CONSENSUS STATEMENT OF

Clinical Care of Patients with Thalassemia in Canada

The consensus Statement on the Care of Patients with Thalassemia in Canada was reviewed and is endorsed by the Canadian Hemoglobinopathy Association (CanHaem)

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PREFACE

Enclosed is the second edition of the Consensus Statement on the care of patients with Thalassemia in Canada, which is a revision of the guidelines for the clinical care of patients with Thalassemia in Canada published in 2009. This edition is developed by physicians and nurses who specialize in the care of patients with Thalassemia in Canada. It is not a comprehensive review of Thalassemia but rather a consensus process written by a working group who has dedicated their careers to the care of patients with Thalassemia in Canada.

My sincere thanks go to each member of the writing group who had prepared and reviewed each chapter. Although this publication does not provide answers to many questions in the Thalassemia field but focuses on the basic management of transfusion dependent and non transfusion dependent Thalassemia.

The autohrs and co-authors hope that this consensus statement will be of help to medical students, house staff, general practionaers, nurses, psychologist, social workers, specialists and sub-specialists as well as patients and their families involved with Thalassemia. We hope that this publication will gauge excellence in the field and will be the benchmark for us to evolve the development of Thalassemia care and research.

Hatoon Ezzat and the writing group
Editor, authors and co-authors
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About this publication

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FOREWORD

I am delighted, on behalf of the Canadian Hemoglobinopathy Association, to present the Consensus Statement on The Care of Patietns with Thalassemia in Canada, which is the revised edition on guideline for the clinical care of patients with Thalassemia in Canada since the first edition in 2009. Canadians affected by thalassemia syndromes have seen a significant improvement in the care available to them. This includes Health Canada approval of additional oral chelators, improved MRI access for iron assessment, and the establishment of new and growing centres of care in all our major population centres. These are staffed by knowledgeable and dedicated healthcare teams.

The future is both now, and bright in thalassemia. The coming decade will likely see the realisation of research to bring successful stem cell transplant and gene therapy more widely into the clinic. It is imperative that we ensure our patients are healthy and well enough to be eligible for these curative treatments. In parallel, emerging novel therapeutics will offer alternative treatments and force us to continue to shift the paradigm of care towards ever better outcomes. CanHaem has, and will continue to be at the forefront of advocacy to ensure high quality care for affected individuals wherever they live. These guidelines outline the expectations that patients and families should expect, and the responsibility of the healthcare system and legislatures to deliver.

Revising these guidelines has been a monumental undertaking and herculean task. We are indebted to Dr. Hatoon Ezzat who has tirelessly worked as editor to bring to fruition this document. My sincere thanks and gratitude go to her and the working group, without whom we would not be able to celebrate the achievements of the last decade and outline the roadmap for the next. I encourage patients and families, legislators, healthcare specialists and family medicine teams that care for thalassemia patients to all read these guidelines. Together, we can ensure thalassemia remains a chronic disease that does not define our patients but one that they can lead productive, fulfilled and happy lives with.

Dr. Richard Ward, MSc, MRCP, FRCPath
Chair, Canadian Hemoglobinopathy Association

September 2017

INTRODUCTION

Overview of Thalassemia

INTRODUCTION & OVERVIEW OF THALASSEMIA

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. More recent migration movements to Canada have challenged health professionals throughout the country in providing equitable access to quality services for the prevention and treatment of hemoglobin disorders in general and thalassemia in particular. 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 centers staffed by professionals experienced in the treatment of the disease and its complications.

The following Consensus Statement on The Care of Patients with Thalassemia in Canada is a revision of the guidelines for the Clinical Care of patients with Thalassemia in Canada written in 2009. This revision is meant primarily for healthcare professionals involved in the care of affected patients and is to provide members of the thalassemia treating the team with relevant information, which should improve health care delivery and patient outcomes. This statement is developed by a Canadian team and intended primarily for application in the Canadian context. Every patient with Thalassemia regardless of location in Canada should have access to optimal management guidance and monitoring. The statement is not intended to offer the full and comprehensive review of thalassemia management, however; it was intended to serve as guidance on delivering services and the way they need to be structured and delivered in Canada. The document will describe the key members and the goal and function of the comprehensive care team in a Thalassemia program. It will provide principles, recommendations, and interventions with a summary of Thalassemia management and its complications.

α-Thalassemia:

α -thalassemia is caused by the reduced or absent production of α -globin chains. Each individual has typically four α-globin genes.

- Hb Bart's hydrops fetalis: 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 with alpha thalassemia major.
- Hb H disease is due to mutations (deletional or non-deletional) 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 minor is due to deletions or mutations of two α -globin genes resulting in mild microcytic anemia. Finally, silent carriers have one α-globin gene deletion or mutation and are clinically asymptomatic.

β-Thalassemia:

β-thalassemia is a genetic disease of hemoglobin production. It is caused by a decreased or absent β-globin chain production, which results in a relative excess of free α-globin chains, and in premature destruction of red blood cells. Each individual has typically two β-globin genes. This disease is common in people from the Mediterranean, Middle East, and South East Asia. It is inherited in an autosomal recessive pattern.

- β-thalassemia major (BTM) is a term that 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. 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.

- β-thalassemia intermedia (BTI) or Non-transfusion Dependent Thalassemia (NTDT) refer 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., δβ). These patients may need occasional transfusional support. Circumstances may change through life requiring long term transfusion support. β-thalassemia trait/carrier refers to a clinically mild phenotype with only one mutated gene resulting in mildly low hemoglobin levels and clinically asymptomatic individuals. NTDT is used now to describe patients with that thalassemia that requires occasional blood transfusions.

PART I

Components of Comprehensive Thalassemia Care

1. Centres of Excellence: Providing a Network for Patient Care

Principles

- To provide thalassemia patients with comprehensive care delivered by a multidisciplinary network of specialized centres and satellite clinics.
- To ensure centres provide excellent routine care adhering to standards of clinical practice. This includes prevention and appropriate management of complications, in order to decrease morbidity and mortality, and improve quality of life for thalassemia patients.
- To ensure all thalassemia patients have access to the same quality of care, regardless of geographic location.
- To ensure patients receive their routine thalassemia care in a convenient, accessible manner with minimal disturbance to their everyday activities.
- To transition the care of thalassemia patients from pediatric clinics to adult clinics in a timely manner while providing high quality of care and support for patients and their families.

Recommendation

- Each program should consist of a collaborative regional network of one or more specialized thalassemia centres and affiliated satellite clinics. These facilities may also provide services for patients with other hemoglobinopathies and transfusion-dependent anemias if patient numbers do not justify the use of separate programs.
- Each program should have a formalized system for specialized thalassemia services that is appropriately configured to both the geographical location and the size of the patient population.
- Patients living within reasonable distance of a specialist centre should have access to this centre for both routine thalassemia-related care and specialized services.
- Patients living in remote areas should have access to a satellite centre for routine thalassemia care. They should access the affiliated specialist centre for services not available locally. This includes regular annual or semi-annual expert clinical review by a hematologist with expertise in treating thalassemia.
- Each program should have effective communication, documentation and accountability between satellite and specialized centres.
- Both the specialized centre and the affiliated satellite clinics should have regular opportunities for self-evaluation and staff development.
- Each program should have a transition plan from pediatric clinics to adult clinics. This includes transition clinics, education, activities planned in advance of the actual transition time.

Background

In order to provide comprehensive, high quality care to thalassemia patients, they must have easy access to both a trained hematologist and to subspecialists that can assist in treating thalassemia-related complications. A network of centres with specially trained staff ensures all patients have access to appropriate care, including those living outside major urban centres. This network consists of both specialized thalassemia centres in major urban areas, and affiliated satellite clinics in outlying areas.

The specialized centre is a facility with a multidisciplinary team of staff that are experienced and focused on the diagnosis, treatment and care of thalassemia. The team is lead by an adult or pediatric hematologist with a special interest or training in thalassemia, and dedicated nursing and subspecialty staff is available to monitor the patients' ongoing care

and complications. A satellite clinic is led by a physician with knowledge of thalassemia, and operates in conjunction with local outreach and hospital services. In this network model, the satellite clinic serves as the primary access point for the patient's routine thalassemia care, while the specialist centre manages the more complex issues that thalassemia patients experience. While the services provided by satellite clinics may vary, it is expected that each is able to adhere to the standards below when providing thalassemia care. Conversely, specialized centres are expected to provide routine thalassemia care to patients for whom this facility is the most easily accessible. By having a network of centres dedicated to providing high quality thalassemia care; patients are assured comprehensive services no matter their residential location.

Interventions

Role of the Specialized Centre

- Provide consultation at key thalassemia-related milestones including diagnosis, initiation of regular transfusions, initiation of chelation therapy, times of major complications, and transfer to an adult clinic. These consultations should be provided in addition to regular annual or semi-annual reviews.
- Provide specialist opinion on the management of complex issues including but not limited to: transfusion management; chelation therapy; phlebotomy management; compliance problems; peri-operative management; management of cardiac, liver, endocrine, and bone complications; fertility issues and genetic counseling; bone marrow transplantation and clinical trials if available; and complex psychosocial issues.
- Provide consultation, education, and training for staff at both the specialized centre and its affiliated satellite clinics.
- Participate in quality improvement including monitoring the program's adherence to standards of care, performance, and care outcomes.
- Be involved in clinical research studies and continuing education to improve overall patient care.
- Advocate for improved care and service delivery at the local, provincial and national levels.
- Provide transition care from pediatric to adult clinics, in a timely manner, planned in advance of transition time.

Role of the Satellite Clinics

- Provide regular transfusions, prescriptions for chelation therapy, and other necessary therapies that constitute routine thalassemia care.
- Monitor growth, development, and general health.
- Monitor psychosocial well-being and provide psychological assessment and treatment when necessary. This may require referral to the specialized centre.
- Organize the routine assessments and monitor tests when locally available. Referrals to the specialized centre should be made for investigations not available in locally.
- Be a local resource of information and support for the family.
- Provide treatment to the patient and family in a way that minimizes disturbance to normal, everyday activities.
- Communicate regularly with the specialized centre, and make referrals for consultation as needed.

Staffing

- The specialized centre should be led by a pediatric or an adult hematologist with experience in thalassemia care, and the satellite clinic by one or more clinicians with knowledge of or interest in thalassemia.
- Each site should have a designated primary nurse to provide support and guidance on routine care and assist in accessing local services. This nurse should be the key contact for the patient and family.
- 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 the medical, nursing, and psychosocial needs of the patients and family.
- Staff should be well-trained in the different aspects of thalassemia, and maintain their knowledge through

various means of continuing education.
- Staff providing routine thalassemia care should 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 specialized centre and satellite clinic should be present, as outlined in Table 1.

Facilities

- Designated facilities with adequate space should be provided for staff-patient consultation and the provision of routine thalassemia care.
- Equipment used in these facilities should be maintained in accordance with each centre's policies.
- Several specialties should be available for consultation at the specialized centre, and if possible, at the satellite clinic. These specialties include but are not limited to audiology, cardiology, endocrinology, genetic counseling, interventional radiology, nuclear medicine, obstetric and fertility medicine and ophthalmology. Multiple consultants from each should be available to assess and provide care for the patient.
- Both specialized centres and satellite clinics should have access to a transfusion medicine laboratory for the provision of correctly collected and matched blood products.
- Facilities at specialized centres should provide special investigations such as MRIs, CT scans, and bone density testing.
- Effort should be made to provide transfusions and other routine care at times that are convenient to patients and families.

Quality Assurance

- Each formalized regional network should have systems in place for regular self-assessment of clinical practice and services.
- Each centre, either specialized 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 service available to patients and families.

Team Members	Services	Sattelite Clinic	Specialized Centre
Physicians	• Consultant pediatric or adult hematologist (depending on age of patients) with experience or training in thalassemia		●
	• Pediatrician, internist, hematologist or general practitioner with knowledge of thalassemia care	●	●
	• On-call physicians for after-hours issues	●	●
Nursing	• Thalassemia nurse specialist to provide training, monitoring, co-coordinating and auditing of patients and program		●
	• Primary nurse contact for patient and family (such same as a nurse specialist)	●	●
	• Registered nurses in outpatient day care unit area who can perform intravenous (I.V.) cannulation and supervise transfusions	●	●
	• Nursing services for community outreach if necessary: home visits, central line care, teaching pump use, etc.		●
Access to other multidisciplinary team members	• Clinical psychologist		●
	• Social Worker	●	●
	• Dietician	●	●
Access to specialist consultants	• Designated endocrinologist		●
	• Designated cardiologist		●
	• Designated hepatologist		●
	• Designated ophthalmologist		●
	• Designated audiologist		●
	• Genetic counselling		●
	• Designated obstetrician and fertility program	●	●
	• Bone marrow transplant service		●
Other support services	• Appropriate laboratory support (transfusion, diagnostics) and diagnostic imaging	●	●
	• Access to equipment for specialized investigations such as MRIs and bone density testing		●
	• Access to translation services	●	●
	• Administrative support sufficient to ensure proper record maintenance and communication between patient and family with clinic, centre, family doctor and all services involved	●	●

Table 1: Staffing Recommendations for Satellite Clinics and Specialized Centres

2. Transition from the Pediatric to Adult Care Setting

Principles

- To ensure transition and continuity of care for adolscent and young adults (AYA) and their families as they move from pediatric to adult care settings.
- To provide psychosocial support to AYA and their families as they face new and different challenges of adulthood.
- To ensure ongoing and optimal multi-disciplinary long-term care throughout adulthood.

Recommendation

- The transition from the pediatric to adult care setting is not a one-time event, but a process implemented over time to ensure adequate preparation of the patient, family, and care providers involved.
- Pediatric care providers should begin planning for transition when patients reach early adolescence a few years in advance of the transfer of care. The process should actively include parents/caregivers well as the patient.
- Transition planning should focus on educating the patients about the biological, medical, and psychosocial aspects of thalassemia, and equipping AYA patients with skills to manage their care responsibly and independently.
- During transition, pediatric and adult centres should collaborate to increase patient familiarity with members of the adult team and the adult system.
- After transition, AYA patients should be followed routinely to ensure they receive optimal care and that complications are identified and managed promptly.

Background

Thalassemia is a condition that requires continuous medical monitoring and treatment throughout the patient's lifetime. The risks, complications and treatment of thalassemia in infancy and childhood can differ than those in adults, therefore it is recommended that young adult patients transition to an adult care team that specializes in thalassemia care. This transition from the pediatric to adult care is a stressful time for AYA patients and their families and often occurs before the patient is emotionally and psychologically ready. During transition period patients are vulnerable both to emotional stress and lack of adherence.

Having a standardized process in place that begins in early adolescence can help to ensure the AYA patient and family are better equipped for transition. As the needs of each patient can be very different, this process should be individualized for more effective planning. The pediatric team initializes the transition process and the adult team should also be actively involved; collaboration and communication between the two teams is imperative. The ultimate goal of transitioning is to promote independence and self-efficacy of the youth, while simultaneously providing a continuous transfer of ongoing care from one team to the next.

Interventions

Preparing for Transition

- The transition from pediatric to adult care setting should be planned well in advance of the actual event. Preparation and discussion with the patient should begin in early adolescence.
- The transition process should actively include all members of the multidisciplinary pediatric team, the patient and the parents/primary caregivers.

- During transitioning, psychosocial support should be provided in both the pediatric and adult settings by means of a social worker, psychologist, nurse, and physician. Patients should to be assessed for transition readiness by several tools available at the pediatric centre.
- If the pediatric site has standardized transition recommendations/policies in place, these should be used to guide the transition process. If available, involve the institution's transition team.

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Implementing the Transition Process

- Transitioning should focus on promoting patients' independence and self-management of their thalassemia. AYA patients should be trained to take charge of their own care and problem-solve health-related issues, including risks and complications, as independently as possible.
- Each patient is unique, and the transitioning process must be flexible to accommodate different developmental stages, readiness for responsibilities, and physical and mental disabilities. Expectations should be adjusted if necessary should challenges arise.
- Needs should be identified and appropriate supports established for patients who may not be able to achieve complete independence or self-management as a result of decreased mental or physical capacity.
- Care should be extended to AYA patients to asses in the ability to navigate the heakthcare system and disability services at colleges and universities.

Transfer of Care

- To ease the transition and reduce anxiety, efforts should be made to organize the transfer when the patient is well. Patients should not be transferred during an acute illness or period of major stress.
- If possible, the pediatric and adult thalassemia teams should schedule a joint clinic in which patients and their families can meet both teams together. This will allow the AYA patient and family to 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. Subsequent overlapping visits with both pediatric and adult services should be considered if possible.
- Prior to the transfer of care, a member of the pediatric team should accompany the AYA patient and family to the new adult clinic so they may become familiar with the new site. At least one member of the adult team should assist in this process.
- The adult team should schedule their first appointment with the AYA patient prior to the transfer of care to avoid delays in care delivery. The medical care of the patient remains the responsibility of the pediatric team until the first appointment so as to ensure the patient has continuous medical coverage.
- Handover from the pediatric team should include: a written comprehensive summary covering the patient's medical history, current treatment, psychosocial concerns and any other relevant information; patient contact information; and all relevant test and imaging results.

3. Screening and Making the Diagnosis

Principles

- To promptly establish the correct diagnosis for a neonate or infant with a thalassemia syndrome (transfusion dependent or non-transfusion dependent thalassemia).
- To correctly diagnosis patients with clinical suspicion of thalassemia syndrome.
- To identify prospective parents who are thalassemia heterozygotes and are at risk for having a child with transfusion dependent thalassemia.

Recommendation

- Prospective parents from high risk areas should be screened before conception.
- Pre-natal diagnois should be offered to prospective parents from high risk areas who did not receive pre-conception testing.
- Universal newborn screening should include testing for thalassemia syndromes.
- Patients with a clinical thalassemia syndrome should be offered testing.

Background

Thalassemia encompasses a wide spectrum of clinical diseases, from asymptomatic carrier to transfusion-dependent thalassemia. Some forms of thalassemias can be detected at birth through sickle cell disease (SCD) newborn screening, where available.

In Canada, high performance liquid chromatography (HPLC and/or and hemoglobin electrophoresis) are the methods most often used by SCD newborn screening program. Neonatal screening for SCD may identify serious thalassemias syndromes such as beta thalassemia major, hemoglobin H disease and Eβ thalassemias. When detected, these infants are referred to specialist centre where diagnosis will be confirmed and delivery of medical care will be ensured. Carriers of the sickle gene and other hemoglobinopathies can also be identified through newborn screening. These patients are usually clinically asymptomatic, but the information may be useful for purposes of genetic counseling.

Screening and confirmatory tests for thalassemia syndromes should be done for patients with a clinical suspicion of thalassemia; or the parents of a suspected child, or prospective/expectant parents where there may be a risk of having a child with a transfusion dependent thalassemia. Common scenarios include preconception screening, prenatal testing in pregnant mothers, newborn screening and clinical situations in which thalassemia syndromes need to be considered.

Further, preconception testing allows prospective parents to make informed reproductive decisions. The most common cause of hemoglobinopathy-related non-immune hydrops fetalis (NIHF) is alpha-thalassemia. It is most common in Southeast Asian populations accounting for 28-55% of NIHF.[3–6] Incidence is lower in other populations (approximately 10%).3,4 Case reports exist of infants with Hemoglobin Bart's surviving to delivery and beyond with use of aggressive intrauterine transfusion and lifelong chronic transfusion similar to individuals with beta-thalassemia major.[8–15]

Several provinces and territories (Ontario, Quebec, British Columbia, PEI, Nova Scotia, New Brunswick, Yukon, Nunavut) have newborn screening available which can detect significant thalassemia syndromes (beta-thalassemia major, Hemoglobin H, Hemoglobin E/beta-thalassemia) in addition to other hemoglobinopathies.

