



**Guidelines for the Clinical Care of
Patients with Thalassemia in Canada**

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Foreword

From the Anemia Institute for Research and Education

The *Guidelines for the Clinical Care of Patients with Thalassemia in Canada* represent an important milestone toward excellence in patient-centred care for all patients and families affected by thalassemia in Canada. Over the years, we have seen significant advances in medical technology, including assessment, monitoring and therapy for thalassemia. These developments, along with better knowledge, supportive care, and self-care, have meant children with thalassemia have been able to participate fully in school, sports, and other activities with their peers. Our young adults have been able to complete their educational goals, including advanced degrees, and to lead full, productive lives with careers and families. In every respect, the opportunity has been here in Canada to provide the highest standard of care to all those affected by thalassemia.

However, the patient (and clinical) community has been well aware that not everyone was achieving that promise. While the Canadian healthcare system is among the best in the world, universal healthcare did not necessarily mean that all patients, especially those with rare disorders, had access to the same standard. The thalassemia community has had to cope with insufficient clinical resources, including the lack of physicians, nurses, social workers and other specialist and supportive care workers. We have experienced the sorrows of patients and families dealing with complications and even deaths that in some cases may have been avoidable. We have also struggled with the lack of awareness and knowledge among the patient community and our inability to reach many families, including those newly arrived to Canada.

We believe these guidelines provide a pathway toward excellence in care and serve as a benchmark for all of us to gauge our success. These guidelines were inspired by the *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK* and are the result of collaboration between the clinical and patient community in Canada. We are indebted to Dr. Isaac Odame who inspired and led this process and to Dr. Farzana Sayani who penned the document as a labour of love. We also salute all of the patients and healthcare professionals who contributed to the guidelines and to the on-going care and support for our thalassemia community. With these guidelines, we must now move forward to challenge the healthcare system and ourselves to provide the resources and support to assure that every patient and family with thalassemia in Canada has access to the highest standard of care available.



Durhane Wong-Rieger, PhD
President, Anemia Institute for Research & Education

Foreword

From The Hospital for Sick Children

It has been a great pleasure and honour to be involved in the development of the *Guidelines for the Clinical Care of Patients with Thalassemia in Canada*. Inspired by the Standards for Clinical Care document produced by the UK Thalassemia Society, the Canadian Guidelines are the result of strong collaboration between Canadian health care professionals and the thalassemia patient community and their families.

I acknowledge the efforts of my fellow colleagues in the Writing Group, in particular Dr. Farzana Sayani, as well as the contributions made by the Canadian and international reviewers.

It is our sincere hope that these guidelines will provide relevant and useful information to health care professionals involved in the clinical care of thalassemia patients across Canada with a goal to optimize health care delivery and patient outcomes. It is also helpful that patients and their families would be able to evaluate their own clinical management and treatment goals.



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Foreword

From the Thalassemia Foundation of Canada

Our dream of national guidelines for the treatment of thalassemia in Canada is now a reality. As President of the Thalassemia Foundation of Canada, I am pleased that these guidelines set a national standard of care that can ensure consistency in delivering the highest quality care for all thalassemia patients regardless of where they live in Canada or the institution that delivers their treatment and care.

To achieve this standard, our thalassemia treatment programs must be appropriately resourced. These guidelines specify the healthcare personnel and other resources necessary for thalassemia centres and other sites to deliver optimal comprehensive preventive and therapeutic care.

The guidelines have the added benefit of serving as a resource to train healthcare professionals new to thalassemia and providing the benchmarks and tools for the healthcare system, providers, and patients to evaluate our performance and to make necessary improvements.

The thalassemia guidelines give patients and their families hope that the scientific and psychosocial progress we have made over the past couple of decades will be a reality for all those affected by thalassemia in Canada.

On behalf of thalassemia patients and the Thalassemia Foundation of Canada, I would like to thank all members of the Writing Group in particular, Dr Odame and Dr Sayani for dedicating their time and effort to completing this document. I also would like to thank the Anemia Institute for Research & Education and Durhane Wong-Rieger for leading this initiative and overseeing it through.



Riyad Elbard
President, Thalassemia Foundation of Canada

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Executive Summary of Standards

Thalassemia is a relatively rare congenital blood disorder, which has life-long implications for patients and families. The care of patients with thalassemia is most adequately delivered by comprehensive care centres staffed by professionals experienced in the treatment of the disease and its complications. The following document is meant primarily for health care professionals involved in the care of affected patients and is to provide members of the thalassemia treating team with relevant information, which should improve health care delivery and patient outcomes. As active participants in their ongoing care, patients and families may also use the document to review their own management and treatment goals.

The guidelines are based on information obtained from published literature, Canadian and international expert opinion, and views of patients and families. The document was reviewed by a team of national hematologists and health care professionals involved in the care of thalassemia patients, international experts and a representative group of patients and their families. Reference was also made to the previously published Thalassemia International Federation's *Clinical Management for Thalassemia and the Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK*.^{1,2} These guidelines are developed by a Canadian team and intended primarily for application in the Canadian context. The document is divided into chapters focusing on

These guidelines serve only as a guide to patient management and should not replace clinical judgement in each individual clinical situation.

components of the comprehensive thalassemia care team, treatment of thalassemia major, complications of thalassemia major and thalassemia intermedia.

A. Components of Comprehensive Thalassemia Care

A1. A Network of Care

- Each program should consist of a collaborative regional network of one or more specialized thalassemia centres and affiliated thalassemia satellite clinics.
- Each program should have a formalized system for specialized thalassemia services that is appropriately configured to the geographical location and size of the patient population.
- All patients should have access to the specialist centre either for routine thalassemia-related care if living nearby or for more specialized services and regular annual expert clinical review if living far away.
- The regional networks may choose to share certain resources but should have effective communication, accountability, and avenues for self-evaluation and staff development.

A2. Lifelong Education and Communication Between Patient and Health Care Team

- Patients and families should be offered comprehensive age-appropriate education about thalassemia.
- Families should be taught to administer home chelation and other treatments, and supervise the child's care. The health care team should provide ongoing support and guidance.
- A key contact health professional, usually a specialized nurse, should be designated for each patient/family and should be readily accessible.

- Adequate monitoring, regular follow up visits, and early identification and management of complications should be provided to minimize hospital admissions.
- The multidisciplinary team should systematically and regularly record and exchange information relating to clinical events, results of investigations, changes in treatment, overall management plans, and changes within the child's family or social system, with each other and the patient/family.
- Information should be communicated to the pediatrician or general practitioner involved in the patient's care at least once a year and after a major event or change in treatment plan.
- Patients and families should be appropriately educated so that they can have a meaningful role in all health care decisions. Patients should be directly involved in decisions appropriate to their age and desire.
- Families should have access to a social worker, psychologist, and peer support networks.
- All information should be tailored to the age, developmental stage, cultural background and educational level of the patient and family. Appropriate programs and support systems should be in place to ease the transition from pediatric to adult care centres.

B. Management of Thalassemia

B1. Initial Management of the Newly Diagnosed Infant

- Diagnosis of a child with a thalassemia syndrome should be done as early as possible after birth and should include hematological and genotypic analysis.
 - The child's clinical course should be closely monitored since the clinical phenotype cannot be accurately predicted from the genotype.
- Qualified experienced professionals should discuss with the family the diagnosis, management and overall psychosocial impact on the child and family in an open, sensitive, and culturally appropriate manner.

B2. Transfusion Support in Thalassemia

I. Starting a Red Blood Cell Transfusion Program

- Irrespective of genotype, all affected infants should be closely monitored for clinical evidence of the need for initiating regular transfusions.
- Patients with thalassemia intermedia phenotype are less likely to have clinical indications for regular routine chronic transfusions in early life and as a result should not be subjected to inappropriate regular transfusions.
- All the necessary baseline laboratory investigations including red cell phenotype and Hepatitis B vaccinations should be initiated prior to initiating transfusions.

II. Red Cell Transfusion Practices and Monitoring

- Patients should receive leucodepleted blood as set out by Canadian Blood Services/ Héma Québec policies and prophylactically matched for D, C, E, c, e, and K1 blood group antigens.^{3,4} (GRADE B)
- Patients with thalassemia major, based on clinical genotype analysis, should receive regular transfusions to maintain pre-transfusion hemoglobin levels between 90 – 100 g/l.⁵⁻⁷ (GRADE B)
- Each patient should have a chart with accurate documentation of transfusion requirements, blood bank antibody monitoring, and transfusion reactions.

B3. Iron Overload and Chelation Therapy

- Transfusional iron loading and body iron stores should be monitored routinely.
- Chelation therapy should be started early in children receiving regular blood transfusions to prevent iron-related toxicities.⁸⁻¹⁰ (GRADE B)
- The chelating agent used should be tolerable and effective in reducing iron load. Intolerance to a chelating agent leads to poor compliance, which results in increased iron overload, subsequent end organ complications, and overall increased morbidity and mortality.
- In patients where deferoxamine is not tolerated or is ineffective, an oral iron chelator should be used.^{8,9,11,12} (GRADE B)
- Regular monitoring for specific chelator-related toxicity should be carried out and the appropriate action taken if toxicity is found.
- The effectiveness of chelation should be routinely monitored and appropriate dose and drug adjustments made when required.
- Patients and families should receive age-appropriate education and access to an experienced multidisciplinary team to provide support in the practical and psychological aspects of chelation therapy and a team that can promote independence and motivation in managing chelation therapy.
- Patients should receive adequate monitoring to identify early signs of inadequate adherence to chelation therapy. If adherence is problematic, they should be provided with appropriate culturally sensitive counseling or therapy to aim for improved treatment outcomes.

B4. Psychosocial Aspects of Thalassemia Care

- The multidisciplinary team at the specialist centre should include a social worker and psychologist with knowledge of challenges faced by thalassemia patients at different developmental stages of life.

- The psychosocial needs of thalassemia patients should be prioritized in ongoing planning for treatment.
- Support should also address age-specific challenges (e.g., needle phobia, treatment compliance, poor-self-esteem, school issues) and cultural influences.

B5. Hematopoietic Stem Cell Transplantation (HSCT)

- The option of HSCT, including its indications and complications, should be discussed with families while the patient is at a young age.
- The discussions should be initiated by the specialist centre and, if appropriate, referral should be made to a HSCT centre with experience in transplanting thalassemia patients where more detailed discussions should take place.
- The options of human leukocyte antigen (HLA)-matched related HSCT (cord blood and bone marrow) should be discussed.
- Post-HSCT, patients should be closely monitored and managed for iron overload and other complications.

B6. Transition from the Pediatric to Adult Care Setting

- Planning for the transition from pediatric to adult care settings should be started several years in advance and should focus on the process of educating the adolescent about the biological, medical, and psychosocial aspects of thalassemia, and equipping the adolescent/young adult with skills to become responsible and independent in caring for his/her health.
- The pediatric and adult centres should collaborate to increase patient familiarity with members of the adult team and the adult system.
- Following transition, adult patients should

be followed routinely to ensure they receive optimal care, psychosocial support, and to ensure that complications are identified and managed promptly.

C. Complications of Thalassemia

C1. Cardiac Complications

- Each thalassemia specialist centre should have access to a pediatric or adult cardiologist with knowledge of managing cardiac complications in thalassemia patients.
- All patients should have routine clinical assessment for signs and symptoms of cardiac dysfunction.¹³ (GRADE B)
- Cardiac iron load should be monitored routinely.¹⁴ Iron overload should be reduced by chelation to lower the risk of iron associated cardiac complications and death.^{8,9,15} (GRADE B)
- Cardiac function should be measured routinely. In the presence of increased cardiac iron load and cardiac dysfunction, more aggressive iron chelation regimens should be initiated.¹⁵ (GRADE B)
- The designated cardiologist should manage cardiac complications, including heart failure and arrhythmia, as per cardiology standards.

C2. Liver Complications

- Every thalassemia specialist centre should collaborate with a designated hepatologist with knowledge of liver complications in thalassemia patients.
- Liver enzymes should be monitored routinely, and abnormalities investigated for etiology, reviewed by a hepatologist if indicated, and managed accordingly.
- Liver iron concentration should be monitored routinely and chelation therapy initiated and adjusted to reduce complications of iron overload.^{8,9,16,17} (GRADE B)

- Every effort should be made to reduce the risk of viral hepatitis by safe transfusions, hepatitis B vaccination programs and regular monitoring.
- Patients with active hepatitis B or C should be referred to the designated hepatologist and managed as per hepatology standards of care.
- Adult patients should be encouraged to avoid liver toxins including alcohol and liver-toxic drugs.
- There should be surveillance for complications in patients with cirrhosis, including hepatocellular carcinoma.

C3. Endocrine Complications

- Each specialist centre should collaborate with a pediatric or an adult endocrinologist with knowledge of endocrine complications in thalassemia.
- Children should be routinely monitored for growth and development until they have attained adult height and full sexual development. Any abnormalities to suggest an endocrinopathy should be investigated and managed accordingly.
- Adolescents and adults should be routinely monitored for endocrinopathies including diabetes mellitus, hypothyroidism, hypoparathyroidism, hypogonadotropic hypogonadism, and growth hormone deficiency.^{8,9,11,18} Abnormalities should be identified early and treatment initiated in consultation with an endocrinologist. (GRADE B)

C4. Bone Complications

- Every specialist centre should have access to a pediatric or an adult endocrinologist, and an orthopaedic surgeon with knowledge of managing thalassemia associated bone disease.
- All children should have routine monitoring of

height, weight, and growth velocity at each visit and these should be plotted.

- All patients should be closely monitored for bone changes and deformities associated with under-transfusion and chelator related toxicity.²⁰ (GRADE B)
- All patients should be encouraged to participate in regular weight bearing, low impact sport activities.
- Transfusion therapy should be started early in children to prevent the bone changes and deformities associated with bone marrow expansion.^{8,9,11,18} (GRADE B)
- Any bone changes should be managed appropriately with adequate transfusions, appropriate iron chelation, or chelating medication dose reduction depending on the underlying cause.^{9,19,20} (GRADE B)
- Adolescent and adult patients should have routine monitoring for osteopenia and osteoporosis, and if detected, should be referred to an appropriate specialist and treated according to treatment guidelines.²¹⁻²⁵ (GRADE B)

C5. Fertility and Pregnancy

- All children should be closely monitored for pubertal development and endocrinopathies, and appropriately treated by an endocrinologist to reduce the risk of long-term hypogonadism and infertility.
- Patients should be assessed by a fertility clinic and available treatment options discussed.
- Women considering pregnancy should be assessed for risks to mother and fetus, and advisability of pregnancy. Detailed assessment and management prior to pregnancy and close monitoring of the health of the mother and fetus during and after pregnancy should be ensured.²⁶⁻²⁸ (GRADE B)
- During pregnancy, women should be managed

by a high-risk obstetrician with knowledge of thalassemia-associated risks, and the specialist centre multidisciplinary team including a cardiologist.

