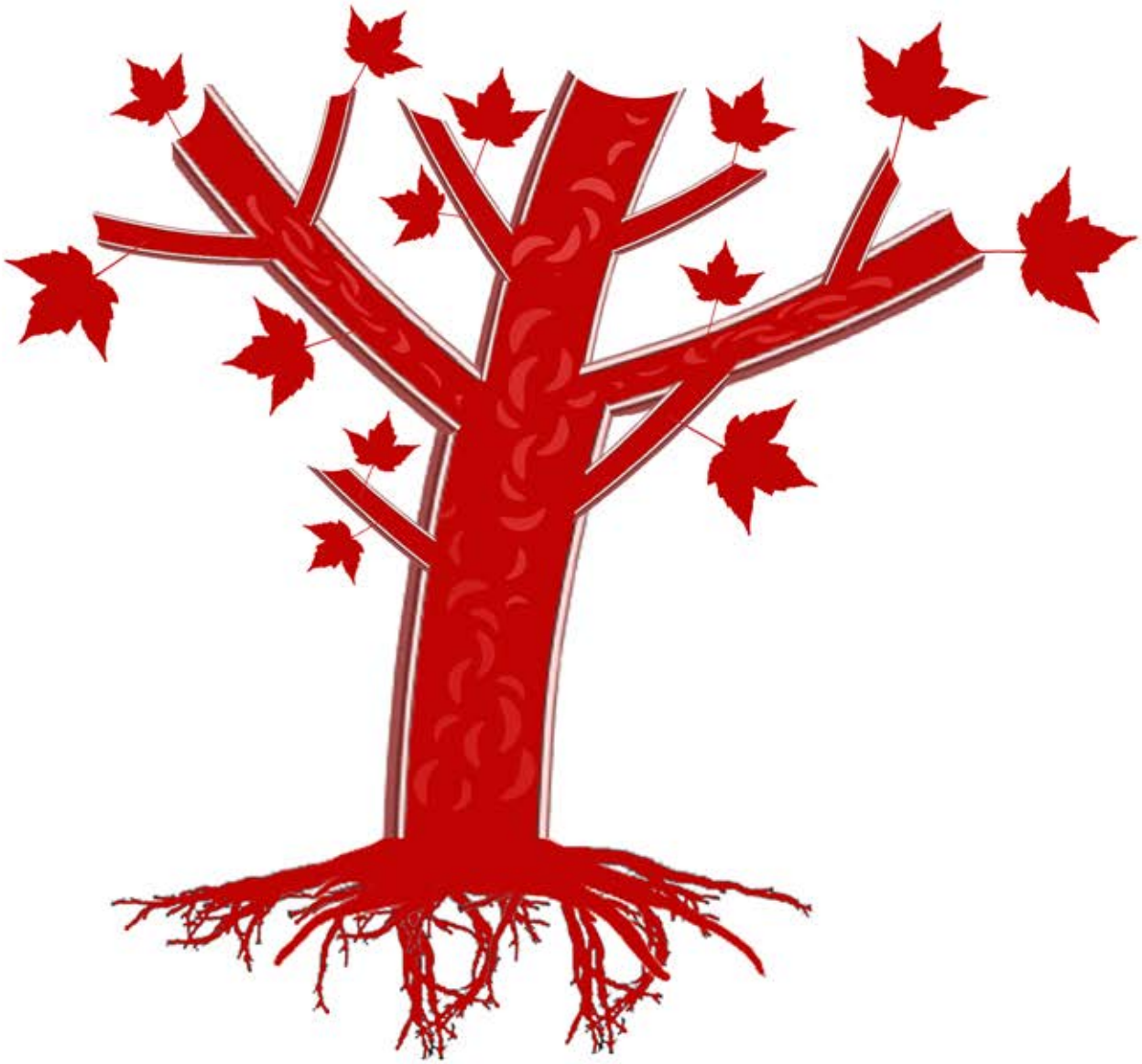

CONSENSUS STATEMENT ON THE CARE OF PATIENTS WITH SICKLE CELL DISEASE IN CANADA

CanHaem
The Canadian Haemoglobinopathy Association

The Consensus Statement on the Care of Patients with Sickle Cell Disease in Canada was reviewed and is endorsed by the Canadian Haemoglobinopathy Association (CanHaem).

Artwork entitled "Tree of Life" by Deon Best

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FOREWORD

The Consensus Statement on the Care of Patients with Sickle Cell Disease in Canada is a comprehensive summary of the current best practices in the prevention and management of sickle-cell-disease complications. It is meant to be a thorough and accessible resource for Canadian health-care providers, with an emphasis on the practical aspects of care for sickle cell disease.

Target audiences for this document include hematologists, internists, pediatricians, emergency physicians, and subspecialists involved in care of patients with sickle cell disease. The Principles and Recommendations sections, in particular, should serve as a quick reference for the above-listed groups, as well as for primary-care providers.

Patients and their family members will also benefit from reviewing this document, and should feel empowered to use it as a tool to ask important questions and to advocate for themselves in medical settings.

Millions of people around the world are affected by sickle cell disease. Approximately 5% of the world's population are carriers of sickle cell disease or thalassemia, and an estimated 300,000 new babies are born with sickle cell disease each year. Sickle cell disease has the highest prevalence in parts of Africa, the Mediterranean, the Caribbean, India, and North America. Sickle cell disease is estimated to affect 90,000 to 100,000 Americans.

In Canada, accurate estimates are not currently available, although it is believed that patients number between 3,000 to 7,000. The number of Canadian patients with sickle cell disease will continue to increase because of high rates of immigration from countries with high prevalence and improved survival with modern medical care. Ongoing efforts to expand newborn screening programs and to develop patient registries will allow us to better grasp the number and distribution of patients with sickle cell disease across Canada, which will in turn facilitate advocacy efforts, education, and resource planning.

Sickle cell disease was identified in 1910. Since that time, incremental improvements in preventive and evidence-based care have led to improved quality of life and life expectancy for patients with sickle cell disease. Much of medical management in sickle cell disease, however, continues to be based on expert consensus, highlighting the need for ongoing participation in well-designed clinical trials.

Our hope is that through the coordinated efforts of researchers, health-care providers, policy makers, patients, family members, and other patient advocates, we can continue to improve the lives of patients with sickle cell disease, ensuring that they can live long, healthy, and fulfilling lives.

Sincerely,

Madeleine Verhovsek, MD and Ewurabena Simpson, MD, MPH

AN INTRODUCTION TO SICKLE CELL DISEASE

Normal Structure and Function of Hemoglobin

Each red blood cell contains millions of hemoglobin molecules, responsible for carrying oxygen from the lungs to the rest of the body's tissues. Hemoglobin is a tetramer, composed of four globin proteins and four heme groups (see Figure). In fetal and newborn life, hemoglobin F (HbF) is the main type of hemoglobin present in red blood cells, formed from two alpha-globin and two gamma-globin chains.

From approximately 6 months of age onward, adult hemoglobin (HbA) is the main type of hemoglobin, made up of 2 alpha-globin and two beta-globin chains. The production of a normal structure and quantity of HbA is dependent on the presence of 4 normal alpha-globin genes (alpha2 and alpha1 on both chromosome 16 alleles) and 2 normal beta-globin genes (one on each chromosome 11 allele).

Sickle Cell Disease

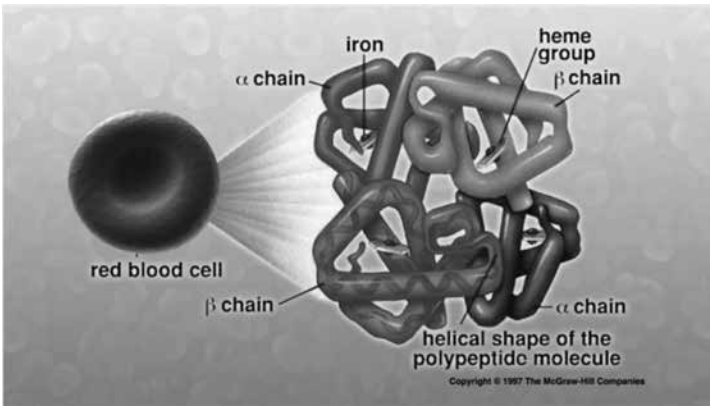
Sickle cell disease is a genetic disorder of hemoglobin. A point mutation in the beta-globin gene causes an amino-acid substitution at position 6 in the beta-globin protein from glutamic acid to valine. Hemoglobin S is formed when altered beta-globin chains ($beta^S$) are incorporated into a hemoglobin tetramer. Hemoglobin S is able to carry oxygen, but when it releases its oxygen, the molecule changes shape so that HbS molecules can "stick" together in long rods, known as polymers. When these polymers form in the usually round red blood cells, the red cell membrane is deformed into an elongated sickle form. Sickled red blood cells are harmful to the body in two main ways:

1) Vaso-occlusion – The sickled red blood cells may block circulation, primarily in the post-capillary venule where the blood vessels are narrowest, and the hemoglobin oxygen concentration is lowest. Vaso-occlusion can cause damage to any organ of the body. Painful episodes (referred to as vaso-occlusive crises) occur due to vaso-occlusion in bone, and are the most frequent complication in many sickle cell disease patients.

2) Hemolysis – Damage to the red cell membrane causes cell breakdown, called hemolysis. The shortened lifespan of sickled red blood cells causes anemia (low hemoglobin concentrations) in individuals with sickle cell disease. Hemolysis is also associated with narrowing or increased pressure in blood vessels in some areas, and can be associated with complications such as pulmonary hypertension and skin ulcers.

There are many genetic forms of sickle cell disease, all with autosomal recessive inheritance. Homozygous hemoglobin S (HbSS) and HbS-$beta^0$ thalassemia (known together as "sickle cell anemia") are the most common forms in much of the world, and are typically the most severe. Two parents with sickle cell trait (HbAS) have a 1 in 4 chance with each pregnancy of having a child with the HbSS form of sickle cell disease. Other genotypes include HbS-$beta^+$ thalassemia, HbSC, HbSO, and HbSD. Disease severity varies widely between patients, influenced by relative concentrations of HbS, HbF, and other hemoglobins, and numerous other genetic and environmental factors.

The Red Blood Cell and Structure of the Hemoglobin Molecule



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PART I — DISEASE-MODIFYING THERAPY

1. Hydroxyurea

Principles

- To identify patients who are likely to benefit from hydroxyurea therapy.
- To initiate hydroxyurea therapy and adjust the dose according to clinical results and results of laboratory monitoring.
- To facilitate optimal patient adherence to hydroxyurea therapy.

Recommendations

Indications and patient counseling

- All adult HbSS or HbS beta^0-thalassemia patients with a history of three or more crises per year should be counseled on the potential benefits and risks of chronic hydroxyurea therapy and strongly encouraged to begin taking it.
- All other HbSS or HbS beta^0-thalassemia patients ≥9 months of age should be counseled on the potential benefits and risks of chronic hydroxyurea therapy, and encouraged to begin taking it.
- After a discussion of the potential benefits and risks, adult patients with HbSC and other compound heterozygous sickle cell disease should be offered hydroxyurea.

Administration and monitoring (modified from Platt 2008)

- Prior to starting hydroxyurea, measure CBC, reticulocyte count, HbF level, renal and liver function.
- For adult patients, consider a starting dose of 1,000 mg. For children, consider a starting dose of 20 mg/kg.
- If creatinine clearance is <60 mL/minute, the starting dose should be reduced.
- After 2 to 4 weeks of daily hydroxyurea, CBC should be performed to look for the expected decrease in white blood cell and platelet count and increase in mean corpuscular volume. If these have not changed:
  - Check that original dose calculation was accurate;
  - Review dosing regimen with patient;
  - Assess adherence and assist with finding strategies for compliance.
- Repeat CBC and reticulocyte count every 2 to 4 weeks, and adjust hydroxyurea accordingly to achieve the patient's maximum tolerated dose.
  - If blood-cell counts are acceptable, strongly consider incremental dose increase(s). If 1 or more parameters fall(s) into unacceptable range at any time (e.g., absolute neutrophil count <1.0, platelet count <80, hemoglobin <50 g/L or decrease in reticulocyte count below 80 x 109/L), hold hydroxyurea until recovery, and consider resuming hydroxyurea therapy at a reduced dose.
  - Individual treatment centres must define their own thresholds for unacceptable hematologic values.
- Once the patient is on a stable dose, monitoring can take place less frequently (e.g., every 3 months).
- HbF levels may be monitored every 3 to 6 months to assess the efficacy of treatment.
- Patients who, despite dose adjustment, active management, and evidence of good adherence, do not respond to hydroxyurea can be considered for enrollment in high-quality clinical trials of other inducers of fetal hemoglobin.
- Contraception is advised for both men and women taking hydroxyurea.
- Women planning a pregnancy should discuss alternative therapeutic options with their treating hematologist, due to concern about teratogenicity of hydroxyurea.
- Hydroxyurea is contraindicated in lactating mothers, as it is excreted in breast milk.

Background

Hydroxyurea has been used for almost 20 years and is currently the only disease-modifying agent proven to prevent complications in patients with sickle cell disease (SCD).

Fetal hemoglobin (HbF) has long been observed to have a protective effect in SCD patients. Higher levels of HbF correlate with a less severe course in SCD patients, including fewer painful episodes, and lower risk of early death.[1,2] This result is due to decreased polymerization of sickle hemoglobin (HbS) in the presence of high concentrations of HbF. In the 1980s, a series of small studies in patients with SCD confirmed the ability of hydroxyurea to increase HbF levels.[3,4] Additional mechanisms of hydroxyurea in SCD include reduced neutrophil counts; decreased adhesiveness of circulating reticulocytes and neutrophils; improved red blood cell (RBC) hydration; decreased adhesiveness; and improved rheology.[5]

In 1995, the Multicenter Study of Hydroxyurea (MSH) was published, in which nearly 300 adult patients with sickle cell anemia and a history of three or more sickle pain episodes per year were randomized to receive either hydroxyurea at maximal hematological tolerated dose, or placebo. After a mean follow-up of 21 months, the hydroxyurea group had significantly fewer crises per year, fewer episodes of chest syndrome, and required fewer transfusions. The medication was well tolerated overall, without any important side effects.

Improved Survival in Adults

Since that landmark paper, there have been numerous additional studies demonstrating the benefits of hydroxyurea in SCD. Long-term follow-up of MSH study participants found an association of hydroxyurea use with improved survival.[6] Long-term follow-up of a similar European study demonstrated a significant reduction in 10-year overall mortality in patients with sickle cell anemia (HbSS) and HbS beta^0 thalassemia.[7]

Infants and Children

Studies in children have shown reduced frequency of vaso-occlusive episodes[8,9] and blood transfusion,[8,9,10] improved transcranial Doppler flow velocities,[11] and reduced rates of hospitalization[9,10,13,14] after starting hydroxyurea, with no unexpected toxicity. Rare episodes of transient neutropenia were reported.[9,14]

The BABY HUG trial was a prospective clinical trial of liquid hydroxyurea (20 mg/kg/day) versus placebo in 193 infants and children with SCD.[15,16] Any child with HbSS or HbS beta^0-thalassemia aged 9 to 18 months was eligible for the study, regardless of clinical severity. Although the study's primary endpoint was not achieved, there were significant reductions in the rates of acute chest syndrome, pain, dactylitis, transfusion, and hospitalization among patients who received hydroxyurea. There were also significant increases in hemoglobin concentration and hemoglobin F levels. There was increased mild-to-moderate neutropenia in the hydroxyurea group, but no increased risk of bacteremia or serious infection. Growth rate was not affected by hydroxyurea. Whether hydroxyurea may have some neuro-protective effect in infants and children remains to be defined.

Hemoglobin SC disease (HbSC)

Although most studies have evaluated patients with more severe forms of sickle cell disease, such as HbSS or HbS beta^0 thalassemia, the few treatment studies in patients with HbSC found similar benefit.[17] To date, however, there have been no high-quality, prospective studies in patients with HbSC.

Hydroxyurea Administration and Monitoring

The goal of hydroxyurea is to titrate to the maximal tolerated dose for each patient, based on maintaining safe blood counts.[18] Laboratory testing of complete blood count (CBC), reticulocyte count, HbF levels, and renal- and liver-function tests should be performed prior to initiating hydroxyurea, and should be repeated at regular intervals thereafter (see Recommendations box for details).

Although the expected decrease in WBC and platelets and increase in HbF can be seen within weeks to months, a clinical response may only be evident after 3 to 6 months of treatment. In addition to laboratory monitoring and dose adjustment, follow-up appointments should be used to assess symptoms and to encourage continued adherence.

The younger the age when first commencing hydroxyurea, the deeper and more sustained the response to the medication.[19] A liquid formulation may be administered to infants and young children.

Once a patient is started on hydroxyurea, the current model of care is to continue this therapy indefinitely. Ongoing research and development of new anti-sickling agents brings hope for future alternatives, however.

Patient Counseling

Prior to initiation of hydroxyurea, patients should be counseled about potential reversible side effects, including nausea, rash, nail changes, hair thinning, and headache.

Concern has existed about the theoretical risk of malignancy after long-term use of hydroxyurea, because of possible increased rates of leukemia and skin cancers in patients with other hematologic conditions who had taken hydroxyurea. Laboratory studies, however, have shown no increased genotoxicity in hydroxyurea-exposed blood from patients with SCD compared with control subjects,[20] and no increased rate of malignancy has been observed in adults or children with SCD who have taken hydroxyurea for up to 20 years.[21,22] Furthermore, there is growing evidence that long-term hydroxyurea therapy is associated with decreased overall mortality, and may have a significant impact on the life expectancy of patients with SCD.[6,7]

Although unsubstantiated in human studies,[23] concern remains about possible teratogenesis based on animal studies. As a result, contraception is advised for both men and women. Patients planning conception should discuss therapeutic options with their treating hematologist. In women for whom the balance of potential risk to the fetus versus benefit to the patient with ongoing hydroxyurea use is uncertain (e.g. a woman with history of severe sickle cell disease complications who has been optimized on hydroxyurea), informed decision-making may include consultation with Motherisk and/or knowledgeable maternal-fetal medicine specialists. When hydroxyurea is discontinued in pregnancy, chronic transfusion may be considered as an alternative means of preventing maternal sickle complications.

Hydroxyurea is also contraindicated in lactating mothers, as it is excreted in breast milk and therefore could potentially lead to adverse effects in the infant.

Some patients and their families may have questions or misperceptions about the balance of risks and benefits of hydroxyurea therapy in SCD. It is important to outline the strong evidence of clinical benefit, and the lack of clear evidence of increased rates of malignancy and teratogenicity. Having a frank and open discussion about these issues is an important element in increasing medication acceptance and adherence.

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2. Transfusion

Principles

- There are specific indications for the use of red cell transfusions for individuals with sickle cell disease.
- Two main indications for red cell transfusion are to treat severe exacerbations of anemia and to treat and/or reduce the complications of sickle cell disease.
- Patients with sickle cell disease should be transfused with phenotypically matched red cells to reduce the risk of alloimmunization and hemolytic transfusion reactions.
- After receiving red cell transfusions, patients should be closely monitored for acute and delayed transfusion reactions.

Background

Individuals with sickle cell disease (SCD) have elevated blood viscosity, which may be further exacerbated by increases in hematocrit. In addition, they are more likely to experience delayed hemolytic transfusion reactions. For these reasons, the indications for transfusion in patients with SCD differ significantly from those in other patients. They are as follows:

1. **Exacerbation of anemia:** In the absence of heart failure, dyspnea, hypotension, or marked fatigue, transfusion should be avoided unless the hemoglobin (Hb) has decreased to <50 to 60 g/L.[1] Note that due to the short circulating life span of sickle erythrocytes, a rapid decrease in Hb can occur if the reticulocyte count falls below a patient's baseline.
2. **Treatment or prevention of SCD complications:** In patients receiving transfusion, hemoglobin concentration should not be increased above 100 to 110 g/L.[2] Note that augmentation of oxygen delivery in patients with SCD is achieved more efficiently through decreasing the sickle hemoglobin percentage (HbS%) than by increasing the total hemoglobin level, particularly at low shear blood flow.[3]

Recommendations

A1. Special Transfusion Requirements

The following apply to patients with sickle cell disease. No special precautions are required for patients with sickle cell trait (HBAS).

- Notify the hospital's Blood Transfusion Service when a patient with SCD presents to the emergency department or is admitted to hospital and transfusion is anticipated. This will allow for sufficient time to prepare specialized blood products. If possible, also provide blood bank with details of prior transfusions, including hospital location.

A2. Phenotypically Matched Red Blood Cells (RBCs)

- Determine the extended RBC phenotype (Rh, Kell, Duffy, Kidd and MNS blood groups) at first visit. Note that by using hypotonic (0.3%) saline lysis, blood samples from even recently transfused sickle cell patients may be phenotyped. Consider referring patients with SCD for genotyping studies, if available, due to the high prevalence of variant RBC antigen alleles. The *RHD-CE(3-7)- D* hybrid gene, for example, found in 22% of individuals of African descent, encodes a partial C antigen which will test as positive by traditional phenotyping, but which may allow the elaboration of an anti-C antibody in response to the transfusion of C+ RBCs if not balanced by a normal C antigen in the patient's other haplotype.[4]
- In patients with no previous alloantibodies, selecting RBCs matched for the patient's Rh (C, c, E, e) and Kell (K1) antigens is considered the most effective means of preventing sensitization, which may occur in up to 30% of sickle cell patients receiving blood matched only for ABO and Rh with D antigen.[5] A high proportion of alloantibodies in sickle cell patients will become undetectable on later testing;[6] if inadvertently challenged with an incompatible unit (e.g., at a health-care facility unaware of a patient's previous antibody history), a delayed hemolytic transfusion reaction may occur, which may trigger a vaso-occlusive pain episode and, in rare cases, may be complicated by hyperhemolysis (see next page).

- Individuals who have previously made alloantibodies may represent "high responders" who are at higher risk of making further antibodies with transfusion.[7] It is therefore prudent to extend prophylactic matching in such individuals by selecting RBCs that are matched for the patient's Rh (antigen D, C, c, E, e), Kell (K1), Kidd (Jk^a, Jk^b), Duffy (Fy^a) and S (S,s) antigens, as well as any antigens to which the patient has already made a clinically significant antibody.[8] Matching for Fyb in sickle cell patients is generally not necessary due to strong association in this population between the FYB gene and a GATA promoter mutation, which blocks only erythroid expression of the antigen; the continued expression of Fy^b in non-erythroid tissues prevents sensitization to this antigen.[9]
- Contacting other hospitals where a patient with SCD may have been transfused is advisable, as there may be a history of antibodies not currently reacting in their pre-transfusion group-and-screen effort; in some regions of Canada, Canadian Blood Services maintains a central registry of patients with SCD to facilitate the sharing of information. In Quebec, all bloods banks use the same information system, and transfusion history is readily available.
  NOTE: Life-saving transfusion should not be deferred if prophylactically phenotype-matched RBCs are not immediately available.