Not all provinces in Canada offer newborn screening for thalassemia. Additionally, Canada welcomes large numbers of immigrants from all over the world every year. These new Canadians may not have had the same access to medical care prior to coming to Canada. Offering testing to all patients with a clinical suspicion of a thalassemia syndrome will ensure appropriate care for the patient and their affected family members.

Pre-conception testing of prospective parents

- Screen parents with ethnic background from high risk areas (Table 2) with: complete blood count with red blood cell indices, serum ferritin and hemoglobinopathy investigation e.g. electrophoresis, high-performance liquid chromatography (HPLC) or Capillary Zone Electrophresis (CZE)[1,2]
- If both parents are found to be heterozygotes of a thalassemia mutation, hemoglobin variant, or combination of the two, referral for genetic counselling is recommended. Ideally, this should be done prior to conception or as early as possible in pregnancy. Additional molecular DNA analysis may be required to clarify the carrier status of the parents and thus the risk to the fetus. Further consultation with specialists in Hematology or Genetics is recommended.[2]

Prenatal Diagnosis

The Society of Obstetricians and Gynecologists of Canada published guidelines for pre-natal screening of thalassemia syndromes in 2008. Their recommendations are summarized below.[2]

1. Prenatal diagnosis should be offered to the pregnant woman/couple at risk for having a fetus affected with a clinically significant thalassemia. Prenatal diagnosis should be performed with the patient's informed consent.

2. Prenatal diagnosis by DNA analysis can be performed using cells obtained by chorionic villus sampling or amniocentesis. Testing of fetal DNA after isolation from maternal blood is a new technique currently under development and is not yet widely available as routing diagnostic testing.

3. For those who decline invasive testing or present after 20 weeks gestational age, the SOGC-CCMG recommend the following:

- Testing of the child should be done as soon as possible to allow for early diagnosis and referral to a pediatric hematology centre if indicated
- For those at risk of Hemoglobin Bart's hydrops fetalis, serial detailed fetal ultrasound for assessment of the fetal C-T ratio (normal <0.5) should be done at a centre with experience conducting these assessments for early identification of an affected fetus.

4. If an abnormality is detected, referral to a tertiary care centre is recommended for further assessment and counselling. Confirmatory studies by DNA analysis of amniocytes should be done if a termination of pregnancy is being considered. Any fetus found to have hydrops fetalis on prenatal ultrasound in the second or third trimester, or any infant born with hydrops fetalis needs to have alpha-thalassemia/Hemoglobin Bart's considered as a possible diagnosis.[7]

- This finding during pregnancy in women with an ethnic background that has an increased risk of alpha-thalassemia should prompt immediate investigation of the pregnant woman and her partner to determine if alpha-thalassemia carrier states are present.[7]
- These investigations should also be done in parents of any infant/stillbirth found to have NIHF to allow for further counselling regarding risks alpha-thalassemia NIHF in future pregnancies.[7]

Newborn Screening

- Newborn screening, by HPLC, is recommended. The finding of a Hemoglobin F only or a Hemoglobin A2 less than 1.5% will identify the majority of babies with beta-thalassemia major. The finding of greater than 25% Hemoglobin Bart's is suggestive of Hemoglobin H.[1,16]. If using HPLC only, this is limited as beta thalassemia cannot be distinguished from more benign conditions (eg. Hemoglobin E/beta thalassemia, Hemoglobin EE - both show FE pattern on HPLC) or detect unusual hemoglobin variants.[17]

- A positive screen result requires confirmatory testing as early as possible to ensure proper clinical follow up of affected infants.
- Recommended confirmatory testing is molecular analysis of globin genes.
- Referral to a pediatric hematology centre and/or genetics is recommended to assist with confirmatory testing and interpretation of results.
- Each provincial newborn screening program has its own policy regarding the notification of asymptomatic carriers.
- However, it is worth remembering that some NTDT are not captured by newborn screening and these children may present later in life when a microcytic anemia is diagnosed.

Clinical Suspicion

The following clinical scenarios should prompt clinicians to consider investigations for thalassemia syndromes:

1. Pallor, hepatosplenomegaly, poor growth/anorexia with a microcytic, hypochromic anemia with normal ferritin and iron studies

- Directly from birth in alpha thalassemia,
- Age 3 to 6 months in beta thalassemia,

These indicate the possibility a transfusion dependent thalassemia. Additional confirmatory testing should be performed immediately to allow for close clinical monitoring and therapeutic intervention. Testing should include haematological and genotype analysis. These tests should be collected before the child receives a blood transfusion.

2. Pallor, hepatosplenomegaly, +/- jaundice, +/- over expansion of skull and facial bones with a hypochromic, microcytic anemia and normal ferritin and iron studies in an older infant or child raise suspicion for a non-transfusion dependent thalassemia, such as beta thalassemia intermedia. Additional confirmatory testing should be performed immediately to allow for close clinical monitoring and therapeutic intervention. Testing should include haematological and genotype analysis. These tests should be collected before the child receives a blood transfusion. Refer to table 3.[1,18]

3. In any individual with a hypochromic, microcytic anemia, splenomegaly and an elevated reticulocyte count, a non-transfusion dependent thalassemia such as Hemoglobin H Disease, should be suspected. Individuals may have symptomatic anemia triggered by illness or pregnancy. Some individuals may present with unexplained hemolytic and microcytic anemia (jaundice, dark urine, +/- gallstones). In others, it may be an incidental finding.[1,18–20]

4.Unexplained microcytosis without anemia, or hypochromic, microcytic anemia in the absence of iron deficiency warrants further investigation for the presence of presence of a carrier (heterozygous) state for alpha or beta thalassemia.[18]

Regions High Risk for Thalassemia
North Africa
Mediterranean
Middle East
India
Southeast Asia
China

Table 2: Regions of the World at High Risk for Thalassemia Syndromes (Adapted from Reference 2)

Stages	Recommended Testing
Initial	Complete blood count with red blood cell indices
	Reticulocyte count
	Serum Ferritin
	Hemoglobinopathy Investigations (Hemoglobin
	Electrophoresis and HPLC)
Confirmatory	Genotype analysis of globin gene mutations

Table 3: Recommended Testing for Investigation of Thalassemia Syndromes

4. Psychological Aspects of Thalassemia Care

Principles

- To help patients and families manage the mental, social, and physical challenges of living with thalassemia during all stages of growth and development and throughout life span.
- To ensure health care providers consider patients' psychosocial functioning when providing care, especially when making treatment decisions.
- To foster healthy coping mechanisms, emotional well-being and effective self-management in patients.

Recommendation

- The multidisciplinary team at the specialist centre should include a social worker, psychologist and an access to psychiatrist referral with knowledge of the challenges faced by thalassemia patients during various stages of life.
- The psychosocial needs of thalassemia patients should be prioritized in ongoing planning for treatment.
- Support should also address age-specific challenges, transition periods, cultural influences and social and economic factors.

Background

Thalassemia is a life long condition requiring ongoing medical treatment and management of complications. This continuous medical management can place significant burdens on both the patient and family in all facets of life. Developmental stages and concerns, behavioural challenges, psychological functioning and social issues all play a role in the patient's treatment adherence, health status, and overall quality of life. In Canada, an increasing percentage of thalassemia patients are from families of recent immigrants, which poses the additional social, economic and cultural challenges. Greater support may be needed under these circumstances to ensure psychosocial well-being. Also, family dynamics must be assessed, especially in the pediatric setting, and the psychological needs of parents and siblings should also be considered during ongoing treatment planning and provision of patient care.

Interventions

Ensuring Adequate Services

- The psychologist and social worker should function as integrated members of the inter-disciplinary team and meet regularly with other professionals to discuss patients in an inter-disciplinary forum.
- Together with the health care team, the psychologist and social worker should regularly review patients, address issues and provide support. This is especially important during critical milestones such as initial diagnosis, commencement of treatment, puberty, transition to adult care, and major life events such as education, employment, marriage, pregnancy, and parenthood.
- Reviews should include all aspects of psychosocial development such as assessing: 1) patient relationships with family, peers, and significant others; 2) functioning 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.
- It is imperative there be good communication between the patient, family, and medical team throughout treatment. Communication should be in both written and verbal forms, as appropriate.

Delivery of Psychosocial Care

- All psychological and social support should be provided in a culturally sensitive manner.
- The health care team should discuss the practical and psychological challenges of transfusions and chelation with patients and families on a regular basis. These discussions should include the consequences of non-compliance with treatment.
- Psychological support should occur through different stages of patient's life. Support should be provided to patient and their caregivers at time of diagnosis, start of blood transfusion, initiation of chelation, school and education, through out development stages including puberty, transition time and major life events as an adult not restricted to employment, marriage and pregnancy.
- 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 in all patients. This should start early in the pediatric population to promote a smooth transition to adult services.
- 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 as appropriate.
- Resources and support should be provided to help patients develop positive coping skills toward their illness and to develop self-management skills, including healthy lifestyle behaviours. The medical team should provide additional support during times of complications, hardship, and major stressors.
- If serious psychological difficulty or psychiatric illness is suspected, patients should be referred to psychiatrists.

5. Quality of Life in Thalassemia

Principles

- Since mortality in thalassemia is fortunately a rare event, health care providers should focus on minimising morbidity and maximising quality of life (QOL). As clearly demonstrated in the pediatric data, better overall health care has a large impact.
- Children treated in developed countries have self-reporting QOL scores that approach that of the healthy population. Safe, regular blood transfusions and access to iron chelation therapy improve patients' QOL.
- State of the art thalassemia care has also been shown to improve fertility.[21] The new oral iron chelation agents have been shown in a randomized control trial to improve SF-36v2 scores in thalassemia patients.22 Finally, bone marrow transplant, the only available cure for the disease, significantly improves PedsQL scores pre-transplant from 63 out of 100 to 94 eighteen months post-transplant.[23]

Recommendation

- Patients with thalassemia should have QOL assessment performed regularly by health care providers.
- QOL impact should be factored into management decisions for patients with thalassemia.

Background

With modern treatment, the life expectancy of patients with thalassemia has improved dramatically.[24] This places a heightened emphasis on evaluating morbidity and quality of life (QOL). The impact of thalassemia on patient's QOL is two-fold. The disease itself can affect patients' primarily thorough decreased energy and disease complications, and the transfusion and iron chelation treatment creates a burden on the patient and family. The World Health Organisation has been defined QOL as "an individuals' perceptions of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns".[25] A systematic review done in 2006 found only 4 studies that measured QOL in patients with thalassemia.[26] Since that time there have been fortunately many more studies published involving both children and adults, which consistently report that patients with thalassemia report lower QOL scores compared to the general population.Studies in children, using the Pediatric Quality of Life Inventory (PedsQL™ 4.0) consistently showed significantly lower scores in all four domains of the measure, including physical, emotional, social and school functioning. Children in developing countries such as Egypt had the worst scores with a mean total score of 64 out of 100, increasing to 77 in Thailand and approaching the normal population in North America at 85.[27,28] One report from Turkey found that 19% of adolescents self-reported significant anxiety and 20% being depressed. Do not forget about the impact of the disease on caregivers, since the same study showed that 29% reported having significant depression.[29] In adults, the Medical Outcomes Study 35-item Short Form Health Survey (SF36V2) is the tool used most often, with a recent Thalassemia Clinical Research Network study finding significantly worse QOL in 5 of the 8 sub domains with the largest effect size being in general health, with a smaller effect size in physical functioning, role-physical, social functioning, and role emotional. Patients with more disease complications and the elderly had the lowest scores.[22, 30] Recently, a disease-specific tool, called the TranQol, was developed in North America for children and adult with transfusion-dependent thalassemia. The tool was found to be valid, reliable and responsive to change, and provides a good option for assessing QOL in this population.[27]

Intervention

- Quality of Life should be assessed at every clinic visit, including physical, emotional, and family health, as well as the impact of the disease on school/career. Areas of concern should be communicated to the rest of the Health Care Providers (HCP) in the team so that appropriate corrective action can be taken.
- A standardized QOL tool, either a generic QOL tool such as the PedsQL for children and the SF 36v2 for adults and/or a disease-specific QOL tool such as the TranQol, should be measured at regular intervals every 1-2 years. The result of the standardised assessment should be tracked in the patient's Electronic Medical Record (EMR).
- When multiple options for therapy are available and of similar medical efficacy, patient preference should be accommodated, with the goal of minimizing negative impacts of treatment on QOL.

PART II

Management of Thalassemia

Part II
MANAGEMENT OF THALASSEMIA

1. Initial Management of 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.

Recommendation

- Affected newborns/infants should be referred promptly to a comprehensive thalassemia program and/or to a pediatric hematologist.
- Treatment should be tailored to the clinical phenotype.
- 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.
- A written summary of the diagnosis, the treatment plan, and the discussions held should be documented and distributed to the family practitioner or pediatrician and the family.

Background

Transfusion-dependent and non-transfusion dependent thalassemias are lifelong medical conditions that require continuous care by a qualified experienced team of health professionals. Trait carriers are usually asymptomatic and they do not require any specific medical care but they should be aware of their status for reproduction purposes.
Early diagnosis of transfusion dependent thalassemia in neonates and children ensures prompt monitoring and treatment for patients who require chronic transfusion support for normal growth and development.

Interventions

Investigation and Diagnosis

- Diagnosis of a child with a thalassemia disorder should be done as early as possible after birth.
- Neonatal screening programs, where present, should be able to identify affected infants and refer them promptly to specialist centre.
- 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.
- Initial diagnostic investigations should include:
    - A complete blood count and a blood smear.
    - Hemoglobin analysis by electrophoresis or high performance liquid chromatography (HPLC).
    - Molecular genetic analysis for both alpha and beta globin gene.
    - Extended red blood cell phenotype if transfusions are anticipated. Red blood cell genotyping should be considered if available.
    - Parents and siblings should be tested if no prior testing has been performed.
- Affected newborns/infants should be referred promptly to a comprehensive thalassemia program and/or to a

pediatric hematologist.
- In symptomatic, previously unidentified infants with suspected thalassemia, investigations and initial assessment should be done immediately at the specialist centre.

Treatment

- The child's clinical course should be closely monitored since the clinical phenotype cannot always be accurately predicted from the genotype. Co-inheritance of alpha-thalassemia mutations and foetal hemoglobi level can modify the clinical phenotype.
- Treatment should be tailored to the clinical phenotype. Figure 1 summarizes the Clinical and laboratory aspects to consider appropriateness for initiating a transfusion program and management of infants with new Thalassemia diagnosis.

Education

- 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.
- 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 family practitioner or pediatrician and the family.

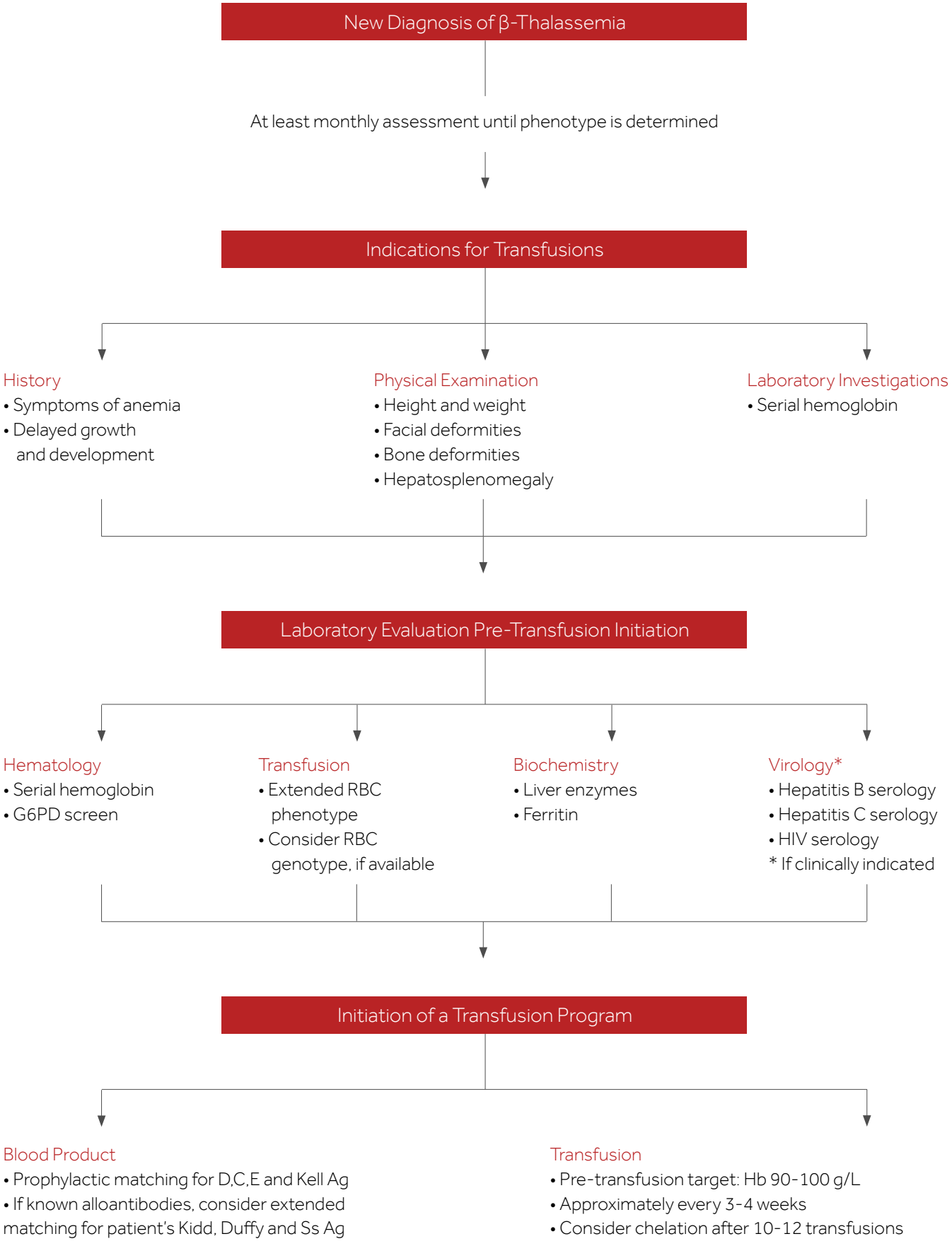

Figure 1: Clinical and laboratory aspects to consider appropriateness for initiating a transfusion program

2. Transfusion Support in Thalassemia

Principles

- To promptly identify the indications to start blood transfusion in thalassemia patients
- To understand the rate and frequency of transfusion in thalassemia patients
- To understand the risk of blood product transfsuions

Recommendation

- Patients with beta-thalassemia major (including more severe forms of HgbE/ß-thalassemia) require transfusion support to prevent life-threatening anemia, which usually first appears by age 4-6 months and then steadily progresses.
- Maintaining a nadir hemoglobin of approximately 90-100 g/L is necessary to prevent disease related complications.
- The decision to transfuse a patient with thalassemia intermia should not be based purely on their hemoglobin level.
- Routine and specialized transfusion requirements needs to be followed as per Canadian Blood Services (CBS) guidelines.