C6. Other Significant Complications: Infection, Dentition, Nutrition

- The physician should be aware of certain infections that are more common in patients that are on chronic transfusion programs or iron overloaded.
- Dental and orthodontic evaluation should be considered to improve appearance and function in patients with facial deformities and malocclusion.
- Regular nutritional assessments should be done by a registered dietician, with specific attention to iron containing foods, calcium, vitamin D, and diabetes.

D. Thalassemia Intermedia

- The α - and β -globin genotypes should be determined when thalassemia is diagnosed.
- The patient with a thalassemia intermedia genotype should be closely followed clinically for signs and symptoms suggestive of the need for intermittent transfusions, or regular chronic transfusion.
- All patients should be routinely monitored and appropriately managed for complications of thalassemia intermedia including iron overload, pulmonary hypertension (especially in splenectomized patients), cardiac dysfunction, extramedullary hematopoiesis, leg ulcers, osteoporosis, thrombophilia, pseudoxanthoma elasticum, and hypersplenism.²⁹⁻³⁶ (GRADE B)
- All patients and families should receive age-appropriate education specific to thalassemia intermedia.
- Patients should be followed in conjunction with the specialist centre.

Introduction

Goals of the Document

Thalassemia is a heterogeneous group of hemoglobin production disorders that is primarily found in the Mediterranean, Asian, Indian, and Middle Eastern regions. These regions account for 95% of all thalassemia births in the world. The epidemiology of thalassemia, however, is rapidly evolving due to migration patterns. In Canada, the number of thalassemia patients continues to grow due to immigration from countries where thalassemia is prevalent. The patient population is characterized by ethnic and phenotypic heterogeneity. The following guidelines are an effort, based on current evidence and existing guidelines, to bring uniform, consistently excellent care to patients affected by thalassemia throughout Canada.

The care of the patient with thalassemia is a life-long commitment encompassing all aspects of care from birth to end of life. Like other rare, life-long, multi-system diseases, thalassemia patients benefit from a comprehensive care approach to management, where experienced professionals work in partnership to deliver the best possible outcomes. Comprehensive care includes a multi-disciplinary team approach focusing on diagnosis, genetic counseling, medical management, primary prevention of complications, and psychosocial support throughout life. Such optimal management is best delivered by comprehensive care teams following universal guidelines.

Canadian thalassemia patients face many challenges in accessing care including the relative rarity and severity of their disorder and the large geographical area of our country, to name a few. *The Guidelines for the Clinical Care*

of Patients with Thalassemia in Canada, which focus on the essential components of a multi-disciplinary team approach and the current best clinical practice, should serve as a guide to Canadian thalassemia treaters and patients alike with the goal of improving the overall health and quality of life for thalassemia patients.

Scope and Organization of the Document

The guidelines outlined in this document will apply to transfusion-dependent thalassemia major patients. Special attention is also given to those patients with thalassemia intermedia phenotype in whom the decision to start transfusions can be a difficult one (Section D).

The document is aimed primarily at healthcare professionals who care for patients with thalassemia. These guidelines are not meant to be a comprehensive review of thalassemia, but rather to provide relevant information to healthcare workers to equip them in the delivery of comprehensive care to thalassemia patients. Special attention has been made to make the document easily readable by patients and their families with the aid of the glossary (Appendix 2).

These guidelines describe the key members, the functions of the comprehensive care team, and the management of thalassemia and its complications. A specific section has been devoted to thalassemia intermedia. Each chapter is divided into principles, guidelines, and interventions with a brief summary of relevant information at the beginning of a few sections as a reference guide. The principles in each chapter describe the desirable goals of a thalassemia treatment centre while the guidelines specify requirements of individual thalassemia treatment

centres. Lastly, the interventions sections detail specific steps that should be taken to implement each guideline.

Levels of Evidence

There are few randomized controlled trials in thalassemia due to the low incidence of the disease and higher prevalence in regions of the world where funds are not readily available for research. We have reviewed the literature, which predominantly consists of retrospective analyses and non-controlled trials, and other guidelines, which also incorporate views of experts in the field. Levels of evidence have been characterized as described in Appendix 1. Most recommendations are level C; however, where they are otherwise, they have been specified.

Reference was made to previously published International and British thalassemia guidelines to assist in the development of these guidelines, with modifications where necessary based on new evidence.^{1,2}

Overview of Thalassemia

The thalassemias are a heterogeneous group of genetic disorders characterized by decreased or absent production of one or more globin chains that make up a hemoglobin molecule. Each hemoglobin molecule is composed of 4 globin chains; normally 2 from the α family and 2 from the β family of globin chains. Each hemoglobin molecule also has a heme group containing iron. The thalassemias are broadly categorized according to the globin chain that is defective.

I. α -thalassemia

α -thalassemia is caused by reduced or absent production of α -globin chains. Each individual normally has 4 α -globin genes.

- Hb Bart's hydrops fetalis: In this condition, all four α -globin genes are deleted resulting in severe intrauterine anemia and death. In the modern era, some patients are surviving to term with intrauterine transfusions and thus need life-long transfusion support for survival after birth.
- Hb H disease: This is due to deletions or mutations in three α -globin genes resulting in moderate hemolytic anemia. Only one α -globin gene is intact. Some patients may need transfusion support and have a thalassemia intermedia phenotype.
- α -thalassemia trait: This is due to deletions or mutations of two α -globin genes resulting in mild microcytic anemia.
- Silent carrier: These patients have one α -globin gene deletion or mutation and are clinically asymptomatic.

II. β -Thalassemia

β -thalassemia is caused by a decreased or absent β -globin chain production, which results

in a relative excess of free β -globin chains, and in premature destruction of red blood cells. Each individual normally has two β -globin genes.

- β -thalassemia major: This term refers to a clinically severe phenotype which is due to the absence of β -globin chain production as a result of homozygous or compound heterozygous β -thalassemia mutations. Severe anemia, ineffective erythropoiesis, and compensatory erythroid marrow hyperplasia necessitate regular red blood cell transfusions, beginning in infancy. The transfusions are important for normal growth and development, improved quality of life, and increased life expectancy.
- β -thalassemia intermedia: This refers to a clinically moderate phenotype, which is due to genotypes such as compound heterozygous states for milder β -globin mutations, thalassemic hemoglobin variants (e.g., HbE) or alternative thalassemic mutations (e.g., $\delta\beta$). These patients may need occasional transfusional support. Circumstances may change through life requiring long-term transfusion support.
- β -thalassemia trait/carrier: This refers to a clinically mild phenotype with only 1 mutated gene resulting in mildly low hemoglobin levels and clinically asymptomatic individuals.

Thalassemia major is a term used to identify patients requiring more than eight transfusions a year, and includes all homozygous β -thalassemia patients, some heterozygous β -thalassemia patients, Hb Barts and some HbH disease patients. Patients with thalassemia major are at risk for impaired growth and development, and decreased survival. This is due primarily to consequences of severe anemia, ineffective

erythropoiesis and compensatory erythroid marrow hyperplasia. The mainstay of treatment is regular transfusion support starting in infancy. The aim of transfusion is to correct the severe anemia to allow for normal growth and development and to inhibit marrow expansion and its sequelae. Extramedullary hematopoiesis results in hepatosplenomegaly. Expansion of marrow results in osteopenia and deformity.

Patients with β -thalassemia major usually become symptomatic by about 4 – 6 months of age and without transfusion support, progressive anemia causes decreased growth and development, heart failure, and eventual premature death. Without transfusions, very few patients survive beyond 5 years of age.

Comprehensive long-term management of thalassemia major patients involves life-long transfusion support approximately every 3 – 4 weeks, reduction of transfused iron, and management of complications of iron overload. Patient-centered services need to be in place to help facilitate optimal comprehensive patient care in ways that are the least disruptive to the patients and family. Comprehensive care also includes assessing and supporting psychosocial needs of children and adults living with a chronic medical condition to enable them to lead normal, self-fulfilling lives and to contribute to society.

A. Components of Comprehensive Thalassemia Care

A1. A Network of Care

Principles

- To provide a high standard of care that is delivered by a multidisciplinary network of specialist centres and satellite clinics.
- To ensure patients can receive regular treatment that is convenient and easily accessible with minimal disturbance to normal, everyday activities.
- To focus on excellent routine care by following high standards of clinical practice, including prevention of, and appropriate management of complications in order to decrease morbidity and mortality, and improve quality of life.

Guidelines

- Each program should consist of a collaborative regional network of one or more specialized thalassemia centres and affiliated thalassemia satellite clinics. These facilities could also provide services for patients with sickle cell disease or other transfusion-dependent anemias where patient numbers are not large enough for separate programs.
- Each program should have a formalized system for specialized thalassemia services that is appropriately configured to the geographical location and size of the patient population.
- All patients should have access to the specialist centre either for routine thalassemia-related care if living near by, or for more specialized services and regular annual expert clinical review if living far away.
- The regional networks may choose to share certain resources but should have effective communication, accountability and avenues for self-evaluation and staff development.

Interventions

I. Role of the Specialist Centre

The specialized thalassemia centre should have a multi-disciplinary team of staff experienced and specialized in the diagnosis, treatment and care of thalassemia. The team should be led by an adult or pediatric hematologist, with special interest in thalassemia. The specialized thalassemia centre should:

- Provide consultation at key milestones including at diagnosis, at initiation of regular transfusions, at initiation of chelation therapy, at times of major complications, and at transfer to an adult clinic in addition to annual review
- Provide specialist opinion on management of complex issues including chelation regimens, problems with compliance, peri-operative management, management of cardiac, liver, endocrine, and bone complications, issues of fertility, genetics, option of bone marrow transplantation, and complex psychosocial issues
- Provide consultation, education and training for staff at satellite clinics and at the specialist centre

- Audit adherence to standards of care, performance and outcomes of care
- Be involved in clinical research studies to improve overall patient care
- Be an advocate for improved patient care and service delivery at the local, provincial and national levels

II. Role of the Satellite Clinic

A satellite clinic should be led by a physician with knowledge of thalassemia, together with local outreach and hospital services. The services offered by satellite clinics may vary but it is expected that each should be able to:

- Provide regular transfusions, prescriptions for chelation therapy, and other necessary therapies
- Monitor growth, development, and general health
- Monitor psychosocial well-being and provide psychological assessment and treatment, when necessary
- Organize the regular assessments and monitor locally available tests
- Be a local resource of information and support for the patient and family
- Provide treatment to the patient and family in a way that minimizes disturbance to normal, everyday activities
- Provide regular communications to the specialist centre, and make special referrals and consultation, as needed

III. Staffing

- The specialist centre should be led by a hematologist with experience in thalassemia care and, the satellite clinic by one or more clinicians with knowledge in thalassemia.
- Each site should have a designated nurse who should be the key contact for the patient and family. This person should provide support

and guidance on routine care and assist in accessing local services.

- A psychologist and social worker should be integral members of the interdisciplinary team.
- Members of the interdisciplinary team should meet on a regular basis to discuss patients with emphasis on medical, nursing, and psychosocial needs of the patient and family.
- Staff should be well-trained in the different aspects of thalassemia and have well-developed intravenous insertion skills.
- Staff turnover should be minimized to allow for the development of effective, long-term relationships between the team and patients.
- Other crucial members of a multidisciplinary team at the specialist centre and satellite clinic should be present, as outlined in Table 1.

IV. Facilities

- Facilities with adequate space should be provided for outpatient consultation, phlebotomy, and transfusion
- Multiple consultants from different subspecialties should be available to assess and provide care for the patient
- Services for phlebotomy and transfusion should be offered at times that are convenient to the patients and families

V. Quality Assurance

- Each formalized regional network should have systems in place for regular self-assessment of clinical practice and services
- Each centre, either specialist or satellite, should design and implement internal audits of clinical practice, adherence to practice guidelines, and services available to patients and families
- When available, each centre should participate in external audits of their clinical practices, adherence to practice guidelines, and services available to patients and families

Table 1: Staffing Recommendations for Satellite Clinics and Specialist Centres

Team Members		Satellite Clinic	Specialist Centre
Physicians	<ul style="list-style-type: none"> • Consultant pediatric or adult hematologist (depending on age of patients) with experience in thalassemia • Pediatrician, internist, hematologist or general practitioner/ internist with knowledge of thalassemia care • On-call physicians for after-hours issues 	<ul style="list-style-type: none"> ■ ■ 	<ul style="list-style-type: none"> ■ ■
Nursing	<ul style="list-style-type: none"> • Nurse specialist for thalassemia service: training, monitoring, co-coordinating and auditing • Registered nurses in outpatient day care unit area who can perform intravenous (I.V.) cannulation and supervise transfusions • Nurse outreach into the community: home visits, teaching pump use, etc. This may be coordinated with local home care programs • Nurse contact for patient and family 	<ul style="list-style-type: none"> ■ ■ ■ ■ 	<ul style="list-style-type: none"> ■ ■ ■ ■
Access to other multidisciplinary team members	<ul style="list-style-type: none"> • Clinical psychologist • Psychologist • Social worker • Dentist • Dietician 	<ul style="list-style-type: none"> ■ ■ ■ ■ 	<ul style="list-style-type: none"> ■ ■ ■ ■
Access to specialist consultants	<ul style="list-style-type: none"> • Designated pediatric or adult cardiologist • Designated pediatric or adult endocrinologist • Designated pediatric or adult hepatologist • Genetic counselling • Designated obstetrician and fertility program • Bone marrow transplant service 		<ul style="list-style-type: none"> ■ ■ ■ ■ ■ ■
Other support services	<ul style="list-style-type: none"> • Appropriate laboratory support (transfusion, diagnostic), diagnostic imaging • Access to translation services • Administrative support sufficient to ensure record maintenance and proper communication between patient and family with clinic, centre, family doctor and all services involved 	<ul style="list-style-type: none"> ■ ■ ■ 	<ul style="list-style-type: none"> ■ ■ ■

A. Components of Comprehensive Thalassemia Care

A2. Lifelong Education and Communication Between Patient and Health Care Team

Principles

- Thalassemia patients and families should be educated, supported, and treated in age appropriate ways so that they can take an active role in optimizing their health and quality of life.
- Patients and their families should work together with professionals in a multidisciplinary team to optimize their care.
- Accurate and effective communication within a family, between the patient and health care team and between health professionals, should be maintained to ensure the successful management of this life-long condition.

Guidelines

- Patients and families should be offered comprehensive, age-appropriate education about thalassemia.
- Families should be taught to administer home chelation and other treatments and supervise the child's care. The health care team should provide ongoing support and guidance.
- A key contact health professional, usually a specialized nurse, should be designated for each patient/family and should be readily accessible.
- Adequate monitoring, regular follow up visits, and early identification and management of complications should be provided to minimize hospital admissions.
- The multidisciplinary team should systematically and regularly record and exchange information relating to clinical events, results of investigations, changes in treatment, overall management plans, and changes within the child's family or social system, with each other and the patient/family.
- Information should be communicated to the pediatrician or general practitioner involved in the patient's care at least once a year and after a major event or change in treatment plan.
- Patients and families should be appropriately educated so that they can have a meaningful role in all health care decisions. Patients should be directly involved in decisions appropriate to their age and desire.
- Families should have access to a social worker, psychologist, and peer support networks.
- All information should be tailored to the age, developmental stage, cultural background and educational level of the patient and family. Appropriate programs and support systems should be in place to ease the transition from pediatric to adult care centres.