A3. Sickledex®-negative Blood

- RBC units that test positive by Sickledex® test (or dithionite solubility test) are from donors with sickle cell trait (HbAS). Since this blood will confound post-transfusion measurements of the patient's HbS%, it should be avoided if possible.[10]

B. Exchange Transfusion

- Ensure patient is euvolemic before initiating an exchange transfusion.
- Depending upon a patient's initial Hb, it may not be possible to achieve a specific target HbS% by top-up transfusion without exceeding a total Hb of 100 to 110 g/L. Exchange transfusion may therefore be required to reach the traditional HbS% goal of <30%. (Note that, for HbSC, it is preferable to state goal as HbA% >70%.)

B1. Manual/Partial-exchange Transfusion:

- A typical protocol for adult manual/partial-exchange transfusion: (Note that, for children, smaller comparable volumes – e.g., 10 mL/kg – would be used.)
  1. Phlebotomize 1st 500 mL of whole blood. Note: For patients who are very anemic at baseline (e.g., Hb <70 g/L), a top-up transfusion may be required before first phlebotomy.
  2. Administer a bolus 500 mL of 0.9% normal saline.
  3. Phlebotomize 2nd 500 mL of whole blood.
  4. Transfuse 2 units of RBCs. (Note that, for children, the total amount of red cells that are infused should correlate to the amount of whole blood that is removed. For small children with Hb near 100 g/L, for every 10 mL/kg whole blood phlebotomized, transfuse 5 mL/kg packed red cells.)
  5. Repeat as necessary to achieve target HbS% (typically a 1.5 blood volume exchange is necessary for first treatment; single cycles may be adequate for maintenance therapy). For patients starting with Hb near 100 g/L, step 4 should alternate between transfusion of 1 and 2 units to keep total Hb from exceeding 120 g/L.

B2. Automated Exchange/Erythrocytapheresis

- Automated exchanges are faster and more precise than manual exchanges, but require specialized equipment and trained personnel. Below is a typical procedure for automated exchange/erythrocytapheresis:
  1. Patient height, weight, and hematologic indices are programmed into an apheresis device.

2. Small aliquots of whole blood are withdrawn under pressure, RBCs separated by centrifugation and discarded, plasma and platelets returned to patient accompanied by donor RBCs (usually through separate line). Depending on the hospital protocol, donor RBCs may or may not be centrifuged in advance to reduce the quantity of optimal additive solution (e.g., SAG-M) infused.
3. Cycle repeats until goal Hb and HbS% achieved.

B3. Venous Access

- A central venous-access device placement is often required for exchange transfusions. If it is left in place between treatments, anticoagulation may be considered due to the risk of line-associated thrombosis.[11]
- Rigid tubing (e.g., dialysis line) or specialized subcutaneous access devices (e.g., Vortex® port) is required for most apheresis devices if the procedure cannot be performed using peripheral veins.

C. First-line Indications for RBC Transfusion

C1. Therapeutic Indications

1. Aplastic Crisis

- Most commonly due to parvovirus B19 infection
- Manifests as profound reticulocytopenia following a viral illness; resolves after 1 week with induction of neutralizing antibodies; 75% of patients develop immunity by age 20.[12]
- Due to decreased lifespan of sickle RBCs (16-20 days), a significant fall in Hb will occur before the reticulocyte count recovers.[13]
- Transfusion support may be required if anemia is symptomatic or if Hb <50 g/L. As there is usually a compensatory increase in plasma volume, however, transfuse cautiously to avoid volume overload (e.g., consider a pre-transfusion diuretic).
- In patients with impaired humoral immunity, intravenous immunoglobulin (IVIG) 0.5 g/kg weekly x 4 may speed viral clearance, but this is usually not required in SCD.[14]

2. Splenic Sequestration Crisis

- Trapping of sickle erythrocytes in sinusoids results in massive, painful enlargement of the spleen and severe anemia over a period of hours, which is accompanied by reticulocytosis and, occasionally, thrombocytopenia and leukopenia.
- If untreated, sequestration crises cause death from hypovolemic shock/anemia; immediate transfusion is often required. Post-transfusion Hb levels are often higher than expected, however, suggesting autotransfusion as sequestered RBCs are released back into circulation. To avoid accidental polycythemia and hyperviscosity, transfuse 1 unit at a time, reassessing Hb level before administering additional red cells. In children, consider administering RBCs in smaller than normal aliquots (e.g., 3 to 5 mL/kg). A single transfusion is often sufficient to reverse a sequestration crisis.[15]
- Following stabilization, immediate splenectomy can prevent recurrences of splenic sequestration crises (50% recurrence rate if treated with transfusion support alone) and chronic hypersplenism.[16]
- In patients for whom splenectomy is contraindicated (e.g., those under age 2 years), chronic transfusion to maintain HbS <30% may be considered as second-line therapy to prevent recurrences.[15]

3. Hepatic Sequestration Crisis

- Less commonly, patients may present with hepatic sequestration crises, characterized by a rapidly enlarging liver accompanied by a decrease in hemoglobin, a rise in reticulocyte count, and a conjugated hyperbilirubinemia. Alkaline phosphatase and transanimases may also be variably increased.
- As with splenic sequestration crises, transfusions should also be administered cautiously due to the risk of autotransfusion and hyperviscosity. Recurrences are common.[1]

4. Acute Chest Syndrome (see Part II, section 2 on Acute Chest Syndrome)

- Broadly defined as a new infiltrate on chest x-ray in a patient with SCD, associated with one or more symptoms of fever, cough, sputum production, tachypnea, dyspnea, or new-onset hypoxia; may progress rapidly to respiratory failure and be complicated by neurologic events.[17]
- May be triggered by infection (often atypical organisms) or marrow embolism as complication of vaso-occlusive pain episode; specific cause not identified in ~60% of cases despite extensive investigations.[17] Empiric treatment with bronchodilators, incentive spirometry and antibiotics (e.g. macrolide or quinolone) advisable in all patients.
- RBC transfusion in the setting of acute chest syndrome results in improved oxygenation.[17] Some studies have observed equivalent outcomes whether patients are treated with exchange transfusion (HbS% goal of 30%) or top-up transfusion (Hb goal of 100 g/L).[18] Other studies have found, however, that patients receiving top-up transfusions may progress to requiring a full exchange.[19]
- In the absence of evidence from randomized controlled trials, most patients with acute chest syndrome should be transfused, with exchange transfusions reserved for patients with more severe or rapidly progressing disease.[20] Signs of severe disease include:
  - altered mental status
  - persistent heart rate >125 beats/minute, respiratory rate >30 breaths/minute, temperature >40°C, or worsening hypotension
  - arterial pH <7.35; peripheral capillary oxygen saturation (SpO2)% <88% despite aggressive ventilatory support
  - serial decline in SpO2% or alveolar-arterial gradient
  - fall in hemoglobin >20 g/L
  - platelet count <200/fL
  - elevated troponin or brain natriuretic peptide (BNP)
  - evidence of multiorgan failure (e.g., renal or hepatic dysfunction)
  - pleural effusions or progressive pulmonary infiltrates

5. Progressive Cholestasis

- This is a syndrome that may occur in the absence of cirrhosis, marked by right upper quadrant pain, nausea, extreme elevation of bilirubin (predominantly conjugated) and alkaline phosphatase and variable elevation in transanimases. It is accompanied by renal failure, thrombocytopenia, and prolonged coagulation times. This syndrome occurs secondary to sickling within hepatic sinusoids, resulting in intrahepatic cholestasis.[21]
- All survivors have been treated with RBC exchange transfusion; platelet and plasma transfusion support have been used to control bleeding due to hemostatic failure.[1]
- In contrast, benign cholestasis (unaccompanied by fever, abdominal pain, gastrointestinal symptoms, or hepatic synthetic failure) resolves within months without specific therapy.[1]

6. Acute Ischemic Stroke or Retinal Occlusion (*see Part II, section 4 on Stroke and Neurological Complications*)

- RBC transfusion is recommended for all pediatric patients. Within 3 hours of the first unit of transfused RBCs, middle cerebral artery (MCA) flow velocity decreases by 20%.[22] Exchange transfusion is associated with lower stroke recurrence rate than top-up transfusion.[23]
- Although there is less supportive evidence for it, RBC transfusion is recommended for adult sickle cell patients without other obvious stroke etiology (e.g., cardioembolism).[15] Note, however, that most strokes in young adult patients with SCD are hemorrhagic, a condition for which the benefits and safety of immediate transfusion therapy are unclear.[24]

C2. Prophylactic Indications

1. Perioperative (see Part III, section 1 on Peri-Operative Management)

- The value of pre-operative transfusion in the prevention of post-operative sickle cell complications was established in the 2013 TAPS trial, in which patients with HbSS or HbS beta^0-thalassemia were randomized to pre-operative transfusion vs no transfusion. The transfusion protocol itself required transfusing to a hemoglobin of 100 g/L within 10 days of surgery, with patients starting with a hemoglobin of >90 g/L undergoing a partial exchange transfusion with a target HbS <60%. The trial was stopped early due to a strong treatment effect: the rate of clinically important complications decreased from 39% in the untransfused group to 15% in the transfused group, and 91% of serious adverse events were acute chest syndromes.[28]
- The 2013 TAPS trial, however, did not enroll patients undergoing high-risk surgeries (e.g., cardiovascular or neurosurgical procedures), and excluded high-risk patients (e.g., patients with previous acute chest syndrome requiring intubation or baseline oxygen saturation <90%). High-risk procedures and high-risk patients were similarly excluded from an earlier randomized controlled trial of patients with HbSS that demonstrated no benefit of an aggressive pre-operative transfusion strategy (target HbS <30%) over a more conservative strategy of top-up transfusion to hemoglobin of 100 g/L (effectively achieving a HbS of 60%).[25] It is therefore unknown whether high-risk patients or those undergoing high-risk procedures might benefit from a more aggressive transfusion strategy than was provided in the TAPS trial.
- There is little evidence to guide transfusion practice in high-risk patients undergoing high-risk procedures. There is also, however, little evidence to guide transfusion practice in low-risk patients undergoing low-risk procedures. While low-risk procedures were included in the TAPS study, relatively few low-risk patients undergoing low-risk procedures were enrolled (13/70) due to the premature conclusion of the trial. Moreover, of the 11 serious adverse events recorded, only 1 was in a patient undergoing a low-risk procedure.[28] It is unknown whether low-risk patients undergoing low-risk procedures require pre-operative transfusion.
- There have been no randomized controlled trials demonstrating the benefit of pre-operative transfusion in patients with milder forms of SCD such as HbSC. Observational studies, however, suggest a benefit of pre-operative transfusion for these patients as well, if undergoing moderate to high-risk procedure.

2. High Stroke Risk (*see Part II, section 4 on Stroke and Neurological Complications*)

- In children, transfusion indicated for secondary prevention of ischemic stroke and for primary prevention in patients with high-risk features (e.g., high MCA or internal carotid blood flow by pediatric transcranial ultrasound, silent cerebral infarct). In the latter group, maintaining HbS <30% while keeping total Hb <120 g/L results in a 92% reduction in stroke incidence.[32]
- Once initiated, transfusions should be continued indefinitely, as discontinuation is associated with a high risk of stroke recurrence.[32] Transfusion has also been shown to be more effective than hydroxyurea in secondary stroke prevention.[33] Even with chronic suppression of HbS to less than 30%, regular monitoring by cerebral magnetic resonance imaging/angiography is advised, as a significant proportion of patients may still demonstrate radiologic disease progression, which in turn predicts overt neurologic symptom development.[34]
- There is little evidence to guide initiation of transfusions for stroke prophylaxis in adults, or following primary hemorrhagic strokes. Note that most strokes in young patients with SCD are hemorrhagic, and may occur despite normal transcranial Doppler screening.[24] However, the underlying pathophysiology for both thrombotic and hemorrhagic strokes in SCD is likely the same and therefore should both be managed with transfusions for secondary prophylaxis.[35]

D. Second-line Indications for RBC Transfusion

- In the absence of evidence from clinical trials, the initial therapeutic goal for the following indications should be HbS% <30%, with scheduled regular review of the transfusion regimen, and re-assessment if the patient's condition changes. Adjustments in transfusion goals and regimen (e.g. exchange versus simple transfusion) should be based on clinical factors.
- Note that some of the following conditions (priapism, pulmonary hypertension, malleolar ulcers) may represent complications of chronic intravascular hemolysis (e.g., nitric oxide depletion) rather than acute vaso-occlusion.[36]

D1. Recurrent Pain Episodes/Acute Chest Syndrome (see Part II, Section 2 on Acute Chest Syndrome)

- In patients who have failed an adequate trial of hydroxyurea (e.g., no benefit despite maximal tolerated dose), chronic transfusion support may be considered as a means of *preventing* recurrent vaso-occlsuive pain episodes or acute chest syndrome. This approach is based on secondary outcome analysis of patients enrolled in randomized controlled trials of chronic transfusion support.[37,38]
- Transfusion is not indicated as *treatment* of uncomplicated acute vaso-occlusive pain episodes, or for treatment of chronic pain syndromes (e.g., avascular necrosis, osteomyelitis, neuropathic pain).[15,39]

D2. Priapism (see Part II, section 10 on Priapism)

- Case series reports[40] and literature reviews[41] suggest that transfusion is of little benefit for priapism, and may be complicated by ASPEN syndrome (Association of SCD, Priapism, Exchange Transfusion and Neurologic events).
- Transfusion should only be considered in cases lasting over 4 hours that are unresponsive to aspiration of blood from the corpora cavernosa and irrigation with dilute epinephrine, and when surgical intervention (shunting and prosthesis) is either ineffective or not immediately available.[41]

D3. Ulcers (see Part II, section 12 on Skin Ulcers)

- The principal management of malleolar ulcers include skin protection, infection control, debridement, compression bandages and wet-to-dry dressings. Ulcers that do not respond to these treatments within 6 months may benefit from other modalities, including blood transfusion, although evidence of benefit is primarily anecdotal.[43,44]

D4. Pregnancy (see Part III, section 2 on Contraception, Pre-conception Counseling and Pregnancy)

- As long as adequate pre-natal care is provided (e.g., bi-weekly obstetrical assessment, switching to weekly in the last month), transfusions may be withheld in the absence of medical or obstetrical emergency without worsening of perinatal outcomes. Chronic transfusion support, however, can decrease the incidence of sickle complications in the mother, and may be considered in pregnant women with a history of frequent pain crises, given the contradiction to hydroxyurea during pregnancy.[37]
- Transfusion support may also be considered for pregnant patients with significant comorbidities (chronic renal, pulmonary, or hepatic disease), history of recurrent fetal loss, and in patients with either multigestational pregnancy or evidence of chronic fetal distress/intrauterine growth retardation.[15]
- Top-up transfusion to improve oxygen carrying capacity is also advised, for fetal indications, in pregnant women with hemoglobin <60 g/L.[44]

E. Transfusion Complications

E1. Delayed Hemolytic Transfusion Reactions

- Without prophylactic phenotypic matching, 30% of transfused patients with SCD will develop alloantibodies – two thirds of them directed towards the C, E and Kell (K1) antigens.[47]

- As 30% to 50% of these antibodies will be undetectable on retesting within the year, patients may be re-challenged inadvertently with subsequent transfusions, resulting in high rate of delayed hemolytic transfusion reactions.[10]
- Delayed hemolysis manifests 1 week to 1 month after transfusion by worsening of hemolytic indices accompanied by new alloantibody in patient plasma (detected by blood group and screen) and/or on patient's RBCs (detected by direct antiglobulin test).
- Patients often present with symptoms typical of a vaso-occlusive pain episode. In some cases, delayed hemolytic transfusion reactions may progress to hyperhemolysis (see below).

E2. Hyperhemolysis

- Hyperhemolysis is defined as post-transfusion RBC destruction accompanied by a fall in Hb to below pre-transfusion levels. Hemolytic indices are increased from baseline, occasionally accompanied by relative reticulocytopenia.[50]
  - Delayed: occurs between 1 and 4 weeks following transfusion, and is often accompanied by new RBC antibodies
  - Acute: occurs less than 7 days after transfusion, often with no new antibodies detectable
  - Enhanced hemolysis appears to involve both transfused and autologous RBCs, and may be exacerbated by further transfusion of even crossmatch-compatible/antigen-negative RBCs.
- Avoid further transfusions if at all possible and treat with IVIG 2 g/kg over 2 to 5 days, accompanied by high-dose steroids (e.g., prednisolone 1 mg/kg/d x 7 days). Consider a brief course of erythropoietin if relative reticulocytopenia is found.[51]

E3. Hyperviscosity

- Be aware of hyperviscosity if sudden-onset hypertension is observed during or shortly after transfusion, accompanied by signs of congestive heart failure and profound alterations in mental status, including stupor, coma, seizures, or features of intra-cerebral infarct or hemorrhage.[52]
- Risk increases if Hb is transfused above 100 to 110 g/L in patients with SCD and HbS% >25%, particularly if the patient is dehydrated and hypoxemic.[3] Hyperviscosity may also occur secondary to autotransfusion following transfusion support of sequestration crises.
- Manage with emergent phlebotomy.

E4. Transfusional Iron Overload (See Part II, section 14 on Iron Overload)

- Each transfused unit of RBCs delivers 200 to 250 mg of iron; in the absence of blood loss or therapeutic phlebotomy, only ~1 mg of iron lost per day. Significant iron overload is therefore likely after repeated top-up transfusions. Selecting fresh RBCs (<7 days old) may slow iron loading in chronically transfused patients to a small degree. Exchange transfusions may more effectively mitigate or even reverse iron loading.[53]

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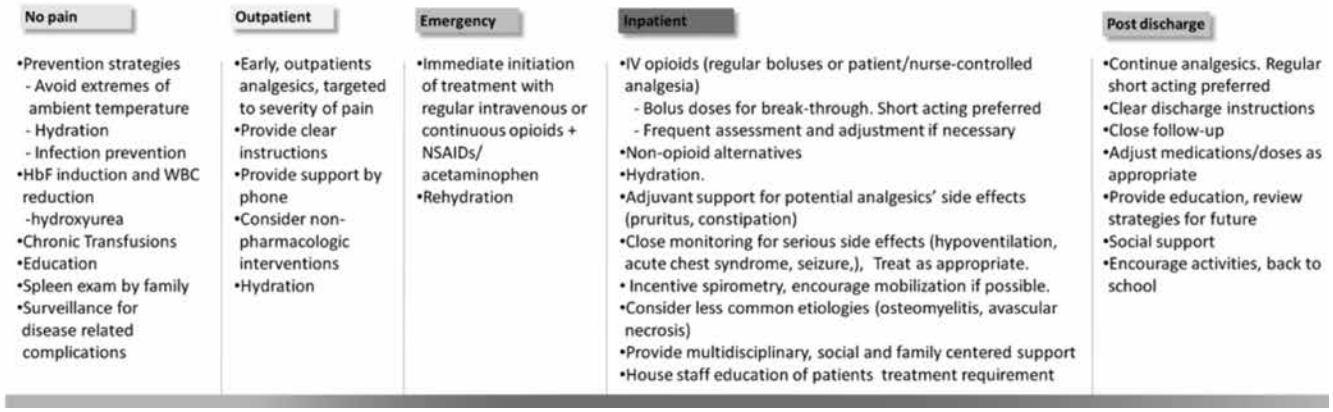
PART II: PREVENTING AND MANAGING COMPLICATIONS OF SICKLE CELL DISEASE

1. PAIN

Principles

- Educating patients, family and other caregivers about rapid identification and prevention of vaso-occlusive crisis forms the foundation for pain management in sickle cell disease.
- Sickle cell disease-related pain should be managed promptly and aggressively to reduce its impact on health-related quality of life.
- Optimal treatment of sickle cell pain requires a combination of pharmacological, psychological and physical therapeutic approaches and may require expertise from a pain specialist.
- Hydroxyurea therapy is effective for preventing or reducing the frequency of pain episodes and should be considered in eligible patients.



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Recommendations

Education and Prevention

Patients or caregivers should be educated for the triggers of vaso-occlusive events and their impact on patients' health and quality of life. A clear instruction should be provided for the prevention of acute pain episodes – preferably at every clinic visit. The benefits of hydroxyurea for the prevention of painful events should be reviewed with patients or their caregivers as early as possible, and on a regular basis. The potential side effects should be reviewed. The fear of triggering pain episodes should not limit patients' activities. If there are no other contraindications, patients with SCD should be encouraged to be as active as their peers.

Home-based Management

- Patients or their caregivers should be provided with clear instructions for the identification of vaso-occlusive pain versus other potential and very serious complications of SCD, including acute chest syndrome or cholelithiasis.
- Caregivers of young children with SCD should be familiar with examination of the spleen. Examination of the spleen is absolutely necessary to ensure that abdominal pain is not due to acute splenic sequestration.

- Patients or their caregivers should be provided written instructions (and preferably in electronic format as well) for the management of sickle cell pain, including the type of medication, dosing options, and administration. This plan should be reviewed in each clinic visit, and modified if required.
- A clear instruction should be provided regarding when and how to seek help or to refer to emergency medicine.
- It should be ensured that patient has access to medication (over-the-counter or prescribed medications) when required. Medications that require a physician's prescription should be provided in advance, so that they can be used when necessary.
- Patients should be provided with the contact information of a health-care practitioner familiar with the management of sickle cell pain.