Background

Beta-thalassemia major

- Patients with beta-thalassemia major (including more severe forms of HgbE/ß-thalassemia) require transfusion support to prevent life-threatening anemia, which usually first appears by age 4-6 months and then steadily progresses. Without regular transfusions, 85% of patients will die before the age of five years[31]. The secondary goal of transfusion, however, and one which requires an even more intensive degree of support, is suppression of ineffective erythropoiesis and the accompanying hypertrophy of myeloid bone marrow that occurs with it. At its extremes, this myeloid hypertrophy may be 10-20 times higher than normal, resulting in bony pain, low bone density, progressive skeletal deformities, and extramedullary erythropoiesis[32]. This latter condition in turn can exacerbate hepato-splenomegaly and promote the formation of benign tumors with associated mass effect (eg., spinal nerve compression).
- Previous studies in patients with beta thalassemia major have established that maintaining a nadir hemoglobin of approximately 90-100 g/L through regular blood transfusions will maintain the patient's erythoid mass at only 1-4x normal[33], which is generally adequate to prevent growth retardation, extramedullary hematopoiesis and dysmorphic bone changes.[34]
- Transfusing to achieve maintain at a Hgb higher than 100 g/L (aka "supertransfusion") will generally only result in more rapid iron loading[35] and in most cases should only be pursued as a short-term strategy to treat extramedullarly hematopoietic pseudotumours. In patients with beta thalassemia major there is insufficient evidence to support the use of higher transfusion thresholds than 100 g/L on the basis of comorbid cardiac disease.
- When transfusing to promote regression of extramedullary hematopoietic pseudotumours consideration must be given to the age of the masses, as over time many will undergo fatty replacement and will be unlikely to shrink in response to aggressive transfusion support.[35] Transfusion protocols that have been demonstrated to effectively shrink ectopic masses of bone marrow may require the administration of up to 2-4 units of RBCs per week over a period of months and will predictably lead to very rapid accumulation of iron.[36] Other modalities such as hydroxyurea, targeted radiotherapy, or rarely surgery, should therefore also be pursued wherever feasible.

Beta-thalassemia intermedia

- Distinguishing a patient with beta thalassemia major from beta thalassemia intermedia is not always straightforward in infancy and monthly monitoring of hemoglobin levels may be required, although genetic studies can be of assistance in predicting the clinical phenotype that will eventually emerge. By conventional definition, patients with beta thalassemia intermedia will require no more than 8 units of RBCs per year for adult patient to maintain a tolerable hemoglobin level.
- Without transfusion support, most patients with beta-thalassemia intermedia (including moderate severity HgbE/ß-thalassemia) will maintain a hemoglobin in the 70-100 g/L range, and transfusion may only be necessary if the hemoglobin transiently drops below the patient's usual baseline, as may occur during acute illness, pregnancy, hemorrhage or in the setting of progressive hypersplenism. Nonetheless, patients with beta-thalassemia intermedia are only able to maintain a tolerable hemoglobin without chronic transfusion support via significant erythroid hypertrophy accompanied by high rates of hemolysis. As a result, untranfused beta-thalassemia intermedia patients, even if able to maintain a hemoglobin level adequate for normal daily function, are still at increased risk of other long-term chronic comorbidities, including extramedullary hematopoietic pseudotumors, growth impairment, osteoporosis, dysmorphic bone changes, hepatosplenomegaly, pulmonary hypertension, pigment cholelithiasis, leg ulcers, and both venous and arterial thrombotic complications.[37] In addition, in comparison to those with beta-thalassemia major, untransfused patients with beta-thalassemia intermedia are at increased risk of developing a pseudoxanthoma elasticum-like condition.[38]
- Thus, the decision to transfuse a patient with thalassemia intermia should not be based purely on their hemoglobin level, particularly if the hemoglobin level has been augmented through interventions such as splenectomy, hydroxyurea, or erythropoietin: at any hemoglobin level, patients with beta thalassemia intermedia generally have greater degrees of erythroid hypertrophy than patients with beta thalassemia major.[33] Monitoring for skeletal abnormalities in these patients is particularly important in the pre-pubertal period so as to avoid the development of permanent deformity.[39] However, many of other complications have a delayed onset (often not becoming apparent until the third decade of life) and therefore the degree of transfusion support offered to patients with beta thalassemia intermedia requires lifelong monitoring of their clinical phenotype. Once a patient begins manifesting complications of erythroid hypertrophy and/or chronic hemolysis, transfusion support should be considered even if the steady state hemoglobin remains > 70 g/L.
- Conversely, however, even a patient with a hemoglobin in the 50-70 g/L range does not necessarily require transfusion support if they are tolerating this degree of anemia well from a symptomatic standpoint and are not manifesting any of the above complications; this may be particularly true in patients with HgbE/ß-thalassemia, who often tolerate even severe degrees of anemia due to a right-shifted oxygen dissociation curve.[40] Caution should be exercised before immediately attributing non-specific concerns such as poor school performance or poor quality of life to the patient's hemoglobin level, particularly given the quality of life impact that regular transfusions (and associated need for iron chelation therapy) will themselves provide. For many patients with beta thalassemia intermedia (and other otherwise non-transfusion-dependent thalassemias) transient decreases in hemoglobin due to intercurrent conditions (eg., pregnancy, acute illness) may require temporary provision of transfusion support but should not be misinterpreted as indicating a need to initiate chronic transfusion therapy. Finally, if transfusions were initiated in response to due fall in height velocity during childhood, or for the prevention of bony changes, it may be reasonable to attempt a weaning off transfusions after maximum height has been achieved and fusion of epiphyseal plates is complete, although ongoing monitoring for the emergence of other complications will be necessary.
- Suggested guidelines for transfusion support of patients with beta thalassemia intermedia have been published[41] but ultimately the decision will still need to be made on a case-by-case basis. If routine transfusion is pursued, targeting an erythropoietin level less than 150 mU/L may be a more reliable strategy for achieving adequate erythropoietic suppression than relying on hemoglobin levels alone. It should be noted that suppression of reticulocytosis is not a reliable indicator of transfusion adequacy in patients with thalassemia.[33] Once initiated, consideration should be given to re-evaluating patient response to transfusion support after six months: if no benefit has been seen in either subjective symptoms or objective indicators of organ dysfunction then discontinuation of routine transfusion is reasonable, although a tapering schedule may be preferable to allow for recovery from erythropoetic suppression.

Alpha thalassemia

- Patients with alpha thalassemia minor (three functioning alpha globin genes) and trait (two functioning alpha globin genes) are generally asymptomatic. Patients with HgbH disease (only a single functioning alpha globin gene), however, may have a degree anemia that occasionally requires transfusion support. Patients with no functioning alpha globin genes (Hgb Barts disease) will die in utero of fetal hydrops without aggressive transfusion support and are therefore encountered very infrequently in clinical practice; if intrauterine transfusions can sustain a developing fetus until delivery, transfusion management should continue in the antenatal period as per patients with beta-thalassemia major. Detailed discussions of intrauterine transfusion protocols for Hgb Barts are outside the scope of these guidelines but have been published elsewhere.[42]
- Patients with deletional HgbH disease tend to have baseline hemoglobin that runs in the range of 90-100 g/L, which is sufficient for most patients to enjoy a near normal quality of life, and because HgbH disease generally does not result in a significant degree of ineffective erythropoiesis, maintaining this baseline hemoglobin level does not generally incur the same complications that a patient with ß thalassemia intermedia might develop at the same hemoglobin level. Thus, transfusion is only required if the hemoglobin temporarily falls below a threshold generally required for adequate functioning (eg., Hgb < 70-80 g/L). This may occur during surgery or other episodes of blood loss, pregnancy, hypersplenism, aplastic crises (eg., infection with Parvovirus B19) or in the face of an oxidative stress that triggers increased hemolysis (eg., infection, fever, ingestion of oxidative drugs). These episodes are usually short-lived but may result in an abrupt fall in hemoglobin by as much as 30 g/L, and shock or organ failure may develop unless prompt transfusion support is provided.[43]
- Patients with non-deletional HgbH disease, however, tend to have lower baseline hemoglobin levels (eg., 70-80 g/L) and are more likely to require transfusion support at an earlier age.[11] Non-deletional HgbH disease diseases are often accompanied by an hemoglobin variant (eg., Hgb-Constant Spring) and the relative instability of this hemoglobin variant may further exacerbate the patient's baseline hemolysis and, with it, the risk of hepatosplenomegaly and gallstones.[44] Other examples of non-deletional HgbH disease include HgbH-Quong-Sze and HgbH-Pakse.
- Rarely, patients with non-deletional HgbH may develop a degree of ineffective erythropoiesis that results in comorbidities similar to those seen in ß-thalassemia intermedia (eg., skeletal abnormalities, extra-medullary hematopoiesis, iron overload). It is generally accepted, however, the primary determinant of anemia in HgbH patients is hemolytic anemia[45] and thus in most cases the goal of transfusion is not to suppress signs and symptoms of erythroid hypertrophy but to achieve a minimum hemoglobin level necessary to prevent acute organ dysfunction (eg., if hemoglobin falls below 50 g/L) and to provide freedom from significant fatigue (eg., when Hgb falls below 70 g/L).

Routine and Specialized Transfusion Requirements

Group, Screen and cross match

Each sample collected from a transfusion recipient must be tested for ABO and Rh groups and should be screened for clinically significant red cell antibodies. With the exception of emergency situations (eg., major hemorrhage or a life-threatening degree of anemia), all transfused RBCs should be crossmatched to detect any incompatibility between the donor and recipient. Approximately 15-20% of thalassemia will become sensitized to RBC minor blood group antigens[76,77] with even higher rates observed amongst patients of Asian descent.[78] A large proportion of these antibodies will be against the C, E, c, e and K antigens, and prophylactic matching for these antigens has been shown to decrease the overall rate of alloimmuization significantly.[76,79] . In keeping with other published recommendations, prophylactic matching for C, E, c, e and K antigens is therefore recommended.80 To facilitate this, and to assist in the investigation of any new antibody specificities that may also develop, patients should be phenotyped for all common clinically significant antigens (D,C,E,c,e,K,k,Fya,Fyb,Jka,Jkb,S,s) prior to their first transfusion or, if not possible, by genotyping using a licensed testing platform.

Blood component production

RBCs provided by licensed manufacturers in Canada meet the general requirements required by the Thalassemia International Federation and are therefore acceptable for use in Canadian patients.[46] For patients travelling abroad, however, clinicians should ensure that any blood products provided in other jurisdictions are also manufactured in accord with the following:[47]

- Blood donors are voluntary and non-remunerated.
- Donations are processed, stored and distributed under the aegis of a rigourous quality assurance program.
- Testing for infectious disease includes highly sensitive assays for HIV, hepatitis B and hepatitis C, with additional testing for other clinically-significant transfusion-transmissible diseases that are known to occur within the local population (eg., West Nile Virus, Chagas Disease).
- Each unit of RBCs is collected and stored under conditions that assure the hematocrit is kept less than 80% at all times, the hemoglobin content kept above 40 g/L at all times, hemolysis kept less than 0.8% at time of expiration, and sterility is maintained throughout.

Notably, the provision of directed blood donations (eg., from parent to child) greatly increases the cost and complexity of blood product provision[48] and places the recipient at increased risk of both transfusion-associated graft-versus-host-disease[49] and transfusion-related acute lung injury.[50] For these reasons, directed donations are discouraged unless it proves impossible to source non-directed blood due to a high degree of patient sensitization to RBC minor blood group antigens.

Irradiation and Cytomegalovirus (CMV)-testing

Cellular blood products should be irradiated with gamma rays to prevent transfusion-associated graft-versus-host-disease in at-risk recipients; the recommended dose is 25 Gy directed towards the centre of the blood product.[58] At-risk recipients include but are not limited to the following:

- intrauterine transfusions.
- recipients of cellular blood components known to be from a blood relative.
- recipients who have undergone hematopoietic progenitor cell (stem cell) transplantation.
- recipients of HLA-selected platelets or platelets known to be HLA homozygous.
- Asplenia in thalassemia patients is not sufficient to justify blood product irradiation.

CMV-sreonegative blood products are generally not indicated in routine transfusions in thalassemia patients unless patient is pregnant, considered for stem cell transplant or in uetro transfusion is indicated.

Blood Product Administration

Informed consent

Documentation that the patient (or their surrogate decision-maker) understands the nature of the blood component that is being offered to them, including the associated risks, benefits, and alternatives, should be maintained in the clinical record[74]. The consent process should be repeated prior to the administration of further transfusion support. Obtaining informed consent is the responsibility of the individual proposing the treatment.[81]

Patient monitoring

To facilitate early detection of acute transfusion reactions, vital signs should be recorded before, during and following a blood transfusion. Close observation and a slower infusion speed is particularly advised for the first 15 minutes of a transfusion[36] Patients should only be transfused while under the care of a healthcare worker (eg., a physician or nurse) and, ideally, with immediate access to resuscitative equipment. Provision of transfusion support after-hours and on weekends is an important consideration in patients who are in school full-time or have regular working hours.

Transfusion dose

For outpatients, it is convenient to set the dose of blood administered to be large enough to allow a repeat transfusion to be delayed by approximately 3-4 weeks while still maintaining the pre-transfusion hemoglobin within target range. It is preferable for most patients to be transfused a fixed quantity of blood at a fixed schedule, making adjustments in response to pre-transfusion hemoglobin levels that are persistently out of range, rather than waiting until the pre-transfusion hemoglobin falls within target range and then ordering a transfusion.

In young children it may be difficult to attain a target pre-transfusion hemoglobin with reasonable precision without ordering blood in weight-adjusted doses (typically 5-15 mL/kg). One recently-proposed formula for precise dosing based on baseline and target hemoglobin levels is listed below:[82]

[Desired – actual Hgb in g/L]/10 x weight [kg] x 3[Hct of transfused unit] = mL to be administered

Notably, when applying the above formula to RBCs with a standard Hct of 0.6, the difference in blood volume required to change the target Hgb by 10 g/L increases to approximately 300 mL once the patient's weight exceeds 50 kg. As this is the approximate volume of a unit of RBCs in optimal additive solution, maintaining a pre-transfusion Hgb in the range of 90-100 g/L in thalassemia patients larger than 50 kg can therefore be achieved with reasonable precision by ordering the transfusion dose in units rather than in mL/kg; ordering in units will decrease wastage of untransfused blood.

If the total transfusion dose necessary to achieve the target hemoglobin is excessive, consideration may be given to splenectomy, a procedure which can decrease transfusion requirements in thalassemia patients by approximately 30%.[53] As splenectomy itself carries risks, an excessive transfusion dose should be defined restrictively, as follows:

- The transfusion dose results in a degree of iron loading which cannot be chelated without inducing significant toxicity.
- The transfusion dose requires either a larger fluid volume than can be accommodated by either pre-transfusion diuresis, plasma-volume reduction, or by administering smaller doses at more frequent intervals.

The above criteria are more likely to be met when the total annual volume of blood administered exceeds 200 mL/kg per year of pure red blood cells (ie., 250-275 mL/kg per year of RBCs in optimal additive solution)[84], which for a 70 kg patient corresponds to 5-6 units per month. However, when this threshold is reached, particularly in patients whose epiphyseal growth plates have already fused, consideration may also be given to decreasing the transfusion dose via the adoption of slightly lower pre-transfusion Hgb targets (eg., 80-90 g/L). Careful monitoring for signs and symptoms of under-transfusion (eg., bony pain, progressive hepatosplenomegaly, pulmonary hypertension) are required if opting to take this approach.

Pre-medication

While there is no evidence from clinical trials that pre-medication decreases the risk of acute transfusion reactions, it is a reasonable intervention to consider in patients with recurrent reactions so as to at least attenuate their severity.[85]

Rate of infusion

To minimize transfusion reactions, blood products should be administered at the slowest feasible rate of infusion (to a maximum of four hours per unit between removal from storage and completion of infusion). The maximal rate of infusion should be determined for each individual patient, taking into consideration the total volume to be administered and the patient's capacity to tolerate a fluid challenge.

Transfusion Reactions

Transfusion reactions that could occur in thalassemia patients are similar to others. These include acute, chronic reactions and iron overload. CBS has an extensive review on management and approach to each reaction.

3. Iron Overload and Chelation Therapy

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.

Recommendation

- 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. 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.
- Deferasirox is the preferred chelator for most patients.
- 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.

Background

Iron Overload Overview

Red cell transfusion is the mainstay of treatment for thalassemia major; however, over time this therapy results in significant iron overload. Beyond tissue iron storage as ferritin or hemosiderin, control of Non-transfusion bound iron (NTBI) is critical to preservation of cardiac function[110] 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, mitochondrial dysfunction, 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 early detection and treatment.[117-119]

Assessment of Iron Overload

In the current era of MRI iron assessment, there is nowdays no role for using surrogate markers such as serum ferritin.[111] 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 1000 or 2500 ug/l.[118] 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 to track chelation efficacy unless it has be shown over multiple timepoints that ferritin correlates with LIC for an individual patient.[112] Regardless, there is poor correlation

between serum ferritin and myocardial iron. In non-transfused dependent thalassemia, the serum ferritin often underrepresents the LIC.[113]

Assessment of liver and cardiac iron using MRI has been shown to affect chelation therapy choices and improve outcomes in TM.[114-116]

MRI evidence of cardiac iron is also suggestive of diabetes and hypogonadism risk[117-125,145] Chelation therapy should be started in patients with a ferritin over 1000 ug/l; however, once chelation has been initiated, the aim of therapy should be to normalise body iron stores and suppress NTBI.

Liver iron concentration (LIC) measured on ultrasound-guided 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] Previous LIC thresholds of 7 or 15mg/g DW [117,110,111] are no longer applicable when the heart can be imaged directly. 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 and validated across platforms.[118, 123,156159]

Transiet elastography (fibroscan) may have a role in the assessment of liver fibrosis, but is not well validated in children and adults with and without concomitant HCV infection.[119-121]

Pancreatic MRI (obtained at the the same time as liver) can be used to assess iron in the pancreas, but its clinical utility is currently uncertain due to a lack of correlation with diabetes and pancreatic iron deposition.[142] However, it may be useful as a tool to risk stratify those patients at greater risk of cardiac iron deposition.[143]

Cardiac iron can accumulate by the age of 6 years in chronically transfused TM patients.[128] Therefore, cardiac MRI should be performed at this age, or earlier if possible with sedation/anesthesia. Iron concentration in the myocardium of the interventricular septum is inversely related to cardiac MRI T2* signal.[123 131]There is no adequate surrogate for assessment of cardiac MRI, and all patients in Canada should have access to cardiac MRI iron assessment.[134,135] Myocardial T2* values less than 25 ms (normal >42ms) are associated with a progressive and significant decline in left ventricular ejection fraction.[122, 123,158,160,161] 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. At the present time there is no consensus on whether a single mean T2* value or multiple regional values is more useful.[124-127] Currently, CMR T2* is validated on 1.5T magnets, but investigation is ongoing to validate 3T and higher magnets, as well as different iron protocols.[138-140] The clinician must be satisfied that the MRI technique used in their centre has been validated and results are reproducible.[136] Asessment of cardiac fibrosis resulting from iron deposition is not yet well defined.

Where cardiac MRI is not possible due to technical reasons such as implanted non-compatible or interefering device, it is reasonable to use tissue Doppler imaging or strain analysis by ECHO as a surrogate of iron depiction as in interval assessment.[129]- ECHO can also be used to detect early diastolic dysfunction or pulmonary hypertension.[137] proNT BNP may correlate with cardiac iron levels but not with cardiac function until late stage of disease.[141]

Initiation of Chelation Therapy

i. Deferoxamine (DFO)

Deferoxamine was the first iron chelator available. Its use has resulted in decreased end organ dysfunction and improved long-term survival. Its main disadvantage is that it must be administered parenterally using an infusion device.[144] However, recent data demonstrates less cardiac deaths with use of oral chelators.[145]

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.[118, 158] Aggressive chelation therapy consists of a 24-hour continuous

infusion of deferoxamine to the maximum daily dose.[146] 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. Deferoxaimne toxicity needs to be watched for when doses are high in the presence of low ferritin levels. the mean daily dose may be adjusted based on ferritin level in order to keep the therapeutic index below 0.025 (i.e. the mean daily dose (mg/kg) of Desferal divided by the serum ferritin level (micrograms/L) should be below 0.025. The therapeutic index is a valuable tool in protecting the patient from excess chelation, but it is not a substitute for careful clinical monitoring.