B. Management of Thalassemia

B1. Initial Management of the Newly Diagnosed Infant

Principles

- To promptly establish the correct diagnosis for the infant with thalassemia.
- To promptly start an appropriate treatment program for the infant with thalassemia.
- To provide education and psychosocial support tailored to the education level, culture and language of the family.

Guidelines

- Diagnosis of a child with a thalassemia disorder should be done as early as possible after birth and should include hematological and genotypic analysis.
- The child's clinical course should be closely monitored since the clinical phenotype cannot always be accurately predicted from the genotype.
- Qualified experienced professionals should discuss with the family the diagnosis, management and overall psychosocial impact on the child and family in an open, sensitive, and culturally appropriate manner.

Interventions

- Where available, the diagnosis of a serious thalassemia syndrome should be predicted from antenatal screening of parents, and may be established by prenatal diagnosis or by neonatal testing. Neonatal screening programs, where present, should also be able to identify affected infants.
- Initial diagnostic investigations should include a complete blood count, peripheral blood film examination, hemoglobin analysis by electrophoresis or high performance liquid chromatography (HPLC), and confirmed by molecular genetic analysis. Both α - and β -globin gene mutational analysis should be conducted to confirm the diagnosis and determine

co-inheritance patterns that may help predict clinical phenotype. Parents should be tested if no prior testing has been performed.

- The initial clinic visit may be at the satellite clinic or at the specialist centre. If initially seen at the satellite clinic, arrangements should be made for a visit to the specialist centre shortly thereafter (within 6 weeks or sooner, if clinically indicated). Each network should develop a system of new patient assessment depending on where the family lives and local resources.
- In symptomatic, previously unidentified infants with suspected thalassemia, investigations and initial assessment should be done immediately at the specialist centre.
- Both parents should be given verbal and written information about the diagnosis and management, and given the opportunity to ask questions. An interpreter may be necessary to communicate in the family's language of first choice, if English or French is not the primary language.
- The key contact specialist nurse should meet and exchange contact information with the family.
- The family should be given information on regional support groups, if available.
- A written summary of the diagnosis, the treatment plan, and the discussions held should be documented and distributed to the satellite clinic, specialist centre, family practitioner and family.

B. Management of Thalassemia

B2. Transfusion Support in Thalassemia

I. Starting a Red Blood Cell Transfusion Program

Principles

- To use clinical and genetic information to help identify thalassemia major patients who will depend on transfusions to maintain acceptable development, health and quality of life, and prolonged life.
- To use clinical and genetic information to help identify thalassemia intermedia patients who do not need routine transfusions to maintain acceptable development, health and quality of life.

Guidelines

- Irrespective of genotype, all affected infants should be closely monitored for clinical evidence of the need for initiating regular transfusions.
- Patients with thalassemia intermedia phenotype are less likely to have clinical indications for regular routine chronic transfusions in early life and as a result, should not be subjected to inappropriate regular transfusions.
- All the necessary baseline laboratory investigations including red cell phenotype, and hepatitis B vaccinations should be started prior to initiating transfusions.

Interventions

i. Deciding When to Start Transfusions

- Infants should be monitored at least once a month until the phenotype of thalassemia major or intermedia has been determined.
- These monthly assessments should include history, physical examination and laboratory investigations as outlined in Figure 1. Parents should be asked about feeding problems,

physical activity, irritability, developmental milestones, and overall health. Physical examination should include assessment for growth curves, head circumference, hepatosplenomegaly, cardiovascular status, facial abnormalities, and bone deformities. Hemoglobin should be checked monthly.

- The genotype may give some information as to the likelihood of the need for transfusions, but ultimately, the decision to transfuse is based on clinical findings and may be subtle and a difficult one to make.
- Indications for transfusion include severe anemia in association with failure to thrive, developmental delay, bone deformities, or unacceptable quality of life.
- The decision to initiate transfusions should be made in consultation with or by the thalassemia specialist at the specialist centre.

ii. Evaluation Prior to Starting Transfusions (Figure 1)

- Patients who are diagnosed early based on neonatal screening should be followed closely with serial hemoglobin measurements to determine if severe anemia is persistent prior to starting regular transfusions.

- Patients without a prior known diagnosis of thalassemia, and with a first presentation of severe anemia and signs and symptoms of chronic hypoxemia, should have a work-up for secondary causes of anemia (e.g., nutritional, hemolytic, intercurrent viral infections, etc.) prior to starting a chronic transfusion program.
- The full red blood cell phenotype should be determined for all patients prior to starting transfusions.
- The baseline serum ferritin and liver enzymes including ALT, AST, bilirubin, lactate dehydrogenase (LDH) should be measured.
- Serologic testing for hepatitis A, B, and C, and HIV should be performed as baseline measures.
- All patients who do not have serologic immunity to hepatitis B should start the vaccination program prior to initiation of a chronic transfusion program if possible.
- All first-degree family members should undergo HLA-typing, if potential future allogeneic hematopoietic stem cell transplant is considered an option.

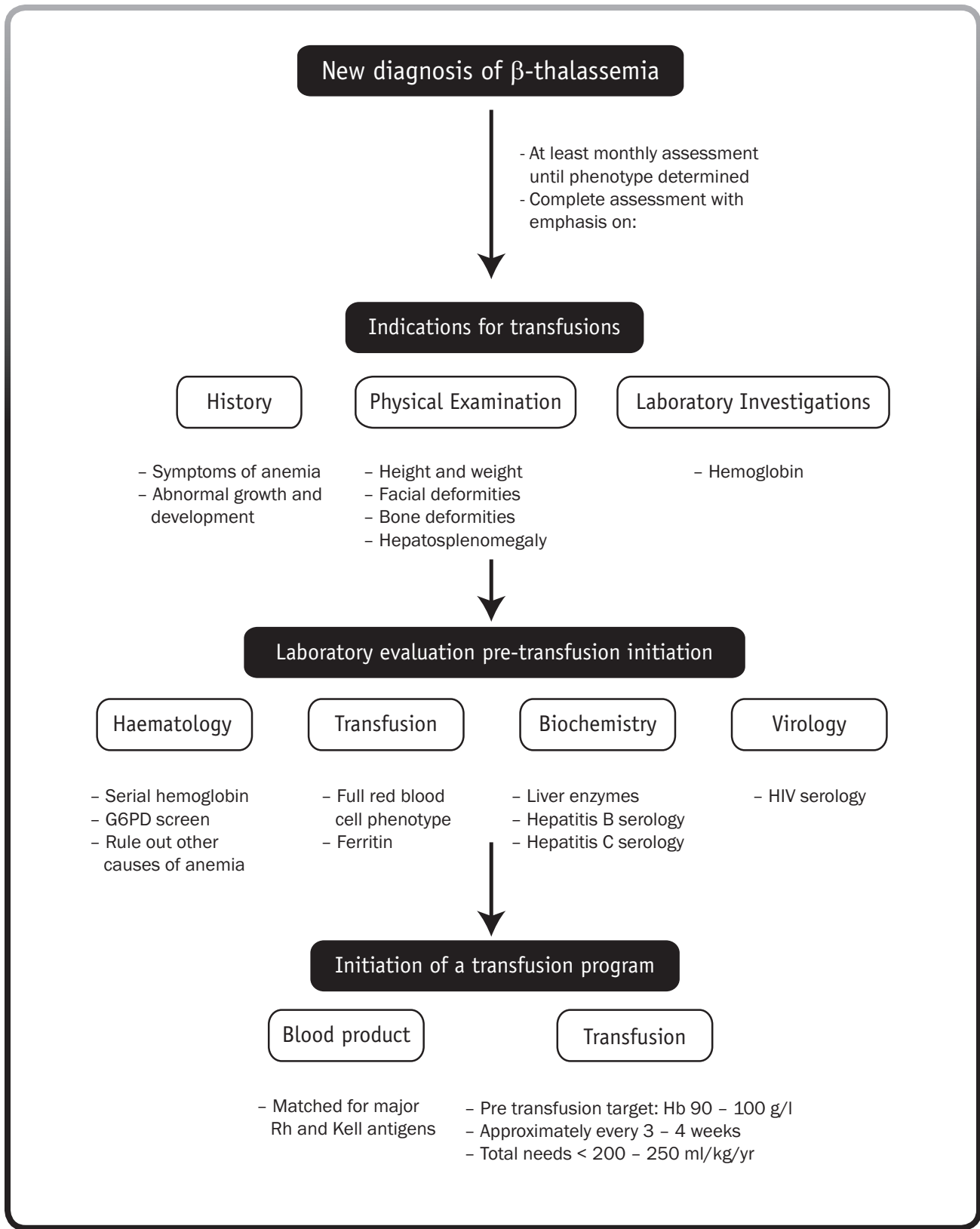


Figure 1: Clinical and Laboratory Aspects When Deciding Appropriateness of Initiating a Transfusion Program

B. Management of Thalassemia

B2. Transfusion Support in Thalassemia

II. Red Cell Transfusion Practices and Monitoring

Principles

- To ensure that children and adults are transfused to an acceptable hemoglobin level necessary to suppress endogenous erythropoiesis and to promote normal development with good quality of life.
- To prevent complications related to under-transfusion.
- To ensure that safe blood transfusion practices are closely followed.
- To deliver transfusion services in a way that is least disruptive to the patient's routine of daily life.

Guidelines

- Patients should receive leucodepleted blood as set out by Canadian Blood Services/Héma Québec policies and prophylactically matched for D, C, E, c, e and K1 blood group antigens.^{3,4} (GRADE B)
- Patients with thalassemia major, based on clinical status and genotypic analysis, should receive regular transfusions to maintain pre-transfusion hemoglobin levels between 90 – 100 g/l.⁵⁻⁷ (GRADE B)
- Each patient should have a chart with accurate documentation of transfusion requirements, blood bank antibody monitoring, and transfusion reactions.

Interventions

i. Blood Product Parameters

- A full cross-match and antibody screen should be performed prior to each transfusion. Every patient should have a complete record of antigen typing, antibodies, and transfusion reactions.

- All patients should be prophylactically matched for D, C, E, c, e and K1 blood group antigens to reduce the risk of alloimmunization.^{3,4} Depending on patient history or other local factors, centres may choose to use extended antigen matching. (GRADE B)

ii. Transfusion Parameters

- Regular transfusions should be administered to maintain pre-transfusion hemoglobin levels between 90 – 100 g/l.⁵⁻⁷ (GRADE B)
- Complete records should be kept and reviewed regularly to identify patients who are being under-transfused or who have increased transfusion requirements.
- Total transfusion requirements should be calculated regularly at 6 – 12 month intervals. If the transfusion requirement is greater than 250 – 275 ml/kg/year, the cause for such high transfusion needs should be determined. These may include hypersplenism, accelerated destruction of donor cells due to allo- or autoantibodies, or blood loss.

iii. Transfusion Safety and Policies

- Transfusions should take place in a designated environment with staff experienced in transfusion and intravenous cannulation. Where possible, efforts should be made to provide extended hour (evening, weekend) services to decrease the impact on patient's quality of life including attending school or work.
- Blood products should be administered in accordance with applicable standards.³⁷ Each centre should have regular reviews and audits by a transfusion committee.
- The patients should be tested at least every 2 – 3 years for transfusion-transmissible infections including Hepatitis B, C, and HIV.

iv. Role of Splenectomy for Management of Transfusion Requirements

- Splenectomy may be considered for patients with thalassemia major with transfusion requirements greater than 250 – 275 ml/kg/year.⁷ However, this should be balanced with known adverse effects of splenectomy including arterial and venous thrombosis, pulmonary hypertension, and life-threatening infection.³⁸ (GRADE B)
- The need for splenectomy due to hypersplenism has significantly decreased due to improved transfusion practices, stressing the importance of adequate transfusion.
- Prior to splenectomy, if not already done, patients should be vaccinated against pneumococcus, Haemophilus influenzae B, and meningococcus as per Canadian Immunization Guidelines.³⁹ (GRADE B)
- Patients and families should be educated about the risks of sepsis post-splenectomy and the need for immediate medical attention, if fever develops.
- The role and duration of antimicrobial prophylaxis in post-splenectomy patients is still

controversial due to lack of sufficient evidence and is reflected by different recommendations in the literature.⁴⁰⁻⁴² The Canadian Pediatric Society recommends antimicrobial prophylaxis post-splenectomy until 5 years of age or in older children for at least 1 year post-splenectomy, but prophylaxis may be continued, depending on individual clinical circumstances.⁴¹

B. Management of Thalassemia

B3. Iron Overload and Chelation Therapy

Background on Iron Overload, Assessment of Iron Overload, and Iron Chelation

I. Iron Overload Overview

Red cell transfusion is the mainstay of treatment for thalassemia major; however, over time this therapy results in significant iron overload. Once the body's ability to store iron is exceeded, free iron accumulates and participates in the formation of reactive hydroxyl radicals, which cause denaturation of proteins and membrane damage. Iron overload, mainly from blood transfusions and, to a lesser degree, from increased gastrointestinal absorption, is the major cause of morbidity and mortality in transfused thalassemia patients. If untreated, it is fatal in the first or second decade of life. Major complications of iron overload, including cardiac, liver and endocrine toxicities, can be avoided or ameliorated by the early detection and treatment of iron overload.⁸⁻¹⁰

II. Assessment of Iron Overload

There are several indirect and direct methods for iron load assessment. Serum ferritin, a simple indirect measure of iron stores, is associated with increased risk of cardiac complications when over 2500 µg/l.⁹ However, ferritin is an acute phase reactant and may be falsely elevated in liver disease, infection, or inflammatory processes. The prediction of iron loading from ferritin is poor and hence it should not be used in isolation.^{16,43} In each patient, the serum ferritin should be periodically correlated with other objective tests of iron overload. Between periodic direct iron assessments, the serum ferritin can be easily used to follow response to treatment. Chelation therapy should be started in patients with a ferritin over 1000 µg/l; however, once

chelation has been initiated, the ferritin should be maintained between 1000 – 1500 µg/l.^{1,2,17}

Liver iron concentration (LIC) measured on ultrasound-guided liver biopsy material directly determines liver iron load. The liver biopsy is invasive and can be associated with morbidity and rarely mortality. In addition, there may be sampling error if iron deposition is patchy, and poor reproducibility if the sample is small or fibrotic.⁴⁴ A liver iron level above 15 mg Fe/g dry weight is associated with increased organ injury and high risk of cardiac death in thalassemia.⁸ Based on data from hereditary hemochromatosis patients, liver iron should be maintained below 7 mg Fe/g dry weight.^{1,2}

Various magnetic resonance imaging (MRI) based techniques have been developed recently to determine organ iron load non-invasively. Calibration curves for MRI R2 and R2* (inverse of T2 and T2*) signals for the liver have been developed and show a curvilinear relationship between liver iron estimated by R2 or R2* and by biopsy.^{14,45-48}

Iron concentration in the myocardium of the interventricular septum is inversely related to cardiac MRI T2* signal.¹⁴ Myocardial T2* values less than 20 ms (normal 20 ms) are associated with a progressive and significant decline in left ventricular ejection fraction. Since other measures of body iron load assessment including serum ferritin, biopsy determined LIC, and liver MRI T2* do not correlate with cardiac MRI T2*, cardiac MRI T2* plays a pivotal role in detection of early cardiac toxicity.^{14,47,49,50} Cardiac MRI is

non-invasive and allows concurrent determination of cardiac function. Early diagnosis of cardiac iron overload and dysfunction may allow for earlier intervention and better outcomes. The major limitation of all MRI modalities at present is their limited availability.