Outpatient Management

- When adequate outpatient management is not sufficient to control the pain, the patient should be assessed in the sickle cell clinic/day hospital setting or in the ED if the clinic is unavailable.
- Patients should be assessed with priority upon arrival, and appropriate management should be started ideally within 30 minutes. The initial treatment should be chosen to achieve appropriate pain control as soon as possible. Patients who have moderate to severe pain or those who were treated with oral morphine without successful pain relief at home should be given intravenous morphine after evaluation.
- The response to treatment and titration of medications should be frequently evaluated. An objective and age-appropriate method for grading the pain and the treatment response should be used.
- Patients should be started on hydration (preferably oral, if tolerated) to ensure that they are not dehydrated. Overhydration, however, should be avoided.
- If intravenous fluid is required, a hypotonic solution (such as 0.45% saline solution) is preferable over isotonic solutions, when there are no other concerns for hyponatremia.
- There is no proven benefit of oxygen therapy for a simple pain event, but it should be given if there is evidence of decreased oxygen saturation or in the presence of respiratory symptoms.
- Depending upon the presenting symptoms, investigations should be considered, including complete blood count (CBC), reticulocyte count, cultures, bilirubin, liver enzymes, blood urea nitrogen and creatinine, blood gas, chest x-rays or other imaging studies. Risk of frequent radiation exposure should be kept in mind.
- Patients should be evaluated for common etiologies of pain that may not be directly caused by SCD.
- For patients with abdominal pain, examination of the spleen is absolutely necessary to ensure that the pain is not due to acute splenic sequestration.
- Antibiotic therapy has no role in the management of a simple acute pain event, and when there is no fever or any other findings suggestive of infection. Physicians should be aware that patients with SCD may have a high baseline WBC count, and leukocytosis in isolation may not be due to infection. Nucleated red blood cells can also be erroneously counted as WBCs on automated CBCs – manual WBC count and WBC differential are often required.
- Red cell transfusions do not have a beneficial role in the management of acute painful episodes in SCD. The benefit of chronic transfusion therapy for the management of chronic sickle cell pain is controversial.
- Patients whose pain has been well controlled with oral medication, and who have been sufficiently observed and deemed safe for outpatient pain management may be considered for discharge, with sufficient education and a clear treatment plan for the next days. Physicians should ensure that each patient has access to the prescribed discharge medications in sufficient quantities.

Inpatient Management

- Patients whose pain cannot be controlled by oral medications should be started on intravenous medications and be admitted to the hospital.

- Those with atypical pain or symptoms should be evaluated for an alternative etiology for the pain that may not be directly caused by SCD.
- Adjunct medications (e.g., non-steroidal anti-inflammatory medications [NSAIDs] and acetaminophen) should be used to reduce the rate of opioid infusion. These medications should be protocolized to optimize their use.
- Smaller doses of analgesics (around 50% of the maintenance dose) should be provided for breakthrough pain.
- Long-acting oral opiates should be considered for basal pain control if patients do not have a continuous IV opiate infusion.
- The response to treatment should be regularly evaluated, and analgesia dose should be reassessed on a regular schedule to titrate the medication dosing to optimize pain control.
- Step-down therapy should not be attempted until the pain is well controlled.
- For those patients whose pain is not controlled upon infusion of analgesics, a team that is expert in the management of pain (e.g., anesthesia, acute pain service) should be consulted, and PCA or NCA should be started.
- All patients, especially those with chest or back pain and those with supplemental oxygen requirement, should be started on age-appropriate incentive spirometry.
- Fluid balance and hydration status should be monitored closely throughout the admission to avoid overhydration.
- The respiratory status of all patients on infusion of analgesics should be monitored. Other potential side effects of treatment (e.g., pruritus) should be addressed.
- Patients should be evaluated for constipation upon admission, and appropriate preventative measures should be provided.
- Provide non-pharmacological measures such as massage, heat pad, and distraction. Involve a pediatric life specialist for children. Encourage activities as tolerated.
- Once sufficient pain control is achieved, de-escalation of therapy can be attempted. Those whose pain is controlled on oral analgesics and deemed safe for discharge, can be sent home, but clear guidance for the management of pain and the possibility of readmission should be provided.
- Transfusion of episodic packed red blood cells for the management of acute pain is not recommended; however, it can be given for the management of symptomatic anemia.
- Patients should receive prophylaxis for venous thromboembolism if mobility is reduced during their hospitalization.

Choice of Analgesics

- Patients should be treated with the most effective therapy with the least potential side effects in each individual patient. The response to treatment should be recorded in each patient's chart so it can be reviewed upon future admissions.
- Patients with adverse reactions to any analgesics should be provided with a written document indicating the type of adverse reaction, so that, in the future, an alternative treatment can be provided as soon as required.
- While on opioid analgesics, patients should also be treated with regular doses of NSAIDs (ibuprofen, naproxen, short-term Ketorolac) and acetaminophen as adjuncts to opioids to reduce the opioid requirement, unless their use is contraindicated.
- For breakthrough pain, short-acting medications are preferable over long-acting alternatives. Long-acting opioids are generally used for pain that is chronic in nature.
- Inhaled nitric oxide, corticosteroids, or magnesium sulfate have not been shown to be effective during acute painful events.

Background

Pain is the most common presentation of sickle cell disease (SCD), and the most frequent cause of hospital admission, with major impact on patient quality of life.[1,2] It has been shown that frequent pain events are associated with early mortality in adults.[3,4] Although patients with sickle cell anemia (HbSS) and HbS beta^0 genotypes generally experience more painful episodes than those with hemoglobin SC disease (HbSC) or hemoglobin S beta$^+$ thalassemia (HbSβ^+), certain patients with HbSC or HbSβ^+ may have severe and frequent painful episodes requiring hospital admissions and aggressive pain management. Within each group of patients, the frequency and the degree of the pain are highly variable.[5] Due to the major impact of the pain on the health and quality of life of patients with SCD, inappropriate pain management may lead to suffering from suboptimal treatment or potentially life-threatening complications.[6]

The pathophysiology of pain in SCD is complex. The initial trigger is vaso-occlusion, with subsequent ischemia of tissues (commonly the bone marrow) and activation of inflammatory cascades, which will lead to inflammation and cytokine release.[7,8] Recurrent reactivation of pain fibers and associated neural networks leads to a hyperalgesic state, which causes amplified pain with each painful stimulus. In SCD, the complex interaction between red blood cells (RBC), white blood cells (WBC), platelets, and endothelium leads to activation of pain fibers, which leads to severe pain.[7]

It should be emphasized that, in addition to acute painful events, many patients with SCD also experience chronic pain. Under these circumstances, recurrent vaso-occlusive injury causes cumulative and chronic tissue insult and chronic inflammation. Physicians and health-care workers should be aware of the nature of chronic pain in these patients.

What defines the sickle cell pain is another challenging aspect of SCD care. Usually, patients are able to recognize vaso-occlusive pain. Other etiologies of pain that are common in patients with SCD, however, should be considered when dealing with a patient with acute or chronic pain (e.g., osteomyelitis, avascular necrosis of bones, cholelithiasis, constipation, acute chest syndrome, stroke, etc.).

Management of Sickle Cell Pain at Home

Most patients with acute painful episodes will be treated at home, and do not require hospital visits or admission. It is therefore crucial to educate patients, families and caregivers of the signs related to sickle cell pain and its appropriate management at home.

Patients, families and caregivers should be educated about the "3 Ps" (or similar) approach to pain management, which incorporates physical, psychological and pharmacological strategies for pain management. In addition, communication with health-care practitioners familiar with the management of pain in these patients would be extremely helpful for providing appropriate guidance for optimal pain management and reduction of hospital admissions.

Non-pharmacologic interventions (e.g., heat packs and massage) as well as behavioral modification (e.g., coping mechanisms and distraction) should be considered as part of the management plan.[13]

Management of Sickle Cell Pain in the Outpatient Setting

Patients should be seen in the day hospital/sickle cell clinic if they have inadequate pain control at home. If the clinic is not available, patients will need to be seen in the nearest emergency department (ED). Studies have shown that whenever available, day hospitals with trained personnel are superior to the ED for the management of uncomplicated painful events.[14] Once in their ED or day hospital, patients should be evaluated with priority and analgesic treatment should be initiated without delay.

In addition, patients should be started on oral or intravenous fluids to ensure adequate hydration or to provide necessary rehydration. This is usually achieved through more than maintenance fluid, but overhydration should be avoided, as it may lead to acute chest syndrome. Studies have suggested that fluids with lower sodium content may be beneficial, due to increased swelling of red cells and reduction of intracellular sickle hemoglobin (HbS) concentration.[15] Although no randomized trial has studied the ideal choice of fluid resuscitation, when no other concerns for hyponatremia exist, it is reasonable to start patients on hypotonic saline solutions (most commonly 0.45% normal saline).

Management of Sickle Cell Pain in the Inpatient Setting

If appropriate pain control cannot be achieved by oral medications, the patient should be started on intravenous medications and be admitted to the hospital. The overall goal should be immediate control of the pain and early discharge, but this should not lead to the potential side effect of oversedation or risk of readmission. Pain-management approaches should follow a similar approach to the "analgesic ladder" for the treatment of cancer-related pain recommended by the World Health Organization. The choice and dosage of analgesic should be given according to the severity of pain in each individual patient.[16, 17]

The inpatient management of sickle cell pain can be challenging, and can lead to patient-caregiver conflicts. Variations in pain management may be caused by differing perceptions about the risk of opioid dependence, the suitability of opioids for SCD pain management, and the efficacy of parenteral opioid administration.[18] In general, patients with SCD may be opioid-tolerant, and will require higher doses for the control of their pain.[6] Due to their higher dose requirements, these patients have an increased risk of opioid-related side effects, including respiratory depression and hyperalgesia. Health-care workers should be educated for this requirement, as suboptimal pain management may result in avoidable patient suffering. It is important to know that patients with SCD have not been shown to be at increased risk of opioid dependency compared with the general population.

In general, all opioids have common side effects that need to be carefully monitored and managed. Morphine, however, has been shown to be associated with an increased risk of acute chest syndrome.[19] Acute chest syndrome, a potentially fatal complication in patients with SCD, is more common in patients admitted for pain, likely due to overhydration, immobility, hypoventilation and/or opioid-induced vascular permeability.[6] Hence, all patients admitted with an acute painful event, and especially those with chest or back pain or patients with decreased O_2 saturation, should be started on incentive spirometry that is appropriate for the patient's age.[22]

If high doses of intravenous infusion of opioids along with adjunctive non-opioid mediation and boluses for breakthrough pain are not sufficient to control the pain, then physicians who are specialized in the management of pain should be consulted. Patient-controlled analgesia (PCA) or nurse-controlled analgesia (NCA) has been shown to be a safe and effective alternative for the management of severe pain.[22]

Choice of Analgesics

Recent evidence has demonstrated that the neurobiology of pain in SCD is more complicated than the simplified concept of ischemia-induced pain. In addition, subclinical studies as well as some clinical evidence indicated that current analgesics, including opioids, may exacerbate some underlying complications of SCD (renal disease, acute chest syndrome, seizures in those with history of stroke, hyperalgesia). Recently, great efforts have been made to investigate and develop new therapeutic options.[23] At the present, however, the mainstay of management of pain in SCD remains NSAIDs, acetaminophen, and opioid analgesics (e.g., morphine or morphine sulfate, hydromorphone; administered by either oral route, as intravenous single doses, or infusion – short acting or slow release). One thing that is certain is that the choice of analgesics should be carefully reviewed for each individual patient based on the past experience of patients and their SCD-related complications.

The recommendations for the dosing of medications for each specific scenario are beyond the scope of this consensus statement. It is encouraged that care centers develop a management guideline for administration of analgesics. Consultation with teams that have expertise in the management of pain should be sought, when the usual management is not sufficient to control the pain optimally or when there are contraindications for common analgesics.

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2. ACUTE CHEST SYNDROME

Principles

- Acute chest syndrome (ACS) is a potentially life-threatening complication of sickle cell disease requiring a high index of suspicion.
- ASC-related complications may be reduced by prompt intervention and appropriate therapy , including the use of blood transfusion.

Recommendations

Early Detection and Prevention

- Pulse oximetry should be a routine part of every medical assessment to identify changes from a patient's baseline oxygen saturation level.[12]
- Patients admitted for a febrile or vaso-occlusive episode should be carefully examined and have continuous oxygen saturation monitoring for early detection of clinical symptoms and/or changes in oxygenation.
- Hydroxyurea therapy should be considered for patients after a single episode of acute chest syndrome.[14]
- There is conflicting evidence about the benefit of chronic red blood cell (RBC) transfusions for the prevention of ACS, and they and are not routinely recommended.[15,16]
- Asthma management for children and adults with both sickle cell disease and asthma should be optimized, and a referral to an asthma specialist should be considered.

Diagnosis and Management

- Once ACS diagnosis is established:
  - Admit to hospital for close care and monitoring.
  - Administer high-flow oxygen to maintain an oxygen saturation of ≥95%.
  - Identify and treat airway, breathing, and circulation issues.
  - Maintain hydration with intravenous and oral intake to keep the total fluid intake at maintenance rate. Monitor fluid balance closely, as overhydration is associated with pulmonary edema and worsened clinical status.[20]
  - Treat pain aggressively by giving adequate analgesia while monitoring oxygen saturation and blood carbon dioxide, as opiates can cause hypoventilation and worsening oxygen saturation. *(see Guidelines for Pain Management, Part III, Section a)*
  - Obtain a complete blood cell count, reticulocyte count, arterial blood gases, and extended cross match for possible exchange or simple transfusion.
  - For febrile patients, obtain blood cultures and consider broad-spectrum antibiotics (including a macrolide for children at risk of atypical bacterial infections).
  - Consult Hematology service urgently prior to transfusion or admission.
  - The use of corticosteroids for the management of ACS has yielded equivocal results, and is not routinely recommended.
  - Patients should use incentive spirometry and/or be assessed by a respiratory therapist.
  - Oxygen saturation and oxygen requirements should be monitored closely.
  - Patients should be reviewed early by a critical care outreach team, if available, if there are concerns about serious or worsening clinical status.

Background

ACS is an acute complication of sickle cell disease defined as the presence of a new pulmonary infiltrate (involving at least one complete lung segment and not atelectasis), fever, chest pain, and/or respiratory signs and symptoms. Clinical signs and symptoms overlap with those of a lower respiratory tract infection. ACS is a leading cause of hospitalization in patients with sickle cell disease, and a significant risk factor for early mortality.

The incidence of ACS is highest among patients with homozygous SS genotypes, and is more common in children than in adults. Causes of ACS include infections (bacteria, viruses, Mycoplasma, Chlamydia and mixed infections), pulmonary infarction, and fat embolism. Patients with sickle cell disease who have undergone abdominal surgery are at risk of developing acute chest syndrome in the immediate post-operative period. Children with sickle cell disease and comorbid asthma are twice as likely to develop ACS as those with sickle cell disease who do not have asthma.[6] Age, hemoglobin F level, degree of anemia, and a higher steady-state white blood cell (WBC) count are also independent risk factors for ACS.[3] In patients with hemoglobin SC disease (HbSC), only WBC count was found to be a statistically significant risk factor.[3]

Up to 50% of hospitalized patients with ACS are admitted for other reasons – most commonly vaso-occlusive crises – and develop ACS during admission.[3] Clinical signs and symptoms of acute chest syndrome are similar in both SS and SC genotypes.[4] At the time of diagnosis, the most frequent symptoms of ACS include fever, cough, chest pain, shortness of breath, and tachypnea.[7] Other symptoms include wheezing, chills, abdominal pain, rib pain, and pain in the arms and legs. Fever and cough are more common in young children, while chest pain, productive cough, and hemoptysis are more common in adult patients. Neurologic complications may also occur. Symptoms observed during a patient's first episode of acute chest syndrome are generally predictive of symptoms during subsequent events.

It is important to note that recurrent ACS is associated with an increased risk of stroke.[3,8] Recurrent ACS is also associated with an increased risk of pulmonary hypertension, interstitial lung disease and pulmonary fibrosis.[9,10,11]

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3. FEVER

Principles

- Infection is the most common cause of sickle cell disease-related mortality.
- Febrile patients with sickle cell disease should be managed promptly to prevent serious infectious complications.
- To review current recommendations for the management of fever in children older than 2 months of age and adults with sickle cell disease. (Penicillin prophylaxis in children with sickle cell disease is discussed separately in the Newborn Screening Chapter.)
- Management of infants younger than two months of age will not be discussed in this section, as they are at risk of serious infections, irrespective of their SCD.

Recommendations

Education of Patients, Families and Caregivers

- Fever is defined as an oral temperature greater than or equal to 38.5°C or 37.5°C by axillary measurement.
- Patients, parents, or caregivers should be educated for the risk of infections on a regular basis.
- Clear instructions should be provided for patients, families, and caregivers (including school personnel) to seek timely and prompt medical attention when a child with SCD has a fever.
- Patients and families should have a functioning thermometer at home for the timely measurement of body temperature when required.
- All patients with sickle cell disease who have a fever should be seen urgently in the nearest Emergency Department or a clinic with available resources, as soon as possible, and regardless of age, disease genotype, vaccination status, or use of antibiotic prophylaxis.
- A Medic-Alert bracelet may be recommended to assist in rapid assessment and triage in the event where a SCD patient is unable to provide their diagnosis.
- Patients should carry a note (ideally both in writing and in electronic form) stating their diagnosis and a suggested management plan, which should be presented to health-care providers who may not be familiar with the specialized care required for SCD patients.

Triage and Initial Management

- Institutions are encouraged to have guidelines for the management of fever in SCD patients.
- All febrile patients with SCD should be seen urgently, and appropriate parenteral antibiotics be administered within 30 minutes of arrival and immediately after blood culture is obtained. The administration of antibiotics should not be delayed, however, for blood-culture sampling.
- In addition to blood cultures, laboratory investigations should include a complete blood-cell count (CBC) with white blood cell differential count and reticulocyte count, bilirubin (total and direct) and blood type and screen.
- Infants younger than 3 years of age should also have a urine culture.
- Further investigations (e.g., blood gas, chest x-ray, throat culture, stool culture, lumbar puncture, evaluation for osteomyelitis) may be indicated based on clinical presentation.
- A chest x-ray should be ordered if the patient has cough, chest pain, fever and/or oxygen saturation below 96%.
- Every patient with SCD and fever should be admitted to hospital and administered intravenous antibiotics with any or more of the following risk factors:

  1. Unwell or hemodynamically unstable appearance
  2. Fever ≥40°C
  3. Age <6 months

4. Leukopenia (white blood cell count <5 x 10^9/L), leukocytosis (white blood cell count >30 x10^9/L), thrombocytopenia (platelet count <100 x10^9/L), hemoglobin <50 g/dL and/or a decline in hemoglobin equal to or more than 20 g/dL from baseline.
5. Respiratory distress
6. Clinical findings suggestive of meningitis, osteomyelitis, acute chest syndrome, or splenic sequestration
7. Pulmonary infiltrate on chest x-ray
8. History of pneumococcal sepsis and/or meningitis
9. Severe pain that cannot be managed at home
10. Severe dehydration
11. Two or more return visits to the emergency department for the same episode
12. Considered unsafe for discharge or close follow-up cannot be ascertained

- Patients who do not meet the above criteria may be candidates for discharge after receiving appropriate intravenous antibiotic (See section E of this chapter on Fever).
- Depending on the other symptoms or signs, patients who are unwell may need to be seen acutely or be transferred to the intensive-care unit.

Choice of Antibiotic

- Second- or third-generation cephalosporins are effective against most common pathogens in patients with SCD and are the antibiotics of choice. Ceftriaxone has the advantage of every-24-hours dosing, especially in low-risk patients who may be discharged home (see below).
- Patients on ceftriaxone should be monitored for ceftriaxone-induced hemolytic anemia.
- Parenteral clindamycin or ciprofloxacin can be used in those patients who have significant allergy to beta-lactam antibiotics. Consult an infectious disease team for guidance.
- In areas where intermediate or high levels of penicillin-resistant pneumococci are prevalent, vancomycin should be added to the second or third general cephalosporin antibiotic.
- In patients who are suspected to have meningitis, those who are hemodynamically unstable, and/ or patients who are unwell, vancomycin should also be added to the second- or third-generation cephalosporin. Consult an infectious disease team for guidance.
- In cases where malaria is suspected, an infectious diseases team should be consulted, and appropriate investigation and treatment should be initiated.
- Febrile SCD patients over the age of 5 years with respiratory symptoms should also be given a macrolide antimicrobial to treat for mycoplasma. Children younger than 5 years of age may also be treated for mycoplasma if there is a high clinical suspicion.
- If infection with influenza is suspected, anti-viral therapy should be considered.
- Patients with osteomyelitis should be covered for common pathogens (e.g., *Staphylococcus aureus and Streptococcus pyogenes*) as well as Salmonella species. Consult an infectious diseases team for guidance.
- Once the results of cultures become available, antibiotics should be modified according to microbial sensitivities.

Disposition and Follow-up

- Low-risk patients can be discharged home, after receiving ceftriaxone in the emergency department. It is strongly recommended that the patient receives the second dose of parenteral ceftriaxone 24 hours after the first dose, while waiting for the 48-hour blood-culture results to become available.

- Low-risk patients whose immunizations are up to date (including vaccination against pneumococci and meningococci) with reliable follow-up may alternatively be considered for discharge on oral antibiotics after receiving the first dose of parental antibiotic (ceftriaxone) and until the result of the blood culture becomes available.
- Patients who are being considered for discharge and who have received ceftriaxone should be monitored in the emergency department for two hours before discharge to monitor for ceftriaxone-induced hemolysis. This is especially important for patients who have been treated with ceftriaxone within the preceding two months or those who have received frequent doses of ceftriaxone in the past. Patients and parents should be provided guidance for monitoring of symptoms of hemolysis at home.
- In low-risk patients who are discharged and in whom no source of infection has been identified, once the results of cultures are available and are negative, antibiotics can be stopped.
- In low-risk patients for whom the result of blood cultures are available and negative but there is a source of infection that can be treated as outpatient (e.g., ear infection), antibiotics can be changed to treat the infection as appropriate.
- If the blood cultures are positive for bacterial growth, the patient should be immediately contacted and admitted into the hospital for treatment with an appropriate antibiotic against the identified infection.
- High-risk patients should be admitted to the hospital and treated until the cultures are negative, the patient looks well, and the patient is considered safe for discharge.