Side effects of deferoxamine include local skin reactions, predisposition to infection with Yersinia enterocolitica and other siderophoric organisms, 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. The incidence of these side effects is increased if TI is >0.025. For intravenous therapy at high doses, renal dysfunction, hypotension and interstitial pneumonitis 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.

ii. Deferiprone (DFP)

Deferiprone, the first oral iron chelator, was approved by Health Canada in February 2015. It is licensed for treatment of iron overload in patients with thalssemia syndromes when alternative chelation is inadequate.[163, 164] Typical dosage is 75-100 mg/kg/d in 3 divided doses with higher doses preferred when used as monotherapy. Deferiprone reduces iron stores, as measured by ferritin or LIC, in thalassemia major patients receiving transfusions. [155-165] 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.[166-168] 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.
A systematic review demonstrated greater efficacy by deferiprone to improvement in cardiac and endocrine function but with insufficiently powered or too few studies to demonstrate efficacy for cardiac and liver iron control.[147] Given the clinical benefit of improvement in LVEF, this makes Deferiprone the preferred cardiac chelator.[148]
The most serious complication of deferiprone is agranulocytosis (neutrophils < 0.5 x 109/L), which occurs in less than 2% of patients and most likely in the first 6 months of treatment.165-172 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.

iii. Deferasirox (DFX)

Deferasirox Dispersible Tablets (DT) (EXJADE) was approved in 2006 as an oral iron 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 – 40 mg/kg/day. It is the most widely used chelator in North America.[149]

A phase III trial (EPIC) demonstrated the efficacy of deferasirox DT and its non-inferiority to deferoxamine at doses of over 20 mg/kg/day when used by thalassemia major patients.[150] Non-inferiority at lower doses of deferasirox DT was not established and may have been due to study design. An extension study of CORDELIA has demonstrated its efficacy for improving cardiac T2* independent of LIC.[151] Individualized assessment of total iron load and a tailored dosing regimen may be needed to achieve optimal iron chelation. There is growing body of data to support its efficacy in chelating the myocardium, though data is lacking for improvement of a previously low LVEF.[152, 153]

Deferasirox DT has also been shown to control liver iron in non-transfusion dependent thalassemia (ESCALATOR study).[154]

Side effects of deferasirox include gastrointestinal symptoms (26%), skin rash (7%), cytopenias, and an increase in serum creatinine and other renal adverse effects (34%). Toxicity is more common at low iron burden.[155] Side effects may be modifiable and efficacy increased by using a BID dosing regimen.[156] Adminstration with food can also increase drug absorption.[157]

Deferasirox film-coated tablets (FCT) (JADENU) were approved by Health Canada in 2016. Public drug plan reimbursement criteria vary by province. There were very limited studies with the new formulation prior to approval though it does appear to have improved gastrointestinal side effect profile compared to DT for Oral Suspension (EXJADE). This may have a positive impact on patient adherence. A useful conversion tool is provided on the manufacturer's website for assisting in switching patients from EXJADE to JADENU formulation of Deferasirox.

Combination chelation therapy

The most commonly reported combination regimen utilises oral Deferiprone with parenteral Deferoxamine. Numbers are small and the dose and scheduling varies widely between studies, making analysis challenging.[159-162] 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.[169-172]

The combination of Deferasirox and Deferoxamine has shown to improve liver and cardiac iron, though with small numbers.[163] More recently, there has been interest in combining two orally available chelators, Deferiprone and Deferasirox.[475] However, coverage for this approach is highly variable among provinces in Canada.

iv. Iron Chelators Under Investigation

Other oral chelating agents are undergoing clinical trials, though with no recent success. There is growing interest in the development of, not only new chelators, but novel agents that target other pathways, such as calcium channel antagonists, hepcidin agonists, apo-transferrin, and silymarin.[166,167]

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 three therapeutic options now exist for iron-overloaded patients in Canada (see table 4), each agent at the present time has benefits and limitations.

Properties	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
Molecular weight (daltons)	560	139	373
Route of Administration	Subcutaneous or intravenous	Oral	Oral
Half-life of iron free drug	20-30 minutes	3-4 hours	12-16 hours
Primary route of iron excretion	Urine and stool	Urine	Stool
Iron chelating efficacy	High (hexadentate)	Low (bidentate)	Moderate (tridentate)
Side Effects	• Local skin reactions • Sensneural hearing abnormalities • Retinopathy and visual changes • Growth retardation • Bone changes • Potential renal and lung toxicity	• Severe neutropenia • Gastrointestinal discomfort • Mild neutropenia • Arthralgias	• Rash • Gastrointestinal discomfort • Renal impairment
Dosage	• 20-50mg/kg/day 3-7 times/week • Children's dose up to 30mg/kg	75-100 mg/kg/day	• 10-40 mg/kg/day (Exjade) • 7–24mg/kg/day (Jadenu)
Contraindications	• Hypersensitivity • First trimester of pregnancy	• Previous agranulocytosis • Pregnancy and lactation	• Hypersensitivity • Creatinine clearance<60ml/min • Pregnancy and lactation

Table 4: Properties of Iron Chelators Available in Canada

Monitoring

- Every patient should have serial serum ferritin levels assessed every 3 months. Chelation therapy should be initiated for a persistently elevated ferritin > 1000 mg/ml or LIC >5mg/gm dry weight.
- Target serum ferritin is between 500 – 1000 mg/ml. Heath care providers should recognize that serum ferritin may not be accurate in assessing iron overload independent of LIC and myocardial iron.
- LIC should be determined by a validated MRI technique after approximately 10 – 20 transfusions, prior to initiation of chelation therapy, and every 6-24 months, as clinically indicated.[110,111]
- Cardiac function and iron should be monitored every 6-24 months using cardiac MRI T2*. Due to the non-linear scale of T2* changes over time should be evaluated using the cardiac iron concentration or by transforming the data.[473]

Treatment

- Young children needing chelation therapy should be started on subcutaneous infusion of Deferoxamine or oral chelation with Deferasirox or Deferiprone. 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 – 30 mg/kg/day for children, and up to 50 mg/kg/day for adults, given over 8 – 12 hours for 5 – 7 days/week.
- 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.

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 and urinalysis, liver enzymes, and blood counts should be monitored prior to commencement of the drug, and then monthly thereafter. Once stabilized, serum creatinine, liver enzymes, and ferritin should be monitored every 1-3 months depending on degree of iron overload, blood test stability and patient compliance. 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 3 months thereafter. Summary for toxicity monitoring is provided in table 5.

Properties	Deferoxamine (DFO)	Deferiprone (DFP)	Deferasirox (DFX)
CBC and differential	Baseline Monthly	Baseline Weekly (neutrophils)	Baseline Monthly
Creatinine, UA	Baseline Monthly	Baseline 3 months	Baseline Two weekly (for one month) Monthly
Liver enzymes	Baseline Monthly	Baseline Monthly (for 3-6 months) Every 3months thereafter	Baseline Monthly Every 3 months if stable
Audiometry	Every 2 years (if stable)	Every 2 years (if stable)	Annual
Ophthalmic testing	Every 2 years (if stable)	Every 2 years (if stable)	Annual
Growth assessment	Bi-annually (Children)	Not required	Not required

Table 5: Recommended Toxicity Monitoring for Available Iron Chelators

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.[168] A study comparing QoL on Deferoxamine or Deferasirox or both showed no difference in a Chinese population.[169] Deferasirox has been shown to provide better QALY than Deferoxamine, though less than Defeiprone.[170-171] 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%).[158] 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
- 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.

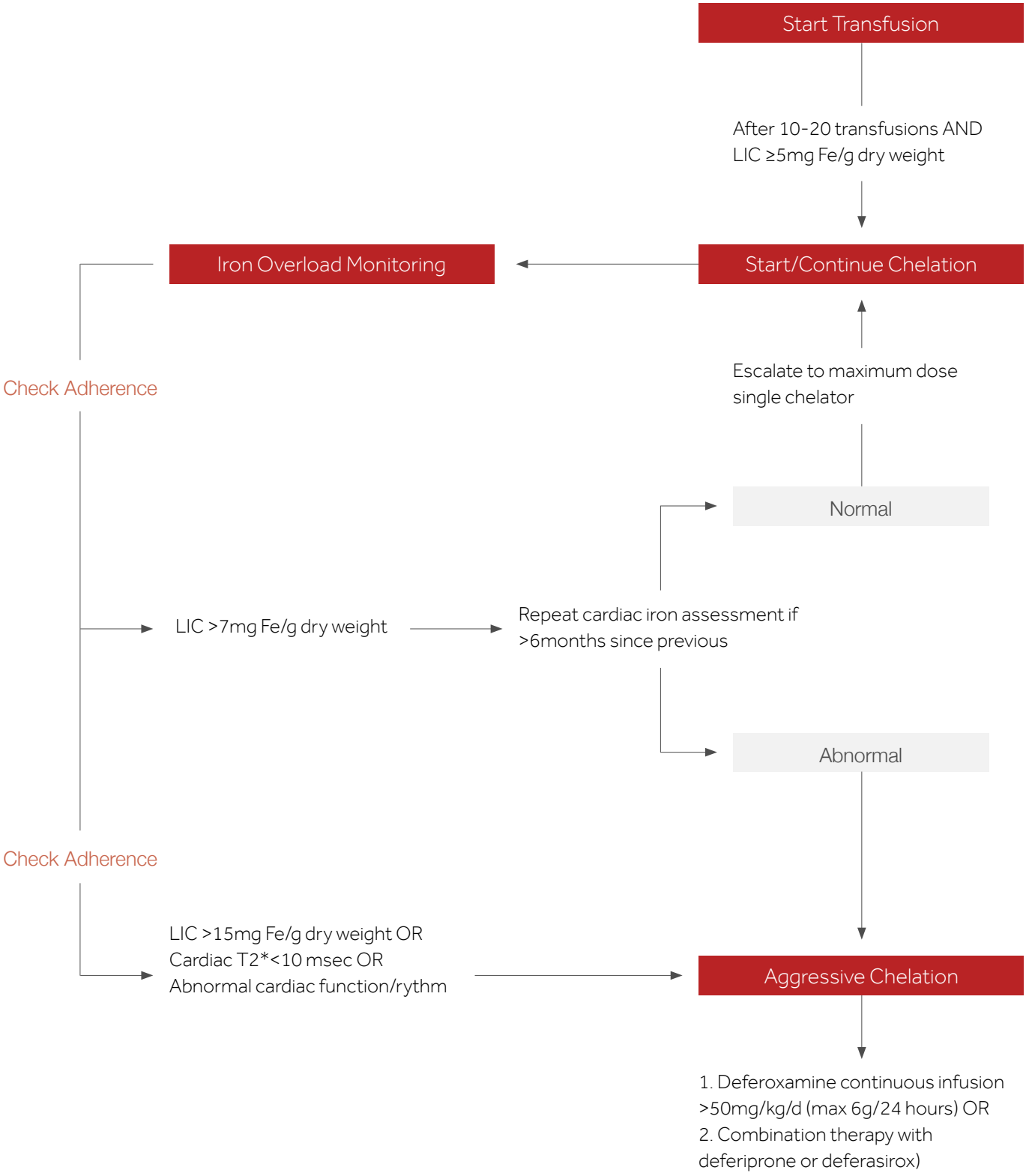

Figure 2: Iron Overload Assessment and Management in TDT patients

4. Hematopoietic Stem Cell Transplantation (HSCT)

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.

Recommendation

- The option of HSCT, including its indications and complications, should be discussed with families while the patient is at a young age, ideally before entering puberty to maximize the likelihood of preserving fertility.
- 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 donor (cord blood or bone marrow) and matched unrelated donor (bone marrow) should be discussed. The option of HLA mismatched related donor (haplo-identical donor) should be also considered.
- The intensity of the conditioning regimen – described as full intensity vs reduced intensity – as well as the advantages and disadvantages associated with each kind of them, should be also included in the discussion.
- Post-HSCT, patients should be closely monitored and managed for iron overload and other complications at least for the first 2 years after HSCT.

Background

HSCT is the only curative option available to thalassemia major patients. HSCT is a complex treatment which requires several weeks of hospitalization and several months of close follow-up. HSCT with a HLA matched (ie compatible) donor, either related or unrelated, and with a full intensity conditioning regimen, is considered as a standard of care for children with thalassemia major[172]. HSCT for adult patients with thalassemia remains unavailable in most centers and needs to be studied carefully given the increased morbidity.

Until recently, HSCT was limited by two main barriers. The first one was availability of a HLA matched donor, which probability is only 25% among siblings and ranges from 10 to 30% among donors from international registries. The second one was complications from thalassemia before HSCT, such as inadequacy of chelation treatment leading to hepatomegaly and portal fibrosis, which increase the risks of complications after HSCT[173] Depending on the importance of these complications before HSCT, patients are ranked in 3 different risk groups called Pesaro class 1 or class 2 (less severe), and Persaro class 3 (more severe).

Patients undergoing HSCT with a HLA-matched sibling donor have an overall survival (OS) ranging from 98% to 91% and disease-free survival (DFS) ranging from 95% to 83%, irrespective of the Pesaro classification.[174,175] Similar outcomes are obtained with matched unrelated donors from registries[176]. Age at HSCT is the main factor for outcome, but the cut-off for age varies among studies from 3 years, to 7 years, to 14-16 years. In the largest reported cohort, children less than 14 years of age have an OS of 96% and EFS of 86%, whereas adolescents and young adults more than 14 years of age have an OS of 82% and DFS of 74%[174]. In adults (age > 16 years), early trials in the 1980 and 90 reported poor outcomes (OS of 66% and DFS of 62%) related to advanced liver disease[177].

Currently, class 1 and 2 are considered similar regarding outcomes after HSCT, with a risk of death related to HSCT about 5% among children. The prognosis of class 3 children, historically with OS of 79% and EFS of 58%[178], has dramatically improved with the development of new conditioning regimens and the use of preconditioning protocols, in order to prevent graft rejection. With modern protocols, class 3 children have now outcomes similar to class 1 and 2, with EFS of 92%[179].

For patients who lack a HLA matched donor, haplo-identical donor (ie the father, the mother or a mismatched sibling) and unrelated cord blood from cord blood bank are the current options. Unrelated cord blood are associated with higher risk of engraftment failure and death. Ongoing protocols based on ex vivo expansion of cord blood before infusion may address this problem. Recently, major breakthroughs have been reported with haplo-identical donors and new protocols of conditioning. Children up to 19 year of age and class 3 have OS of 96% and EFS of 96%[180]. These very promising results open the door to an era of universal cure for every children suffering from thalassemia major.

The main complications related to HSCT are acute graft versus host disease (GvHD) and chronic GvHD, engraftment failure and secondary bone marrow rejection, hypofertility and sterility. The incidence of grade 2-4 acute GVHD is 9% and the incidence of extensive chronic GVHD is 6% in the european experience[174]. The incidence of graft failure is variable, from 5 to 30% depending on several factors of the patient, the donor and the protocol of HSCT. The main causes of deaths are infectious complications after HSCT rejection, Severe GVHD may also cause the death of the patient.

The incidence of sterility and gonadal deficiency is estimated about 60% after HSCT with full conditioning regimen[181], Higher risk are documented in girls transplanted in post-menarchial[182], and lower risk in children transplanted before puberty (62% of spontaneous puberty after HSCT)[182]. Better control of iron overload before HSCT, younger age at transplantation and new protocol of HSCT based on lower doses of alkylators chemotherapy should improve gonadal function.

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.
- Possible long-term complications of HSCT include iron overload, chronic GVHD, delayed pubertal development, growth and endocrine deficiencies and infertility. There is also a theoretical but yet not proven, higher risk of malignancy after HSCT.
- Preservation of fertility should be part of the preparation to HSCT. For prepubertal children, enrolment in investigational trial of tissue preservation (either ovarian or testicular tissue) should be considered.
- 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 counselled that they would still pass on a mutant thalassemia gene to each of their children.

5. Gene Therapy (GT)

Principles

- To ensure patients and families receive adequate information on gene therapy for informed decision-making.
- To ensure close follow-up of patients who have undergone gene therapy.

Recommendation

- The discussions of Gene Therapy should be initiated by the specialist centre and, if the patient is serious about pursuing gene therapy and it is appropriate, referral should be made to a centre where experimental trial is opened.
- Before referring to a GT trial, search for a HLA matched donor should be done in order to state no matched donor is available.

Background

Gene therapy is a promising curative option for patients with thalassemia major. It is still in its beginning and is available only through experimental trials. No trials are currently opened in Canada, but several trials are ongoing or in late phase of development in the United States and Europe.

The hematopoietic stem cells (HSC) of the patient are collected in peripheral blood by apheresis after stimulation by GSCF and Plerixafor. Then, the normal gene of hemoglobin is introduced within autologous HSC in a dedicated laboratory for gene therapy. Several technologies can be used to transfer the gene into HSC[183]. Currently, the most common technology is based on a viral vector called lentivirus[184]. This virus does not cause infectious disease. Once the corrected HSC are produced, the bone marrow of the patient has to be destroyed by high doses of chemotherapy, similar to conditioning regimen of autologous HSCT, before infusing the corrected HSC intravenously.

Current GT trials enroll only patients who lack a HLA matched donor. Since 2004, more than 25 patients have been treated by GT[184,185]. In the largest reported trial, 18 patients from 12 to 35 years of age were included. All patients without the β0/β0 form of thalassemia became transfusion independent, while the 8 patients with β0/β0 thalassemia remained transfusion dependant but at lower rate[186]. In another trial based on the same vector, 4 patients, all without β0/β0 thalassemia, achieved transfusion independence[187].

The main risk associated with GT is secondary leukemia related to dysregulation of normal genes by the random insertion of the viral vector into the genome of HSC. So far, it has not been observed in GT for thalassemia but the length of follow-up is still too short to conclude. GT induced leukemia have been observed only in several GT trials based on a retrovirus vector, different from the lentivirus vector used in GT for thalassemia, for treatment of various immune deficiencies[188-190]. Also, patients enrolled in GT trials are at risk of secondary loss of the corrected HSC due to clonal exhaustion[183]. Moreover, patients are exposed to long term sexual hormone insufficiency and hypofertility related to high doses of chemotherapy. Patients have to be informed that GT brings a corrected hemoglobin gene to HSC only, but not to egg cells and spermatozoids which will always carry the mutated gene.

Finally, there has been recent advent of the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated protein 9 (Cas9) systems for precise genome editing. Inherited haematological disorders represent ideal targets for CRISPR-Cas9-mediated gene therapy. Correcting disease-causing mutations could alleviate disease-related symptoms in the near future. Similar to virus-mediated gene therapy, CRISPR-Cas9-mediated genome editing is used to correct HBB gene mutations in patients via HDR, leading to normal erythropoiesis. In the past two years, several research groups have successively applied CRISPR-Cas9 technology to correct β-thalassaemia mutations in patient-derived induced pluripotent stem cells (iPSCs).[476]

Interventions

- Discussions about gene therapy for thalassemia should include benefits, risks, short and long-term complications, quality of life and psychosocial impact.
- The patient's risk factors and organ function should be assessed prior to GT.
- Possible short and long-term complications of gene therapy include secondary leukemia or lymphoma, secondary loss of corrected HSC, delayed pubertal development, endocrine deficiencies, and infertility.
- Preservation of fertility should be part of the preparation to gene therapy. For prepubertal children, enrolment in investigational trial of tissue preservation (either ovarian or testicular tissue) should be considered.
- Transplanted individuals should be counseled that they will still pass on a mutant thalassemia gene to each of their children.