Liver iron estimation using the Superconducting QUantum Interference Device (SQUID) also correlates with liver iron load.⁵¹ It cannot be used on the heart, and is available in only a few centres. It therefore, has a limited role in routine management.

III. Initiation of Chelation Therapy

Iron chelation with deferoxamine has been used for more than 30 years and has prevented or delayed complications of iron overload and has also extended life.^{8,9,11} In the last few years, new oral iron chelating agents have been developed, adding new interest to the field and posing many new questions.

i. Deferoxamine

Deferoxamine was the first iron chelator available. Its use has resulted in decreased end organ dysfunction and improved long-term survival.^{8,9,11} Its main disadvantages are that it must be administered by the parent or the patient either by intravenous or subcutaneous infusion driven by a pump.

The dose of deferoxamine is adjusted according to body iron load and age, and ranges from 20 – 40 mg/kg/day for children and up to 50 mg/kg/day for adults given for 8 – 12 hours for 5 – 7 nights per week.

More aggressive chelation therapy is required for patients with significant iron loading with ferritin > 2500 µg/ml, liver iron concentration

> 15 mg/g dry weight or cardiac T2* < 10 ms.^{9,47}

Aggressive chelation therapy consists of a 24-hour continuous infusion of deferoxamine to the maximum daily dose. While an increase in the dosage of deferoxamine can increase the amount of iron chelation, the chelation efficiency of the same dose of drug is significantly increased by prolonging the duration of infusion, likely decreasing the organ damage due to non-transferrin bound iron. The constant presence of chelator decreases damaging reactive radical formation.

Side effects of deferoxamine include local skin reactions, predisposition to infection with *Yersinia enterocolitica*, severe allergy, divalent ion deficiency (e.g., zinc) and dose-related complications. Dose-related toxicities include auditory problems, including high frequency bilateral sensory neural loss, tinnitus, and deafness. High doses of deferoxamine increase the likelihood of night blindness, impaired color vision, impaired visual fields, and decreased visual acuity. For intravenous therapy at high doses, renal dysfunction and hypotension have been noted. Growth retardation can occur especially in children under 3 years and on high doses. Excessive doses of deferoxamine in patients with low iron loading can cause skeletal changes including vertebral demineralization and flattening of vertebral bodies. Rare complications include renal impairment and interstitial pneumonitis at very high doses.

ii. Deferiprone

Deferiprone, the first and most studied oral iron chelator, is currently approved in Europe and other parts of the world but not in North America. In Europe, it is licensed for treatment of iron overload in patients with transfusion-dependent anemias when deferoxamine is contraindicated

or inadequate.^{52,53} Typical dosage is 75 mg/kg/d in 3 divided doses up to a maximum of 100 mg/kg/day. Deferiprone reduces iron stores, as measured by ferritin or LIC, in thalassemia major patients receiving transfusions.^{53,54} It causes less iron excretion compared to deferoxamine on a molecule-to-molecule basis. Because of its small size and lipophilic nature, deferiprone is able to penetrate cells better and chelate iron from organs such as the heart more effectively.⁵⁵⁻⁵⁷ Myocardial T2* values and left ventricular ejection fraction (LVEF) improve more rapidly in deferiprone-treated patients compared to deferoxamine-treated patients.

While deferiprone clearly has selectivity for cardiac iron, deferoxamine chelates iron more efficiently from the liver. Combination treatment with deferoxamine and deferiprone is increasingly being used to remove total body iron. Combination treatment reduces myocardial iron load, lowers ferritin and improves LVEF in thalassemia major patients with mild to moderate cardiac iron loading as defined by T2* values of 8 – 20 ms.⁵⁸⁻⁶²

The most serious complication of deferiprone is agranulocytosis (neutrophils < 0.5 x 10⁹/L), which occurs in less than 1% of patients.^{54,63} Milder neutropenia (0.5 – 1.5 x 10⁹/L) occurs in 8% of patients. Common side effects of deferiprone include arthropathy, transient elevation in ALT, and gastrointestinal upset. Initial concerns about drug-induced fibrosis have not been supported by multiple subsequent studies, and progressive liver disease attributable to the drug has not been reported in large clinical trials.^{54,63,64}

iii. Deferasirox

Deferasirox is the only oral iron chelator approved in Canada. It has been approved for the treatment of chronic iron overload in patients with transfusion-dependent anemias aged 6 years or older and in those patients aged 2 – 5 years who cannot be adequately treated with deferoxamine. Dosing is adjusted based on the patient's transfusion rate and trend of iron load; treatment ranges from 10 – 30 mg/kg/day.

A phase III trial demonstrated the efficacy of deferasirox and its non-inferiority to deferoxamine at doses of over 20 mg/kg/day when used by thalassemia major patients.¹² Non-inferiority at lower doses of deferasirox was not established and may have been due to study design. Individualized assessment of total iron load and a tailored dosing regimen may be needed to achieve optimal iron chelation.

Side effects of deferasirox include gastrointestinal symptoms (26%), skin rash (7%), cytopenias, and an increase in serum creatinine (34%). The optimal dose of deferasirox for an individual patient, its effectiveness at reducing cardiac iron, its role in combination therapy, and its long-term safety profile remain to be clarified.

A randomized, open-label, Phase III trial evaluated Patient-Reported Outcomes (PROs) at the end of one year and found that significantly more patients on deferasirox as compared to those on deferoxamine reported treatment satisfaction (89% vs. 41%, respectively) and treatment convenience (93% vs. 11%).⁶⁵ Of those previously treated with deferoxamine, 97% of those in the deferasirox arm indicated a preference for deferasirox and 86% indicated a willingness to continue treatment as compared to 14% of those assigned to the deferoxamine group. All of these findings suggest a greater likelihood of compliance with deferasirox therapy.

iv. Iron Chelators Under Investigation

Other oral chelating agents are undergoing clinical trials. Studies with newer chelators (deferitron) or modifications of old chelators (starch attached to deferoxamine) are under way. With limited available evidence, recommendations cannot be made regarding the use of these other drugs.

v. Chelating Agents Summary

The ideal chelating agent should be highly efficient at binding iron, and be able to penetrate cells effectively and remove intracellular iron. It should be easy to administer orally, have a long half-life, and lack significant side effects. Lastly, the ideal chelating agent should be inexpensive and accessible. Although two therapeutic options now exist for iron-overloaded patients in Canada, each agent at the present time has benefits and limitations. Deferoxamine (Desferal) is a parenteral drug with proven efficacy and a well-defined long-term toxicity profile. Deferasirox, which can be administered orally and is now commercially available in Canada, presents a new option for patients for whom deferoxamine

is not effective or tolerated or those who are noncompliant. Although Deferiprone has a relatively well-defined efficacy and toxicity profile, access to this oral agent is restricted because it is not licensed for use in Canada.

Guidelines

- Transfusional iron loading and body iron stores should be monitored routinely.
- Chelation therapy should be started early in children receiving regular blood transfusion to prevent iron-related toxicities.⁸⁻¹⁰ (GRADE B)
- The chelating agent used should be tolerable and effective in reducing iron load. Intolerability of a chelating agent leads to poor compliance, which results in increased iron overload, subsequent end organ complications, and overall increased morbidity and mortality.
- In patients where deferoxamine is not tolerated or is ineffective or in those patients who are noncompliant, oral iron chelators should be used.^{8,9,11,12} (GRADE B)
- Regular monitoring for specific chelator-related toxicity should be carried out and the appropriate action taken if toxicity is found.
- The effectiveness of chelation should be routinely monitored and appropriate dose and drug adjustments made when required.
- Patients and families should receive age-appropriate education and access to an experienced multidisciplinary team to provide support in the practical and psychological aspects of chelation therapy and to promote independence and motivation in managing chelation therapy,
- Patients should receive adequate monitoring to identify early signs of inadequate adherence to chelation therapy. If adherence is problematic they should be provided with appropriate culturally sensitive counseling or therapy to aim for improved treatment outcomes.

Principles

- To be aware of complications of iron overload, to monitor routinely and accurately for iron overload, and to reduce iron accumulation using iron chelators with the goal of preventing organ damage and dysfunction.
- To reduce body iron load quickly in patients with iron overload and end organ toxicity.
- To monitor for and treat adverse side effects of iron chelators.

Interventions

I. Monitoring

- Every patient should have serial serum ferritin levels assessed every 3 months. Chelation therapy should be initiated for a persistently elevated ferritin > 1000 µg/ml and a liver iron concentration > 7 mg Fe/g dry weight.^{2,9,17}
- LIC should be determined after approximately 10 – 20 transfusions, prior to initiation of chelation therapy, and every 1 – 2 years (or as clinically indicated) thereafter.^{1,2} Modalities for measuring LIC may include liver biopsy, liver MRI R2 or R2*, or SQUID.
- Cardiac function should be monitored every 1 – 2 years using echocardiography or radioisotope studies (MUGA) and ECG. Both cardiac iron load and function can be measured more accurately using cardiac MRI T2* every 1 – 2 years.

II. Treatment

- Young children needing chelation therapy should be started on subcutaneous infusion of deferoxamine. To help with adjustment, the drug can be administered less frequently and increased to the target dose over 1 year.
- The target dose of deferoxamine should be 20 – 40 mg/kg/day for children, and up to 50 mg/kg/day for adults, given over 8 – 12 hours for 5 – 7 days/week.
- Deferasirox, as an alternative, should be available to patients who are intolerant to deferoxamine or in whom it is ineffective.¹²
- Deferiprone is currently not approved in Canada; however, it should be considered for patients in whom deferoxamine and deferasirox are intolerable or ineffective. It may also be considered in combination with deferoxamine in certain clinical situations such as cardiomyopathy.⁵⁸⁻⁶²

- The treating thalassemia specialist should have access to the different drug options for chelating iron and should be able to tailor the use of the drugs based on specific individual patient requirements and evidence from clinical trials.

III. Toxicity

- For patients on deferoxamine, investigations should include yearly audiometry and ophthalmology examinations, bi-annual growth assessments for children, and regular screening x-rays for bone complications. Baseline assessments for the above should be done prior to initiating chelation.
- For patients on deferasirox, serum creatinine, liver enzymes, and blood counts should be monitored twice prior to commencement of the drug, and then weekly for the first month and then monthly thereafter for 3 – 6 months. Once stabilized, serum creatinine, liver enzymes, and ferritin should be monitored every 3 months. Complete blood count should be performed monthly. Audiometry and ophthalmic testing should be done annually or earlier, if clinically indicated.
- For patients on deferiprone, complete blood counts with differential should be performed weekly and ALT measurements done monthly for 3 – 6 months, and every 6 months thereafter.

IV. Support

- Patients and families should be educated on the role and importance of iron chelation therapy and the rationale for the treatment regimen.
- Deferoxamine infusions are burdensome and therefore compliance is poor. Every effort should be made to provide education for patients and their families. Issues such as drug preparation, choice of infusion site,

types of needles and infusers used, and strategies for treatment of local reactions should be addressed. Children should be encouraged to participate in part of the routine of drug administration at an early age. This should be encouraged by the team based on the development level of the child, the family structure, and the cultural ideas of the family around the illness and treatment. The importance of chelation therapy should be reinforced at every clinic visit.

- All patients and families should have access to a multidisciplinary team to provide support in the practical and psychological challenges arising from daily chelation therapy and regular transfusions.
- The satellite clinic and specialist centre should have similar treatment and monitoring protocols. Good communication between the patient, family, local clinic, and specialist centre should be maintained to optimize patient care.

Table 2: Comparison of Currently Available Iron Chelators

Characteristics	Deferoxamine	Deferiprone	Deferasirox
Route of administration	<ul style="list-style-type: none"> • Subcutaneous or intravenous 	<ul style="list-style-type: none"> • Oral 	<ul style="list-style-type: none"> • Oral
Plasma half-life	<ul style="list-style-type: none"> • Short • 20 minutes 	<ul style="list-style-type: none"> • Moderate • 2 hours 	<ul style="list-style-type: none"> • Long • 8 – 16 hours
Primary route of iron excretion	<ul style="list-style-type: none"> • Urine and stool 	<ul style="list-style-type: none"> • Urine 	<ul style="list-style-type: none"> • Stool
Iron chelating efficiency	<ul style="list-style-type: none"> • High (hexadentate) 	<ul style="list-style-type: none"> • Low (bidentate) 	<ul style="list-style-type: none"> • Moderate (tridentate)
Charge of iron (III) complex (hydrophilic or lipophilic)	<ul style="list-style-type: none"> • Charged • Hydrophilic 	<ul style="list-style-type: none"> • Uncharged • Lipophilic 	<ul style="list-style-type: none"> • Uncharged • Lipophilic
Side effects	<ul style="list-style-type: none"> • Hearing abnormalities • Visual changes • Growth retardation • Bone changes • Local skin reactions • Potential renal and lung toxicity 	<ul style="list-style-type: none"> • Severe agranulocytosis • Mild neutropenia • Arthritis • Gastrointestinal discomfort 	<ul style="list-style-type: none"> • Rash • Gastrointestinal discomfort • Mild increase in creatinine
Specific guidelines for monitoring treatment	<ul style="list-style-type: none"> • Annual audiometry and retinal exams • Regular growth assessment. • Annual bone x-rays 	<ul style="list-style-type: none"> • Weekly complete blood count and differential— ALT monthly for 3 – 6 months then every 6 months thereafter 	<ul style="list-style-type: none"> • Weekly serum creatinine for 1st month • Creatinine, liver enzymes monthly for 3 – 6 months, then every 3 months once stabilized • Blood counts monthly • Annual audiometry and retinal exams
Advantages	<ul style="list-style-type: none"> • Long-term experience • Effective chelator – Intensive therapy can reverse cardiac disease • May be combined with deferiprone 	<ul style="list-style-type: none"> • Oral • Established safety profile • Better at removing cardiac iron • May be combined with deferoxamine 	<ul style="list-style-type: none"> • Oral • Once a day dosing
Disadvantages	<ul style="list-style-type: none"> • Prolonged parenteral infusions • Eye, ear, bone, growth toxicities • Poor compliance 	<ul style="list-style-type: none"> • Agranulocytosis requiring weekly monitoring 	<ul style="list-style-type: none"> • Limited, long-term data, including safety profile • Close monitoring of renal function

