometimes calcium supplementation.

The aim of treatment is to place the corrected serum calcium at the lower limit of the normal range in order to avoid complications of hypercalciuria and subsequent nephrocalcinosis.

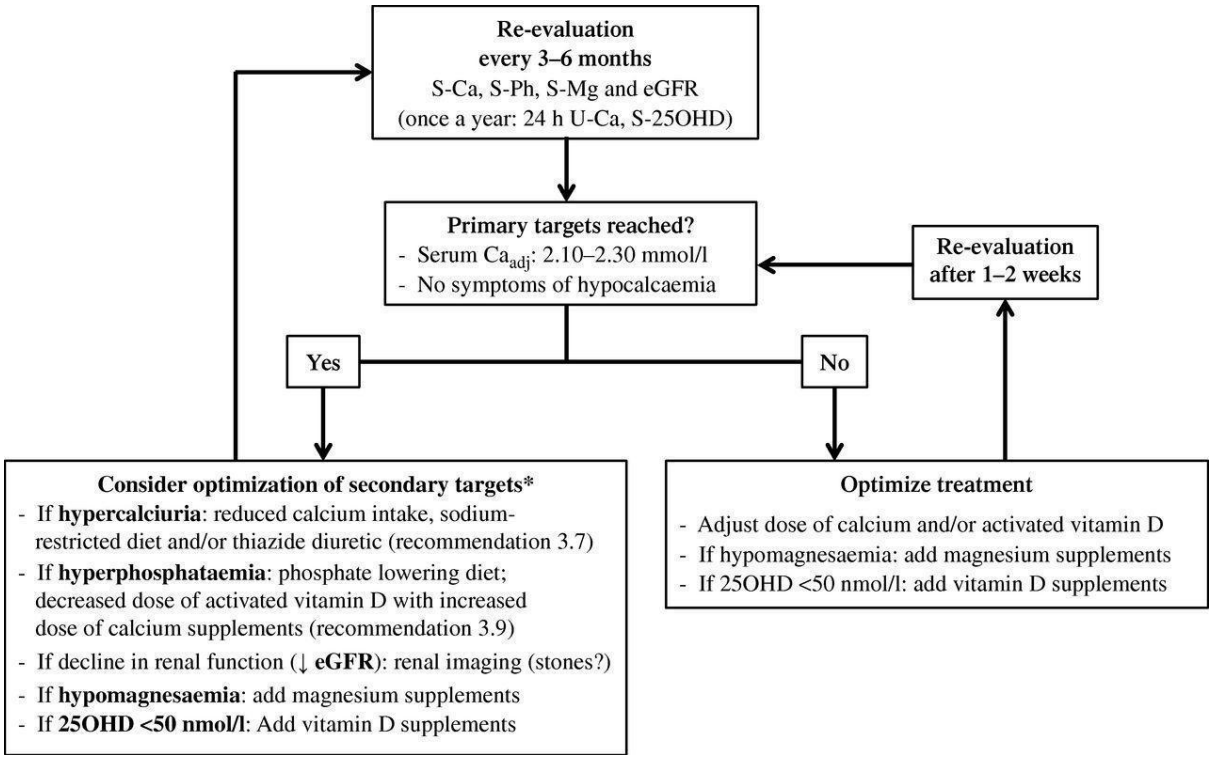
Table 8.8: Diagnosis of hypoparathyroidism and vitamin D deficiency

	PTH	Corrected calcium	Phosphate	Vitamin D level
Primary hypoparathyroidism	Low	Low or low normal	Normal to high	Normal
Secondary hypoparathyroidism	Low	High	Normal to low	Normal
Vitamin D deficiency	High	Normal or low	Normal to high	Low

Table 8.9: Vitamin D metabolites in the management of chronic hypoparathyroidism

Medication	Typical dose
Calcitriol ($1,25(OH)_2D_3$)	0.25–2.0 µg once or twice daily
Alfacalcidol ($1\alpha(OH)D_3$)	0.5–4 µg once daily
Dihydrotachysterol	0.3–1.0 mg once daily
Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol)	Patients with vitamin D (25-OH) D_3 level <20 ng/mL (50 nmol/L): Loading dose of vitamin D followed by maintenance dose Patients with vitamin D (25-OH) D_3 level >20 ng/mL (50 ng/mL): Maintenance dose of vitamin D

Figure 8.4: Monitoring and treatment of chronic hypoparathyroidism (Bollerslev et al., 2015)



*If dose of calcium or activated vitamin D is changed, re-evaluation of serum calcium levels is recommended after 1–2 weeks.

Hypercalciuria can be diagnosed by measuring 24-hour urine excretion or rapidly by checking urine test for calcium/creatinine ratio. If hypercalciuria suspected a confirmation with renal ultrasound scan would be useful for further management and monitoring.

Adrenal insufficiency

AI is a recognised but probably underestimated complication of thalassaemia. It occurs due to excess iron deposition in the pituitary gland (secondary AI) or in the adrenal gland (primary AI) (Elsedfy et al., 2011). Increasing evidence suggests that subclinical AI is common (between 15–53.6%) in children and adolescents with thalassaemia, but adrenal crisis is rare (Srivasta et al., 2005).

The clinical manifestations of AI, such as fatigue and weight loss, often overlap with the symptoms of thalassaemia, making it difficult to diagnose clinically *(*Nakavachara and Viprakasit, 2013). Both primary and secondary adrenal failure should be considered in unwell patients (Elsedfy et al., 2011).

Endocrine Society Clinical Practice Guidelines advise measuring serum cortisol levels at 08:00–09:00 in the morning as the first-line test for diagnosing central AI, and recommend against using a random cortisol level check to diagnose AI. A cortisol level <3 µg/dL (80 nmol/L) is indicative of AI and a cortisol level >15 µg/dL (400 nmol/L) likely excludes an AI diagnosis (Fleseriu et al., 2016).

Endocrine Society Guidelines also advise performing a cosyntropin stimulation test (Short Synacthen test) when morning cortisol values are between 3 µg/dL and 15 µg/dL to diagnose AI. Peak cortisol levels <18.1 µg/dL (500 nmol/L) at 30 or 60 minutes indicates AI. Clinicians should perform biochemical testing for the hypothalamic–pituitary–adrenal axis at least 18–24 hours after the last hydrocortisone dose or longer for synthetic glucocorticoids (Fleseriu M., 2016).

Please refer to the relevant chapters for the diagnosis and management of diabetes and bone disorders.

Requirements

- Patients with TDT should receive optimal transfusion to prevent excessive bone expansion.
- The recommended DFO dose in childhood should not be exceeded.
- Regular assessments of growth, including weight and height (standing and sitting), should be recorded every 6 months from diagnosis until final adult height is attained, with referral to a paediatric endocrinologist if there is any concern. Data should be charted, and height velocity calculated, to ensure any change is detected promptly.
- Puberty should be systematically assessed annually from the age of 10 years, with referral to a paediatric endocrinologist if there is any suspicion of delayed (no pubertal changes in girls by age 13 years and boys by age 14 years) or arrested puberty (puberty starts but then does not proceed). Progress should be documented using Tanner staging.
- Assessment of bone age is useful, by plain hand and wrist X-ray, if there are concerns about pubertal delay or a fall in height velocity.
- Evidence of faltering growth, with declining centiles for height and height velocity, is often apparent around the age of 8–12 years. This should be investigated thoroughly with consideration given to DFO toxicity and GH deficiency. IGF-1 should be measured annually, and a GH stimulation test should be considered based on clinical, auxological and IGF-1 data. If there is evidence of GH deficiency, GH therapy should be instituted as per NICE guidance, under the supervision of a paediatric endocrinologist.

- Delayed puberty should be fully investigated, including with LH, FSH and testosterone (ideally early morning)/oestradiol. Adolescents with evidence of hypogonadism should be treated with HRT, under guidance from a paediatric endocrinologist.
- FT4 and TSH measurement should be checked annually from age 12 years, or if any symptoms of hypothyroidism develop in between times, and hypothyroidism should be treated promptly with regular checks as to the adequacy of replacement thyroxine dose. Secondary hypothyroidism requires confirmation of a fully functional cortisol axis before initiating treatment.
- A random (ideally morning) cortisol level check should be conducted annually, with consideration of a standard-dose Short Synacthen test and morning adrenocorticotropic hormone level if cortisol deficiency is considered.
- The bone profile (calcium, phosphate and alkaline phosphatase) and PTH level should be monitored at least annually from the age of 12 years.
- Vitamin D should be checked at least annually from age 2 years at the latest and supplemented as necessary.

Table 8.10: Summary of endocrine screening in thalassaemia

Disorder	Frequency	Evaluation	Action
Growth delay	6-monthly from diagnosis until attainment of adult height	Height (standing and sitting), weight, growth velocity If growth delay concerns consider to check; Bone age (X-ray wrist) IGF-1 and IGF-BP3 GH stimulation test	● GH treatment in GH deficiency ● Treatment of anaemia and appropriate chelation ● Treat nutritional deficiencies (Zn and minerals) ● Treat concurrent endocrinopathy
	6-monthly from age 10 years	Tanner staging **If pubertal delay:** Oestradiol	● Hypogonadism: HRT (oestrogen/testosterone)

Gonadal dysfunction		Testosterone LH/FSH/GnRH stimulation test	
Diabetes mellitus	From age 10 years	OGTT at ages 10, 12, 14 and 16 years, and annually thereafter	● Impaired glucose regulation: chelation therapy, diet ● Diabetes management
Hypothyroidism	Annually from age 10 years	Thyroid function test: TSH, FT4	● Hypothyroidism: thyroxine replacement (LT4); exclude cortisol deficiency prior to treatment in central hypothyroidism
Hypoparathyroidism	Annually from age 10 years	Vitamin D Ca/PO_4/Mg/ALP Check PTH if ↓Ca	● Active vitamin D analogues ● Treat symptomatic hypocalcaemia with 10% calcium gluconate
AI	Annually from age 10 years	Random (ideally morning) serum cortisol If abnormal: Short Synacthen test	● AI; hydrocortisone supplementation ● Stress dose hydrocortisone in
Bone disease	Vitamin D: check yearly from age 2 years DXA: check once I adolescence Further scans dependent on results and clinical picture	Vitamin D Bone density scan (DXA)	● Vitamin D replacement if required ● Consider bisphosphonate treatment in the presence of any vertebral fracture or recurrent long bone fractures with low BMD

↓, low; Ca, calcium; DXA, dual-energy X-ray absorptiometry; GnRH, gonadotropin hormone-releasing hormone; LT4, Levothyroxine; Mg, magnesium; PO_4, phosphate; Zn, zinc.

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Chapter 9

Reproductive Health Across the Lifespan

"I didn't know I needed to be on contraception because of my iron chelation medication. No one told me this until I became pregnant and lost my baby."

"I didn't know my fertility would have been affected when I was ready to grow my family."

Part A: Age of Consent, Sexual Health, Contraception and Treatment

Sexual health understanding is essential for the general wellbeing of individuals and a key factor in building a healthy community. Within these guidelines, we aim to provide individuals with sufficient information to help them have safe and healthy relationships. It is important that individuals learn the facts and the law about sex, sexuality and sexual health in an age-appropriate and inclusive way. The ability to achieve sexual health and wellbeing depends on different factors, such as access to comprehensive information about sex and sexuality, understanding about the risks of unprotected sexual activity and access to sexual health services (WHO, 2023).

In the UK, any capable individual aged ≥16 years, including those with a disability/impairment, are entitled to consent to their own medical treatment and sexual activities including contraception, unless it is proven that there is significant evidence to indicate otherwise (British Medical Association, 2020). For young individuals aged <16 years, their entitlement to consent depends on their maturity and understanding of the objectives involved in their treatment. Otherwise, parents or individuals with parental responsibilities can consent (Legislation.gov.uk, 1969a,b, 1991, 2000, 2005; Court of Appeal, 1984). However, we at the UKTS encourage young individuals to involve their parents or their guardians in important decision-making.

Regarding sexual activities, legally the age of 16 years is considered appropriate to consent regardless of gender identity and sexual orientation (National Society for the Prevention of Cruelty to Children, 2023). In the meantime, information about contraception, abortion and sexually transmitted diseases can be provided to young individuals under the age of 16 years without parental consent or knowledge, as long as the young person understands the advice provided and its implications (General Medical Council, 2023).

There are several methods of contraception. Permanent options include female sterilisation and male sterilisation (vasectomy). Non-permanent methods include caps or diaphragms, the COCP, condoms, contraceptive implant, contraceptive injection, contraceptive patch, female condoms, an intrauterine device or coil, an intrauterine system or hormonal coil, natural family planning (fertility awareness), the progestogen-only pill and vaginal rings (NHS, 2021).

Part B: Infertility in Men

Aims

To screen and diagnose at the earliest for effective management of male hypogonadism and infertility.

Background

Testicular function is regulated by the pulsatile release of GnRH from the hypothalamus, which stimulates the secretion of pituitary gonadotropins. Then, in the testis, LH mainly stimulates testosterone production and FSH promotes spermatogenesis (Amory and Bremner, 2001). The cause of male infertility in patients with beta thalassaemia is classically considered to be the result of iron deposition in the endocrine glands, whilst in the general population potential causes are multiple (De Sanctis and Giovannini, 2011). Adult male patients with beta thalassemia, on regular blood transfusions, are prone to developing acquired hypogonadism, with the frequency depending mostly on the degree of compliance with blood transfusion and chelation programmes (De Sanctis et al., 1986, 2016a).

Hypogonadism is a common complication in patients with TDT due to iron overload and has been reported in approximately 50% of cases (Prati, 2000). In a study by Safarinejad (2008), the prevalence of HH was 76.2% and almost one-half of the male patients with thalassemia had failure of pubertal development. In another study, hypogonadism was encountered in 32.63% of patients but its frequency was not significantly different when

comparing patients who were post-transplant with patients with TDT (36.59% versus 30.77%). It is also notable in this study that about 80% of post-transplant patients with hypogonadism had hypergonadotropic hypogonadism, whilst most of the TDT patients had HH (Rostami et al., 2020).

Allogeneic HSCT is currently the only definitive treatment for beta thalassaemia and the number of long-term survivors following HSCT have increased noticeably in recent years (Yes ilipek, 2003; Tauchmanovà et al., 2002). Patients with thalassaemia who have undergone allogeneic HSCT have lower fertility potential, mainly in sperm parameters, compared with patients treated with blood transfusion and chelation. This information is important for patients living with thalassaemia who are considering HSCT (Rostami et al., 2020). In a multicentre European study, suspected infertility was less frequent in males who received HSCT treatment at the age of 13 years or later than in those for whom treatment started at the age of 1–12 years (Borgmann-Staudt et al., 2012).

Delay of pubertal sexual maturation in adolescents and decreased libido, erectile dysfunction, and lower quality of life in adults could all be part of clinical manifestations of hypogonadism. At very low levels of gonadotropins and testosterone, spermatogenesis is impaired and the volume of ejaculate is decreased (Silveira et al., 2002; Salenave et al., 2012).

A diagnosis of acquired HH is confirmed by low serum concentrations of testosterone and gonadotropins, whereas hypergonadotropic hypogonadism is confirmed by low testosterone and high gonadotrophin levels. There is a correlation between pituitary hormones, testosterone, testicular volume and the degree of pubertal development, sperm count and quality (Ansari et al., 2018).

Individuals with high iron burden have decreased pituitary volume and low gonadotropin levels. Additionally, their seminal environment has a detrimental effect on sperm vitality and quality. In patients with consistent adherence to iron chelation, pituitary size and fertility measures are better preserved (Singer et al., 2015).

In a study by Soliman et al. (2000), testosterone levels were correlated significantly with all sperm parameters. A similar finding was shown in another study as patients who had lower levels of serum FSH, LH, and testosterone had significantly lower ejaculate volumes, sperm concentrations, percentages of motile and progressively motile sperm, and testicular volumes (Ansari et al., 2016). In men with thalassaemia, testicular volume on ultrasound has significant correlation with concentrations of serum testosterone, LH, FSH and sperm parameters (Ansari et al., 2016).

Chen et al. (2018) demonstrated that males with beta TDT have a high proportion of fertility impairment, and that iron overload in testes might contribute to disturbed sperm

quality and testicular tissue injury. Such findings might explain the high prevalence of impaired fertility in patients with beta TDT with normal pituitary function.

Treatment of infertility

Treatment of hypogonadism and fertility in men must include good iron chelation, appropriate testosterone replacement therapy and the induction of fertility.

Patients with beta TDT who fail to enter puberty or whose puberty is arrested before complete sexual maturation used to be considered sterile for life. However, this does not seem necessarily true as gonadotropin treatment (human chorionic gonadotropin [hCG] and human menopausal gonadotropin [hMG]) can achieve spermatogenesis (De Sanctis et al., 1988; De Sanctis et al., 2018). Because of advances in fertilisation and sperm banking technologies, all individuals, even those with extremely low sperm counts and motility, should be considered candidates for sperm cryopreservation (De Sanctis et al., 1989).

Exogenous testosterone does not induce testicular growth or spermatogenesis in men with HH. Equally, exogenous oestrogen does not induce ovulation (findings that clinch the diagnosis), and induction of fertility in both sexes requires treatment with either pulsatile GnRH (Pitteloud et al., 2002a,b; Warne et al., 2009) or exogenous gonadotrophins (Warne et al., 2009). Fertility outcomes with each regimen are variable, with poorer responses in patients with signs of absent mini-puberty (prepubertal testes, cryptorchidism and/or low inhibin) (Pitteloud et al., 2002b; Lui et al., 2009).

Table 9.1: Society of Endocrinology published predictors of the success of spermatogenesis induction in male patients with HH

Positive predictors	Negative predictors
TC ≥4 mL, consistent with milder LH/FSH deficiency	Absent mini-puberty
Normally descended testes	Absent spontaneous pubertal development (testicular volume <4 mL)
Higher baseline serum inhibin B level (i.e., >100 pg/mL)	History of maldescended testes (cryptorchidism) with a surgical correction; late surgical correction (past first year of life)
Spermatogenesis achieved in prior gonadotropin treatment cycles	Low baseline serum inhibin B level (<60 pg/mL) Mutation in *ANOS1* (formerly *KAL1)*, an X-linked form of Kallman syndrome

Induction of puberty in adolescent males with either hCG monotherapy, or with combinational therapy of hCG and recombinant FSH, may result in better testicular growth and improvement in potential fertility compared with treatment with testosterone therapy (Barrio et al., 1999).

If the patient has spontaneous onset of pubertal development, they can begin with hCG monotherapy. FSH can be added in cases where azoospermia persists after 6–12 months of treatment. Early induction of spermatogenesis may increase sperm production capacity and reduce the time required for the appearance of sperm once fertility is desired. Monotherapy of hCG alone is at least theoretically less efficacious in the induction of spermatogenesis than combinational therapy of hCG and FSH (Barrio et al., 1999; Dunkel and Quinton, 2014; Dwyer et al., 2013).

Men with post-pubertal gonadotropin deficiency might respond to hCG monotherapy, but men with prepubertal onset of gonadotropin deficiency virtually always benefit from combination hCG plus FSH therapy. Sperm concentrations typically take at least 4–6 months to rise with hCG monotherapy, and FSH therapy is added if sperm concentrations remain below 10 million/mL and conception has not occurred.

The initial regimen of hCG is usually 1000–2000 IU. This is administered intramuscularly two times per week. The clinical response is monitored, and testosterone levels are measured every 2–3 months. Dosage adjustments of hCG may be needed to determine the optimal schedule. The disadvantages of hCG include the need for more frequent injections and the higher cost (De Sanctis et al., 2018).

Table 9.2: Treatment of fertility in boys and men

Drug and formulation	Treatment of fertility in boys and men	Side effects and cautions
Pulsatile GnRH	Initial: 5–25 ng/kg per pulse every 90–120 minutes; increase to 25–600 ng/kg per pulse	Requires extensive experience Most physiological form of replacement
hCG plus recombinant FSH	hCG: dose 500–3000 IU twice weekly; increased to every 2 days; dose adjusted based on serum testosterone levels Recombinant FSH: dose 75–225 IU 2–3 times weekly	hCG: inflammation locally in the testis, may induce apoptosis of germ cells In HH with prepubertal onset it is necessary to add FSH to induce testicular growth and spermatogenesis No data on effects on future fertility

The optimal regimen to maximise the potentiality for fertility in severe cases, in those with testicular volume <4 mL, is unknown (Sørensen et al., 2012). FSH pretreatment may plausibly maximise the Sertoli cell population before exposure to hCG or GnRH-induced endogenous LH, and thus has the potential to improve fertility outcomes (Santhakumar et al., 2014).

Requirements

- Treatment of hypogonadism and fertility in men must include good iron chelation, appropriate testosterone replacement therapy and induction of fertility.
- All boys with thalassaemia should be checked annually for hypogonadism with LH, FSH and testosterone/SHBG (preferably morning and fasting) levels tested from 10 years of age.
- All men considering fertility evaluation should be referred promptly to specialists (fertility clinics or endocrinologists with expertise in fertility management) for investigations and fertility management. Testicular ultrasound scan and semen analysis should be considered as part of investigations if required to guide initial fertility management.
- Building a family is a key concern for many patients and their extended families. They greatly value discussion with a specialist to discuss realistic options and the likelihood of success. It is also important to address unrealistic expectations and consequent psychological and emotional problems.

- Because of advances in fertilisation and sperm banking technologies, all individuals, even those with extremely low sperm counts and motility, should be considered candidates for sperm cryopreservation.
- Men with thalassaemia and hypogonadism are at risk of developing low BMD and fractures (mainly vertebral) if testosterone deficiency is not diagnosed and replaced promptly. It is important to monitor BMD with DXA whilst testosterone is replaced to an adequate level.

Recommendations

- The evaluation of infertile male patients is crucial to recognise potentially treatable causes of infertility.
- All boys with thalassaemia should be checked annually for hypogonadism with LH, FSH, testosterone (preferably morning and fasting) levels and SHBG from 10 years of age.
- Early discussion and screening are essential to detect fertility issues in men; these patients should be promptly referred to specialists (fertility clinics or endocrinologists with interest in fertility management) for further evaluation and management. Testicular ultrasound scan and semen analysis should be considered as part of initial investigations to guide fertility management.
- Partner screening should be offered to detect clinically significant Hb variants. If the partner has a clinically significant variant, the couple should be counselled together about the risk of their baby having a major Hb disorder, and offered PND or PGT.
- Prior to fertility treatment, it is essential to check that the couple have had a normal semen analysis result and confirmation of tubal patency. Assumptions should never be made, as overlooking simple tests can cause unnecessary delays in starting definitive treatment.
- Because of advances in fertilisation and sperm banking technologies, all individuals, even those with extremely low sperm counts and motility, should be considered candidates for sperm cryopreservation.
- Induction of fertility in both sexes requires treatment with either pulsatile GnRH or exogenous gonadotrophins.

Part C: Treatment of Fertility in Women

"There was nothing I wanted than more than having a healthy family of my own. It took a lot for me to become pregnant but with God's will I had my baby."

Aims

The primary aim for the younger patient is to optimise iron chelation from infancy to reduce the likelihood of infertility.

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

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

Standards

- Each Specialist Centre will identify a paediatric endocrinologist with experience in the management of thalassaemia.
- Pubertal development, growth, and endocrine function will be closely monitored in girls with thalassaemia, and prompt referral made if there is any suspicion of problems.
- At any time when the patient wishes they should be referred to a fertility/endocrine/assisted conception clinic with experience of thalassemia patients, to allow discussion about treatment options; culturally appropriate advocacy will inform these discussions.

Background

HH caused by the effects of iron overload is common among women with TDT. Advances in the management of iron overload have resulted in a lower prevalence of this endocrine problem; however, it still affects up to 60% of adult patients (NICE Clinical Guideline [CG156] 2012).

Iron overload and ovarian function

Little is known about the effect of iron overload on ovarian follicles, and whether ovarian reserve is affected by the disease or treatment status. The medical literature contains multiple reports of successful pregnancies in women with TDT (with optimal chelation) with use of gonadotropins for ovulation induction and/or IVF, suggesting that the ovaries may be spared from the damage caused by iron overload in earlier years of life (Bajoria and Chatterjee, 2011; Chang et al., 2011). However, there are limited data on the effect of iron overload on ovarian reserve, and it is unclear whether iron accumulation and oxidative stress cause ovarian damage leading to low ovarian reserve and poor reproductive outcomes in women with TDT.

There are many factors that can hinder the effective assessment of ovarian reserve over time in women with TDT, including continuous use of HRT and the dynamic nature of the extent of iron overload. The data from studies that have assessed ovarian reserve and fertility in women with TDT are heterogeneous as there is variation in study types, the population under study, ethnicity, degree of iron load, extent of multiorgan involvement, types of investigations/interventions used and the inclusion criteria for participants.

With regards to biochemical markers of ovarian function, FSH levels in the early follicular phase are not reliable in women with HH as markers of gonadal function (Chang et al., 2011). Anti-Mullerian hormone levels appear to be a useful marker to estimate ovarian reserve and time to the onset of the menopausal transition (determined by the onset of menstrual irregularities in women with menstrual function) (Knauff et al., 2009; Broekmans et al., 2008). A recent study demonstrated that other markers of ovarian reserve – serum anti-Mullerian hormone level and antral follicle count on pelvic scan – were significantly lower in women with TDT compared with age-matched healthy controls, suggesting a direct impact of disease activity or iron overload on the ovary (Talaulikar et al., 2019). Low ovarian reserve could therefore be an important contributor towards subfertility in many women with TDT. Suppressed levels of anti-Mullerian hormone were also noted in women with TDT without HH who had regular menstrual cycling, suggesting a likely deleterious effect of the background diagnosis and/or treatment (transfusional iron overload) on ovarian reserve (Talaulikar et al., 2019).

It has been suggested that iron-induced damage impairs oocyte function, with demonstrated increased levels of redox-active iron in follicular fluid, thus contributing to subfertility (Chang et al., 2011; Pafumi et al., 2011; Reubinoff et al., 1996). However, there are insufficient data on the direct effects of iron on the gonads (Castaldi and Cobellis, 2005; Pafumi et al., 2011). It is possible that ovarian damage starts with the accumulation of small amounts of iron from an early stage (pre- or during puberty), as ovarian follicles are highly sensitive to endocrine disruptors such as free radicals or chemotherapy (Chatterjee and Bajoria, 2013; Lutchman Singh et al., 2005). It is possible

that chronic iron-induced oxidative damage can result in earlier or accelerated follicular ageing, a mechanism postulated to be responsible for reduced fertility and early menopause in women with thalassaemia. Further studies are required to elucidate the mechanisms by which iron overload could adversely affect ovarian reserve and hormone production, and the best treatment strategies to prevent such damage.

Investigation and management of hypogonadism and ovulation induction

British Society of Haematology national guidelines are available for pubertal induction if required (Conway and Critchley, 2013). Many older patients have hypogonadism and therefore will need fertility support for conception. The role of the fertility specialist is twofold: in the treatment of ovulation induction using injectable gonadotrophins, and in the use of PGT to identify non-thalassaemia embryos prior to a clinical pregnancy in a high-risk couple as discussed in **Chapter 10: Reproductive Informed Choice – Prenatal Diagnosis and Preimplantation Genetic Testing**.

There are national guidelines for the assessment and treatment of fertility problems (NICE, CG 156). A full fertility workup for both partners is mandatory prior to treatment with gonadotrophins:

1. The minimal investigations based on NICE guidelines (which are focused on heterosexual couples) are:

    a. Semen analysis (after 3 days abstinence) for the male partner.

    b. For the female partner, follicular-phase (cycle day 2–5) oestradiol (E2), FSH and LH analysis. Ovulation should be estimated with a 7-day premenstrual progesterone (P4) assay. However, as the patient with thalassaemia will be amenorrhoeic, blood tests can be performed at any stage once there has been elimination of their maintenance oestrogen/progestogen.

2. A transvaginal ultrasound to estimate ovarian volume, morphology, antral follicle count and assess uterine morphology. Patients should be counselled that the ovarian reserve, ovarian volume and antral follicle count will be reduced because the ovary has not been stimulated (Bajoria and Chatterjee, 2011; Talaulikar et al., 2019). Anti-Mullerian hormone levels in patients with thalassaemia are reported to be lower than in age-matched controls (Chang et al., 2011).

3. Assessment of tubal patency.

Patients must be fully counselled about the potential risks and complications – such as over-/under-response, the requirement for monitoring by ultrasound and blood tests, the possibility of a multiple pregnancy – and the chances of success with treatment, which is mostly closely related to the age of the patient at the time of conception. The obstetric risks overall must be discussed prior to initiation of treatment.

The aim of ovulation induction is the maturation of a single follicle. At the start of treatment, a baseline ultrasound must be done to confirm ovarian quiescence and to check the endometrial size, which should be ≤4 mm. Patients then self-administer exogenous hMG daily until there is a dominant follicle 18 mm in size with an endometrial thickness of at least 7 mm. At this point, a trigger injection is given to promote follicle rupture and ovulation approximately 38 hours later. A trigger injection should not be given if there are more than two follicles >14 mm on the day of the trigger injection to reduce the likelihood of multiple pregnancy (NICE CG 156). Couples are then advised to have unprotected intercourse daily for 2 days commencing on the day of trigger (Yasmin et al., 2013). Intrauterine insemination is not routinely used unless there are separate fertility indications (NICE CG 156), such as when donor sperm is required.

If the treatment is successful, the earliest a urinary pregnancy test can be performed is approximately 15 days following the trigger injection. If the treatment is unsuccessful then treatment can restart on the second day of the menstrual cycle.

Table 9.3: Example of ovulation induction schedule

Time of intervention	Intervention	Details	Grade and level
Baseline	Transvaginal ultrasound scan	Assess pelvis Endometrium <4 mm and no follicle >10 mm	1B
Initiation of therapy	Initiation of hMG (Menopur or Meriofert)*	75 IU daily	1B
Days 10–12 after initiation of stimulation	Assessment of follicles	No follicles >10 mm: continue same dose for a further 5 days and reassess**	1B

Days 10–21	Assessment of follicles and trigger injection	If fewer than 2 follicles >14 mm on day of trigger, then trigger with 5000 IU hCG or choriogonadotropin alfa (e.g., Ovitrelle)***	1B
Day 7 after trigger injection	Measure serum progesterone	Levels of more than 30 nmol/L are confirmatory****	1B
Days 14–18 after trigger	Measure blood (day 14/15) or urine beta-hCG (17/18)	Confirmation of pregnancy	1C
Day 2 of withdrawal bleed	Option to initiate next ovulation induction cycle if unsuccessful		
Clinical review		If no follicular development achieved or 6 cycles of successful ovulation but no pregnancy	1C

*If recombinant FSH medication (e.g. GonalF) is being used then it is essential to add in recombinant LH activity. **Continue low-dose stimulation for at least 21 days before considering increasing the dose to 150 IU/75 IU alternate days. ***Multiple pregnancy will always be a possible outcome, and a patient should not have a trigger injection if more than two follicles >14 mm are present on the day of trigger without clear and documented counselling. ****Progesterone support is not necessary as long as ovulation has been confirmed.

Recommendations

- A full fertility workup of both partners should be undertaken prior to any ovulation induction therapy.
- Patients should be fully informed of individualised risk factors relating to assisted conception, the underlying thalassaemia syndrome and any associated complications prior to treatment.
- Multiple pregnancy will always be a possible outcome, and a patient should not have a trigger injection if more than two follicles >14 mm are present on the day of trigger without clear and documented counselling.
- Patients who have failure of treatment or conception after 6 cycles should be discussed in an MDT.

Part D: Management of Menopause and Post-Reproductive Health

"This is not discussed with patients and we don't know what to expect with these changes that happen a lot sooner than women my age, we need more support with this."

Aims

To ensure that women with thalassaemia experiencing menopausal transition have access to evidence-based information and guidance regarding management of menopause-related health issues through their healthcare practitioners.

To ensure that women are adequately supported in making informed decisions regarding treatment of their menopausal symptoms and the protection of their long-term health.

Standards

- In women with thalassaemia aged ≥45 years presenting with menopausal symptoms, the diagnosis of perimenopause or menopause should be considered based on their symptoms.
- Women with thalassaemia presenting with menopausal symptoms should be made aware of resources available for guidance, and should be offered treatment (lifestyle, non-hormonal interventions and HRT) after information and support to help them make an informed decision about their management.
- Women with thalassaemia having treatment for menopausal symptoms should ideally have a review 3–4 months after starting treatment and should continue to be reviewed at least annually after that.
- Duration of treatments such as HRT should be individualised. No arbitrary limits should be placed on the dose of HRT, duration of usage or age of women having treatment.
- Women with thalassaemia aged <40 years presenting with premature ovarian insufficiency (POI) or early menopause (women aged 40–45 years) should be advised to take HRT and to continue to do so until at least the natural age of the menopause.

Background

Thalassaemia and menopause

Chronological and ovarian ageing are two concurrent processes that influence the pace and duration of the menopausal transition process. In the UK, the average age of menopause is 51. About 10% of women can have an early menopause (<45 years) and 1% can experience POI (<40 years) (Coulam et al., 1986).

Age at menopause is influenced by multiple factors such as ethnicity, diet, exercise levels, smoking status, socioeconomic background, BMI, ethnicity, cultural beliefs and concurrent medical/gynaecological health issues (Gold, 2011; Schoenaker et al., 2014). Every individual's experience of menopausal transition is unique. Whilst some experience minimal menopausal symptoms, others experience severe symptoms that can have a major impact on their quality of life and work. Common menopausal symptoms include hot flushes, night sweats, sleep disturbance, fatigue, joint aches, brain fogging, mood fluctuations, low libido, vaginal dryness and dyspareunia.

Menopausal hormone changes also impact long-term bone, muscle, metabolic, heart and brain health. There are several lifestyle, non-hormonal and hormonal interventions that can help improve quality of life, and protect long-term health, after the menopause. There is very little data about menopausal transition, symptoms, and the safety and efficacy of treatments for menopausal symptoms in women with thalassaemia, especially for women with HH who are on long-term HRT. POI can follow chemotherapy treatment, which is associated with SCT treatment for TDT. Despite the large number of patients with TDT for whom HRT is prescribed, few prospective data exist to assist clinicians in making evidence-based decisions regarding optimal treatment regimens. No evidence-based guidelines for the management of women with thalassaemia in menopause exist, and recommendations are usually based on theoretical knowledge about the physiology of the menopause or extrapolated from evidence relating to the use of HRT in women without thalassaemia (De Sanctis et al., 2016).

Thalassaemia and HRT

No data are available to evaluate the impact of HRT in women with TDT. Specific studies in this group of women are lacking and risks associated with long-term use of HRT – such as breast cancer, endometrial cancer, venous thromboembolism (VTE) and cardiovascular events – have not been characterised. There is an urgent need to develop guidelines based on robust research into menopause and HRT to guide care for this group of women. Women with TDT and HH are offered long-term HRT for relief of symptoms of hypogonadism, and to prevent long-term health complications of oestrogen

deficiency, such as osteoporosis and increased risk of heart disease. The type of HRT, dosage and route of administration are complex in women with thalassaemia due to associated medical risks and comorbidities (Gallagher, 2007). Sequential oestrogen–progestogen replacement therapy is the mainstay of treatment for women with HH. Both the contraceptive pill and HRT have been used for oestrogen replacement in women with thalassaemia. Oestrogen can be replaced using oral, vaginal and transdermal preparations. Progestogen cover can be provided through oral, transdermal and intrauterine coil routes. HRT is not contraceptive.

Limited data suggest the superiority of HRT over the contraceptive pill for more physiological oestrogen concentrations and long-term bone outcomes (Torres-Santiago et al., 2013). In non-thalassaemia populations, the prothrombotic effects of oestrogen in HRT can be circumvented by transdermal administration of oestrogen (Santen et al., 2010). Transdermal oestradiol and micronised progesterone appear to be the safest HRT preparations, particularly in women with risk factors for thrombosis and other comorbidities (North American Menopause Society, 2012; Katz et al., 1993). Women who have chosen HRT for the management of menopausal symptoms need regular reviews to assess the benefits (quality of life and bone and heart health) versus the risks (thrombosis, stroke and breast/endometrial cancer) of continuing HRT.

Recommendations

- Consider the diagnosis of perimenopause or menopause in women with thalassaemia aged ≥45 years presenting with menopausal symptoms.
- Make women with thalassaemia presenting with menopausal symptoms aware of resources available for guidance, and offer treatments (lifestyle, non-hormonal interventions and HRT) after information and support to enable them to make an informed decision about their management.
- Discuss a healthy lifestyle including avoiding excess alcohol, having a healthy diet, quitting smoking and regularly exercising as part of the menopause consultation.
- Before starting HRT, assess each patient carefully to identify any contraindications or increased risk of thrombophilia, or comorbidities such as liver or heart disease, and tailor the laboratory testing and HRT advice accordingly. Close liaison with the haematology team is important, especially for women with splenectomy.
- Transdermal oestradiol and micronised progesterone seem to be the preparations with the best safety profiles, particularly in women with risk factors for thrombosis or other comorbidities.
- Review women with thalassaemia having treatment for menopausal symptoms for 3–4 months after starting treatment and continue with annual reviews to discuss benefits versus risks after that.