Background

Infections are the most common cause of mortality in patients with sickle cell disease (SCD) worldwide. Fortunately, the practice of early identification of patients with SCD through neonatal screening, antibiotic prophylaxis and expanded immunization schedules have significantly reduced infection-related mortality in countries with available resources.[1] Patients with SCD are especially at risk of severe infections (sepsis, meningitis) caused by encapsulated bacteria including *Streptococcus pneumoniae, Haemophilus influenzae* type b, and non-typhi salmonella species.[2,3] In endemic areas, malaria infection with secondary severe hemolysis is a major cause of mortality among patients with SCD.[4]

The susceptibility of SCD patients to infection is mutifactorial. The process of functional asplenia starts early in life, and, by the age of 5 years, more than 95% of children with sickle cell anemia (HbSS) will have functional asplenia.[5] Patients with hemoglobin S beta-^{0} disease (HbSβ^0) have a similar progression of asplenia to those with HbSS. Patients with hemoglobin SC disease (HbSC) and hemoglobin S beta$^+$ thalassemia, however, will generally have a later and slower progression of asplenia.[6] Patients with SCD also have abnormalities of the alternative complement pathway.[8] Viral and bacterial respiratory infections may trigger acute chest syndrome, which is another serious and potentially fatal complication in these patients.[9]

Despite the implementation of effective newborn hemoglobinopathy screening, antibiotic prophylaxis, and immunization against *S. pneumoniae* and *H. influenzae,* which have significantly reduced the mortality of infections in SCD patients,[10,11] the protection is not complete, and serious bacteremia does occur.[12] As a result, prompt and specific management of fever and infections in patients with SCD is of utmost importance.

It is imperative to educate patients, families, and care providers about the significance of fever and its optimal management, considering the severe complications that are associated with infection in patients with SCD.[12, 13]

Considering the potential serious complications of infection in patients with SCD, urgent administration of antibiotics for febrile patients with SCD is critical.[14] The landmark randomized trial by Wilimaset has demonstrated that a carefully selected subgroup of low-risk patients with SCD may be managed as outpatients with daily doses of ceftriaxone until blood cultures are negative.[15] It is important to note that fever can also be observed with other serious complications of SCD (e.g., acute splenic sequestration), which may require admission and aggressive treatments.[16]

In patients with SCD and fever, the prescribed antibiotic must be effective against common pathogenic bacteria in SCD.[14] In addition, the incidence of penicillin-resistant *S pneumoniae* in the community and the possibility of other serious infections (e.g., meningitis) should be considered. Ceftriaxone is the most widely used antibiotic in patients with SCD in Canada, due to its good coverage for common SCD pathogens and once-daily administration. Ceftriaxone-induced hemolytic anemia is a potentially serious complication that is thought to be immune-mediated, and is more common in SCD patients compared with the general population.[16]

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4. STROKE AND NEUROLOGICAL COMPLICATIONS

Introduction

Patients with sickle cell disease (SCD) may be affected by various disorders of the central nervous system, including ischemic and hemorrhagic stroke, transient ischemic attack, silent cerebral infarction, cerebral vasculopathy, and Moyamoya disease.[1] Prevention and early recognition of the neurological complications of sickle cell disease are necessary to reduce the long-term impact of these disorders.

A. Management of Stroke in Children with Sickle Cell Disease

Principles

- To identify children with SCD who are at an increased risk of stroke, and to implement measures to prevent stroke occurrence.
- To carry a high index of suspicion in patients with clinical signs and symptoms of stroke, and to urgently implement appropriate management to reduce stroke-associated morbidity and mortality.
- To prevent the recurrence of stroke among children with SCD who have already experienced a stroke event.

Recommendations

Education, Screening and Prevention of Ischemic Stroke in Children

- Parents and caregivers of children with SCD should be educated about the common presenting signs and symptoms of stroke, and advised to present emergently to the nearest hospital if any of these symptoms occur. Teaching should be reinforced at every follow-up visit.
- Annual TCD ultrasound screening should be performed in patients with SCD starting at 2 years of age. Available literature on this subject mainly comprises patients with HbSS and HbSbeta 0-genotypes.
- Patients with abnormal TCD screening results (TAMM velocities ≥200 cm/s) should have repeat testing within 2 weeks, and should be counseled regarding the risk of stroke and the benefits of prophylactic blood-transfusion therapy. Referral to a hematologist with expertise in sickle cell disease is strongly recommended.
- Where long-term transfusions are not feasible (e.g., due to red-cell alloimmunization and/or family refusal), physicians should consider hydroxyurea therapy and/or a referral for hematopoietic stem-cell transplantation.[16,17,18]
- Patients with ≥1 conditional TCD velocity (170 to 199 cm/s) are at risk of conversion to abnormal TCD, and are at a higher risk of developing a first stroke than are patients with normal TCDs. Currently, no specific therapeutic intervention is recommended for these patients, and no randomized control trial has been performed to assess whether there is any benefit to treating these patients. More frequent TCD screening (every 3 to 6 months), however, has been recommended for these patients.[19]
- For secondary stroke prevention, chronic transfusions to maintain the HbS level <30% are also recommended.[20] The recently published results from the Stroke With Transfusions Changing to Hydroxyurea (SWITCH) trial have demonstrated that children with SCD who have already experienced a stroke are still at risk of stroke recurrence if they are switched from chronic transfusion therapy to hydroxyurea and phlebotomy.[21]
- For patients who receive chronic red-cell transfusions, optimal chelation therapy is necessary *(see Part II, section 14 on Iron Overload)*.

Management of Acute Ischemic Stroke in Children

- Admit to hospital.
- Administer high-flow oxygen to maintain an oxygen saturation of ≥95%.
- Identify and treat airway, breathing, and circulation issues.
- Maintain hydration with intravenous and oral intake to keep the total fluid intake at maintenance rate.

- Maintain normal body temperature, normal blood pressure, normoglycemia, and control seizures.
- Urgent computed tomography (CT) scan of the brain without contrast may be negative within the first 12 hours of ischemic stroke event.[22]
- If there is a high index of suspicion, and CT is negative, diffusion weighted magnetic resonance imaging/angiography (MRI/MRA) of the brain is more sensitive than CT for detecting early and small infarcts as well as hemorrhagic conversion of infarcts.[19] MRI may be performed acutely, if a CT scan is normal, but is usually deferred until after the initiation of acute therapy.
- Exchange red-cell transfusion (erythrocytapheresis) to target an HbS <30% is recommended for the acute management of acute ischemic stroke, although there are no randomized control trials to support this recommendation.
- Consider initial simple transfusion when an urgent exchange transfusion cannot be initiated within 4 hours of presentation, or for children in whom the stroke is secondary to severe anaemia from splenic sequestration or aplastic crisis.[23,24]
- Other risk factors for acute ischemic stroke should be excluded, including infections, Moyamoya disease, cardiac disease, arterial dissection, and prothrombotic abnormalities. Also, consider computed tomography venography/magnetic resonance venography (CTV/MRV) (especially if MRA is normal) to investigate for cerebral sinovenous thrombosis (CSVT).
- Consultations with a pediatric hematologist and a pediatric neurologist are recommended.
- The use of thrombolytic therapy is not routinely recommended in children with ischemic stroke outside of a clinical trial.[25]
- Patients should be started on a chronic transfusion program to maintain HbS levels below 30%, and to prevent stroke recurrence.[11]
- Once the patient is stable, consider investigations for other potential causes of acute ischemic stroke (e.g., echocardiography, ECG, MRI/A, carotid Doppler ultrasonography, fasting lipid profile, thrombophilia investigations).
- Consider the long-term use of anti-platelet and/or anti-thrombotic therapies.
- Long-term follow-up should be coordinated between multiple disciplines, including hematology, neurology, physical therapy, occupational therapy, and speech therapy.

Management of Hemorrhagic Stroke in Children

- For hemorrhagic stroke, there is no clear evidence on the role of exchange blood transfusion in the acute phase. Long-term transfusions are often considered for maintenance therapy.
- Supportive care is the same as with acute ischemic stroke (see section i. above, *Acute ischemic stroke*).
- Investigate for concurrent bleeding diathesis, and correct coagulopathy, if present. Consultation with a pediatric hematologist is recommended.
- Urgent neurology and neurosurgical consultations should be obtained to evaluate for the need for surgical intervention.
- Referral for hematopoietic stem-cell transplantation (HSCT) should be considered for children with SCD who have sustained a stroke event *(see Part II on Transfusion)*.[15]

Background

Stroke is a rare but significant cause of disability in children with SCD; neurologic deficits will occur in approximately two-thirds of survivors.[2] SCD is the most common cause of stroke in children. Overt stroke occurred in approximately 1 in 10 children with sickle cell anemia (HbSS) in the era prior to active screening by transcranial Doppler (TCD) and the use of transfusion prophylaxis in high-risk patients.[1] By 18 years of age, the cumulative risk of overt stroke is reduced to 1.9% (95% confidence interval [CI], 0.6% to 5.9%) with active screening by TCD and transfusion as primary stroke prophylaxis.[3] Patients with HbSS disease have the highest risk of stroke, and have an 11% chance of developing a first stroke by the age of 20 years compared with a 2% risk for patients with

hemoglobin[5] SC disease (HbSC).[1] Children with SCD who are between the ages of 2 and 5 years have the highest incidence of first stroke followed by those between 6 and 9 years of age.[4] Most strokes in children with SCD are ischemic, and commonly involve the large arteries supplying the brain such as the middle cerebral and internal carotid arteries.

Primary hemorrhagic stroke is less common than arterial ischemic stroke among children with SCD. Presenting signs and symptoms of hemorrhagic stroke may include severe headache, nausea and vomiting, nuchal rigidity, focal neurologic deficits, seizures, and altered levels of consciousness. Some factors that have been reported to be associated with hemorrhagic stroke in children with SCD include hypertension, corticosteroid use, and a recent history of blood transfusion.[5]

Clinical features of ischemic stroke include focal weakness (usually hemiparesis), seizures, altered consciousness and mentation, confusion, visual, speech, and sensory disturbances. In children, these symptoms may be transient.

Recognized risk factors for ischemic or hemorrhagic stroke among patients with SCD include high blood-flow velocity on transcranial Doppler ultrasonography, low steady state hemoglobin levels, high white-cell count, hypertension, and a recent history of acute chest syndrome.[3] Genetic factors (such as a family history of SCD and stroke, comcomitant alpha thalassemia, hemoglobin F levels) and nocturnal hypoxemia may also modify the risk of stroke.[6,7]

TCD is used as a screening tool to evaluate stroke risk among children and adolescents with SCD. TCD is a non-invasive approach for measuring the time-averaged maximum mean (TAMM) velocity in the middle cerebral artery, distal internal carotid artery, anterior cerebral artery, posterior cerebral artery, and basilar artery. Patients with TAMM velocities ≥200 cm/second in any of the arterial segments are considered to have abnormal results, while velocities between 170 and 200 cm/second are termed conditional. Abnormal blood velocities reflect arterial narrowing, and predict a stroke risk of 40% over the subsequent 3 years.[8]

The Stroke Prevention Trial in Sickle Cell Anemia (STOP 1) trial showed a clear benefit for prophylactic blood transfusions in children with abnormal TCD, with a 92% reduction in stroke risk when compared with observation only.[9] A decision-analysis model by Mazumdar *et al* suggests that the optimal stroke-prevention strategy using TCD is annual screening until age 10 years, with transfusions for children at high risk until age 18 years.[10] This finding has not been evaluated within the parameters of a randomized controlled trial, however, and the optimal duration of transfusion therapy is unknown.[11,12] During the STOP II trial, discontinuation of prophylactic red-cell transfusions caused a high rate of reversion to abnormal TCD blood-flow velocities and strokes in high-risk children.[13] A 2011 analysis of the STOP II data demonstrated that the cessation of prophylactic red-cell transfusions is also associated with an increased risk of silent brain infarction in high-risk children with SCD.[14]

Patients with SCD who have already had a first stroke also benefit from regular blood transfusions. If left untreated, these patients have a 67% risk of a second stroke over the subsequent 9 years.[15] Transfusions for primary and secondary prophylaxis of stroke are aimed at keeping the total sickle hemoglobin (HbS) level below 30%.[11]

B. Management of Stroke in Adults with Sickle Cell Disease

Principles

- To carry a high index of suspicion in patients with clinical signs and symptoms of stroke.
- To urgently implement appropriate management to reduce stroke-associated morbidity and mortality.

Recommendations

Patient Education

- Patients and caregivers should be educated about the common presenting signs and symptoms of stroke, and advised to present emergently to the nearest hospital if any of these symptoms occur. Teaching should be reinforced at every follow-up visit.

Management of Acute Ischemic Stroke in Adults

- Admit to hospital.
- Administer high-flow oxygen to maintain an oxygen saturation of ≥95%.
- Identify and treat airway, breathing, and circulation issues.
- Maintain hydration with intravenous and oral intake to keep the total fluid intake at maintenance rate.
- Emergent imaging of the brain should be performed prior to initiating any specific therapy for treating acute ischemic stroke. Non-contrast CT is sufficient to provide this information in most cases.
- If there is a high index of suspicion and CT is negative, diffusion-weighted MRI/MRA is more sensitive than CT for detecting early and small infarcts as well as hemorrhagic conversion of infarcts.[19] MRI may be performed acutely, if a CT scan is normal, but is usually deferred until after the initiation of acute therapy.
- As in the case of adult ischemic stroke in the absence of SCD, the use of a fibrinolytic agent (e.g., tissue plasminogen activator) may be considered within the first 3 hours of the acute phase.[27] Thrombolytic therapy may be pursued in consultation with a neurologist, with the caveat that its use in patients with SCD is associated with an increased risk of intracerebral hemorrhage.
- Consultations with both hematology and neurology subspecialists are recommended.

NOTE: The majority of the recommendations below are based on pediatric research literature. To date, there are insufficient data from randomized clinical trials to provide evidence-based recommendations.

- Exchange transfusion is recommended to reduce the HbS level below 30%. This recommendation is extrapolated from clinical literature, but there have been no randomized controlled trials to support this.
- Long-term simple or exchange red-cell transfusion is recommended to maintain an HbS level ≤30%. Exchange transfusion, either manual or automated, is favored over simple transfusion in adults with SCD, to maintain iron balance or to assist in reducing iron overload.[28]
- Consider hydroxyurea therapy if chronic transfusions are not feasible (e.g., due to severe alloimmunization or patient refusal).
- Once the patient is stable, consider investigations for other potential causes of acute ischemic stroke (e.g., echocardiography, ECG, MRI/A, carotid Doppler ultrasonography, fasting lipid profile, thrombophilia investigations).
- Consider the long-term use of anti-platelet and/or anti-thrombotic therapies.

Management of Hemorrhagic Stroke in Adults

- For hemorrhagic stroke, there is no clear evidence on the role of exchange blood transfusion in the acute phase. Long-term transfusions are often considered for maintenance therapy.
- Supportive care is the same as with acute ischemic stroke (see Recommendations above for Acute Ischemic Stroke).
- Investigate for concurrent bleeding diathesis, and correct coagulopathy if present. A consultation with a pediatric hematologist is recommended.
- Urgent neurology and neurosurgical consultations should be obtained to evaluate the need for surgical intervention.

Background

Although ischemic strokes are more common among individuals with HbSS who are younger than 20 years of age, patients with HbSS who are aged 30 years and older (especially those ≥50 years of age) are also at risk of ischemic stroke. Within the adult population of individuals with HbSS, the rate of ischemic stroke is lowest in the 20- to 29-year-old age group. Interestingly, this group of patients also had the highest incidence of hemorrhagic stroke.[3]

To date, there have been no clinical trials to evaluate approaches for primary stroke prevention for adult patients with sickle cell disease (SCD). The use of TCD ultrasound is not generally recommended as screening tool for the prevention of stroke among adults with SCD.[21]

C. Silent Cerebral Infarction

Principles

- To identify children and adults with SCD who have silent cerebral infarcts.
- To implement close neuroradiological and neurocognitive follow-up in children and adults with SCD.

Recommendations

- A screening MRI/MRA at least once during childhood is recommended.[37] The need for sedation or general anesthesia and the presence of neurocognitive abnormalities may depend upon the age at initial screening.
- Follow up MRI/MRA may be indicated if abnormal radiographic findings are found, and/or if neurocognitive difficulties occur.
- Children with SCD who are found to have cognitive/learning difficulties should also have follow-up MRI/MRA studies.
- Regular neuropsychological testing and review of school performance is recommended for school-aged children with SCD.
- In the multicentre Silent cerebral Infarct Transfusion (SIT) trial, therapy with regular red-cell transfusions to keep HbS<30% led to a significant reduction in the incidence of recurrent cerebral infarction in children with SCD.[36]

Background

Silent cerebral infarcts (SCI) are more frequent than overt strokes among individuals with SCD. Upon MRI, these SCI present as abnormalities not associated with overt symptoms or focal neurological abnormalities. Silent infarcts commonly occur in the frontal and parietal lobes, and may be seen in 20% to 35% of children with SCD.[29] Silent infarcts are associated with impaired cognitive function and an increased risk of stroke.[1] SCI may also progress over time.[31] Risk factors for SCI include positive history of seizures, presence of the SEN beta-S globin gene haplotype, white blood cell (WBC) count $\geq 11.8 \times 10^9$/L and less than one painful event per year.[32] In the Silent Cerebral Infarct Multi-Center Clinical Trial, lower baseline hemoglobin concentration, higher baseline systolic blood pressure, and male sex were identified as risk factors associated with SCI.[35] In this trial, therapy with regular red-cell transfusions led to a significant reduction in the incidence of recurrent cerebral infarction in children with SCD.[36]

D. Cerebral Vasculopathy

Principles

- To identify children and adults with SCD with Moyamoya disease.
- To implement close neurological and/or neurosurgical follow-up in children and adults with SCD and Moyamoya disease.

Recommendations

Investigation

- A screening MRI/MRA at least once during childhood is recommended.[42] The age at initial screening may depend on the need for sedation/general anesthesia and the presence of neurocognitive abnormalities.
- Follow-up MRI/MRA may be indicated if abnormal radiographic findings are found and/or if neurocognitive difficulties occur.
- Children with SCD who are found to have cognitive/learning difficulties should also have follow-up MRI/MRA studies.
- Regular neuropsychological testing and review of school performance is recommended for school-aged children with SCD.

- A screening MRI/MRA at least once during childhood is recommended.[42] The age at initial screening may depend on the need for sedation/general anesthesia and the presence of neurocognitive abnormalities.
- Follow-up MRI/MRA may be indicated if abnormal radiographic findings are found and/or if neurocognitive difficulties occur.
- Children with SCD who are found to have cognitive/learning difficulties should also have follow-up MRI/MRA studies.
- Regular neuropsychological testing and review of school performance is recommended for school-aged children with SCD.

Management

- Moyamoya disease usually requires a referral to a neurosurgeon for possible surgical intervention with or without prophylaxis with antiplatelet agents.
- Under the direction of a neurologist, medical therapy (such as antiplatelet therapy and/or calcium channel blockers) may be used in individuals who are poor surgical candidates or those with mild disease. Short- and long-term efficacy data are very limited, however.[43]
- Consultation with a neurology and/or stroke subspecialist is recommended for guidance on acute management and follow-up.

Background

Moyamoya disease results from progressive occlusion of the circle of Willis arteries and particularly the distal internal carotid artery (ICA) (less often the proximal anterior cerebral artery by [ACA], the middle cerebral artery [MCA], the basilar artery. and the posterior cerebral arteries [PCAs]). This progressive occlusion causes the development of characteristic collateral, the appearance of which on angiographic imaging may be described as a "hazy puff of smoke," which is the direct Japanese translation. Children with Moyamoya disease typically develop acute ischemic stroke or transient ischemic attacks, while adults may have ischemic or hemorrhagic events.[38] The highest known prevalence of the disease is in the Japanese population.[39] Moyamoya is associated with a higher risk of cerebrovascular events among affected individuals with SCD, and more children tend to progress to occlusion than adults.[40]

Diagnosis is made by MRI/MRA/cerebral angiography; diagnostic criteria using these neuro-imaging techniques have been described.[41]

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5. EYE COMPLICATIONS

Principles

- To rapidly assess and treat patients with new vision changes or eye trauma.
- To use appropriate screening tests for patients at increased risk of eye disease.
- To identify proliferative sickle retinopathy early.
- To initiate appropriate monitoring and treatment as soon as eye complications have been identified.

Recommendations

Investigation

- Any patient with SCD who develops new changes in vision should be referred to an ophthalmologist immediately.
- Any patient with SCD who sustains eye trauma should be referred to an ophthalmologist immediately to rule out hyphema.
- By the age of 10, all patients with sickle cell disease should have had a full ophthalmologic examination, which should include:
  - Assessment of visual acuity
  - Intraocular pressure
  - Evaluation of anterior structures with slit-lamp biomicroscopy
  - Examination of posterior and peripheral retina, with fluorescein angiography when indicated

  If eye examination is normal, routine follow-up should take place every 1 to 2 years.
- If proliferative or other eye complications are identified, the patient should have more frequent follow-up with an ophthalmologist.
- Patients with eye complications should ideally be followed by a retinal specialist who has experience with sickle cell disease.

Treatment

- All patients with proliferative retinopathy should be followed by an ophthalmologist who has experience with SCD, and who will determine the appropriate timing and modality of therapy.

Background

a. Proliferative Sickle Retinopathy

While many ocular complications of sickle cell disease can occur, the most recognized complication is proliferative retinal vascular disease. Occlusion of the peripheral retinal pre-capillary arterioles produces local retinal ischemia, which triggers neovascularization and formation of fibrovascular lesions referred to as "sea fans."[1] Only arterioles and capillaries are occluded in children, whereas both arteries and veins occlude in adults, possibly because sickled red blood cells are the only insult in children, but leukocyte and endothelial activation over time with cumulative damage to the vascular system causes additional occlusion in adults.[1] The new, fragile vessels are prone to vitreous hemorrhage, and fibrovascular lesions can cause traction on the retina and subsequent retinal detachment and visual loss. The Goldberg staging system (stages I to V) reflects this spectrum of disease progression.[2] Another classification system has also been proposed.[3] See table 1 for a summary of ocular complications of sickle cell disease.

Proliferative sickle retinopathy (PSR) is more prevalent in patients with hemoglobin SC disease (HbSC) (33%)[4] than in patients with sickle cell anemia (HbSS) (3%).[5] The typical age of onset is earlier in men with HbSC (ages 15 to 24) than in women with HbSC (ages 20 to 39) and than HbSS patients of both genders (ages 25 to 39).[6] There can be evidence of PSR as early as 8 to 10 years of age in patients with HbSC[7,8,9] and as early as 13 years of age in patients with HbSS.[9] The risk factors for closure in HbSS disease are a low total hemoglobin, low fetal hemoglobin (HbF),

and high irreversibly sickled cell count.[1] Autoinfarction of a sea fan causes spontaneous regression, and is more common in patients with HbSS.[10]

PSR is usually asymptomatic, unless the patient develops complications, such as vitreous hemorrhage or retinal detachment, in which case he or she may complain of floaters or visual field loss. If macular ischemia occurs, vision loss can arise from a single macular infarct or cumulative insult to the small vessels surrounding the fovea, causing enlargement of the foveal avascular zone and reduced visual acuity over time.