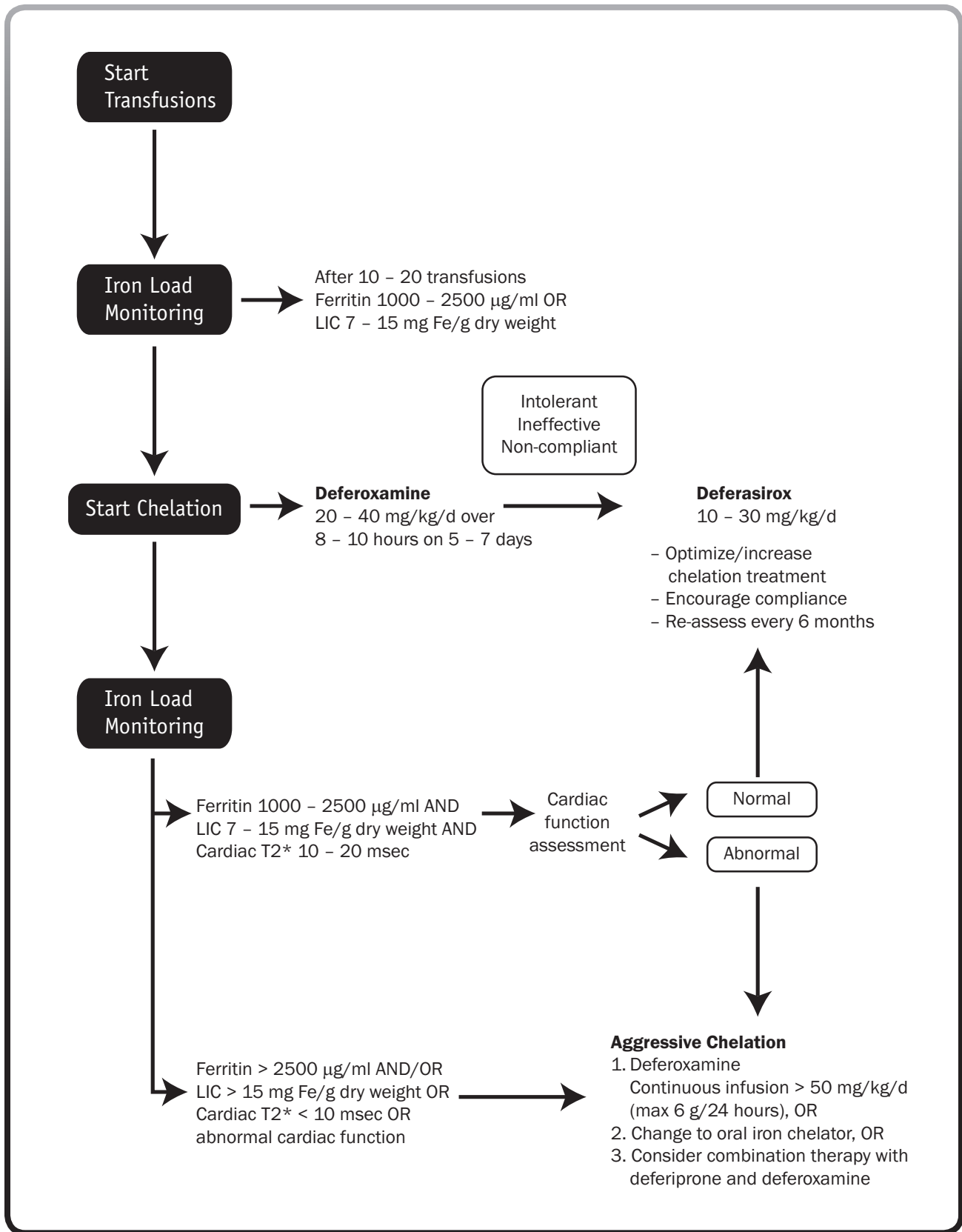


Figure 2: Monitoring of Iron Load and Appropriate Chelation Therapy

B. Management of Thalassemia

B4. Psychosocial Aspects of Thalassemia Care

Principles

- To help patients and families cope with the changing social and psychological aspects of living and growing up with thalassemia.
- To ensure patients' emotional well-being and promote self-management.

Guidelines

- The multidisciplinary team at the specialist centre should include a social worker and psychologist with knowledge of challenges faced by thalassemia patients at different developmental stages of life.
- The psycho-social needs of thalassemia patients should be prioritized in ongoing planning for treatment.
- Support should also address age-specific challenges and cultural influences.

Background

Thalassemia is a life long condition requiring ongoing medical treatment and management of complications, and hence, is a significant burden on the patient and family in all facets of life. Many diverse cultural, social, developmental, psychological and behavioural issues affect these patients and have bearings on the overall effectiveness of treatment, survival, and quality of life. In Canada, an increasing percentage of newly diagnosed patients are from families of recent immigrants, which poses additional challenges of socio-cultural adaptation. Greater social support may be needed under these circumstances.

Interventions

- The psychologist and social worker should regularly review patients, address issues and provide support, especially at critical milestones such as time of diagnosis, first transfusions, initiation of chelation, puberty, transition to adult care, and major life events such as marriage, pregnancy, and parenthood.
- The psychologist and social workers should function as integrated members of the interdisciplinary team and meet regularly with other professionals to discuss patients in an inter-disciplinary forum.
- Reviews should include all aspects of psychosocial development such as assessing: 1) patient relationships with family, peers, and significant others, 2) function at school, work and within the community including neuropsychological assessments, when necessary, 3) adolescent concerns of adjustment, 4) sexuality 5) self-esteem, identity, autonomy, and coping-skills, 6) search for and adaptation to vocations.
- All members of the multidisciplinary team should emphasize the importance of good communication between patient, family, and the medical team. Communication should be in both written and verbal forms, as appropriate.
- Resources and support should be provided to help patients develop a positive, coping

attitude toward their illness and to develop self-management skills, including healthy lifestyle behaviours. The medical team should provide support during times of complications, hardship, and major stressors.

- The practical and psychological challenges of regular transfusion and chelation, including the consequences of non-compliance, should be discussed with patients and families. The team should encourage shifting age-appropriate responsibilities from parent to child on a continuous basis, allowing the child to take control of disease management, including drug administration. Psychological issues such as needle phobia or fear of blood should be treated at an early age to allow for a smoother shift of responsibilities during adolescence. The team should help facilitate building a sense of autonomy, self-reliance, and self-esteem.
- Adolescents and adults should receive phase-specific support with regard to adjustments, relationships, work, marriage, parenthood, life-goals and societal expectations.
- Patients should have easy access to psychology services.
- If serious psychological difficulty or psychiatric illness is suspected, patients should be referred to a psychiatrist.
- All psychological and social support should be provided in a culturally sensitive manner.

B. Management of Thalassemia

B5. Hematopoietic Stem Cell Transplantation (HSCT)

Background

HSCT is the only curative option available to thalassemia major patients. Three major risk factors that affect overall outcome include inadequacy of chelation treatment, hepatomegaly, and presence of portal fibrosis.⁶⁶ Patients undergoing HLA-matched related allogeneic HSCT with no risk factors (Class 1) have an overall survival (OS) of 93% and disease-free survival (DFS) of 91%. OS and DFS are 87% and 83% for Class II (1 or 2 risk factors), and 79% and 58% for Class III (3 risk factors) patients respectively. Treatment-related mortality is approximately 10%. The best results are seen with children under the age of 3 years. In adults (age > 16 years) overall survival is 66% and event-free survival (EFS) 62%.^{66,67} Therefore, HSCT should be considered for patients at an early age before complications due to iron overload ensue. Transplant related complications including acute and chronic graft versus host disease should be weighed against the potential for cure in making a decision for HSCT.

HLA-matched unrelated donor transplants are associated with similar outcomes with high-resolution donor typing, however, treatment-related mortality is significant at 5–30% in some series.⁶⁸⁻⁷⁰ Acute and chronic graft-versus-host disease is a major complication and is much higher in unrelated donor transplants and in adult patients.

Related and unrelated umbilical cord transplants are another potential curative option for thalassemia patients and are associated with less graft-versus-host disease (GVHD), quicker access to stem cells, and no harm to the donor.^{71,72} The cord transplants yield low total cell numbers which limits their use to children or small adults. The cord transplants are also associated with slower engraftment and higher rejection risks.

Principles

- To ensure patients and families receive adequate information on hematopoietic stem cell transplantation (HSCT) for informed decision-making.
- To ensure close follow-up of patients who have undergone HSCT.

Guidelines

- The option of HSCT, including its indications and complications, should be discussed with families while the patient is at a young age.
- The discussions should be initiated by the specialist centre and, if the patient is serious about pursuing HSCT and it is appropriate, referral should be made to a HSCT centre with experience in transplanting thalassemia patients where more detailed discussions should take place.
- The options of HLA-matched related HSCT (cord blood and bone marrow) should be discussed.
- Post-HSCT, patients should be closely monitored and managed for iron overload and other complications.

Interventions

- HSCT should be performed in centres with experience in transplanting patients with thalassemia.
- Discussions about the role of HSCT in thalassemia should include benefits, risks, short and long-term complications, quality of life after HSCT and the psychosocial impact.
- The patient's risk factors and organ function should be assessed prior to HSCT.
- Long-term complications of HSCT include

iron overload, chronic GVHD, delayed pubertal development, growth and endocrine deficiencies, infertility and secondary malignancies. Complications should be managed in collaboration with the appropriate sub-specialist.

- After HSCT, reduction of pre-existing iron overload should continue by routine phlebotomy with or without chelation.^{73,74} Phlebotomy is safe and effective for iron removal after HSCT and has been shown to reduce iron load and liver fibrosis. Patients should be phlebotomized to achieve a ferritin < 300 ug/l.
- If the patient's mother becomes pregnant, the option of chorionic villous sampling (CVS) or amniocentesis for pre-natal diagnosis should be discussed. If the fetus does not have beta thalassemia, the cord blood should be harvested and stored for potential future transplant. If antenatal testing has not been done, all cord blood should be collected and subsequently tissue typed and stored, if matched.
- Transplanted individuals should be counseled that they will still pass on a mutant thalassemia gene to each of their children.
- Other modes of HSCT such as the use of multiple cord blood units are currently undergoing clinical trials. Updated recommendations might be made as new evidence becomes available.

B. Management of Thalassemia

B6. Transition from the Pediatric to Adult Care Setting

Principles

- To ensure a smooth transition and continuity of care for adolescents/young adults and families as they move from pediatric to adult care settings.
- To provide psychosocial support to the adolescents/young adults and families as they face new and different challenges of adulthood.
- To ensure ongoing and optimal long-term care throughout adulthood.

Guidelines

- Planning for the transition from pediatric to adult care settings should be started several years in advance and should focus on the process of educating the adolescent about the biological, medical, and psychosocial aspects of thalassemia, and equipping the adolescent/young adult with skills to become responsible and independent in caring for his/her health.
- The pediatric and adult centres should collaborate to increase patient familiarity with members of the adult team and the adult system.
- Following transition, adult patients should be followed routinely to ensure they receive optimal care and that complications are identified and managed promptly.

The transition from pediatric to the adult care setting is a stressful time for young adults and their families. A standardized process can help to ensure the proper steps are taken to equip and prepare the individual for transition. As the needs of each patient can be very different, this process should also be individualized.

Interventions

- The transition from pediatric to adult care setting should be planned well in advance of the actual event (at least 2 years) and should be discussed with the patient and family.
- Preparation for transition should consider the child's developmental stage and the readiness of the patient and family to take on new responsibilities.
- The patient and the family should be educated and equipped with tools to deal with the transition. The multidisciplinary pediatric team should focus on promoting independence in the young adult to take charge of his/her own care, and to problem solve on health-related issues including risks and complication that might arise.
- The pediatric and adult thalassemia teams should schedule a joint clinic where patients and their families can meet both teams together and become familiar with members of the adult team assuming their care. Optimally, the transition clinic should occur in the familiar setting of the pediatric site where patients and families feel most comfortable.
- A familiar member of the multidisciplinary pediatric team should take the young adult and family to the new adult clinic and where

they can become familiar with the new site. At least one member of the adult team should assist in this process and the visit should occur prior to the patient's first appointment.

- The pediatric team should ensure that there is a good transfer letter summarizing all the pertinent patient information, including medical, psychosocial care, and other relevant aspects.
- To ease the transition and reduce anxiety, the patient should not be transferred during an acute illness or during a period of other stress. Attempts should be made to organize the transfer when the patient is well.
- Psychosocial support in both the pediatric and adult settings should include a social worker, a psychologist, an education nurse, a specialist nurse, and a physician.

C. Complications of Thalassemia

C1. Cardiac Complications

Background

Iron-induced heart failure and arrhythmias are the most common causes of death in thalassemia major patients accounting for as many as 67% of all deaths.^{9,75} Deaths from cardiac disease are unusual before the age of 15 years unless iron chelation has been inadequate. Appropriate iron chelation as assessed by serum ferritin and liver iron concentration reduces the risk of cardiac disease and improves survival.^{8,9}

There are still many unanswered questions as to the best diagnostic and monitoring modalities, the frequency of testing, and the optimal treatment of iron-related cardiotoxicity. Recommendations will need to change as new evidence arises.

Principles

- To reduce cardiac morbidity and mortality by optimal iron chelation starting in childhood and continuing throughout adulthood.
- To monitor closely for cardiac dysfunction.
- To treat urgently cardiac dysfunction according to standards of care.
- To escalate chelation of cardiac iron if cardiac toxicity is identified.

Guidelines

- Each thalassemia specialist centre should have a pediatric or an adult cardiologist with knowledge of managing cardiac complications in thalassemia patients.

- All patients should have routine clinical assessment for signs and symptoms of cardiac dysfunction.¹³ (GRADE B)
- Cardiac iron load should be monitored routinely.¹⁴ Iron-overload should be reduced by chelation to lower the risk of iron associated cardiac complications and death.^{8,9,15} (GRADE B)
- Cardiac function should be measured routinely. In the presence of increased cardiac iron load and cardiac dysfunction, more aggressive iron chelation regimens should be initiated.¹⁵ (GRADE B)
- The designated cardiologist should manage cardiac complication, including heart failure and arrhythmia, as per cardiology standards.

Interventions

I. Monitoring for Cardiac Dysfunction and Iron Load

- All patients should be asked for symptoms of cardiac disease on each visit and have a cardiac physical examination every 6 months. Any abnormality should trigger specific cardiological evaluation.
- Cardiac function, including LVEF, can be measured by several techniques including echocardiography, MUGA scan, and cardiac MRI T2*. Since decreased LVEF is associated with subsequent development of symptomatic cardiac disease and death, cardiac function should be measured yearly starting at the age of 10 years.¹³ Assessment may be done sooner or more frequently if clinically indicated or if compliance with chelation has been poor.
- If there is a suspicion of arrhythmias based on history or physical examination,

an electrocardiogram and 24-hour Holter monitoring should be done.