- Individualise duration of treatments such as HRT. Do not use arbitrary limits based on the dose of HRT, duration of usage or age of women having treatment.
- Offer women with thalassaemia aged <40 years presenting with POI or early menopause (women aged 40–45 years) HRT at least until the natural age of the menopause, in addition to lifestyle advice.
- Referral to (or seeking advice from) a specialist menopause service should be considered for women who have complex medical backgrounds and who are having difficulties with HRT or management of menopausal health problems.

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Chapter 10

Reproductive Informed Choice – Prenatal Diagnosis and Preimplantation Genetic Testing

"As a patient growing up, I didn't know if I would live to the age of becoming pregnant so when this stage of my life came, everything was new to me and my team. I wish we were told about our options earlier."

Aims

To ensure that all couples at risk of having children with a thalassaemia disorder – including beta thalassaemia major, beta thalassaemia intermedia, alpha zero thalassaemia hydrops fetalis and severe HbH disease – are enabled to make informed choices concerning their reproductive options, through specialist genetic counselling.

To support couples to have a healthy family.

Standards

- All couples at risk of having children with a thalassaemia disorder should be referred for specialist genetic counselling as soon as the risk is recognised.
- Counselling is provided by a genetic specialist with specific experience in both Prenatal Diagnosis (PND) and Preimplantation Genetic Testing (PGT) for Hb disorders.
- DNA analysis is provided for all at-risk couples
- All at-risk couples are informed of PND and PGT as options to achieve a healthy family.
- A couple at risk of having a child with a thalassaemia disorder should be offered PGT if the female partner is aged <40 years at the time of treatment, and there is no living unaffected child from the current relationship.
- If the woman has a thalassaemia disorder, her treating haematologist should be involved in the management plan prior to PGT.

Background

Prenatal Diagnosis

PND using chorionic villus sampling (CVS) is available to all at-risk couples and at-risk women, from 11 weeks gestation onwards. PND, undertaken by experienced operators, carries a risk of miscarriage of 0.5% (Jauniaux and Petrou, 2013). If a woman presents in later pregnancy and the placenta is not accessible for CVS, then amniocentesis may be carried out from 15 weeks gestation instead.

DNA testing should be offered to both partners (ideally before any pregnancy) to identify the precise mutations they carry and to enable genotype–phenotype correlations. The woman should be encouraged to self-refer for counselling for PND as soon as a pregnancy is confirmed, so that CVS, if chosen, can be planned by the 11th week of pregnancy.

If PND shows an affected fetus, the woman should be offered termination of pregnancy. If this is her choice, termination should take place as a matter of urgency and within 5 days of the woman receiving the result, so she has the option of an early surgical termination of pregnancy.

If PND shows an unaffected fetus and the couple have an existing affected child, it is technically feasible to HLA-type the fetus. If the fetus and the affected child are HLA-compatible, then it is possible to collect cord blood and store for transplant for the affected child. However, collection and storage of cord blood is not covered by an NHS tariff. Some couples consider collection and storage of cord blood by going privately.

Preimplantation Genetic Testing

PGT is the only way for an at-risk couple to ensure a fetus is unaffected, whilst avoiding the risk of an invasive procedure and the risk of termination of pregnancy associated with conventional PND. It may be acceptable to some couples who would not accept a termination of pregnancy on religious or other grounds. It allows the diagnosis of single-gene disorders such as thalassaemia or chromosomal abnormalities, or HLA typing, in IVF embryos before they are transferred to the woman's uterus.

The indication for monogenic PGTM includes couples with or without infertility, at risk of transmitting autosomal dominant, autosomal recessive and X-linked monogenic disorders. 'PGT-A' is performed to screen for chromosomal aneuploidies in order to improve success rates, and PGT-SR is performed to identify structural chromosomal abnormalities. There is now excellent evidence that they are safe and accurate. Ever since it was introduced in 1990 (Handyside et al., 1990; Verlinsky et al., 1990), the

number of indications for PGT has increased steadily, as has the number of couples requesting PGT. In 2015, it was estimated that >16,000 children were born using PGT (no current figures are available).

However, PGT is a long and complex process that combines IVF techniques with DNA testing. The overall clinical pregnancy rate for monogenic PGT (European Society of Human Reproduction and Embryology [ESHRE] data from 61 centres) is 35% per embryo transfer (van Montfoort et al., 2021).

Seven main steps are involved:

1. The couple has a 'genetic workup' to determine the best method for embryo testing. This may involve a family genetic study using a method called karyomapping, a technique used to test embryonic cells for genetic mutations using genetic markers within the genome to assess the likelihood of an embryo carrying a gene mutation. Karyomapping uses genome-wide linkage-based analysis of single-nucleotide polymorphisms and can detect if the region containing the mutation has been inherited in the embryo (Wang et al., 2019). This method circumvents the need for locus-specific preclinical genetic workup, therefore reducing the workload and waiting time for couples.

2. The woman undergoes controlled ovarian stimulation. This results in multifollicular growth and the suppression of ovulation.

3. Approximately 36/37 hours before the egg collection, a one-off injection of hCG is given, when three or more follicles measure >18 mm. Under sedation, the ovarian follicles are aspirated under transvaginal ultrasound control via a needle passed through the vaginal wall. Eggs are identified within the follicular aspirate.

4. A sperm sample is provided by the man. The eggs are fertilised using intracytoplasmic sperm injection (ICSI), to prevent paternal contamination from excess sperm lodged in the zona pellucida (Harton et al., 2011). Only mature eggs can be injected by ICSI.

5. Eggs using polar body biopsy (although rarely carried out) or embryos are biopsied at day 3 (blastomere biopsy) or at 5–6 days (trophectoderm biopsy) after fertilisation. The trophectoderm biopsied embryos are cryopreserved to provide sufficient time for genetic analysis (Cohen et al., 2012).

6. Embryos that do not have a thalassaemia gene disorder are identified by DNA testing of the embryonic cells or polar body.

7. One or two unaffected embryos are transferred into the woman's uterus either in the stimulated cycle or a subsequent cycle if embryos are frozen. Guidance from the Human Fertilisation and Embryology Authority (HFEA) states that embryos can remain in storage for up to 55 years (HFEA, 2023). The chance of successful thaw is not affected by the duration of storage. Current guidelines allow transfer of a maximum of two embryos in women aged <40 years (HFEA, 2021).

A pregnancy test is carried out 14–16 days after embryo transfer. The likelihood of becoming pregnant is strongly linked to the age of the woman being treated. On average, a woman aged 18–34 years of age is more likely to conceive than an older woman.

Misdiagnosis after PGT is complex and difficult to identify: however, there is agreement on an overall misdiagnosis rate of 0.14–0.27% after embryo transfer (Harper et al., 2012; De Rycke et al., 2015). All women who become pregnant following PGT should be offered PND by CVS.

A cycle may need to be cancelled due to understimulation of the ovaries, or overstimulation that may lead to ovarian hyperstimulation syndrome. On occasion, there may be no suitable embryos to transfer as some may not have been fertilised, some may have not survived the biopsy procedure or all embryos may be affected.

Couples should avoid unprotected intercourse before the procedure and afterwards until the outcome of the procedure is known, to avoid the risk of a natural conception and the risk of an undiagnosed affected child.

The treating haematologist should be involved in the management plan with the IVF team. If the woman has a thalassemia disorder, then the haematologist should review the suitability of the woman to undergo IVF treatment, including a review of the chelation regimen, when iron chelation treatment and other medication should stop prior to the procedure, optimal transfusion therapy during treatment, a cardiology review, liver assessment and the requirement for thromboprophylaxis during treatment.

Access

PGT is available at several centres in the UK. Current data available list 10 centres that carry out PGT on the NHS, two of which are located in London (Genetic Alliance UK, 2020).

At present, PGT is available on the NHS only to couples who meet the criteria in Table 10.1. Such couples are entitled to receive three complete cycles (NHS England, 2014). If

couples choose to have PGT and fall within the criteria for PGT funding, or are prepared to pay privately, they should be referred for PGT. The access criteria have been under review by NHSE.

Table 10.1: Access criteria for PGT on the NHS

Access criteria
The couple is at risk of having a child with a serious genetic condition
The risk of conceiving a pregnancy affected by a serious genetic condition should be ≥10%
The couple has been referred to the PGT provider by an NHS Clinical Genetics Service
The couple has received genetic counselling from a clinical geneticist or a registered genetic counsellor
The female partner is aged <40 years at the time of treatment
There is no living unaffected child from the current relationship
The female partner has a BMI of >19 and <30 (but can be referred if she undertakes to lose weight)
Both partners are non-smokers or undertake to stop smoking
The HFEA has licensed the indication for PGT. Licence is already in place for beta thalassaemia, alpha thalassaemia and HbE/beta thalassaemia
The test is included in the list of UK Genetic Testing Network-approved tests, or suitable for inclusion
The couple must not be seeking PGT primarily because they are infertile, although it is recognised that individuals with thalassaemia disorders may have to be treated for infertility

It is possible to HLA-test unaffected embryos for compatibility with an existing affected child; however, HLA testing is not included in the NHS criteria for PGT funding. It requires a specific application to NHS England, including evidence from the treating paediatric haematologist and the PGT centre. The process may be drawn out and the application may not be successful.

Which couples should be referred for PGT?

- At-risk couples who wish to avoid the risk of having an affected child, but would not consider termination of an affected pregnancy.
- Couples undergoing fertility assessments: couples who have been referred for IVF, or if the male partner has been referred for ICSI, may be suitable candidates for PGT.
- Couples where one partner has a thalassaemia disorder (or has had a successful bone marrow transplant for thalassaemia) and the other is a healthy carrier. These couples are at 50% risk of an affected child in every pregnancy. In such couples, it is essential to store DNA before the transplant so this can be used for the PGT 'genetic workup'.
- Couples at risk of more than one diagnosable genetic disorder. The chance of being at risk of two disorders is highest for couples who are close blood relatives. One in 10 related couples at risk of thalassaemia is also at risk of another recessive disorder. Such couples have a 43.75% risk of having a child with one disorder and a 6.25% risk of a child with two disorders.
- Counselling for related couples at risk of thalassaemia should include a basic family history designed to identify other possible genetic disorders in the extended family. If any potential disorder is identified, the couple should be referred to a clinical genetic service for expert assessment of additional risk, including DNA testing when this is feasible.
- Both partners need to stop smoking as smoking has been shown to reduce the chances of conceiving, and cut down on alcohol consumption to <2 units/week as excessive alcohol consumption can decrease sperm production and reduce motility. Women who conceive should stop consuming alcohol.

Evidence base

The ESHRE PGT Consortium has been collecting data from international PGT centres since 1997. Yearly data collections are published from approximately 60 centres offering PGT worldwide. This data collection is an extremely valuable resource for monitoring the accuracy, reliability, effectiveness and safety of PGT. For more technical details about PGT, readers are referred to Dahdouh et al. (2015) and Konstantinidis et al. (2015).

A summary of the first 10 years of international data collection (1997–2007) showed that 17% of 27,000 cycles that reached oocyte retrieval were at risk of single-gene disorders. The commonest indication was for Hb disorders: 530 PGT cycles were for beta thalassaemia and sickle cell disorders, and 170 cycles for beta thalassaemia and HLA selection. The overall pregnancy rate was 23% per oocyte retrieval and 29% per embryo transfer (Harper et al., 2012). However, the proportion of successful embryo diagnoses

is rising (De Rycke et al., 2015), as is the proportion of successful pregnancies. The current clinical pregnancy rate reported by the ESHRE for monogenic PGT is 35% per embryo transfer (van Montfoort et al., 2021).

The rate of referral for PGT is steadily increasing (Harper et al., 2012) and there is continuous improvement in available DNA diagnostic techniques (Konstantinidis et al., 2015; Lathi et al., 2012; Thornhill et al., 2015). There has been improvement in pregnancy rates of up to 63% of live births per embryo transfer with trophectoderm biopsy, vitrification of blastocysts and transfer in a subsequent normal cycle (Lathi et al., 2012,). Approximately 5–10% of pregnancies achieved in this way will result in a miscarriage.

Currently, the Centre of Reproductive and Genetic Health in London, where a significant number of PGT cases for single-gene disorders are managed, has excellent success rates. For haemoglobinopathies, the live birth rate per embryo transfer is 55.9% (UK Forum on Haemoglobin Disorders Conference 18.05.2022). The improved clinical outcomes are most likely due to the implementation of trophectoderm biopsy and frozen embryo transfer.

Requirements

- All at-risk couples should be referred to a genetic specialist or genetic counsellor, with expertise in the genetic aspects of the Hb disorders and prevention, to ensure the couple fully understand the risk of having an affected child, and the benefits and limitations of available options for PGT and PND.
- DNA testing should be carried out on both partners to identify the beta-globin gene mutations and to assess genotype–phenotype correlations.
- The couple should be referred for PGT if they choose, and if they fulfil the criteria in Table 10.1 or elect to pay for private treatment.
- Couples opting for PND should be given the contact details of the PND centre so they can self-refer as soon as a pregnancy is recognised, or the genetic counsellor should refer immediately on their behalf.
- If the woman chooses to terminate an affected pregnancy following PND, this should be carried out within 5 days of the woman receiving the results.

Recommendations

Couples seeking PGT should be advised that:

- A cycle may need to be cancelled due to understimulation of the ovaries, or overstimulation that may lead to ovarian hyperstimulation syndrome, or that

there may be no suitable embryos to transfer as some may not have been fertilised, some may have not survived the biopsy procedure or all embryos may be affected.

- They should avoid unprotected intercourse before the procedure and afterwards until the outcome of the procedure is known, to avoid the risk of an undiagnosed affected child.
- All women who become pregnant following PGT should be offered PND to confirm the results of PGT, because the techniques used for PGT have technical limitations including the possibility of a misdiagnosis.

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Chapter 11

Management of Pregnancy

"Early pregnancy was a scary time for my family and I as we didn't know whether I and the baby would have been well enough. But fortunately for me my team knew exactly what to expect and were involved in every stage which really put me at ease and I delivered a healthy, gorgeous baby boy. I am grateful for them. "

Aims

To optimise iron chelation from infancy; this will reduce the likelihood of infertility. This is a primary aim for the younger patient.

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

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

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

Standards

- Patients contemplating pregnancy will be assessed for possible risks to themselves and their babies; this evaluation should be updated as needed.
- At any time the patient wishes, they should be referred to a fertility/endocrine/assisted conception clinic with experience of thalassemia patients, to allow discussion about treatment options; culturally appropriate advocacy will inform these discussions.
- Pregnant patients will be jointly managed during pregnancy and delivery by a 'maternal medicine' obstetrician experienced with Hb disorders and by their haematologist.

Background

Many people with TDT who are well managed from childhood remain naturally fertile; however, older patients may be subfertile (58% of those aged <30 years, 68% of those aged between 30 and 40 years, and 75% of those aged >40 years) (Ang et al., 2014). Some may need specialist evaluation and, where appropriate, fertility induction treatment.

Fertility in thalassaemia can be reduced due to HH, which develops due to iron toxicity in the pituitary and hypothalamus. HH used to be a frequent complication in iron-overloaded patients with thalassaemia; however, incidence has fallen in recent years with better chelation therapy (Belhoul et al., 2013). Diabetes and hypothyroidism can also impair fertility. Building a family is a key concern for many patients and their extended families, and they greatly value discussion with a specialist who is able to explain the options and realistic likelihood of success, minimising unrealistic expectations and consequent psychological and emotional problems.

Patients with TDT who have undergone bone marrow transplantation for thalassaemia will commonly be infertile. Although they may be ‘cured’ from the condition clinically, it is essential for them to understand that they still have, and will pass on to any children, their thalassaemia globin genes. Partner testing and counselling is essential before fertility treatment is undertaken.

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

Patients with NTDT will have mild to moderate degrees of anaemia that can pose significant challenges during pregnancy. Patients may also have pre-existing iron overload that can vary between mild (in the majority of patients with alpha NTDT) or severe (beta NTDT). The severity of the anaemia can affect both fetal growth and maternal health during pregnancy (Origa et al., 2007, 2010). Transfusions initiated during pregnancy may be associated with an increased risk of alloimmunisation (Roumi et al., 2017; Voskaridou et al., 2014).

Other challenges common to both TDT and NTDT thalassaemia are the increased thrombotic risk in splenectomised patients, and the presence of skeletal deformities that may increase the risk of fetal complications during labour, as well as maternal risk of fractures due to osteoporosis (Taher et al., 2010, 2006; Chan et al., 2002; Poggi et al., 2016; Inati et al., 2015). Management of pregnancy in thalassaemia syndromes therefore requires a multidisciplinary approach to ensure successful outcomes.

Increased risks during pregnancy principally relate to:

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

For the baby, issues include:

- The possibility of having a major Hb disorder, depending on the globin genotype of the other parent.
- If the mother has diabetes, there is a fourfold increased risk of fetal anomaly and a threefold increase in perinatal mortality (NICE, 2015).
- If ovulation induction results in a multiple pregnancy, there is increased risk of premature delivery, growth restriction and disability in the infants.

Careful assessment of patients considering pregnancy should be undertaken, ensuring that cardiac iron status and function are sufficiently good to manage the extra demands of pregnancy, and that other possible complications are detected and optimally managed.

A full review of medication is necessary, ensuring patients remain on necessary medications including penicillin in splenectomised patients, thyroxine if needed, medications to ensure glycaemic control and vitamin D supplements if there is any deficiency. Vitamin D is needed for fetal bone development and to avoid neonatal rickets, as well as for the expectant mother. Any potentially teratogenic medications must be discontinued, including angiotensin-converting enzyme inhibitors, bisphosphonates and oral chelating agents.

Folic acid 5 mg daily should be started 3 months prior to planned conception and, if not, started as soon as possible after a positive pregnancy test. This needs to be continued throughout pregnancy (De-Regil et al., 2015; Lam and Tang, 1999).

Oral chelation regimens should be switched to DFO ideally 6–12 weeks prior to planned conception. Both DFP and DFX have shown some reproductive toxicity in animal studies (SPC); however, case reports of spontaneous pregnancies in patients with thalassaemia have not shown any maternal or fetal toxicity. Termination of pregnancy is not required

and chelation should be stopped as soon as a pregnancy is confirmed (Ahmad et al., 2019; Diamantidis et al., 2016; Anastasi et al., 2011)

Most patients with NTDT are fertile and will have no thalassaemia-related complications impacting their ability to conceive. However, in patients who become pregnant there is a possibility that they will need blood transfusion during pregnancy or delivery. Their RBC genotype and phenotype should be documented and reviewed, as well as any previous antibodies that may increase the risk of transfusion-related complications during pregnancy (Voskaridou et al., 2014; Origa et al., 2010, 2017; Origa and Comitini 2019).

Recent guidelines on the management of conception and pregnancy in thalassaemia syndromes should be referred to for more comprehensive details on the management of patients (Shah et al., 2023).

Table 11.1: Preconception optimisation patients with TDT and NTDT, modified from British Society for Standards in Haematology guidelines on the management of conception and pregnancy in thalassaemia syndromes (Shah et al., 2023)

Aspect of care	Investigations/ management	Aim	References	Quality and grade
Genetic counselling	Partner screening and patient genotype PGT or PND for appropriate couples		National screening standards	1B
Fertility unit assessment	Evaluation of both patient and partner, including tubal patency, sperm count, hormonal assessment		Standard practice	1B
Iron chelation	Optimise chelation regimen Change chelation regimen to avoid DFP or DFX within 3 months of planned conception	SF ~1000 µg/L	Borgna-Pignatti & Marsella, 2015; Di Maggio and Maggio, 2017; Singer and Vichinsky, 1999; Saliba et al., 2016	1B

Transfusion	Increased RBC requirement in patients with TDT Consider transfusion in patients with NTDT; ensure extended RBC phenotype or genotype before transfusion Rh- and Kell-matched units should be used in patients with TDT and NTDT	Target Hb 100 g/L during pregnancy	(Origa 2017, 2019; Taher, 2014)	1B
Cardiac	Electrocardiogram, echocardiogram, 24-hour Holter monitor, cardiac T2*, cardiology review	Cardiac T2* >20 msec, LVEF <56%	Carlberg et al., 2018 Yardumian et al., 2016	1B
Liver	SF levels, liver R2 or T2*, liver ultrasound (gallstones and fatty liver, especially in thalassaemia intermedia)	LIC <7 mg/g	Royal College of Obstetricians and Gynaecologists Green-top Guideline 66	1B
Infection	HBV and HCV, HIV, especially in TI, hepatitis B antibody titre in vaccinated patients Ensure splenectomised patients are fully vaccinated		Standard practice Green book	1B

Endocrine	OGTT, fructosamine, thyroid function, DXA, vitamin D, adrenal function; ensure adequate calcium and vitamin D intake	Fructosamine< 300 nmol/L for >3 months prior to conception	Royal College of Obstetricians and Gynaecologists Green-top Guideline 66; Barnard and Tzoulis, 2013	1B
Medication	Cessation of bisphosphonates, angiotensin-converting enzyme inhibitors; commence 5 mg folic acid; ensure patients on DFO are taking vitamin C; splenectomised patients should have penicillin V prophylaxis and initiate aspirin		Royal College of Obstetricians and Gynaecologists Green-top Guideline 66	1B

Antenatal care should follow NICE guidance (NG201), with general and thalassaemia-specific management delivered by an MDT including an obstetrician, midwife and a haematologist linked to a special haemoglobinopathy team.

Physiological plasma volume expansion in pregnancy exacerbates anaemia leading to increasing transfusion requirements in patients with TDT, and initiation of transfusion in late pregnancy in some patients with NTDT (Tongsong et al., 2009; Voskaridou et al., 2014; Nassar et al., 2008).

For patients with TDT, the pretransfusion Hb level should be maintained >100 g/L to avoid maternal and fetal morbidity. Severe maternal anaemia affects placental function and predisposes to fetal growth restriction, low birthweight and preterm birth (Origa et al., 2010; Tongsong et al., 2009).

For patients with NTDT, the indications for transfusion are primarily based on maternal tolerance of anaemia and fetal development. If there is symptomatic anaemia or evidence of fetal growth restriction at any time point in the pregnancy, then top-up transfusions should be offered with the aim of maintaining pretransfusion Hb at >10g/L. If a patient is tolerant of the anaemia and fetal growth is progressing without concerns, then a plan should be formulated at around 36 weeks gestation. If the Hb level is >80 g/L at 36 weeks then delivery can be planned with a possible risk of transfusion if the Hb level drops during labour or postnatally. If the Hb levels is <80 g/L at 36 weeks

gestation then transfusion should be offered to the patient at around 37/38 weeks. All patients with NTDT should have crossmatched blood available at the time of admission to the labour ward if they have not been transfused regularly during pregnancy.

Plans for transfusion should be clearly documented in the clinical notes of the patient and antenatal records.

Thrombosis risk is increased in patients with thalassaemia, with the highest risk in splenectomised women with NTDT and those with high platelet counts (Panigrahi and Agarwal, 2007; Taher et al., 2008). Thrombosis risk assessment for all patients with thalassaemia should occur at booking, 28 weeks gestation, and during any admissions including delivery and postpartum. Low-molecular-weight heparin (LMWH) should be given to patients as per local VTE guidelines and NICE recommendations.

Patients with cardiac iron overload are at increased risk of complications due to the absence of chelation in the first trimester. If a patient has cardiac iron overload, a joint decision should be made between the cardiology and haematology teams as to the optimal time to initiate chelation. There is experience of safe use of DFO from 20 weeks gestation onwards. Should a pregnant patient develop cardiac decompensation then DFO iron chelation should be started immediately, regardless of gestation, as this is a lifesaving intervention.

Schedule of antenatal care

- Aspirin prophylaxis with 75–150 mg at night is recommended from around 12 weeks (Rolnik et al., 2017; Hoffman et al., 2020) as the risk of pregnancy-induced hypertension and pre-eclampsia is increased in thalassaemia syndromes (Lao, 2017). Consideration should be given to stopping at 36 weeks as there may be a risk of postpartum haemorrhage (Hastie et al., 2021).
- Assisted conception patients should have an early viability scan as miscarriage and fetal loss rates are high (Nassar et al., 2006).
- Third trimester growth scans should be performed for early detection of growth restriction to allow planned transfusion and appropriate timing of delivery, to reduce perinatal morbidity and mortality.
- Pregnant patients with thalassaemia should be reviewed monthly until 28 weeks gestation and fortnightly thereafter. The MDT should provide routine as well as specialist antenatal care.
- Pregnant patients with TDT require specialist cardiac assessment at 28 weeks gestation and thereafter as appropriate.

- Monitor thyroid function in hypothyroid pregnant patients with thalassaemia as thyroxine requirements increase during pregnancy.
- Monitor monthly serum fructosamine in patients with thalassaemia who are pregnant and have diabetes.
- Splenectomised patients with a platelet count >600 × 10^9/L should be offered LMWH thromboprophylaxis in addition to low-dose aspirin 75–150 mg daily.
- Consider LMWH thromboprophylaxis from 28 weeks gestation to 6 weeks postpartum, or throughout pregnancy if additional risk factors are present.
- All pregnant patients with thalassaemia require LMWH during hospital admissions.
- Pregnant patients with myocardial iron loading need a first trimester specialist cardiology review, and imaging for assessment of iron burden and cardiac function.
- Patients with no myocardial iron loading should be assessed at 28 weeks gestation to formulate a delivery plan based on cardiology advice.
- Patients presenting with palpitations should be assessed for arrhythmias.

Peripartum and postpartum care

Most patients with thalassaemia should have uncomplicated pregnancies if preconception optimisation is well managed. For delivery, local and national guidelines should be followed (NICE NG207, 2021; NICE NG121, 2019).

Patients with TDT should be receive a DFO infusion (2000 mg over 24 hours subcutaneously or intravenously) on admission to the labour ward to reduce circulating toxic NTBI, which can cause free radical damage and cardiac dysrhythmia during the stress of labour. Patients should expect to have a normal vaginal delivery unless there are maternal or fetal indications for caesarean section. Continuous intrapartum fetal heart rate monitoring is recommended during labour and delivery.

After delivery, patient Hb levels should be checked and, for patients with TDT, a top-up transfusion undertaken to ensure that the Hb level is >120 g/L at discharge.
Routine postnatal care should follow national guidance (NICE NG194, 2021). Breast feeding should be encouraged as DFO is not orally absorbed. Patients with thalassaemia are at high risk of VTE, particularly splenectomised patients with NTDT. Patients who have been splenectomised should receive LMWH for 6 weeks postpartum.

Patients should expect to continue with DFO infusion for the duration of the hospital stay after delivery. If breast feeding is to be continued, patients need to be prescribed DFO infusion subcutaneously on 5 days/week at 40–50 mg/kg/day for as long as breastfeeding is undertaken. Once a patient stops breastfeeding they can safely switch to oral iron chelation or combination therapy if indicated.

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Chapter 12

Transition from Paediatric to Adult Services

"No decision about me, without me"

"Every patient should be as actively involved in making decisions about their health and healthcare as they wish to be"

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

Aims

To prepare and support young people with a long-term condition regarding their health, educational and psychosocial needs when moving from paediatric to adult services through:

- A flexible but planned process to equip the young person with the skills and knowledge to navigate the adult healthcare system.
- Education and support of the young person to foster independence, self-management and empowerment.
- Ongoing engagement with adult health services to optimise health outcomes and wellbeing.

Standards

- Young people should be supported to take responsibility for their health needs and choices. Education should be given to the young person and their parents or carers over time, to nurture and empower independence.

- Each young person requires a named/key worker for transition. The transition process should commence by age 12–14 years; this is dependent on development stages.
- Adult and paediatric teams will work collaboratively with the young person and their parents or carers to provide a timely and smooth handover. Primary, secondary and tertiary healthcare providers and community teams should be involved in the process, and in the young person's ongoing care.
- Any anxieties that the young person and their parent(s) or carer(s) may have, arising from the change from paediatric to adult health services, should be addressed.
- Psychosocial stresses that may negatively impact on adherence with their transfusion regimen, medication and/or self-care should be identified and managed.
- Close monitoring of thalassaemia treatment should continue over the transition period, with particular attention to the monitoring of iron stores and adherence to iron chelation therapy.
- Use of a recognised health transition framework, such as 'Ready Steady Go Hello', may be utilised to support the transition pathway protocols.
- A structured approach should be used to support the young person and their family to facilitate their transition journey in a gradual way.

Background

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

The process, should be flexible in meeting a level of standardisation whilst being specifically tailored to individual needs, and should incorporate the following.

- Preparation of the young person and their family through education, support and communication about thalassaemia, its management and potential complications.
- Communication with both the young person and their parents or carers, together and independently, to gather their views, concerns and aspirations and to address these.

- Introductions to and familiarisation with adult staff and facilities.
- Transfer to the adult team, and ongoing education, support and communication with the young person within the adult services.

Transition occurs at a time when patients are already affected by change; a time of physical, biological, developmental and psychosocial changes due to adolescence occurring in the young person's life. As far as possible, all efforts must be made to ensure that there is engagement with the young person and their family throughout the process, and that the process proceeds at a rate that is appropriate for the needs and maturity of the young person (Yacobovich and Tamary, 2014). Although the family is usually the main source of support to young people, especially for those with long-term conditions, it is important to acknowledge the wishes and expectations of both the young person and their parents/carers, which may differ, and to offer peer support as well. Cultural sensitivities should also be considered and managed in a respectful manner.

In addition to the usual young person's concerns regarding independence, self-image, peer acceptance, emotional and sexual maturation, career, family and employment prospects, the young person with thalassaemia also must manage their health needs: transfusion, chelation, multiple hospital attendances and possible complications of the condition, such as iron overload, delayed puberty due to HH and/or bone thinning (Department of Health, 2012).

Growing up with thalassaemia, and particularly leaving familiar paediatric healthcare providers, can have a major psychological effect on young people, causing feelings of apprehension, anxiety and abandonment, unless well managed (Bryant et al., 2011; Musallam et al., 2008). These feelings may have a negative impact on subsequent engagement with adult healthcare services, treatment adherence and hospital attendance. Thus, the transition process requires time, commitment and resources from professionals to facilitate an effective transition pathway, and to achieve best outcomes (Department of Health, 2006; National Alliance to Advance Adolescent Health, 2020). Transitional care must be flexible and developmentally appropriate to meet the varying needs of young people with thalassaemia (Viner, 1999).

Teenagers and young adults with thalassaemia are particularly at risk of serious disease complications due to iron overload. This is because the toxic effects of progressive iron accumulation often present clinically in this age range, and also because adherence to iron chelation therapy is often compromised when young people begin to take responsibility for their own treatment. Young people can often focus more on social and psychological challenges rather than their long-term

health condition. Ensuring that transfusion iron loading remains within an acceptable range can also present a challenge to the thalassaemia care team, who need to find ways of supporting the young person to continue with effective chelation.

Transition for all young people with long-term conditions to adult services has been highlighted in the UK as an area requiring improvement (Bryant et al., 2011; Care Quality Commission, 2014; Department of Health, 2011). Recently published NICE guidance recommends the involvement of health and social care managers and commissioners in the development and delivery of transition pathways (NICE, 2016).

Requirements

- Transition planning should take account of the young person's maturity and developmental stage, and may start from 12 years onwards. For young people who join the service later than age 12 years, the transition process should be commenced immediately.
- A named/key worker to support the young person and their parent(s) or carer(s) is required in both paediatric and adult settings. The worker may be their specialist nurse, a youth worker or their paediatrician, who will provide support, education and continuity until the young person is settled and confident within the adult services.
- Transition should be a dynamic, interactive process involving the young person and their family, with the transfer of care presented in a positive manner rather than an inevitable, undesirable event. All efforts must be made to listen to and address any concerns raised by the young person and/or their family.
- A transition plan should be created with input from the young person and their parents or carers that describes the transition process, and its purpose, and introduces the key worker for transition who should be well known to the young person and their family or carers.
- An assessment of the young person's understanding of their condition, potential complications and their medication should be undertaken, and also an assessment of their confidence/maturity and their readiness to move to adult services.
- The young person should be given the opportunity – and encouraged – to speak with clinicians in the absence of their parents, if they so choose.
- In addition to explaining and providing information about their condition, the key worker should also be able to signpost young people to voluntary, charity and

community sector services who can provide support and information about thalassaemia, such as the UKTS, and other services that provide information about careers, finance, relationships, and emotional and sexual health.

- The named worker can also help the young person to understand the roles and responsibilities of the primary, community, secondary adult and paediatric tertiary health services, and how to navigate the different services.
- The young person with their key worker should be introduced to the adult team, through a joint appointment with both adult and paediatric teams in either the paediatric or adult setting, or through a transition clinic. Introductions to other team members, such as the staff of the day unit or ward where the young person will receive blood transfusions and a clinical psychologist (if attached to the team), are also valuable.
- SHCs should have transition guidelines and information about transition in place, which should be shared with their local hospitals and other centres within the network. If the young person with thalassaemia is transfused at a local clinic or LHT, it is important that robust links are made in the same way so that blood transfusions can continue seamlessly when moving from paediatric to adult services.
- Peer support is invaluable during the transition process. Opportunities to meet with other young people with thalassaemia should be provided, through facilitated support groups at the centre if patient numbers and geography allow.
- Psychosocial support through individual or group meetings is also valuable in promoting confidence, wellbeing, communication skills and healthy independence.
- Summary information regarding the young person's health – including any complications, medication and test results – should be prepared and discussed with the young person, to form the basis of a transfer summary for the adult team. The young person should also receive a copy of the transfer summary.
- The transition plan should be reviewed regularly to assess progress in terms of their understanding of their condition, ability to communicate with professionals, maturity and readiness for transfer.
- Transfer to adult services should occur when the young person is adequately prepared and ready to leave paediatrics; the age can vary between Trusts from the age of 16–18 years and flexibility is encouraged where possible.
- The named/key worker should attend the adult clinic with the young person for the first appointment if possible, and continue to support the young person for a defined period following transfer of their care to adult services. A minimum of 6 months is recommended.

- All efforts should be made to make the young person feel comfortable and welcomed into the adult services, both in the outpatient setting and in the unit where they will be receiving blood transfusions.
- An adult equivalent named/key worker – who may be a specialist nurse, youth worker or a haematologist – will continue the transition process, providing support and education through other significant 'transitions', such as moving onto college, university or the workplace. As they reach adulthood, the young person may leave the family home, so will require advice and support on independent living, such as managing financial affairs, student life, housing and relationships, whilst still attending for blood transfusions, managing their regular medications and attending outpatient appointments.
- Delivery of thalassaemia care – including convenient and flexible access to transfusions, monitoring of iron stores, adjustment of chelation therapy considering adverse effects, efficacy and tolerability, and evaluation of treatment adherence – must be robust and organised to ensure continuity during the transition pathway and to avoid loss of follow-up.
- It is particularly important for services to audit outcomes in young people to continually improve services.
- Feedback from patients is also essential to improve future patient experiences and quality of care.

Recommendations

- Throughout transition, the young person should be treated in age-appropriate facilities and, where possible, be seen as an outpatient and attend day-care settings with other similarly aged patients.
- The concept of transition to adult services and allocation of a key worker, preferably a clinical nurse specialist, should be introduced early on to allow adequate preparation, adjustment, education and readiness to move on to adult services. Guidance, support, openness and information sharing with the young person, and their parents or carers, are key.
- Information provided about transition, thalassaemia, and other aspects of adolescence and adulthood should be age-appropriate, and be delivered in a convenient format for the young person, such as written/digital materials, email, text messaging and/or signposting to useful websites.
- Routine involvement with psychology specialists during adolescence, and especially during transition, is ideal. This can familiarise the young person and their family with the service, and provides professional support to the young person if they are struggling with the challenges associated with both adolescence and living with thalassaemia.

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

https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Services/Child-health/Ready-Steady-Go/NHS-Ask-three-questions.pdf

https://www.byc.org.uk/uk/nhs-youth-forum/youth-rights-in-healthcare#:~:text=All%20young%20people%20have%20a,they%20have%20in%20healthcare%20settings

https://www.readysteadygo.net/rsg.html

The UK's leading charity for children and young people's mental health:
https://youngminds.org.uk/

The UK's leading support service for young people:
https://www.themix.org.uk/

An online mental wellbeing community:
https://www.kooth.com/

Catch it
Learn how to manage anxiety or depression:
https://www.nhs.uk/apps-library/catch-it/

Thrive
Helps you prevent and manage stress and anxiety:
https://www.nhs.uk/apps-library/thrive/

Calm
The #1 App for Meditation and Sleep:
https://www.calm.com/

Chapter 13

Acute Clinical Presentations of the Unwell Patient

Aims

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

To enable timely escalation and transfer, where appropriate, for specialist management.

To optimise outcomes for patients who become acutely ill.

Standards

- HCCs will have network responsibility for:
    a. Agreeing regional escalation pathways for the management of acute/emergency complications.
    b. Coordinating regional training for SHTs and LHTs.
    c. Supporting the development of locally agreed clinical guidelines.
    d. Facilitating access to urgent advice.
- SHTs will:
    a. Offer education about thalassaemia-specific acute presentations to patients and healthcare professionals, including emergency department and primary care colleagues, with details of how to access specialist advice and agree pathways for shared care with local teams and patients, with guidance on how to access urgent clinical advice.
    b. Patients presenting with acute clinical problems will be assessed with consideration given to the range of thalassaemia-specific complications they might develop.
    c. Appropriate management should be instituted as quickly as possible and all cases escalated for specialist haematology input.

Background

The majority of medical management of thalassaemia takes place in the outpatient clinic and day unit. Staff, patients and the parents of children with thalassaemia need to be aware of thalassaemia-related health risks. Patients and parents should have access to their health records, and be aware of their diagnoses and relevant test results.