Eye examinations, therefore, should be performed in response to new symptoms, and as part of a routine screening program. Examination should include: assessment of visual acuity, intraocular pressure, evaluation of anterior structures with slit-lamp biomicroscopy, and examination of posterior and peripheral retina, including fluorescein angiography, when indicated.[9] Diagnosis of PSR is suspected on funduscopy by the characteristic appearance of the retinal vasculature, and is confirmed by documenting retinal ischemia on fluorescein angiography. There is no known method of preventing PSR, although hydroxyurea and other inducers of HbF, theoretically, could be protective.

Laser photocoagulation is the established treatment of PSR. Intravitreal anti-vascular endothelial growth factor agents may complement laser treatment, but their use is not yet supported in the literature. Current evidence indicates that no active interventions are required for new vessels that are asymptomatic or do not threaten the macula. Sectoral or circumferential retinal photocoagulation destroys the ischemic retina, which is responsible for the proliferative retinopathy. Patients are usually treated if there is bilateral disease, spontaneous hemorrhage, a high degree of neovascularization, or if they have already lost vision in one eye due to proliferative retinopathy.[9]

In patients with early disease, prophylactic photocoagulation may prevent visible progression.[11] One study, however, showed no absolute difference in visual acuity between eyes that had undergone photocoagulation and those that had not.[12] This may be due in part to the relative rarity of visual loss as a result of PSR. In a natural history study of a cohort of 59 patients with sickle cell disease (SCD) and PSR, vitreous hemorrhage was rare with no longstanding visual sequelae, and prolonged vision loss due to retinal detachment only occurred in 2 patients.[8] Further study is required.

Chronic phlebotomy to a target hemoglobin (Hb) of 90 to 100g/L has been suggested as a means of preventing progression, but this has not been tested in a prospective, randomized fashion, and is not routinely performed in clinical practice.

b) Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) can cause sudden, painless onset of blindness. CRAO is rare, with only 17 cases reports identified in a recent systematic review of the literature, mostly in patients with HbSS.[13] Patients were 5 to 32 years of age. About one-third of events occurred during a vaso-occlusive crisis, supporting the hypothesis that CRAO is caused by acute thrombus formation.

There is no proven treatment for CRAO in SCD. As with other severe complications of vaso-occlusion, simple or exchange red blood cell (RBC) transfusion may help ameliorate symptoms by decreasing sickle hemoglobin (HbS) cells. Thirteen of the patients in this series had at least partial recovery. There was no clear association between those patients who received exchange transfusion and those whose vision improved. Other treatments included: oxygen, chronic transfusion, acetylsalicylic acid, heparin, and/or nifedipine.

c) Hyphema

Trauma to the eye can cause bleeding into the anterior chamber, known as hyphema. In a patient with SCD, or even sickle-cell trait, sickled RBCs can block drainage of the anterior chamber, increasing the risk of elevated intraocular pressure and subsequent retinal or optic-nerve ischemia. Because of this risk, it is prudent for all patients and carriers with SCD to have an ophthalmologic evaluation after any ocular trauma.

Table 1. Ocular Complications of Sickle Cell Disease

Retrobulbar and Orbit	Orbital compartment syndrome with inflammation: orbital cellulitis, orbital wall infarction
	Recurrent bilateral lacrimal gland enlargement
Anterior Segment	Conjunctival vessel dilation
	Ischemia associated with retinal surgery or extensive panretinal photocoagulation
	Iris ischemia resulting in iris atrophy, pupillary abnormality, and, rarely, iris neovascularization
	Traumatic or post-surgical hyphema with induced glaucoma
Posterior Segment	Vascular occlusion (arterial and or venous)
	Central or branch retinal artery occlusion (spontaneous or following trauma or surgery with elevated intraocular pressure)
	Branch retinal artery occlusion
	Submacular choroidal infarction
	Macular infarction or enlargement of the foveal avascular zone
	Epiretinal membrane
	Macular hole
	Retinal schisis and/or holes
	Retinal neovascularization
	Choroidal ischemia, neovascularization
	Optic disc neovascularization
	Angioid streaks

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6. PULMONARY HYPERTENSION AND CHRONIC PULMONARY DISEASE

Acute chest syndrome is covered in detail in Part II, section 2.

Principles

- To screen all individuals with SCD for pulmonary hypertension.
- To evaluate with echocardiogram, and determine which patients require further testing with right heart catheterization.
- To evaluate for possible underlying causes of pulmonary hypertension.
- To prevent new-onset or progression of pulmonary hypertension.
- To diagnose asthma, sickle cell chronic lung disease, and obstructive sleep apnea in affected patients.
- To appropriately manage chronic pulmonary disease following diagnosis.

Recommendations

A. Pulmonary Hypertension

- All SCD patients should have regular clinical evaluation for cardiorespiratory symptoms, including shortness of breath on exertion, exertional chest pain, syncope, palpitations, peripheral edema, hepatic congestion and ascites.
- Regular pulse oximetry monitoring of oxygen saturation (SpO_2) during medical visits is recommended to determine baseline status. Patients with deteriorating or low (≤94%) measurements should be referred to a respiratory specialist. (Note that transcutaneous monitoring can underestimate oxygen saturation, so appropriate follow-up is recommended to avoid misdiagnosis.)[14,15]
- All SCD patients should have a baseline screening echocardiogram starting at the age of 3 years, including measurement of tricuspid regurgitant jet velocity (TRV).
- Echocardiogram should be repeated at least every 5 years if normal and if the patient is asymptomatic.
- Adult patients should be considered for right-heart catheterization (RHC) as the gold standard for pulmonary hypertension (PHTN) diagnosis if (see Figure 1):
  - TRV ≥2.8 m/sec, or
  - TRV ≥2.5 m/sec and symptoms of PHTN, high NT-proBNP testing (>164.5 pg/mL), and/or low six-minute walk distance (≤333 m)
- In patients with PHTN confirmed on RHC, thromboembolic disease, iron overload, systemic hypertension, obstructive sleep apnea, and chronic hypoxemia must be ruled out and treated.
- Hydroxyurea and/or transfusion (simple or exchange) may be considered in patients with PHTN confirmed on RHC. Selection of therapeutic strategy may depend upon the physician and patient preference, and the severity of PHTN.
- Targeted therapy may be considered in consultation with a PHTN specialist. When possible, patients should be considered for enrollment in an available clinical trial.
- Hydroxyurea therapy should be considered even if RHC shows normal pulmonary-artery pressure, as raised TRV on echocardiogram remains a poor prognostic marker, with increased mortality in adults with SCD.

B. Chronic Pulmonary Disease

- Patients should be screened for respiratory symptoms associated with asthma, chronic lung disease, and obstructive sleep apnea (OSA) on routine clinical visits.
- Routine screening pulmonary function testing (including lung-volume measurements and DL_{CO}) should be considered for both adult and pediatric patients to identify subclinical abnormalities.

Asthma

- Patients describing symptoms suggestive of asthma should have spirometry testing with bronchodilator challenge.
- Young children (e.g., those under 6 years of age) with respiratory signs and/or symptoms who are unable to perform pulmonary function testing may benefit from consultation with an asthma specialist, as a diagnosis of asthma can be difficult to establish.
- Medical management of asthma in patients with SCD should follow established clinical practice guidelines.
- Consultation or co-management with an asthma expert is recommended.

Obstructive Sleep Apnea

- Patients with symptoms of obstructive sleep apnea or sleep-disordered breathing should be referred for overnight polysomnography and/or consultation with a sleep specialist physician or ENT specialist.

Smoking

- Patients with SCD should be discouraged from smoking, as smoking has been independently associated with mortality in young adults with SCD.

Background

A. Pulmonary Hypertension

Chronic hemolysis in sickle cell disease (SCD) results in depletion of nitric oxide, and probable resultant increase in pressures in the pulmonary arterial circulation. Pulmonary embolization, fat emboli, or in situ thrombosis may also be involved in the pathophysiology.[1]

B. Other Chronic Pulmonary Disease

a) Asthma

Patients with SCD have been reported to have either similar or higher rates of asthma compared with peers. Asthma is associated with increased rates of sickle pain, acute chest syndrome, stroke, and premature death.[16-18] As per the Canadian Thoracic Society (CTS) guidelines, "a diagnosis of asthma should be considered in individuals of all age groups with recurrent symptoms (e.g., frequent episodes of breathlessness, chest tightness, wheezing or cough, that are often worse at night and in the early morning) and signs of variable airway obstruction".[19] These symptoms may present after exposure to certain triggers (e.g., allergens, cold air, exercise, viral upper respiratory tract infection). Physical findings may include diffuse, high-pitched expiratory wheezes on respiratory exam, but this exam finding has poor positive- and negative-predictive value. Diagnosis is based on the demonstration of airflow limitation on spirometry, and reversibility with bronchodilator. Methacholine challenge should only be performed in consultation with sickle cell disease (SCD) and asthma experts, due to the theoretical risk of bronchoconstriction triggering a vaso-occlusive episode.[20]

Patients with SCD and asthma should receive attentive management to improve symptoms and prevent complications.[20] Established clinical practice guidelines, such as those from the Canadian Thoracic Society, should be followed.[19] Consultation or co-management with an asthma expert is recommended.

b) Sickle Cell Chronic Lung Disease

In adult patients with sickle cell anemia (HbSS), 90% of the population has abnormalities upon pulmonary function testing, with the most common abnormalities being mild restrictive defects (74%) and isolated low diffusing capacity for carbon monoxide (DL_{CO}) (13%).[21] These changes may occur as a result of repeated episodes of acute chest syndrome, causing patchy areas of lung fibrosis. Recurrent chest wall vaso-occlusive episodes, spinal osteoporosis, and osteomalacia have also been postulated to play a role in the development of these changes. In children, restrictive patterns and progressive decline in lung volumes have also been observed.[22]

c) Obstructive Sleep Apnea

Children and adolescents with SCD have higher rates of obstructive sleep apnea (OSA) and sleep-disordered breathing (SDB) than their peers, with estimated prevalence of 10% to 20%.[23,24] Studies have demonstrated a link between nocturnal desaturations and cerebrovascular ischemia,[25] sickle painful episodes, left ventricular hypertrophy, and diastolic dysfunction.[26]

OSA in patients with SCD may be related to a relatively increased size of oropharyngeal lymphoid tissue and reduced airway dimensions.[24] Therapeutic options may include medical treatment, continuous positive airway pressure, or surgery. Adenotonsillectomy has been shown to decrease the severity of OSA in children with SCD, with fewer obstructive respiratory events and less severe nocturnal oxygen desaturation post-operatively.[27] Specialist hematologist, respirologist, and/or ear, nose and throat specialists should assess the patient, selecting optimal therapy based on individual patient factors.

d) Smoking

Patients with SCD should be discouraged from smoking, as smoking has been independently associated with mortality in young adults with SCD.[18]

Diagnosis

a) Clinical Evaluation

With current screening practices in SCD, many patients are asymptomatic at diagnosis. Symptoms of moderate or severe pulmonary hypertension may include shortness of breath on exertion, exertional chest pain, exertional syncope, peripheral edema, palpitations, hepatic congestion, and ascites.

b) Echocardiogram

Estimates of the prevalence of pulmonary hypertension (PHTN) in patients with SCD vary based on the testing method employed. Echocardiogram is a simple, noninvasive method to screen for PHTN. Estimated right-ventricular and pulmonary-artery systolic pressure are calculated from the measured tricuspid regurgitant jet velocity (TRV); TRV ≥2.5 m/sec corresponds to elevated pulmonary artery pressure.

Echocardiogram findings suggestive of PHTN are present in 11% to 32% of children and adolescents with SCD,[2,3] and approximately 30% of adults with SCD.[4,5,6] Furthermore, elevated TRV (≥2.5 m/sec) in adults is associated with an increased risk of death,[4,6] regardless of its etiology, and is thus a biomarker of severe SCD. Elevated TRV can be seen in children with SCD as early as the age of 3 years.[7,8] No association has been clearly established between elevated TRV and morbidity or mortality in children.[9,10]

c) Right-Heart Catheterization

Compared with right heart catheterization (RHC), which is the gold-standard method for diagnosis of PHTN, echocardiography had a false positive rate of 75% in one large adult SCD study – a positive predictive value of only 25%.[5] In this study, the prevalence of PHTN by RHC in the adult SCD population was approximately 6%. The authors found that when TRV was ≥2.5 m/sec, propeptide of brain natriuretic peptide (NT-proBNP) was high (>164.5 pg/mL), and the six-minute walk distance was low (≤333 m); the positive predictive value of echocardiography was 62% with a false negative rate of 7%. Using the above criteria may be beneficial in selecting patients for RHC after positive echocardiogram screening. There are limited data available on the role of RHC in diagnosis of PHTN in pediatric SCD patients.

A recent study found that survival estimates for subjects with PHTN diagnosed by RHC versus those subjects without PHTN by RHC were 63% versus 83% at 5 years from diagnosis.[11] Further study of the relative importance of echocardigraphic versus RHC findings is required, as is the development of more predictive non-invasive screening tools. The current body of available evidence indicates that echocardiogram alone is insufficient for the diagnosis of pulmonary hypertension in adult SCD patients. Of note, the role of RHC in diagnosing PHTN in pediatric patients with SCD has not been reported.

Prevention and Treatment

Since hemolysis is believed to play a central role in the pathophysiology, reducing the hemolytic rate is likely to be beneficial. Thromboembolic disease, iron overload, systemic hypertension, obstructive sleep apnea, and other causes of chronic hypoxemia must be ruled out and treated, if identified.[12]

Higher levels of fetal hemoglobin F (HbF) are associated with a reduced risk of PHTN.[13] HbF-inducing therapies such as hydroxyurea, therefore, may be beneficial in preventing PHTN onset or progression. Prospective studies are required to evaluate this hypothesis.

There is no current standard of care for pharmacologic treatment of symptomatic PHTN in SCD. Hydroxyurea and chronic exchange transfusion may be beneficial in preventing disease progression, although there have been no prospective trials studying PHTN as an outcome. Targeted therapeutic options for RHC-confirmed PHTN should be guided by a team of PHTN specialists and hematologists specializing in SCD care.

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7. CARDIAC COMPLICATIONS

Principles

- To identify cardiac complications in patients with sickle cell disease (SCD), including left ventricular dysfunction and myocardial ischemia.
- To appropriately monitor and manage cardiac complications.

Recommendations

Left-ventricular Dysfunction

- All asymptomatic adult patients should have a baseline echocardiogram performed.
- Consider baseline echocardiogram in asymptomatic children starting at age 10.
- Any new signs or symptoms of cardiac dysfunction should be investigated with echocardiogram.
- If echocardiogram demonstrates high right-ventricular systolic pressure (RVSP) or pulmonary artery systolic pressure (PASP), right-heart catheterization should be considered to assess for pulmonary hypertension (see Part III, section f on *Pulmonary Complications and Chronic Pulmonary Disease* for more detailed recommendations).
- Patients who have evidence of left-ventricular dysfunction should be evaluated by a cardiologist.
- Newer load-independent methods such as strain imaging should be considered.

Myocardial Ischemia

- Clinical evaluation in patients presenting with acute chest pain should include screening for possible myocardial ischemia.
- ST changes on ECG or other markers of myocardial ischemia (e.g., cardiac troponin) should prompt cardiologist involvement.
- Echocardiography or MUGA scan can be used to evaluate for fixed focal-wall motion abnormalities.
- Stress-perfusion cardiac MRI or Thallium-201 SPECT scanning at rest and with exercise may be performed to evaluate for fixed and reversible perfusion defects.
- Serial noninvasive studies may be useful to ascertain whether focal abnormalities or perfusion defects are reversible or permanent.
- Optimal management of myocardial ischemia in SCD requires further study, as the underlying pathophysiology appears to differ from typical coronary artery disease.

a. Pulmonary Hypertension and Right-ventricular Dysfunction

Patients with SCD are at increased risk of pulmonary hypertension and right-ventricular hypertrophy (RVH). In children and young adults, a small series study of 32 children found RVH in 25% of subjects, and resting pulmonary hypertension in 16% as estimated by the tricuspid regurgitant jet velocity (TRV).[1] Pulmonary hypertension may be over-diagnosed by echocardiography, and, therefore, direct measurement of pulmonary arterial pressure by right heart catheterization is the gold standard for diagnosis.[2]

See Part II, section 14 on *Pulmonary Complications and Chronic Pulmonary Disease* for in-depth discussion of pulmonary hypertension.

b. Cardiac Iron Overload

Patients requiring chronic transfusion are at increased risk of iron overload. SCD patients on chronic transfusions have lower rates of cardiac iron overload than similarly transfused patients with thalassemia major. Longer duration of chronic transfusion and poor adherence to prescribed chelation therapy are associated with a higher risk of cardiac iron overload in SCD patients.[3]

See Part II, section 14 on "Iron Overload" for in-depth discussion of cardiac iron overload.

c. Left Ventricular Dysfunction

Chronic anemia in SCD often leads to left ventricular (LV) dilatation, which may progress to eccentric LV hypertrophy with increasing age, and can result in LV diastolic dysfunction. Subclinical cardiac dysfunction may be evident on routine echocardiography screening, but clinical heart failure from LV dysfunction is a late and uncommon occurrence.[4]

The largest study in adolescents and adults was a prospective, multicenter, observational study evaluating 191 stable outpatients over 13 years of age.[5] Compared with normal controls, patients had increased left and right ventricular dimensions, increased left-atrial dimensions, and increased interventricular septal thickness. Diastolic dysfunction was present in 18% of patients, and was an independent risk factor for mortality. Dilated left-chamber dimensions were associated with low hemoglobin level and increased age.[6] Despite these changes, contractility generally remained normal.

Pediatric studies demonstrate LV hypertrophy, LV dilatation and LV diastolic dysfunction compared with controls but normal LV systolic function.[7] Increase in left-ventricular size is inversely proportional to hemoglobin.[8] Using different methods of measurement, contractility is variably reported as normal[9] or reduced.[8,10] Newer echocardiographic methods provide a less load-dependent measure of cardiac function, and offer potential early identification of dysfunction. Using strain imaging, peak longitudinal strain was reduced in patients with normal left-ventricular ejection fraction (LVEF) during a sickle cell crisis[11] and RV longitudinal systolic strain was reduced in children with SCD with normal LV systolic function.[12] Further study of these methods is required to ascertain their role in screening, diagnosis, prognosis, and management of cardiac disease in patients with SCD.

d. Myocardial Ischemia

In patients with SCD and chest pain, myocardial ischemia should be considered in the differential diagnosis. In a group of adult patients prospectively evaluated for chest pain during painful crisis, significant ST-T wave changes were present upon electrocardiogram (ECG) in half of patients (10 of 20). When other noninvasive evaluations were performed, 6 of these patients had focal-wall motion abnormalities on multigated acquisition (MUGA) scan, and/or perfusion defects with thallium-201 scans, suggesting myocardial ischemia. The study was not able to determine whether these defects were permanent or reversible.[13]

Evidence of myocardial infarction has been found in a small proportion of adult SCD patients at autopsy. In a study of 72 patients with SCD autopsied between 1955 and 1982, 10% (7 of 72) showed evidence of myocardial infarction, although no gross obstructive or artherosclerotic lesions were identified in the coronary arteries. During life, 6 of the 7 patients had chest pain clinically.[14] Mechanisms contributing to ischemia in SCD may include microthrombi in the arteriolar circulation, anemia, coronary vasospasm, and red blood cell sickling. Endothelial dysfunction and increased arterial stiffness in the larger vessels also contribute to the vasculopathy, and have a global effect on cardiovascular function in SCD.[15]

Stress-perfusion cardiac MRI may be superior to radionuclide techniques for the detection of myocardial ischemia. A small study in asymptomatic SCD found reduced perfusion reserve and diffuse fibrosis using MRI techniques.[16]

In a few small studies in children, thallium-201 single-photon emission computerized tomography (SPECT) scanning has shown myocardial perfusion abnormalities in a proportion of asymptomatic[17,18] and symptomatic patients with SCD.[19] In one small case series, myocardial perfusion improved after six months of hydroxyurea treatment.[19] Rates, clinical importance, optimal diagnostic strategy, and management of myocardial ischemia in children with SCD all require further study.

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8. SPLENIC SEQUESTRATION

Principles

- To ensure the early detection of acute splenic sequestration in patients with SCD.
- To institute urgent therapy for patients with acute splenic sequestration crises to restore intravascular volume and improve tissue oxygenation.
- To prevent recurrent episodes of splenic sequestration crises.

Recommendations

Education and Monitoring

- All parents and caregivers of children with SCD should be taught how to palpate the spleen *at their first clinic visit*. Teaching should be reinforced at subsequent follow-up visits.
- At clinic visits, steady state splenic size should be accurately and consistently documented by physicians or nurses.
- Palpating for the spleen must be done in the clinical assessment of any patient with SCD who presents to an emergency department.
- Patients with newly enlarged or enlarging spleen size should be assessed emergently in a health facility; urgent bloodwork for complete blood count (CBC), reticulocyte count, and blood type and cross match must be performed.

Acute Management

- Transfusion of packed red blood cells must be performed using guidelines for blood transfusions in patients with SCD (see Part II, section 8 on Acute Splenic Sequestration).
- Immediate transfusion of packed red blood cells must be performed *using guidelines for blood transfusions in patients with SCD.*
- Exchange transfusions aimed at reducing the concentration of sickle hemoglobin (HbS) to below 30% have not been shown to be superior to simple red-cell transfusions, and are not routinely recommended.
- Emergency splenectomy should be performed in patients who do not respond to red-cell transfusions. Lack of response may include inability to maintain hemoglobin level despite blood transfusions, increasing splenic size, and persistent hypovolemia.

Long-term Management

- Recurrent splenic-sequestration crises occur in up to 50% of patients. *Following one episode of acute splenic sequestration*, treatment options to prevent recurrence should be discussed with the patient and family.
- Elective splenectomy and chronic transfusion therapy are the two most common approaches to preventing recurrent episodes of splenic sequestration.[11,12,13,14] To date, there are no randomized control trials comparing each of these options. It is strongly recommended that patients consult with a hematologist specialized in the care of patients with SCD.
- Acute splenic sequestration should be considered in the differential diagnoses of any patient with SCD who presents with hypovolemic shock and exacerbated anemia.