PART III

Complications of Thalassemia

Part III
COMPLICATIONS OF THALASSEMIA

1. Cardiac Complications

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 escalate chelation of cardiac iron if cardiac toxicity is identified.
- To treat urgently cardiac dysfunction according to standards of care.

Recommendation

- All thalassemia comprehensive care centers should have a cardiologist with expertise in managing cardiac complications and iron overload in thalassemia patients.
- The cardiologist should manage cardiac complications as heart failure or arrhythmias as per cardiology standard.
- All patients with thalassemia should have routine assessment for signs and symptoms of cardiac dysfunction and/or arrythmias.
- Cardiac function and pulmonary artery pressure should be monitored routinely.
- Cardiac iron overload must be monitored routinely in patients with thalassemia.
- Cardiac iron overload should be lowered by iron chelation therapy to reduce complication and avoid mortality.
- In the presence of cardiac dysfunction or complication from iron overload, aggressive management with iron chelation must be used.

Background

Iron-induced heart failure and arrhythmias are one of the most common causes of death in patients with thalassemia major.[199, 252] Deaths from cardiac disease are unusual before the age of 15 years. Appropriate iron chelation reduces the risk of cardiac disease and improves survival.[198,199] Effective chelation involves control of tissue iron levels as well as suppression of non-transferrin bound iron (NTBI) which cause free-radical mediated oxidative damage to organelles.[253]

Interventions

- Each thalassemia specialist centre should have a cardiologist with knowledge of managing cardiac complications in thalassemia patients.
- All patients should have routine clinical assessment for signs and symptoms of cardiac dysfunction.[203]
- Diabetic patients and males are at greater risk of cardiac related iron complications[254, 255]
- Splenectomy status may also play a role[256, 257,267]
- Cardiac iron load and function should be measured routinely by MRI T2*.[204]
- Iron-overload should be reduced by chelation to lower the risk of iron associated cardiac complications and death.[198, 199,205, 227]
- In the presence of increased cardiac iron load and/or cardiac dysfunction, more aggressive iron chelation regimens should be initiated.[205]
- The specialist cardiologist should manage cardiac complication, including heart failure and arrhythmia, as per cardiology standards, but with appreciation of specific thalassemia-related considerations.

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 or if new symptoms present. Any abnormality should trigger specific cardiological evaluation.
- Cardiac function, including LVEF, can be measured by several techniques including echocardiography (ECHO) , MUGA scan, and cardiac MRI. MUGA should be avoided due to cumulative radiation exposure. 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 6 years.[203, 258,259]
- Assessment may be performed 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 (ECG) and Holter/event monitor should be performed[260, 261]
- NT-pro BNP may be helpful in the assessment of cardiac iron[262-264]
- Vitamin D levels should be normalised as there may be a correlation with cardiac disease[265]
- Baseline ECHO assessment should be ordered for pulmonary hypertension (PHT), though the prevalence is low in Thalassemia Major. In Thalassemia Intermedia, ECHO for PHT screen may be performed more frequently. LV non-compaction may be more prevalent in Thalassemia and can be screened with ECHO[266]
- With the availability of Cardiac MRI T2* assessment, there is no role for using the serum ferritin or liver iron concentration as a marker of cardiac risk. Furthermore, particularly in chelation-exposed patients there can be discrepancy between these different markers.[198, 267-271]
- Due to the major impact on outcomes, where cardiac MRI T2* is not available locally, there should be arrangement for patients to undergo cardiac MRI T2* analysis at another centre.[272]
- Each centre should have a radiologist with expertise in CMR T2* and the technique should be employed using a validated protocol.[215, 273] A segmental approach to T2* analysis is controversial and is not required as a basic requirement of analysis (15, 84, 85)
- ECHO with strain analysis can be used as an interim assessment of iron related cardiomyopathy where it is difficult to obtain frequent MRI T2* or where there may be a contraindication to MRI.[210, 276-278]
- Pancreatic MRI can predict those patients at risk of developing cardiac iron overload.[279]
- Cardiac MRI T2* values greater than 30ms are considered normal, and >20ms not usually associated with significant iron load.
- Cardiac MRI T2* less than 10ms correlates with a progressive and significant decline in LVEF.[204]
- CMR T2* should be repeated every 1 – 2 years in patients with high MRI T2* values (> 20 ms), and every 6 months in patients with low MRI T2* values <10ms. Additional imaging is recommended 6 months after changing chelation regimen or if there has been deterioration in compliance to chelation therapy. The timing and frequency of testing should be individualized to each patient.
- Detection of cardiac fibrosis is still at the experimental phase and results are controversial.

Treatment Based on Cardiac Dysfunction and Iron Load Assessment

- Chelation therapy to reduce high iron load lowers the likelihood of developing cardiac dysfunction. However, longstanding iron deposition in the heart can lead to late cardiac events such as restrictive cardiomyopathy and arrhythmia, even if successfully chelated. For this reason, current T2* value does not predict for longterm morbidity from prior iron accumulation, and vigilance should be maintained in old patients with a prior history of sustained non-adherence or suboptimal chelation.[474]
- Lack of compliance with chelation therapy should be identified and importance of chelation stressed.[237]
- 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 patients with T2* <10ms or a drop in LVEF by 7-10% or to below the normal range.
- Conversion to an aggressive chelation program in patients with heart failure can improve LVEF and myocardial MRI T2* measurements.[205]
- 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.[237, 266] Aggressive chelation therapy

should be started immediately and cardiac function monitored at least every 6 months.

- 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 arrythmogenic tissue. Amiodarone should be avoided due to risk of thyroid and liver disease in Thalassemia.
- Ablation may be unsuccessful due to widespread fibrosis and should be undertaken by an experience Electrophysiologist cardiologist, ideally in cooperation with a thalassemia specialist cardiologist.
- Implantable cardiac devices should be considered in the setting of cardiogenic shock as a bridge to effective chelation.
- If heart transplantation is being considered, a panel reactive antibody should be requested early on to determine likelihood of successful engraftment and blood transfusions limited to reduce further sensitisation.
- Deferiprone has been shown to increase both T2* and RVEF & LVEF in patients with severe cardiac iron overload and cardiac dysfunction[250]
- Deferasirox has been shown to increase both T2* and LVEF in patients with moderate-severe cardiac iron overload and normal cardiac function.[241-245] It has not yet been determined if liver iron concentration affects the efficacy of Deferasirox to chelate the myocardium[239]
- Continuous infusion of Deferoxamine can effectively chelate non-transferrin bound iron and improve iron and cardiac dysfunction.
- First line management of a T2*<10ms with reduced LVEF should be high dose CIV Deferoxamine with Deferiprone tid.[233, 234,237,238, 247]
- Second line management of a T2*<10ms with reduced LVEF should be Deferiprone tid at 100mg/kg/d with or without intermittent Deferoxamine, especially in the presence of significant liver iron overload[238, 247]
- For patients with a low T2* and normal LVEF Deferiprone and Deferasirox have both been shown to be effective.
- Combination of Deferoxamine and Deferasirox for severe myocardial iron is limited but efficacious for those with normal LVEF.[263]
- There is insufficient data at present to recommend combination therapy with Deferasirox and Deferiprone for cardiac iron overload.
- Intermittent Deferoxamine should not be used as chelation monotherapy in patients with significant cardiac iron overload.[234]
- At present, use of Calcium Channel Antagonists as an adjuvant to chelation is experimental and should be limited to clinical trials.[266]

Pulmonary Hypertension (PHT)

- Markers of platelet and endothelial activation as well as hemolysis and splenectomy status have been associated with pulmonary hypertension (PHT) in non-transfused thalassemia patients. The prevalence of PHT (overall ~2% - 33% depending on diagnostic criteria) in TDT and deletional HbH disease is very low compared to NTDT.[267-276] ECHO has a high positive predictive value when TRJV>3.2.
- Chronic blood transfusion was found in one study to reduce ECHO – defined pressures and improve six minute walk test in a group of Hb/Ebeta thal patients.[277]
- The OPTIMAL study showed benefit of Hydroxyurea or transfusion in reducing risk of PHT.[278]
- At the current time there is insufficient evidence to support the use of sildenafil for improving TRJV in thalassemia syndromes. A pilot study demonstrated safety but with no improvement in 6MW.[279]
- There is limited data to suggest possible benefit from L-carnitine in reducing TRJV.[280]

2. Liver Complications

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.

Recommendation

- 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.,[288,298]
- 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.

Background

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

Interventions

- HFE mutation may contribute to the degree of liver iron overload in thalassemia syndromes[281].
- Liver enzymes including ALT, and bilirubin should be routinely monitored every 3 months and any abnormalities investigated[282].
- Various MRI protocols are available for liver iron quantification. The hematologist should be familiar with their institution's protocol and its limitations, and ensures it is validated[283-285]. All patients should have regular objective assessment of liver iron load by MRI. 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 the normal range to avoid liver damage, fibrosis and cirrhosis.
- A target LIC of 5mg/gDW has been suggested for NTDT patients requiring chelation[286].
- Serum ferritin often dramatically underestimates LIC in NTDT[287].
- Fibroelastography has been used in a few studies for assessment of iron related liver damage in thalassemia. However a lack of validated reference range for this indication prevents widespread uptake[288-291].
- Serum hyaluronic acid (HA) has been investigated as a non-invasive marker of liver fibrosis in TM[292].
- 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.
- Deferiprone has been shown to to be safe in regards to the liver with no progression of fibrosis[296].

- Splenectomy may contribute to the speed of iron loading in the liver[297].
- There is preliminary data to suggest Deferasirox has benefits on liver fibrosis beyond a chelating effect[166].
- Due to better overall care of thalassemia and iron overload, HCV is becoming a more common cause of morbidity and mortality, particularly in areas with high HCV prevalence[309,310].
- The magnitude of effect of HCV infection and iron on liver fibrosis and progression is controversial[298-301].
- Traditional HCV therapy used PEG IFN alone or with Ribavarin[302-307].
- Active HCV may downregulate hepcidin, contributing to increased liver iron deposition[294].
- Ribavarin therapy for HCV does not increase liver iron as much as would be expected from the increased transfusion requirements[294]. It is hypthesised that chelation is more effective when the virus is less active.
- Deferiprone should be avoided, if possible, with concomitant IFN therapy due to increased risk of significant neutropenia[295].
- Where genotype (and SNPs) permits[311,312], novel HCV therapies should be used in preference to IFN and Ribavarin treatment due to higher rates of SVR and minimal side effect profile.
- Patients with end stage liver disease and cirrhosis should be followed by a hepatologist[313].
- Patients with cirrhosis should be followed for the development of hepatocellular carcinoma with six-monthly albumin, INR, PTT and liver ultrasound[314,315].
- 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.
- Management of HCC should be by a comprehensive tumour board with options including radiofrequency ablation and surgery as well as liver transplantation[316].

3. Endocrine Complications

Principles

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

Recommendation

- Each specialist centre should collaborate with a pediatric or an adult endocrinologist with knowledge of endocrine complications in thalassemia.[325]
- 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, hypogonadotrophic hypogonadism, and growth hormone deficiency.[8,9,11,18] Abnormalities should be identified early and treatment initiated in consultation with an endocrinologist.
- There may be a role in the future for MRI pituitary assessment.[326]

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 the anterior pituitary and endocrine glands.[317,318] Over half of patients have evidence of an endocrinopathy with more than a third having multiple, though prevalence varies by geographic region and chelation history.[319,320] The prevalence of endocrine disorders is lower in Non-Transfusion Dependent Thalassemia, though oxidate stress still contributes.[321,322] Bone marrow transplantation cannot fully restore endocrine function, and depending on conditioning regimen and transplant complications may worsen them.[324]

Interventions

Short Stature

All children should be assessed for short stature with standing and sitting height measurements every 6 months.[343,344]
Ethnic appropriate growth charts should be used, where available.
Endocrine evaluation should be initiated if there is a fall-off on growth curves, decreased height velocity, or delayed bone age.[345]

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.[327,328,344]

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 (topical or parenteral[329]), and subsequent follow-up by an endocrinologist.[329,350-354]

Adults should be routinely assessed for secondary hypogonadism, impotence, or infertility. Patients with cardiac iron deposition are at greater risk of HH (188). Pituitary MRI, may in the future have a role for risk stratification of hypogonadism.[331]

Correction of hypogonadism is not as beneficial to bone disease in thalassemia as in other causes of premature gonadal failure.[332]

There may be a role for supplementation with L-carnitine on supporting pubertal development.[333]

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.

Serum ferritin is a marker of risk for hypothyroidism.[334] Central hypothyroidism is an uncommon cause of hypothyroidism n TM.[335]

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. Ncoturnal calcium and PTH levels may assist in making the diagnosis.[336] Hypoparathyroidism should be managed as per endocrine standards.[336]

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.[337-339]
There is a correlation between diabetes and age, serum ALT, HCV status, and ferritin, and cardiac iron deposition. There has not been shown to be a direct relationship between diabetes risk and pancreatic iron.[330,337,338]
A fasting plasma glucose test should be done regularly starting at puberty.[337]
An oral glucose tolerance test can detect early impairment of glucose metabolism .

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.

Fructosamine is often preferred to HbA1c for monitoring of glycemic control in Thalassemia, though there is moderate correlation between the two measurements.[339]

Improvement of iron load with adequate combination chelation therapy may decrease insulin resistance and decrease glucose intolerance.[346,348,349]
Patients with diabetes are at higher risk of cardiac complications and should be monitored more closely in consultation with a cardiologist.[254]

Adrenal Insufficiency

Adrenal insufficiency has not been frequently reported in thalassemia patients.[340,341]If symptoms are reported, it can be screened for using morning cortisol and the cortisol responses following ACTH stimulation.[342]

4. Bone Complications

Principles

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

Recommendation

- All Thalassemia centres should have a pediatric and an adult endocrinologist with expertise in management of thalassemia bone complication.
- All children with thalassemia should have routine monitoring of height, weight, growth velocity and assessment of setting to standing height at each visit.
- All children needs close monitoring for bony complications resulting from under transfusion and iron chelation toxicity.
- Transfusion therapy needs to be started early in childhood to prevent bone marrow expansion resulting in irreversible bony deformities.
- All bony changes needs to be managed with adequate transfusion or monitoring of iron chelation dose depending on the underlying etiology.
- All adult thalassemia patient s should be encouraged to quit smoking to improve bony health.
- Vitamin D level needs to be optimized in all patients with Thalassemia.
- Routine monitoring of zinc and other trace elements is advisable with possible replacement if deficient.
- All patient should be encouraged to participate in regular weight-bearing low impact sport activity.
- All patients should have routine monitoring of bony health by a DEXA scan.
- If low bone density is detected, all patients needs to be referred to an endocrinologist for managment.

Background

Bone disorders are common and multifactorial in patients with thalassemia and may be related to inadequate transfusion, iron overload, adverse effects of chelation with Deferoxamine or Deferiprone, nephrolithiasis, and other endocrine disorders.[100,101] These factors contribute to the development of low bone mineral density (BMD), which is seen in >50% of adult patients, and is more common at the spine than hip. The pathophysiology of low bone density differs between thalassemia major (high bone turnover) and intermedia (low bone turnover). Bone pain and fracture has been reported in up to 1/3rd of patients[356]. Low BMD has also been associated with cardiac iron overload. Bone disorders may additionally present as skeletal deformities, growth retardation, arthropathies, disc degeneration, fractures, or back pain.

Interventions

- Every specialist centre should have access to an endocrinologist 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 on ethnic- appropriate standardised growth charts.
- All patients should be closely monitored for bone changes and deformities associated with under-transfusion and chelator-related toxicity.[382]
- Transfusion therapy should be started early in children to prevent the bone changes and deformities associated with bone marrow expansion.[378, 379,380,381]
- Bone expansion should be managed by adjustment of transfusion regimen to further suppress endogenous erythropoiesis.[379, 381-383]
- 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.[389]

- Use of Deferoxamine under the age of 6 years and at high doses (> 50 mg/kg/day) should be avoided to limit its effect on bones (dysplastic changes in the spine and long bones, and growth retardation) [382,383]
- All patients prescribed Deferiprone should be assessed clinically for arthralgias and arthropathy
- Deferiprone arthropathy may be managed with dose reduction or cessation and NSAIDs
- Bone mineral density of the hip and spine should be measured using dual energy x-ray absorptiometry (DEXA) and commence at 12 years of age.[357, 384-388]
- Neither the WHO Fracture Risk Assessment tool or Canadian Association of Radiologists and Osteoporosis Canada tool are validated in young Thalassemia patients.[358]
- Quantitative ultrasound or CT should not be used as an alternative to DEXA scan in assessment of thalassemia related bone densit.[359, 360]
- Frequency of repeat DEXA scan should be determined on a per patient basis in consultation with an endocrinologist.
- Patients reporting new or worsening back pain should be screened with x-ray for vertebral fractures.[361]
- Low BMD for age should be managed with 1200mg elemental calcium and 1000IU – 2000IU vitamin D, preferably from dietary sources, regular exercise to improve core stability and resistance training as well as weight bearing exercise, limitation of caffeine intake, and cessation of smoking.[362]
- Serum 25-hydroxyvitamin D should be measured after three to four months of adequate supplementation and should not be repeated if an optimal level (≥ 75 nmol/L) is achieved.
- Patients with low bone density despite optimisation of lifestyle and dietary factors should be referred to a specialist for consideration of drug therapy.
- Care should be taken to treat men and women equally when considering bone health.[363]
- Whole body vibration therapy may have a beneficial impact on bone density content, though adherence to therapy reduced over time.[364]
- Neridronate[365, 366] Pamidronate[367-370], Zolendronic Acid[371-374] and Alendronate[369,375] has been shown to improve BMD in thalassemia major patients and benefit may persist after stopping the drug.[388,390,391]
- Patients with thalassemia intermedia may respond less well to bisphosphonates.[376]
- Bisphosphonates should be avoided in women of child bearing potential due to possible effects on future fetal bone health.
- Hypogonadism contributes to short stature and low BMD.[384]
- Patients with hypogonadism should be referred to an endocrinologist and consideration given for hormone replacement therapy (HRT). However, HRT is not as effective in Thalassemia as in premature ovarian failure at normalising spinal DEXA score.
- All other endocrine abnormalities should also be sought for and corrected since they are contributory factors.

5. Renal Complications

Principles

- To prevent renal complications associated with thalassemia both transfusion and non-transfusion dependent thalassemias.
- To provide effective monitoring and treatment for patients with evidence of renal disease.
- To provide effective monitoring of renal function for patients on iron chelation

Recommendation

- Renal abnormalities, both tubular and glomerular, are frequent in patients with TDT and NTD.
- Contributing factors likely include chronic anemia and hypoxemia, iron overload, and iron chelators.
- Serum creatinine needs to be checked monthly to every 3 months according to iron chelator and baseline creatinine.
- Proteinuria needs to be monitored on regular basis.
- Refer to a nephrologist with expertise in the thalassemia management need to be considered when appropriate.

Background

Advances in the management of thalassemia patients have improved morbidity and mortality. Previously under-recognized end organ complications are becoming more apparent. Emerging data have demonstrated that renal abnormalities, both tubular and glomerular, are common in patients with both transfusion dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT).