Recommendations

- Healthcare professionals responsible for managing acutely unwell patients should be aware of the spectrum of acute complications in thalassaemia, and consider whether thalassaemia could explain the presentation.
- Network-agreed clinical guidelines should be in place detailing management of acute complications in children and adults with thalassaemia.
- The patient should be discussed with the SHT as soon as possible to ensure escalation and, if appropriate, transfer.
- All patients should be referred for follow-up with the SHT after discharge; plans for follow-up at the SHT should be communicated clearly to all teams and the patient to minimise delays.
- Any adverse events arising from acute presentations should be reviewed at local morbidity and mortality meetings, and at the next HCC MDT.
- Serious adverse events should be registered on the NHR.

Part A: Early Recognition of the Acutely Unwell Patient

Patients with thalassaemia often have complex care needs, acute presentations are uncommon and expertise among healthcare providers will vary. Patients may present as acutely unwell or decompensate rapidly. They therefore need prompt assessment and management, and will often need admission to hospital. Early consultation with the specialist team will be important to support acute/emergency management, agree a treatment plan and establish the level of care required. If transfer is required, the level of priority established and optimum timescales for transfer should be agreed.

Multidisciplinary and high-dependency support may be required, e.g., input from cardiology and management on a coronary care unit.

One requirement of SHTs is to educate staff in emergency departments, acute assessment units and primary care to allow the cascading of knowledge, the means to access specialist advice to be known and recognition of the role of the 'expert patient'.

Acute presentations may be of a general medical or surgical nature, coincident with the diagnosis of thalassaemia, but there are also specific clinical presentations that occur more frequently in thalassaemia and can result in rapid clinical deterioration with associated morbidity and mortality, if not recognised and treated promptly. A history of severe iron overload and poor compliance with chelation therapy is obviously a risk factor for iron overload-related complications, especially cardiac failure and arrhythmia, but other factors also play a role. Where possible, these patients may be 'flagged' to alert clinical teams of the possibility of thalassaemia-related presentations.

Some examples of acute presentations in thalassaemia are:

- cardiac failure and cardiac arrhythmias
- sepsis, including post-splenectomy, with a different profile of organisms
- VTE, including line-related, atypical site and unprovoked
- osteoporotic fracture
- spinal cord compression after fracture or from extramedullary haematopoiesis
- endocrine dysfunction, including diabetes, thyroid, calcium and adrenal
- gallstones and cholangiopathy
- renal stones, renal colic and urosepsis
- acute chronic liver decompensation: cirrhosis or concurrent viral hepatitis.

The questions to cover in assessing an acutely ill thalassaemia patient are listed in Table 13.1. The use of these in conjunction with local Trust policies (e.g., antibiotic policies, Sepsis Six, transfusion policies and VTE assessments) should facilitate early diagnosis and relevant care.

Table 13.1: Assessment of the acutely unwell patient, examples of specific acute presentations (see also the relevant chapters on specific complications)

Key questions	Consider	Remember
What is the transfusion history?	Is the patient on a regular transfusion programme, intermittently transfused or not transfused? When was the last transfusion? Are the symptoms compatible with a transfusion reaction?	Baseline Hb/pretransfusion Hb Alloantibodies Transfusion reactions including delayed transfusion reaction, hyperhaemolysis syndrome, bacterial TTI, transfusion-transmitted acute lung injury, fluid overload, anaphylactic reactions
Is there an indwelling venous device?	Sepsis: local or systemic? VTE?	Check when line last accessed Any anticoagulation: is this therapeutic?

Any features of sepsis? **(NB Sepsis Six: consider as immune-compromised patient cohort)**	Does the patient have an indwelling line? Has the patient had splenectomy and, if so, has appropriate post-splenectomy infection prophylaxis been continued? Is the patient chelating with DFP and, if so, has neutrophil count been checked to exclude agranulocytosis? Is the patient chelating with DFO and, if so, are the clinical features compatible with *Yersinia* or *Klebsiella* sepsis? Also consider gallstones, central nervous system sepsis, urinary tract infection, endocarditis, acute COVID-19 infection	*Klebsiella* and *Yersinia* sepsis more common in iron-loaded patients; may include meningitis, cerebral abscess, urinary tract infection *Yersinia enterocolitica* may mimic appendicitis Malaria if relevant travel
Has the patient had a splenectomy and are they up to date with their vaccinations?	Sepsis VTE	Pneumococcal, meningococcal and haemophilus infections risk Local antibiotic resistance patterns Risk of VTE, especially in NTDT

What drugs are used for iron chelation?	Drug side effects	DFP: neutropenia and agranulocytosis DFX: renal and liver toxicity, upper gastrointestinal ulceration and haemorrhage, acquired Fanconi's syndrome (acute renal tubular damage) DFO: sepsis with *Yersinia* or *Klebsiella*, mucormycosis (See Chapter 6 and product SPCs for full range of possible adverse effects]

What is the degree of iron overload: is this patient at risk of cardiac iron? **Any history of palpitations?** **Any history of liver disease?**	Trends in ferritins Recent MRI results: cardiac T2*, liver iron Cardiac drugs – angiotensin-converting enzyme inhibitor, amiodarone, digoxin	Highest risk of cardiac failure seen when Cardiac T2* <10 msec Those with previous cardiac iron may still develop arrhythmias T-wave abnormalities are common in patients with thalassaemia and non-specific Other symptoms and signs should be used to support a diagnosis of ischaemic cardiac complications Liver disease may be advanced if the patient also has hepatitis, or a history of poor iron chelation over a prolonged period or alcohol excess
Is the patient diabetic? What is their control like?	Hypo-/hyperglycaemia?	Review fructosamine to consider control; if this is not available, the HbA1c level can be used but this is diluted with blood transfusion and may mask poor control
Is there any other endocrine complication, treated or undiagnosed?	Hypocalcaemia, hypothyroidism hypoparathyroidism, AI, undiagnosed diabetes	May impair cardiac function/rhythm Adrenal function presentation may be subacute manifesting with acute stress

Could thalassaemia explain acute pain?	Wide range of complications including gallstones, renal stones, fracture, pancreatitis, pulmonary embolism	Use wider history to focus on underlying cause

Table 13.2: Acute symptoms and important pathologies to consider

Key questions	Consider	Remember
Acute breathlessness?	Assess for pneumonia, congestive cardiac failure, pulmonary embolism, sepsis, acidosis, severe anaemia	Blood pressure may normally be low in these patients, check previous records
Acute abdominal pain?	Gallstones, biliary tract sepsis Renal stones (hypercalciuria) Hepatic congestion from congestive cardiac failure? *Yersinia* infection NTDT post-splenectomy, VTE? Portal vein thrombosis, mesenteric infarction Pancreatitis	Review medical pathologies prior to any surgical intervention Pancreatitis ± gallstones NB Measure splenomegaly: compare with baseline, consider splenic infarcts Consider ultrasound, abdomen computed tomography, MRI/magnetic resonance cholangiopancreatography

Acute back pain?	On treatment for osteoporosis? Recent DXA results: risk of osteoporotic fracture? At risk of extramedullary haematopoiesis (e.g., NTDT, undertransfused patient with TDT)?	Confirm any history of trauma Assess for spinal cord compression, e.g., weakness, paraesthesia, bladder control; urgent spine MRI should be undertaken if suspected
Acute neurological presentation?	Any features of sepsis: consider specific infections above Leg weakness, bladder or bowel dysfunction Extramedullary haematopoiesis with spinal cord compression Acute ischaemic stroke	Neuroimaging, blood and cerebrospinal fluid cultures where indicated Urgent spine MRI if any possibility
Acute anaemia?	Baseline Hb, transfusion history? Any intercurrent illness, fevers, diet issues? G6PD status?	Parvovirus (and, if considered possible, any other family members with thalassaemia should have review/Hb check) Folate deficiency

Part B: Specific Acute Complications

Acute back pain/spinal cord compression

Osteopenia and osteoporosis are seen commonly in thalassaemia, frequently as a result of multifactorial aetiologies, and are usually defined by DXA scanning. Minor trauma may lead to fracture and a low threshold for imaging is recommended.

Extramedullary haematopoiesis, typically paraspinal, can be seen, especially in undertransfused patients with TM or NTDT. This can present with acute neurological symptoms, back pain, referred pain, bladder or bowel dysfunction, and spinal cord compression. Urgent investigation with MRI is required and urgent discussion with the Specialist Centre is recommended. Transfusion, with or without hydroxycarbamide, can lead to rapid resolution of symptoms and is preferred to DXT for most patients, except where there is spinal cord compression. Rarely, surgical decompression may be necessary (Taher et al., 2010).

Anaemia

Review of a patient's transfusion history is important to distinguish those with TDT or with NTDT. Rarely, patients on a regular programme present for urgent transfusion away from their local centre if they have missed their regular appointments. In any patient with recent transfusion with acute unexplained anaemia, a delayed transfusion reaction must be considered, although this would usually be accompanied by jaundice. Any intercurrent illness such as parvovirus may disproportionately affect the anaemia in thalassaemia.

In patients with NTDT, worsening anaemia may be due to sepsis, pregnancy, folate deficiency, G6PD deficiency and, if the presentation is not to the patient's usual centre, their baseline haematology results should be sought and the presentation discussed with the specialist team, as transfusion may or may not be necessary.

Bone marrow transplant patients

Any acute presentation in a patient who has undergone allogeneic bone marrow transplantation should be discussed immediately with the transplant centre. Complications can include sepsis, GvHD, veno-occlusive disease, steroid-induced diabetes and metabolic disturbances.

Cardiac

Patients with cardiac iron (highest risk when MRI T2* <10 msec) can present acutely with cardiac arrhythmias (e.g., atrial fibrillation [AF], ventricular dysrhythmias, heart block) and heart failure. They can present in ways that are not typical (e.g., reduced appetite/early satiety, abdominal pain with hepatic congestion) and at ages when health professionals unfamiliar with thalassaemia may not expect to see such cases. Those with previous cardiac iron may still present years later with arrhythmias, typically atrial. Without a comprehensive assessment, the severity of a patient's presentation or risk may be underestimated. The electrocardiogram (ECG) and echocardiogram changes may be non-specific or subtle, and the LVEF can appear to be preserved, but it should be remembered that well patients with thalassaemia have ejection fractions of 63–75% and findings should be used in conjunction with the patient's clinical history and MRI results. Concurrent infection can be a precipitant as can other factors, e.g., hypocalcaemia, hypothyroidism, uncontrolled diabetes and pulmonary embolism. Pericarditis may be a less common presentation.

Management should include discussion with a cardiologist experienced in managing thalassaemia, and care in an appropriate setting, e.g., high-dependency/intensive-therapy or coronary care unit. There must be discussion with the SHC, and consideration of transfer when clinically stable. Blood pressure support should be targeted to clinical measures of renal and cerebral perfusion, and care with diuresis is needed to avoid precipitating prerenal acute kidney injury. Intensification of chelation should be started immediately, usually with a combination of DFO (50–60 mg/kg/day, continuous intravenous infusion) and oral DFP (75–100 mg/kg in three divided doses).

Endocrine

Diabetes mellitus is a common complication seen in thalassaemia, with incidence increased in those with a first-degree relative with type 2 diabetes. Acute and chronic complications of diabetes (e.g., hyperglycaemia, hypoglycaemia, nephropathy) may be seen. Although OGTTs form part of the regular monitoring for complications, patients may present with previously undiagnosed diabetes.

Calcium metabolism abnormalities may be seen (hypocalcaemia, hypocalcaemia tetany) and review of vitamin D level, bone profile, PTH, arterial blood gas and renal losses is required. Resistant chronic hypocalcaemia may impair cardiac function and input from the SHT's endocrine and renal teams should be considered.

Thyroid abnormalities are seen, with iron overload-related hypothyroidism typically presenting with insidious symptoms or identified through routine monitoring tests. Less commonly, a patient may present after taking inappropriate doses of levothyroxine (e.g., poor compliance or self-medicating with higher doses than advised).

Gallstones and renal stones

Both are seen more frequently in thalassaemia and standard assessments should be initiated. Renal stones are a particular problem in older patients, with an incidence of around 10%. If the patient is symptomatic or has an unexpected decline in renal function, with or without symptoms, a renal tract ultrasound to look for hydronephrosis should be undertaken as a matter of urgency. If hydronephrosis is found, it should be managed as a matter of urgency with urology and interventional radiology input.

Any surgical interventions should be planned with the Specialist Centre, with detailed consideration of all thalassaemia-related issues as described in **Chapter 14: Management of Surgery**.

Liver

Transfused patients are at risk of TTI. If a patient presents with jaundice, possibilities also include haemolytic transfusion reaction or gallstone obstruction. The history and symptoms and signs, as well as laboratory investigations – including alkaline phosphatase, OGGT, direct antiglobulin test, reticulocytes, blood film and RBC antibody screen – should help differentiate between the two. Some patients with thalassaemia have advanced liver disease, typically related to iron overload, with or without TTI. There may be features of cirrhosis, and such patients are at risk of acute hepatic decompensation and variceal bleeds. Details of the care plan should be urgently confirmed and input from the liver team experienced in thalassaemia sought. If a patient is accepted for liver transplant, hepatitis E virus (HEV)-negative blood products should be given. Urgent transfer to the regional liver unit should be discussed with the SHT.

Sepsis

Patients presenting with features of acute sepsis require urgent assessment and resuscitation in line with the ‘Sepsis Six’ interventions. Suitable laboratory samples such as blood cultures (peripherally and from any indwelling venous access device), viral swabs, stool and urine cultures should be obtained. Antibiotics must be promptly

administered depending on the possible site of infection and suspected organism, in line with local patterns of resistance and hospital antibiotic policies, within 1 hour of presentation. These should cover any identified relevant risk (e.g., line-related infection and features of focal risk such as *Klebsiella*, *Yersinia* and malaria).

Some thalassemia patients, particularly those with severe iron overload, can present with non-specific symptoms and no fever, or only low-grade fever. It is important to monitor these patients very carefully as a rising white blood cell count and elevated C-reactive protein level may be the only indication of sepsis. Iron chelation with DFO must be paused, especially when infection with *Yersinia* or *Klebsiella* is suspected. Patients on DFP or DFX should be assessed on a case-by-case basis, and treatment continued only where the benefits of ongoing therapy outweigh the risks. Specific pathogens are discussed in Part C of this chapter.

Venous thromboembolism

Some patients may be on therapeutic anticoagulation (e.g., those with indwelling lines or previous VTE), and should have compliance reviewed at presentation, although thrombi can occur even if the patient is anticoagulated. For others, there is an increased risk of VTE, particularly in patients with NTDT following splenectomy, so as with any clinical presentation raising suspicion of deep-vein thrombosis, pulmonary embolism or unusual site (e.g., portal vein thrombosis), therapeutic anticoagulation should be considered whilst arranging diagnostic tests. Please refer to Part D of this chapter for more information.

Part C: Specific Infections in Thalassaemia

Standards

- All patients should receive prompt resuscitation and antibiotics should be started within national sepsis and local antibiotic guidelines.
- DFO should be temporarily discontinued during the acute sepsis episode.

Background

Infection is a leading cause of mortality in patients with thalassaemia. Factors associated with increased risk of infectious complications include therapy-related factors such as splenectomy, transfusions and iron overload; disease-related factors such as anaemia, ineffective erythropoiesis and neutrophil function; and comorbidities

such as poorly controlled diabetes. Clinicians managing patients with thalassaemia should be aware of commonly implicated infectious foci and organisms, and of the potential for rapid deterioration in patients presenting with infection. Acute infection may be the precipitant for deterioration in high-risk patients with cardiac iron overload or diabetes. Patients who are immunocompromised, such as those who are post-bone marrow or solid organ transplant, need special consideration depending on the time from transplant, immunosuppressive medications and transplant complications.

Viral aetiologies

Human parvovirus B19

Human parvovirus B19 infection can present as a flu-like illness. RBC aplasia may develop due to direct cytotoxicity on erythroid precursors that temporarily suppresses erythropoiesis, resulting in severe anaemia. The presentation is with reticulocytopenia usually <1%, beginning about 5 days after exposure and lasting 7–10 days, and anaemia (more severe than normal) develops shortly after reticulocytopenia resulting in an increased transfusion requirement. The diagnosis is confirmed by raised parvovirus IgM levels and/or parvovirus DNA detection during the acute phase of infection. Recovery is accompanied by outpouring of nucleated RBCs and reticulocytosis. Family members with major haemoglobinopathies should also be screened.

Transfusion-transmitted infections

The acute phase of infection is similar to that in other patient groups. The commonest TTIs in the UK include HBV, HCV, HEV and HIV, but the risks are low. Patients who receive transfusions abroad who present with fever should be screened for a wider range of pathogens such as malaria. There are other less common pathogens to consider (e.g., dengue virus).

COVID-19

Patients with thalassaemia, and risk factors such as severe liver or cardiac iron overload and other comorbidities, may be eligible for COVID-19-directed therapies as per national guidance. However, one registry study showed that patients with both TDT and NTDT who developed COVID-19 infection had lower overall all-cause mortality and fewer in-hospital complications compared with age-matched controls.

Bacterial and other infections

The most commonly reported sites of infection are the lungs (pneumonia) and the hepatobiliary and soft tissues. Other possible sites of infection are indwelling central venous access devices (CVADs), leg ulcers and meningitis in asplenic patients with NTDT who may have distorted sinuses due to extramedullary haematopoiesis.

The organisms most often isolated are *Klebsiella pneumoniae*, *Escherichia coli*, *Streptococcus pneumoniae*, *Salmonella typhi* and *Yersinia enterocolitica*. The pathogenicity of these organisms is increased in the presence of iron overload. Certain organisms utilise DFO as a siderophore to increase their virulence, and temporary interruption of DFO must be considered in acutely unwell septic patients. The evidence for oral iron chelators is less clear; other factors to consider would be renal function and neutropenia.

Yersinia enterocolita infections may manifest as fever, abdominal pain and enterocolitis that can mimic appendicitis. Other clinical presentations are tonsillitis and polyarthritis. Severe systemic infection may develop in patients with thalassemia leading to significant morbidity.

Asplenic patients are at risk of developing overwhelming post-splenectomy infections, such as meningitis, pneumonia and sepsis. Implicated organisms are encapsulated bacteria (*Streptococcus pneumonia*, *Haemophilus influenzae* type B and *Neisseria meningitidis*). Other pathogens responsible for post-splenectomy infections include *Escherichia coli*, *Pseudomonas aeruginosa*, group B streptococci and *Enterococcus* spp.

Malaria should be considered for patients returning from travel to a malaria-endemic region. The treatment is similar to that for other patient groups. Fungal infections are uncommon and are mostly seen in the transplant setting.

Recommendations

- Clinicians must be made aware of the potential life-threatening nature of infections in patients with thalassaemia.
- Vaccinations must be discussed with patients as part of the annual review. Patients must be educated about the presenting signs and symptoms of infection.

Part D: Hypercoagulability and Thrombosis

Aims

To identify risk factors for thrombosis in thalassemia.

To guide clinicians on the role of anticoagulation in the prevention and management of VTE.

Standards

- Clinicians should assess thalassemia-related thrombotic risk factors in addition to other conventional risk factors to optimise thromboprophylaxis in these patients.
- An indwelling central venous catheter (CVC) should be considered a risk factor for thrombosis.

Background

Thromboembolism is well described in patients with thalassemia. The presence of a high incidence of thromboembolic events, mainly in beta thalassemia intermedia, has led to the description of a hypercoagulable state (Musallam and Taher, 2011; Taher et al., 2019). Possible aetiologies for thromboembolism in beta thalassemia include exposure of phosphatidylserine on abnormal RBCs, increases in platelet activation and aggregation, elevation of endothelial microparticles, increased endothelial activation, decreased NO secondary to haemolysis, thrombocytosis and an increase of nucleated RBCs after splenectomy, and organ dysfunction caused by iron overload (Natesirinilkul, 2020; Taher et al., 2019). Deficiencies of protein C and protein S, the natural anticoagulant proteins, have also been reported as risk factors of thromboembolism in patients with beta thalassemia (Natesirinilkul, 2020).

Prevalence and sites of venous thromboembolism

The incidence of thromboembolic events is not well established; one study of 8860 patients with beta thalassemia described an overall thrombotic rate of 1.65%, with rates of 0.9% and 4% in for patients with TDT and NTDT, respectively. Most patients with NTDT had venous thrombosis (66%), whilst arterial events were seen more commonly in patients with TDT (Taher et al., 2006). Data from a multicentre study

conducted in Italy on survival and causes of death in patients with TM indicated VTE as a complication in 1.1% of patients with TDT (Borgna-Pignatti et al., 2004). An observational study from Italy reported that 4% of 683 patients with TDT and 9.6% of 52 patients with NTDT had experienced a thrombotic event (Borgna-Pignatti et al., 1998; Saliba and Taher, 2016). In another cohort of 83 splenectomised patients with NTDT, 29% experienced a venous thrombotic event over a 10-year follow-up period (Cappellini et al., 2000; Saliba and Taher, 2016).

The common sites for VTE include deep venous thrombosis, stroke, pulmonary embolism, portal vein thrombosis, cerebral veins and CVC thrombosis in those who have indwelling catheters. Arterial events are less common and can present as thrombotic strokes, transient ischaemic events or myocardial infarcts (Panigrahi and Agarwal, 2007).

The thalassemia-related thrombosis risk scoring system

A thalassemia-related thrombosis risk scoring system (TRT-RSS) was introduced in 2019 (Taher et al., 2019) that aims to predict first thrombotic events in patients without prior incidents, and provides long-term (>10 years) risk assessment considering the chronic, lifelong nature of the disease (see Table 13.3).

Advancing age, splenectomy, chronic anaemia of <90 g/dL in patients with TDT, iron overload and NTDT are known independent risk factors for the development of thrombosis. This risk scoring should be evaluated at the moment of decision-making to assess the contribution of thalassemia to thrombosis risk, and should be interpreted in the context of other conventional risk factors to determine management decisions for patients. The thrombosis risk factor scoring process can identify aspects of clinical care for optimisation, such as improving anaemia, intensifying chelation, initiating a regular transfusion programme and reducing thrombosis risk.

Table 13.3: The TRT-RSS

Risk factor at time of assessment	Score
Age >35 years	2.5
Hb level <9 g/dL	2.5
SF level ≥1000 µg/L	2.0
Not regularly transfused	3.5
Splenectomised	6.5
TRT-RSS total score minimum	0.0
TRT-RSS total score maximum	17.0

Managing thrombosis risk in patients with a central venous catheter

An indwelling CVAD (CVC) is sometimes necessary to facilitate regular RBC transfusions or iron chelation for a subpopulation of patients with thalassaemia. Most of the evidence comes from patients with sickle cell disease; there is limited evidence on CVC-related thrombosis in thalassemia.

There is a paucity of data on catheter-associated thrombosis in patients with thalassaemia that is limited to two small case series. Davis and Porter (2000) and Miskin et al. (2003) reported that 8 out of 25 catheters were linked to catheter-associated VTE, and that 4 out of 7 patients were affected with incidence of 0.48 and 0.41 VTE events per 1000 catheter days, respectively. Data on children with thalassaemia are even more limited. Since 2000, the 3rd edition of the Thalassaemia International Federation (TIF) guidelines has recommended the use of prophylactic anticoagulation in patients with TM, as line thrombosis is relatively common.

Treatment of thrombosis and future plans for indwelling catheters

The treatment of CVC-associated thrombosis in patients with thalassaemia should follow principles described for other patient groups (Citla Sridhar et al., 2020; Geerts, 2014), as there are insufficient data for this specific patient group regarding choice of anticoagulants. Anecdotally, direct oral anticoagulants have been used; however, this is an unlicensed indication (the treatment course is usually 3–6 months). For all patients, a detailed bleeding risk assessment should be conducted to identify risk factors that can help in selecting the appropriate anticoagulant drug, consider what

may be a safe dose for initial and extended treatment, and the optimal treatment duration; there are no validated bleeding risk assessment tools for patients with thalassaemia.

Indications for line removal with a CVC-associated thrombus are associated infection, non-functioning CVC or progressive symptoms despite anticoagulation. The decision to remove a CVC should be discussed with the patient first. There are rare anecdotal reports of line removal provoking embolism.

Recommendations

- Thromboprophylaxis should be considered for all patients with thalassaemia aged >16 years (or those post-pubertal) with CVCs, balancing the patient's individual risk of VTE versus their risk of bleeding. This risk assessment should follow the NICE VTE guidelines (NICE 2023) noting contraindications or unacceptable bleeding risks.
- An individual risk assessment should be performed for prepubescent patients with thalassaemia.
- In the context of CVC-associated VTE, CVC lines should only be removed if they are infected, non-functional or if there are progressive symptoms despite anticoagulation.
- If a CVC is removed, the patient should complete a minimum of 3 months of anticoagulation, then consider ongoing therapy based on their relative thrombotic and bleeding risk factors.
- If the line remains in situ, the patient should continue anticoagulation for this period.
- Repeat imaging may be considered after 6–12 weeks, to ensure no thrombus progression.
- Advancing age, splenectomy, iron overload and long-term anaemia of <90 g/dL in patients with TDT and NTDT are known risk factors for VTE. Optimising both thalassemia and non-thalassemia risk factors is important to prevent and manage VTE.
- Patients identified to be at highest risk on their TRT-RSS should have their thalassemia care optimised to further reduce the risk of thrombosis.

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Chapter 14

Management of Surgery

Aims

To optimise outcomes for the patient with thalassaemia requiring surgery and to minimise associated risks.

To plan elective surgical procedures in a timely manner, with involvement of perioperative specialists, to allow optimisation of the thalassaemia-related health of the patient at the time of surgery.

To facilitate close working relationships between surgical, anaesthetic and paediatric/haematology teams around the time of any elective or urgent surgery.

To ensure the risk of perioperative complications related to thalassaemia are considered by all the clinical teams involved and by the patient/parent giving consent.

Standards

- All patients listed for elective surgery should undergo an assessment of risk related to the planned procedure, taking their underlying thalassaemia and comorbidities into consideration. Any discussions should involve patients/parents in shared decision-making and make specific reference to cardiac, thrombotic, endocrine and metabolic disturbances.
- All patients undergoing major surgery should undergo a review by an anaesthetist with a specialist interest in perioperative assessment and optimisation.
- Patients undergoing urgent surgery should be discussed with the SHT and escalated to the thalassaemia HCCs as required.
- Patients listed for planned surgical procedures can be referred to the thalassaemia HCC MDT for preoperative discussion if deemed to be high risk or to require specific input. All splenectomy cases should be discussed and referred to the NHP in line with referral guidelines (NHP, 2020).

- Patients should be given access to all relevant information regarding thalassaemia-specific and anticipated issues related to surgery to allow for informed consent.

Background

Preoperative assessment

Surgical procedures are more frequently required in people with thalassaemia. This may relate to a complication of their thalassaemia condition, its treatment or an unrelated diagnosis. All patients should have a clear understanding of the indication for, benefits of and risks involved with the surgery procedure planned. Patients on long-term transfusion (TDT) and those with NTDT may have significant medical issues, often related to iron overload, that can affect the outcomes of surgery. Surgery should be planned collaboratively between the specialist surgical team, the SHT and the LHT. Some complex cases may require discussion with the regional thalassaemia HCC and local procedures should be in place to facilitate urgent referrals if required.

There is also increasing recognition that surgical outcomes are improved by preoperative optimisation. Optimisation of known thalassaemia complications, such as those relating to iron overload, will be relevant and should be discussed with patients as part of shared decision-making. This may not be possible in emergency surgery, but should be taken into consideration among the wider MDT prior to any planned elective procedures. An assessment of thrombotic risk is also important and should consider the patient's splenectomy status, previous history of thrombosis and presence of indwelling lines. For patients currently taking anticoagulation medication, this should be acknowledged and managed in line with local guidance.

There are robust national guidelines on how patients listed for surgery should be risk assessed in terms of the anticipated surgical outcome (Centre for Perioperative Care, 2021). Risk assessment tools, such as the Surgical Outcome Risk Tool (SORT), take several factors into account, such as the grade according to the American Society of Anaesthesiologists (ASA) classification system, which was developed to take a patient's physiological status into account when considering surgical risk (Knuf et al., 2018). Although this assessment is subjective, it is likely that patients with TDT would be classified as at least ASA grade 3, which is defined as severe systemic disease, and those with additional comorbidities such as cardiovascular disease may be classified as even higher risk.

In line with national guidance, all hospitals should have provisions in place to provide appropriate perioperative assessment of patients undergoing elective and emergency

surgical procedures. Any preoperative evaluation of risk should take all comorbidities into consideration, with diabetes, endocrine disease, anaemia and cardiac arrhythmias specifically highlighted. Airway assessment is also important and may be relevant if orofacial malformations are present or previous dental procedures have caused changes to the orofacial anatomy. The use of long-term opioid medication for chronic pain is also recognised as requiring specific attention as it can lead to complex postoperative pain management. Occasionally, patients may require a functional capacity assessment to judge their fitness for elective surgery, which may involve formal cardiopulmonary exercise testing. Such decisions will be taken by specialist anaesthetists, but close liaison with haematology teams is important to take thalassaemia into consideration. It is also important to ensure patients are involved throughout the process to enable them to be fully informed in any decision-making.

Specific issues

Transfusion

Blood transfusion for patients with TDT should be planned around elective surgery to allow surgery to be undertaken with an optimal Hb level (100–120 g/L). Special blood requirements should be communicated well in advance to the surgical unit's transfusion laboratory; this applies to patients with TDT and with NTDT. Any alloimmunisation issues should be highlighted and managed in advance. For emergency situations, any transfusion support should be considered in line with the patient's clinical condition and local transfusion policy, after discussion with the SHT.

In considering transfusion for the NTDT patient, the risks and benefits of elective preoperative transfusion should be assessed with the SHT. Preoperative transfusion may be considered for specific procedures, particularly if the patient is splenectomised and has a high nucleated RBC count. In these patients, there is some evidence that a period of hypertransfusion prior to a surgical procedure may reduce the thrombotic risk (Chen et al., 1996; Musallam et al., 2013; Taher et al., 2006).

Endocrine

Diabetes is widely recognised as a risk factor for prolonged postoperative length of stay and higher rates of adverse postoperative outcomes (Sampson et al., 2007). This is irrespective of other medical conditions such as thalassaemia. There are therefore clear national guidelines on how diabetes should be managed perioperatively and this should form part of the preoperative assessment and optimisation (Centre for Perioperative Care, 2021). Other endocrine complications should be tested for if no recent routine monitoring results are available. Thyroid function and serum calcium

levels should be normalised. If not already performed, patients with TDT should be screened for subclinical adrenocortical deficiency, which could manifest clinically during surgery. Where possible, specialist endocrinology input should be requested to advise on the possible need for surgical replacement therapy to cover the procedure. In the case of emergency surgery, deficiency should be assumed if no recent results are available and replacement therapy with hydrocortisone should be given perioperatively.

Cardiac

Where possible, cardiac and liver iron should be optimised preoperatively to reduce the risks of perioperative complications. Those with a history of iron loading and previous organ dysfunction should have this evaluated as part of their preoperative assessment. For patients with current evidence of severe cardiac and/or liver iron loading, the risk of perioperative decompensation is potentially high, and all cases should be discussed with the thalassaemia HCC for advice on further management. For urgent surgery, continuous intravenous DFO at 50–60 mg/kg should be considered during the perioperative period. In all cases, anaesthetic and surgical teams should carefully maintain the fluid and electrolyte balance, and monitor for cardiac arrhythmias.

Yersinia infection

Patients with iron overload who are being chelated with DFO are at risk of *Yersinia* infection, which can present with acute abdominal symptoms that may mimic acute appendicitis. The treatment for this is appropriate antibiotics, but patients should be reviewed by surgeons to ensure that there is no surgical sequelae of infection such as perforation of the bowel.

Splenectomy

The use of splenectomy to decrease transfusion need in patients with TDT has decreased from 57% in the 1960s to 7% in the 1990s (Piga et al., 2011), and likely further still because of appropriate transfusion from early childhood. It is sometimes indicated for those with splenomegaly with a high transfusion requirement of >200–220 mL RBCs/kg/year (Rebulla and Modell, 1991). In patients with NTDT the spleen is often enlarged, and splenectomy is sometimes used to increase the total Hb level by 10–20 g/L and avoid the need for transfusion. Routine splenectomy is not recommended because of the long-term risks of sepsis, thrombosis, PHT and enhanced iron loading. In lower-income countries where reliable blood supply may not

be available, splenectomy may be useful for patients with NTDT to reduce their need for transfusions. Splenectomy can either be performed with an open or laparoscopic approach, with the latter possibly preferred, if clinically available, because of a shorter recovery time.

When discussing splenectomy with a patient, the generic risks of surgery should be outlined in addition to the specific risks of post-splenectomy infection and the increased risk of thrombosis. Individuals with thalassaemia have an increased risk of thrombosis in the periprocedural period, partly because of the increased platelet count and prothrombotic thalassaemia cells (Taher et al., 2010). Therefore, a perioperative and postoperative thromboprophylaxis plan should be discussed and documented in the patient's notes. Extended prophylaxis should be considered as well as aspirin for those who have a platelet count of $>500\times10^9$, and possibly continued if this persists.

For elective splenectomies, patients should be vaccinated and this should be completed ≥2 weeks before the procedure. The vaccine schedule is outlined in Chapter 7 of the UK Health Security Agency (2020) guidelines. This should be documented in the patient's notes and a vaccination record given to the patient.

Patients should also be offered lifelong prophylactic antibiotics with oral penicillin (or macrolide if allergic/intolerant), mainly to reduce the risk of severe pneumococcal infection, and they should be taken regularly, especially during childhood. However, it is recognised that adherence can be poor and so we suggest that patients have access to a treatment dose of antibiotics such as penicillin V 500 mg twice daily/amoxicillin 500 mg three times daily, or if penicillin-allergic erythromycin 500 mg twice daily, at home should they develop a fever. Patients should be counselled on when and how to use these antibiotics, and if symptoms do not improve or their temperature is >38 °C then patients should be advised to seek urgent medical attention, ideally with letters explaining the need for empirical broad-spectrum antibiotics in line with local antibiotic protocol/ microbiology advice.

Patients should be offered a post-splenectomy card to alert medical professionals to the risk of severe infection; they may wish to buy an alert pendant or bracelet. They should be informed about the procedure and post-procedural risks, and the risks of overseas travel, especially regarding malaria and tropical infection.

Cholecystectomy

Cholecystectomy is recommended if there is a history of complications related to gallstones such as biliary colic, cholecystitis, cholangitis, gallstone-related pancreatitis or biliary obstruction. This can be via the laparoscopic route. It is generally not

recommended for asymptomatic gallstones but may be considered if the patient is having a splenectomy. If indicated, the laparoscopic approach may be preferred.

Orthopaedic surgery

Patients with thalassemia are at increased risk of developing osteoporosis, putting them at risk of needing elective or urgent surgery, including large joint replacement. Any surgical cases should be managed in line with the recommendations above.

Thrombotic risk and management of anticoagulation

As previously discussed, splenectomy is a specific indication for the consideration and documentation of thromboprophylaxis. However, it is recommended that thrombotic risk is assessed in all patients with thalassaemia undergoing surgery in line with local guidance. If there are concerns about additional thrombotic risk factors then they should be taken into consideration reflecting the surgical procedure involved.

In addition, patients on long-term anticoagulation should have a clear plan for perioperative management of their anticoagulation, taking the bleeding risk of the procedure into consideration. This should be carried out in line with local management guidelines and escalated to SHTs if there are any specific concerns.

Requirements

- All patients undergoing planned surgery should have a clear management plan that includes input from surgical, anaesthetic and haematology teams. This should include a preoperative risk assessment related to the planned procedure, taking their underlying thalassaemia and comorbidities into consideration. Any discussions should involve patients/parents in shared decision-making and make specific reference to cardiac, thrombotic, endocrine and metabolic disturbances.
- All patients should have an individualised risk assessment for thrombosis and be appropriately managed to reduce the risk.
- It is preferable that surgery be undertaken at a centre with an SHT. If this cannot be facilitated, there should be clear communication with the specialist team and this should be escalated to the HCC if there are any concerns.
- If there appears to be an acute surgical problem, medical pathologies that could explain the presentation should be excluded prior to surgery.

- Urgent surgical intervention should be undertaken without undue delay, but close liaison with the LHT should occur to reduce the risk of adverse outcomes.
- Blood transfusion support should be planned with input from the SHT.
- All patients undergoing splenectomy should be discussed with the HCCs and escalated to the NHP.

Recommendations

- All staff involved in the care of the patient should have access to relevant and recent correspondence, including information relating to medical history, current medication and investigation results before any procedure is undertaken, even in the event of urgent treatment.
- Patients with cardiac iron overload should be reviewed by the named cardiologist at the SHT and have a clear management plan for any elective procedure.
- Patients should give informed consent for surgery and be aware of the potential risks and benefits.
- Long-term risks of surgical procedures, such as infection and thrombosis, should be clearly discussed and explained at the time of consent.
- Information at discharge should be shared with the patient, SHT and primary care.
- Outcomes of surgery, including any adverse events should be discussed locally and escalated to the HCC MDT for the purpose of learning, and to highlight if any changes to clinical pathways are required.