- Regular echocardiography will also help monitor for the development of pulmonary hypertension.
- Ferritin greater than 2500 µg/L or a liver iron concentration > 15 mg Fe/g dry weight is associated with high risk of cardiac death in thalassemia.⁸
- Since ferritin and liver iron may not correlate with cardiac iron load, cardiac iron can be specifically and reproducibly measured using cardiac MRI T2*. Cardiac MRI T2* less than 20 ms correlates with a progressive and significant decline in LVEF.¹⁴
- The specific timing and frequency of MRI T2* testing has not yet been established. However, as it becomes more widely available, it may be reasonable to consider doing this test every 1 – 2 years in patients with high MRI T2* values (> 20 ms), and every 6 months – 1 year in patients with low MRI T2* values. Timing and frequency of testing should ultimately be individualized to each patient. These recommendations may change as we obtain more experience with this diagnostic modality.

II. Treatment Based on Cardiac Dysfunction and Iron Load Assessment

- Chelation therapy to reduce high iron load lowers the likelihood of developing cardiac dysfunction. Cardiac MRI T2* values greater than 20 ms are not usually associated with significant iron load and cardiac dysfunction. Lack of compliance with chelation therapy should be identified and importance of chelation stressed.⁴⁷
- Cardiac MRI T2* values between 10 and 20 ms indicate cardiac iron deposition with a risk of eventual cardiac decompensation. A more aggressive chelation program should be implemented in such patients, and cardiac iron load and function re-evaluated every 6 months. Conversion to an aggressive chelation program in patients with heart failure can improve LVEF and myocardial MRI T2* measurements.¹⁵ Compliance with chelation therapy should be explored and its importance stressed. (GRADE B)
- Cardiac MRI T2* values < 10 ms indicate significantly increased iron loading and are associated with significant risk of more immediate cardiac decompensation without aggressive intervention.^{47,76} Aggressive chelation therapy should be started immediately and cardiac function monitored at least every 6 months.
- Where cardiac MRI T2* is not available, chelation decisions should be based on ferritin, LIC and cardiac function assessment. Patients with ferritin > 2500 µg/ml and LIC > 15 g Fe/g dry weight should be chelated more aggressively, while those with ferritin < 2500 µg/ml and LIC 7 – 15 g Fe/g dry weight should have chelation adjusted accordingly and compliance encouraged.
- A cardiologist with knowledge of thalassemia and iron-related cardiotoxicity should be involved in every affected patient's care and be consulted when problems arise.
- Cardiologic intervention and management for heart failure and arrhythmia should follow cardiology standards and should include medications such as ACE inhibitors, beta-blockers, diuretics, digoxin, and anti-arrhythmic agents, pacemakers with or without cardioversion capacity, and ablation of arrhythmogenic tissue.

C. Complications of Thalassemia

C2. Liver Complications

Background

Liver disease is a common complication in older thalassemia patients. Common causes of liver disease include transfusion-related viral hepatitis (Hepatitis B, C), iron overload, drug toxicity, and biliary disease due to gallstones.

Principles

- To prevent liver disease caused by viral hepatitis, iron overload, drug toxicity or hepatocellular carcinoma.
- To monitor liver abnormalities routinely, and provide treatment for iron overload and any underlying liver disorder.

Guidelines

- Every thalassemia specialist centre should collaborate with a designated hepatologist with knowledge of liver complications in thalassemia patients.
- Liver enzymes should be monitored routinely, and abnormalities investigated for etiology, reviewed by a hepatologist if indicated, and managed accordingly.
- Liver iron concentration should be monitored routinely and chelation therapy initiated and adjusted to reduce complications of iron overload.^{8,9,16,17} (GRADE B)
- Every effort should be made to reduce the risk of viral hepatitis by safe transfusions, hepatitis B vaccination programs and regular monitoring.
- Patients with active hepatitis B or C should be referred to the designated hepatologist and managed as per hepatology standards of care.
- Adult patients should be encouraged to avoid liver toxins including alcohol and liver-toxic drugs.
- There should be surveillance for complications in patients with cirrhosis, including for hepatocellular carcinoma.

Interventions

- Liver enzymes including ALT, AST, alkaline phosphatase and bilirubin should be routinely monitored every 3 months and any abnormalities investigated.
- All patients should have regular objective assessment of liver iron load by ultrasound-guided liver biopsy or liver MRI R2/R2* where available. The interval between assessments should depend on the clinical situation, but in general it should be every 1 – 2 years. Iron should be appropriately chelated to reduce liver iron concentration to below 7mg Fe/g dry weight to avoid liver damage, fibrosis and cirrhosis.
- All patients should start the full hepatitis A and B vaccination course prior to starting a transfusion program. Viral serology including HepBsAg, anti-HepB sAb, and anti-Hep C Ab should be monitored annually and if there is a two-fold rise in liver enzymes.
- Hepatitis B and C should be managed in collaboration with a designated hepatologist and as per Canadian consensus guidelines.^{77,78} Thalassemia-specific complications of hepatitis treatment should be monitored for and appropriate medication adjustments made.
- Patients with end stage liver disease and cirrhosis should be followed by a hepatologist.
- Patients with cirrhosis should be followed for the development of hepatocellular carcinoma with yearly liver ultrasound and alpha-fetoprotein measurements.
- In the presence of elevated liver iron, liver fibrosis, and cirrhosis may be accelerated by alcohol, liver-toxic drugs, and untreated viral hepatitis. Patients should be encouraged to minimize alcohol intake and physicians should limit exposure of patients to hepatotoxic drugs.

C. Complications of Thalassemia

C3. Endocrine Complications

Background

Endocrine complications including short stature (34%), delayed puberty, hypogonadotropic hypogonadism (35 – 55%), hypothyroidism (10%), hypoparathyroidism (4%), and diabetes mellitus (5.6 – 20%) are common in thalassemia major, and are primarily due to iron overload of endocrine glands.^{11,18,79-81}

Principles

- To ensure normal growth, sexual development and fertility.
- To prevent treatment-related endocrine complications.
- To detect and treat endocrine disturbances promptly and effectively.

Guidelines

- Each specialist centre should collaborate with a pediatric or an adult endocrinologist with knowledge of endocrine complications in thalassemia.
- Children should be routinely monitored for growth and development until they have attained adult height and full sexual development. Any abnormalities to suggest an endocrinopathy should be investigated and managed accordingly.
- Adolescents and adults should be routinely monitored for endocrinopathies including diabetes mellitus, hypothyroidism, hypoparathyroidism, hypogonadotropic hypogonadism, and growth hormone deficiency.^{8,9,11,18} Abnormalities should be identified early and treatment initiated in consultation with an endocrinologist. (GRADE B)

Interventions

I. Short Stature

- All children should be assessed for short stature with standing and sitting height measurements every 6 months.^{80,82}
- Endocrine evaluation should be initiated if there is a fall-off on growth curves, decreased height velocity, or delayed bone age.⁸¹
- The diagnosis of growth hormone deficiency, other hormonal or nutritional deficiencies or deferoxamine toxicity should be considered.
- Growth hormone stimulation testing should be done and, if indicated, growth hormone therapy started.⁸²⁻⁸⁴ (GRADE B)

II. Delayed Puberty and Hypogonadism

- Delayed puberty and hypogonadism is the most common endocrine complication, and thus, all children should be assessed yearly from the age of 10 years. If there is pubertal delay characterized by no pubertal changes in girls by age 13 years and in boys by age 14 years, or arrested puberty, a pediatric endocrinologist should be consulted. Hypogonadism in boys is suggested by the absence of testicular enlargement (less than 4 ml), and in girls by the absence of breast development by the age of 16 years.
- All patients with delayed puberty or hypogonadism should receive appropriate investigations including bone age and hormonal assessments, hormonal replacement therapy, and subsequent follow-up by an endocrinologist.⁸⁵⁻⁸⁹
- Adults should be routinely assessed for secondary hypogonadism, impotence, or infertility.

III. Hypothyroidism

- TSH levels should be measured annually beginning at 12 years of age since hypothyroidism often develops after adolescence. Hypothyroidism should be treated with thyroid hormone replacement.

IV. Hypoparathyroidism

- Hypoparathyroidism usually develops after the age of 16 years. All patients over the age of 12 years should have calcium and phosphate levels checked at least every 6 months. If these are abnormal, parathyroid hormone level should be measured. Hypoparathyroidism should be managed as per endocrine standards.^{79,90}

V. Impaired Glucose Tolerance and Diabetes

- Risk factors for developing diabetes in this population include age, iron overload, poor chelation compliance, chronic liver disease, cirrhosis, viral hepatitis, and genetic factors.⁹¹⁻⁹³
- A fasting plasma glucose test should be done regularly starting at puberty.^{91,94,95}
- Impaired glucose tolerance and diabetes should be managed as per Canadian Diabetes Association Guidelines⁹⁶ and in conjunction with a diabetes clinic with emphasis on glycemic control, diet, exercise, and management of complications.
- Improvement of iron load with adequate combination chelation therapy may decrease insulin resistance and decrease glucose intolerance.^{95,97-99} (GRADE B)

C. Complications of Thalassemia

C4. Bone Complications

Background

Bone disorders are common and multifactorial in patients with thalassemia and may be related to inadequate transfusion, iron-overload, over-chelation, and other endocrine factors.^{100,101} These factors contribute to the development of osteopenia and osteoporosis. Bone disorders may present as skeletal deformities, growth retardation, arthropathies, fractures, or pain.

Principles

- To prevent the bone disorders associated with thalassemia.
- To provide effective monitoring and treatment for patients with evidence of bone disease.

Guidelines

- Every specialist centre should have access to a pediatric or an adult endocrinologist and an orthopaedic surgeon with knowledge of managing thalassemia associated bone disease.
- All children should have routine monitoring of height, weight, and growth velocity at each visit and these should be plotted.
- All patients should be closely monitored for bone changes and deformities associated with under-transfusion and chelator related toxicity.¹⁹ (GRADE B)
- All patients should be encouraged to participate in regular weight-bearing, low impact, sport activities.
- Transfusion therapy should be started early in children to prevent the bone changes and deformities associated with bone marrow expansion.^{8,9,11,18} (GRADE B)
- Any bone changes should be managed appropriately with adequate transfusions, appropriate iron chelation, or chelating medication dose reduction depending on the underlying cause.^{9,18-20}
- Adolescent and adult patients should have routine monitoring for osteopenia and osteoporosis, and if detected, should be referred to an appropriate specialist and treated according to treatment guidelines.²¹⁻²⁵ (GRADE B)

Interventions

- Inadequate transfusion leads to bone marrow expansion, which causes skull and skeletal deformities. These increase the risk of fracture, vertebral collapse, cord compression, dental deformities, and pain. These complications are preventable by early initiation of adequate transfusions. (GRADE B)
- Adequate chelation therapy should be maintained in patients on a chronic transfusion program since iron overload is associated with abnormalities of the synovium and articular cartilage.¹⁰¹
- Over-chelation of iron with deferoxamine causes dysplastic changes in the spine and long bones, and growth retardation especially when chelation therapy is started under 3 years of age and at higher doses (> 50 mg/kg/day).^{19,20} High doses should be avoided in young children. (GRADE B)
- All patients on deferoxamine should have regular radiological investigations to rule out chelator-related changes. If detected, appropriate dose reductions should be made.
- Bone mineral density of the hip and spine should be measured using dual energy x-ray absorptiometry (DEXA) every 1 – 2 years in all patients over the age of 10 years. Osteopenia

and osteoporosis occur in approximately 90% of thalassemia major patients and osteopenia can be seen in children under 10 years old.^{21,22} Osteoporosis is associated with increased risk of fractures.

- Osteopenia (z score -1 to -2.5) should be managed by an endocrinologist and with calcium- and vitamin D rich diet, regular exercise, and no smoking.
- Adult patients with osteoporosis (z score below -2.5) should follow all recommendations as per osteopenia and be started on bisphosphonates. Bisphosphonates decrease pain, improve bone mineral density, and decrease bone resorption in thalassemia patients.^{25,102,103} Options for bisphosphonates include alendronate, pamidronate, or zoledronic acid. (GRADE B)
- Hypogonadism contributes to short stature and osteoporosis.²¹ Patients with hypogonadism should be referred to the specialist centre endocrinologist and consideration given for hormone replacement therapy. All other endocrine abnormalities should also be sought for and corrected since they are contributory factors.
- Patients with severe back pain or neurological findings should be evaluated immediately with MRI and promptly seen by an orthopaedic surgeon. Pain should be managed appropriately.

C. Complications of Thalassemia

C5. Fertility and Pregnancy

Background

As thalassemia care improves overall, patients are living longer into adulthood and are able to attain reproductive capacity. Optimal care of such patients includes addressing infertility and endocrinopathies, optimizing prenatal care, as well as assessing cardiac impairment, liver dysfunction, and the risk of viral transmission. Good overall care during and after pregnancy are vital to improved outcomes for both mother and child.^{26,27,104}

Principles

- To improve the opportunity for thalassemia patients to have children, if desired.
- To ensure optimal management during pregnancy.

Guidelines

- All children should be closely monitored for pubertal development and endocrinopathies, and appropriately treated by an endocrinologist to reduce the risk of long-term hypogonadism and infertility.
- Patients should be assessed by a fertility clinic and available treatment options discussed.
- Women considering pregnancy should be assessed for risks to mother and fetus, and advisability of pregnancy. Detailed assessment and management prior to pregnancy, and close monitoring of the health of the mother and fetus during and after pregnancy should be ensured.²⁶⁻²⁸ (GRADE B)

- During pregnancy, women should be managed by a high-risk obstetrician with knowledge of thalassemia-associated risks, and the specialist centre multidisciplinary team including a cardiologist.

Interventions

- All children should be started on a chelation program early in life to reduce iron-associated endocrinopathies especially hypogonadotropic hypogonadism. If identified, endocrinopathies should be appropriately investigated and managed by an endocrinologist.
- When patients reach the age when they may be contemplating pregnancy, a referral to a fertility clinic should be made to discuss options and realistic goals. If the patient is infertile, non-thalassemia causes of infertility should also be sought.
- A couple should be referred to a genetic counselor to discuss the risks of having a child with thalassemia or another hemoglobinopathy. The partner should be tested to determine his/her carrier state for thalassemia and sickle cell disease. The risk of having an affected child and the options for pre-natal diagnosis and subsequent interventions if the fetus is affected should all be discussed with the couple.
- In patients with hypogonadism, ovulation or spermatogenesis may need to be induced and should be done by an experienced fertility centre.