Low-molecular weight proteinuria is nearly universal in patients with TDT.[392-394] Other tubular abnormalities described include increased urinary excretion of N-acetyl-β-D-glucosamide (NAG) and/ or β2-microglobulin (indicators of proximal tubular damage), calcium, phosphate, magnesium, uric acid, amino acids, and malondialdehyde.[392-402] In addition to tubular changes, glomerular abnormalities have also been reported ranging from hyperfiltration, overt proteinuria, to long-term decrease in glomerular filtration rate. [394,395,397, 401-407]

Diverse mechanisms are thought to contribute to renal dysfunction although these need to be further elucidated. These factors include chronic hypoxia and anemia, iron overload, and medication effect from iron chelators.[407] In vitro and animal studies have suggested that tubular and endothelial cells are susceptible to apoptosis under hypoxic stress with resulting tubular dysfunction and interstitial fibrosis. [409-414] In comparison, anemia appears to contribute to glomerular dysfunction by altering renal vascular flow and inducing renal hyperperfusion and glomerular hyperfiltration.[400, 406,415] In the longer-term this may result in progressive renal damage. Quinn et al also speculated on the role of hemolysis through the release of free heme and resulting decreased nitric oxide bioavailability on renal dysfunction as opposed to chronic anemia alone.[406] Supporting this hypothesis is the effect of free heme on renal injury.[416]

Various studies support the nephrotoxicity of iron. An animal model demonstrated iron deposition in the glomeruli, proximal tubules and interstation with associated proteinuria. [417] Similarly, there appears to be a correlation between increased serum ferritin and the urinary excretion of N-acetyl-β-D-glucosaminidase and β2-microglobulin, markers of proximal tubule damage.[397, 418] With adequate iron chelation, there was reversal in the observed tubular defects. [399, 418] In another study, a decreased MR T2* value was the only independent predictor of nephropathy.[404] The mechanism proposed for this iron toxicity to kidneys is similar to that seen in other target organs: 1) production of reactive oxygen species 2) lipid peroxidation and mitochondrial stress resulting in cell injury and death 3) release of cytokines and growth factors 4) fibrosis and sclerosis.[392, 419, 420]

Acute renal injury and even failure requiring dialysis have been demonstrated in a few patients receiving

deferoxamine.[421-425] Fortunately, the kidney injury was reversible in these patients. Significant renal dysfunction has also been described in some patients with bone marrow failure taking deferasirox.[426-430] In TDT patients; an increase in creatinine from baseline has been seen in patients receiving deferasirox or deferoxamine with some requiring dose modifications for normalization of their creatinine whereas others resolved spontaneously without intervention. [405,431] The prospective EPIC study which monitored patients for up to five years did not show any progressive increase in serum creatinine.[432, 433] It remains unclear how iron chelators affect the kidney. It has been suggested that over-chelation and relative iron depletion may be implicated in the renal changes observed during chelation therapy perhaps by affecting energy metabolism and/or altering prostaglandin production impacting renal hemodynamics.[392, 408]

Interventions

- There is a paucity of data in terms of kidney-specific management. One might infer from the proposed pathophysiology that renal injury may be reduced by simultaneously 1) minimizing hypoxia and anemia by regularly transfusing TDT patients 2) preventing iron overload through adequate chelation therapy 3) while avoiding over-chelation. Various other measures have been suggested but are lacking clinical data in thalassemia patients: prolyl hydroxylase inhibitors, renin angiotensin system blockage, antioxidants such as vitamin E and acetylcysteine, VEGF, arginine.[408] Additionally, one study has suggested that renal tubule function may improve in beta-thalassemia patients after hematopoietic stem cell transplant.[434]

- Baseline screening:

    - Serum creatinine levels should be assessed before initiating iron chelation therapy

- Monitoring:

    - Serum creatinine monthly deferasirox, q3 months deferoxamine
    - Patients who with additional renal risk factors should be monitored weekly during the first month after initiation or modification of deferasirox therapy, and monitored monthly thereafter. Consider GFR measurement
    - Monitor regularly for proteinuria. Fluctuations are expected; however, upward trend in the protein/creatinine, interruption or dose reduction should be considered.
    - Other causes of increasing creatinine should also be considered, example concomitant nephrotoxic medication, renal stones, etc.

- Iron chelation adjustment

    - Refer to iron chelation chapter

6. Thromboembolic Disease

Principles

- Patients with thalassemia have a hypercoagulable state.
- Patients with thalassemia should have individualized risk assessments to determine whether a thrombosis risk reduction strategy should be employed.

Recommendation

- Patients should have an individualized risk assessment for thrombosis. Known risk factors for thrombosis include: splenectomy, age >35, NTDT, transfusion naivety, elevated platelet count, elevated nRBC count, pulmonary hypertension, pregnancy, as well as conventional cardiovascular risk factors.
- Patients who develop thrombosis should be treated according to national standards of practice.
- There is no evidence to support routine thromboprophylaxis in all patients.
- Consider low dose aspirin as primary prophylaxis in splenctomized patients with high platelet counts.
- Consider VTE prophylaxis for 2-4 weeks post splenectomy.

Background

Beta thalassemia is characterized by a hypercoagulable state and an increased risk of thrombosis. The mechanisms contributing include platelet activation, alteration of red cell membranes, adhesion molecules on endothelial cells, and of the hemostatic factors. The risk is significantly higher in NTDT than TDT. There is also an increased risk of arterial thromboses, namely cerebral infarcts. VTE risk is reduced by regular blood transfusions, and increased by splenectomy. (13 Similar risk factors are associated with ECHO-defined pulmonary hypertension.

Thrombotic complications in thalassemia patient are well known, however, there is still a paucity of robust clinical evidence to derive evidence-based recommendations[435]. Overall the rates of thrombotic complications are higher in NTDT than in TDT. In a pediatric study the thrombosis rate was 4% for TDT and 9.6% for TDT[436]. In the OPTIMAL CARE study, a large study of over 8000 patients, thrombosis occurred 4.38 times more frequently in NTDT patients compared to TDT patients[435]. This study found that age >20, splenectomy, family history of thrombosis, and prior thrombosis were risk for thrombotic complications in TDT patients. Further patients on aspirin had lower rates of recurrent thrombosis. The majority of thrombotic complications in NTDT patients are venous, including deep vein thrombosis, pulmonary embolism, and portal vein thrombosis[437], while a history of transfusions and a hemoglobin > 90 g/L were protective against thrombosis.

There are higher rates of cerebral vascular events in TDT and NTDT patients, with overt stroke in one study reported at 28% of NTDT and 9% of TDT patients[436]. Recent data demonstrate high rates of silent infarcts on MRI are evident on a large percentage of NTDT patients. The risk factors associated with stroke in NTDT are still unclear.

Intervention

- Splenectomy significantly increases the risk of thrombosis, and careful risk to benefit analysis should be done prior to recommending splenectomy[435].
- Post splenectomy patients with elevated platelet counts should be considered for primary thrombosis prophylaxis with low dose aspirin.
- Patients should have an individualized risk assessment of thrombosis.
    - High risk factors for thrombosis include: NTDT, high number of circulating nRBCs, age >35, a

ferritin > 1000 mcg/L, pulmonary hypertension and splenectomy[435]

- Protective risk factors against thrombosis include: chronic transfusion therapy, maintaining a Hb > 90 g/L

- Transfusion therapy should be considered in NTDT patients that develop thrombosis, or in patients at high risk for developing thrombosis.
- Patients with TDT and NTDT should be considered at high risk for thrombosis when hospitalized or undergoing surgery, and should have appropriate thromboprophylaxis[437].
- Pregnant and post-partum patients with TDT and NTDT are at higher risk of thrombosis espically splectonomized patients, and should be given appropriate thromboprophylaxis.
- There is no role for inherited thrombophilia screening in thalassemia patients.
- For patients with indwelling central venous catheters the risk of catheter associated thrombosis is low, and there is no evidence to support routine thromboprophylaxis[440].
- For adults with thalassemia classical cardiovascular risk factors (atrial fibrillation, hypertension, diabetes, hyperlipidemia) should be routinely screened for and treated according to national guidelines[439].
- Patients who develop VTE or ATE should be treated according to the current standards of practice[437].
- There is currently insufficient evidence to support the use of hydroxyurea or chelation for the prevention of thrombosis.

7. Fertility and Pregnancy

Principles

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

Recommendation

- 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]
- 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.

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 is vital to improved outcomes for mother and child[441, 442, 455, 456, 457]

Intervention

- 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. Successful pregnancy and fertility are feasible in patients utilising an array of artificial reproductive techniques, more so with females than males[443, 444].

Pre-pregnancy Assessment

- It is possible to undertake HLA typing of IVF embryos to establish a pregnancy that is HLA compatible with an affected sibling with Thalassemia who requires stem cell transplantation[445].
- Fetal genotyping of paternal mutations in maternal plasma from pregnancies at risk of beta-thalassemia can be an option for genetic screening in high risk partners[446].
- There are various blood markers that are altered in HbBarts affected pregnancies, including inhibin-A and PlGF[447,448].

- 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[458].
- Several medication changes may need to be made including initiation of folic acid supplements, stopping possible teratogens such as chelation, 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. There are a number of case reports of continued oral chelaton in pregnancy, but this is not recommended due to known teratogenic potential of the drug class[449-452].

During Pregnancy

- The patient should be closely followed by the high-risk obstetrician and hematologist through the specialist centre. Cardiac function should be monitored closely and referral to cardiologist needs to take place if patients is at a risk of cardiac complication during pregnancy. Transfusion requirements will likely increase. Serial ultrasounds should be done to monitor for fetal anomalies or growth restriction.
- Significant adverse pregnancy outcomes have been described in HbH disease even when the Hb is maintained >70[452,453].
- MRI to asses iron overload could be performed safely during pregnancy if needed.

Mode of Delivery

- There is a high incidence of delivery by Caesarian-section primarily due to cephalopelvic disproportion[458]. Risks of vaginal and Cesarean-section delivery should be discussed with consideration of other medical issues including cardiac dysfunction.
- Vaginal delivery needs to be encouraged since there is lower risk of cephalopelvic disproportion given adequate transfusion and blood product avaliability

Post-delivery

- The mother should be encouraged to restart chelation with deferoxamine 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. Post-partum VTE prophylaxis is recommended in NTDT patinets, particularly when splenectomised[454].

8. Non-Hepatitis Infections, Nutrition and Dentition

Principles

- To screen for and treat non-hepatitis infections in patients with TDT
- To screen for and manage nutritional deficiencies in patients with TDT
- To recognize patients with TDT may require for dental and orthodontic interventions

Recommendation

- Physicians should be aware that patients with TDT or iron overload are at higher risk for certain infections as compared to the general population.
- Patients with TDT should be regularly assessed for nutritional deficiencies by a multi-disciplinary team, ideally including an assessment by a dietician.
- Patients with TDT may have facial bone deformities, and should be offered dental and orthodontic consultation to improve and maintain functional dentition.

Background

I. Infections

Patients with TDT have increased susceptibility to infections for multiple reasons. There are reported decreases in both innate and adaptive immunity in thalassemia patients[459]. Further many patients with TDT have undergone splenectomy, increasing their risk of infection from encapsulated organisms (S. pneumoniae, H. influenzae, and N. meningitides). Additionally, certain bacterial organisms, Yersinia enterocolitica, Klebsiella species, E. coli, S. pneumoniae, Pseudomonas, Listeria, and Legionella) are more virulent in the presence of excess iron[460]. Parvo B19 can cause transient marrow aplasia, and may result in increased transfusion requirements for patients with TDT[463]. Parvo B19 is typically transmitted through respiratory transmission, however, it can be transmitted through blood products. Pregnant patients with thalassemia are at increased risk of CMV and varicella infections. Patients should be aware that there may be emerging pathogens in the future may be discovered to be transmitted through blood products.

II. Nutrition

Patients with TDT are known to have inadequate nutritional intake of many vitamins and nutrients. Studies have shown inadequate levels of fat soluble vitamins including A, D, E and K, as well as low levels of folate, B6, thiamine, calcium, magnesium and zinc[465]. The deficiencies in calcium, magnesium, vitamin D, zinc, vitamin K have been associated with decreased bone health. There is emerging evidence of amino acid deficiencies (glutamine and arginine) secondary to chronic hemolysis may exist in patients with TDT[466]. The role of essential amino acid supplementation is currently unclear.

III. Dentition

Patients with TDT who are not transfused, under-transfused, or initiate transfusions later in life may have craniofacial bone malformations which can affect dentition and cause malocclusion[462].

Infections

- Physicians should know that TDT patients are at risk for infections, specifically parvovirus B19, Yersinia enterocolitica and Klebsiella.
- Patients undergoing splenectomy should have the appropriate vaccines, as per the National Advisory Committee on Immunization, prior to splenectomy.
- Splenectomized patients should have appropriate fever counseling.
- Patients with TDT should have annual screening for blood borne pathogens.
- Patients should be aware there may be emerging pathogens in the future that are currently not known.
- Patients who develop parvo B19 may require a transient increase in transfusion support.

Nutrition

- Physicians should recognize patients with TDT are at high risk for nutritional deficiencies, and regular nutritional assessments should be done by a multidisciplinary team, ideally including a dietician assessment.
- Patients with TDT should be treated for any deficiencies with appropriate nutritional supplements, including nutrients key to bone health such as calcium, magnesium, zinc, vitamin D and vitamin K[464].

Dentition

- Patients with TDT should be transfused to minimize bone malformations.
- Patients with TDT should be referred for re regular dental assessments and orthodontic assessments when required.

System	Investigation	Age to Start	Frequency
Iron Load	1. Serum Ferritin 2. Liver MRI 3. Cardiac MRI	• Pre-Transfusion	1. q 3 months 2. q 6-24 months 3. q 6-24 months
Chelation associated	Refer to table 5 for chelator specific side effects and monitoring		
Liver Function	Liver enzymes	• Pre-Transfusion	q 3 months
Cardiac Function	1. Physical Examination 2. Echo, MUGA scan or T2*MRI Holter PRN	• At diagnosis	1. q 6 months 2. Annually
Endocrine Function	1. Growth chart, sitting and standing height 2. Hypogonagism (Puberty staging) 3. Hypothyrodism (TSH) 4. Hpoparathyrodism (Ca, PO4, PTH) 5. Diabetes (OGTT, Fructosamine if available)	• At diagnosis • 10 years • 10 years • 10 years • 10 years	1. q 6 months until reached final growth? 2. Annually until complete puberty 3. Annually 4. Annually 5. Annually
Bone	Ostepenia/Osteoporosis (DEXA scan)	• 10 years	1. q 3-5 years
Infections	1. Hepatitis B sAg, sAb 2. Hepatitis C serology 3. HIV serology	• Pre-Transfusion	1. q 2-3 years

*unless ferritin is low, serum ferritin monitoring is indicated every month

Table 6: Recommended Monitoring for Complications of β Thalassemia

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PART IV

Non-transfusion Dependent Thalassemia

Part IV
NON-TRANSFUSION DEPENDENT THALASSEMIA (NTDT)

Principles

- To diagnose NTDT at early stages of life and perform all necessary investigations.
- To be able to screen for complications and prevent them before development.
- To be able to treat complications including iron overload in patients with NTDT.
- To recognize patients with NTDT that needs blood transfusion or other disease specific therapies as Hydroxyurea.

Recommendation

A. Diagnosis

- NTDT should be suspected in patients with a chronic microcytic anemia, often in the range of 70-90 g/L, presenting with symptoms secondary to chronic hemolysis and/or ineffective erythropoiesis. Such patients include beta-thalassemia intermedia, Hemoglobin H disease and Hemoglobin E/Beta-thalassemia and rare forms of unstable hemoglobins.
- Laboratory diagnostic approach should include:
    - Red cell and hemolytic markers.
    - Hemoglobinopathy investigations (HPLC, electrophoresis).
- Confirmatory DNA analysis of alpha and or beta globin genes as appropriate for the suspected diagnosis.
    - Consider further DNA analysis in cases where alpha tri/or quadriplication is suspected to cause NTDT in the presence of a simple beta-thalassemia trait.

B. Complications

<u>Extramedullary hematopoiesis</u>

- Screening:
    - Clinical examination for organomegaly and bony deformities (ex. frontal bossing, zygomatic bone prominence, depression base of nose, shortening of long bones) at each clinic visit.
    - Screen for neurologic symptoms or back pain at regular clinic visits.
- Prevention:
    - There is insufficient evidence to recommend specific primary prevention strategies but treatment with hydroxyurea and red cell transfusions may be of benefit in select populations.
- Treatment:
    - Consider red blood cell transfusions, hydroxyurea, radiation therapy, and surgical decompression depending on severity.

Hypercoagulable state and thromboembolic events

- Screening:
    - Have a high index of suspicion for thromboembolic events.
- Prevention and Treatment:
    - Acute VTE management is generally in accordance with standard TE guidelines.
    - Further evidence is required to adequately provide recommendations regarding prophylactic anticoagulation or anti-platelet therapy as well as long-term management of patients with thrombotic or cerebrovascular disease.
    - Consider low-dose aspirin in splenectomized NTDT patients with platelets > 500 x 10^9/L.

Pulmonary Hypertension

- Screening:
    - Annual routine echographic assessment of TRV.
    - In asymptomatic patients with a TRV >3.2m/s or >2.5 m/s if they are symptomatic, confirmation by right heart catheterization.
    - If pulmonary hypertension is found, rule out other causes of pulmonary hypertension, particularly thromboembolic causes.
- Treatmet:
    - Further studies are required for providing adequate evidence for management of pulmonary hypertension in the context of NTDT but referral to a cardiologist/pulmonary hypertension specialist is recommended.
    - Consider hydroxyurea and/or transfusions. Selection of therapeutic strategy may depend upon the severity of the pulmonary hypertension, as well as physician and patient preference.

Leg ulcers

- Screening:
    - Inspection of the skin (particularly of the lower limbs) during each clinic visit.
- Prevention:
    - There is insufficient evidence to recommend specific primary prevention strategies.
    - Consider leg elevation and /or sleeping with the end of the bed elevated.
- Treatment:
    - Referral to dermatology or plastic surgery is suggested.
    - Further studies are required for adequate evidence in specific management of leg ulcers but treatment considerations include 1) local management with leg elevation, occlusive dressings, topical antibiotics, sodium nitrite cream, skin grafting, 2) systemic treatments such as red blood cell transfusions, hydroxyurea, arginine butyrate.

Iron overload

- Screening:
    - Initiate iron burden screening by imaging (ex. MRI T2*) by 10 years of age. One can consider delaying this to 15 years of age in patients with deletional HbH disease as they accumulate iron more slowly.
    - NTDT patients requiring frequent blood transfusions over a prolonged period of time should be screened according to TDT guidelines.
- Treatment:
    - Consider starting chelation treatment in NTDT patients ≥10 years of age with an LIC ≥ 5mg Fe/g dry weight. Start at half the usual starting dose in TDT (DT deferasirox 10mg/kg/day.)
    - Adjust dosing according to LIC and ferritin after 6 months.
    - Ongoing monitoring by imaging yearly and serum ferritin every 3 months.
    - Suggested parameters for discontinuation of therapy: LIC < 3mg Fe/g dry weight or (serum ferritin < 300 µg/L if LIC not available).

Low bone density and other bone diseases

- Follow recommendations outlined for osteoporosis in TDT
- Screening:
    - Monitor for changes in facial bone structure and head circumference.
    - Assess bone mineral density of the spine, hips, radius, and ulna by dual-energy X-ray absorptiometry (DXA) starting at age 10 years.
    - Screen for bone pain, particularly back pain and neurologic symptoms. If present, imaging is necessary to look for fractures.
    - Hormone and nutritional profile screening.
- Prevention:
    - Vitamin D and Calcium.
- Treatment:
    - If osteopenia or osteoporosis is present, referral to an endocrinologist for management (ex bisphosphonates).