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SECTION C: Prevention and Management of Complications

Chapter 15

Management of the Cardiovascular System

"Getting iron out of the heart can be one of the most difficult and scariest parts of having thalassaemia. It is important for us patients to realise this as early as possible as its easier to prevent by taking chelation. I allowed iron to build up and damage my heart and it has never been the same again."

Aims

To guide clinicians and patients with thalassaemia on strategies to prevent cardiovascular complications arising through their thalassaemia, or through the consequences of medical interventions used to treat it, especially blood transfusion.

To guide clinicians and patients with thalassaemia on the use of appropriate monitoring to detect cardiovascular complications prior to the development of symptoms, or damage to the heart and circulatory system.

To illustrate the limitations of current clinical approaches in preventing every manifestation of cardiovascular dysfunction in this group of individuals.

To promote awareness of other risk factors that may impact on cardiovascular health, such as diabetes and poor lifestyle habits, including smoking and sedentary living.

Standards

- Every patient must have access to a cardiology service with experience in the management of cardiac consequences of thalassaemia.

- Children should be referred for their first cardiac evaluation – including clinical assessment, ECG, echocardiogram and CMR T2* – between the ages of 6 and 8 years, dependent on their ability to do breath holds for the scan.
- Cardiology assessments thereafter should be at intervals guided by symptoms, adequacy of chelation and the findings of previous assessments.
- A high-risk time for the development of cardiac problems is 16–25 years of age, and during this period assessments should be undertaken at least yearly.
- Patients with myocardial iron and LV impairment with new-onset symptoms must be discussed with the SHT, and reviewed urgently for consideration of inpatient intensive chelation.
- Patients must be considered for anticoagulation if they have indwelling venous lines or AF, including paroxysmal AF.

Background

Pathophysiology of the heart and circulation in thalassaemia

The heart and circulation are affected by the consequences of the ineffective erythropoiesis that characterises the thalassaemia genotype. The characteristics of cardiovascular effects are determined by the severity of the beta-globin gene mutation, by the coinheritance of other genetic modulators, and by the type and intensity of treatment, including blood transfusion and iron chelation.

Chronic anaemia and the cardiovascular system

Severe anaemia affects individuals with thalassaemia not receiving regular transfusion, but even with regular blood transfusions chronic anaemia of variable severity persists. Physiological responses to anaemia in the healthy person with thalassaemia lead to a chronic hyperdynamic circulation, characterised by an increased cardiac output, reduced peripheral vascular resistance due to vasodilatation and resultant low blood pressure. Cardiac chamber dilatation is common, so that parameters of cardiac size on chest X-ray, echocardiography and MRI scanning are larger than for an age-matched population. Measures of cardiac function often have higher values than for an aged-matched non-anaemic population. In anaemias of other causes an increased resting heart rate is to be expected, but in thalassaemia, normal or relatively low heart rates are common, and are associated with reduced heart rate variability that probably represents disordered autonomic function, which is not well characterised.

Important consequences of these physiological adaptations are that physicians and cardiac departments with little experience interpreting data from this group of patients may imply disease where there is none (an 'enlarged heart'). Conversely, and more worryingly, they may report 'normal' values, which are inappropriate for the thalassaemia population. An important example is the LVEF. Values of 60% are frequently assumed to be normal in non-thalassaemia populations, but may represent dysfunction in this group of patients; the lower limit for LVEF in patients with TM, using MRI scanning, is approximately 63% (Pennel et al., 2013). LV end-diastolic dimensions on echocardiograms, and LV volumes and LV mass estimated by CMR or echocardiogram, are all increased in healthy patients with TM, although precise normal ranges are not available. Parameters should also be related to body size in this group of patients, many of whom are of smaller habitus than their peers.

Some of the age-related changes in cardiac function in this population may be the consequences of chronic anaemia. There is an increased incidence of ventricular diastolic dysfunction in the older population of patients with transfused TM, which may progress to features of heart failure with normal ejection fraction (known as heart failure with preserved ejection fraction). Increased sizes/volumes of the atria are commonly encountered, attributable to volume expansion in anaemia plus changes in LV compliance.

The increased shear forces associated with anaemia and a hyperdynamic circulation may account for remodelling of the arterial vessel walls, particularly in the large, compliance arteries. This may lead to abnormal vascular dynamics, which in turn exacerbate a tendency to develop LV diastolic dysfunction (Cheung et al., 2002).

Anaemia may account for some of the symptoms encountered in the population with TM. The symptoms are non-specific, consisting primarily of exercise limitation and breathlessness, but may cause confusion because of their similarity to the clinical presentation of cardiac failure.

Blood transfusion

Blood transfusion is essential for people with TM but inevitably leads to iron overload. Chelation therapy is required to deal with excess iron accumulation and is lifesaving in the context of tissue, and in particular cardiac iron load (Modell et al., 2008).

With regular transfusions from infancy, it is possible to detect iron in the heart from as early as 6 years of age (Wood et al., 2008; Berdoukas et al., 2013). Maintaining a good Hb level by transfusion will mitigate the profound ill effects of severe anaemia on growth and development, as well as the physiological consequences of anaemia discussed above (Shah et al., 2019).

Myocardial accumulation of iron through blood transfusion occurs once transferrin is fully saturated and is closely linked to the levels of NTBI in the blood. The heart has a significant buffering capacity for iron, but when this is exceeded the risk of deterioration in myocyte contractile function appears, culminating in the clinical syndrome of cardiac failure. This is systolic heart failure (heart failure with reduced ejection fraction) and carries a high risk of mortality if intensive, continuous iron chelation is not instituted urgently (Pennel et al., 2013).

It is uncommon for blood transfusion to cause volume overload problems for patients with TM, but in those with poor LVEF and in the older age groups with restrictive ventricular physiology, slower transfusion rates, limited-volume blood products and more frequent, smaller transfusions may be helpful. Occasionally loop diuretics (furosemide or bumetanide) may be given at the time of transfusion, but the potentially serious consequence of volume contraction needs to be avoided by careful clinical assessment.

Cardiovascular investigations

Clinical history and examination

The insidious development of cardiac dysfunction can be difficult to detect, as symptoms are frequently non-specific. Exercise limitation, breathlessness and exhaustion are all symptoms frequently associated with anaemia. Changes in status are generally the key and mandate investigation. Chest pain and palpitations are relatively common, and may not always relate to clinically significant pathology, cardiac dysfunction or iron overload, but require investigation.

There are no thalassaemia-specific cardiovascular features to be found on examination. However, it is common to encounter a low normal blood pressure, frequently with systolic blood pressure <100 mmHg and anaemia-associated, usually innocent, systolic murmurs at the base of the heart. Of particular importance is the appearance of changes in signs, particularly the development of indicators of cardiac failure or PHT. Clinical examination – including recording of pulse, blood pressure, oxygen saturation by pulse oximetry and cardiovascular findings – should be recorded at least at every annual review visit, or even more frequently as dictated by the clinical needs in cases of known cardiovascular involvement.

Electrocardiogram and ambulatory recording

A standard 12-lead ECG commonly shows non-specific abnormalities, particularly of repolarisation (non-specific T-wave changes), but these are of unclear significance if

longstanding. They are more common in patients with a history of severe iron overload, but are not a reliable indicator of current cardiovascular iron status. An early baseline ECG is important to enable changes across time to be identified. The frequency of surveillance ECGs is dependent on individual circumstances, but a minimum of once every 2 years for completely stable, non-iron-overloaded patients with TM is useful to detect subtle but uncommon developments, such as conduction disturbance, QT prolongation, ventricular hypertrophy or right ventricular (RV) overload. ECGs should be obtained at least annually for those with iron overload and an abnormal baseline ECG.

As intermittent arrhythmias will frequently be missed on a standard ECG, ambulatory recordings need to be considered. The standard 24-hr Holter monitor will miss many intermittent and potentially important abnormalities of rhythm and conduction. Longer-term monitoring – using Holter recorders, patient-activated recorders, adhesive patch ECGs and implantable loop recorders – need to be considered in individual cases. In this era of personal electronic devices, the use of smart phones or watches can be useful to explore intermittent symptoms in an economical and patient-orientated fashion.

There is no clear indication to embark on prospective arrhythmia surveillance in asymptomatic patients with TM, with the exception of those who have had a neurological or other possible embolic event, where silent AF must be excluded and anticoagulation strongly considered.

Echocardiography

Echocardiography is the most practical means of regular long-term monitoring of cardiac anatomy and function, and can be used for annual or more frequent follow-up. Despite not providing direct assessment of iron loading, it allows for readily available assessment of cardiac and pericardial structures.

The most frequently used parameter of ventricular function is the ejection fraction, although this parameter alone cannot fully describe cardiac function and is subject to significant interscan variation. More sophisticated measures of cardiac function, such as tissue Doppler imaging and global longitudinal strain, have demonstrated their usefulness in TM and other cardiomyopathies, achieving greater sensitivity and specificity, particularly for detecting minor changes in function. Global longitudinal strain in particular seems to be an efficient echocardiographic parameter that can detect hemochromatosis-related cardiac dysfunction earlier than LVEF. It is particularly important to identify these early changes in this patient group so that appropriate chelation treatment can be introduced.

Echocardiography remains the best method of detecting PHT and diastolic ventricular dysfunction, or restrictive physiology, and is of particular usefulness when valve disease is suspected.

It is imperative that cardiac departments undertaking surveillance testing are aware of the issues and importance of including objective assessments of cardiac function, so that these may be followed in the long term and subtle changes are not missed. Thus, the methodology of LVEF measurement should be standardised and it is important to discourage subjective visual estimates of function. Automated LVEF and the use of 3D and 4D volumetric assessment are all more likely to reduce interscan variability.

Table 15.1: Parameters for an adequate echocardiogram in patients with TM

Parameter	Comment	Essential (E) or desirable (D)
Chamber dimensions	LV end-diastolic and end systolic Left atrial diameter or area RV size	E
Ventricular systolic function (radial)	Systolic function by Biplane analysis, 4D analysis if possible Not a visual estimate	E
Ventricular diastolic function	E/E' plus other parameters	D
Tricuspid jet V_{max}	To detect PHT Preferable to calculate pulmonary arterial systolic pressure <2.5 m/sec is normal, >3.0 m/sec is abnormal No tricuspid regurgitation jet in many cases, generally means normal right heart pressures	E
Ventricular function (longitudinal)	Tricuspid annular plane systolic excursion, LV and RV Better by tissue Doppler imaging systolic myocardial velocity parameters	D
Strain imaging	Global longitudinal strain	D
3D volume analysis	3D volumes and derived ejection fraction improve accuracy of surveillance	D

Cardiac magnetic resonance imaging

The diagnosis of cardiac iron has been transformed since the introduction of the T2* CMR method (Anderson et al., 2001). This gold-standard diagnostic tool has replaced the need for biopsies and allows for accurate non-invasive assessment of cardiac and liver iron burden. It is a robust, reliable method and has been validated histologically (Carpenter et al., 2011).

T2* is one of the three fundamental tissue signal MRI rate constants. Cardiac iron levels are inversely related to myocardial T2* values. The most recent international expert consensus suggests eight equally spaced echo times ranging from 2 to 18 msec acquired on a 1.5T scanner for myocardial assessment (Messroghli et al., 2017). More artefacts are seen in T2* measured on 3T with lower reproducibility resulting in difficulty quantifying low T2* values with high tissue iron (Alam et al., 2016).

Although both bright-blood and black-blood techniques are validated and widely used, the black-blood method has superior reproducibility, less artefact susceptibility and is the preferred method to use clinically (Menacho et al., 2019).

T2* measurements are derived from a single, mid-ventricular short-axis slice and a homogenous region of interest encompassing the subepicardial and subendocardial regions, as iron is preferentially stored in the subepicardial layers. Values ≥20 msec indicate the absence of clinically important iron overload and carry the lowest risk, between 10–19 msec indicates mild to moderate cardiac iron but a relatively low risk of heart failure, and <10msec indicates severe iron overload with substantial risk of immediate cardiac complications. Heart failure risk rises from 14 to 30% within 1 year if values are 6–9 msec, and there is a 50% risk of heart failure within 1 year if <6 msec (Kirk et al., 2009). Although T2* is supported by long-term adoption, its inverse relationship with iron loading continues to cause confusion, particularly among patients and non-experts, so that a case for undertaking a simple conversion to iron loading to mg/g could be justified: T2* in msec to mg/g is 45/(T2*msec) (Carpenter et al., 2011).

Table 15.2: A grading scheme for assessing myocardial iron and guiding changes in chelation therapy

Risk of heart failure if untreated	T2* (msec)
No cardiac iron, low risk	≥20 msec
Mild to moderate cardiac iron, low risk	10–19 msec
Moderate risk	6–9 msec
High risk	<6 msec

In principle, elevated liver iron deposition according to liver MRI-T2* single or repeated measurements is associated with increased morbidity, but is not a reliable marker to predict cardiac iron levels.

Native T1 mapping, a novel imaging biomarker sensitive for the assessment of tissue abnormalities (mainly interstitial fibrosis and oedema), has shown potential in the assessment of myocardial iron loading in patients with TM. Although T1 lacks appropriate calibration against histological samples, the combined use of both segmental native T1 and T2* values could improve the sensitivity for detecting iron overload, particularly in low/early overload cases. Native T1 has been associated with cardiac complications in patients with TM (Meloni et al., 2021); therefore, completing the CMR protocol with native T1 sequences (at no significant additional scan time or risk) is advisable, although it would not be sufficient alone to guide management at present. A number of T1 methods have been described with MOLLI (modified Look-Locker inversion recovery) the most used sequence. Despite the advantages of T1 as a complementary assessment, there are challenges facing its clinical use including the variation of absolute T1 values between sequences and scanners (Menacho et al., 2017). Current consensus guidelines advise the establishment of site-specific reference ranges (Messroghli et al., 2017).

All patients receiving regular transfusions should have a quantitative tissue iron load assessment by CMR scanning at the earliest possible opportunity.

- CMR should be performed in transfused patients as soon as they are able to lie in a scanner without sedation (usually aged between 5 and 10 years). An ECG and echocardiogram should also be performed at each visit.

- Surveillance scans in children receiving blood transfusions should be performed at 2-year intervals.
- Repeat CMR scanning every year in the most vulnerable danger period, as the patient's care moves from paediatric services to adult medicine, is to be encouraged.
- Surveillance scans should be performed at regular intervals on all adults receiving regular blood transfusions.
- The interval of surveillance should not exceed 2 years for well-chelated individuals able to take their treatment, but should be more frequent in patients having difficulties with treatment, with abnormal baseline results or suggestive cardiac symptoms. Investigations at less than 6-monthly intervals are unlikely to detect meaningful changes, the rate of iron removal being relatively slow in the heart.
- Patients who are not regularly transfused but have an SF level >1000 µg/L should undergo CMR for iron quantification, and non-transfused patients should undergo CMR if the SF level is >800 µg/L.
- In non-iron-loaded patients, a search must be made for alternative causes of ventricular function impairment.

The nature of the CMR scans should be discussed with patients to reassure them that the scans are free from ionising radiation. Some patients find the scan stressful; ultrafast sequences focusing on the diagnostic images can be acquired in such cases (Abdel-Gadir et al., 2016). Recent technological advances allow for a wider selection of patients to be accommodated (wide-bore machines and the feasibility of scanning patients with non-MR conditional devices).

Overall, echocardiography is more readily available for serial and frequent assessment of dimensions and function, whilst CMR is being utilised more sparingly for comprehensive assessment, including iron loading, cardiac anatomy and function evaluation. The relative need for concomitant routine use of both techniques should be decided on an individual basis upon any specific clinical questions exceeding the classical evaluation of function of iron loading (e.g., PHT, valve disease or diastolic function).

Blood biomarkers

Brain natriuretic peptide (BNP) and its prohormone N-terminal pro-BNP are serum biomarkers that are highly sensitive indicators of the presence of cardiac failure. There are conflicting data from small cohorts on the usefulness of BNP in the routine surveillance of patients with TM (Pennel et al., 2013); however, raised BNP or N-terminal pro-BNP levels make heart failure (with preserved or reduced ejection

fraction) diagnosis possible and should prompt further assessment. In individual cases of established heart failure, measurement of BNP can help guide volaemic status and may be useful in differentiating breathlessness due to pulmonary problems versus that due to cardiac failure.

Troponin levels should be assessed if indicated from the clinical context (e.g., chest pain or suspected myocarditis), but the results should be interpreted with caution and in combination with the rest of the clinical and laboratory findings because mild, clinically insignificant troponin elevation is not unusual in the setting of chronic anaemia.

Additional cardiac investigations, such as exercise testing or right heart catheterisation, should be subject to a multidisciplinary decision if prompted by symptoms.

Acute presentations

Assessment of chest pain syndromes: pericarditis, myocarditis and coronary artery disease

Assessment of chest pain in patients with TM requires special attention and watchful interpretation. The population of patients with TM is a relatively young group, with improving life expectancy as a result of the advances in their management. They are also exposed to traditional risk factors, such as diabetes mellitus, from a young age and prone to a wide range of infections, which could theoretically increase the risk of myocardial or pericardial inflammation. The non-specific nature of cardiac sounding symptoms in patients with TM should also be taken into consideration.

The high prevalence of pericarditis (nearly 50%) that was previously seen in non-chelated young patients has been drastically reduced in recent years due to better management of iron overload and more efficient control of blood-borne infections (Engle et al., 1964; Kremastinos and Farmakis, 2011). There are no significant data on the occurrence of either pericardial or myocardial inflammation in this setting, which had been historically estimated at 5% and 4%, respectively, in well-treated patients (Farmakis et al., 2020).

Evidence on the prevalence of ischaemic heart disease is scarce. The possibility of either myopericarditis, and of epicardial or microvascular coronary disease, should not be neglected, as despite being relatively uncommon in patients with TM these conditions are associated with incremental risk in patients who are already exposed to a significant burden of cardiovascular pathologies. Appropriate testing is recommended depending on the clinical presentation (Gulati et al., 2021). The

particular role of CMR in this setting should be considered, as it could allow the assessment of cardiac function, iron loading, myopericardial inflammation and myocardial perfusion in a single examination (Collet et al., 2021).

Acute arrhythmias

A variety of arrhythmias have been described as complicating thalassaemia. These are mostly supraventricular and ventricular tachycardias, but in inadequately chelated patients, bradycardia and heart block may be seen. The heart block will usually, but not always, respond to the removal of myocardial iron. Pacemakers are rarely required, but if symptomatic bradycardia or heart block does not improve despite intensive chelation, the use of MRI-compatible pacemakers is preferred to allow subsequent evaluation of iron loading. Patients with previous cardiac iron may also present several years later with arrhythmias, which are most typically atrial.

Ventricular tachycardia is a grave indicator of heart dysfunction that requires urgent and expert assessment. It is almost uniquely a feature of severe myocardial iron overload in patients with TM and usually responds to intensification of chelation.

Ventricular tachycardia is a medical emergency necessitating admission to hospital. Severe cardiac decompensation or non-responsive ventricular tachycardia mandates the use of direct-current cardioversion to restore sinus rhythm as quickly as possible. Intravenous chelation with DFO 50–60 mg/kg/day, 24 hours/day, should be started as soon as possible via a central line. Early addition of oral treatment with DFP 75–100 mg/kg/day in three divided doses is also advised. Other therapies are dependent upon the response to chelation, but would include beta-blockers and/or amiodarone, as well as normalisation of electrolyte disturbance, particularly potassium and magnesium.

Consideration of device therapy via an implantable cardioverter defibrillator after the initial event should be delayed until the response to chelation has been fully assessed. Unlike virtually all other cardiomyopathies faced by cardiologists and electrophysiologist physicians, ventricular tachycardia in this group of patients can be considered to be a toxic manifestation of iron and its removal associated with minimal risk of further ventricular tachycardia, unless there is evidence of irreparable damage to ventricular function.

Atrial arrhythmias including AF, atrial flutter and intra-atrial re-entrant tachycardias are the most common rhythm disturbances in patients with TM. AF may be the precipitating event that causes acute cardiac decompensation in severely iron-overloaded hearts. Patients should be assessed and treatment actioned depending on the acute nature of presentation. Early consideration of direct-current cardioversion is advised for haemodynamically unstable patients, those presenting with heart failure

symptoms, chest pains or signs of reduced cerebral perfusion. Short-term drug therapy with amiodarone is often successful in controlling atrial arrhythmias during intensive chelation treatment, and can often be stopped after 6 to 12 months. Ablation strategies to restore sinus rhythm can be considered following successful removal of cardiac iron as demonstrated by CMR.

It is increasingly observed that AF is a risk faced by a large proportion of patients with TDT after the age of 40 years, most often without any current cardiac iron loading or cardiac function impairment. It is more frequently encountered in those with diabetes and a previous history of cardiac iron loading, sometimes decades in the past. Conventional risk scores aiming to predict the risk of stroke (e.g., CHA_2DS_2-VASc) are not applicable to this group of patients, who may face a particular risk of stroke and other emboli. Lifelong anticoagulation should be considered in patients with proven or suspected AF.

Acute decompensated heart failure

The development of acute heart failure complicating thalassaemia is now thankfully rare, but still has a high immediate mortality risk, approaching 50%. This emphasises the importance of avoiding this complication by adherence to regular chelation, guided by CMR T2* measurements.

All patients presenting with heart failure symptoms should be assumed to have high cardiac iron levels until they undergo a CMR assessment. Patients with a T2* <6 msec have an ~50% risk of developing heart failure within 12 months (Kirk et al., 2009). However, even with acute severe decompensated heart failure, restoration of completely normal ventricular function is possible with intensive continuous chelation. The potential for the complete reversal of heart failure in patients with TM may not be appreciated by clinicians who are not familiar with the management of these patients. Improvements in ventricular function assessed by echocardiography or CMR precede demonstrable improvements in iron content measured by T2*.

The management of acute heart failure in patients with thalassaemia differs to that of those with non-anaemia-related heart failure due to the physiological adaptations described previously and, as such, the following are recommended for the management of acute heart failure in patients with thalassaemia (Pennell et al., 2013).

- Admission to an inpatient ward with facilities to provide ECG and haemodynamic monitoring. Contact with a specialist cardiology service with expertise in RBC cardiology should be made at the earliest opportunity.

- For symptomatic relief of fluid overload, cautious administration of diuretic therapy is recommended to ensure preload is maintained. Excessive reduction of preload by overdiuresis can cause acute renal failure.
- Commence continuous DFO therapy (24 hours/day, 7 days/week) at 50–60 mg/kg over 24 hours, administered either intravenously or subcutaneously, depending on the patient's access and tolerance. Introduce DFP 75 mg/kg/day in three divided doses when possible.
- All efforts should be made to support the circulation, but care must be taken to ensure that intensivists are aware of the particular haemodynamic features of this patient group. Inotropic support must be used cautiously in these patients, who often improve on much lower central systemic blood pressures than seen in non-thalassaemia patients with heart failure. Support should be continued for long enough to allow adequate removal of the toxic iron accumulation, which may take days or weeks in some circumstances, particularly if renal function is impaired.
- Arrhythmias are common in patients presenting with acute decompensation and should be treated promptly. Amiodarone can be used as the first-line antiarrhythmic agent. Beta-blockers must be used with caution and if blood pressure allows. Derangement of serum electrolytes, particularly potassium and magnesium, must also be normalised.
- Patients should be screened for thiamine and vitamin D deficiency, hypoparathyroidism, hypothyroidism and diabetes. Patients should receive hydrocortisone for presumed AI.
- A bedside echocardiogram should be performed to confirm the diagnosis of heart failure and exclude other diagnoses that may present similarly.
- CMR should be performed as soon as practicable for cardiac and liver iron quantification.

As soon as practicable, the introduction of conventional heart failure medication, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with beta-blockers and aldosterone receptor blockers, should be considered (Pennel et al., 2013), although conventional doses may not be tolerated because of low blood pressure. Whilst these medications are prescribed for long-term use in patients with non-thalassaemia heart failure, the length of time of exposure for patients with TM has not been established. Patients are usually advised to avoid alcohol for at least a few months after an episode of acute heart failure.

Pulmonary hypertension

PHT is a particular feature of non-transfused patients. It is believed that intravascular haemolysis plays a major part in the development of pulmonary vascular endothelial

dysfunction. Thus, the emphasis of treatment has been to transfuse thalassaemia intermedia patients intensively if PHT is diagnosed or, preferably, transfusion is initiated early to prevent the development of PHT.

Patients with TM rarely develop PHT but do so at a higher frequency than the non-thalassaemia age-matched population. In all patients with TM, chronic pulmonary thromboembolism may contribute to the mechanism and should be considered in all cases. Consideration should be given to lifelong anticoagulation.

Once established, PHT carries a poor prognosis, with the development of RV dilatation followed by RV dysfunction and failure, for which no adequate treatments are available.

The gold-standard method for the diagnosis of PHT is invasive and requires careful catheterisation of the right heart. Echocardiography can be used as a non-invasive screening measure to identify patients at risk of developing PHT. The tricuspid regurgitation jet velocity (TRV) estimates RV systolic pressure and correlates with mean pulmonary artery pressure. It is suggested that patients with thalassaemia with TRV persistently >3.0 m/sec should be considered for a right heart catheter study.

There is some experience to support the use of phosphodiesterase-5 inhibitors (sildenafil, tadalafil) in the treatment of PHT. Individual patients should be referred to national PHT centres to be considered for more complex therapies, such as endothelin antagonists or phosphodiesterase-5 inhibitors.

Iatrogenic PHT has been observed in patients with indwelling CVCs due to undetected chronic pulmonary thromboembolism. There have been instances where surgical pulmonary thromboembolectomy has been used successfully to treat these patients, but this high-risk surgical intervention must be avoided if possible. This experience has led to the recommendation for full anticoagulation of all patients fitted with inferior vena cava devices, usually with vitamin K antagonists.

Management of the cardiovascular system in pregnancy

Please read in conjunction with **Chapter 11: Management of Pregnancy**.

Fitness considerations in pregnancy

Fertility is commonly reduced in patients with thalassaemia due to iron loading in the anterior pituitary gland, and patients will often require assisted reproductive methods to successfully conceive. Thalassaemia poses an increased risk to both the mother

and fetus, and the risk of cardiac complications ranges from 1% to 15% (Pennel et al., 2013).

The RCOG recommends review by a cardiologist with expertise in thalassaemia during the planning stages (RCOG, 2014). A thorough assessment is required to determine the mother's cardiac status prior to embarking on pregnancy and this must include an ECG, transthoracic echocardiogram for cardiac anatomy and function, CMR for cardiac iron quantification and a 24-hour tape recording to check for rhythm disorders.

Reduced LV function is a relative contraindication to pregnancy. If LV dysfunction is demonstrated, women should be strongly advised against planning a pregnancy at that time. It is recommended that cardiac T2* values should be >20 msec, indicating no significant iron loading, and that LV function should be normal (ejection fraction >65%). T2* values <10 msec indicate severe myocardial iron and patients should be advised to avoid pregnancy, at least until a period of intensive chelation has improved cardiac iron, due to the risk of developing overt heart failure.

Surveillance and antenatal care

Pregnant patients should undergo assessment of cardiac function with transthoracic echocardiography. Iron loading should be assessed by CMR scanning, which is safe from 20 weeks gestation if it was not undertaken preconceptually. Women with T2* values <20 msec are at risk of decompensation and therefore require regular clinical assessment. In the event of unplanned pregnancy, an iron-overloaded patient must have immediate and regular cardiovascular investigation including echocardiography, and chelation therapy with low-dose subcutaneous DFO (20 mg/kg/day) for 4–5 days/week can be considered starting from 20 weeks. Chelation therapy discussions with the patient in pregnancy should be clearly documented.

Management of labour

Timing of labour is dependent on comorbidities identified throughout the antenatal period. Patients with cardiac iron who are off chelator medication have high serum concentrations of NTBI that may cause free radical damage and arrhythmias during labour, and some centres recommend that peripartum chelation therapy with low-dose DFO is started.

Requirements

- Clinical examination – including recording of pulse, blood pressure, oxygen saturation by pulse oximetry and cardiovascular findings – should be recorded at least at every annual review visit.
- Referral to a cardiology service with specific experience in the management of the cardiac consequences of thalassaemia should first be made when the child is 8–10 years of age.
- See Table 15.3 for assessment frequencies for uncomplicated, well-chelated patients on stable therapy, and without symptoms or abnormalities on previous testing.

Table 15.3: Frequency of assessment for stable, well-chelated patients

Assessment	Age at first visit	Surveillance interval	Comment	Essential (E)/desirable (D)
Clinical cardiology visit and examination	8–10 years	2 years 1 year 2 years	If no symptoms or abnormalities Between 16–25 years old After age 25 years	E D E
ECG			At each visit	E
Echocardiogram	8–10 years		At each visit	D
MRI	8–10 years	2 years if >20 msec on last assessment		E

See Table 15.4 for frequency of assessment for

- patients who are poorly chelated without heart failure or impaired LV function
- patients who have recovered from an episode of heart failure
- patients with impaired LV function but with no symptoms.

Table 15.4: Frequency of assessment for patients who are poorly chelated

Assessment	Surveillance interval	Comment	Essential (E)/desirable (D)
Clinical cardiology visit and examination	Immediate, then 3–6 months	Dependent on severity of T2*; perform every 3 months if T2* <6 msec	E
ECG	At each visit		E
Echocardiogram	6 month	At each visit	D
MRI	6 months if T2* <10 msec 1 year if T2* <20 msec		E

Particular vigilance is required before and during pregnancy (see Table 15.5).

Table 15.5: Cardiac assessments around pregnancy

Assessment	First visit	Surveillance	Essential (E)/desirable (D)
Clinical cardiology visit and examination	When planning pregnancy	Preconception	E
		At ~12 weeks gestation	E
		At 28 weeks gestation	D
		3 months post-delivery	D
ECG		First visit	D
Echocardiogram		Every visit	E
MRI		Preconception and at post-delivery visits	E

- If abnormalities on testing or significant symptoms, may need more intensive monitoring

- Echocardiographic assessment must be undertaken and reported by an operator experienced in cardiac assessments in thalassaemia. A minimum data set, detailed in Table 15.1, should be recorded each time.
- Findings of any cardiac iron on T2*, impairment of cardiac function or new arrhythmia should lead to an early review of the patient's chelation regimen, to ensure it is optimised with regard to reducing myocardial iron.
- Patients with ventricular arrhythmias or clinical cardiac failure must be admitted to hospital, and started on continuous intravenous DFO 50–60 mg/kg/day, with

oral DFP 100 mg/kg/day in three divided doses being introduced as soon as possible, in the absence of any contraindications.

- Patients with ventricular arrhythmias or clinical heart failure must be managed in liaison with the SHC, and preferably transferred for inpatient management there.
- Patients found to have PHT must be managed in conjunction with the most convenient national PHT service team.
- Patients who have an indwelling venous device should be fully anticoagulated.
- Patients with AF, including paroxysmal, must receive anticoagulation therapy.
- Patients who have had a neurological or other possible embolic event must be investigated for silent or paroxysmal AF.

Recommendations

- Lifestyle factors likely to affect cardiovascular health should be explored, and patients strongly advised to undertake physical exercise and not to smoke tobacco.
- Comorbidities such as diabetes mellitus and hypothyroidism should be optimally managed so as not to contribute to cardiovascular morbidity.
- Repetition of T2* measurements within 6 months of a previous measurement is not recommended.
- A T2* >20 msec and ejection fraction >65% is recommended prior to embarking on pregnancy.

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Chapter 16

Management of Impaired Glucose Tolerance and Diabetes Mellitus

"I thought living with thalassaemia was difficult, until I developed diabetes and had to learn how to deal with both."

Aims

To optimise quality of life and prevent diabetes complications and premature death by:

- Encouraging meticulous adherence to iron chelation medication to lower the risk of developing diabetes, as well as other complications, and possibly to improve or normalise glucose metabolism if impaired.
- Diagnosing impaired glucose regulation and diabetes early.
- Preventing the progression of impaired glucose regulation to diabetes.
- Optimising glycaemic control and other cardiovascular risk factors.
- Detecting and treating diabetic complications early.
- Supporting patient self-management.

Standards

- A paediatric and adult consultant diabetologist should be identified for each SHT.

- Patients should be checked annually for impaired glucose regulation and diabetes from puberty, or from the age of 10 years if there is a family history of diabetes.
- Patients with diabetes should have a full annual diabetes review, including glycaemic control, cardiovascular risk factors and diabetic complications.
- Patients with diabetes should have access to a clinical health psychologist with experience in diabetes management.

Background

Impaired glucose regulation and diabetes mellitus are common and significant complications of thalassaemia. In adult patients attending a UK thalassaemia service, around 20% will have impaired glucose regulation and up to 41% will have diabetes (Ang et al., 2014; Jobanputra et al., 2020). The main aetiological factor is transfusional iron overload, which damages pancreatic beta cells reducing insulin secretion. The other key factors for some patients are insulin resistance secondary to liver disease and HCV infection affecting glucose metabolism (Mowla et al., 2004). Risk factors for diabetes also include poor compliance with chelation therapy or advanced age at onset of chelation (Gamberini et al., 2004), increasing patient age, an average SF over 10 years >1250 µg/L and myocardial T2 <20 msec (Ang et al., 2014). In addition, with the global pandemic of diabetes, patients can develop type 1 or type 2 diabetes independently of their thalassaemia.

Impaired glucose regulation and diabetes must be detected early to allow prompt treatment of hyperglycaemia and intensification of iron chelation therapy. Very intensive combined chelation can improve or normalise glucose metabolism in patients with impaired glucose regulation or non-insulin-dependent diabetes, mainly through marked increase of insulin secretion (Farmaki et al., 2006, 2010). Intensive chelation can prevent progression to frank diabetes.

Screening for impaired glucose metabolism remains dependent on the OGTT (De Sanctis et al., 2022a), which includes measurement of fasting plasma glucose (FPG) and plasma glucose 2 hours after oral ingestion of 75 g of glucose. According to the recommendations of the WHO (WHO and International Diabetes Federation, 2006), results should be interpreted as follows.

A. FPG:
    i. FPG ≤6.0 mmol/L = normal
    ii. FPG 6.1–6.9 mmol/L = impaired fasting glycaemia
    iii. FPG ≥7.0 mmol/L = diabetes.

B. 2-hour plasma glucose:
    i. 2-hour plasma glucose <7.8 mmol/L = normal
    ii. 2-hour plasma glucose 7.8–11.0 mmol/L = IGT
    iii. 2-hour plasma glucose ≥11.1 mmol/L = diabetes.

If diabetes develops, a critical aim of care must be the prevention, early detection and management of diabetic complications, including macrovascular complications (cardiovascular disease, cerebrovascular disease and peripheral vascular disease) and microvascular complications (diabetic retinopathy, nephropathy, neuropathy and erectile dysfunction). These complications can cause major patient morbidity and mortality, and account for 80% of direct patient care costs in the UK. In patients with thalassaemia and diabetes, the prevalence of diabetic nephropathy is 13–55% (Tzoulis et al., 2014; Loebstein et al., 1998) and the prevalence of diabetic retinopathy is 13–26% (Tzoulis et al., 2014; Incorvaia et al., 1998). Macrovascular disease is uncommon, but is expected to increase as the life expectancy of patients with thalassaemia rises. Further, diabetes significantly increases the risk for cardiac complications, heart failure, hyperkinetic arrhythmias and myocardial fibrosis in patients with thalassaemia (Pepe et al., 2013). Expert recommendations for the diagnosis and management of disturbances of glucose metabolism have been formulated for patients with TM (De Sanctis et al., 2016). Oral glucose-lowering agents have been demonstrated to be safe and effective in this patient group (De Sanctis et al., 2022b).

Living with diabetes and thalassaemia can have a major psychological effect, with feelings of treatment burden, being different, dependence, damage, anxiety and impacts on daily life. Healthcare professionals need to be able to support their patients to manage their diabetes and enable them to apply self-management skills to lead a full and rich life.

Requirements

- All non-diabetic patients should be screened by OGTT and fructosamine testing annually from puberty, or from the age of 10 years if there is a family history of diabetes.
- In patients with impaired glucose regulation (impaired fasting glycaemia/IGT) or non-insulin-treated diabetes, iron chelation therapy should be intensified, with consideration given to using combination chelation regimens, with the aim of normalising the iron load as judged by CMR and hepatic MRI.
- Patients with evidence of diabetes must be referred to the nominated consultant diabetologist in each SHT for further evaluation and treatment guidance, and their management kept under regular review by the specialist diabetes team. This is essential to provide adequate care for complex cases.
- Overall glycaemic control should be monitored using fructosamine levels. Fructosamine is a circulating glycated protein that measures overall glucose control in the previous 2–3 weeks. Normal ranges vary in different laboratories but are generally 205–285 mol/L. HbA1c or glycated Hb testing should be avoided for patients with thalassaemia as it is unreliable after repeated transfusions. Patients with impaired glucose regulation (impaired fasting glycaemia IGT) should have their fructosamine level measured every 6 months to identify trends in glycaemic control, aiming to keep their fructosamine levels ≤325 µmol/L. Patients diagnosed with diabetes should have their fructosamine levels measured every 3 months.
- Any patient with symptoms of hyperglycaemia (e.g., thirst, polyuria, polydipsia or *Candida* infections) should have urgent measurement of their random plasma glucose and fructosamine levels. If random plasma glucose ≥11.1 mmol/L, which is diagnostic of diabetes, then blood or urinary ketones should be measured to exclude diabetic ketoacidosis.
- Patients with diabetes who are acutely unwell and who are hyperglycaemic (plasma glucose >12 mmol/L) should have blood or urinary ketones measured to exclude diabetic ketoacidosis.
- Patients with diabetes should test their capillary blood glucose at home in order to monitor glycaemic control and identify hypoglycaemia or severe hyperglycaemia. The frequency of monitoring depends on their treatment, with increased frequency needed for patients on insulin.
- Patients with mild to moderate hyperglycaemia should be treated with antidiabetic drugs. The choice of agent should be individualised and depends on the balance of impaired insulin secretion versus insulin resistance, and on the patient's comorbidities. There are very limited data on the efficacy and safety of antidiabetic drugs in patients with thalassaemia. Metformin is the first-

line drug of choice, except in patients with significant chronic kidney disease (estimated glomerular filtration rate <30 mL/min), acute heart failure or acute respiratory failure. The choice of second-line agent must be personalised. There are currently 5 classes of antidiabetic drugs, some of which are associated with weight loss and low rates of hypoglycaemia.