Background

Splenic sequestration is an acute and life-threatening complication of sickle cell disease (SCD), caused by the trapping of blood within the spleen. Acute splenic sequestration may result in hypovolemic shock and death, if not rapidly recognized and treated. It is characterized by the presence of an enlarging spleen and a sudden drop in hemoglobin concentration. The reticulocyte count is usually increased, and thrombocytopenia may be present. Although most episodes occur between the ages of 6 months and 5 years, cases of acute splenic sequestration have been described in infants younger than 6 months as well as in adults. Splenic sequestration is more commonly associated with sickle cell anemia (HbSS) SCD. Patients with compound heterozygous genotypes

such as hemoglobin SC disease (HbSC) and HbS beta thalassemia may remain at risk of this complication during adolescence and into adulthood, however, due to persistent splenic enlargement.[1,2,3,4,5,6,7,8] Patients with acute splenic sequestration often present with sudden weakness, pallor, tachycardia, tachypnea, abdominal fullness, left upper quadrant pain, and palpable splenomegaly. Atypical symptoms such as back pain, left flank pain, chest pain, or mental obtundation may also occur.[2,7] Acute splenic sequestration in the absence of a palpably enlarged spleen has also been reported.[9] During an acute splenic sequestration crisis, the mean decline in hemoglobin is usually ≥3 g/dl from baseline.[7,10] Patients who have had one episode of splenic sequestration are more likely to have recurrent episodes, and to have an increased risk of mortality with subsequent episodes.[11]

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9. RENAL COMPLICATIONS

Principles

- To institute methods of primary prevention for renal complications.
- To monitor for and identify renal complications in a timely manner.
- To effectively prevent progression of sickle cell nephropathy.
- To appropriately manage patients with end-stage renal disease.

Recommendations

Primary Prevention

- Consideration should be given to starting hydroxyurea in early childhood.

Monitoring and Diagnosis

- Renal function should be monitored at least annually.
- Monitoring should include serum creatinine, urine routine and microscopy (including urine protein), and urine microalbumin (ACR and PCR).
- Any serum creatinine level near the upper limit of the normal range (or upper limit of age-matched controls for children) should be identified and followed closely, with consideration of referral to nephrologist.
- BP should be monitored at least annually.

Secondary Prevention

- Patients with proteinuria should be assessed by a nephrologist.
- ACE inhibitor or ARB therapy should be considered if there is proteinuria, even in the absence of hypertension.
- If ACE inhibitors or ARBs are used, potassium levels should be monitored closely.
- Patients with proteinuria and hypertension should have careful attention to blood pressure control, avoiding diuretics when possible.
- Patients with evidence of sickle cell nephropathy should avoid long-term use of NSAIDs.
- Urinary-tract infections should be identified and treated promptly with appropriate antibiotics.

Management of Chronic Kidney Disease Stage 5

- Patients with CKD should be managed by a nephrologist.
- Hemodialysis and/or renal transplantation may be considered in the treatment of renal failure in SCD patients.
- ESAs may be used.
- In patients receiving ESAs, the baseline hemoglobin preceding renal failure should serve as the target hemoglobin level.
- High doses of erythropoietin may be required.

Pathophysiology

The kidneys of patients with SCD are susceptible to structural and functional abnormalities affecting many parts of the nephron.

Two main mechanisms are responsible for the majority of renal problems in SCD patients. The first is renal medullary sickling. The naturally acidotic, hypertonic, and hypoxic environment in the renal medulla promotes red blood cell (RBC) sickling. Sickling leads to vaso-occlusion in the vasa recta, where severe and recurrent damage can result in loss of medullary blood vessels and nephrons. Clinically, these injuries manifest as: hyposthenuria, tubular dysfunction, and hematuria. Although less common, hemoglobin AS (HbAS) cells can also sickle in the extreme conditions of the renal medulla, leading to similar renal complications in some patients with sickle cell trait.

Secondly, changes occur at the level of the glomerulus. These changes are typically benign in childhood, but can progress with age. Early in life, there are changes in renal physiology characterized by increased renal plasma flow, and increased glomerular filtration rate (GFR). Enhanced creatinine secretion from the proximal tubules in sickle cell anemia (HbSS) patients, in combination with increased GFR, leads to serum creatinine levels that are lower than those seen in control subjects.[1]

Glomerular involvement can progress into sickle glomerulopathy over time. Focal segmental glomerulosclerosis is the most common pathology of the glomerulus, and the most common cause of renal failure in SCD.[2]

Epidemiology

In a prospective, 25-year follow-up study of 934 patients with sickle cell anemia, approximately 4% of patients with HbSS, and 2.4% of patients with hemoglobin SC disease (HbSC) developed renal failure, at median ages of 23 and 50 years, respectively.[3] The Bantu haplotype was also a risk factor for renal failure. Sixty percent of patients over age 40 had proteinuria, and 30% had renal insufficiency. Another large study of 300 adult patients showed increased protein excretion in 68% of SS patients and 32% of patients with other sickling hemoglobinopathies (SC, SD, and S-beta thalassemia). Prevalence increased with age.[4]

Microalbuminuria is present in approximately 20% to 27% of young people with SCD (ages 2 to 20).[5] At the older end of this age group, the prevalence increases to 46%, approaching the rates seen in adults.[6]

Clinical Presentation, Investigation and Management

Hyposthenuria

Hyposthenuria is the inability to concentrate urine maximally, and is the most frequent clinically recognized renal abnormality in SCD patients. It is due primarily to the loss of deep juxtamedullary nephrons, which are necessary for maximal urine concentration.[7] Hyposthenuria may occur in childhood in patients with HbSS, often presenting as enuresis.[8,9] It is more likely to occur later in life in patients with Hb S-beta thalassemia, other SCDs, and sickle trait. Hyposthenuria may be suspected based on a history of urinary frequency, nocturia or enuresis, and polyuria. The maximum urine osmolality is around 400 to 450 mosm/kg at age 10 years as compared with normal children where the maximum osmolality is up to 12 mosm/kg.[10] A low urine osmolality in the presence of normal or increased serum osmolality can confirm the diagnosis. Although data are very limited, intranasal DDAVP may help to decrease symptoms.[9] Patients should be educated on the importance of liberal oral hydration to prevent RBC dehydration.

Tubular Dysfunction

Due to an incomplete distal renal tubular acidosis, SCD patients can have impaired urinary acidification. The degree of this effect is related to the extent of hyposthenuria. Patients rarely become acidotic unless other causes of acidosis are also present.

Impaired potassium excretion as a result of impaired distal nephron function has also been described in SS patients.[11] Even when present, serum potassium concentration is usually normal unless the patient develops renal insufficiency. Patients with impaired potassium excretion are at additional risk of hyperkalemia with the use of drugs such as ACE inhibitors or aldosterone antagonists, or when other factors are present such as volume depletion or rhabdomyolysis.

Hematuria

Hematuria is one of the most common renal complications in patients with SCD and other sickle hemoglobinopathies. Ischemia due to medullary sickling can lead to hematuria, which is typically mild and self-limiting.[10] Interestingly, in 80% of cases the bleeding comes from the left kidney.[12,13] This is thought to be due to compression of the left renal vein between the aorta and superior mesenteric artery, which may slow flow to the renal medulla and promote sickling.[33]

More severe ischemia can result in renal medullary infarction or papillary necrosis, which often presents with gross hematuria. Although renal infarction is typically painless, it can be complicated by obstruction or pyelonephritis. In addition to hematuria, patients with acute, large renal infarcts are likely to present with pain in the flank, abdomen or lower back.[14] This may be accompanied by nausea and vomiting, fever,[14] and hypertension.[15] The diagnosis is confirmed with contrast-enhanced CT or angiography.

Renal medullary carcinoma is a rare malignancy of the kidney that can present with hematuria, flank pain, urinary-tract infection, or abdominal mass. It occurs almost exclusively in sickle hemoglobin (HbS) carriers but has also been diagnosed rarely in patients with sickle cell anemia (SCA).[16] It has a significant male preponderance in childhood. Renal medullary carcinoma can be suspected based on imaging studies, but definitive diagnosis is based on pathology.[17] This is a highly aggressive malignancy, which is typically resistant to conventional chemotherapy, and average survival is less than 12 months.

Sickle Glomerulopathy: Proteinuria and Chronic Kidney Disease

Clinically, proteinuria is the most common manifestation of glomerulopathy. Furthermore, as many as 40% of patients with HbSS and nephrotic syndrome may go on to develop progressive chronic kidney disease (CKD), leading to CKD stage 5. Increased urinary albumin and immunoglobulin G (IgG) excretion are the earliest detectable abnormalities.[4,18] Routine urinalysis may be used to screen for proteinuria; urinary protein to creatinine ratio and albumin to creatinine ratio (ACR) can be measured on a spot urine sample. In patients with positive protein on urinalysis or elevated protein-to-creatinine ratio (PCR) or ACR, 24-hour urine collection can quanitify protein excretion.

Serum creatinine and urea should also be measured. Because of the increased physiologic tubular secretion of creatinine, it has been proposed that the upper limit of "normal" serum creatinine for patients with HbSS be decreased to 80 µmol/L for men and 68 µmol/L for women.[1] There are no data on upper limit of "normal" serum creatinine for pediatric patients with HbSS. If significant abnormalities are detected, consultation with a nephrologist, and consideration of renal biopsy, may be indicated.

Focal segmental glomerulosclerosis is the most common cause of CKD in SCD. A kidney biopsy may be indicated to exclude other renal pathology, such as membranoproliferative glomerulonephritis, and to confirm FSGS.

Primary prevention may be possible if hydroxyurea is started in early childhood.[19]

Secondary Prevention of Sickle Cell Nephropathy

1. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) may be initiated to prevent progressive renal disease in patients with glomerulopathy, even in the absence of hypertension.[20,21] A small, randomized, controlled trial demonstrated a significant improvement in albuminuria with ACE inhibitor treatment.[21,22] During an average of 2 years of follow-up in a large longitudinal cohort of children, treatement with hydroxyurea or ACE inhibitors led to complete reversal of microalbuminuria in 44% and 56% of subjects, respectively.[5] Close monitoring of serum potassium level is required when using ACE inhibitors and ARBs in these patients.
2. Patients should avoid long-term use of NSAIDs because of the physiologic effect of reduced glomerular filtration rate (GFR) and renal blood flow in patients with SCD.[23,24] If non-steroidal anti-inflammatory drugs (NSAIDs) are used, careful patient education is required.
3. Blood pressure control – ACE inhibitors (or ARBs) should be first-line therapy, followed by standard approaches, but diuretics should be avoided due to the likelihood of concomitant hyposthenuria, causing volume depletion and risk of RBC dehydration. To our knowledge, there have been no studies examining specific target blood pressure in this population.
4. Early and complete treatment of urinary-tract infection.

Erythropoietin

Because of the combination of decreased endogenous erythropoietin production and chronic hemolysis, the required dose of erythropoietin may be higher than what is typically used in CKD – even more so in patients receiving hydroxyurea. The baseline hemoglobin preceding renal failure should serve as the target hemoglobin level.[25] Risks and benefits of erythropoiesis-stimulating agents (ESAs) need to be carefully balanced, particularly in patients with previous thrombotic or cardiovascular complications.

Management of CKD Stage 5

Diagnosis of CKD stage 5 is associated with an increased relative risk of mortality in patients with SCD.[3] In a study of 77 patients with SCD and CKD stage 5, most were treated with hemodialysis, and survival was similar to that seen in other non-diabetics with CKD stage 5 (actuarial survival of 59% at 30 months vs 48% in diabetics and 66% in non-diabetics).[26] Although hemodialysis has been the traditional treatment of choice, multisystem disease – including cardiovascular disease, susceptibility to infections, anemia and decreased ability to excrete potassium – can pose additional risks. This has led some to suggest early consideration of renal transplant.[27,28]

There is increasing experience with renal transplantation in SCA.[28,29] A case-control study of 82 patients post-renal transplant for sickle cell nephropathy (SCN) showed short-term outcomes that were similar to age-matched kidney-transplant recipients with other causes of end-stage renal disease, including delayed graft function, pre-discharge acute rejection, and 1-year graft survival. There was a trend, however, to lower 3-year, deceased donor graft survival, and a significant 3-year risk of graft loss. Furthermore, the adjusted mortality risk was higher compared with non-SCN controls at 1 year (relative risk [RR]=2.95, *P*=0.001) and at 3 years (RR=2.82, *P*=0.0001). More recently, the graft survival at 6 years was found to be around 70% for patients transplanted between 2000 and 2011.[30,31] Renal transplantation appears to be relatively safe and effective in adolescents, with 60% graft survival and 89% patient survival following 10 renal transplants in 9 patients, but results were poorer than those observed in adolescents with other causes of renal disease.[32] Acute sickling episodes may increase in frequency in some patients following transplantation.[28]

There is an overall trend toward improved survival in patients with renal transplant for SCN when compared to those treated on hemodialysis.[34] This must be weighed against the risks associated with renal transplantation and, ultimately, the decision regarding the most appropriate therapy should be made on an individual basis.

Acute Kidney Injury

A broad differential diagnosis should be considered when a patient with SCA develops acute kidney injury. Multi-organ dysfunction syndrome can be related to infection or a vaso-occlusive episode in patients with SCD.[35] Treatment with simple or exchange transfusion should be considered in these cases.

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10. PRIAPISM

Principles

- To educate patients about the risks of priapism in boys, adolescents and men with SCD.
- To teach patients to recognize priapism and bring it to rapid medical attention.
- To ensure rapid medical treatment by the emergency medical team.
- To appropriately involve consultants, including Urology and Hematology.
- To select appropriate medical and/or surgical intervention, tailored to the individual patient and episode.

Recommendations

Patient Education

- Educate patients about risk of priapism in boys, adolescents, and men with SCD.
- Educate as to possible measures for self-treatment of priapism at home.
- Instruct patients to seek medical attention if the episode lasts for longer than 2 hours.
- Emphasize the nature of this problem as a medical emergency that requires rapid assessment and attention, so that the patient can advocate for himself at the emergency department.

Acute Treatment

- Patients should be treated rapidly and in a sensitive manner.
- First-line therapy includes:
  - Intravenous fluids and narcotic analgesia
  - Supplemental oxygen should be administered if the patient is hypoxic
  - Oral pseudoephedrine may be considered
- If first-line therapy is not rapidly effective, and the total duration of priapism has been or will soon be longer than 4 hours, urologist consultation should be obtained.
  - Urologist to consider corporeal aspiration and irrigation with or without vasoactive agent.
  - Consider cavernosum-spongiosum shunts if the above measures are ineffective.
- Hematologist to consider risks vs. benefits of exchange transfusion.

Prevention

- No preventive measure has been confirmed in randomized studies.
- Chronic hydroxyurea use may be effective in preventing episodes of priapism.
- Other preventive measures that may be considered include daily pseudoephedrine, sildenafil, or chronic RBC exchange transfusion.

Background

Priapism is a prolonged, full or partial erection that "persists beyond or is unrelated to sexual stimulation".[1] Prolonged priapism lasting more than 4 hours is a medical emergency. Prolonged or recurrent priapism can result in erectile dysfunction.

Priapism occurs when there is an imbalance in the arterial inflow and venous outflow from the penile vascular chambers. SCD-related priapism is classically low-flow (ischemic), with sickle veno-occlusion and endothelial dysfunction causing a pathological decrease in venous outflow, in contrast to increased arterial flow seen in high-flow (non-ischemic) priapism.[1] Minor episodes can be uncomfortable but tolerable and self-limiting, lasting up to several hours. Recurrent self-limiting "minor" episodes, referred to as stuttering or intermittent priapism, may be a precursor to a major episode. Major episodes can last a few hours to several days, and are often extremely painful.[2] Patients may not report episodes until they are very severe or prolonged.[3]

Epidemiology

In regions of high prevalence, sickle cell disease is the most common cause of priapism. Priapism can first occur in early childhood, sometimes as early as 5 or 6 years of age.[4] The lifetime risk of priapism in men with SCD is estimated at 29% to 42%.[5,6] Based on patient questionnaires, the probability of having at least one episode by 10, 15, or 20 years of age is 12.9%, 50.3%, and 89%, respectively.[7]

Risk Factors and Triggers

Risk factors for priapism include higher sickle hemoglobin (HbS) levels,[25] increased hemolytic rate,[26] and sleep hypoxemia.[27] It is more common in sickle cell anemia (HbSS) than HbSS-alpha thalassemia and hemoglobin SC disease (HbSC).[28] Priapism may occur spontaneously, but potential triggers include sexual activity, fever, dehydration, and cold weather.[3,8]

Diagnosis and Triage

Diagnosis is made by patient report of erection lasting beyond or unrelated to sexual stimulation, typically more than 30 minutes.[1,9] A history should be taken to determine the time of onset and any potential precipitating events.[9] Priapism can be confirmed by physical examination and Doppler penile ultrasound. Priapism in patient with SCD is usually bicorporal – affecting both corpora cavernosa bodies but leaving the glans penis and corpus spongiosum soft, which enables normal urination during the episode. Patients with prior episodes or at high risk should be instructed not to wait for the arbitrary 4-hour cut-off time to seek care. Instead, they should be instructed to go to the emergency room urgently while fasting (in case surgical treatment is required). Triage staff should be notified about the critical nature of the condition and the need to be urgently evaluated by specialists familiar with this condition.

Management

Management of priapism in patients with SCD is based largely on small case series and expert opinion.

a) Home Management

Initial self-treatment by patients has some reported benefit, including analgesia, oral hydration and light exercise.[8] There may also be benefit in voiding, ejaculating, or having a warm shower or bath.[7]

b) First-line Medical Therapy

First-line medical interventions include supportive-care measures such as intravenous hydration, narcotic analgesia, and supplemental oxygen (if the patient is hypoxic). Oral vasoactive agents (terbutaline, phenylephrine, and pseudoephedrine) have been reported to be effective in reversing pharmacologically induced priapism,[9] and may be considered.

If the episode persists for more than two hours, additional measures must be considered.

c) Aspiration/Irrigation

Institution of supportive measures should not delay urological consultation and consideration for decompression, which includes corporal aspiration, irrigation, and administration of intracorporeal epinephrine solution.[10]

- Study: Prospective, case series of 15 boys and teenagers.
- Indication: Priapism persisting 1 hour after arrival at the emergency department (total duration of episode = 4 to 6 hours).
- Procedure (more detailed instructions available in reference 9):
  1. Conscious sedation and local anesthesia.
  2. Aspiration of blood from corpus cavernosum with 23-gauge needle. A sample should be sent to the lab for blood gas, which confirms a low-flow (ischemic) state.

3. Irrigation of the corporus cavernosum with normal saline, followed by diluted epinephrine (1:1,000,000 dilution of epinephrine to saline). This should be done under hemodynamic monitoring (heart rate, blood pressure).

- Results of the study: Rapid detumescence in 37 of 39 episodes.

d) Surgical Shunts

If the above measures are ineffective, surgical procedures may be required to create a cavernosum-spongiosum distal shunt.[4,11]

e) Transfusion

Depending on the patient's hemoglobin level, exchange transfusion may be used, although there is conflicting evidence as to its efficacy.[12,13] Transfusion may be associated with equivalent or worse clinical outcomes compared to more conservative management, including risk of neurological events (referred to as ASPEN syndrome).[14,15]

Prevention

One study has suggested that patients with high levels of fetal hemoglobin (HbF) are unlikely to suffer from priapism.[16] Hydoxyurea has been demonstrated in case reports to be effective in preventing recurrent priapism.[17,18]

There is some scientific evidence that chronic phosphodiesterase type 5 (PDE5) inhibitor therapy in patients with recurrent priapism reconditions PDE5 regulation in the penis (Burnett, Bivalacqua *et al.* 2006). Long-term, continuous PDE5 inhibitor (tadalafil or sildenafil) was shown retrospectively to be associated with decreased priapism recurrences over 2 years of clinical follow-up in 3 out of 4 SCD patients with a history of disease-associated "stuttering" priapism.[19] A small, randomized controlled trial of 13 patients showed no difference in priapism frequency between the sildenafil and placebo groups during the eight-week double-blind phase. Mild reductions in priapism were seen during eight weeks of open-label assessment,[21] suggesting a possible role for further study of this therapy.

Other prevention methods that have not been extensively studied include: oral or self-administered intracavernous injection of etilefrine[22]; self-administered intracavernosal metaraminol[23]; ketoconazole and prednisone[24]; daily, oral pseudoephedrine[9]; or chronic exchange transfusion.[9] Well designed, randomized trials are required to further evaluate these and other potential therapies.

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11. BONE COMPLICATIONS

Introduction

In patients with sickle cell disease (SCD) presenting with bone pain, clinicians must distinguish between common causes, including acute vaso-occlusive crisis (VOC), osteomyelitis (OM), and avascular necrosis (AVN), while also considering more rare complications such as abscesses, myositis, or septic arthritis. It is useful to know that bone pain in SCD is much more likely to be due to VOC than to OM. In one pediatric series, VOC was at least 50 times more likely.[1]

A thorough evaluation begins with assessing historical features of the pain. If the onset of symptoms was acute, it may be suggestive of VOC or OM, versus the chronic pain and disability caused by AVN. Concurrent infectious symptoms (e.g., fever, rigors) may suggest OM. Any prior history of bone complications can also guide further investigations.

Physical examination should include a musculoskeletal examination, targeting the joint or other location of symptoms. Selection of appropriate laboratory investigations and imaging should be guided by clinical suspicion.

a. Acute Vaso-occlusive Crisis

Principles

- To recognize clinical syndromes suggestive of acute vaso-occlusive crisis.
- To undertake appropriate investigations to diagnose acute vaso-occlusive crisis.
- To provide supportive therapy in acute vaso-occlusive crisis, including appropriate pain management.
- To prevent acute vaso-occlusive crisis.

Recommendations

- The clinician should take a careful history of the pain, including onset, location, and quality
- Imaging studies are only necessary if there is concern that the pain may be due to a cause other than acute vaso-occlusive crisis
- Pain management with opiate analgesia – medication, dose, and route must be selected based on the severity of pain
- Adjunctive use of non-steroidal anti-inflammatory agents
- Respiratory status should be monitored in patients receiving high doses of opiates
- Active hydration with frequent reassessments; oral fluid is preferable to intravenous if the patient is able and motivated to drink
- Supplemental oxygen (if hypoxemic)
- During an episode of VOC, patients should be monitored clinically for onset of acute chest syndrome
- There is no role for red blood cell transfusion or empiric antibiotic therapy in an uncomplicated vaso-occlusive episode
- Upon resolution of pain episode, the patient should be assessed for chronic hydroxyurea therapy to prevent recurrent episodes

Further discussion of analgesia in vaso-occlusive crisis can be found in Part III, section A "Pain Management."