Endocrinopathies

- Screening:
    - In children, growth parameter monitoring with particular attention to growth velocity, especially in young children and adolescents where it is expected to be at its highest.
    - In children ≥ 10 years of age, yearly Tanner staging. Puberty delay defined by lack of breast bud development in girls ≥ 13 years or no testicular enlargement in boys ≥ 14 years. If present, consider: gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone/estradiol, pelvic ultrasound, zinc level, thyroid-stimulating hormone (TSH) and T4.
    - Annual screening in patients≥10 years: free T4, thyroid-stimulating hormone, calcium, phosphate, vitamin D, and fasting blood glucose.

- Treatment:
    - Patients with diagnosed endocrinopathies should be managed by an endocrinologist and managed according to recommendations for TDT with regards to chelation therapy and hormone supplementation.
    - If presence of growth failure, consider initiating chronic transfusion therapy with weaning and or discontinuation as appropriate once catch up growth has been achieved.

Infections, hemolytic and aplastic crises

- Manage asplenic patients as per asplenia guidelines.
- During periods of infection, monitor closely for acute drops in hemoglobin that could indicate a hemolytic or aplastic crisis.
    - Hemolytic crisis: maintain Hb > 70-90 g/L, hydrate adequately and monitor renal function and electrolytes closely. Consider looking for bacterial (or parasitic) causes as appropriate.
    - Aplastic crisis: send parvovirus IgM to diagnose. Maintain Hb > 70 g/L.

Cholelithiases

- Screening:
    - Screen yearly by ultrasound for the presence of gallstones.
- Treatment:
    - Symptomatic cholelithiases should be managed with a cholecystectomy.

Liver disease

- Screening:
    - Liver enzymes/function tests should be monitored every 6 months in NTDT patients ≥10 years.
    - Consider measuring liver fibrosis by transient elastography in patients with an LIC ≥ 5mg Fe/g dry weight or serum ferritin ≥800ng/ml.
    - Albumin, INR and PTT monitoring in patients with cirrhosis or ≥ 40 years old.
- Prevention:
    - Adequate iron chelation therapy as described in iron overload section.
    - Immunizations for Hepatitis A and B prior to starting blood transfusion therapy as well as regular monitoring of Hepatitis B titers.
    - Annual serologic monitoring for Hepatitis B and C in transfused patients. Positive results should be confirmed by polymerase chain reaction and managed by sub-specialists as per institutional guidelines.
- Treatment:
    - Patients with evidence of hepatic disease should be referred to a hepatologist for further management.

NTDT-directed therapies

- All patients should receive folic acid supplementation.
- Red blood cell transfusions
    - Occasional transfusions should be considered in periods of (anticipated) acute stress or hemoglobin drop
        - Pregnancy
        - Surgery
        - Infections
    - Chronic transfusions: The goal of chronic transfusion is to improve anemia and decrease effects from ineffective erythropoiesis. Benefits must be balanced with long term complications including iron overload and red cell alloimmunisation. Patients should be considered for chronic blood transfusion if they develop:
        - Growth failure
        - Poor school performance / developmental concerns
        - Delayed puberty
        - Bone deformities
        - Patients with symptomatic anemia and secondary decreased quality of life / poor exercise tolerance
        - Rapid splenic enlargement (> 3cm/year) accompanied by drop in hemoglobin, particularly during periods of rapid growth
        - Primary prevention in high-risk patients as well as management and or secondary prevention of NTDT complications:
            - Pulmonary hypertension
            - Chronic leg ulceration
            - Thrombotic or cerebrovascular disease
            - Extramedullary hematopoietic pseudotumors
    - If chronic transfusions are initiated, monitor for red cell alloimmunization and manage the expected iron overload.

- Hydroxyurea
    - While there are no randomized clinical trials to provide strong evidence for use of hydroxyruea, observational studies have suggested some benefit in certain β NTDT subgroups and for management of NTDT complications (pulmonary hypertension, leg ulcers, extramedullary hematopoietic pseudotumors.)
        - Starting dose 10mg/kg/day, escalating to a maximum of 20mg/kg/day with concomitant folic acid supplementation.
        - Assess for response by 6 month and discontinue if no clinical benefit. In patients having responded, continue to monitor for sustained response.
        - Monitor for adverse effects: CBC+diff, renal function, liver enzymes.
        - Contraindicated in pregnant women as well as patients with hepatic or renal failure.

- Splenectomy
    - Routine splenectomies should not be performed but rather reserved for specific clinical situations such as:
        - Worsening anemia with poor growth/development and chronic transfusions or iron chelation therapy are not possible.
        - Hypersplenism with worsening cytopenias resulting in clinical problems, ex bleeding or infection.
        - Massive splenomegaly with risk of splenic rupture significant left upper quadrant pain or early satiety.

- Immunize pre-splenectomy and manage post-splenectomy as per asplenia guidelines.
- There is a lack of evidence to provide a recommendation on post-splenectomy thromboprophylaxis. Based on expert opinion, consider low-dose aspirin in splenectomized NTDT patients with platelets > 500 x 109/L.

Background

The term Non-Transfusion Dependent Thalassemia (NTDT) refers to a thalassemic spectrum of disease that is milder than transfusion-dependent thalassemia but more severe than trait. By definition, these patients do not require transfusions to sustain life; however, they may require transfusional support in certain clinical settings such as poor growth, excessive extramedullary hematopoiesis, and periods of acute stress or profound anemia (hemolytic crises, aplastic crises, pregnancy, infection, surgery). The baseline hemoglobin often lies between 70-90 g/dL.[1]

By referring to NTDT, we primarily include forms of:

- Beta Thalassemia Intermedia, where there is an excess of α-globin chains in relation to available β-globin chains
- Hemoglobin E/Beta thalassemia
- Hemoglobin H disease, where there is an excess of β-globin chains in relation to available α-globin chains[2]
- Rare forms of unstable hemoglobin.

The degree of severity of NTDTs is quite variable and is largely related to the underlying molecular defects, the presence of additional polymorphisms, and the resultant degree of chain imbalance[3]. Therefore, the specific genotype may provide some information; however, the diagnosis of NTDT is a clinical one and the genotype may not necessarily correlate with the phenotype. Despite its genotypic variability, all manifestations of NTDT are primarily due to ineffective erythropoiesis, hemolytic anemia, and iron overload.

1. Diseases

Beta Thalassemia Intermedia

Beta thalassemia intermedia describes a spectrum of disease in which there in an increase in the ratio of alpha globin to beta globin. Diverse genetic modifiers contribute to this ratio of alpha/beta globin resulting in the phenotypic variability of beta thalassemia intermedia. These genetic modifiers include :

- The degree of deficit in β-globin chain production. There are greater than 200 β- globin gene mutations described ranging in decreased to absent β-globin production. These may be present in the homozygous or compound heterozygous state. Larger deletions may affect other globin genes (ex. hereditary persistence of fetal hemoglobin (HPFH), δβ thalassemia, Hb Lepore.) There also exist rare dominant β-globin mutations. In addition, β-globin synthesis can be modulated by various transcription factors (ex. TFIIH, GATA-1.)[3,4]
- The presence of α gene deletions or duplications results in variations in the α- to β-globin chain imbalance (deletions improve the ratio of α- to β-globin whereas triplications and quadruplications worsen it.)
- Polymorphisms and mutations in genes modulating γ-globin production (ex. Xmn1-HBG2, HBS1L-MYB, and BCL11a) can alter the capacity for continued γ chain synthesis after birth. [3-5] Increased γ-globin chains reduces the imbalance of α to β-like globins.
- Excess α-globin chains, whether through decreased γ /β -globin and or increased α-globin production, precipitate as hemichromes forming inclusion bodies in early erythroid precursors as they are unable to form stable tetramers.[6] These inclusions damage the membranes of red blood cells and their organelles as well as trigger the formation of reactive oxygen species, which further damage the red blood cells.[7,8] This process of red blood cell injury leads to the intramedullary destruction of erythroid precursors and results in the ineffective erythropoiesis that is a hallmark of beta thalassemias. In comparison to transfusion dependent thalassemia (TDT) where there is little to no β globin, the residual β globin production as well as the variable γ-globin synthesis in NTDT moderate the consequences of the excess α-globin, which leads to the less severe phenotype of NTDT.

Hemoglobin E/ beta thalassemia

Hemoglobin E /beta thalassemia is present in high frequency in South East Asia and Bangkadesh, and accounts for approximately half of all severe beta thalassemia patients globally.[9,10] It is caused by compound heterozygosity for beta thalassemia and the hemoglobin variant HbE. HbE is the result of a single point mutation substituting G to A in codon 26 of the β-globin gene. This point mutation creates in an alternate mRNA splicing site, decreasing β-globin production. In addition, the resultant beta-globin binds more weakly to α-globin leading to instability in high oxidative states.[11] This thalassemia subgroup's disease severity can range from entirely transfusion independent to transfusion dependent and, like thalassemia intermedia, multiple other genetic factors will affect a patient's phenotype.

Hemoglobin H disease

Alpha thalassemia caused by deletion and or mutation of alpha globin genes (on chromosome 16p13.3) is the most common genetic disorder affecting up to 5% of the world's population.[12] When three of the four alpha globin genes are inactivated, unpaired beta globin chains form beta tetramers (hemoglobin H) in red cells, ultimately resulting in a chronic hemolytic anemia. This form of alpha thalassemia was first described in 1955 and is called Hemoglobin H disease (HbH disease).[13] This condition is most prevalent in Southern/Western China, Indochina, and South-East Asia; however, its prevalence has increased worldwide due to population migration. It is estimated that at least 10,000 babies are born every year with this condition.[10] A review of a Canadian cohort of HbH disease patients in Ontario showed that the majority of patients were of Chinese, Filipino, Laotian, and Vietnamese descent, with a minority of Mediterranean, Middle Eastern or East Indian descent.[14]

While HbH disease is generally thought to be one of the milder forms of NTDT, clinical severity can be heterogeneous but can largely be divided into the less severe "deletional" and more severe "non-deletional" forms.[15] The type and location of the alpha globin molecular defect(s) play into the disease severity modifying the α- to β-globin ratio and α-globin stability.[16]

- Deletional mutations: Deletional mutations are more frequent than non-deletional. They can occur in cis resulting in α^0 or no production of α-globin from one chromosome (ex. $--^{SEA}$, $--^{FIL}$, $--^{THAI}$, $--^{MED}$). Deletions can also affect a single α- globin gene on a chromosome leading to α^+ or reduced alpha globin production (ex. $-\alpha^{3.7}$, $-\alpha^{4.2}$.)
- Non-deletional mutations: There are >70 forms of non-deletional mutations (ex. Constant Spring (CS), Quong Sze, Pakse, and polyA.) The majority of these mutations involve the α2 gene which is located closest to the α-globin regulatory region and has the stronger gene expression resulting in 2-3:1 gene product production over α1.[16] Hence, an α2 mutation will have more significant impact on α-globin production.
- In the deletional type, the HbH amount is variable but is usually less than 30%. HbH is unstable and is oxidized to form intracellular inclusion bodies in older red blood cells causing oxidative damage, membrane dysfunction, and shortened red cell survival with premature destruction in the spleen resulting in moderate to severe hemolysis. Hemoglobin H has high oxygen affinity, lacks heme-heme interaction and has poor oxygen delivery capacity. Hence, patients are functionally more anemic than their hemoglobin may indicate.[17,18] In non-deletional types, the situation is made worse by the instability of the mRNA transcribed, which results in the production of hyper-unstable globin variants. They are unable to assemble in stable tetramers and thus rapidly degraded, further aggravating the globin chain imbalance resulting in increased hemolysis.[18] The oxidative damage and membrane dysfunction results in rigid overhydrated cells with a shortened red cell survival. The loss of phospholipid asymmetry with phosphatidylserine exposure increases the risk of thrombosis.[19]

Clinically, HbH disease manifests as microcytic anemia present from birth. Most individuals with deletional HbH disease remain relatively asymptomatic, and hence may not be diagnosed until later on in life. Some may be misdiagnosed and treated inappropriately for iron deficiency anemia. Their hemoglobin level after infancy is approximately 95g/L, MCH 16pg.[15] There may be mild pallor with no or minimal jaundice and usually mild splenomegaly from childhood. This condition is 1) most often compatible with a normal unrestricted physical life 2) rarely requires red blood cell transfusions 3) may result in the development of gallstones in adulthood 4) results in a slower rate of iron accumulation than other NTDT patients.[15,20]

In comparison, individuals with non-deletional HbH disease have a more severe hemolytic anemia with average hemoglobin

around 72g/L, MCH 18.6pg, and a higher reticulocyte count.[15] Other findings include mild to moderate pallor with jaundice as well as early onset splenomegaly, which can progress quite significantly later on in life., Growth delay, intermittent transfusion requirements particularly around infections, and iron overload in the first decade of life are additional fairly frequent features..[15] Rarely and in its most severe form, hydrops fetalis can result.

In summary, the heterogeneous clinical features of HbH disease, like NTD beta thalassemias, underscore the importance of early and accurate diagnosis with proper management.

2. Complications

The imbalance in the α and β chains in this spectrum of disease results in a number of complications, primarily as a result of ineffective erythropoiesis, hemolytic anemia, and iron overload. Various studies have suggested risk factors for morbidity to include increased age, lower hemoglobin, and prior splenectomy.[21-26] Transfusion support with adequate chelation and hydroxyurea use appears to reduce the frequency of NTDT-associated complications in patients who are on the more severe end of the spectrum.[21,26]

Extramedullary hematopoiesis

As a result of chronic hemolytic anemia and ineffective erythropoiesis, there is a physiologic response with erythroid hyperplasia leading to expansion of hematopoietic tissue. The expansion of hematopoietic tissue results in osteoporosis, bone deformities, and extramedullary hematopoiesis, which can manifest as hepatosplenomegaly and or hematopoietic pseudotumors .[27] Extramedullary hematopoiesis can arise in any tissue normally contributing to hematopoiesis in the developing fetus. While hematopoiesis normally ceases in these sites at birth, the vascular connective tissue retains the ability to be activated to produce red cells under conditions of chronic ineffective erythropoiesis. [28] Age, more severe ineffective erythropoiesis and anemia, as well as lower HbF levels are thought to increase the risk for developing this complication. [22,25,29] It is hypothesized that the chronic red cell therapy in TDT patients shuts down the erythropoietic drive, reflecting some of the differences in morbidity observed between NTDT and TDT patients.[1,26] Indeed hematopoietic pseudotumors arise in 20% of NTDT patients as opposed to <1% of adequately transfused TDT patients.[1,26]

One of the most concerning regions for hematopoietic pseudotumors is the paraspinal region as serious neurologic sequelae can result from spinal compression.[28] These account for 11-15% of extramedullary hematopoietic pseudotumors. [30,31] Management strategies for spinal pseudotumors as well as other areas of extramedullary hematopoiesis include red blood cell transfusions, hydroxyurea, radiation therapy, and surgical decompression depending on severity. [28,30-33]

Hypercoagulable state and thromboembolic events

Venous and arterial thromboembolic events are fairly common in patients with thalassemia.[23-25,34,35] The pathogenesis of hypercoagulality in thalassemia remains to be fully elucidated. However, contributing factors are thought to include oxidative stress, red cell membrane abnormalities, endothelial injury and dysfunction, as well as platelet activation and thrombin generation.[36-44]

The prevalence of thromboembolic events has been reported to range from 4 to 14 % in NTD thalassemia, with an approximately 2 to 4 fold increased risk as compared to TD thalassemia patients.[23,26,34,35] Identified risk factors include splenectomy, age > 35 years, serum ferritin > 1000 ng/ml, Hb level of < 90g/L.[23-26] In fact, in one study over a 10 year period, 29% of splenectomized NTD patients had developed a venous thrombotic event.[23]

In addition, while strokes are less common in NTDT patients as compared to TD patients [34], there is an increased risk for silent cerebral infarcts in NTDT patients. White matter lesions in otherwise asymptomatic individuals with NTDT have been reported in 16-60%, with a higher risk of these in older, transfusion naïve, and splenectomized patients. [45-49] Interestingly, the presences of arterial stenosis, particularly of the internal carotid[49], as well as increased velocities by transcranial Doppler (as compared to normal controls but below the conditional threshold defined in sickle cell disease) [50-51] have been

identified, although the significance of these findings is unclear.

Further evidence is required to adequately provide recommendations regarding prophylactic anticoagulation or anti-platelet therapy as well as long-term management of patients with thrombotic or cerebrovascular disease. Acute management is generally in accordance with standard VTE guidelines. Expert opinion suggests considering low-dose aspirin in splenectomized NTDT patients with platelets > 500 x 10^9/L.[52]

Pulmonary hypertension

Even though NTDT patients are not generally affected by severe cardiac hemosiderosis, multiple cardiac anomalies have been described in NTDT patients. These include congestive heart failure, pericarditis, pericardial changes, valvular defects, and most importantly for this group of patients, pulmonary hypertension.53

The precise pathophysiology of pulmonary hypertension in NTDT remains unclear and is likely multifactorial. Hemolysis with resulting endothelial dysfunction is likely a dominant contributing factor to pulmonary hypertension.[54,55] Additionally, hypercoagulability and thromboembolic disease may play a role in causing secondary pulmonary hypertension; however, further research is needed to clarify their role in NTDT patients.[56] The prevalence of pulmonary hypertension in beta NTDT has varied widely across studies, ranging between 11-59%. However, these findings are based largely on echocardiogram findings: a tricuspid-valve regurgitant jet velocity (TRV) > 2.5-2.8 m/s corresponding to a pulmonary arterial systolic pressure > 30-35 mm Hg, without confirmation by cardiac catheterization.[6, 57-59] In one study, the prevalence of pulmonary hypertension by cardiac catheterization in beta NTDT patients was 4.8%, up to 5 times more frequent than in patients with TDT.[60] Risk factors include age, prior splenectomy , hydroxyurea naïve, iron chelation naïve, transfusion naïve, prior TE event, increased WBC, higher number of transfusions, higher nRBCs, increased non transferrin bound iron (NTBI), and hypoxia.[56,59-62] While fewer studies have been performed in alpha thalassemia patients with regard to pulmonary hypertension, the prevalence of pulmonary hypertension is reported to be 4.7 to 7% by similar echographic criteria.[63,64]

Patients with NTDT should be screened annually for pulmonary hypertension by echocardiogram with measurement of the TRV. A TRV threshold of >3.2m/s has positive predictive value of 93.3%.[59] Therefore, asymptomatic patients with a TVR >3.2m/s or symptomatic patients with a TVR >2.5 m/s, should undergo right heart catheterization for confirmation of pulmonary hypertension. Patients with confirmed pulmonary hypertension should be referred to a cardiologist and treated according to pulmonary hypertension guidelines. For management of pulmonary hypertension in the context of NTDT, further studies are required to study the response to various therapies including hydroxyurea [65-67] and chronic transfusions.[68]

Leg ulcers

Leg ulcers are a more common and problematic issue in patients with NTDT than in those with TDT.[1,25,26] Factors thought to contribute to their development include friable tissues from chronic tissue hypoxia as well as hypercoagulability, abnormal red cell rheology, increased venous pressure, and perhaps non-transferrin bound iron injury. [16,23,26,69-71]

Managing ulcers is generally difficult and inspection for these at each clinic visit is recommended. Based on expert opinion, referral to dermatology or plastic surgery is suggested and treatment approaches can include leg elevation, topical antibiotics and occlusive dressings, sodium nitrite cream, chronic blood transfusions, hydroxyurea, skin grafting, arginine butyrate, platelet-derived wound healing factors.[16,52]

Iron overload

Iron overload is seen across the spectrum of NTDT subgroups [72]; however, it occurs more slowly in patients with deletional HbH disease.[15] Iron overload in NTDT is a consequence of ineffective erythropoiesis and anemia leading to inappropriately decreased hepcidin levels. Decreased hepcidin results in increased intestinal absorption of iron via ferroportin.[73-75] As a consequence, in these patients, the rate of iron absorption is approximately 2-4 times faster as compared to the normal population.[75,76] The distribution of iron deposition is different from TD thalassemia with preferential loading of iron in hepatocytes and slower loading in cardiac myocytes and endocrine cells in NTDT patients[75,77-80]. This may perhaps be

related to the higher episodic dose of iron during transfusions in TDT as opposed to slow but increased iron absorption from the gut in NTDT.