- Patients with severe hyperglycaemia or worsening glycaemia on multiple oral antidiabetic drugs should be treated with insulin. Severely insulin-deficient patients should be considered for a multiple daily injection (MDI) or a basal-bolus insulin regimen, which involves slow-acting basal background insulin being administered usually once per day and rapid-acting insulin being taken with each meal.
- Continuous glucose monitoring may be considered for close monitoring in a few situations, including in pregnancy and for people with diabetes complications, but has poor compliance compared with capillary blood glucose monitoring.
- Insulin, C-peptide, and venous glucose level testing may be required if a diagnosis of diabetes is unclear, to rule out type 1 diabetes and to check pancreatic reserve in advance of the initiation of insulin treatment.
- Patients must have further diabetes specialist input in specific situations requiring excellent glycaemic control, including preconception, pregnancy and surgery.
- Women with diabetes who are planning to become pregnant should be informed that establishing good glycaemic control before conception and continuing this throughout pregnancy will reduce the risk of miscarriage, congenital malformation, stillbirth and neonatal death. It is important to explain that risks can be reduced but not eliminated.
- Patients with diabetes must be regularly assessed, at least once per year, for other endocrinopathies because they are at high risk of hypogonadism, hypothyroidism, hypoparathyroidism and bone thinning.

Recommendations

- Patients with impaired glucose regulation or diabetes should be encouraged to undertake 150 minutes of moderate-intensity activity each week that accelerates the heart rate (such as brisk walking). This can be taken in 10-minute bouts (NICE, 2012).
- Overweight patients with impaired glucose regulation or diabetes should be encouraged and supported to make lifestyle changes in diet and exercise, aiming to lose 5–10% of their body weight per year to reach a BMI <25 kg/m^2, or <23 kg/m^2 if of South Asian or Chinese descent (NICE, 2012).

- Healthcare professionals should help patients to assess their diet and encourage them to increase their consumption of foods high in fibre (e.g., vegetables and fruit), as well as to avoid foods high in saturated fat.
- The nominated consultant diabetologist and their team must work in close partnership with the Haematology team to enable integrated care, ideally in joint clinics.
- Patients with diabetes should have a planned programme of recommended checks each year that includes the nine key care processes: measurement of glycaemic control (fructosamine), serum cholesterol, serum creatinine and estimated glomerular filtration rate, urinary albumin excretion (urinary albumin/protein-to-creatinine ratio), smoking status review, weight, blood pressure, diabetic foot examination and diabetic retinal screening. This should be part of personalised care planning that enables patients and their healthcare professionals to jointly agree actions for managing their diabetes, and to meet their individual needs.
- Patients with diabetes should be managed according to treatment targets and recommendations for type 1 and type 2 diabetes set by NICE, which are available on their website, including targets for blood pressure and cholesterol.
- Patients with diabetes should be invited to attend structured education in diabetes self-management. For patients on MDI insulin regimens, this should include training in carbohydrate counting and insulin dose adjustment.
- Healthcare professionals must be aware of the psychological impact of having both diabetes and thalassaemia. They should offer patients counselling with a clinical health psychologist who has experience of working with patients with diabetes.

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Chapter 17

Management of Bone Complications

"Bone pain is the one of the worse things about having thalassaemia. Nobody seems to know what to do about it or know anything that could help."

"Bone pain makes me feel older than I am which depresses me."

Aims

To prevent the variety of bone diseases that can occur in people with thalassaemia.

In those with bone thinning, to monitor and provide effective treatment to lessen associated morbidity, fractures and reduced quality of life.

Standards

- Transfusion therapy will be initiated in time to prevent irreversible deformities associated with bone marrow expansion.
- Doses of DFO will be kept within a range to minimise the risk of bone toxicity or reduce height velocity. Any bone changes possibly related to DFO toxicity should be suspected and investigated in children with bone/joint pain or short stature.
- Management of the maturing skeleton should focus on achieving peak bone mass.
- All patients should have vitamin D measured with supplements given if needed.
- All patients should be advised of the need for adequate dietary calcium for healthy bones.
- All patients should be advised on lifestyle changes that promote the achievement of peak bone mass and the maintenance of bone BMD: smoking

cessation, avoiding excessive alcohol consumption and undertaking weight-bearing exercise.

- Diagnosis of hypogonadism and other endocrinopathies should be prompt, and appropriate HRT given.
- Adult patients should be monitored for low bone mass/osteoporosis.
- Bisphosphonates and other bone specific agents should be considered in patients with deteriorating BMD/osteoporosis confirmed on DXA BMD scan, particularly if there have been fractures.
- Osteoporosis treatments should be reviewed regularly.

Background

Bone disease is an important cause of morbidity in patients with thalassaemia with problems related to inadequate transfusion, DFO use, failure to reach peak bone mass and progressive bone thinning in adults.

Characteristic bone disease is seen with inadequate transfusion causing deformities of the skull and face. Dental and sinus complications should be managed by early referral to a specialist dental service (see **Chapter 18: Managing Dental Complications**). These problems are related to marrow expansion and can be prevented by adequate blood transfusion regimens (Weatherall, 2001); they should now occur only rarely in optimally transfused patients, although those with thalassaemia intermedia who are not regularly transfused remain at risk.

DFO-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 DFO (15–35 mg/kg) in young children (Olivieri and Brittenham, 1997) and have become rare in younger patients since treating physicians became aware of the issue. It remains to be seen whether newer chelating agents will have any adverse effects on growing bones; to date they do not appear to. Defective calcium absorption might be a cause of bone disease in people with thalassaemia (Lertsuwan et al., 2018).

Vitamin D

In the absence of supplementation, vitamin D deficiency is very common in people with thalassaemia (Vogiatzi et al., 2009). Vitamin D is essential for calcium homeostasis and mineralisation of the skeleton, and vitamin D levels directly correlate

with BMD. Assays for 25-OH vitamin D are now widely available and supplementation is possible with a variety of supplements available, both prescribed and over the counter (including Halal, etc.). Vitamin D3 should be the replacement of choice by an oral route (ROS guidance, 2018. In the absence of research evidence, expert opinion is that the target vitamin D level should be >75 nmol/L, somewhat above the traditional 'normal range' of 50 nmol/L. Maintenance therapy is likely to be required.

Loading regimens for the treatment of deficiency are available up to a total of approximately 300,000 IU, given either as weekly or daily split doses. The exact regimen will depend on the local availability of vitamin D preparations but will include one of the following:

- 50,000 IU capsules, one given weekly for 6 weeks (300,000 IU)
- 20,000 IU capsules, two given weekly for 7 weeks (280,000 IU)
- 800 IU capsules, five per day given for 10 weeks (280,000 IU).

Supplements should be taken with food to aid absorption. Calcium/vitamin D combinations should not be used as sources of vitamin D for the above regimens, given the resulting high dosing of calcium.

Maintenance regimens may be considered with doses equivalent to 800–2000 IU daily (occasionally up to 4000 IU daily), given either daily or intermittently at a higher equivalent dose. Where available, high-dose weekly supplementation such as 10,000-IU capsules or 20,000 IU fortnightly may help compliance.

Where oral compliance remains very poor or gut absorption prevents successful oral replacement, administering intramuscular vitamin D (ergocalciferol) during transfusion visits could be considered (given as 150,000 IU every 3 months).

The following treatment approaches have been demonstrated to work poorly, lead to toxicity or are associated with an increased risk of falls, and are therefore not recommended.

- Annual depot vitamin D therapy either by intramuscular injection or orally (Sanders, 2010).
- The use of activated vitamin D preparations (calcitriol and alfacalcidol). These agents should only be considered if there is proven primary hypoparathyroidism. This diagnosis should be made when persistent hypocalcaemia and hypoparathyroidism co-exist.

Vitamin D levels should be monitored every 3–6 months after loading doses are complete, and should be monitored intermittently depending on levels and compliance with therapy.

Calcium

The Recommended Dietary Allowances (covering requirements of ≥97.5% of the population) for calcium range from 700 to 1300 mg/day for life-stage groups ≥1 year of age. For adults the recommended daily intake is generally 1000 mg (Ross et al., 2011).

Total daily calcium intake should be 700–1000 mg/day (in diet or as supplements) from age 11 years upwards. For younger children, total daily intake should be 350 mg for children aged 1–3 years, 450 mg for those aged 4–6 years and 550 mg for those aged 7–10 years. A screening tool such as the University of Edinburgh CGEM Calcium Calculator (https://webapps.igc.ed.ac.uk/world/research/rheumatological/calcium-calculator/) can be helpful to estimate daily calcium intake.

Dietary modification should be explored as the first option to achieve target intake. Signposting to information to help choose calcium-rich food may be helpful (see Royal Osteoporosis Society, 2022).

Supplementation should be considered when dietary modifications are insufficient to reach recommended daily intakes. Calcium is better absorbed with food and in split doses. Advice should be given around the timing of tablets to achieve optimal absorption (with food and split doses), as well as to minimise the possibility of them reducing the absorption of other medications (e.g., do not take with levothyroxine).

Even for patients with hypercalciuria and stones, the recommendation is for normal calcium intake (not low) as intestinal calcium will bind oxalate.

Bone mineral density

Low bone mass is present in children with thalassaemia aged <10 years (Vogiatzi, 2004); however, there are technical issues with performing DXA scans on children as they need to be adjusted for bone size and also for pubertal stage. There is no evidence supporting the treatment of low bone mass in children with thalassaemia, therefore there is little rationale for performing DXA scanning on patients until they reach pubertal maturity. Management of bone disease in children should focus on lifestyle measures such as calcium intake and weight-bearing exercise, as well as ensuring adequate levels of serum vitamin D. Peak bone mass is only achieved when an individual is in their late 20s so the focus should remain on maximising the opportunities to achieve this peak.

Low BMD is seen in a high proportion of adults with thalassaemia and the prevalence increases with age (Vogiatzi et al., 2009). DXA scanning is the most widely used modality for the assessment of bone mineralisation in clinical practice. There are some limitations to DXA interpretation in people with thalassaemia (Pellegrino et al., 2019; Wong et al., 2014). These include smaller bone size (giving lower BMD readings) and degenerative changes of the spine (giving higher BMD readings). Trabecular bone score, a tool to measure bone connectivity from DXA images of the spine, can help assess bone quality but is not widely available in clinical practice (Baldini et al., 2014; Silva et al., 2014).

The pathology of this low bone mass is complex and not fully understood, but includes delayed sexual maturity, parathyroid gland dysfunction and hypogonadism. There are high reported rates of fracture (Chatterjee, 2001); however the relationship between BMD and fracture risk is not fully understood. Low bone mass in patients with thalassaemia has been shown to be related to raised levels of bone turnover markers and increased rates of bone resorption. BMD assessments should be undertaken regularly, usually by DXA scanning, from the completion of puberty.

Bisphosphonates are potent inhibitors of bone resorption and short-term studies have shown increases in BMD, reductions in bone turnover and reductions in bone pain. Regimens used include daily oral alendronate (Morabito, 2002), monthly intravenous pamidronate (1 mg/kg) with (Chatterjee, 2012) and without HRT (Voskaridou, 2003), and intravenous zoledronate 4 mg every 6 months (Voskaridou, 2006).

There are no studies in thalassaemia that have shown fracture reductions with bisphosphonate treatment. There are significant concerns about long-term bisphosphonate use. Osteonecrosis of the jaw is a condition of exposed necrotic bone in the maxillofacial region that does not heal after 6–8 weeks. In patients treated with high-dose bisphosphonates for malignancy (similar doses to some of those used in the thalassaemia studies) the reported incidence is 1.4% with 3 years of treatment. In patients treated with oral bisphosphonates for postmenopausal osteoporosis, rates of 1:10,000 are quoted. Rare cases have been seen in patients with thalassaemia treated with intravenous bisphosphonates (Chatterjee et al., 2014).

There have been reported cases of atypical femoral fractures seen with bisphosphonate use. These are fractures along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. A specific case definition of these fractures has been described (ASBMR task force report, 2013), and anecdotal cases have been seen in patients with thalassaemia.

Due to these rare but significant side effects, long-term bisphosphonate therapy should not be advised without reassessment of fracture risk and, if possible, an opinion

from a specialist in osteoporosis (rheumatology, endocrinology or care of the elderly depending on local provision). Current practice would suggest first ensuring adequate vitamin D levels and supplementing testosterone/oestrogen for a period of ≥2 years before starting bisphosphonate treatment for osteoporosis in this group. If bisphosphonate treatment is started, this should be reviewed after ≤5 years of oral bisphosphonates or 3 years of intravenous treatment, and a 'drug holiday' should be considered (Gregson et al., 2022; National Osteoporosis Guidelines Group, 2021). Bisphosphonates adhere strongly to hydroxyapatite and remain in bones for long periods, providing fracture protection after discontinuation except in those at highest risk of fracture, where careful consideration of the need for extension may be appropriate. Caution should be taken in giving bisphosphonates to women of childbearing age. The bone half-life of these drugs is several years and the impact on a developing fetus is not known.

Denosumab (an anti-receptor activator of nuclear factor kappa beta monoclonal antibody) has been shown to increase BMD and reduce bone turnover in patients with TM within 1 year of treatment (Yassin, 2014). If this is considered, it is advisable that treatment is supervised by a clinician with an interest in osteoporosis and experience of this drug. Stopping denosumab leads to rapid bone loss and increased risk of vertebral fractures (Cummings et al., 2018), so it should not be discontinued without being replaced with an alternative antiresorptive agent.

Bone pain in thalassaemia

Persistent pain is a common complaint. A questionnaire-based study conducted in North America identified that pain was a significant symptom in >50% of adults with thalassaemia aged >35 years, and affected patients with both TDT and NTDT. The commonest sites of pain are the lower back, followed by the mid-back, legs and head (Green et al., 2013). Pain of this sort contributes to a reduction in quality of life. Pain may be localised or of a more generalised nature. In many cases, a causative factor can be identified, such as osteoporotic fractures of the spine, extra medullary haematopoietic masses causing nerve root compression or entrapment, disc disease or arthritic changes in the large joints. These findings may be amenable to treatment with resolution of pain symptoms. Chronic pain not amenable to corrective treatment requires management by a specialist team with careful choice of analgesic drugs (preferably avoiding long-term use of strong opioids), and use of non-pharmacological and cognitive methods. A description of these is beyond the scope of the *Standards of Care*. There are many resources to assist patients and healthcare professionals in formulating a management plan (Opioids for Persistent Pain, British Pain Society, 2010; Pain Tool-kit booklet, 2012).

Requirements

- Children with TM should receive optimal transfusion to prevent excessive bone expansion.
- The recommended DFO dose in childhood should not be exceeded.
- Regular assessment of standing and sitting height should be undertaken in children with thalassaemia, until full height is achieved.
- HRT should be initiated after assessment by a paediatric endocrinologist if hypogonadism is diagnosed. Other endocrine derangements should be sought and corrected.
- Vitamin D levels should be measured regularly from age 2 years, and replacement with oral supplements should be advised if insufficient until an optimal level (~75 nmol/L) is achieved.
- BMD should be measured by DXA scan of the spine and hip. A suitable screening regimen should start at completion of puberty and occur every 2–3 years. The ongoing frequency of scanning should be determined by results and therapy, but expert opinion suggests that the minimal interval between scans should be 18 months.
- Bisphosphonates and other bone-active drugs should be considered in patients with a low BMD for their age (z-score less than -2.0 if premenopausal or age <50 years, t-score less than -2.5 if postmenopausal or age >50 years), if there are fragility fractures and/or falling BMD despite adequate vitamin D levels, and hormone supplementation if there is hypogonadism. Bisphosphonate treatment should be reviewed after a maximum of 5 years for oral agents and 3 years for intravenous agents, and it is recommended after these intervals that a pause in treatment be considered for a period of 2–3 years (a bisphosphonate ‘holiday’).
- Bisphosphonates should be stopped if there is suspicion of atypical femoral fractures or osteonecrosis of the jaw.
- Chronic pain not amenable to corrective treatment requires management by a specialist pain team with careful choice of analgesic drugs (preferably avoiding long-term use of strong opioids), and use of non-pharmacological and cognitive methods.

Recommendations

- In children and adolescents who are treated with DFO, and who experience bone or joint pain, radiological investigations to rule out treatment-related bone disease should be requested.
- Dietary calcium should be assessed and advice given to achieve adequate calcium levels for the patient's age.
- Children and adults should be encouraged to undertake regular weight-bearing exercise, and high alcohol intake and cigarette smoking should be strongly discouraged.
- BMD changes in people with thalassaemia are better assessed in the femur compared with the spine (Pellegrino et al., 2019; Wong et al., 2014).
- Treatment of hypoparathyroidism with activated Vitamin D should aim to achieve adjusted calcium levels below the normal range (2–2.2 mmol/L) to reduce the risk of causing or exacerbating hypercalciuria.

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Chapter 18

Managing Dental Complications

"My teeth started falling out one day which was absolutely terrifying but I didn't know I was meant to be monitored regularly by specialist dentists after starting bisphosphates. No one told me."

Aims

To improve awareness of the potential orofacial and dental manifestations of thalassaemia.

To ensure that appropriate pathways for dental care are in place, including prevention and the timely management of dental infections.

To outline the dental implications in relation to the use of medications known to be associated with a risk of medication-related osteonecrosis of the jaw (MRONJ).

Standards

- RBC transfusion in children with thalassaemia should be sufficient to prevent the development of marrow overgrowth and facial bone changes, and some of the associated dental problems.
- All patients should access regular dental care to prevent oral infection and manage the potential orofacial features of thalassaemia.
- Patients presenting with acute dental infections/abscesses should receive urgent dental care and antimicrobial therapy as required.
- Close liaison with the haematology team is required to determine the potential complications when delivering invasive dental treatment, and to put measures in place to reduce risk.

- All patients should ideally have a comprehensive dental assessment with their local dentist prior to the commencement of medication associated with the risk of MRONJ to ensure that they are as dentally fit as feasible.

Background

Oral health is an important component of a person's general wellbeing and quality of life (Haag et al., 2017; Department of Health and Social Care, the Welsh Government, the Department of Health Northern Ireland, Public Health England, NHS England and NHS Improvement, 2014). For people with thalassaemia, this is particularly important as there are numerous potential orofacial manifestations where early recognition can enable appropriate management and prevent complications.

Many dentists do not have experience in providing dental treatment for a patient with thalassaemia and may fail to recognise the associated oral manifestations (Duggal et al., 1996). This is in part due to the significant variation in the geographical prevalence of thalassaemia in the UK related to its predominant occurrence in people of certain ethnic origins (Mediterranean, Asian, Middle Eastern and African).

Fear of the unknown may be associated with reluctance to provide anything other than basic dental care. Indeed, many general dentists may prefer to refer these patients to either the community dental services or to hospital-based specialist dental units (special care dentistry, paediatric dentistry and oral surgery), especially when extractions of teeth are required. When dental treatment is provided, the dentist may not be fully aware of the impact of thalassaemia on dental management, and hence may not liaise with the haematologist when appropriate.

Enhancing awareness of the importance of regular dental care and the potential orofacial manifestations of thalassaemia is key to the removal of barriers to oral care.

Orofacial manifestations of thalassaemia

Many orofacial features have been described in people with thalassaemia, as summarised in Table 18.1 (Helmi et al., 2017; Singh et al., 2013). The extents of these changes depend on the severity of the anaemia, the patient's age, the duration of the clinical symptoms and when blood transfusion is commenced, especially when transfusion is started later in life or is less intensive than recommended. In addition to people with TM, those with thalassaemia intermedia who are untransfused are most at risk of orofacial manifestations.

Table 18.1: Orofacial manifestations of thalassaemia

Site	Feature	Reason
Facial/jaw bones	Enlargement of the upper jaw (chipmunk face)	Bone marrow expansion
	Maxillary sinus reduction/nasal obstruction	Bone marrow expansion
	'Chicken wire-like' appearance of tooth-bearing bone on radiographs	Bone marrow expansion
	MRONJ	Medications including antiresorptives and antiangiogenics
Teeth	Delayed dental development	Physical growth delay
	Teeth with enlarged pulp chambers and short crowns/roots	Iron deposits
	Discoloured teeth	Iron deposits/bilirubin in the dentinal tubules
	Varying degrees of malocclusion (overbite, open bite)	Changes to facial bones
	Migration and spacing of upper anterior teeth	Changes to facial bones
	Developing tightness, discomfort and ulceration from dentures	Changes to facial bones
	Dental decay	Lack of regular dental care; dry mouth, change in quality of saliva, fatigue/poor motivation
Soft tissues	Pale gingivae and oral mucosa	Anaemia
	Discoloured gingivae	Iron deposits
	Painful swelling of salivary glands and dry mouth	Iron deposits
	Reduced salivary protection	Reduced IgA in saliva
	Sore or burning tongue	Folate deficiency

Facial/jaw bones

Bone marrow hyperplasia may result in malformation/enlargement of the facial bones, including the maxilla and mandible (Movahhedian et al., 2020; Abu Alhaija et al., 2002). This is usually more significant in the upper jaw, resulting in a characteristic appearance with prominent high cheekbones and relatively smaller lower facial bones.

Bone marrow overgrowth may also result in a reduction in the size of the maxillary sinuses and nasal obstruction (Di Mauro et al., 2016). Thinness of the cortical bone, absence of the inferior dental canal and a 'chicken wire' appearance of the lower jaw is often observed on radiographs.

Antiresorptive medications such as bisphosphonates are commonly used in thalassaemia care for the management of osteoporosis, and cases of MRONJ have been reported in relation to their use (Chatterjee et al., 2014). MRONJ is defined as exposed bone or bone that can be probed through a fistula, in the maxilla or mandible, which has been present for >8 weeks (Ruggiero et al., 2014). It can occur spontaneously, but more commonly presents following trauma due to dental extraction(s).

In addition to bisphosphonates, other medications have been associated with the development of MRONJ, including antiangiogenic agents such as vascular endothelial growth factor inhibitors and tyrosine kinase inhibitors (Kanwar et al., 2020).

The reported incidence of MRONJ in relation to the use of higher-potency intravenous bisphosphonates ranges between 2 and 28%, with the majority of studies suggesting an incidence of 5–8%; however, these studies are in patients with different underlying conditions, predominantly myeloma or other malignancies. Incidence is time- and dose-dependent, with the time to onset ranging from 4 to 120 months.

The incidence of MRONJ associated with oral bisphosphonates is lower and is generally accepted to be <1% (0.01–0.34%) (Fedele et al., 2009). Incidence is again time- and dose-dependent, with the time to onset ranging from 3 to 10 years (Scottish Dental Clinical Effectiveness Programme, 2017).

Teeth

Delayed dental development/eruption may occur and teeth may have short crowns in addition to features of taurodontism (enlarged pulp/nerve chambers) (Hazza'a and Al-Jamal, 2006). The roots of the teeth may be short and slender with the lamina dura (bundle bone around the tooth) appearing faint/attenuated on radiographs.

The permanent teeth may appear discoloured because of progressive iron accumulation within the tooth tissue as it is forming (darker teeth) and/or incorporation of bilirubin in the dentinal tubules (yellow discoloration of teeth). Changes in the jaw dimension can result in spacing of the upper teeth and rotation or forward drift of the upper front teeth.

Although it has been suggested that people with thalassaemia may also have an increased risk of dental decay, the evidence is not conclusive (Singh et al., 2013; Hattab et al., 2001). Factors that may contribute to an increased risk include variable access to dental care, reduction in the quality and quantity of saliva, and increased levels of *Streptococcus mutans* in the mouth (Lugliè et al., 2002), in addition to patient factors such as poor motivation, fatigue, depression and financial/time constraints.

Dental care is often sought at a late stage when individuals experience pain and try to access emergency dental services. In this situation, the dental decay is often advanced with fillings no longer viable, with increased risk of infection and abscesses spreading into the tissues of the face and neck. This risk is compounded by thalassaemia-related iron overload, splenectomy (Wang et al., 2003) and multiple immune abnormalities, including defective neutrophils and macrophage chemotaxis, described in patients with thalassaemia (Vento et al., 2006).

Certain organisms are particularly common causes of dental infection in people with TM. In particular, *Klebsiella* dental infections can act as a source of generalised septicaemia (Sarma, 2007), which can be serious or fatal when not identified in a timely manner.

Unfortunately, as a consequence of late presentation, dental extractions may be more likely to be provided than fillings, leading to individuals losing more and more teeth. Where teeth have been lost, the dimension of the dental arch can slowly expand making dentures feel tight or uncomfortable, causing ulceration.

Soft tissues of the mouth

The oral mucosal lining and gingivae may appear pale due to anaemia, but can also have areas of discoloration due to iron deposition. Oral ulceration and burning tongue may be present secondary to chronic anaemia. Necrotising stomatitis, possibly linked to agranulocytosis due to DFP treatment, has also been described (Tewari et al., 2009).

Iron deposition in the parotid glands can result in a dry mouth and painful facial swelling. A reduction in salivary IgA and phosphorous may occur, leading to a potential increase in risk of dental decay (Siamopoulou-Mavridou et al., 1992). Increased oral

Candida albicans colonisation has also been noted in patients with thalassaemia (Hazza'a et al., 2010).

Dental care

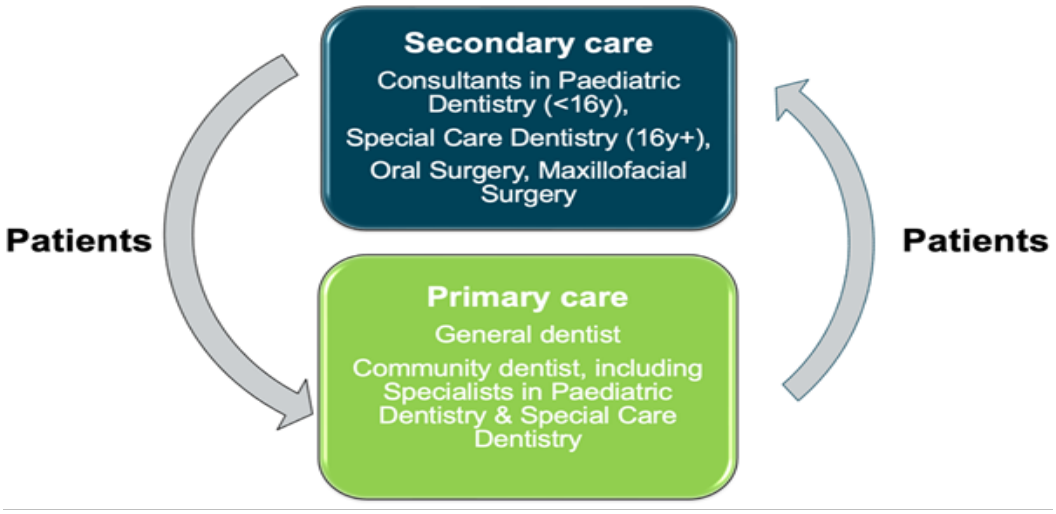
Accessing care

Patients with thalassaemia should be encouraged to register with their local primary care general dental services at an early age so that preventive regimens can be put in place and regular care provided (Kumar and Hattab, 2014). Dental care should be delivered as a coordinated team approach, ensuring close liaison between the dentist, the haematologist and, where appropriate, the paediatrician.

Dental care is provided on a shared-care basis (Figure 18.1). Most patients with thalassaemia can receive routine dental treatment under local anaesthesia from a local general dentist. This means that routine check-ups and treatments are mainly provided by the local general dentist, but referral may be required to specialist services in the community or hospital dental services. This may be for specific courses of treatment, such as dental extractions if the patient receives regular blood transfusions. Occasionally, patients may have multiple associated medical comorbidities that increase their risk and require special adaptations to be put in place. In such cases, regular care within specialised primary care-based special care dentistry/paediatric dental services may be more appropriate.

Hospital-based special care dentistry services also exist but are limited. They provide care for the most complex cases, particularly those who may require surgical intervention/dental extractions and/or general anaesthesia. They do not usually provide continuing care; on completion of treatment, patients are discharged to the primary dental services for regular review. Referral to hospital-based oral surgery/maxillofacial surgery services may be required occasionally.

Figure 18.1: Shared dental care



The most important principle of dental care is that prevention is better than cure. It is therefore extremely important that people with thalassaemia keep their teeth and gums in as clean and healthy a state as possible, by brushing teeth twice per day with a medium-textured small-headed toothbrush. Alternatively, an electric toothbrush can be used, and the dentist will be able to advise which ones are suitable. A fluoride toothpaste is recommended to reduce the risk of dental decay.

Regular check-ups are essential to ensure that problems can be picked up at an early stage and treated before acute infections arise. Individuals with thalassaemia who present with acute dental infections and abscesses should be treated at the earliest opportunity, especially if they have had a splenectomy. If the patient is not registered with a dentist, they should seek urgent care from their local emergency dental services or hospital so that antibiotics can be prescribed until suitable care can be arranged. Alternatively, their general medical practitioner may be able to assist.

For patients who are receiving regular transfusions, invasive dental treatment (e.g., dental extractions/deep scaling) should be planned within 1 week of the last transfusion when the patient's Hb profile is optimised. Increased risk of infection should be considered with perioperative antibiotic prophylaxis occasionally used, although there is a lack of evidence regarding its appropriateness.

Where there is misalignment of teeth due to maxillary expansion, orthodontic treatment or cosmetic dentistry may be required to correct alignment, although the result may not be stable and requires close review. Orthodontic treatment can be more complex due to the hypercellular nature of the bone, short roots and changes in dental arch parameters.

Although there is a theoretical risk associated with dental local anaesthetic containing adrenaline (may lead to impairment of local circulation), this is used routinely for patients with thalassaemia without reported problems.

Prevention of MRONJ in patients taking antiresorptive/antiangiogenic medication involves pretreatment screening, extraction of teeth with poor prognosis prior to commencement, adjustment of prostheses to prevent mucosal trauma, oral hygiene instruction, and cessation advice in relation to smoking and alcohol. This approach has been demonstrated to reduce the incidence of MRONJ by up to 50% (Vandone et al., 2012).

There is currently no clear evidence for the efficacy of any intervention to manage MRONJ; in the case of non-vital teeth/dental abscesses, root canal treatment should be considered to try and stabilise the infection, although dental extractions are unavoidable where this is not possible. Key principles are outlined below.

- When a patient is already on medications and a dental extraction is unavoidable, straightforward extractions can be undertaken in primary care, although a second opinion can be sought when necessary. Surgical extractions should be undertaken by a specialist in oral surgery or maxillofacial surgeon.
- There is no evidence supporting the temporary discontinuation of bisphosphonates as the drugs persist in skeletal tissues for years (Ottesen et al., 2020). There is also no conclusive evidence supporting the use of antibiotics or topical antiseptic prophylaxis in reducing the risk of MRONJ.
- If a patient has spontaneous or chronic bone exposure, referral to an oral surgery or oral and maxillofacial surgery specialist should be considered.

Comorbidities that may affect dental care

Individuals with thalassaemia may have multiple secondary effects of their disorder. These can impact on the delivery of dental care as summarised in Table 18.2, with a risk assessment undertaken prior to invasive dental intervention and appropriate treatment modifications put in place.

Table 18.2: Comorbidities associated with thalassaemia that may impact on dental care

	Risk assessment	Details	Dental treatment modification
Medical	Chronic anaemia	• Fatigue • Poor motivation • Oral manifestations of anaemia	• May need to reduce appointment time/adapt care • If sedation/general anaesthesia required, haematology input required for preoperative assessment
	Infection	• Increased risk due to splenectomy, immune abnormalities, iron overload, severe anaemia • Bacterial and fungal infections more common	• Manage infections early and more aggressively • Consider postoperative antibiotics after invasive dental treatment
	Transfusion	• Patients with TM ± intermedia receive regular blood transfusion	• Avoid dental treatment on the same day as the transfusion • Ideally schedule dental appointment within 1 week of transfusion • Consider referral to community dental service or hospital dental services for invasive dental procedures
	Liver dysfunction	• Due to iron overload leading to severe haemosiderosis and hepatic fibrosis	• Clarify extent of liver damage and related precautions, e.g., prescribing drugs, assessing bleeding risk

	Cardiomyopathy	• Due to iron overload • Risk of increased cardiac stress • Antidysrhythmics and occasionally anticoagulation may be prescribed for AF	• Close liaison between the haematology and dental teams to identify risks, e.g., management of anticoagulant medication perioperatively • Minimise stress/anxiety for the patient and avoid lengthy appointments • Consider referral to community dental service or hospital dental services for invasive dental procedures
	Diabetes	• Due to iron overload	• Determine severity and appropriate perioperative management • Consider increased infection risk
	Blood-borne viruses	• TTIs: HBV, HCV, hepatitis G virus • HIV	• Follow cross-infection control protocol • Confirm status of infection and management • Clarify presence/extent of liver cirrhosis: caution when prescribing drugs, bleeding risk (preoperative blood test may be required)
	Depression	• Related to lifelong adherence to a complicated medical regimen • Leads to poor motivation, reduced tolerance, acceptance and increased fatigue	• Consider impact on patient motivation and ability to accept dental intervention (Mednick et al., 2010) • Consider tolerance to dental procedure • Adapt treatment plan accordingly

Dental	Malocclusion	• Enlargement of maxilla due to bone marrow expansion/hyperplasia • Spacing of maxillary incisors	• May require orthodontic intervention • Where appropriate, adhesive dentistry may be appropriate (white fillings to mask the gaps)

	MRONJ	• Antiresorptive drugs for osteoporosis
		  • Oral or intravenous bisphosphonates
		  • Denosumab
			• Follow Scottish Dental Clinical Effectiveness Programme guidelines on MRONJ

	Caries	• Dry mouth • Reduced salivary IgA • Higher levels of salivary *Streptococcus mutans* • Poor motivation	• Follow NHS England toolkit for prevention
	Periodontal disease	• Short crowns and roots • Splenectomy • Poor motivation	• Regular monitoring and maintenance

Requirements

- Dental care should be delivered as a coordinated team approach, ensuring close liaison with the haematologist and, where appropriate, the paediatrician. This will help to identify the risk factors associated with thalassaemia and the potential associated comorbidities, and help manage/reduce them. The appropriate setting for any given dental treatment, namely primary or secondary (hospital-based) care, can then be determined.
- For all patients with thalassaemia receiving regular transfusions, invasive dental care should be delivered as close as possible to a planned transfusion, when the patient's Hb profile will be optimal. This can be up to 1 week after transfusion, depending on the extent of treatment planned.
- Where dental infection is present, it should be managed early and aggressively.
- All patients should have a comprehensive dental assessment with their local dentist prior to commencing medication associated with the development of MRONJ, to ensure that they are as dentally fit as feasible. To minimise the risk of osteonecrosis of the jaw, emphasis is on the reduction of mucosal trauma and the avoidance of subsequent dental extractions. Preventive

dental advice should be given, emphasising the importance of reporting any symptoms such as loose teeth, pain or swelling as soon as possible.

- If sedation or general anaesthesia is planned, close liaison with the haematology team is required. This will allow appropriate transfusion support to be arranged and the patient's Hb profile to be optimised. Inhalation sedation is preferable to intravenous sedation but may not be sufficient to enable the delivery of longer/more complex treatment, particularly when the patient is very anxious.
- Anaesthetists assisting with general anaesthesia/sedation for dental treatment should also be made aware of any additional cardiac, liver and or renal complications.
-

Recommendations

- Individuals with thalassaemia should have access to early, regular and preventive dental care. This will help reduce the impact of any associated oral manifestations and allow dental development to be monitored. This should include preventive oral care to reduce the risk of dental decay, including fluoride application/prescription, fissure sealants and dietary advice.
- Comprehensive oral assessment of children at age 12–13 years will enable the planning for/prevention of difficulties from overcrowding/misplaced teeth.
- If maxillofacial surgery is planned to manage severe facial deformity associated with bone marrow expansion due to thalassaemia, careful consideration should be given to the medical and surgical risks, including the risk of more extensive bleeding from the hypervascular bone.
- All patients prescribed medication known to be associated with increased risk of MRONJ should be advised of the risk and asked to have a dental assessment prior to commencement.

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Chapter 19

Miscellaneous Complications in Thalassaemia

This chapter describes complications in various systems that are not covered elsewhere in this document.