I. Pre-pregnancy Assessment

- A thorough pre-pregnancy assessment, prior to considering conception, should include detailed assessment of iron load, cardiac

status, liver function, viral infection status, and endocrinopathies.¹⁰⁵

- Several medication changes may need to be made including initiation of folic acid supplements, stopping possible teratogens such as deferoxamine, ACE inhibitors, oral hypoglycemics, and bisphosphonates, and initiating calcium and vitamin D supplementation to prevent worsening of osteoporosis.
- Iron load should be minimized by more intensive chelation before a planned pregnancy due to the fact that transfusion requirements (and iron loading) increase during pregnancy, and iron chelators have to be discontinued at least during early pregnancy.

II. During Pregnancy

- The patient should be closely followed by the high-risk obstetrician, cardiologist and hematologist through the specialist centre. Cardiac function should be monitored closely. Transfusion requirements will likely increase. Serial ultrasounds should be done to monitor for fetal anomalies or growth restriction.

III. Mode of Delivery

- There is a high incidence of delivery by Caesarian-section primarily due to cephalopelvic disproportion.¹⁰⁵ Risks of vaginal and Cesarean-section delivery should be discussed with consideration of other medical issues including cardiac dysfunction.

IV. Post-delivery

- The mother should be encouraged to restart chelation with deferoxamine (not deferasirox) since it is safe while breastfeeding. Calcium and vitamin D should be continued, while bisphosphonates should only be restarted

after breastfeeding is stopped. The mother should be advised on the use of contraception or the reinitiation of estrogen replacement therapy after delivery.

C. Complications of Thalassemia

C6. Other Significant Complications: Infection, Dentition, Nutrition

Principles

- To investigate and treat appropriately for infections other than hepatitis in thalassemia patients.
- To ensure good dental hygiene and function.
- To assess and manage nutritional deficiencies.

Guidelines

- The physician should be aware of certain infections that are more common in patients that are on chronic transfusion programs or iron overloaded.
- Dental and orthodontic evaluation should be considered to improve appearance and function in patients with facial deformities and malocclusion.
- Regular nutritional assessments should be done by a registered dietician, with specific attention to iron-containing foods, calcium, vitamin D, and diabetes.

Interventions

I. Infections

i. Parvovirus B19

- Parvovirus B19 infection can cause a transient aplastic crisis characterized by an acute drop in hemoglobin, absence of reticulocytes, and absence of red blood cell precursors in the bone marrow.
- Treatment includes supportive transfusions.
- Thalassemia major patients on a regular transfusion program may require more frequent transfusions until recovery from the infection, while thalassemia intermedia patients may require initiation of a short-term transfusion program.

ii. *Yersinia enterocolitica*

- Thalassemia patients are susceptible to infection with *Y. enterocolitica* due to iron overload and chelator therapy.^{106,107}
- It should be suspected in the presence of fever, abdominal pain, diarrhea and vomiting.
- If there is a high clinical suspicion, iron chelation must be stopped immediately, cultures sent, and antibiotics started. An ultrasound of the abdomen should be performed in patients with abdominal pain to rule out an abscess.
- Iron chelation should be restarted only after symptoms have completely resolved.

II. Dental Complications

- Thalassemia patients who are untransfused, undertransfused, or begin transfusion at a later stage may have malformations of the facial bones due to bone marrow expansion. This can cause deformities, affect growth of the teeth and lead to malocclusion.
- Patients should have regular examinations since orthodontic care can improve appearances and masticatory function.

III. Nutrition

In general, patients with thalassemia have similar nutritional requirements as the general population.

- Iron supplements should be avoided.
- Calcium rich foods or calcium supplements should be encouraged to reduce the risk of osteoporosis. Vitamin D may need to be supplemented.
- Folic acid levels should be checked and replaced if low in all non-transfused patients.
- Vitamin C supplements should only be taken with deferoxamine therapy to increase the chelatable iron pool, since on its own, it can increase iron toxicity.
- Trace minerals (zinc, selenium, copper) should be monitored while on chelation therapy and replaced as necessary.
- Patients should be evaluated routinely by a nutritionist and recommendations made based on diet history and complications of thalassemia. Diabetic patients require specific counseling by a dietician and an endocrinologist.

Table 3: Recommended Monitoring for Complications of β -Thalassemia

System	Investigation	Age to start	Frequency of Monitoring
Iron Load	<ol style="list-style-type: none"> Serum ferritin Liver iron content <ul style="list-style-type: none"> - Liver biopsy - Liver MR Cardiac iron load 	<ul style="list-style-type: none"> • Pre-transfusion initiation • After 10 – 20 transfusions • 10 years 	<ul style="list-style-type: none"> • Every 3 months • Yearly • Every 1 – 2 years
Chelation associated	<ol style="list-style-type: none"> Audiometry Ophthalmological Bivalent ion levels (e.g., zinc, copper) Chelator specific laboratory tests 	<ul style="list-style-type: none"> • When chelation starts 	<ul style="list-style-type: none"> • Yearly • Yearly • Yearly • Every 1 week to 3 months
Liver Function	<ol style="list-style-type: none"> Liver enzymes <ul style="list-style-type: none"> - ALT, AST, ALP, Bilirubin 	<ul style="list-style-type: none"> • Pre-transfusion initiation 	<ul style="list-style-type: none"> • Every 3 months
Cardiac Function	<ol style="list-style-type: none"> Physical examination Echocardiogram, MUGA scan, or cardiac MRI T2* 	<ul style="list-style-type: none"> • At diagnosis • 10 years 	<ul style="list-style-type: none"> • Every 6 months • Yearly
Endocrine Function	<ol style="list-style-type: none"> Short stature <ul style="list-style-type: none"> - Standing and sitting height Hypogonadism <ul style="list-style-type: none"> - Puberty staging Hypothyroidism <ul style="list-style-type: none"> - TSH Hypoparathyroidism <ul style="list-style-type: none"> - Calcium - Phosphate Diabetes <ul style="list-style-type: none"> - Random glucose 	<ul style="list-style-type: none"> • At diagnosis • 10 years • 12 years • 12 years • Pre-transfusion 	<ul style="list-style-type: none"> • Every 6 months • Yearly until puberty complete • Yearly • Yearly • Every 6 month
Bone Complications	<ol style="list-style-type: none"> Osteopenia/ Osteoporosis <ul style="list-style-type: none"> - DEXA scan 	<ul style="list-style-type: none"> • 10 years 	<ul style="list-style-type: none"> • Every 1 – 2 years
Infections	<ol style="list-style-type: none"> Hepatitis B sAg, sAb Hepatitis C serology HIV serology 	<ul style="list-style-type: none"> • Pre-transfusion initiation 	<ul style="list-style-type: none"> • Every 2 – 3 years

D. Thalassemia Intermedia

Background

I. Clinical Presentation

The term thalassemia intermedia (TI) is used to describe a less severe form of thalassemia in which regular transfusions are not required for patient survival. By definition, these patients require fewer than eight transfusions per year. The manifestations of TI are primarily due to ineffective erythropoiesis, anemia, and iron overload. TI includes a heterogeneous group of patients ranging from those who are asymptomatic and never need transfusions to those who may need intermittent transfusion.

The severity of the manifestations depends on the underlying molecular defects, which determine the amount of excess alpha globin chains and the amount of residual gamma globin chains. TI may result from a variety of different genotypes. The excess amount of free α -chains determines the degree of ineffective erythropoiesis and subsequent complications. TI can be due to:

- homozygosity for a mild β mutation
- co-inheritance of β -thalassemia with another thalassemia like variant (e.g., HbE)
- co-inheritance of α -thalassemia mutations in otherwise more severe β -thalassemia
- coinheritance of extra α -genes with heterozygous β -thalassemia
- inheritance of a dominant thalassemia mutation with hyper-unstable β -chains.

The specific genotype may provide some information; however, the diagnosis of TI is a clinical one and the genotype may not necessarily correlate with the phenotype.

Certain manifestations are more common in TI than in thalassemia major (TM).³⁴

Hypersplenism is more common in TI and is associated with subsequent splenectomy complications including thrombocytosis, sepsis, cerebrovascular accidents, thrombosis and pulmonary hypertension (PHTN).^{30,36,108} Cardiac complications in TI are different from TM and include a high incidence of PHTN (61%), right heart failure (5.4%), valvular disorders (48%), pericarditis, and left ventricular dysfunction (less common).³¹ PHTN is more common in TI. Its optimal management is not clear and includes several options including transfusion therapy, antiplatelet agents, hydroxyurea, prostacyclin analogues, and phosphodiesterase-5 inhibitors.²⁹ Other manifestations more common in TI than TM are thromboembolic complications (10% vs. 4%),³⁸ extramedullary erythropoietic masses,¹⁰⁹ gallstones, bone deformities, osteoporosis, leg ulcers³² and diffuse elastic tissue defects causing pseudoxanthoma elasticum (skin lesion, retinal angioid streaks, calcified arterial walls, and cardiac valve and pericardium involvement).³³ TI patients may have iron-overload in the absence of transfusions due to increased gastrointestinal absorption of iron and low hepcidin levels.

II. Treatment

The decision to transfuse in TI is mainly clinical and can be a difficult one. Severe forms of TI may need regular transfusions, usually started after 3 years of age, to maintain normal growth and development until puberty. The indications for initiation of a chronic transfusion program include symptomatic anemia, growth failure, delayed puberty, bone deformities, symptomatic extramedullary hematopoietic pseudo tumors, and chronic ankle ulceration. Milder forms of TI do not require regular transfusions except during acute anemia episodes due to infection (especially parvovirus infection) or acute hemolysis due to G6PD deficiency.¹¹⁰

Iron overload is less severe in TI patients unless they are routinely transfused. When not regularly transfused, the main source of iron accumulation is from increased intestinal iron absorption. Monitoring for iron load need not be as frequent as in TM and chelation may not start until later in life if needed at all.

Hemoglobin F induction with hydroxyurea may increase fetal hemoglobin and thus reduce transfusion requirements, decrease extramedullary erythropoietic masses, decrease leg ulcers and increase the general sense of well being.^{35,111} Patients with specific genotypes such as hemoglobin E/ β -thalassemia, α -deletions, and Xmn1 polymorphism may have better responses to hydroxyurea.¹¹²

Hematopoietic stem cell transplantation (HSCT) is rarely indicated in TI patients.

Principles

- To maintain normal growth and development, and good quality of life for patients with thalassemia intermedia.
- To avoid unnecessary transfusions.
- To monitor routinely and manage complications of thalassemia intermedia appropriately.

Guidelines

- The α - and β -globin genotype should be determined when thalassemia is diagnosed.
- The patient with thalassemia intermedia genotype should be closely followed clinically for signs and symptoms suggestive of the need

for intermittent transfusions or regular chronic transfusion.

- All patients should be routinely monitored and appropriately managed for complications of thalassemia intermedia including iron overload, pulmonary hypertension (especially in splenectomized patients), cardiac dysfunction, extramedullary hematopoiesis, leg ulcers, osteoporosis, thrombophilia, pseudoxanthoma elasticum, and hypersplenism.²⁹⁻³⁶
- All patients and families should receive age-appropriate education specific to thalassemia intermedia.
- Patients should be followed in conjunction with the specialist centre.

Interventions

- Thalassemia intermedia has variable presentations, and thus, input from the specialist centre in all aspects of care is very important.
- Patients should be educated on, and followed closely, for signs and symptoms of anemia that require occasional transfusions.
- The decision to start regular transfusions should be made in collaboration with the specialist centre.
- All red cell units should be phenotypically matched for ABO, C, D, E, and Kell to reduce the risk of alloimmunization. Red cell alloimmunization may be more likely in transfused children with TI than TM since their first transfusion is usually at an older age (after 3 years of age).⁴
- All patients not on a chronic transfusion program should be on folic acid supplements.
- Iron load should be measured regularly with consideration for the severity of anemia, number of transfusions, and organ iron load. Chelation therapy should be initiated

and adjusted accordingly if iron overload is present as previously described. It should be noted that iron overloading can be more than what is expected from transfusions alone as the active bone marrow in TI patients should significantly increase iron absorption through the gastrointestinal tract. Total body iron load may be higher than what the serum ferritin may suggest. If in doubt, objective iron quantitation is indicated.

- In patients with hypersplenism, the decision for splenectomy should consider the indications and risks. At the time of splenectomy, a liver wedge biopsy can be taken to determine iron loading.
- Regular cardiac monitoring for complications of TI is important and should assess for PHTN, right and left ventricular dysfunction and valvular abnormalities. Echocardiography should be done regularly after 10 years of age depending on the amount of transfusions the patient has received. Initiation of transfusions in patients with early cardiac dysfunction should be considered. Management of cardiac complications should be done in consultation with a cardiologist.
- If pulmonary hypertension is identified, treatment with regular transfusions should be considered.^{31,110} Several medications have shown some benefit and may be considered in consultation with a cardiologist/pulmonologist.³⁴
- Growth and puberty should be monitored yearly for children 10 years and older, and an endocrinologist consulted if abnormalities arise. If there is stunted growth or hypogonadism, regular transfusions should be considered during puberty.
- Symptoms due to extramedullary hematopoietic masses should be investigated and acted upon immediately with radiation

if urgent, or hydroxyurea or hypertransfusion if non-urgent.¹¹³⁻¹¹⁵

- Patients with moderate to severe TI should be monitored at the specialist centre at least annually.
- Allogeneic HSCT may be an option for severe patients and appropriate referral should be made. Decision making for HSCT is difficult and should consider the complications of transplant, the improved outcomes of transfused and well-chelated patients, and the difficulty in predicting disease behaviour in TI.