Iron overload in NTDT predisposes patients to liver complications such as liver fibrosis, cirrhosis, and hepatocellular carcinoma [75,81-83] as well as endocrinopathies. [25,70] Other complications linked with increased NTBI include thrombotic disease, pulmonary hypertension, cerebrovascular disease such as silent cerebral infarcts, as well as osteoporosis. [25,70,74]

In addition, unlike TDT, serum ferritin levels appear to correlate more poorly with iron burden as measured by liver biopsy liver iron content (LIC) or MRI assessment.[81] In NTDT, ferritin underestimates LIC. Moreover, ferritin was not effective in predicting the development of iron-related morbidities.[70] Therefore; iron overload assessment by imaging modalities is imperative to more accurately evaluate an NTDT patient's iron burden.

Treatment for iron overload in NTDT patients consists of iron chelation therapy with a few studies demonstrating improvement in the LIC and or serum ferritin. [84-94] Based on the period of onset of iron-related morbidities, monitoring and, when needed, treatment of iron overload should begin at the age of 10 years in NTDT patients .[25] However, there remain important gaps in existing literature, specifically with regards to the long-term safety and efficacy as well as the threshold at which to begin iron chelation therapy in these patients.

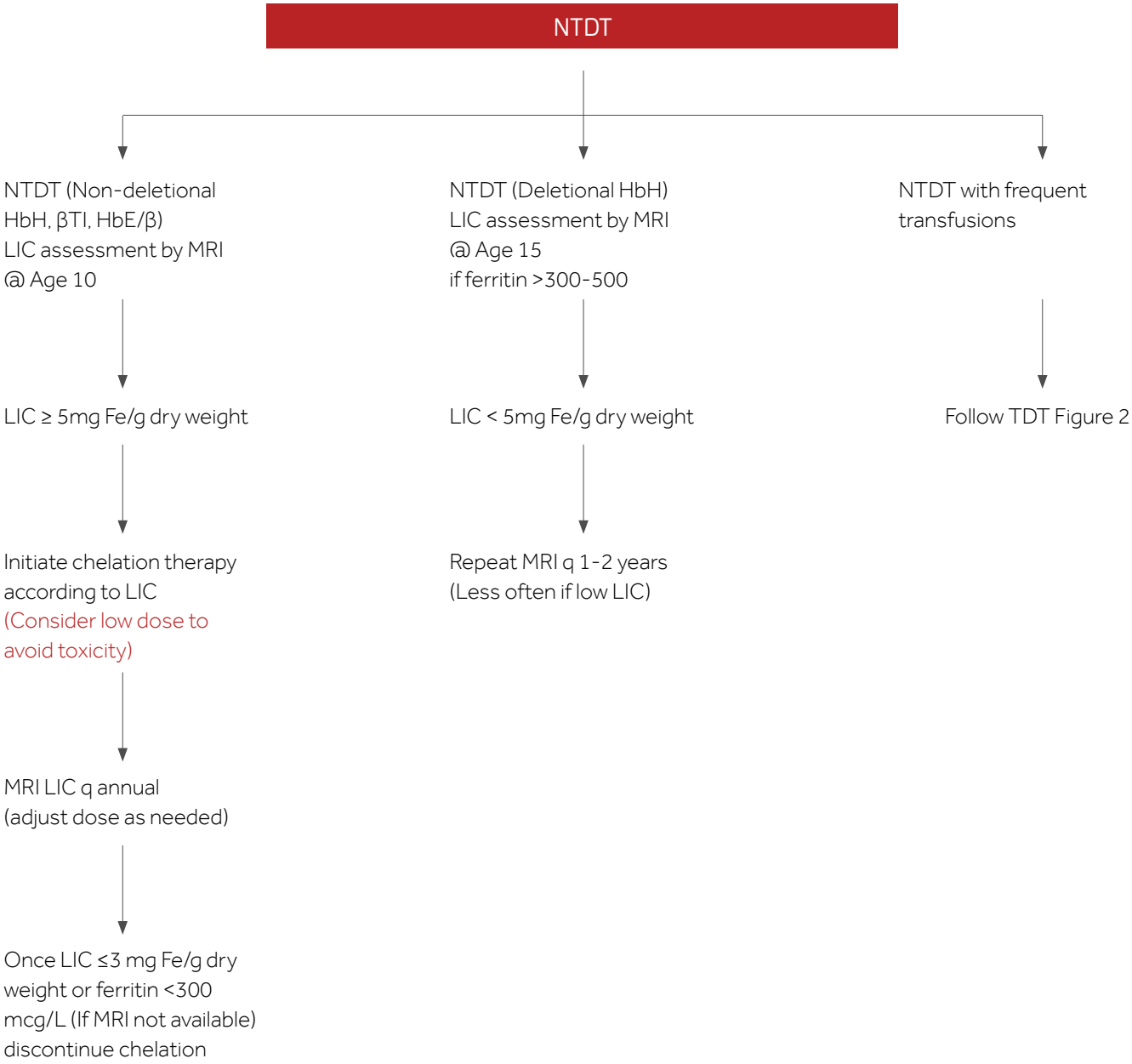

Figure 3: Iron Overload Assessment and Management in NTDT patients

Low bone density and other bone abnormalities

Bone abnormalities are a frequent complication in NTDT. Bony changes can include frontal bossing, prominence of the zygomatic bones, depression of the base of the nose, shortening of long bones, excessive thinning of cortices and dilatation of the medullary cavities. [16,95] These changes are a consequence of ineffective erythropoiesis and resulting bone marrow hyperplasia, which can expand up to 30 times the normal volume. [96]

This process also contributes in part to the development of osteopenia. Other contributing factors to bone disease in NTDT can include iron toxicity directly impacting bone metabolism and or causing endocrinopathies, vitamin D deficiency, and chelation therapy resulting in micronutrient deficiencies. [97-99] In fact, osteopenia and or osteoporosis are nearly universal and often present by age 10 in patients.[100,101] Pain and fractures are also common.102

Therefore, bone mineral density screening should be initiated by age 10. There are few studies on the prevention and management of bone disease in NTDT. The OPTIMAL care study found that osteoporosis was less frequent in patients receiving hydroxyurea and chelation therapy.[26] Vitamin D and calcium are frequently prescribed [15,101] although the efficacy of this supplementation has not been well studied. Therefore, supplementation should be based on general practice guidelines for vitamin D and calcium replacement. Bisphosphonates have been shown, in a small number of studies, to improve thalassemia patients' (NTDT and TDT) back pain symptoms, to increase their bone mineral density, and to be well-tolerated.[103,104]

Endocrinopathies

Endocrine complications, while less prevalent in NTDT than TDT patients, are still a frequent complication in NTDT patients.[1,15,97] While this difference in prevalence has not been fully studied, the differential rate, degree, and location of iron loading between the two are thought to play a role.[98] Indeed, endocrinopathies in NTDT, like TDT, have been mainly attributed to iron overload. [26, 70] Other contributing factors include splenectomy, severity of ineffective erythropoiesis, and lower HbF. [26, 29,105]

The endocrinopathies most frequently reported in NTDT patients are growth retardation, delayed puberty, hypogonadism, diabetes mellitus, dyslipidemia as well as thyroid, parathyroid, and adrenal dysfunction. [26,101, 106] Short stature is reported in 7-46% of NTDT patients [97, 107,108], although final height difference from mid-parental height was -0.72±1.23 standard deviations (SD) in one study.[97] Growth failure is likely multifactorial in etiology. Chronic anemia/hypoxia, increased metabolism, nutritional deficiencies, and iron overload resulting in growth hormone - insulin like growth factor axis dysregulation as well as hypogonadism are some of the potential factors impacting growth. [101]

Screening for endocrine disorders should include monitoring of growth parameters well as annual Tanner staging in children. Other suggested annual testing for NTDT patients ≥ 10 years includes: free T4, thyroid-stimulating hormone, calcium, phosphate, vitamin D, and fasting blood glucose.[52]

Patients with diagnosed endocrinopathies should be managed by an endocrinologist and managed according to TDT recommendations for chelation therapy and hormone supplementation. The presence of growth failure would be an indication to initiate chronic/frequent transfusion therapy with weaning and or discontinuation as appropriate once catch up growth has been achieved.[52]

Infections, Hemolytic and Aplastic Crises

Infection is a significant cause of morbidity and mortality in TDT patients. Patients with NTDT are also at increased risk of infection and secondary complications from these infections. Predisposing factors include anemia, iron overload, splenectomy, and immune abnormalities due to nitric oxide depletion, presence of plasma iron, as well as macrophage dysfunction due to iron. [109] In addition, many patients have undergone a splenectomy, increasing their risk for infection by encapsulated organisms. Infections in asplenic patients can be reduced through the use of immunizations to Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae, prophylactic antibiotics, as well as urgent fever management with intravenous antibiotics.

Patients with NTDT are also at risk for hemolytic and aplastic crises. This is particularly in true for patients with HbH disease and is generally worse for patients with non-deletional HbH due to the more rapid rate of hemolysis. Triggers for hemolytic crises include infection, pyrexia, oxidative challenge, hypersplenism, and pregnancy. The hemolytic crises can result in hemolysis as brisk as one might expect with glucose-6-phosphate dehydrogenase deficiency with risk for severe anemia as well as renal dysfunction.

Aplastic crises are a result of exposure to parvovirus B12. The virus targets red cells including erythroblasts, resulting in a halt in erythropoiesis. Most recover spontaneously but some patients require red blood transfusion(s) and or immunoglobulin therapy [12].

Cholelithiases

Similarly to other chronic hemolytic conditions, patients with NTDT are predisposed to forming cholelithiases due to increased production and excretion of bilirubin. Studies report a prevalence of 15.7 to 63%.[110-114] NTDT is occasionally co-inherited with Gilbert's syndrome, which further increases the risk for development of cholelithiases.[114]

Gallstones can be screened for by abdominal ultrasound. Symptomatic gallstones should be managed with a cholecystectomy.

Liver disease

Liver complications such as liver fibrosis, cirrhosis, and hepatocellular carcinoma have been described in patients with NTDT. [81-83] While viral hepatitis may contribute to liver disease in a subgroup of patients with NTDT who require transfusions [82,83], the majority of patients are at risk for liver disease due to chronic hepatocellular iron deposition. Based on extrapolations from other liver diseases such has hereditary hemochromatosis, iron is likely key in the development of liver fibrosis and cirrhosis and possibly carcinogenesis in NTDT patients.[115-118] Iron-related liver damage is supported by the correlation seen between higher serum ferritin levels in NTDT patients and higher transient elastography values measuring liver fibrosis as well as increased transaminases. [25,26,119] In addition, hepatocellular carcinoma has been described in some NTDT patients without viral hepatitis.[120, 121]

Based on expert opinion, liver function tests should be monitored every 3 months in NDTD patients ≥10 years as well as liver ultrasounds yearly in patients with an LIC ≥ 5mg Fe/g dry weight or serum ferritin ≥800ng/ml.52 For measuring liver fibrosis and cirrhosis, transient elastography has been demonstrated to be comparable to a liver biopsy with the advantage of being non invasive.[122] Patients with evidence of hepatic disease should be referred to a hepatologist for further management.

3. Treatment

Management of NTDT is complex and must take into consideration the screening and prevention of complications, as well as the treatment of established complications, as described in previous sections. The decision to initiate treatment in NTDT patients is often a difficult one to make given the wide array of clinical presentations and should be patient-specific. [1,2,6,10,11,14,15,19-21, 123-129].

NTDT treatment modalities include:

- Observation
- Blood transfusion
- Fetal Hemoglobin induction
- Splenectomy
- Erythropoietin (EPO) stimulating agents

Observation

Due to the wide clinical variability of NTDTs, a number of patients are simply mildly anemic, asymptomatic or minimally symptomatic, and may be brought to clinical attention only later in adult life.[29,105] It is imperative to screen regularly for potential complications and treat them accordingly. All patients should receive folic acid supplementation.

Blood transfusions

By definition, patients with NTDT do not need chronic red cell transfusions to sustain life, but periodic transfusions may be required in specific situations, such as surgery, pregnancy and aggravated anemia (acute hemolysis, viral-induced pure red cell aplasia, sepsis, etc.) In addition, chronic transfusions may be necessary in certain circumstances after weighing the risks and benefits. These can include but are not limited to growth failure, developmental concerns, extramedullary hematopoiesis (excessive splenomegaly, facial changes, paraspinal pseudotumors,), pulmonary hypertension, and poor quality of life. Hemoglobin level should not be the sole determining factor for implementing chronic transfusions.

More specifically, in the pediatric setting, patients with growth failure, as evidenced by inadequate growth velocity, should be started on chronic transfusion therapy[52]. Such patients are often identified early, sometimes requiring chronic transfusions as early as 2 years of age, and are closer on the spectrum of disease to TDT. They may also present with complications such as delayed puberty, developmental concerns, bone deformities, symptomatic anemia with decreased quality of life, and worsening splenomegaly.

Milder forms of NTDT can present with distinct challenges for which starting chronic transfusion should be considered: symptomatic extramedullary hematopoiesis, symptomatic anemia with decreased quality of life, pulmonary hypertension, bone deformities, and chronic leg ulceration. [68,130-133] The decision to start chronic transfusion therapy needs to be balanced with the risks of 1) chronic iron overload and need for iron chelation therapy 2) red cell alloimmunization. In spite of these risks, the prevention of NTDT complications linked to chronic anemia and hemolysis is desirable, and chronic transfusion therapy may be considered in certain patients even before these occur. [130]

Fetal Hemoglobin Induction

Hydroxyurea, known to induce hemoglobin F, is a common medication used in sickle cell disease as well as in certain myeloproliferative diseases. Its use has been reported in patients with beta thalassemia intermedia as well as Hemoglobin E/beta thalassemia. It is theorized that, by increasing γ globin production, there is a decrease in the α/β globin imbalance resulting in decreased ineffective erythropoiesis.[134] While there have not been any large randomized controlled trials comparing hydroxyurea use versus placebo or standard of care, hydroxyurea therapy has been associated with decreased blood transfusion requirements, total and fetal hemoglobin rise, decreased splenomegaly, decreased ferritin, as well improvement in some NTDT complications such as pulmonary hypertension and extramedullary hematopoietic pseudotumors.[26,32,65-67,114,134-153]. There appears to be an association between hematological response to hydroxyurea and certain genotypes and polymorphisms (MAP3K5, KLF10)[138-140]; however, there is however not enough evidence thus far to screen patients for certain polymorphisms prior to hydroxyurea use.

Hemoglobin F induction with hydroxyurea may be an attractive option when chronic transfusions are not desired and treatment for NTDT is warranted. In all trials, hematologic responses were seen at dosages from 8 to 20mg/kg/day.[134-153] Overall, hydroxyurea is well tolerated, particularly at the lower dose of 10mg/kg/day. In comparison, there was a higher risk of developing neutropenia in patients receiving 20mg/kg/day.[137] No additional side effects to hydroxyurea have been described in this particular population. Standard hydroxyurea monitoring and follow up is recommended in any patient receiving this medication.

Given the correlation between disease severity and HbF level as well as response to hydroxyurea for some patients, other HbF inducers are being examined and developed. These include butyrate derivatives, decitabine, as well as genetic therapeutic blockade with knockdown of γ globin gene repressors. [5,154-156] At this time, there are insufficient data to recommend the use of other hemoglobin F inducers in the NTDT population.

Splenectomy

Due to chronic hemolysis and ineffective erythropoiesis resulting in extramedullary hematopoiesis and chronic splenic congestion, patients with NTDT generally have splenomegaly, which at times may be massive. Historically, splenectomies were routinely performed in NTDT patients to increase their hemoglobin level and decrease symptoms attributed to chronic severe anemia; however, it should no longer be routinely performed, as it is associated with a number of potential adverse outcomes.[52]

In all patients, there is an increased risk for sepsis and thrombosis post splenectomy.[157-159] The risk of sespsis can be in part mitigated by pre-splenectomy immunization to S. pneumoniae, N. meningitidis, and H. influenzae as well as by following asplenia guidelines with regard to antibiotic prophylaxis and fever management. However, with regards to thrombosis risk, patients with NTDT are already hypercoagulable and have evidence of endothelial dysfunction. Not surprisingly, patients with NTDT who have undergone a splenectomy are at further increased risk for thrombosis, as compared to the general population and even other NTDT patients.[23,24,26,59,64] Careful prophylaxis must be employed in the peri-operative setting. It is unknown whether prolonged prophylaxis, and if so which therapeutic agent reverses those risks. Therefore, further evidence is required to adequately provide recommendations regarding prophylactic anticoagulation or anti-platelet therapy. Expert opinion suggests considering low-dose aspirin in splenectomized NTDT patients with platelets > 500 x 10^9/L.[52]

In addition, an increase in other NTDT complications have been reported post-splenectomy, including pulmonary hypertension as well as iron overload, ulcers, nephrolithiasis, and some endocrinopathies.[26,72,159-161]

Therefore, splenectomies should be reserved for patients with significant complications such as 1) worsening anemia with poor growth/development and chronic transfusions or iron chelation therapy are not possible/available 2) hypersplenism with worsening cytopenias resulting in clinical problems: bleeding, infection, severe anemia with lack of post-transfusion hemoglobin increment 3) massive splenomegaly with risk of splenic rupture, significant left upper quadrant pain, or early satiety. [52,162] Thus the decision to perform a splenectomy in NTDT patients must be carefully balanced between indications such as these and the potential risks described above.

Erythropoietin Stimulating Agents

The level of endogenous erythropoietin (EPO), has been reported to be low relative to the degree of anemia and hemolysis in NTDT. [163] In addition, EPO levels also tend to decrease with age.[164] Based on this premise, erythropoietic stimulating agents (ESAs) have been assessed in few studies. While some improvement in hemoglobin level was observed, there was concern for potentially worsening marrow expansion and which could result in symptomatic extramedullary disease.[165] Hence, hydroxyurea in combination with ESA may be a desirable option; however, such regimens cannot be routinely recommended at this time due to lack of published data confirming long-term benefit.[166]

Novel interventions

As the pathophysiology of NTDT is better understood, possible targets for interventions are being examined. These novel therapies aim to improve various aspects of NTDT including anemia, ineffective erythropoiesis, red cell deformities, HbF levels, and iron loading. Examples of these include activin receptor ligand traps, [167,168] HbF inducers,[154-156] altered iron metabolism with decreased TMPRSS6, [169,170] hepcidin,[171] transferrin,[172] as well as gene editing.[5,173] These interventions are at various stages of development ranging from animal to clinical trials and demonstrate the exciting advances in the field; however, at this time, there are insufficient data to recommend these therapies outside of clinical trials.

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