Background

The oldest cohort of patients with thalassaemia were born at a time when regular blood transfusion was not standard of care and iron chelation was experimental. Many patients aged >50 years have had prolonged periods of heavy iron overload as chelation was not standard of care until the late 1970s. Complications may develop as a long-term sequelae of heavy iron overload many years prior, even though the patient may not have had significant iron overload for many years after that. Complications such as hepatocellular carcinoma, AF and pancreatic exocrine insufficiency were previously not well described in patients with TDT, but are now increasing in frequency as patients age. Other complications such as renal stones, renal impairment and ophthalmological complications may be related in part to iron chelation, iron overload-mediated damage or underlying disease, and leg ulcers are often encountered in patients with NTDT but may also be seen in undertransfused patients with TDT.

One of the biggest challenges for patients is the long-term impact on mental health due to the constant need for treatment, be it transfusion, iron chelation or other treatments. Fatigue is a common symptom identified by patients on patient-reported outcome questionnaires, with about 45% of patients complaining of significant fatigue within the last 7 days. More significantly, using a standard validated EQ-5D questionnaire, 61% of patients surveyed reported anxiety and depression, and 59% reported impairment in activity on the day of completing the questionnaire (Li et al., 2022). These are all issues that need careful thought and consideration by the clinical team to ensure that the burden of treatment does not result in a serious deterioration in quality of life for the patient. Proactive questioning of a patient's mental and emotional wellbeing should be undertaken as part of standard of care, either during transfusion episodes with the support of the nursing teams or formally in the clinic.

Many of these issues are identified in older patients and it is important to ensure that patients have treatment options that help reduce the burden of disease. Proactive monitoring for early warning signs of complications developing to help reduce additional long-term health problems is integral to improving quality of life and supporting long-term health.

Liver disease is common in patients with TDT and NTDT. Several contributory factors may co-exist, including hepatic toxicity due to iron loading of the liver parenchyma, viral hepatitis, biliary disease and drug toxicity. The spectrum of clinical presentations includes acute and chronic hepatitis, obstructive jaundice, cholangitis, portal hypertension, hepatic insufficiency and hepatocellular carcinoma. It is important to recognise that liver fibrosis may occur in patients with normal liver function tests and so should be assessed in patients at risk of liver disease.

Part A: Gallstones

Gallstones are a common occurrence in people with thalassemia with a prevalence of 8.7–35% (Shahramian et al., 2018; Alhawsawi et al., 2019; Wanchaitanawong et al., 2021); incidence is higher in people with NTDT than those with TDT, primarily due to increased haemolysis, and increases with age. Gallstone complications may develop due to infection and inflammation of the gallbladder and biliary duct (acute cholecystitis, gallbladder empyema or ascending cholangitis), or due to obstruction of the biliary ducts and acute pancreatitis.

The management of gallstones/complications should mirror that of the general population as described in national guidelines (NICE, 2014). Ultrasonography is usually the first modality of imaging to detect gallstones. Magnetic resonance cholangiopancreatography may be indicated if the duct is dilated and/or liver tests are abnormal.

Elective cholecystectomy is appropriate after acute complications such as cholecystitis or pancreatitis settle. In some instances, endoscopy and/or surgery may be required on a more urgent basis. When gallstones are symptomatic and require surgical intervention, cholecystectomy should be done via the laparoscopic route as this is associated with fewer postoperative complications and a shorter hospital stay. There is some evidence to suggest more complications in the perioperative period (Premawardhena et al., 2019). Removal of the gallbladder during splenectomy is a common practice as acute cholecystitis can be severe in the splenectomised individual.

Recommendations

- When gallstones are symptomatic and require surgical intervention, cholecystectomy should be done via the laparoscopic route as this is associated with fewer postoperative complications and a shorter hospital stay.

Part B: Leg ulcers

Leg ulceration causes significant debility in patients with Hb disorders. Leg ulcers are reported to occur in 7.9% of patients with NTDT and up to 22% of patients with HbE/beta thalassaemia (Taher et al., 2010; Mehta et al., 2022). There are multiple hypotheses regarding the aetiology of leg ulcers, including chronic hypoxia due to anaemia, increased oxygen affinity of HbF, a hypercoagulable state and iron overload through the generation of reactive oxygen species (Matta et al., 2014). Increasing age, iron overload, hypercoagulability and splenectomy are risk factors for the development of leg ulcers (Taher et al., 2010).

Leg ulcers typically appear in the second decade of life after minor trauma, most commonly on the medial or lateral malleoli, and may be either unilateral or bilateral (Mehta et al., 2022). They heal slowly and tend to recur or become chronic, causing pain impacting adversely on quality of life and disability.

Optimal management is unclear as there are no proven treatment approaches. A variety of therapies have been described in small studies: compression bandages, various modalities of dressings, growth factors and pentoxifylline (currently unlicensed for the treatment of leg ulcers in the UK). The results of blood transfusion have been variable, from rapid healing with a 100% recurrence rate to slower rates of healing (Matta et al., 2014; Aessopos et al., 2006). Oral zinc is widely prescribed; however, a recent review found that oral zinc does not appear to aid the healing of arterial and venous ulcers in the leg (Nelson and Bell-Syer, 2014).

Recommendations

- Patients with leg ulcers should be assessed by an MDT familiar with the management of leg ulcers in patients with haemoglobinopathies.
- Standard principles apply such as good wound hygiene, compression therapy if appropriate, and managing complications such as pain and infections.
- Patients should be offered lifestyle advice to promote ulcer healing and reduce the risk of recurrence, such as regular walking, avoiding leg trauma and the use of frequent emollients.

- Hypertransfusion regimens are frequently used to improve anaemia, although there are no data on the optimal pretransfusion target Hb level. Maintaining pretransfusion Hb levels >105 g/L may be useful in some patients in addition to standard leg ulcer care.
- Referral to specialist dermatology and plastic surgical teams for skin grafting may be needed in severe cases.

Part C: Liver

Aims

To preserve liver function and avoid liver damage related to iron toxicity, viral hepatitis and adverse effects of therapy, including iron chelation therapy.

To investigate and treat liver abnormalities promptly.

To diagnose and manage common complications in thalassaemia as they arise as patients age.

Standards

- Liver function tests should be monitored at regular monthly intervals.
- Liver iron levels should be maintained within safe limits to avoid hepatic damage, using the range of available chelation options, and taking steps to encourage adherence to treatment.
- Adjustments to chelation and other treatment should be made promptly if abnormalities of liver function are detected on routine monitoring tests.
- Vaccination against hepatitis A virus and HBV infection should be ensured.
- Liver disease should be managed jointly with a designated specialist hepatologist.
- Management of chronic HCV infection should include histological assessment of fibrosis on biopsy and/or non-invasive techniques.
- Antiviral therapy aimed at sustained viral clearance should be planned and managed in collaboration with a designated specialist hepatologist.
- Patients with established cirrhosis should have regular surveillance checks for hepatocellular cancer.
- Patients presenting with deranged renal function and/or renal colic should be assessed for renal stones, with appropriate referral for specialist care as required.

- Weight loss, abdominal pain and diarrhoeas with or without steatorrhea should prompt investigation for pancreatic exocrine deficiency and/or other gastrointestinal complications.

Iron overload and chelation therapy

The liver is the main site for iron storage and clears NTBI from the plasma and incorporates it into ferritin. When the storage capacity of ferritin is exceeded, free iron accumulates in the hepatocyte leading to the production of reactive oxygen species that in turn causes lipid peroxidation and protein damage. This contributes to hepatic inflammation and necrosis, and leads to the development of fibrosis (Sikorska et al., 2016).

LIC values between 7 and 15 mg/g dw are associated with moderate and severe iron overload, respectively (Allali et al., 2017), whilst LIC >16 mg/g dw is associated with an increased risk of hepatic fibrosis.

In general, where possible, the LIC should be maintained <7 mg/g dw and ideally <5 mg/g dw. MRI iron assessment of the liver is also mandatory as a pre- and post-transplant evaluation in cases of HSCT (Mavrogeni et al., 2018).

MRI assessment of LIC enables monitoring of liver iron levels without the need for serial biopsies and is considered less subject to variability than analysis of liver biopsy samples (Anderson et al., 2001; St Pierre et al., 2005; Wood et al., 2005). The frequency of monitoring for liver iron is described in **Chapter 6: Iron Overload and Management**.

Non-invasive assessment of liver fibrosis using transient elastography Fibroscan® may be helpful in assessing liver disease in people with thalassaemia. Liver stiffness measurements have been shown to correlate with LICs assessed by MRI T2* (Pipaliya et al., 2017; Atmakusuma et al., 2021) but further validation is required. Liver biopsy should be reserved for the investigation of complex liver pathology, and for the staging of liver fibrosis, when clinical signs and non-invasive assessment are in conflict or equivocal.

Mild elevations of transaminase levels are relatively common in patients receiving DFP, particularly in patients with HCV infection, but these changes are usually non-progressive and are rarely of sufficient severity to warrant treatment discontinuation (Ceci et al., 2002; Cohen et al., 2003). Initial concerns about DFP and the progression of liver fibrosis were not confirmed in subsequent studies, which suggest that fibrosis was more related to hepatic iron loading in the presence of

HCV infection (Olivieri et al., 1998; Wanless et al., 2002; Maggio et al., 2002; Töndury et al., 1998).

Transaminitis is observed in patients treated with DFX and is generally three to five times the upper limit of normal. Liver function tests should be checked before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, DFX should be interrupted. Once the cause of the liver function test abnormalities has been clarified or after return to normal levels, cautious reinitiation of treatment at a lower dose followed by gradual dose escalation may be considered. DFX treatment is not recommended for patients with severe hepatic impairment (Child–Pugh class C) (DFX SPC) and it should be used with caution in those with Child–Pugh class B impairment.

All three chelators can be considered in patients with raised transaminases and Child–Pugh class A hepatic impairment, and they are effective in reducing liver iron (Maggio et al., 2011); DFX can stabilise or reverse liver fibrosis (Deugnier and Turlin, 2011; Maira et al., 2017; Sousos et al., 2018)

Viral infections and liver disease

There is a wide global variation in the prevalence of HCV infection in patients with thalassaemia in published data. Patients were infected with HCV prior to routine testing of blood donors and hence there is a population of patients aged >30 years who were infected via transfusions administered in the UK. The vast majority of these patients have either spontaneously cleared the infection, have negative polymerase chain reaction tests for HCV RNA, or have been successfully treated and the infection eradicated. Currently active HCV infection is usually seen in patients who were treated outside of the UK. The risk of TTI in the UK remains extremely low (Narayan et al., 2021).

Hepatocellular carcinoma is increasingly reported, particularly in older patients (mean age 48 years) (De Sanctis et al., 2020). Risk factors include high iron levels and chronic viral hepatitis (Fianianos et al., 2018; Marsella et al., 2019), but hepatocellular carcinoma is not restricted to those with chronic viral hepatitis and is well recognised in patients with NTDT (Borga-Pignatti et al., 2014). Hepatocellular carcinoma was not a common cause of death in survival studies published over the past 20 years; however, it is becoming a more important cause of mortality (Borgna-Pignatti et al., 2004; Telfer et al., 2006; Moukhadder et al., 2017). There is a paucity of published data on optimal management although recent management guidelines have been suggested (Mancuso et al., 2020).

The indication for HCV treatment in the thalassaemia population is similar to that of the general population. Treatment of HCV infection previously required lengthy periods on unpleasant medication, including interferon and ribavirin, but has been revolutionised by the introduction of highly effective directly acting oral antiviral agents that can clear infection in the majority of patients with very few side effects. The effectiveness of directly acting oral antiviral agents has been demonstrated in patients with thalassaemia (Mangia et al., 2017; Kamal et al., 2019; Ponti et al., 2019; Maffei et al., 2020). In some cases ribavirin can now be avoided, but it is still indicated for the treatment of patients with established cirrhosis. Ribavirin provokes haemolysis and transfusion requirements are substantially increased during combination treatment; thus, chelation needs to be intensified during and after the completion of therapy. There is no consensus about the use of DFP or DFX during antiviral therapy. In one trial, some of the patients did use DFP during therapy; however, assessment of neutropenia becomes more problematic, since both DFP and interferon may cause a decrease in neutrophil count (Telfer et al., 1997).

HBV infection is now rare among patients with thalassaemia in the UK as a result of the exclusion of high-risk donors, and the screening of units before transfusion and for HBV infection in recipients. Patients who are infected with HBV should be reviewed at a specialist liver unit where a decision can be made about antiviral therapy for the management of hepatitis. These patients remain at high risk of complications such as cirrhosis and hepatoma, and need to be on long-term surveillance programmes.

Lifestyle and other factors

Iron overload alone in the absence of hepatitis infections or chelation drugs results in raised transaminase levels (Jensen et al., 2003; Angelucci et al., 2000), and this should be taken into account when monitoring iron chelation side effects.

Patients with thalassemia are still susceptible to liver disease from non-transfusion, non-infective and non-drug-related causes. Underlying liver problems related to the above are worsened by the impact of excessive alcohol use. Patients should be advised to use alcohol within the national gender-based guideline limits and to avoid binge drinking.

Non-alcoholic fatty liver disease is common in both adults and children (European Association for the Study of the Liver et al., 2016). Non-alcoholic fatty liver disease can result in iron overload in the non-thalassaemia patient population and this is known as dysmetabolic iron overload. Non-alcoholic fatty liver disease results in liver damage due to non-alcoholic steatohepatitis. Patients with thalassaemia who may be at risk of

this complication as a consequence of obesity should be given lifestyle advice, and referred to dieticians and hepatologists for appropriate advice.

Requirements

- A hepatologist should be designated for each thalassaemia SHT.
- Serological tests to monitor for viral hepatitis (anti-HCV, hepatitis B surface antigen, and anti-HB core antigen) should be conducted every year. Adequate protection from HBV should be ensured by a full course of vaccination initiated before the first transfusion or as soon as possible after it, and then by serial monitoring of anti-HB antibody titre and 'booster' vaccination as needed.
- Liver iron levels should be maintained <7 mg/g dw, and ideally <5 mg/g dw. Assessments of liver iron should be by MRI (R2 or T2*) rather than liver biopsy.
- Patients with active HCV (HCV RNA-positive) or chronic active human papilloma virus infection should be referred to the designated hepatologist for further virological studies (genotype, quantitation of viral load), assessment of liver fibrosis and decisions about management.
- Antiviral therapy is recommended in all patients with HCV viraemia.
- Patients with unexplained abnormalities of liver function tests should have a detailed drug and alcohol history taken, and be investigated promptly. Liver biopsy remains the only modality able to provide a histopathological diagnosis but non-invasive tests of liver fibrosis should be considered for assessment of liver fibrosis if histological examination of the liver parenchyma is not essential.
- Patients with previous HCV infection and/or severe iron overload should undergo Fibroscan® assessment to assess for severity of fibrosis. If this is identified then referral to hepatology should be done to ensure appropriate risk assessment for hepatocellular carcinoma and, if needed, surveillance should be initiated.
- Patients with established cirrhosis should be reviewed regularly by the designated hepatologist. Surveillance for hepatocellular carcinoma (measurement of alpha fetoprotein, liver ultrasound, or cross-sectional abdominal imaging by MRI or computed tomography) should be done at least every 6 months. Surveillance for oesophageal varices should be undertaken at the time of diagnosis of cirrhosis and every 2–3 years thereafter. If varices are detected they should be treated by a specialist hepatologist.
- The management of hepatocellular carcinoma should be individualised, taking into account the patient's comorbidities.

- Patients with a history of excess alcohol use should be supported with regular advice on safe consumption and carefully monitored for the development of alcoholic liver disease.

Part D: Ophthalmological Manifestations in Thalassaemia

The ophthalmic changes seen in thalassaemia may be due to the disease itself, iron overload or iron chelation therapy, with an overall frequency varying between 41.3–85% (Gartaganis et al., 2000; Taneja et al., 2010; AbdelMalik et al., 2012). The following manifestations have been described.

- Ocular surface changes such as dry eyes and conjunctival vascular abnormalities (Gartaganis et al., 2003).
- Lens opacification (cataract) with incidence reported to be between 9.3 and 44% (Aksoy et al., 2014; Taneja et al., 2010; AbdelMalik et al., 2012).
- Ocular fundus abnormalities characteristic of pseudoxanthoma elasticum (Barteselli et al., 2014), which is more common in patients with NTDT who are older, have been splenectomised, and who have required transfusions and iron chelation. Some of these changes may predispose to sight-threatening complications and regular eye checks are recommended. Pseudoxanthoma elasticum-like fundus changes have also been noted in various studies (Liaska et al., 2016). Other retinal degenerative appearances have been described (Jethani et al., 2010).
- DFO retinopathy is well described (Di Nicola et al., 2015). This complication is more likely to develop in younger patients treated with high doses of DFO with low SF levels. Ocular toxicity usually manifests as night blindness, blurred vision, decreased visual acuity, colour vision impairment or cataract formation. Findings on fundoscopy can vary (Haimovici et al., 2002; Lakhanpal et al., 1984; Cohen et al., 1990). Further assessment includes techniques such as electrodiagnostic methods, angiography and fundus autofluorescence (Viola et al., 2014; Dettoraki et al., 2017). The pathophysiology is felt to be chelation of metals such as iron, copper and zinc, which are essential for normal retinal function (Chaston et al., 2003; Chaston and Richardson, 2003). Severe irreversible retinopathy can be prevented by regular monitoring of SF levels and review of DFO dosing (Porter et al., 1989).
- There have been isolated case reports describing ophthalmic complications in patients treated with DFX-toxic maculopathy (Pan et al., 2010), reversible retinopathy (Walia and Yan, 2013) and lens opacities (DFX SPC).

Patients reporting symptoms such as night blindness, visual field defects, visual loss and loss of colour vision should be promptly assessed by ophthalmology teams with experience of thalassaemia ocular pathology.

Recommendations

- All patients with thalassaemia who describe changes to their vision or other ophthalmological symptoms should be reviewed by an ophthalmology team; assessments should include electrodiagnostic tests.
- All patients who are on continuous intravenous DFO infusion should have a baseline assessment and then have close ophthalmological monitoring, as prompt drug discontinuation might arrest retinal damage.
- Patients on high doses of DFO should have regular measurement of their SF level and the therapeutic index of DFO should be maintained <0.025.
- Patients treated with DFX should have a baseline ophthalmological evaluation and further assessment if new visual symptoms occur.

Part E: Pancreatic Exocrine Insufficiency

Pancreatic exocrine insufficiency is being increasingly identified as a problem in older patients with thalassaemia. This arises when the pancreatic parenchyma has been damaged, which may be seen in patients secondary to iron overload. This is a late presentation as a consequence of pancreatic iron overload and, even if a patient currently has a well-controlled iron burden, historical iron burden is important (Jansen et al., 1984; Santos García et al., 2018). Many patients with pancreatic enzyme insufficiency will have diabetes mellitus and a history of cardiac or severe liver iron overload (Kaser et al., 2023).

Abdominal cramps and weight loss are the commonest symptoms reported by patients. Fatty stools that are difficult to flush may occur in some patients. Malnutrition is frequently encountered due to malabsorption (Hopson et al., 2022).

Stools should be sent for faecal elastase testing and low levels are indicative of pancreatic exocrine insufficiency. Coeliac disease should be ruled out and an endoscopy and an MRI may be needed. Blood tests should be taken to ensure vitamin B12, folate, vitamin D, zinc and magnesium levels are maintained, and appropriate replacement provided if needed. Patients should be referred to gastroenterology for specialist investigations and appropriate management.

Management is with pancreatic enzyme replacement therapy. Patients should be advised to limit/stop alcohol use and smoking.

Standards

- Patients presenting with weight loss and abdominal pain should have a detailed history and examination followed by a faecal elastase test.
- Patients should be referred for specialist gastroenterology input if faecal elastase is low.
- Patients should be encouraged to stop smoking and reduce/limit alcohol.

Part F: Renal Complications

Renal complications have become more relevant for patients with thalassaemia. A high frequency of renal stones in patients is thought to be linked to an increased predisposition to hypercalciuria (Aliberti et al., 2022; Bakr et al., 2014). Iron chelation and the impact of anaemia caused by the underlying disease/iron overload may cause renal glomerular dysfunction manifesting as any of the following: proteinuria, hypercalciuria, hypouricaemia with uricosuria or hypophosphataemia with phosphaturia (Thongsaen et al., 2023).

Chronic anaemia and subsequent hypoxia can cause oxidative stress and associated lipid peroxidation, leading to functional abnormalities in tubular cells (Nagababu et al., 2008), and may accelerate the deterioration of renal function by inducing tubulointerstitial hypoxia (Kaissling et al., 1992). There is some evidence to support iron overload itself causing tubular dysfunction in patients with thalassaemia who are transfused (Koliakos et al., 2003; Ali and Mahmoud, 2014). Glomerular dysfunction has also been identified in patients with higher than normal creatinine clearance levels and evidence of microalbuminuria and raised cystatin C levels (Aldudak et al., 2000; Hamed and El Melegy, 2010), with and without chelation therapy.

Iron chelation itself can cause renal injury and is well described in patients receiving DFX (Naderi et al., 2013; Dee et al., 2014; Economou et al., 2010). There is some evidence in the literature that high doses of chelators at low levels of iron burden, or a rapid fall in iron burden due intensive chelation, are more likely to result in deterioration in renal function and the development of tubulopathy (Yui et al., 2021).

Management of patients with thalassaemia should include routine assessment of renal function as part of chelation monitoring. In addition, if their biochemistry profile shows

any electrolyte abnormalities suggestive of tubular dysfunction then it should be investigated, and if the patient is taking DFX this should be stopped.

Standards

- Renal function should be assessed monthly for patients on DFX.
- In the presence of unexplained electrolyte abnormalities and or glycosuria/microalbuminuria, consider renal Fanconi syndrome.
- Input from a renal specialist team should be obtained if renal function does not improve following dose reduction or omission of iron chelation.

Part G: Urological Complications

Patients with thalassaemia can develop urological complications such as renal stones, which are present in around 18% of patients (Abrahams and Stoller, 2003). Presentation can vary from asymptomatic to the development of acute kidney injury and hydronephrosis from a stone causing obstruction. This may first be identified as unexplained renal impairment via biochemistry assessment done as part of routine monitoring. It is important to ask about renal/loin/groin pain and check for haematuria. Renal impairment can be assumed to be due to iron chelation if a patient is using DFX; if renal function does not improve after 1 week of withdrawal of DFX, an urgent scan should be considered to look for renal stones, especially if there are symptoms suggestive of a renal stone. Patients presenting with symptoms suggestive of renal stones should be referred to a specialist urology team for management of renal stones.

Patients may develop recurrent urinary tract infections as renal stones can harbour bacteria, and a low threshold should be used for use of prophylactic antibiotics (Wong et al., 2013).

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Chapter 20

Optimising Venous Access

"Listen to the patient preference; we know what we need"

"I know what cannula suits me and where to put it and to warm my arm up with a heat pad before insertion"

"I was taught how to look after my line (CVAD) at home and had step by step written instructions for if I forgot something."

Aims

To ensure that intravenous access required for therapeutic or diagnostic purposes is performed safely, minimising risk and with consideration/participation of the patient.

Standards

- Peripherally inserted venous cannulas (PIVCs) are suitable for periods of therapy lasting fewer than 5 days. The goal is to use the smallest gauge cannula in the largest vein available in a position suitable for the patient.
- Consider CVADs when peripheral access becomes difficult or for longer-term therapy with intravenous DFO.
- Adult patients with CVADs should be considered for thromboprophylaxis for the duration of the use of the CVAD, unless there is a contraindication or unacceptable risk of bleeding.

Patients with TDT need frequent blood sampling and cannulation throughout their lives; therefore, preservation of veins and taking steps to avoid the development of needle phobias is paramount to ensure a good patient experience. In childhood, careful support and management of patients and their families around the time of blood sampling and transfusion builds confidence for future cannulations, and a

bad experience with difficult cannulation or venepuncture can result in significant psychological trauma that can make future cannulations more difficult.

Adults are expert patients and very familiar with their venous anatomy, and will know which veins are best for cannulation and for blood sampling.

If cannulation is difficult in children then CVADs can help support them until their venous access improves. For adults, CVADs have additional risks of thrombosis and patients should be counselled about the increased thrombosis risk and advised to take thromboprophylaxis if a CVAD is inserted; they should also be considered for therapeutic anticoagulation if there are additional risk factors for thrombosis such as a previous history of thrombosis or if the patient has been splenectomised.

Background

Cannulation

Tips for paediatric cannulation

The aim for paediatric patients with thalassaemia is to make this the best experience possible, and to avoid or minimise complications and distress, where possible, in order to reduce long-term anxiety and negative associations for the child.

- Consider use of distraction/play therapy in preparation for cannulation to reduce anxiety in a child.
- Use local anaesthetic creams such as LMX4® Ametop® (as per local policy) prior to cannulation.
- Sucrose 24% solution can be helpful in babies for procedural pain management.
- Young children will need to be held securely for the procedure (Royal College of Nursing, 2019).
- Involve psychology professionals to support children/young people with cannulation procedures to try and avoid needle phobia.
- Take steps to preserve small veins. Use a butterfly needle for blood tests from smaller veins to preserve larger veins for cannulation.
- Restrict the number of attempts to cannulate each time.
- Avoid leaving peripheral cannulas during ambulatory homecare, as this can lead to further vein damage.

- Offer rewards or treats, if appropriate, following the procedure to encourage trust, compliance and co-operation.
- Allow parents/carers to be involved during the cannulation procedure, in order to support the baby/child/young person (parents will also need their own support because it will be emotional and challenging for them too).

Tips for adult cannulation

There are patients who and situations when it can be difficult to cannulate. It is important to not label the patient as this offers no advantage to the patient or the healthcare professional who needs to perform the procedure. Many thalassaemia units and haematology units have professionals who are expert in obtaining access, and this is often through experience, but all can improve by sharing 'tips'. Some of these are covered below

- Take time to assess and listen to the patient as they will often know their venous anatomy quite well.
- Assistance methods include heat pads, air gloves, Veinplicity®, Accuvein® and good hydration prior to the need for access, when possible. Where possible, insert the smallest cannula into the largest vein available.
- If the procedure requires more than one attempt, then it is important to adhere to local policy on the number of attempts before passing on to a colleague or escalating. At these times, it is important to communicate with your patient(s); they may prefer you to continue with cannulation but, in this scenario, it is important to document the patient's decision and consent.
- When seeking assistance consider what type of help is needed. This may be someone with similar skills, expert skills or equipment, or you may need to advocate that cannulation should stop and alternatives to peripheral cannulation be sought in the patient's best interests.
- Healthcare professionals managing patients with thalassaemia are responsible for caring for veins in patients who will need PIVCs over long periods. It is paramount that care is taken throughout the whole process.

Monitoring peripheral cannulas

All PIVCs should be monitored at least every 8 hours for phlebitis and infiltration or extravasation.

Phlebitis

All hospitals will use some form of phlebitis monitoring tool; the Royal College of Nursing standards for infusion therapy (2010) provide a visual infusion phlebitis (VIP) scale for use (Jackson, 1998). Clinical indication replaces the 3-day remove/replace standard because rates of phlebitis increase after 96 hours in situ (Loveday, 2014).

Infiltration or extravasation

This is when the fluid or drug leaks from the veins into the surrounding subdermal or subcutaneous tissue; the term 'tissuing' is often used. The Royal College of Nursing provides an infiltration scale that can be used. Infiltration is where the fluid is non-vesicant. Extravasation is where the fluid/drug is vesicant, and action should be taken quickly to minimise damage to the surrounding tissue. All hospitals will have an extravasation policy. Extravasation should prompt immediate discontinuation of the infusion and requires immediate intervention (BNF, 2016). Extravasation should be identified and assessed by the healthcare professional and appropriate interventions/actions should be implemented to minimise its effects (Fidalgo et al., 2012).

Blood transfusions

Blood administration should be through a sterile PIVC specifically designed for blood administration using a 170–200-µg integral mesh V filter (J pack, 2014. It should be changed when a transfusion episode is complete, every 12 hours, or if there is contamination or the integrity of the product has been compromised.

Central venous access devices

Peripherally inserted central catheters

These can be inserted at the bedside (in some hospitals) or by interventional radiology, and are easy to remove as they are only held in place with a stat lock. They are now the most commonly used devices for adult patients, especially for intravenous DFO. They are easy for patients to hide or cover. Caution should be used for blood sampling due to the length of the line and the potential for the line to become blocked. Some patients may need assistance to use it one-handed.

Short-term central venous access devices

These are only in site for 10–14 days. They are not used for long-term treatments for patients with thalassaemia.

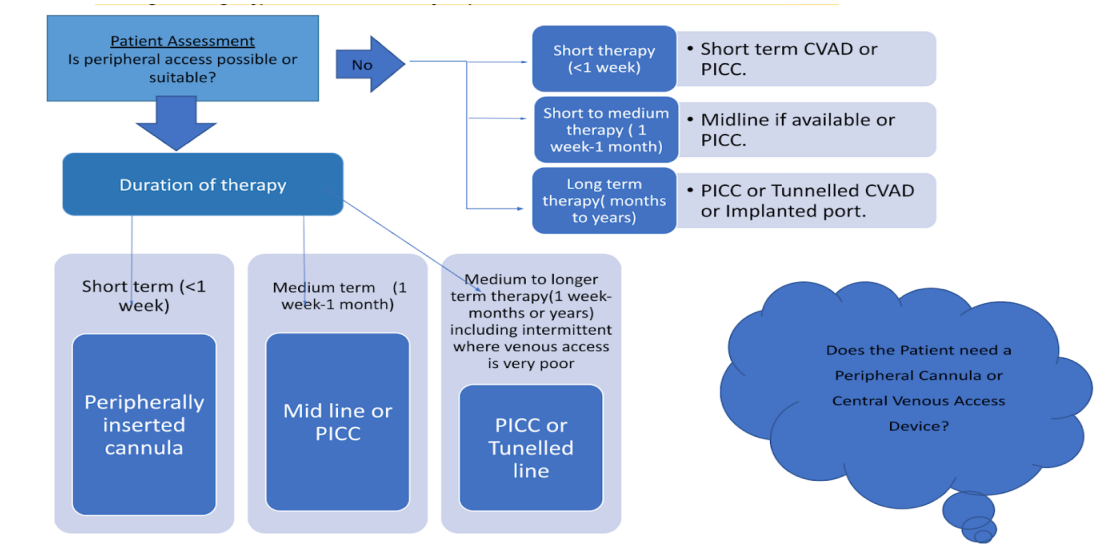
Skin-tunnelled central venous access devices

These lines (Groshong® and Hickman®) were previously used frequently. They have an internal cuff that grafts the line in place in the skin tunnel. They are good for blood sampling and the administration of all types of intravenous therapies, and can stay in place long term if free from infection/thrombus. Patients can learn to use these devices by themselves.

Implanted ports

These indwelling ports (portacaths) are often used in children. The port is under the skin and is not visible when not in use. They can stay in long term if kept free from infection/thrombus. Accessing the port requires training and patients cannot access the port themselves.

Figure 20.1: Deciding on the right type of venous access for patients



Recommendations

Competence

Registered healthcare practitioners undertaking the insertion of vascular access devices, their care and management, and the administration of infusion therapy will have undergone theoretical and practical training in the following as part of a competency assessment. Local policy procedures and guidelines should be followed regarding the specific initial and ongoing training and education that each healthcare practitioner requires.

Flushing technique

Flushing is a vital part of maintaining patency in CVADs of all types and should occur before and after their use. Normal saline at a minimum of 10 mL using a push–pause technique is used. Aspiration before use of a CVAD to remove the dead space is the ideal practice.

Patient care

A patient going home with a CVAD has extra safety implications and therefore assessment of the patient is paramount:

- Assessment of the home setting to include the preparation, administration and storage of intravenous therapy equipment.
- The patient or carer should be able to demonstrate understanding of and the ability to perform procedures.

Patients should be given a set of verbal and written instructions about all aspects of the therapy that should be tailored to their cognitive, psychomotor and behavioural abilities. This should include troubleshooting or what to do ‘when something goes wrong’.

Patients should have knowledge of/and written information about who to contact regarding line concerns at any time of the day. In some settings, this may be the specialist nurses during the day and the emergency department out of hours. This should include presenting to the hospital if they develop a temperature of ≥38 °C.

Documentation

There should be an organisational policy that sets out the requirements of documentation for insertion and recording the monitoring of CVADs.

Complications

Healthcare professionals who manage CVADs need to be educated, deemed competent, and constantly updated about their correct use and care. Additionally, clinicians should be skilled in the strategies and methods necessary to reduce device complications (Gorski, 2021), and must be able to recognise and manage the complications of these devices.

All organisations will have guidance on managing the commonest complications, which are infection and clots. Patients should be aware of the early signs of these potential complications.

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Chapter 21

Review of Patients Previously Treated Outside the UK

Aims

To ensure that patients starting, or returning, to use thalassaemia services in the UK can be assessed thoroughly at the outset, and start receiving care without delay.

To ensure that patients and their families have a proper understanding of the condition and any complications.

To address any unidentified or unmanaged problems.

To ensure the patient and family is introduced to and integrated into local continuing care arrangements.

Standards

- Children and adults who have been receiving treatment outside the UK will be seen, as soon as possible after they arrive, at an established SHT for a thorough assessment.
- Transfusion treatment will be restarted without delay.
- Any complications that may have developed will be detected and discussed with the individual and family, and management plans put in place.

Background

Thalassaemia services in many countries are of the highest quality and it is unlikely that a patient previously managed in, for example, Italy will have undetected problems. However, in some lower-income countries blood supplies may be erratic, screening of donor units may not be complete or iron chelation may be unaffordable; therefore, it is

possible that a patient may have problems or complications that they are unaware of and/or that are untreated. Optimising transfusion and chelation treatment regimens, and actively managing any complications that have not been recognised to date, are likely to improve wellbeing and reduce morbidity and mortality.

Patients who have recently arrived in the UK may present to the emergency department with anaemia or infection, may be referred by their GP, or may make contact through the local support organisation or another patient. It is necessary to make an early appointment, to establish in the first instance when the patient's next transfusion is due, and to start to make an overall assessment of their condition and its treatment. They may arrive with a full understanding about their condition and plentiful documentation about their management to date, or they may have very little or none.

Their initial assessment will include a full medical history covering:

- age at diagnosis and age at first transfusion
- transfusion history including transfusion reactions
- chelation treatment (current and previous), including frequency, doses, route, and any chelator intolerances or complications
- any coincident diagnoses
- any other current medications
- developmental history including puberty if relevant age
- surgical procedures, particularly splenectomy
- complications from iron overload including cardiac failure, dysrhythmia and endocrinopathies: diabetes, hypothyroidism, hypoparathyroidism or hypogonadism
- history of bone problems such as fractures and treatment for osteoporosis.

The results of any investigations they are aware of should be explored, including haematology, biochemistry, virology and any recent MRI iron quantitation of the heart and/or liver, and where the tests were done.

A family history is important for general clinical assessment, and will help elucidate whether other family members should be screened for thalassaemia.

Patients should have a full medical examination, recording height (sitting and standing), weight, the presence of thalassaemia-specific facies or dental problems, signs of cardiac failure, the presence of an enlarged liver or spleen, surgical scars, stigmata of chronic liver disease, the stage of pubertal development and any clinical signs suggesting endocrinopathy.

Requirements

- Any newly arriving patient should be offered an early review with the team at the most convenient SHT, with appropriate translation services available if needed. This will include a full discussion of their condition from the time of diagnosis, and previous and current treatment regimens, together with the results of any investigations that they are aware of and a comprehensive medical examination.
- Baseline investigations (Table 21.1) should be undertaken after discussion with the patient and with their consent.

Table 21.1: Baseline investigations

Immediate investigations	FBC, blood film, Hb HPLC (although may not be informative if recently transfused; family study may help)
	SF or plasma ferritin assay
	Blood group and antibody screen
	RBC genotyping, offered through the NHSBT
	HBV and HCV serology to include HBV surface antibody titre
	HIV serology preceded by pretest counselling
	Full renal, liver, bone and sex hormone profiles, thyroid function tests, random glucose, fructosamine if diabetic, PTH, vitamin D level, G6PD level
	Globin genotyping (alpha- and beta-globin genotype, -158 ^{G}yXmn1 C→T polymorphism)

	Parental samples may be informative
Semi-urgent investigations	OGTT if no established diabetes mellitus
	Abdominal and pelvic ultrasound to access for gallstones, liver fibrosis or cirrhosis, spleen size and renal tract pathology (renal stones), uterine/ovarian tissue in females
	Cardiac T2*
	Liver iron quantification using T2* or R2
	DXA scan
Other specialist assessments and clinical reviews	Audiology baseline
	Ophthalmology baseline
	Cardiac review
	If diabetic, specialist diabetic clinic
	Abnormal OGTT: dietician and diabetes nurse review
	If other endocrinopathies, endocrine clinic
	If hepatitis B surface antigen- or C antibody-positive, hepatology clinic
	Patient and family members should be offered genetic counselling, as appropriate

- An early review visit should be planned to discuss the results of these investigations and any necessary treatment changes.
- Vaccination for HBV should be undertaken as soon as possible if the patient has been tested and is non-immune.
- Arrangements for continuing care should be carefully discussed with the patient and family, either at the local clinic with review visits at the SHT or entirely at the SHT if this is closer.
- The family should be introduced to their key contact(s) and contact numbers exchanged.

Recommendations

- The patient/family should be given written information about the services available and how to make contact as needed, in or out of hours.
- A ‘first clinic visit checklist’ should be completed.
- As soon as possible, they should be taken to visit the transfusion unit that they will be attending and meet the staff there. If possible, they should be put in touch with some other patients and families.
- They should be given contact details for any local support groups or organisations, and for the UKTS.