Background

Vaso-occlusion in patients with SCD causes infarction leading to bone pain. Common locations for acute VOC include the long bones, ribs, sternum, spine, and pelvis, although infarcts can occur in any bone in the body.[2] In young children, dactylitis (painful swelling of the fingers or toes) is a common presentation, due to infarction of the small bones in the hands or feet.

Dactylitis: Microinfarcts in the small bones of the hands and feet can lead to tenderness and swelling of the digits, known as dactylitis or "hand and foot syndrome". This typically occurs in infants and young children under the age of 5, in whom there is still hematopoietic bone marrow in the small bones. In a prospective study of 233 children with sickle cell anemia (HbSS), 45% of children had experienced dactylitis between birth and 2 years of age. Episodes were more common during the colder months of the year. Affected patients had lower fetal hemoglobin (HbF) and higher reticulocytes than unaffected children.[3] Dactylitis in infancy helps to predict a more severe course later in life.[4] Patients present with painful, often symmetrical swelling of the hands or feet, often accompanied by mild skin erythema and low-grade fever. In this clinical setting, the differential diagnosis of osteomyelitis should be considered, although osteomyelitis affecting several digits would be unusual. Dactylitis should be treated in the same manner as other VOCs – with supportive care and pain management. Hydroxyurea should be considered in infants and children with SCD to prevent dactylitis and other end-organ complications.[5]

The clinical presentation of a VOC of bone is dominated by the acute onset of deep-seated pain, often described by the patient as "typical sickle cell pain." Mild erythema and warmth, as well as local tenderness, are usually present. Many patients also have a low-grade fever. Pain can vary from mild (i.e., barely interfering with normal lifestyle) to excruciating.

Diagnosis of acute VOC is generally based on the findings of clinical assessment. Laboratory investigations may reveal non-specific elevations of the white blood cell count and/or erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Abnormalities on plain x-ray, radioisotope bone scan, and radiolabelled leukocyte scan are often difficult to distinguish from those seen in OM. Ultrasound may reveal a subperiosteal fluid collection, which is typically smaller in VOC (<10 mm) than in OM (>10 mm). Subperiosteal fluid aspirate is likely to be hemorrhagic with a negative culture (versus turbid or purulent fluid with a positive culture in OM).[6]

Empiric treatment in presumed acute VOC includes active hydration, and supplemental oxygen (if hypoxemic). Symptom management strategies include heat packs applied to the painful site. Analgesia with opiates should be tailored to the severity of pain; for example, oral morphine for mild pain versus frequent intravenous opioid (ideally via PCA) or continuous infusion for severe pain. Anti-inflammatory medications may be used adjunctively. During an episode of VOC, patients should be monitored clinically for onset of acute chest syndrome, which can develop due to fat embolism following bone infarction.

Chronic hydroxyurea therapy can prevent VOC in patients with HbSS or patients with HbS-beta 0-thalassemia with repeated episodes. (*For more detailed discussion, see Part I -Hydroxyurea*.)

b. Osteomyelitis

Principles

- To recognize clinical syndromes suggestive of osteomyelitis.
- To undertake appropriate investigations to diagnose osteomyelitis.
- To provide appropriate treatment.
- To monitor for improvement while on therapy or following treatment.

Recommendations

- Consider osteomyelitis in the differential diagnosis of a patient with bone pain that is "not like their typical sickle pain", particularly in the presence of other clinical or laboratory markers of infection.
- Ultrasound may be helpful in evaluating for osteomyelitis.
- Definitive diagnosis requires aspirate of periosteal fluid collection or bone biopsy, performed by an Orthopedic specialist or Interventional Radiology expert.
- Treatment should include a minimum of six weeks of antibiotics to cover the cultured organisms.

- Oral therapy should only be used when the organism is found to have good sensitivity and adequate serum bactericidal levels can be attained.
- Consultation with an Infectious Disease expert may be beneficial in determining optimal choice and duration of antibiotics.
- The role for operative decompression as part of first-line therapy is unclear; surgical debridement may be beneficial in cases that do not improve as expected on antibiotics.

Background

Mechanisms responsible for the increased risk of osteomyelitis in SCD likely include: hyposplenism, impaired complement activity, bowel infarction leading to migration of bowel flora to the bloodstream, and the presence of infarcted or necrotic bone. Typical organisms include *Salmonella* species, *Staphylococcus aureus* and Gram-negative enteric bacilli.[7,8]

Elevated temperature may be suggestive of OM or other infectious etiology, while other abnormalities in vital signs (e.g., tachycardia, hypotension) potentially indicate progression to sepsis.

Leukocytosis and increased ESR or CRP are non-specific laboratory findings that may be present in both infectious and non-infectious processes. A definitive diagnosis of OM in SCD requires positive cultures from blood, subperiosteal fluid collection, or bone.

Plain radiography, radioisotope bone scanning, and radio-labelled leukocyte scanning are not useful in the routine diagnostic evaluation of bone pain in SCD, as these modalities can detect acute infarction, but changes are often difficult to distinguish from those seen in OM.[9]

Ultrasonography is a rapid, simple, and non-invasive modality that is moderately sensitive for detecting acute osteomyelitis.[10] The main ultrasonographic finding in OM is subperiosteal fluid. Larger fluid collections ([>4 mm][10] or [>10 mm][6]) are more characteristic of OM versus smaller collections that may be seen in VOC. Aspiration of subperiosteal fluid under ultrasound guidance may aid diagnosis; the aspirate is typically hemorrhagic in VOC and turbid or purulent, with positive cultures in OM. Diagnosis based on ultrasound has led to successful management in a prospective, pediatric study.[32] In a retrospective study comparing OM patients with control cases presenting with VOC, 76% of OM patients had periosteal elevation and/or fluid collection on initial ultrasound, and 84% of patients had a positive ultrasound at some time during their hospital stay. Although 9% of patients with VOC had an initial positive ultrasound, all ultrasounds demonstrated small fluid collections (<4 mm), and repeat ultrasounds were all negative. Mean CRP levels and white blood cell (WBC) count at presentation were significantly higher in the OM group.[11]

Magnetic resonance imaging (MRI) can be useful in the diagnosis of OM. As with other imaging modalities, there is overlap between the changes seen in infection and infarction. Although still not 100% specific for differentiating OM from VOC,[12] gadolinium enhancement improves the accuracy of MRI.[13]

OM must be treated with at least 6 weeks of antibiotic therapy, tailored to the organism identified. If culture sensitivities offer the option of oral antibiotics, oral therapy may be considered only if adequate serum bactericidal levels can be attained. Assessment by an Infectious Disease and/or Orthopedic specialist should be performed, if possible. In more complicated or refractory cases, adjunctive therapies may include operative decompression or drainage of any fluid collections identified on imaging. Infection resolved in twenty-nine of thirty affected bones in a study of SCD patients with osteomyelitis confirmed on bone culture and treated with operative decompression and a minimum of six weeks of parenteral antibiotics (97%).[7]

MRI may be a useful imaging modality for monitoring response to therapy.[14]

c. Avascular Necrosis

Principles

- To recognize clinical syndromes suggestive of avascular necrosis.
- To undertake appropriate investigations to diagnose avascular necrosis.
- To provide appropriate supportive care in early avascular necrosis.
- To identify progression to bone deformity and consider the role for surgical intervention.

Recommendations

- Consider the possibility of AVN in any patient with ongoing, localized bone pain. Clinicians should have a high degree of suspicion for AVN in patients with pain and/or decreased range of motion in the hip.
- MRI may be performed to detect early disease.
- Supportive care should include adequate analgesia.
- A physiotherapist and/or Orthopedic specialist with interest in SCD may be consulted to advise on appropriate exercises and parameters for physical activity (see Figure 1).
- There is no evidence currently for the use of hip core decompression.
- Patients with advanced femoral- or humeral-head disease should be evaluated by an Orthopedic specialist with interest in SCD for possible arthroplasty.
- Any arthroplasty should be performed with special attention to decreasing the risk of perioperative complications (see Part III, section 1: *Peri-operative Management*).

Background

Osteonecrosis (avascular necrosis, AVN) occurs when sickling of cells in the bone microcirculation leads to infarction of the bone marrow and death of osteoblasts. The most common locations for AVN are the femoral and humeral heads, with a prevalence of 10% and 6%, respectively, in a group of patients with SCD who are over the age of 5 years old[15,16]; however, prevalence is higher in older groups.[17,18]

Cohort studies have demonstrated that AVN may be asymptomatic when originally detected,[18] but symptoms and bone deformity often progress rapidly over time.[19] Clinical symptoms may include pain, deformity, limb shortness, stiffness, or limited range of motion of the joint.

Diagnosis is based on imaging. MRI is the most sensitive method of detection, and is, therefore, particularly helpful for early detection of disease. Characteristic findings on plain x-ray make it a useful modality in advanced disease.[8] Staging of disease severity can be performed using the Ficat and Arlet[20] or Steinberg systems.[21,22]

Initial treatment is conservative: bed rest with progressive weight bearing in the case of hip AVN (see Figure 1) or rest with part-time shoulder splinting in the case of shoulder AVN. Symptomatic treatment with analgesics is crucial. Application of heat, such as use of heating pads or whirlpools may also help to improve symptoms.[23]

Unfortunately, no additional intervention has been shown definitively to slow progression of early disease. Hip core decompression followed by physiotherapy was not superior to physiotherapy alone in a prospective, multicenter study. The study suffered several limitations, however; it was inadequately powered with short duration of follow-up (3 years).[24]

AVN of the hip can lead to femoral-head collapse, which requires hip arthroplasty.[18,19] Surgery should be performed in a specialized centre, with special attention to minimizing the risk of perioperative complications (*see "Peri-operative Care" section of current guidelines*). Revision is frequently required.[16,25]

Joint replacement is also the treatment of choice in advanced shoulder AVN. Patients have variable outcomes, however, in terms of function and pain relief with this procedure.[26,27]

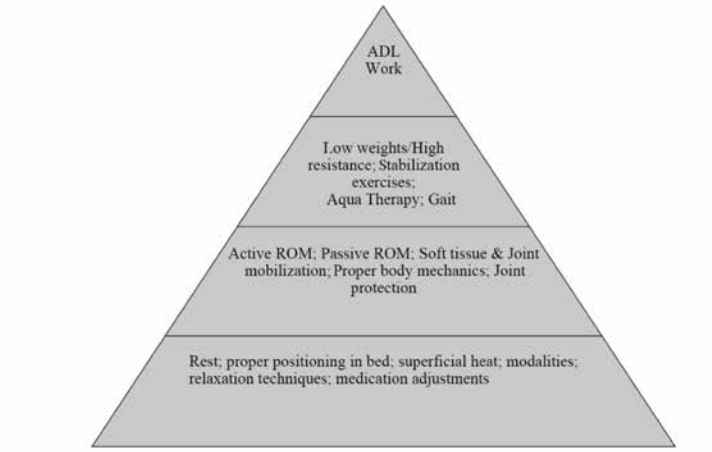

Fig. 1. A therapeutic treatment pyramid.

ADL: activities of daily living; ROM: range of motion

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d. Low Bone Mineral Density

Principles

- To recognize low bone mineral density (BMD) in patients with SCD.
- To assess for and manage underlying risk factors for low bone mineral density.
- To provide appropriate pharmacologic and non-pharmacologic therapy to improve bone mineral density in patients with low bone mineral density.

Recommendations

- All patients should have height, weight, and BMI measured, at least annually.
- History of fractures should be recorded.
- 25-hydroxy-vitamin D levels should be assessed at baseline, starting in infancy.
  - If levels are normal, they should be reassessed regularly (e.g., every 1 to 2 years).
  - If levels are low, supplementation should be prescribed according to current guidelines (e.g., vitamin D 1,000 to 2,000 IU daily).
- All patients should have a baseline Dual-energy X-ray absorptiometry (DXA) scan, repeated at intervals appropriate to their risk category (e.g., every 5 years for low risk and every 1 to 3 years for patients with moderate- and high-risk T-scores who are being actively managed).
- Non-pharmacologic approaches to building bone strength include resistance training and/or weight-bearing aerobic exercise, and a diet high in calcium-rich foods.
- Intake of calcium and vitamin D should be reviewed, with supplementation doses selected based on dietary intake, serum vitamin D levels, and risk level.
- Patients with osteoporosis (defined T-score ≤-2.5), should be assessed by an Endocrinologist or Osteoporosis specialist, with careful consideration of the role of anti-resorptive therapies.

Background

Based on clinical experience and a small number of studies, children and adults with SCD are known to have higher rates of low bone mineral density (BMD) than the general population. As in other patient groups, low BMI and low vitamin D levels are risk factors for low BMD.[28,29] Other potential contributing variables include lower

hemoglobin level, higher ferritin, male gender, and low serum zinc concentration.[29,30] Further study is required to clearly elucidate the pathogenesis of disproportionately high rates of reduced BMD in patients with SCD. The natural history, fracture risk, and specific therapeutic approach to low BMD in SCD also warrant further investigation.

In the absence of strong evidence to guide therapeutic decision-making, guidelines such as the "2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada"[31] should be followed. Non-pharmacologic approaches to building bone strength include resistance training and/or weight-bearing aerobic exercise, and a diet high in calcium-rich foods. Intake of calcium and vitamin D should be reviewed, with supplementation doses selected based on dietary intake, serum vitamin D levels, and risk level. Pharmacologic therapy should be considered for all patients with osteoporosis (defined as a T-score ≤-2.5), in the context of their other risk factors. Assessment by an Endocrinologist or Osteoporosis specialist may be beneficial.

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12. SKIN ULCERS

Principles

- To recognize the clinical presentation of sickle cell skin ulcers.
- To provide appropriate treatment of skin ulcers.
- To provide supportive therapy for skin ulcers, including appropriate pain management.
- To prevent de novo and recurrent skin ulcers.

Recommendations

- Patients should be educated on the importance of avoiding trauma, especially to the lower leg and feet, and carefully attending to any small injuries.
- Patients should be instructed to seek medical attention quickly if evidence of a leg ulcer is noted, since early diagnosis and management are critical.
- Wound care is the mainstay of therapy, and should be administered and/or prescribed by an individual with expertise in skin ulcers.
- RGD peptide matrix is likely to speed healing.
- Wound swabs should only be performed if there is clinical evidence of infection.
- If a wound swab is positive, systemic antibiotics should only be administered if there is clinical evidence of infection.
- Bed rest, elevation of the leg, and supporting elastic bandages may be beneficial, but should be considered on a case-by-case basis.
- Interruption or discontinuation of hydroxyurea may be considered in a patient on hydroxyurea with a non-healing or slowly healing skin ulcer.
- Pain from the ulcer should be treated with oral analgesics at optimal doses.

Background

Skin ulcers associated with sickle cell disease (SCD) are rare before 10 years of age. Usually the first episode will occur between the ages of 10 and 50 years.[1,2] Known risk factors include sickle cell anemia (HbSS) genotype, low hemoglobin level, and venous insufficiency.[3] High fetal hemoglobin (HbF) levels appear to be protective.[2] There may be geographic variation in rates, with higher incidence reported in Jamaica than the United States.

The mechanism of onset of skin ulceration can vary. Approximately half of cases are caused by local trauma, which can result from insect bites, simple scrapes, or injury. The remaining cases are apparently spontaneous, likely caused by skin infarction. There is a higher prevalence of skin ulcers in areas with lower amounts of subcutaneous fat, thinner skin, and decreased blood flow.[4] Most ulcers occur around the medial or lateral malleoli, but can also begin on the anterior shin or dorsum of the foot. Ulcers are typically well demarcated, with a punched-out appearance and a base of granulation tissue. Healing generally takes months to years, with subsequent recurrence of 25% to 52%.[2] The risk of secondary bacterial infection in these open wounds is high. One must be cautious in interpreting results of bacterial swabs, however, as the wound is colonized almost universally.

Treatment

Treatment consists of measures to keep the lesion clean and to reduce hemostasis and lymphedema. Randomized, controlled trials of Solcoseryl or Duoderm[5] or propionyl-L-carnitine[6] did not show benefit; however, arginine-glycine-aspartic acid (RGD) peptide matrix does result in nearly three times faster healing than control (saline) treatment.[7] Debriding may be required to facilitate healing. The role of topical antimicrobial products is unclear.[8] Systemic antibiotics should only be administered if there is clinical evidence of infection. Bed rest, elevation of the leg, and supporting elastic bandages have been beneficial anecdotally.[1] Daily cleansing of the affected area may also aid healing.

There is limited evidence of modest benefit in ulcer healing for other measures, including oral zinc supplementation[9] and transfusion to normal hemoglobin.[10] Patients with recurrent or refractory skin ulcers may benefit from chronic simple or exchange transfusions, although there is a lack of high quality studies to support this practice.

There are conflicting reports as to the role of hydroxyurea. In other hematologic diseases, hydroxyurea has been associated with new ulcer formation,[11] and some observational reports in SCD have shown potential association with new ulcers[12] or worsening of existing ulcers.[13] Conversely, a systematic review found that hydroxyurea treatment in adults with SCD was not associated with skin ulcers, although this conclusion was based on limited evidence from the literature. Further study is required. Decisions about chronic use of hydroxyrea should take into consideration the balance of all potential benefits and risks to the individual patient.

Pain

Pain from the ulcer may be substantial, and should be managed with appropriate oral analgesia. Successful adjunctive therapy with topical opioids has been reported in patients with refractory pain.[14]

Surgery

Surgical management of leg ulcers requires further study. Skin grafts using pinch grafting techniques may improve healing, but most ulcer recurrence occurs within 2 years.[15]

Prevention

The only clear way of preventing ulcers is to avoid trauma. Any injury, even small scratches or insect bites, should be attended to conscientiously to encourage rapid healing. Once an ulcer has healed, support stockings may reduce the risks of skin breakdown.[1]

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13. GROWTH AND ENDOCRINE COMPLICATIONS

Principles

- To maintain a system for close monitoring of growth and development.
- To prevent transfusion-related endocrine complications.
- To enable early detection of endocrine disorders with timely and appropriate intervention.

Recommendations

Monitoring

- The growth, nutritional status, and development for children with SCD should be monitored every 6 to 12 months during routine, follow-up, pediatric-clinic visits, and plotted on an appropriate growth chart until patients have attained adult height and full sexual development.
- Each specialist centre should collaborate with a pediatric or an adult endocrinologist who has knowledge of endocrine complications in SCD.
- Children should be referred to a pediatric endocrinologist if there is a clinical suspicion of growth failure or any endocrine-related complication.
- Adolescents and adults with SCD should be routinely monitored for endocrine disorders including diabetes mellitus, hypothyroidism, hypoparathyroidism, hypogonadotrophic hypogonadism, and growth-hormone deficiency. Any abnormalities should prompt a consultation with an endocrinologist.

Delayed Growth and Growth Failure

- Height and weight monitoring should be performed at each visit (and at least every 6 to 12 months) for all children with SCD, and plotted on an appropriate growth chart.
- Nutrition counseling should be provided during routine clinic visits.
- Folic-acid supplementation is recommended due to increased folate utilization and red blood cell turnover.
- Patients should be tested for zinc deficiency. Zinc supplementation has been shown to improve growth and gonadal function and decrease infection rate among children with SCD.[5,15,16]
- Children with heights <5th percentile for age, despite adequate nutritional status, should be referred to a pediatric endocrinologist for growth-hormone stimulation testing and, if indicated, growth-hormone therapy.
- Patients with poor growth associated with severe anemia should be strongly considered for hydroxyurea therapy, unless they are already on a chronic transfusion program.
- The diagnosis of growth-hormone deficiency, other hormonal or nutritional deficiencies, or deferoxamine toxicity should be considered for children with short stature or growth failure.

Hypogonadism and Delayed Puberty

- Children and adolescents with SCD who lack any pubertal signs by the age of 13 years in girls and 14 years in boys should be referred to a pediatric endocrinologist for evaluation.
- All patients with delayed puberty or hypogonadism should undergo investigations for bone age and hormonal assessments, as well as referral to an endocrinologist for further management.
- Adults with sickle cell disease should be routinely evaluated for secondary hypogonadism, impotence, or infertility.

Adrenal dysfunction

- Children and adults with SCD are at risk of pituitary-adrenal axis dysfunction secondary to hemorrhagic or thromboembolic injury and iron deposition.
- Clinicians should have a low threshold to investigate for adrenal insufficiency among patients who have hemodynamic compromise during sickle cell crises or with sepsis.

Thyroid Dysfunction

- There are conflicting data regarding the significance of thyroid dysfunction among children and adults with sickle cell disease.
- Chronically transfused children and adults with SCD are at increased risk of hemosiderin-associated thyroid dysfunction and should undergo annual thyroid screening.
- Children and adults with evidence of hypothyroidism should receive thyroid-hormone replacement therapy, and should be referred to an endocrinologist.

Impaired Glucose Tolerance and Diabetes Mellitus

- Diabetes mellitus (DM) affects approximately 2% of chronically transfused patients with SCD.[13] Duration of chronic transfusions and age at the initiation of chronic transfusion therapy are the most important risk factors for these patients.[13]
- Hemoglobin A1c may not be a reliable indicator of hyperglycemia in patients with SCD.[17,18]
- Chronically transfused children and adults with SCD should undergo annual glucose tolerance screening with fasting plasma glucose from 10 years of age.
- Impaired glucose tolerance and diabetes should be managed as per the Canadian Diabetes Association Guidelines,[19] and in conjunction with a diabetes clinic, with emphasis on glycemic control, diet, exercise, and management of complications.

Parathyroid Dysfunction

- Hyperparathyroidism is rare, but may occur as an incidental finding (no known association with SCD). Symptoms are non-specific, but, more importantly, may mimic other complications of SCD, such as bone pain, polyuria, and fatigue. [20]
- In patients with severe and recurrent bone pain, consider screening with serum calcium, phosphorus, alkaline phosphatase, renal function, parathyroid hormone levels, and neck ultrasound to exclude hyperparathyroidism.
- Hypoparathyroidism may occur from iron overload as seen in transfusion-dependent beta thalassemia patients.[21] Consider screening chronically transfused patients from 10 years of age.
- Children and adults with evidence of hyperparathyroidism should be referred to an endocrinologist.