Appendix 1: Levels of Evidence

Level	Type of Evidence (Based on AHCPR 1992)
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of Recommendations

Grade Recommendation (Based on AHCPR 1994)

A (Evidence Levels Ia, Ib)

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

B (Evidence Levels IIa, IIb, III)

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

C (Evidence Level IV)

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

Appendix 2: Glossary

adherence	the degree to which a person is able to take medication exactly as prescribed
agranulocytosis	absence or very low levels of granulocytes (neutrophils)
alkaline phosphatase	a protein found in body tissues, especially in liver, bile ducts, and bone
allele	one of a number of different forms of a gene. Each person inherits two alleles for each gene, one allele from each parent. These alleles may be the same or may be different from one another.
alloantibody	an antibody that develops to an antigen that is foreign to the person
allogeneic	belonging to or obtained from the same species but genetically different
alloimmunization	formation of an alloantibody to foreign antigens on the donor red cells after red blood cell or plasma transfusion; can result in a serious transfusion reaction
alpha-fetoprotein	a protein that is normally only produced in the fetus during development, but may also be produced by certain cancers and be measured in the blood
anemia	low level of hemoglobin
antenatal	literally “before birth”, meaning during pregnancy
antibody	protein made by the body’s immune system usually in response to infection, to fight it off
antigen	a molecule stimulating an immune response
aplastic crisis	when the bone marrow stops producing red blood cells. A common cause is parvovirus B19.
arrhythmia	irregular heart beat
artery	a blood vessel that carries oxygenated blood from the heart to the rest of the body
arthritis	painful inflammation and swelling in joints

arthropathy	general term for a joint disorder
audiology	clinical specialty focusing on hearing, hearing disorders, and hearing loss
auditory	of, or related to, the sense and organs of hearing
autoantibody	an antibody that acts against the cells and tissues of the individual from which it was formed
bidentate	having two teeth-like projections
biliary	of, or relating to bile
bilirubin	a breakdown product of hemoglobin during the destruction of red blood cells: a high level in the blood produces the yellow skin symptomatic of jaundice
biopsy	removal of a small sample of tissue from the living body for microscopic or other examination, in order to aid diagnosis or guide treatment
bisphosphonates	a group of drugs that are used to prevent and treat osteoporosis
bone marrow	fatty, vascular tissue found in most bones which produces red blood cells, platelets and most white cells
caesarian section	delivery of a fetus by surgical incision through the abdominal wall and uterus. Also known as C-section.
cannula	a small hollow plastic tube which is inserted into a blood vessel via a needle and used to give intravenous fluids
cannulation	insertion of cannula
cardiac	of, or pertaining to, the heart
cardiologist	a physician specializing in diseases of the heart
cardiology	clinical specialty of managing heart disorders
cardiotoxic	toxic or poisonous to the heart
carrier	an individual carrying one unexpressed gene for a trait

cartilage	a fibrous connective tissue that lines joints and forms the flexible portions of the outer ear and nose
catalyze	to enhance or accelerate a chemical reaction
cephalopelvic	pertaining to the fetal head size and its relation to pelvic size
chelation	removal of excess iron from the body, using a specific medication called a chelator
chelator	small molecules, which bind to metals, such as iron
Chorionic villous sampling	procedure, usually undertaken at 11 or 12 weeks of pregnancy, to remove a small piece of the placenta in order to test for a condition which may affect the fetus
cirrhosis	a liver disease that can be caused by a range of problems, in which the liver is scarred and the liver cells damaged, leading to reduced liver function
clinical trial	a scientifically controlled study of the safety and effectiveness of a therapeutic agent
complete blood count	a blood test to examine the cell components of blood including red blood cells, white blood cells and platelets
compliance	degree of accuracy or constancy which a patient follows a prescribed regimen
consultant	specialist physician who gives expert advise, generally to the attending health care provider
cord compression	compression or pressure added to the spinal cord, caused by a mass, tumor, abscess, or ruptured intervertebral disc
creatinine	waste product produced by muscles and excreted in the urine; measurements in the blood are used to evaluate kidney function
crossmatch	testing for compatibility of donor and recipient blood prior to transfusion by mixing serum and red blood cells
cytopenia	decrease in the number of blood cells
deferasirox	only oral iron-chelating drug commercially available in Canada

deferiprone	An oral iron chelator unavailable in Canada or US, which has been found very useful in reducing iron load in the heart
deferoxamine	the first available iron chelator which is administered by intravenous or subcutaneous injection
denaturation	a structural change in molecules brought about by an external stressor such as a heat or acid
Diabetes mellitus	a condition in which the body is unable to process carbohydrates and sugars properly, thus the levels of sugar in the body are high
diagnostic imaging	a general term for any sort of X-ray or scan used to aid diagnosis
dietician	specialist in the principles of nutrition
Dual energy x-ray absorptiometry (DEXA or DXA)	a method for measuring bone density and predicting the risk of fracture due to osteoporosis
echocardiogram	a noninvasive ultrasound scan of the heart in which the heart chambers, muscle wall, major blood vessels and heart valves can be seen
ejection fraction	a measure of the fraction of blood pumped or ejected from the heart with each beat
Electrocardiogram (ECG)	a graphical recording of the heart's electrical activity
electrophoresis	a test to identify types of hemoglobin chains in an individual. The chains are sorted by size and electrical charge using differential migration through a gel
endocrine	relating to hormones
endocrinologist	a medical specialist in conditions causing hormone disturbance
endocrinopathy	a condition affecting the hormone producing glands
engraftment	process in which the newly transplanted stem cells begin to function and reproducing in the recipient's body
enzyme	proteins made by living cells that speed up or catalyze a metabolic process

epidemiology	branch of medical science dealing with the cause, transmission and control of disease in populations
erythroid	relating to red blood cells
erythroid marrow hyperplasia	overgrowth of the bone marrow caused by increased red cell production
erythropoiesis	the process of red cell formation
event-free survival (EFS)	time from study entry to disease progression or relapse
ferritin	a soluble transport form of iron, which can be measured in the blood and used as an indication of the total amount of iron in the body
fibrosis	the formation of fibrous tissue in an organ
folic acid	a vitamin of the B group which is required for red cell formation; it is found in green leafy vegetables and nuts
G6PD deficiency	low level of an enzyme called glucose-6-phosphate dehydrogenase in red blood cells due to inheritance of a mutation; patients usually have no problems unless they ingest certain medications or fava beans; these may cause rapid destruction of affected red cells
gallstone	hard solid material developing in the biliary system or gall bladder
gastrointestinal	of, or related to, the stomach or intestines
gene	a physical unit of heredity which contains instructions about how to make a protein or enzyme; genes are inherited from parents in packages called chromosomes.
genetic	relating to one or more genes
genetic counseling	guidance provided by a medical professional to individuals at an increased risk of having an offspring with a genetic disorder, including advice, prenatal tests and available treatments
genotype	a particular type or combination of genetic changes

globin	the protein parts of the hemoglobin molecule
graft-versus-host-disease; acute, chronic	a condition following an hematopoietic stem cell transplant in which the functioning donor immune cells in the transplanted tissue react against and damage tissues of the person receiving the transplant
half-life	the time it takes for the amount of a drug in the patient's body to decrease by half
heart failure	the inability of the heart to pump blood adequately
hematopoiesis	the formation of blood cells in the body, particularly in the bone marrow
hematopoietic stem cell transplant	the transplant of blood stem cells derived (taken from) the bone marrow or blood; usually because of a condition such as thalassemia or leukemia
hematologist	medical specialist managing blood disorders
hematology	the study of the nature, function, and diseases of the blood and of blood-forming organs
hemoglobin	the red, oxygen-carrying pigment contained in the red blood cells
hemoglobinopathy	a general term which covers all the inherited medical conditions which are due to abnormal or under-produced hemoglobin proteins
hemolytic	resulting from abnormal red blood cell breakdown
hepatitis	inflammation of the liver
hepatocellular carcinoma	cancer of the liver
hepatologist	medical specialist in liver disorders
hepatomegaly	liver enlargement
hepatosplenomegaly	liver and spleen enlargement
hemochromatosis	a hereditary disorder of metabolism leading to deposition of iron in the tissues; may lead to bronzing of the skin, arthritis, diabetes, cirrhosis, or heart disease if untreated

heterozygote	an individual who inherits one type of a gene from one parent, and another type from the other; relating to hemoglobin disorders it most usually describes inheritance of a normal gene from one parent together with a thalassemic or sickle gene from the other—the healthy carrier
hexadentate	having six tooth-like projections; ligand that can bind six iron atoms
high performance liquid chromatography (HPLC)	an automated, rapid and accurate way of identifying different proteins in solution, for example, different types of hemoglobin from a blood sample
Human Leukocyte Antigen (HLA) typing	test to determine if a patient has a suitable transplant donor; HLA antigens are detected on the surface leukocytes (white blood cells)
Holter monitoring	recording of the heart's electrical rhythms via electrodes continuously for 24 hours
homozygous	a person who has two copies of the same mutation, one inherited from each parent; for example, beta- thalassemia major or sickle cell anemia
hormone	a product of living cells circulating in the body fluids producing a stimulatory effect on the target cells, e.g., insulin
hormone replacement therapy (HRT)	usually used to describe female sex hormone therapy given to women after the menopause, but can also relate to the replacement of any hormone which is lacking because of underactivity of the endocrine glands
hydrophilic	tending to dissolve in water
hydrops fetalis	excess accumulation of fluid in the tissues or in an internal cavity (peritoneal, pleural, pericardial) of the fetus due to heart failure
hydroxyurea	a medication used for many years for bone marrow over-activity syndromes, but more recently found to be of use in sickle cell anemia and to some extent in thalassemia
hyperplasia	an unusual increase in the cells composing tissue
hypersplenism	overactive spleen, often also enlarged, resulting in lowered blood counts
hypertension	elevated blood pressure

hypoglycemic agent	any of various agents used to decrease the level of glucose in the blood, used in the treatment of diabetes mellitus
hypogonadotropic/hypogonadism	decreased activity of the gonads (ovary and testis) due to underproduction of gonadotropin hormones by a small gland below the brain
hypoparathyroidism	under activity of the parathyroid glands, which control body calcium levels
hypothyroidism	under activity of the thyroid gland, which controls the body's metabolic activity levels
hypoxemia	insufficient oxygen in the blood
infertility	inability to produce offspring; for women inability to conceive, for men, inability to impregnate
infusion	the act of putting a fluid into the body, usually through a vein
intermedia	when relating to thalassemia, describes a condition with intermediate severity in which a person can generally make enough hemoglobin to manage without regular blood transfusions; it may be due to a variety of different types of mutations affecting hemoglobin production or stability.
interstitial	between the cells found in a structure
interventricular septum	the wall separating the left and right ventricles of the heart
intrauterine	inside the uterus or womb
leucodepletion	removal of leukocytes (white blood cells) from whole blood in order to prevent certain transfusion reactions (i.e. fever, chills, alloimmunization)
ligand	a molecule such as an antibody, hormone, or drug that binds to a receptor
lipophilic	having the ability to dissolve in a lipids (fats)
liver enzymes	enzymes usually found within the liver cells; these may be released into the blood when the liver is injured or diseased
magnetic resonance imaging (MRI)	a diagnostic procedure that uses magnetic fields to provide three-dimensional images of body structures

malocclusion	when the teeth do not meet properly when the jaws close
masticatory	for chewing
membrane	outer surface of a cell
molecule	a compound made of two or more atoms held together by chemical bonding
morbidity	illness
mortality	death
MUGA scan	multigated acquisition scan, which uses injection of a radio-isotope to assess heart function, specifically the ability to pump blood
mutation	a permanent change in genetic material usually in a single gene which causes a change in function of the protein or enzyme produced by the gene
myocardium	the middle muscular layer of the heart wall
neurological	of, or relating to, neurology (nerves or brain)
neutropenia	abnormally low number of neutrophils
neutrophils	the white blood cells that fight off bacterial and fungal infections
obstetrician	physician specializing in obstetrics
ophthalmic	relating to the eye
ophthalmology	the clinical specialty of managing eye disease
oral glucose tolerance test	laboratory test that checks how the body controls (metabolizes) blood sugar, used to diagnose diabetes
orthodontic	the branch of dentistry dealing with the prevention and correction of irregular teeth, by means of braces
orthopaedics	the clinical specialty of managing bone and joint problems, particularly by surgery
osteopenia	a mild degree of bone thinning

osteoporosis	a more severe degree of bone thinning which can cause pain and increased risk of fracture
overall survival	percentage of study subjects who have survived for a defined period of time, also called survival rate
ovulation	egg production
parathyroid	the glands that control calcium levels in the blood and bones, by producing parathyroid hormone
parenteral	administration of a substance or drug by a method other than via the intestine, such as intravenously, intramuscularly or subcutaneously
Parvovirus B19	single-stranded DNA virus belonging to the Parvoviridae family of viruses, B19 is the only known pathogenic human parvovirus
pathogenic	capable of causing disease
pediatrician	a physician specializing in pediatrics or the care of children
pediatrics	the clinical specialty of caring for illness in children
pericarditis	inflammation of the fibrous sac which surrounds the heart
peri-operative	around the time of an operation
peripheral blood film	a film of blood on a glass slide which can be examined using a microscope
phenotype	describes the structure or appearances resulting from different gene makeup, or genotype
phlebotomy	blood removal from the body
pneumonitis	inflammation of the lung(s)
polymorphism	(literally “many forms”) usually describing the possibility of different forms which can occur at a single gene site
portal fibrosis	referring to scarring in the liver, specifically, the portal tracts

precursor	a substance, cell, or cellular component from which another substance, cell, or cellular component is formed especially by natural processes
prenatal diagnosis	diagnosis on a baby before birth
prophylaxis	treatment given to try to prevent a problem, rather than waiting until it develops and then treating it
pseudoxanthoma elasticum	chronic degenerative disease affecting elastic tissues, defined by small yellowish papules and plaques on regions of abnormally loose skin
psychologist	a specialist in one or more branches of psychology, or the study of the mind and behaviour
puberty	the stage of adolescence when an individual becomes physiologically capable of sexual reproduction
pulmonary	of, or pertaining to, the lungs
radiation	transmission of energy in the form of electromagnetic waves or particles
red blood cells	cells in the body containing hemoglobin that deliver oxygen and remove carbon dioxide from the body
rejection	the failure of a recipient's body to accept a transplanted tissue or organ as the result of immunological incompatibility; immunological resistance to foreign tissue
resorption	process of losing substance; when bone is remodeled it undergoes new formation and is resorbed through cells called osteoclasts
reticulocyte	an immature red blood cell
retina	light-sensitive surface at the back of the eye, which detects light and sends messages to the brain, where they are interpreted into vision
risk factor	an element increasing risk
sensorineural	usually used to describe a form of deafness due to damage to the auditory or hearing nerves

sepsis	severe infection, usually bacterial of the blood
skeletal deformities	abnormalities of the skeleton: in thalassemia these abnormalities are caused by improper chelation or insufficient transfusion, resulting in increased red cell production by the bone marrow
spermatogenesis	process in which spermatagonia develop into mature spermatozoa (sperm cell)
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
Superconducting QUantum Interference Device (SQUID)	test used to assess hepatic iron storage; results are compared to liver biopsy and ferritin levels to evaluate consistency of the three measurements of overload in populations
stem cells	the earliest, most primitive cells in the body which can mature into almost any of the tissues
subcutaneous	under the skin
synovium	lining of the joints
teratogen	a drug or substance that causes malformation of an embryo or fetus, resulting in birth defects
thalassemia	any of a group of inherited forms of anemia occurring primarily in people of Mediterranean descent, caused by faulty synthesis of part of the hemoglobin molecule
thrombocytosis	state of increased number of platelets in the blood
thrombophilia	increased tendency of the blood to clot
thrombosis	formation of a blood clot in the blood vessels
thyroid	the gland that produces thyroxin hormone, which controls the body's activity levels
tinnitus	a ringing in the ears due to auditory nerve damage

trait	a characteristic determined by genetics
tridentate	having three tooth-like projections; ligand that can bind three iron atoms
transfusion	the transfer of whole blood or blood products from one person to the other
ultrasound	a type of scan using high frequency sound waves used to visualize internal organs
vaccination	injection to provoke an immune response to an infectious agent, and therefore protect against it
venous	of, or pertaining to a vein
ventricles	the main pumping chambers of the heart
vertebra	a bone in the spinal column
<i>Yersinia enterocolitica</i>	bacterial organism in the bowel and/or blood resulting in severe pain, fever and sepsis; people who have high iron levels and are on chelation therapy are especially susceptible

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