SECTION D: Non-Transfusion-Dependent Thalassaemia

Chapter 22

Non-Transfusion-Dependent Thalassaemia

"People think thal intermedia is just a less severe type of thal major, but it has its own problems, especially as you get older."

This section addresses issues covered by preceding chapters as they apply to NTDT. Where the same standards and key interventions apply, they are not repeated; where there are differences, they are highlighted. Comprehensive guidelines for the management of people with NTDT have recently been published by the TIF (Taher et al., 2023). This chapter outlines the care of patients with beta thalassaemia intermedia, compound heterozygous states such as HbE/beta thalassaemia and HbH.

Aims

To maintain the good health, normal growth and development, and good quality of life during childhood, adolescence and adulthood of people with NTDT, avoiding unnecessary treatment with regular transfusions in those with milder clinical features, but intervening with appropriate transfusion as needed.

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

Standards

- A comprehensive DNA diagnosis (beta-globin mutations, alpha-globin genotype, Xmn1 C→T polymorphism) should be undertaken as soon as the diagnosis of thalassaemia has been established.
- Parents, carers and patients should be counselled at diagnosis, and as often as needed thereafter, about the likely course of the condition and the therapeutic options available.

- During the first 3–5 years of life, children with thalassaemia should be monitored carefully and systematically for evidence of thalassaemia features that may require regular transfusion therapy. Older children, adolescents and adults with a diagnosis of NTDT should continue to be monitored regularly, for consideration of indications for transfusion, and for iron loading, PHT and extramedullary haematopoietic masses in particular.
- Complications of NTDT should be identified at an early stage and treated promptly.

Background

Definition

NTDT encompasses the spectrum of clinically significant thalassaemia syndromes that do not require regular transfusions in early childhood to sustain acceptable health, growth and development. The definition includes a broad range of phenotypes and genotypes, and patients can be subdivided into those who have never been transfused and those who require occasional transfusions. These groups not been formally defined but may include people who receive up to six transfusions per year (Taher et al., 2010; Weatherall 2012). The pathophysiology and severity of iron overload in these two groups will differ, and in general iron overload and the need for chelation is likely to be increased in the latter group.

In NTDT, ineffective erythropoiesis due to imbalance in alpha/beta-globin chain production results in a multitude of pathophysiological manifestations such as chronic anaemia, primary iron overload and hypercoagulability, and changes due to medullary expansion (skeletal deformity, osteoporosis and extramedullary haematopoiesis). An Hb level >10 g/dL has been shown to be a predictor for absence of mortality and improved overall survival (Musallam et al., 2022). In addition, chronic anaemia causes fatigue, reduced exercise tolerance and has an adverse effect on quality of life (Taher et al., 2015; Mihailescu et al., 2020; Cappellini et al., 2019).

Genetics and clinical phenotypes

Genetics

Beta NTDT can be the result of the inheritance of milder beta-globin gene mutations, allowing sufficient beta-globin chain production for some HbA production. Additional genetic factors, such as coinheritance of alpha thalassaemia or the inheritance of a genetic determinant of enhanced HbF 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 alpha chains within the developing erythroblast. The clinical phenotype can usually be predicted from knowledge gained from beta-globin, alpha-globin and Xmn1 polymorphism analysis (Table 22.1), but sometimes the clinical phenotype is not what is predicted from genetic analysis. The alpha thalassaemia syndrome HbH has a relatively variable phenotype ranging from mild to moderate anaemia, but some mutations may be severe enough to result in patients requiring regular transfusions.

Table 22.1: Genetic determinants of NTDT

Genetic determinants of NTDT	
Homozygous (or compound heterozygous) for **mild beta mutation** (such as IVS1-6 T→C, codon 9 C→T)	
Homozygous for **severe beta mutation** but persistence of HbF due to	Homozygous for Xmn1 polymorphism
	HPFH
	Other factors increasing HbF
Coinheritance of beta thalassaemia (heterozygous) and a thalassaemia-like Hb variant (these may result in a TM or intermedia phenotype)	HbE/beta thalassaemia
	Hb Lepore beta thalassaemia
Coinheritance of alpha thalassaemia mutations (homozygous alpha+ or heterozygous alpha^{0}) with homozygous beta thalassaemia resulting in decreased globin chain imbalance	

Coinheritance of extra alpha gene(s) with heterozygous beta thalassaemia resulting in increased globin chain imbalance
Inheritance of a 'dominant thalassaemia' mutation (hyperunstable beta-globin variant)
HbH
Alpha thalassaemia inherited with another **alpha-globin variant** (e.g., HbH Constant Spring)

Clinical phenotypes

Moderate/severe

This includes up to 10% of patients with homozygous beta thalassaemia, the majority of those with HbE/beta thalassaemia and a very small proportion of those with HbH. At the severe end of the spectrum 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 osteoporosis, and will gradually accumulate iron, particularly in the liver, due to increased gastrointestinal iron absorption. The majority in this group end up requiring regular transfusions (Taher et al., 2014).

Mild

This group includes a small proportion of patients with homozygous beta thalassaemia (usually predictable from genotype analysis), some patients with HbE/beta thalassaemia and the large majority of patients with HbH. It is important to identify this mildly affected group and to provide information tailored to their long-term complications. PHT, hypersplenism, gallstones, endocrinopathies, osteoporosis, chronic ankle ulceration, thromboembolic disease and iron overload can occur, but usually not before the age of 30 years.

Clinical presentations and complications

Pulmonary hypertension

The international standard for the diagnosis of PHT is right heart catheterisation. The prevalence of PHT in studies that assess PHT using echocardiographic criteria is high, averaging 30% in untransfused adults. The confirmed prevalence of pulmonary arterial hypertension on right heart catheterisation was 2.1% in patients with TDT and higher (4.8%) in those with NTDT. The positive predictive value for a TRV ≥3.2 m/sec threshold in echocardiography for the diagnosis of PHT is reported to be as high as 93.9% (Derchi et al., 2014). The incidence of PHT is high in untransfused adults, particularly those who have been splenectomised, and PHT causes significant morbidity and mortality (Musallam et al., 2011; Taher et al., 2010, Teawtrakul et al., 2015).

Autopsy studies show pulmonary vascular occlusion with thrombus, presumably a result of hypercoagulability, increased platelet count and activation. NO depletion through scavenging by free plasma Hb may also play a role in promoting pulmonary vascular changes. Echocardiography is a useful screening test, particularly if done sequentially. If there is a suspicion of PHT on the basis of clinical symptoms and signs, and/or findings on echocardiography, referral should be made to a specialist unit for assessment and consideration of right heart catheterisation to confirm the diagnosis. Patients with PHT should be managed jointly with a national specialist PHT unit. Treatment options include hypertransfusion and hydroxycarbamide. Anticoagulant therapy may be beneficial in some cases. Decisions about specific therapy for PHT, including sildenafil and endothelin antagonists, should be guided by the PHT Specialist Centre.

Thrombosis

Patients with NTDT have a hypercoagulable predisposition. The incidence of thrombosis ranges from 9.6 to 29% in various studies (Borgna Pignatti et al., 1998; Cappellini et al., 2000; Taher et al., 2010). Factors contributing to this hypercoagulable state include thrombogenic RBCs, activated platelets and thrombocytosis, splenectomy, endothelial activation and iron overload. The patients at highest risk are:

- adult patients
- splenectomised patients
- never or previously minimally transfused patients
- patients with elevated platelet counts (≥500 × 10^9/L)
- patients with Hb <100 g/L
- patients with a history of PHT
- patients with iron overload (LIC ≥5 mg/g dw or SF level ≥800 ng/mL)

- pregnant patients
- patients with other risk factors for thrombosis such as limited mobility, malignancy, or personal or family history of thrombosis.

In high-risk situations (e.g., pregnancy or periods of immobility) these patients should receive thromboprophylaxis. The management of patients who develop thromboses should be similar to other patient groups according to local hospital policy.

Extramedullary haematopoiesis

Asymptomatic paravertebral masses are observed in 15–20% of patients. Symptoms can be subtle, for example a feeling of incomplete bowel emptying can indicate a presacral mass, and spinal cord compression may be present in individuals who complain of minor symptoms of weakness or discomfort in a knee joint. A full neurological examination should be undertaken if there is any suspicion, with consideration of MRI scanning of the spine. Masses causing spinal cord compression, root compression or pressure symptoms in other anatomical sites require urgent management. The optimal treatment modality is not established but radiotherapy can induce rapid resolution of pressure effects. Good results, although generally slower in onset, have been described with hypertransfusion and hydroxycarbamide. Asymptomatic masses may require therapy depending on their position (e.g., if impinging on the spinal cord), but may simply be monitored if not threatening vital structures (e.g., lying in the paravertebral gutters in the thorax).

Low bone mineral density

Low BMD is very common in people with NTDT. One cross-sectional study found Z scores less than -2 in 67% of adult patients, a similar prevalence to that seen in people with TM. Low BMD affects the spine and femora, and results in a significantly increased risk of fractures (Vogiatzi et al., 2009). The prevalence of osteoporosis increases with age, and is reported in 30% of patients aged ≥32 years (Taher et al., 2010). The high prevalence is probably a result of expanded ineffective erythroid marrow combined with reduced growth, deficiency of endocrine function and a high rate of bone turnover. BMD should be assessed every 5 years. There is very little data on different treatment options for osteoporosis in NTDT. Recommendations for the treatment of patients with TM apply and, in addition, osteoporosis with fractures may be an indication for regular transfusion in a patient with NTDT, as this may reduce the rate of loss of bone mass by suppressing ineffective erythropoiesis in the spine, femora and other affected bones.

Pregnancy

See **Chapter 11: Management of Pregnancy**.

Leg ulcers

Leg ulcers are more prevalent in people with NTDT than those with TDT. The management of leg ulcers is discussed in **Chapter 19: Miscellaneous Complications in Thalassaemia**.

Management

Blood transfusion

Considerations to be taken into account in deciding whether to start a child on regular transfusion include those listed below.

- Episodes of acute anaemia may be related to intercurrent infection and are not necessarily an indication for long-term transfusion.
- Parvovirus B19 and other viral or atypical infections are common causes of acute resolving anaemia. The Hb level returns to baseline once the infection resolves.
- It is important to remember that acute haemolysis may also be exacerbated by G6PD deficiency and that folate deficiency may occur; patients with NTDT should be prescribed folic acid supplements.
- Transfusion initiated for delayed growth and pubertal development in children with NTDT should be reviewed once growth is complete.
- Older patients may become increasingly symptomatic with anaemia and regular transfusion programmes may be indicated.
- Since RBC alloimmunisation is common in people with NTDT, with incidence varying between 4 and 37% (Taher et al., 2015), use of phenotype-matched units for transfusion is mandatory. Patients who begin regular transfusions as adults have higher rates of alloimmunisation and haemolytic transfusion reactions (Ang et al., 2021). The risk of alloimmunisation is highest in splenectomised patients and during pregnancy (Al-Riyami and Daar, 2019).

Managing iron overload

In people with NTDT, ineffective erythropoiesis and hypoxia lead to increased intestinal iron absorption, which results in primary iron overload. Intermittent transfusions also contribute to iron overload and patients receiving regular transfusions develop secondary iron overload similar to that seen in patients with TDT. The ROIL due to increased intestinal absorption is slower than transfusional iron overload; however, it is cumulative and can result in clinically significant LIC and clinical sequelae from the age of 10 years (Musallam et al., 2014).

Recent data have shown that iron overload complications are associated with considerable morbidity in patients with NTDT and that this is under-recognised. SF levels are unreliable in people with NTDT and underestimate the degree of liver iron loading. Iron-related cardiomyopathy is rare in people with NTDT but endocrinopathies are encountered (Taher et al., 2014, 2012). Patients should be offered liver iron monitoring by either T2* or R2 (Ferriscan) to assess the degree of iron burden (discussed later).

Serum ferritin

Although levels of SF correlate with LIC in NTDT, potentially toxic LIC levels are associated with lower SF levels than in people with TM, and the range of values of SF used to predict morbidity and mortality in people with TM may not be directly applicable to people with NTDT. In one study, the authors found elevated LIC levels in patients with SF levels <1000 µg/L, a level generally considered safe in people with TM (Taher et al., 2008, 2012; Pakbaz et al., 2007; Taher et al., 2008; Origa et al., 2008).

SF levels of ≥800 ng/mL in people with NTDT are associated with an increased risk of iron overload-related morbidity and death (Musallam et al., 2022). One study reported that patients with SF levels ≤300 ng/mL did not develop any morbidity (Musallam et al., 2014).

Non-transferrin-bound iron

Detectable NTBI was reported in one study to associated with the frequency of previous transfusions. This may relate to increased uptake and mobilisation of iron, which is thought to relate to low hepcidin levels in people with NTDT. Thus, NTBI may be apparent before serum transferrin is fully saturated, in contrast to in people with TM, where NTBI is detected when erythropoiesis is suppressed, hepcidin levels are normal and transferrin is fully saturated. It is not yet clear how NTBI levels correlate with clinical outcomes in people with NTDT, and whether NTBI levels can be used

clinically for decision-making relating to the initiation and adjustment of chelation therapy.

Liver iron concentration

The relationship between LIC and total body iron, which has been established in people with TM, is not applicable to people with NTDT and the mechanism of iron deposition differs. Therefore, LIC values of people with NTDT should be interpreted with caution. LIC increases by an average of 0.35 mg/g dw per year in people with NTDT. Higher values of LIC measured by MRI have been associated with a significantly increased risk of complications such as thrombosis, PHT, endocrinopathies and osteoporosis (Musallam et al., 2011). LIC ≥5 mg/g dw is associated with poorer survival in patients with HbE/beta thalassaemia (Premawardhena et al., 2022). Some studies have shown an association between age and LIC, but others have not been able to demonstrate this (Pakbaz et al., 2007; Taher et al., 2008, 2012; Origa et al., 2008).

Myocardial iron

In cross-sectional studies using myocardial T2* MRI, non-transfused or rarely transfused people with NTDT do not appear to have measurable cardiac iron loading. There is insufficient published data to assess the long-term risk of cardiac iron loading beyond the age of 40 years. Furthermore, for patients who switch to regular transfusions, there is a risk of cardiac iron accumulation, as seen in people with TM (Taher et al., 2009, 2010).

Iron chelation

There have been a number of small uncontrolled trials of chelation therapy with DFO (Cossu et al., 1981) and DFP (Olivieri et al., 1992; Voskaridou et al., 2012; Liu et al., 2011), which have demonstrated that these agents can chelate iron in patients with NTDT with an acceptable short-term safety profile. An initial pilot trial (Voskaridou et al., 2010) and subsequent placebo-controlled trial (Taher et al., 2013) have shown that DFX is safe, effective and acceptable for reducing LIC and SF (Taher et al., 2013, 2016) at doses of 5, 10 and 20 mg/kg (dispersible tablets). The lower limit of LIC for inclusion was 5 mg/g dw. There have been no studies that have compared different levels of liver iron to see at which levels chelation therapy should be started, and no studies have demonstrated a beneficial effect of chelation on morbidities in people with NTDT.

Role of hydroxycarbamide

Hydroxycarbamide is a cytotoxic agent that can suppress intra- and extramedullary erythropoietic activity and enhance HbF production. The potential clinical benefits include alleviation of the symptoms of anaemia, a reduction in clinical jaundice, relief of bone pain, reduced bone marrow and spleen enlargement, and regression of extramedullary masses. Transfusion requirements may be reduced.

In general, the clinical experience and results published in case series show that the response is variable. Better results have been reported for specific genotypes, notably those who are homozygous for the Xmn1 polymorphism (Karimi et al., 2009, Bradai et al., 2007). Some patients are particularly sensitive to bone marrow suppression and become leukopenic with relatively modest doses, and too high a dose may suppress erythropoiesis rather than enhance Hb levels.

Splenectomy

Splenectomy should generally be avoided in patients with NTDT aged <5 years, but should be considered for patients with:

- hypersplenism resulting in clinically important leukopenia, thrombocytopenia, bleeding or symptomatic anaemia
- massive splenomegaly with clinical symptoms
- massive splenomegaly (largest dimension >20 cm) with concern about possible splenic rupture.

Splenectomy used to be recommended in order to increase patients' Hb levels and avoid regular transfusions; however, it is increasingly clear that splenectomy does not provide a permanent alternative to transfusion in these patients, and probably increases the risk of long-term complications such as thromboembolic disease and PHT. Avoidance of transfusion is no longer a standard indication for splenectomy in the UK, where blood is readily available and safe, and several options for iron chelation exist.

Stem cell transplantation

Since many patients with a moderate/severe phenotype of NTDT have relatively poor quality of life, and many will eventually require transfusions and chelation therapy, SCT should not be ruled out. The decision whether or not to pursue this option is especially difficult given the established risks of the procedure, the improving outlook for those

managed with transfusions and chelation therapy, and the difficulty in predicting the long-term consequences of NTDT in a young child.

The discussion requires careful counselling, accurate and consistent information, and good communication between the family, the transplant centre and the SHT/HCCs.

Requirements

General

- The organisation of services for patients with NTDT should be similar to those for people with TM. Input from the HCC and SHT is especially important as the conditions are relatively rare, and optimal management is often finely balanced and patient-specific.
- Patients should receive regular folic acid supplementation.
- Patients should be reviewed at least annually at/with the SHT.

Transfusion

- Transfusion may be required short term during acute infection, pregnancy and following surgery (Taher et al., 2021).
- After transfusion for an episode of acute anaemia, the patient should be observed carefully for several months to determine their steady-state symptoms and Hb level.
- The decision to give regular transfusions should be made in collaboration with the HCC. Indications for long-term transfusions include symptomatic anaemia, slowing growth velocity, delayed puberty, bone problems (facial deformities, recurrent fractures and premature epiphyseal fusion), PHT, symptomatic extramedullary haematopoietic masses and chronic ankle ulceration. Regular transfusions result in lower rates of these complications and improved survival (Musallam et al., 2021), but these benefits must be balanced against the risk of iron overload.
- RBC units transfused must be matched for A, B, O, Rh (DCcEe) and K.

Monitoring of iron load and chelation therapy

- LIC is the most important parameter for assessing iron overload in people with NTDT and should be assessed using R2 or T2* MRI. Assessments should start from age 10 years and be repeated every 2–5 years.
- SF should be measured at least once per year and correlated with LIC. Increasing SF levels (particularly >800 µg/L) should prompt a repeat LIC assessment.
- Myocardial T2* should be considered for assessment of myocardial iron loading in older patients and those who require more frequent transfusions (3–6 per year).
- Iron chelation is recommended in older children and adults whose LIC is >5 mg/g dw.
- DFX-FCT is recommended as first-line chelation, with the goal of reducing the LIC and maintaining it within the range 3–7 mg/g dw. The starting dose should be 7–10 mg/kg/day and the dose adjusted up to 14 mg/kg/day on the basis of monthly SF and periodic LIC assessment. DFX should be discontinued when LIC <300 µg/L (Deferasirox SPC).
- DFO or DFP can be considered for chelation in patients who are unable to tolerate or have adverse effects with DFX.

Splenectomy

- Careful consideration should be given to the risks/benefits of splenectomy. The decision must be made with the HCC team.
- Patients with NTDT should be transfused for several months prior to splenectomy to reduce spleen size, suppress marrow activity and reduce the numbers of circulating, prothrombotic thalassaemic RBCs.
- The vaccination schedule and antibiotic prophylaxis are discussed in **Chapter 13: Acute Clinical Manifestations of the Unwell Patient**.

Growth and pubertal development

- Growth and pubertal development should be monitored regularly from the age of 10 years, and referral to the designated endocrinologist made if abnormalities are documented.
- A period of regular transfusion should be offered during adolescence if growth spurts and/or pubertal development are delayed.

Pulmonary hypertension

- People with NTDT should have regular echocardiography from age 15 years. If there is clinical or echocardiographic evidence to suggest significant PHT, patients require assessment and consideration of right heart catheterisation to confirm the diagnosis and plan management. Screening criteria for TRV values on echocardiography are:
    - TRV >2.5 m/sec and asymptomatic: 'possibly' has PHT
    - TRV >2.5 m/sec and symptomatic or with other echocardiographic criteria suggestive of PHT: 'likely' to have PHT
    - TRV >3.2 m/sec: 'likely' to have PHT (Taher et al., 2023).
- Treatment of PHT should be coordinated in close collaboration between the LHT, SHT and PHT centre. Regular transfusion is normally recommended for these patients.

Extramedullary haematopoietic masses

- Suspected extramedullary haematopoietic masses should be investigated promptly, particularly if causing pressure effects. Radiotherapy can be considered if there is an urgent need to alleviate pressure effects. Hypertransfusion and/or hydroxycarbamide may be appropriate therapy if there are mild or moderate clinical consequences.

Other treatments

- The treatment goals should be discussed and agreed between the patient, carer and HCC haematologist before initiating hydroxycarbamide therapy. The patient should be made fully aware of possible adverse effects of the drug and supplied with written information. Hydroxycarbamide should be started at a dosage of 10–15 mg/kg/day, and the FBC monitored regularly and systematically. It is unlikely that patients will tolerate dosages >20–25 mg/kg/day.
- Referral to a centre with experience of transplanting for thalassaemia should be offered to families, for detailed discussion of transplantation as an option.

Recommendations

- The rationale for transfusion in patients with thalassaemia intermedia should be carefully discussed with the patient and/or their 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 association with regular transfusion.
- If splenectomy is planned, an abdominal ultrasound scan should be done prior to the procedure to detect gallstones. If present, a cholecystectomy should also be considered.
- Clinical trials are needed to determine the optimal management of PHT in these patients.

Suggestions for regular monitoring tests, which differ in some respects from those for patients with TM, are given in Table 22.2.

Table 22.2: Regular monitoring tests for patients with NTDT

	Frequency	Age at start
Clinical examination to include: Height Weight Spleen size Liver size Assessment of facial bone deformity and dental state	3 monthly, but according to severity of clinical syndrome, can be less frequent if mild	From birth or time of diagnosis
Pubertal development	6 monthly	10 years
Cardiac assessment	Annually for HbE/beta thalassaemia; 5 yearly for alpha thalassaemia	15 years
Blood tests FBC Liver function, renal function, urate SF	3 monthly, but according to severity of clinical syndrome, can be less frequent if mild	From birth or time of diagnosis
DXA bone density	5 yearly	15 years
Echocardiogram, including assessment for PHT (TRV should be quoted)	Annually for moderate/severe and post-splenectomy 5 yearly for mild beta or alpha	15 years
Formal assessment of body iron stores/MRI if available	5 yearly, or more frequently if abnormal	15 years

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Section E: Psychosocial Wellbeing

Chapter 23

Psychosocial Needs Requirements

"It would be a dream to have access to psychology services like patients with other conditions. This would have really helped me throughout my life to cope with the highs and lows of the condition."

Psychological care is an essential component of holistic care for people with thalassaemia. It can help patients cope with the emotional impact of their illness, reduce anxiety and depression, and improve their quality of life. Psychological care can also help patients develop coping strategies to manage the physical symptoms of thalassaemia and the demands of treatment. Furthermore, it can promote adherence to treatment and improve clinical outcomes by addressing psychosocial factors that may influence patients' abilities to manage their illness effectively.

Aims

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

To improve quality of life and emotional wellbeing among patients.

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

To minimise the negative impact of thalassaemia on the emotional wellbeing of patients.

Standards

- Consideration of the psychosocial demands and supporting needs associated with living with thalassaemia is a key role and responsibility for all professionals involved in the provision of care for people with this condition.
- Consideration of the family context and developmental/life stage of the person with thalassaemia is key to ensure that care and treatment recommendations are individually tailored to and appropriate for each patient.

- Psychosocial support, alongside specialist psychological care, should be provided as a standard part of thalassaemia clinical care, in both paediatric and adult services.
- Core staffing of SHCs should include a clinical/health psychologist with a special interest and experience in thalassaemia.

Background

Thalassaemia is a genetic disorder that can lead to multiorgan failure and a reduced life expectancy. The condition is progressive, stressful to manage, and needs complex and time-consuming treatments, leaving patients and carers worried about the challenges of the treatment burden (Nabavian et al., 2022).

As a chronic, lifelong and life-limiting condition, thalassaemia poses multiple and severe challenges (Kaewkong et al., 2021). Alongside the physical symptoms of thalassaemia and its impacts on family, relationships, emotional wellbeing and quality of life, the child or adult with thalassaemia must also cope with invasive, complex and demanding treatments, frequent hospital visits and a lifelong reliance on health services.

Thalassaemia also has an impact on both physical and emotional functioning, as the individual must adjust to the impact that their illness has on their physical wellbeing and hopes and ambitions for life. Feelings of difference, uncertainty, anxiety, depression, helplessness and loss are common, and the individual must make physical and emotional adaptations to build a life that incorporates illness and the management of their physical symptoms and treatments, whilst struggling to maintain a sense of self-worth and normalcy (Jordan et al., 2022.).

Not only does growing up with a chronic medical condition present significant challenges to children in accomplishing developmental tasks (Wang et al., 2022), but high rates of depression and anxiety are consistently found among seriously physically ill adult populations (Palareti et al., 2020). Given that a number of psychosocial factors are known to influence patient adjustment and adherence (Goldbeck et al., 2014; Joshi, 1998), failing to provide psychosocial care, as part of standard care, to people with thalassaemia runs the risk that higher levels of untreated emotional distress will lead to lower treatment adherence, poorer self-management and poorer clinical outcomes.

Many patients acknowledge that the ways in which their doctors and nurses approach them, and the messages and expectations they convey in clinical interactions, are centrally important to the way in which they think about themselves and their illness.

The psychosocial wellbeing of the individual needs to be a significant concern for the whole team.

Requirements

- The psychosocial needs and challenges faced by individuals living with thalassemia across their lifespans should be prioritised, to provide comprehensive and effective care. Psychological support should be available to address a variety of challenges associated with thalassaemia including, but not limited to, adjustment difficulties, poor self-esteem, low mood, health anxieties, needle phobia (this also can develop later in life due to cannulation difficulties and trauma), school and work difficulties, relationship problems and cultural issues.

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

- A clinical or health psychologist should be an embedded member of the MDT.

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

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

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

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

- Diagnosis of a child with thalassemia is a challenging time for families and appropriate support should be available to enable the family to discuss the

diagnosis, management, and overall psychosocial impact on the child and family. Such support may be provided by a psychologist or another professional trained in genetic counselling.

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

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

- Transition from paediatric to adult care is stressful for young adults and their families, and it is important to provide psychosocial support to ensure that optimal care continues throughout adult life. Paediatric and adult centres should collaborate to ease transition using a standardised process to ensure that the proper steps are taken to equip and prepare the young person. Transition should not take place during a time of acute illness or another period of stress (see **Chapter 12: Transition From Paediatric to Adult Services**).

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

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

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

- Information should be made available in a variety of formats, including verbal and written. Information given verbally should be adequately documented and written information should be provided in the patient's preferred language. Information should be age-appropriate and given at

repeated points during the course of the condition, and at times when changes in treatment or in the course of the condition occur.

Recommendations

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

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

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

- Recommended treatments should take into account the individual living with thalassaemia's (and carers') developmental level, family structure, cultural ideas around illness and treatment, social context and life demands. The constraints imposed by treatment should also be considered and, wherever possible, some flexibility incorporated to accommodate any minor difficulties and issues. Individuals with thalassaemia should, whenever possible, be involved fully in decisions and details about treatment regimens. Changes in treatment should always be discussed in full, and the rationale and reasons for any changes made clear. Information about treatment options, including the relative benefits or disadvantages and the potential consequences of non-adherence, should be made available to patients. Patients should also be involved in monitoring their progress (for example, SF levels and the results of imaging tests quantifying tissue iron) so that their understanding of the impact of adherence and non-adherence is enhanced. More regular reviews can prove helpful in initially establishing a routine for a new treatment regimen.

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

appropriate psychosocial support (**see Chapter 12: Transition from Paediatric to Adult Services**).

- Standard annual reviews of patients should include a measure of emotional wellbeing to monitor psychosocial wellbeing among patients in order to identify any difficulties proactively, providing prompt psychological assessment, early support and treatment, if necessary (see **Chapter 2: Annual Reviews**).

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

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Chapter 24

Adherence

"No one told me the most difficult part of thalassaemia treatment was the daily internal fight to take my iron chelation. People underestimate how hard this really is."

Aims

To facilitate open and honest conversations about adherence.

To increase levels of adherence to treatment.

Standards

- Care teams should regularly discuss adherence with patients and families.
- Care teams should consider how they are able to best facilitate conversations around adherence with patients and families so that these can be continued in future appointments. This will include how they communicate with each other within the MDT.
- Conversations around adherence should be collaborative and non-judgemental.

Background

Working with issues around adherence can be a challenge for both individuals living with thalassaemia and healthcare professionals. Thalassaemia is a long-term condition with considerable treatment demands, and to accurately understand someone's presentation we need to know exactly how much treatment they are receiving and have helpful conversations around this. These conversations are not isolated events and may require long-term follow-up. Working with ambivalence around treatment will be familiar to many healthcare professionals. This section aims

to help us think about how we can work with this ambivalence in the most effective ways to encourage behaviour change.

When talking about adherence in this section, we are working on the assumption of capacity. There might be circumstances in which either safeguarding procedures for children or the Mental Capacity Act require consideration alongside this guidance (in which case the relevant guidance should be referred to).

Communication styles

Communication between healthcare professionals and patients and patient adherence have been shown to be related (Channon et al., 2007). It is recommended that teams create a culture in which the struggles around adherence can be openly acknowledged whilst still holding expectations of increased adherence levels (Duff and Latchford., 2013). Conversations about adherence need to be non-judgemental, empathic and collaborative; we are working *with* our patients to understand their individual circumstances, why certain treatments are difficult and what would need to be different for them to be able to start to increase their adherence. The aim of such conversations is to equip people to make their own decisions, acknowledging that people are generally better persuaded by their own arguments rather than being told what is 'right' (Miller and Rollnick, 2013). Communication around adherence should aim to encourage patients to talk about why health/treatment matters for them; responsibility for change is shared.

There can be a sense that having open conversations about adherence takes time that is not readily available. It needs to be acknowledged that some approaches shown to increase behaviour change (e.g., motivational interviewing [MI]) originated within therapy settings. However, MI has also been shown to be effective in brief appointments (Evans et al., 2011), with the likelihood of change being increased when such conversations are followed up at a later consultation. Therefore, what is a priority for a particular clinic visit could be considered.

Subtle differences in how we ask questions can help people be open about how they are managing adherence. This can include the use of open questions and not making assumptions, approaching the issue of adherence with empathic curiosity. For example, asking '*how much* [treatment] do you manage on average each week/month?' rather than 'do you manage your treatment?'. Such subtle changes in language aim to open up wider conversations about adherence and we can consider many aspects:

- Family and individual beliefs about a person's health status.
- Family and/or individual goals about treatment and healthcare.
- Daily routines and how these fit with adherence.

- How treatments impact on different areas of their life (home, social, school, work, etc.).
- Any barriers to taking treatments (e.g., multiple demands, difficulties accessing prescriptions/hospital, side effects, financial concerns, cultural beliefs, and psychological barriers, such as what taking treatment means to them and their sense of identity).
- Times in the past when adherence had been greater; what can be learned?
- What needs to be different for someone to increase their adherence to treatments?
- What are the first steps for someone?

We are often most motivated by what matters to us now (West and Michie, 2020). Therefore, linking treatment goals to patient goals can be particularly helpful (e.g., I want to have enough energy to attend a family celebration).

Information sharing

There is a positive correlation between knowledge about thalassaemia and adherence; not making assumptions about what our patients know about their treatment is crucial. Giving information (and having information available in different languages) is an important part of conversations around adherence. How we give information can also make a difference. For example, whilst acknowledging that MI is an overall approach and not a series of techniques, when it comes to giving information, it recommends that we first elicit what the patient already knows (ensuring they are engaged and primed), then deliver new and relevant information, and then elicit what the patient understands from our conversation (which gives a chance to correct their understanding and be clear that they do understand accurately) (Miller and Rollnick, 2013).

Examples of such questions are given below.

- What do you understand about the term iron overload?
- Tell me what you know about how your chelation therapy works?
- Can I just let you know how I would explain it [as a doctor/nurse]?
- For you, what is the key part of the conversation that we have just had?

In paediatric settings, there can at times be complexities around what information carers would like to share with young children. At such times, it is important to have open conversations with carers (just as you would with patients). There may be times when healthcare professionals are working with carers to enhance a child's adherence. Also, adolescence and young adulthood are times when taking treatments

becomes more difficult due to someone's developmental stage. Here, the family and individual dynamics require careful consideration (Naar-King and Suarez, 2011).

Psychological support

Sometimes, people are unable to adhere to treatments due to psychological difficulties, procedural distress and/or mental health problems. For example, if someone is experiencing depression, motivation to engage in many behaviours (including, but not exclusive to, adherence) can be impacted. In such examples, it is important to consider intervention for the psychological difficulties alongside, or even before, further conversations about adherence.

Specific aspects of adherence in patients

Children

This is a very difficult time for parents as there will be a lot of anxiety over iron overload and the need for chelation. If DFO is being used then one-to-one training is needed for patients to build confidence in their parents for needle insertion and administration of treatment.

It is important in this setting that administration of chelation should not become a battle of wills between parents and children. Proactive support and engagement with parents and the child is essential to support understanding of the importance of good adherence to treatment, and age-appropriate support and discussion with the child is critical in supporting good adherence.

Children should be supported with open discussion about side effects so that treatment can be adjusted to support adherence. As a child grows older, periodic education on reasons for taking chelation should happen either during the transfusion visit or clinic appointments.

Children should be encouraged to start to take control of medication administration once they are in their teenage years and are deemed able to self-medicate by parents and healthcare providers. All children should be able to self-medicate by the age of 16 years in preparation for transition to a more independent life. It is important that parents remain actively engaged in supporting adherence during this time by checking in with the child that medication has been taken, and raising concerns with healthcare providers about side effects or adherence.

Adults

An open and frank dialogue between healthcare providers and patients is critical in ensuring good adherence to treatment. There are many factors that impact a patient's ability to adhere to medication and non-adherence may be intentional or unintentional. It is important to be non-judgemental and understand the challenges that are impacting the patient's ability to take medication.

Non-adherence will affect not just chelation but other therapies a patient takes, and working through the challenges regarding taking therapy will take time and patience. It is important to remember that adjusting therapy to support adherence is critical to improve outcomes. Please refer to **Chapter 6: Iron Overload and Management** for more details on chelation options and the management of side effects.

When discussing chelation, it is important to not ask direct questions with 'yes' and 'no' answers, but to ask a more descriptive question such as 'how often are you missing/forgetting chelation over a period of time?', in order to get an idea of average compliance.

In addition, once a patient states that they have missed chelation therapy, it is important to follow that up by determining what the factors were that resulted in them missing treatment, and to work out solutions with the patient in the context of their lifestyle to help them avoid missing chelation. MI and cognitive behaviour therapy are helpful interventions to support patients with adherence to treatment regimens. Setting goals and helping a patient achieve what is important for them (e.g., developing independence to go to university, optimising iron chelation to support a planned pregnancy, spermatogenesis induction, and optimising chelation for planned gene therapy or bone marrow transplantation etc.) is a very powerful driver for patients, and helps them to remain committed to the goal of an improved iron burden.

Seniors

As patients age there are other issues that need to be taken into account. In particular, the complexity of therapy with other medications they may need, such as those for diabetes, hypertension or cardiac issues. Dosages of therapy may need to be adjusted for renal or liver issues. Patients are often very set in their chelation regimen at this age and will often have very well-controlled iron burdens, so compliance may not be an issue, but over chelation may become an issue and will need appropriate discussion.

As patients age and approach the end of life it is important to rationalise regimens appropriately to reduce the burden of treatment at times when quality of life is paramount.

Recommendations

- All healthcare professionals should have an understanding of the complex factors that can underpin difficulties with adherence.
- Healthcare professionals should be able to facilitate constructive conversations around adherence, acknowledging that these conversations need to be collaborative to be most effective (engaging with further training, such as MI, when appropriate).
- It should be acknowledged that working with issues around adherence can evoke strong feelings (in patients, families and healthcare professionals alike).
- Patients and families should have a choice in choosing treatment that may work best for their lifestyle.

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Chapter 25

Holistic Care and Quality of Life

Aims

To ensure patients with thalassaemia have a holistic approach to their care.

To give an overview of how clinical teams can support the different aspects of the patient journey.

Standards

- To optimise the quality of life of people with thalassaemia through both self-care and medical intervention.
- To support clinical teams in managing older patients with thalassaemia in acute settings.
- To recognise the need to review the goals of care of patients' management plans when appropriate.
- To give patients who are deteriorating and may be approaching the last year of their life the opportunities to discuss their wishes for their future care.
- To involve and support patients and their loved ones in developing an individualised plan of care that meets their needs.

Background

People with thalassaemia can benefit from a holistic approach to care that includes self-care and lifestyle changes (Pouraboli et al., 2014). The WHO definition of quality of life is 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' (Centre for Disease Control and Prevention, 2023).

Holistic care, paying attention to quality of life and recognising early the importance of palliative care input, is an essential component of thalassaemia management in the UK. Healthcare professionals should provide effective communication, symptom management, emotional and spiritual support, planning for end-of-life care and referral to specialist services as needed. By providing comprehensive palliative care, patients living with thalassaemia and their families can experience improved quality of life and a greater sense of control over their care.

Quality of life assessment

Quality of life can be assessed with the following tools, some of which are specific to thalassaemia.

- The Specific Thalassaemia Quality of Life Instrument (STQOLI) (Lyrakos et al., 2012).
- The WHOQOL (WHO Quality Of Life) Questionnaire (Telfer et al., 2005; WHO, 2012).
- TranQol in adults and children with TM (Klaassen et al., 2014).
- The Short Form Health Survey – SF36 (Musallam et al., 2011; Sobota et al., 2011).
- The Dartmouth Primary Care Cooperative Information Chart System (Pakbaz et al., 2005).

Self-care

Self-care measures for patients with thalassaemia include:

- regular exercise tailored to the individual patient's ability
- ensuring adequate rest
- avoiding smoking, drinking alcohol and drug abuse
- good nutrition with a balanced diet; for some patients this may include limiting foods that are high in iron
- having adequate zinc supplementation with regular monitoring from the clinical team.

Flexibility in transfusion and outpatient clinics

SHCs and local centres should try to support children and adults with thalassaemia, in education and employment, by providing more flexible times for clinics and

transfusion. This can include evening clinics, the setting up of joint clinics with other specialities, and facilitating evening or weekend transfusion times. This will allow greater social integration of patients with thalassaemia into society.

A survey on the education and employment of individuals with thalassaemia in the US and Canada in 2011 revealed that 70% of adults were employed, of which 67% were in full-time employment. A more recent survey of 151 patients with TDT found that 30% of patients were unemployed or unable to work because of their TDT, whilst 32.3% were in full-time employment (≥32 hours/week). Participants reported spending a median of 15.8 hours per month managing their condition, a median of 7.0 hours per month at medical appointments and 2.0 hours per month travelling to medical appointments (Li et al., 2022). Extending the interval between crossmatch sampling and blood transfusion will also allow more flexibility for patients (**see Chapter 5: Red Blood Cell Transfusion**).

Evolving comorbidities in thalassaemia

Survival in thalassaemia has steadily improved over the years (Farmakis et al., 2020). However, despite improving survival trends, the median age of death in England has been reported to be 45 years and the crude 10-year mortality rate for patients with TDT to be 6.2%, more than five times greater than the age/sex-adjusted mortality rate of the general population (Jobanputra et al., 2020). Another retrospective cohort study of patients with TDT in England demonstrated that the mean percentage of deaths of patients with TDT at age 55 years was higher than for age-matched controls (7.17% versus 1.18%) and >30 years lower than the modal age of death for the general population in the UK (Li et al., 2023).

The causes of death have changed. Earlier identification and management of cardiac iron with T2* MRI and intensification of chelation have led to a 71% risk reduction in death due to iron overload cardiomyopathy (Modell et al., 2008). Hepatocellular carcinoma has been reported to have replaced infections as the second most frequent cause of mortality after heart disease in Greek registry data, with an increasing frequency, responsible for 12.6% and 16.8% of deaths in the periods 2000–2010 and 2010–2015, respectively (Voskaridou et al., 2019).

The improved survival of people with thalassaemia brings with it an evolving list of comorbidities. Advancing age in conjunction with chronic exposure to iron-related oxidative stress, immunogenic blood products and disease-specific medications such as iron chelators may accelerate the presentation of conditions not frequently seen in the past. For example, atherosclerotic-related cardiovascular disease was previously not commonly seen. However, coexisting cardiovascular risk factors such as diabetes,

which may arise as a result of suboptimal iron chelation, and smoking may modify the clinical spectrum of the disease.

Cardiac disease has been reported in 18% of patients with thalassaemia overall, with the most common conditions being AF (11%), heart failure (9%) and acute arrhythmias (4%) (Jobanputra et al., 2020). A 14% prevalence of cardiopulmonary complications (heart failure, PHT, and AF being the most common) has been reported for patients in England (Li et al., 2023).

For patients in England, diabetes has been reported to affect 34% of patients overall, osteoporosis 40%, and non-diabetes endocrine disorders – including hypoparathyroidism, hypopituitarism and hypothyroidism – the most common comorbidities, affecting 40% of patients (Jobanputra et al., 2020). A high rate of comorbidities was noted in younger patients in the same series. There were two comorbidities that occurred in >40% of patients aged 15–19 years: endocrine disorders (excluding diabetes) in 48% and osteoporosis in 44%. Rates of comorbidities generally increased with age. The prevalences of endocrinopathies and osteoporosis (29.11%), diabetes (28.27%) and hypopituitarism (28.27%) have also recently been reported by Li et al. (2023).

A range of cancers have been described in people with thalassaemia, with iron implicated as a significant factor in the aetiology (Zanella et al., 2016). Hepatocellular carcinoma is an important cause of mortality, with other cancers including haematological ones and those arising from endocrine glands (Farmakis et al., 2020). Patients with thalassaemia aged >65 years have also been reported to be 2.24-fold more likely to develop dementia compared with age-matched controls, with the risk greater in patients with NTDT.

There is a significant impact on health-related quality of life that can be underestimated. In a recent survey of 151 patients with TDT, most participants reported problems with pain (73%), anxiety or depression (61%), and the ability to conduct their usual activities (59%); 41% reported moderate-to-severe pain or discomfort, and 29% reported moderate-to-extreme anxiety or depression (Li et al., 2023).

As with other chronic and life-limiting conditions, patients living with thalassaemia will require a holistic approach to manage their symptoms, improve their quality of life, and support themselves and their families as they navigate the challenges of living with a chronic illness. It is important to practise shared decision-making with this group of patients and give them opportunities to discuss any wishes for their future care, including when they are approaching the ends of their lives. Teams can consider referring to their local specialist palliative care team if patients who are deteriorating

have needs that their generalist team are struggling to meet. This may be for symptom control, emotional and practical support, and carer support.

An MDT approach is required for patients presenting with progressive complications despite best available therapies. It is helpful to start these conversations earlier on in the disease trajectory to give patients opportunities to make their wishes known.

Examples of complications that may be indicative of a change in disease trajectory to trigger these conversations can include:

- debilitating cerebrovascular disease
- decompensated liver cirrhosis
- hepatocellular carcinoma
- chronic heart failure (not iron-mediated)
- multiorgan failure from whatever aetiology (for example end-stage diabetic complications).

Factors that require consideration include:

- altered drug metabolism in patients with liver or renal dysfunction
- a decision on iron chelation based on prognosis and rationalising medications
- transfusions may need to be tailored to individual needs (for example, adjustment of transfusion volumes in patients with cardiac or renal failure).

Recommendations

- Early integration of the concept of holistic care: Holistic care should be integrated into the management of thalassaemia as early as possible. This will allow patients and their families to become familiar with the concept of palliative care and to access support and resources when needed.

- Communication: Effective communication is key to providing holistic care to patients with thalassaemia. Healthcare professionals should have open and honest conversations with patients and their families about the patient's prognosis, treatment options and end-of-life care. Patients should also be given opportunities to express their wishes and preferences regarding their care.

- Symptom management: Patients with thalassaemia may experience a range of symptoms, such as pain, fatigue and shortness of breath. Healthcare professionals should work with patients to manage these symptoms effectively, using a combination of pharmacological and non-pharmacological

interventions. Referral to appropriate specialist teams (e.g., pain or palliative care teams) should be considered.

- Emotional support: Patients with thalassaemia may experience anxiety, depression and other emotional distress as a result of their condition. Healthcare professionals should provide emotional support to patients and their families, and refer them to specialist services, such as counselling, as needed.

- Spiritual support: Patients with thalassaemia may have spiritual or religious beliefs that influence their care. Healthcare professionals should be aware of these beliefs and provide appropriate spiritual support, such as access to religious leaders or spiritual advisers.

- Planning for end-of-life care: Turning points in the patient's disease trajectory may be an appropriate trigger to start discussions around future care. If it is felt a patient may be nearing the last year of their life, healthcare professionals should work with them and their family to give them the opportunity for discussions around their wishes for the future and their plans of care. This may include decisions about resuscitation, artificial nutrition and hydration, and other interventions. Patients can also be given information around writing advance decisions to refuse treatments and appointing a lasting power of attorney for health and welfare, to make decisions on their behalf if they become unable to do so. Teams involved in the patient's care should work collaboratively with each other and the patient and their loved ones to develop an individualised plan of care to meet their needs.

- Holistic care: Clinical teams should take a holistic approach to the management of thalassaemia, addressing the physical, emotional, spiritual and social needs of patients and their families. This may involve working with the UKTS and other healthcare professionals, such as pain specialists, psychologists, social workers, nutritionists etc.

- Referral to specialist palliative care services: Patients with thalassaemia who require specialist palliative care should be referred to specialist services, such as hospice or palliative care teams. These services can provide additional support, such as symptom management, emotional support and spiritual care.

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Chapter 26

Social Welfare

Aims

To ensure all individuals living with thalassaemia and their families have access to equitable specialised thalassaemia care and support services, irrespective of where they reside in the UK.

To assess the diverse lifespan-specific challenges families may face and recommend suitable adjustments or services that may help to improve their quality of life.

To signpost families and other healthcare professionals to the types of financial welfare services available in the UK.

To provide healthcare professionals with insight into completing Personal Independence Payment (PIP) applications.

Background

Thalassaemia can result in significant quality-of-life challenges for individuals and their carers. In the UK, social welfare programmes play a crucial role in supporting those living with and affected by thalassaemia.

The primary reasons why social welfare is necessary for people with thalassaemia is to ensure individuals have access to quality healthcare. Thalassaemia management requires regular blood transfusions as often as every 2 weeks, daily iron chelation therapy and specialist management.

Social welfare initiatives provide financial support, ensuring that individuals can attend these treatments and afford necessary lifesaving medications. This assistance is particularly crucial for low-income families who may struggle to meet the high costs associated with thalassaemia management, or those who are unable to work full-time due to attending hospital appointments and being unwell. By alleviating the financial strain, these initiatives enable individuals with thalassaemia to focus on their health and wellbeing, rather than worrying about the financial implications of their condition.

Living with thalassaemia can be emotionally challenging for individuals and their families. Social welfare programmes often establish support groups where individuals can connect with others facing similar challenges, share experiences and seek emotional support. These support networks play a vital role in reducing feelings of isolation, providing a safe space for individuals to discuss their concerns and fostering a sense of belonging.

Religious leaders can provide emotional support, counselling and guidance to help individuals cope with the challenges they face. They can offer prayers, spiritual solace and a sense of community to those affected by thalassaemia.

Translators and interpreters are also an imperative component of basic care needs for families affected by thalassaemia where English is not a first language. Interpreters act as advocates for individuals with thalassaemia and their families, ensuring their voices are heard and their rights are respected. They not only help patients to navigate complex healthcare systems and communicate their needs and concerns effectively, but also to access appropriate services and support. By empowering patients with the ability to communicate, translators and interpreters enable them to actively participate in decision-making regarding their healthcare and wellbeing and should form part of their team if required.

Additionally, public welfare initiatives must also recognise the importance of education and employment for individuals with thalassaemia. Scholarships, grants and special educational programmes should be provided to support their academic pursuits. By ensuring equal access to education, individuals with thalassaemia can develop the skills necessary to lead fulfilling lives and contribute to society. Social welfare programmes should also collaborate with all employers to create an inclusive workplace that offers equitable employment opportunities to accommodate transfusions and appointments, enabling individuals with thalassaemia to maintain some financial independence.

Thus, social welfare programmes are essential in thalassaemia management in the UK. They ensure access to healthcare, provide financial assistance, offer emotional support, promote education and employment opportunities, and enhance genetic counselling and awareness. By addressing the various needs of individuals with thalassaemia and their families, social welfare initiatives play a crucial role in improving their quality of life and fostering a more inclusive society. It is imperative that continued support and investment are provided to sustain and enhance these programmes, ensuring that individuals with thalassaemia receive the necessary resources and support to thrive.

Types of financial welfare support that are available.

In the UK, individuals with thalassaemia are eligible for various forms of social welfare support to help manage their condition and improve their quality of life. It is essential that individuals with thalassaemia and their carers seek advice from relevant government departments, such as the Department for Work and Pensions or Citizens Advice or speak with a healthcare professional or a social worker; they can provide detailed information on the available benefits and guide individuals through the application process based on their specific circumstances.

Disability Living Allowance

Individuals living with thalassaemia who have care needs or mobility difficulties may be eligible for the Disability Living Allowance. This benefit provides financial support to help with the extra costs associated with their condition. This has now been replaced by the PIP for new claimants.

The Personal Independence Payment

The PIP is a UK Government benefit that is available to individuals aged 16–64 years with long-term health conditions or disabilities. Individuals who are eligible for the PIP receive regular payments to assist with the additional costs they may face due to their disability or health condition. Individuals with thalassaemia may be eligible for the PIP if they experience difficulties with daily living or mobility. It is not means tested.

It is important to note that the PIP is not a recognition- or achievement-based programme. Instead, it focuses on providing financial assistance to individuals who require support with daily living or mobility activities due to their disability or health condition.

The amount of PIP received is determined through an assessment process that evaluates an individual's ability to carry out specific activities and the impact that their disability or health condition has on their daily life via two components: daily living and mobility. The assessment considers factors such as mobility, personal care and the ability to manage daily tasks independently. For each task, the Department for Work and Pensions will assess:

- whether the person can do it safely
- how long it takes the person
- how often the condition affects this activity

- whether they need help to do it, from another person or by using extra equipment.

Whilst there are no awards associated with the PIP, it is a valuable resource that helps individuals with disabilities or long-term health conditions to maintain their independence and improve their quality of life.

Daily living

The applicant may be awarded the PIP under the daily living component if they need help with:

- eating, drinking or preparing food
- washing, bathing and using the toilet
- dressing and undressing
- reading and communicating
- managing medicines or treatments
- making decisions about money
- socialising and being around other people.

Mobility

The applicant may be awarded the PIP under the mobility component if they need help with:

- working out a route and following it
- physically moving around
- leaving their home.

Employment and Support Allowance

The Employment Support Allowance is a benefit for individuals who are unable to work due to illness or disability. It provides financial support to help with living costs and recipients are divided into two groups: the support group for those with severe disabilities and the work-related activity group for those who may be able to work in the future.

Access to Work

Individuals with thalassaemia who are employed or self-employed can access support through the Access to Work scheme. This programme provides practical assistance, such as adaptations to the workplace or specialised equipment, to help individuals overcome work-related barriers.

Universal credit

Individuals with thalassaemia who are unable to work due to the severity of their circumstances can apply for this benefit.

Carer's Allowance

The Carer's Allowance is a benefit that is available for individuals who provide regular and substantial care to someone with a serious long-term medical condition (parents, children, spouses, relatives etc.).

Blue Badge Scheme

Individuals with mobility difficulties may be eligible for a Blue Badge, which allows them to park in disabled parking spaces and provides other parking concessions.

Travel concessions

Individuals with thalassaemia in receipt of certain welfare benefits or with a disability may be eligible for discounted or free travel on public transport, such as the Disabled Persons Railcard or the National Concessionary Bus Pass.

Housing support

Individuals with thalassaemia who require adapted or specialised housing due to their condition may be eligible for housing support through local authorities or housing associations.

Occupational housing support

Individuals with thalassaemia who require adapted or specialised equipment (bathroom rails, wheelchairs etc.) because of their condition may be eligible for grants or support through local authorities.

Council tax reduction

Families who receive the PIP may be eligible to apply for a reduction of their council tax bill. The amount of reduction varies depending on factors such as income, savings, household size and local council policies.

Recommendations

You may be contacted by Department for Work and Pensions officials to complete a Factual Report as they may need further information about the patient's medical condition(s) and the impact their condition(s) have on their day-to-day life, in order to award the claim.

It is important to take the following points into consideration when preparing the letter of support for the applicant:

- Physical symptoms: Outline any physical symptoms or complications related to thalassaemia, such as fatigue, shortness of breath, jaundice, bone deformities, and pain or organ dysfunction, and how they may affect the patient on a daily basis. Include copies of scans, investigations and clinic notes.

- Treatment and management: Outline the current treatment plan for thalassaemia, including blood transfusions, iron chelation therapy, and any other medications or interventions being used. Discuss the frequency and duration of treatment and any challenges, side effects or concerns related to adherence. Include a detailed list of all medication, including any over-the-counter pain medication used and how this may affect the patient on a daily basis.

- Emotional wellbeing: Outline the emotional impact of thalassaemia on the patient and their family members. Discuss any feelings of anxiety, depression, stress or isolation. Include coping strategies and support systems that are already in place.

- Quality of life: Discuss how thalassaemia affects the patient's daily life, including limitations on physical activities, school or work attendance, and social interactions due to the number of treatments or appointments that the applicant attends on a weekly or monthly basis. Determine any adjustments or accommodations that may be necessary to improve the patient's quality of life.

- Family dynamics and support: Explore the impact of thalassaemia on the patient's family, including their understanding of the condition, involvement in treatment decisions and emotional wellbeing. Assess the availability of social support and resources for the patient and their family.

- Transition to adulthood: Young individuals with thalassaemia and their families require assistance with transitioning from paediatric to adult care, including support for educational and career planning, financial independence and navigating the healthcare system. This ensures continuity of care and support as they transition into adulthood.

- Financial burden: Outline the financial impact of thalassaemia, including costs associated with treatment, medication, transportation and other related expenses. Identify any financial support options or assistance programmes that may be available.

- Education and empowerment: Detail the patient's and family's understanding of thalassaemia, its management and potential complications. Assess their knowledge of available resources, educational materials and support groups. Providing information and resources will empower them to make informed decisions and actively participate in their care.

It is important that PIP assessors are told how the condition (and secondary conditions) may affect the patient. If only the name of the condition is included without a description, the claim may not be awarded.

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Appendices

Appendix 1

Annual Review Template

Annual Review Template for Thalassaemia/RIA (ADULTS/PAEDIATRICS)

Patient Info.	**Date**		**Patient Name**		**NHS No.**	
	ADULT / UNDER 18					
	Diagnosis					
	Comorbidities					
	Vaccination status (if new to UK / Hep B / splenectomised)					

Patient Monitoring	**Height (cm)**		**Centile *(under 18s)***	
	Weight (kg)		**Parental heights (cm) *(under 18s)***	
	Tanner score (from age 10)		**Growth velocity satisfactory? *(under 18s)***	**Y / N (if not satisfactory refer to Endocrinology)**
	Transfusing Hospital			
	Not regularly Transfused: Transfusion indicated (in last 12 months, no. of transfusions, indications)			

	On Transfusion: Transfusion Regimen	**Units**		**Frequency/ Interval**		**ROIL (mg/kg/OD)**		
	MRI iron assessment		**Cardiac T2* * (ms) (2-5 yearly depending on previous result. Start at 20+ years or earlier if need >3 transfusions/year)**			**Ferriscan (mg/g/dry wt.)**		
			Liver T2* (ms) (2-5 yearly depending on previous result. Start at 10+ years or earlier if need >3 transfusions/year)			**Ferritin**		
	Pretransfusion Hb							
	Iron chelation (drug/dosage/frequency)							
	Adherence/compliance documentation							
	Other Medications							

Investigation Results	**Creatinine**		**UPCR (if on DFX)**		**ALT**		**AST**	
	Bilirubin		**Vit. D (from age 2)**		**Calcium**		**LH/FSH**	

	TSH		OGTT (from puberty)		PTH		Free T4	
	Morning cortisol				Testosterone/oestradiol			
	Virology (Hep B, C, HIV)				Spleen Size			
	Liver size		DXA scan		Eye test completed (if on chelation)			Y / N
	Audiometry test completed (if on chelation)			Y / N				
	Echo (mild phenotype: 5 yearly, moderate/severe: 1-2 yearly from age 15)							
	Assessment for facial bone deformity/dental state/EMH (e.g. rib expansion, masses in spine)							

Discussion	1. Details of activities over last 12 months (e.g., acute admissions/AED visits/surgery/school/university/starting family etc.) 2. Transition (under 18s) 3. Wider health determinants (e.g., community mental health/social care/DLA/PIP. Use local tool if further psychological/social input needed)

Extra	**Psychology assessment needed**	**Y / N**	**New treatment discussion (Gene therapy/Luspatercept etc.)**	**Y / N**
	Baseline genetic test available	**Y / N**	**Transplant discussion**	**Y / N / NA**

Actions	**Tertiary Hospital**	
	Patient	
	Local/ Transfusing Hospital	
	Community	
	GP	

Multisystem Review ^	**Puberty/menses/sex characteristics**	
	Cardiorespiratory	
	Neurology symptoms	
	Ophthalmology symptoms	
	Leg ulcers	

	Infections	
	Joint pains	
	Chronic pain	
	Pancreatic insufficiency	
	Extramedullary haematopoiesis	
	Fractures	

Misc. ^	**Additional Comments**	

Appendix 2

Schedule of Testing

Endocrine dysfunction	Tests	Frequency	Age	Instructions
Puberty and fertility	Tanner staging	Yearly	10	
	LH, FSH, Oestradiol	Yearly	10	In girls
		Yearly	10	
	Anti-Mullerian hormone	Ad hoc		When seeking fertility
	Prolactin	Yearly		If other pituitary hormones deficient
	LH, FSH, Testosterone, SHBG	Yearly	10	In boys, preferably morning test
Growth	Bone age	1-2 Years	From Diagnosis	Careful monitoring whilst on Deferoxamine
	Height and Weight	6 monthly	From Diagnosis	
	IGF-1	Yearly	8-12	
	GH stimulation test	Ad hoc		To confirm diagnosis If GH deficiency is suspected
Hypothalamo–Pituitary–Gonadal axis	Morning Cortisol (8-9 AM)	Yearly	12	
	Short Synacthen Test, ACTH	Ad hoc		If morning cortisol <200 nmol/L

	Prolactin, IGF-1, LH, FSH, oestrogen/ testosterone, TFT			If other pituitary hormones deficient and suspecting central cause
Thyroid function	Free T4, TSH	Yearly	12	Subclinical and primary hypothyroidism common than secondary hypothyroidism
Calcium & bone metabolism and hypoparathyroidism	Corrected Calcium, Phosphate, ALP	6 monthly	12	
	PTH	Yearly	12	
	Vitamin D (25 OH vitamin D3 levels)	Yearly	2	
	Bone density	2-5 Yearly	12	DXA or pQCT scan MRI scan if osteoporotic vertebral fracture is suspected
	Urine calcium creatinine ratio	Yearly	12	Spot urine test (can be done rapidly), but will need to check serum creatinine simultaneously
	24-hour urine calcium excretion	Ad hoc		Laborious but gold standard test
Diabetes	OGTT	Yearly	Since puberty	
		Yearly	10	If there is family history of Diabetes
	Fasting glucose	Yearly	Since puberty	
		Yearly	10	If there is family history of Diabetes

	Capillary blood glucose monitoring (CBG)	Ad hoc	After Diabetes diagnosis	In people with poorly controlled Diabetes and in who predispose to hypoglycaemia /hyperglycaemia
	Continuous glucose monitoring	Ad hoc		Consider use in pregnancy and poor compliance with CBG monitoring
	Fructosamine	3-6 monthly		To monitor glycaemic control
	Insulin, C-peptide, venous glucose	Ad hoc		When diagnosis is unclear, when to rule out Type 1 Diabetes and to check pancreatic reserve for initiation of Insulin
General	Clinical examination	Yearly or soon if required	From diagnosis	Ideally in joint Thalassemia/ Endocrine clinics

Appendix 3

Abbreviations and Acronyms

AF	atrial fibrillation
AI	adrenal insufficiency
ALT	alanine aminotransferase
ASA	American Society of Anaesthesiologists
BMD	bone mineral density
BMI	body mass index
BNP	brain natriuretic peptide
BSPED	British Society of Paediatrics and Endocrinology
Cas9	CRISPR-associated protein 9
CDGP	constitutional delay in growth and puberty
CMR	cardiovascular magnetic resonance imaging
COCP	combined oral contraceptive pill
COVID-19	coronavirus disease 2019
CRISPR	clustered regularly interspaced short palindromic repeats
CRG	Clinical Reference Group
CVAD	central venous access device
CVC	central venous catheter
CVS	chorionic villus sampling
DFO	desferrioxamine
DFP	deferiprone
DFX	deferasirox
DFX-D	deferasirox dispersible tablet
DFX-FCT	deferasirox film-coated tablet
dw	dry weight
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
ESHRE	European Society of Human Reproduction and Embryology
FBC	full blood count
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
G6PD	glucose-6-phosphate dehydrogenase
GH	growth hormone
GP	general practitioner
GvHD	graft versus host disease
Hb	haemoglobin
HbA	adult haemoglobin
HbF	fetal haemoglobin
HbH	haemoglobin H disease
HBV	hepatitis B virus

HCC	Haemoglobinopathy Coordinating Centre
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDR	homology-directed repair
HEV	hepatitis E virus
HFEA	Human Fertilisation and Embryology Authority
HH	hypogonadotropic hypogonadism
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hMG	human menopausal gonadotropin
HPFH	hereditary persistence of fetal haemoglobin
HPLC	high-performance liquid chromatography
HRT	hormone replacement therapy
HSC	haematopoietic stem cell
HSCT	haematopoietic stem cell transplantation
IAT	indirect antiglobulin test
ICSI	intracytoplasmic sperm injection
Ig	immunoglobulin
IGF-1	insulin-like growth factor-1
IGF-BP3	insulin-like growth factor binding protein 3
IGT	impaired glucose tolerance
IVF	in vitro fertilisation
LH	luteinising hormone
LHT	Local Haemoglobinopathy Team
LIC	liver iron concentration
LMWH	low-molecular-weight heparin
LPI	labile plasma iron
LV	left ventricular/ventricle
LVEF	left ventricular ejection fraction
MDI	multiple daily injection
MDT	multidisciplinary team
MI	motivational interviewing
MRI	magnetic resonance imaging
MRONJ	medication-related osteonecrosis of the jaw
NHEJ	non-homologous end joining
NHP	National Haemoglobinopathy Panel
NHR	National Haemoglobinopathy Registry
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NHSSCTSP	NHS Sickle Cell and Thalassaemia Screening Programme
NICE	National Institute of Clinical Excellence
NO	nitric oxide
NTBI	non-transferrin-bound iron
NTDT	non-transfusion-dependent thalassaemia
OGTT	oral glucose tolerance test
PGT	preimplantation genetic testing
PHT	pulmonary hypertension
PIP	Personal Independence Payment
PIVC	peripherally inserted venous cannula

PND	prenatal diagnosis
POI	premature ovarian insufficiency
PTH	parathyroid hormone
RBC	red blood cell
RCOG	Royal College of Obstetricians and Gynaecologists
rhGH	recombinant human growth hormone
ROIL	rate of iron loading
RV	right ventricular/ventricle
SaBTO	Advisory Committee on the Safety of Blood, Tissues and Organs
SCS	Sickle Cell Society
SCT	stem cell transplantation
SF	serum ferritin
SHBG	sex hormone binding globulin
SHC	Specialist Haemoglobinopathy Centre
SHOT	Serious Hazards of Transfusion
SHT	Specialist Haemoglobinopathy Team
SPC	Summary of Product Characteristics
SSQD	Specialist Services Quality Dashboard
FT4	free thyroxine
TDT	transfusion-dependent thalassaemia
TIF	Thalassaemia International Federation
TM	thalassaemia major
TRT-RSS	thalassemia-related thrombosis risk scoring system
TRV	tricuspid regurgitation jet velocity
TSH	thyroid-stimulating hormone
TTI	transfusion-transmitted infections
UKTS	United Kingdom Thalassaemia Society
VTE	venous thromboembolism
WHO	World Health Organization
WMQRS	West Midlands Quality Review Service

Appendix 4

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 that fight off bacterial and fungal infections.

alpha fetoprotein a chemical marker that can be measured in the blood. This is raised in certain circumstances, for example, in liver cancer and sometimes during pregnancy.

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 manufactured by the body's immune system to fight infection. 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 blood cells.

appendicitis/appendectomy 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 the joints.

arthropathy pain in the joints.

audiology the speciality relating to hearing.

audiometry measurement of hearing.

autosomal recessive a gene that can be passed on to offspring by a mother or a father, and that, 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 caused by bacterial organisms circulating in the blood.

Bart's hydrops fetalis an unusual condition, which usually causes a late miscarriage or stillborn baby, caused by the fetus 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, carrying bile. This has the dual purpose of aiding digestion and carrying waste products such as bilirubin to be broken down in the liver. The gallbladder is a small storage pouch for bile between the liver and the bowel.

biopsy a small sample of tissue removed for microscopic or other examination, in order to aid diagnosis or guide treatment.

bisphosphonates a group of drugs that help put calcium back into the bones.

bone marrow transplant a 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. Accompanied by new bone formation,

the result of the two being called bone remodelling.

carcinoma the most common type of cancer or tumour.

cardiac arrythmia disturbance of the normal, regular heart rhythm.

cardiac decompensation failure of the heart's pumping mechanism to work strongly enough.

cardiologist heart specialist.

cardiology speciality of 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 that causes 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.

cholecystectomy surgical removal of the gallbladder.

cholecystitis inflammation of the gallbladder.

cholelithiasis stones in the gallbladder or biliary tract.

chorionic villus sampling procedure, usually undertaken at or around 12 weeks of pregnancy, to remove a small piece of the placenta in order to make a diagnosis of a condition that may affect the fetus.

cirrhosis a liver disease that can be caused by a range of problems, in which the liver is scarred with areas of functioning liver tissue trapped between these scar-tissue bands.

colic spasms of pain caused when a hollow organ is blocked, for example, the bowel or tubes of the biliary tract.

compound heterozygote a person who is heterozygous at two different genes (for example, who might have alpha^0 thalassaemia trait and sickle cell trait).

deferasirox an iron-chelating drug that is active when taken by mouth, licensed under the name Exjade.

deferiprone an iron-chelating drug that is active when taken by mouth, licensed under the name Ferriprox.

densitometry (bone) measurement of bone density or strength of the bones.

desferrioxamine the original 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.

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 that increases the kidneys' output of salt and water, causing an increase in urine output.

dysrhythmia disturbance in the heart's normal, regular rhythm.

echocardiography a simple 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 any condition affecting the hormone-producing glands.

enzyme a protein chemical that speeds up metabolic processes in the cells of the body. The level of enzymes can also be measured and sometimes 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 bone ends lock together or fuse in certain areas, after which no more growth can occur.

erythroid relating to red blood cell production.

erythroid marrow hyperplasia overgrowth of the bone marrow caused by increased red blood cell production.

erythropoiesis the process of red blood cell formation.

erythropoietin the hormone produced by the kidneys that drives red blood cell production.

fallopian tube connects the ovary to the body of the uterus or womb.

ferritin a soluble transport form of iron, which needs to be measured by blood testing as an indication of the total amount of iron in the body.

fetus the unborn baby.

folic acid a vitamin of the B group that is required for red blood cell formation. It is found in green leafy vegetables and nuts.

fracture breakage (of a bone).

G6PD deficiency low levels of a chemical called glucose 6 phosphate dehydrogenase, found in the red blood cells, which is used by the red blood cells to resist damage by certain chemicals. Deficiency is an inherited condition, usually causing few problems but which can lead to red blood cell breakdown, especially if a person takes certain medications, which should therefore be avoided.

gallstone a lump of hard material developing in the biliary system or gallbladder

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 part of the haemoglobin molecule.

glucose intolerance a mild form of inability to handle glucose and sugars optimally, not as severe as diabetes mellitus.

gonadal relating to the organs of reproduction; ovaries in women and testicles 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 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 that 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 that is chiefly responsible for controlling growth.

haematocrit percentage of the blood that is taken up by the blood cells as opposed to the fluid plasma.

haematologist medical specialist in blood disorders.

haematology the medical specialty relating to blood disorders.

haematopoiesis the process of blood cell formation, which usually takes place within the bone marrow. 'Extramedullary 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 in the red blood cells. From infancy onwards, the majority type is haemoglobin A, and it is the beta-globin protein part of this that 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 too many clinical problems.

haemoglobinopathy a general term that covers all the inherited medical conditions that are due to abnormal or underproduced haemoglobin proteins.

haemolysis premature red blood cell breakdown.

haemolytic resulting from premature red blood cell breakdown.

hepatic relating to the liver.

hepatitis inflammation of the liver.

hepatocellular carcinoma cancer of the liver cells.

hepatologist medical specialist in liver disorders.

hepatomegaly liver enlargement.

hepatosplenomegaly liver and spleen enlargement.

hereditary persistence of fetal haemoglobin the continuation of production of fetal or baby-type haemoglobin into adult life. This is an inherited feature.

heterozygote an individual who inherits one type of a gene from one parent and another type from the other. Relating to haemoglobin disorders, it most usually describes inheritance of a normal gene from one parent together with a thalassaemia or sickle cell gene from the other – the healthy carrier state.

high-performance liquid chromatography an automated, rapid and accurate way of separating different protein bands in a solution, for example, different subtypes of haemoglobin in a blood sample.

histology the appearance of tissue examined under a microscope.

histopathology the medical specialty of analysing tissue specimens for abnormality.

HIV human immunodeficiency virus, which causes AIDS.

HLA/human leukocyte 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 chemical substances produced by the endocrine and other glands or cells, which are released into the bloodstream to act upon specific receptor sites in other parts of the body to bring about various effects.

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 that is lacking because of underactivity of the endocrine glands.

hydroxycarbamide (also known as hydroxyurea) a medication used for many years for bone marrow overactivity 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 low blood counts.

hypertension high blood pressure.

hypertransfusion describes the regimen for treating chronic anaemias such as thalassaemia, in which the haemoglobin is not allowed to fall below approximately normal levels.

hypocalcaemia low calcium level in the blood.

hypogonadism failure of the normal activities of the testes in men or ovaries in women.

hypogonadotropic hypogonadism hypogonadism resulting from underproduction of gonadotropic hormones, which are produced by a small gland inside the brain and normally drive gonadal function.

hypoparathyroidism underactivity of the parathyroid gland, which controls body calcium levels.

hypothalamus a small gland situated deep in the brain that, 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.

intermedia when relating to thalassaemia, describes the condition in which, although a person inherits a thalassaemia gene from both parents, they can make enough haemoglobin to get along without always needing regular blood transfusions.

intrauterine inside the uterus or womb.

intravascular inside a blood vessel

laparoscopy a procedure for looking and/or operating inside the abdomen through small, keyhole incisions.

laparotomy an operation to open up the abdomen, using an ordinary surgical incision.

leukaemia cancer of the primitive white blood cells.

malocclusion (dental) the teeth do not meet properly when the jaws close.

meningitis inflammation, usually caused 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 technique that gives very clear pictures and exposure to minimal radiation.

necrosis tissue death, resulting from lack of blood supply.

nephropathy kidney problem.

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

oesophageal relating to the gullet down which food is swallowed.

ophthalmology the medical specialty of managing eye disease.

orthopaedics the medical specialty 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.

ovary the organ in females that produces eggs.

ovulation egg production.

paediatrics the medical specialty of caring for children.

pamidronate a medication (one of the bisphosphonates) that can help put calcium back into bones.

parathyroid the gland that controls calcium levels in the blood and bones, by producing parathyroid hormone.

paravertebral around the vertebral bones.

pathogenic causing illness.

pericarditis inflammation of the fibrous sac that surrounds the heart.

perinatal around the time of birth.

perioperative around the time of operation.

perioral around the mouth.

peripheral towards the edges, in medicine this term is usually used to describe towards the hands and feet.

phenotype describes the structure or appearance resulting from a gene, 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, that (with the **hypothalamus**) controls most of the body's hormone-producing glands.

pneumococcus a type of bacteria (also known as ***Streptococcus pneumonii***) that 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 describes the possibility of different forms that can occur at a single gene site.

prenatal diagnosis the diagnosis of 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.

radiology the medical specialty of interpreting X-rays and other diagnostic images.

radiotherapy the medical specialty of giving treatment with radiation therapy.

renal relating to the kidneys.

retina the membrane at the back of the eye that senses light and sends messages to the brain, where they are interpreted into vision.

retinopathy disease problem affecting the retina.

rheumatology the medical specialty of managing joint disease (with medicine, not surgery).

rickets a condition that arises when the bones are softened by a lack of vitamin D or calcium (**osteomalacia**), causing bone deformity, especially at the knees.

rubella (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.

serology testing of serum.

serum the clear fluid remaining when blood has been allowed to clot and the clot removed.

sickle cell disorders a group of inherited conditions in which the altered structure of haemoglobin can give rise to anaemia, sudden severe pain 'crises' and a range of other health problems.

sinus 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 that 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 cell type.

subclinical 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 that falls with increased iron content

tachycardia rapid heart rate.

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 that produces thyroxine hormone, which controls the body's activity levels.

transaminases liver enzymes.

type 1 diabetes or insulin-dependent diabetes is a chronic autoimmune condition where the immune system mistakenly attacks and destroys the insulin-producing cells (beta cells) in the pancreas.

type 2 diabetes a type of diabetes that is usually of later onset, and which frequently responds to diet or tablets rather than needing insulin.

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.

ventricle/ventricular when relating to the heart, indicates the main pumping chambers.

vertebra(e) bone(s) in the back or spine.

vertebral dysplasia abnormality in development of the vertebrae.

Yersinia **(*enterocolitica*)** bacterial organism that can cause infection in the bowel, causing severe pain and fever, which can mimic appendicitis. It particularly infects people who have high iron levels and are on iron chelation.