Background

Delayed growth, skeletal maturation, and pubertal development are the most common endocrine disorders among children with sickle cell disease (SCD). Children with SCD often maintain a lower average height and weight than children without SCD.[2] A widely accepted definition of pubertal delay is the absence of pubertal signs by 14 years of age for boys and 13 years of age for girls.[3] Children and adolescents with SCD are frequently affected by delays in sexual maturation and late pubertal onset.[4,5]

These growth abnormalities are seen more commonly among children and adolescents with homozygous hemoglobin SS disease than among those with SCD.[6] There are several factors that contribute to growth delay and failure among children with SCD.[1,7,8,9,10] Infants and young children are particularly at risk for suboptimal nutritional intake during/following an acute illness.[11] Careful counseling and close follow-up are necessary to monitor for and prevent these common complications.

Other endocrine disorders that may occur include adrenal, thyroid, pancreatic, and parathyroid dysfunction. Although these disorders can manifest among non-transfused patients with SCD, these complications tend to be more common among chronically transfused children and adolescents with SCD as a consequence of iron overload.[12,13,14] For children and adults with SCD, the etiologies for these endocrine abnormalities are multifactorial, and these disorders may arise as a consequence of chronic anemia, tissue hypoxia, high basal energy demands, iron overload, genetic factors, and malnutrition.[13]

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14. IRON OVERLOAD

Principles

- To prevent transfusional iron overload in SCD.
- To diagnose and monitor transfusional iron overload.
- To initiate the appropriate iron chelation therapy at the appropriate time.
- To monitor chelation therapy.

Recommendations

Prevention

- Red blood cell transfusions should only be administered when medically necessary.
- Avoid transfusion for uncomplicated acute painful episodes if: i) the patient's hemoglobin concentration is near their baseline level, ii) there is appropriate reticulocyte response, and iii) the patient has no symptoms of anemia.

Monitoring and Diagnosis

- Maintain an accurate record of volume of red blood cell transfusions.
- In chronically transfused patients, serum ferritin should be measured regularly (e.g., every 3 months).
- Liver iron should be assessed yearly in chronically transfused patients who are not undergoing chelation.

Chelation Therapy

Initiation

- Chelation should be started in each patient who has evidence of increased total body iron; individual patient factors must be considered in determining the best timing for initiation.
- Deferoxamine or deferasirox are appropriate first-line therapy.
- Deferasirox should be avoided in patients with renal insufficiency.
- Data are lacking regarding combination chelation therapy for patients with SCD.

Baseline investigations prior to starting chelation therapy

- Serum ferritin, transferrin saturation, creatinine and liver enzymes.
- Liver iron content and cardiac iron should be assessed by MRI:
  - Liver iron content may be assessed by liver biopsy if MRI is contraindicated or unavailable, or if there are additional indications for liver biopsy (e.g., assessment in co-existing chronic hepatitis infection).
- Ancillary testing of cardiac function may also be performed (e.g., echocardiogram).
- Auditory and ophthalmic testing should be performed in all patients.

Monitoring in Patients on Chelation Therapy

1. Deferoxamine (DFO)
   - Serum ferritin, creatinine, and liver enzymes should be measured regularly (e.g., every 3 months).
   - Maintain therapeutic index of <0.025 calculated quarterly:

$$\frac{\textbf{Mean daily dose of DFO in mg/kg}}{\textbf{Serum ferritin in ug/L}}$$

- Auditory and ophthalmic testing annually.
- Liver iron and cardiac iron should be assessed every 6 to 12 months, depending on iron overload severity.

2. Deferasirox (DFX)
   - Serum ferritin, creatinine, and liver enzymes should be measured regularly (e.g., every 3 months).
   - Patients on DFX should be monitored for proteinuria monthly.
   - Auditory and ophthalmic testing annually.
   - Liver iron and cardiac iron should be assessed every 6 to 12 months, depending on iron overload severity.

I. End-organ Effects of Iron Overload

In healthy individuals, 1 to 2 mg of iron is absorbed daily from dietary intake, and an equal amount is lost, mostly from the gastrointestinal tract. The majority of body iron is present in hemoglobin. Additional iron is stored in the liver, spleen and bone marrow as ferritin or hemosiderin. The body does not have a homeostatic mechanism for excreting excess iron; therefore, if levels in the body increase, as occurs with repeated blood transfusions, iron can be deposited in the organs, starting with the liver.

Patients with sickle cell disease (SCD) who receive recurrent red blood cell transfusions are susceptible to iron overload,[1] which can be associated with significant morbidity and mortality.[2] One unit of red blood cells contains approximately 200 mg of iron (1 mL of erythrocytes = 1 mg iron).[3]

Avoiding unnecessary transfusion can prevent iron overload. Patients presenting with acute SCD pain episodes generally do not require RBC transfusion; as long as their hemoglobin level is at baseline, there is appropriate reticulocyte response, and there are no symptoms of anemia (*see Part II, section 1 – Pain*). Nonetheless, patients with SCD may require transfusions for medical reasons, including primary or secondary stroke prevention, acute chest syndrome, or surgery. SCD patients will develop iron overload proportional to the volume of blood transfused.[5,6] Iron overload is often under-recognized and under-treated in previously transfused patients with SCD.[7]

II. Assessment of Iron Overload

i) *Serum Ferritin and Other Laboratory Tests*

Serum ferritin level is the most commonly used test to screen for iron overload. It is inexpensive and widely available. False positives can occur in the presence of inflammation, liver disease and vitamin C deficiency. In patients with SCD, ferritin is elevated during vaso-occlusive episodes and for several weeks thereafter.[8] Trends in serum ferritin are poor predictors of changes in liver iron concentration in patients with SCD.[9,10] Nevertheless, when SCD patients are clinically stable, serum ferritin may be used in conjunction with monitoring transfusion volumes[6] and evaluating liver and cardiac iron (see below) to track response in patients on chelation therapy. Elevated transferrin saturation (>50%) should only be present in states of true iron overload,and may therefore be used as an additional test to evaluate iron stores.

ii) *Evaluation of Hepatic Iron*

In the presence of increasing body iron stores, the liver is the first organ to become overloaded with iron. Liver magnetic resonance imaging (MRI) is a safe, non-invasive, and accurate method of assessing liver iron content (LIC).[11,12] Although MRI machines are accessible in many medium- and large-sized centres in Canada, they may not available in smaller communities. Furthermore, MRI protocols specific to this indication are required (e.g., R2 Ferriscan or R2*), and staff must be trained in their application.

Previously, liver biopsy was the gold standard in measuring hepatic iron, reported in “mg/g dry weight”. Liver biopsy provides a direct, quantitative assessment of LIC. Biopsy is associated with procedural risks[13], however, and, since liver iron deposition is not uniform, liver biopsy can be associated with sampling error.[14,15] Liver biopsy is still performed to assess for potential complications in selected patients, including liver fibrosis, cirrhosis, or hepatocellular carcinoma.[16] Decisions about the role of liver biopsy in SCD patients should be made together with a liver specialist.

iii) Evaluation of Cardiac Iron

In chronically transfused patients, cardiac iron loading typically occurs more slowly than liver iron loading and generally appears with increasing age. Nonetheless, cardiac iron deposition can occur even at low liver iron levels.[5] In comparison with patients with thalassemia, patients with SCD are less likely to have abnormal cardiac iron at the same levels of liver iron.[17,18] This may be due to an overall lower transfusion burden in patients with SCD compared with thalassemia major. Longer duration of chronic transfusion and poor adherence to prescribed chelation therapy are associated with a higher risk of cardiac iron overload.[19]

Cardiac MRI is used to assess myocardial iron.[20] Measurements — expressed as T2 or T2* — correlate with cardiac dysfunction: T2* <20 msec is associated with presence of cardiac iron and ventricular dysfunction. Conversely, T2* is >20 msec when no cardiac iron or ventricular dysfunction are present.[20]

As cardiac iron overload occurs more slowly than liver iron loading, the corollary is also true – cardiac iron is also removed more slowly.[20]

iv) Other Laboratory Tests

Non-transferrin-bound iron (NTBI) is present in the blood when transferrin is highly saturated and, therefore, measurement of NTBI is an intriguing method for quantifying iron overload. There is little standardization of NTBI testing, however. Until reproducible protocols are available, it is primarily used in scientific research.[21]

III. Treatment of Iron Overload

i) Dietary Iron

For patients with sickle cell anemia (SCA) with iron overload, dietary iron intake should be minimized, including iron-containing supplements, red meat, and other high-iron foods. In addition, increased vitamin C intake can increase iron absorption from the diet.

ii) Reviewing Transfusion Regimen

Erythrocytapheresis, also referred to as "red cell exchange", is a process by which the patient's red blood cells are removed via an apheresis machine and replaced by donor packed red blood cells. For patients requiring a program of chronic red blood cell transfusion, erythrocytapheresis can be used in place of simple transfusion. Small, nonrandomized studies of patients who have received exchange transfusion show that they have less iron overload than patients receiving simple transfusion,[8] and that existing iron overload can be improved or stabilized.[22,23,24]

Despite evident decrease in iron loading, apheresis also has drawbacks. Firstly, blood utilization is increased by approximately 50% compared with a simple transfusion program.[22] This results in increased exposure to the risk of alloimmunization and transfusion-related adverse effects. Furthermore, the blood banking and other associated costs of apheresis make it more expensive.[22] Secondly, although iron levels are better controlled on an apheresis program, the majority of patients still require chelation therapy.[22.24]

It has been argued that the increased costs of apheresis need to be weighed against the potential costs saved by preventing iron-related organ damage.[22] Erythrocytapheresis is an appealing concept to prevent iron overload or control existing iron overload in patients on a chronic transfusion program, but the apparent benefits do not clearly outweigh the potential harms. Further study would be informative.

Partial manual exchange is a less resource-intensive method of red cell exchange that appears to be an effective method of slowing the rate of iron loading in chronically transfused patients with SCD.[25]

ii) Chelation Therapy

Chelation therapy is used to treat or prevent the accumulation of high levels of iron in the body. It works by binding excess iron and facilitating its excretion. Continuous blood levels are optimal to maximize chelation. The goal is to have a negative iron balance.

Clinical judgment is required when selecting the optimal time to begin chelation therapy. In one study of chelation in SCD,[26] serum ferritin ≥1000 g/L was required for study entry; Superconducting Quantum Interference Device testing (SQUID) was then performed to determine LIC. To be enrolled, patients had to have a liver iron concentration of ≥2 mg/g if receiving simple transfusions and ≥5mg/g if receiving exchange transfusions.

No studies to date have established specific thresholds for initiation of chelation in patients with SCD, or the effectiveness of chelation treatments specific to patients with SCD.[27] Consideration should be given to:

- Serum ferritin level;
- Liver iron concentration (by biopsy or MRI);
- Cardiac iron.

Although there are differences in the pathophysiology and natural history of iron overload in patients with SCD and thalassemia, in the absence of strong evidence to guide chelation therapy in SCD, clinicians may wish to use guidelines for chelation therapy in thalassemia major as a reference.[28,29]

Presently in Canada, two chelators are licensed for use:

1) Deferoxamine (DFO) has been in use for many years, and is widely available. Because of its high molecular weight, it has poor gastrointestinal absorption and is thus administered parenterally (intravenously or subcutaneously). DFO works by mobilizing iron in parenchymal cells and macrophages, and increasing iron excretion in the urine and feces. Clinical trials of DFO in chronically transfused patients with thalassemia major have shown high effectiveness in controlling body iron burden.[30] One small, randomized controlled trial (RCT) in patients with SCD showed a reduction in serum ferritin and improved hepatic function in all patients, with an apparent dose-response relationship.[31]

DFO removes iron more rapidly from the liver than from the heart,[33] making it a suboptimal choice for patients with documented cardiac iron accumulation. Patients may find it inconvenient because of the need for overnight subcutaneous infusions most nights of the week. Although DFO has long been the standard of care for transfusional iron overload in SCA, adherence is often suboptimal.[33] Adverse effects may include: reactions at infusion sites; abnormalities in vision or hearing; skeletal and growth abnormalities; zinc deficiency or Yersinia infection.[3] Several of these potential side effects have the potential to overlap with complications of sickle cell disease.[30] Typically, DFO is administered by subcutaneous infusion into the upper arm or abdomen over 8 to 12 hours. The daily dose of 20 to 60 mg/kg in infused 5 to 7 days of the week using a portable pump.[34] Dose adjustments are made to maintain a Porter index under 0.025.

In severely iron-overloaded patients with thalassemia, DFO has been given by continuous, 24-hour intravenous infusion with good improvement in serum ferritin, arrhythmias, and ventricular dysfunction.[35]

2) Deferasirox (DFX) is an oral iron chelator licensed in Canada in 2006. It has been studied in one Phase III randomized clinical trial (RCT) in which it was compared with DFO in patients aged 2 years and older with thalassemia major.[36] Dosing of both drugs was based on baseline liver iron concentration (LIC) as measured by liver biopsy. The researchers found that patients with LIC ≥7 mg iron/g dry weight had "significant and similar dose-dependent reductions in LIC and serum ferritin". Noninferiority was not shown in the group of patients with lower LIC, however, possibly because of disproportionately low dosing of DFX relative to DFO.

One Phase II RCT comparing DFX and DFO in 195 patients with SCD who were aged 2 years or older found similar dose-dependent LIC reductions in both groups, with doses of DFX of 30 mg/kg and DFO of ≥50 mg/kg showing absolute change in ferritin.[26] Discontinuation rates were equivalent for DFX (11.4%) and DFO (11.1%). In a substudy of this trial, however, patient satisfaction was higher for those on DFX.[37] In a five-year follow-up study of patients on DFX,[38] ferritin levels were significantly reduced, and there were few drug-related adverse events.

Cochrane reviews demonstrated similar efficacy between DFX and DFO.[39]

Adverse effects of deferasirox noted in clinical trials include: rash, gastrointestinal (GI) symptoms (nausea, diarrhea), mild elevation of transaminases, hearing impairment, and nonprogressive elevation of serum creatinine. More recently, cases of acute kidney injury have been reported, particularly in patients with pre-existing renal impairment. In addition, there have been reports of hepatic failure and gastrointestinal hemorrhage (www.drugs.com/pro/exjade.html).

DFX is taken orally once daily at a starting dose of 20 mg/kg/day.[36] It may be increased in increments of 5 to 10 mg/kg/day every 3 to 6 months, based on trends in ferritin level.[40] Based on data from a subgroup of 264 patients with beta-thalassemia, SCD, and myelodysplastic syndromes pooled from four clinical trials, doses over 30 mg/kg/day appear to be effective and safe.[41]

3) Deferiprone (L1) is an oral iron chelator available in Europe and other countries, but not licensed in Canada. Data from randomized clinical trials in thalassemia patients[42-44] suggest that L1 is as effective as DFO at decreasing iron load. In a randomized trial comparing L1 with DFO, patients with SCD also had similar reductions in body iron burden.[45] Studies showed more effective chelation of cardiac iron by L1 compared with DFO.[32]

Adverse effects can include: agranulocytosis, arthalgias, zinc deficiency; mild GI symptoms, and mild aminotransferase elevations.[3] L1 may be obtained in Canada through an industry special-access program.

4) Combination therapy with two or more chelating agents can increase the rate of iron excretion, but is rarely required in patients with SCD. Studies in patients with thalassemia and severe iron overload have shown improved cardiac iron levels and left-ventricular function in patients randomized to receive combination deferoxamine and deferiprone versus deferoxamine alone.[46,47]

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PART III: COMPREHENSIVE CARE

1. PERI-OPERATIVE MANAGEMENT

Principles

- To minimize the risk of morbidity and mortality in patients undergoing surgical procedures.

Recommendations

1. Pre-operative Care

- All patients should undergo consultation with an anesthesiologist prior to surgery.
- There should be close communication between the anesthesia, medical and surgical teams.
- The patient's treating hematologist, or another hematologist with expertise in sickle cell disease, should be directly notified of the upcoming surgery so that all important peri-operative factors are reviewed.
  - Pre-operative transfusion:
  - Decisions about the role and optimal method of pre-operative transfusion must take into account the risk category and individual patient factors (e.g., comorbidities and severity of sickle cell disease phenotype).
  - Patients undergoing moderate-risk surgery should typically receive prophylactic RBC transfusions to a target hemoglobin of 100 mg/L, or, if pre-transfusion hemoglobin is >=90 g/L, partial manual exchange to target HbS <60%.
  - Automated red cell exchange transfusion to target HbS <30% must be considered in high-risk procedures, and in patients with complex comorbidities or a history of post-operative complications.
- Cross-match compatible, phenotype-matched, Sickledex-negative units of red blood cells should be on hold in the blood bank (number based on risk of intra-operative blood loss).
- All patients should receive adequate hydration prior to surgery.
- If the patient is required to remain in NPO status prior to surgery, they should be admitted for intravenous hydration with isotonic solution during the NPO period.

2. Intra-operative Care

- The anesthesiologist should avoid regional anesthesia, when possible.
- Tourniquets or arterial clamping may be used when surgically required. but duration should be minimized.
- Intraoperative monitoring should include temperature, heart rate, blood pressure, and oxygenation.
- Temperature optimization may include use of warmed intravenous fluids and warming blankets.
- Careful attention should be paid to hydration and volume status.

3. Post-operative Care

- Isotonic intravenous fluids should be administered until the patient is drinking and eating well.
- Supplemental oxygen should be provided as needed.
- Consider involvement by respiratory therapy for deep breathing exercises and/or incentive spirometry.
- Clinical monitoring, including temperature, heart rate, blood pressure, oxygenation.
- Laboratory monitoring should be undertaken as indicated: hemoglobin, lactate dehydrogenase (LDH), reticulocyte count, bilirubin, arterial blood gas, chest x-ray.
- Pain control must be optimized. Patients with SCD may have increased opiate requirements compared with the general population. Good pain control will facilitate mobilization, and may help prevent splinting and atelectasis.
- Patients should receive post-operative thromboprophylaxis, as post-surgical bleeding risk permits.

Assessing and Managing Surgical Risk

Surgical procedures such as tonsillectomy, splenectomy, cholecystectomy or orthopedic surgery are commonly required in patients with sickle cell disease (SCD) because of hypersplenism, chronic hemolysis, or bone complications, respectively. In addition, patients with SCD may require unrelated surgeries during their lifetimes.

Patients with SCD have a higher risk of perioperative complications than the general population, for several reasons.

1. Anemia – Patients with SCD are already anemic, and procedural bleeding will further decrease hemoglobin levels, leading to more severe anemia, and decreasing the oxygen-carrying capacity of blood cells.
2. Hypoxemia – Intraoperative hypoxia, local tissue hypoxemia, or post-operative atelectasis can trigger sickling of red blood cells. Sickling of red blood cells can lead to a painful crisis or acute chest syndrome, among other SCD-related complications.
3. Dehydration – Several factors in the perioperative period can predispose the patient to dehydration, including pre-operative nothing-by-mouth (NPO) status and reduced oral intake following some surgeries (e.g., tonsillectomy or bowel surgery). Systemic dehydration can lead to dehydration of the red blood cells, and a subsequent increased rate of sickling.
4. Hypothermia – Intraoperative skin and tissue exposure, and the use of unwarmed intravenous infusions can lower body temperatures, leading to increased risk of red blood cell (RBC) sickling.
5. Acidemia – Use of prolonged tourniquets or arterial clamping required in some procedures can cause acidemia, leading to increased risk of RBC sickling.
6. Infection – Asplenia, either surgical or due to recurrent infarction, contributes to the risk of postoperative infection.
7. Chronic organ disease related to SCD can make certain patients more susceptible to organ-specific complications.

The risk of complications increases with the age of the SCD patient, and certain surgeries are known to be high-risk.[1] Risk must be assessed individually for each patient, however, depending on medical condition and the procedure to be undertaken. Tonsillectomy, for example, is classically a moderate-risk procedure in other patient populations; however, it may carry increased risk in an SCD patient because of the risk of airway compromise and hypoxia, the risk of excessive bleeding, and possible decreased oral intake during the post-operative recovery period.

The Cooperative Study of Sickle Cell Disease used the following classification for surgical risk:[1]

- Low-risk – Procedures of the eyes, skin, nose, ears, distal extremities, and also of the dental, perineal, and inguinal areas;
- Moderate-risk – Procedures of the throat, neck, spine, proximal extremities, genitourinary system, and intra-abdominal areas;
- High-risk – Procedures of the intracranial, cardiovascular, and intrathoracic systems.

Adverse outcomes may be minimized by optimal selection of anesthetic methods. Higher rates of postoperative painful crisis are associated with regional anesthesia than with local or general anesthesia.[1]

Use of tourniquets or arterial clamping are thought to increase the risk of sickling, because of hypoxia, acidosis, and venous stasis in the distal tissues. There have been several case series and case reports of generally successful outcomes with these surgical techniques, however.[2-4] Surgeons and anesthesiologists should be made aware of a patient's diagnosis of SCD and his or her pre-operative condition. Informed decisions about surgical technique and anesthetic approach must aim to best balance risks and benefits for the individual patient. The patient's treating hematologist, or another hematologist with expertise in sickle cell disease, should be directly notified of the upcoming surgery so that all important peri-operative factors are reviewed.

Role of Pre-operative Transfusion

Regarding pre-operative transfusion, the following questions must be considered for each patient:

1. Should this patient receive transfusion pre-operatively?
2. If so, what will be the transfusion parameters (i.e., target Hb and/or target sickle hemoglobin (HbS) concentration) and optimal method (i.e., simple vs. exchange)?

The risk category of the planned surgery plays an important role in risk stratification. As with all medical decision-making, individual patient factors (e.g., comorbidities and severity of sickle cell disease phenotype) must be considered in decisions about pre-operative transfusion.

Moderate-risk surgeries

The majority of surgeries performed on SCD patients are moderate-risk, including cholecystectomy, splenectomy, orthopedic and gynecologic surgeries.[1] Compared with low-risk procedures, moderate-risk surgeries are associated with higher rates of development of complications, including acute chest syndrome.[5]

In a randomized controlled trial of patients with sickle cell anemia (HbSS) undergoing a total of 604 operations, the Preoperative Transfusion in Sickle Cell Disease Study found that a pre-operative simple transfusion regimen (target pre-operative hemoglobin level of 100 g/L) offered outcomes equivalent to those of a pre-operative exchange transfusion regimen (target sickle hemoglobin [HbS] level <30%), specifically a similar incidence of serious peri-operative complications (31% vs. 35%) and acute chest syndrome (10% in both study groups). Furthermore, there was a higher rate of transfusion-related complications in the exchange transfusion group (14% vs. 7%, odds ratio [OR] 2.15, 95% confidence interval [CI] 1.23 to 3.77).[5] Seventy-five percent of the procedures were moderate-risk, with only one high-risk surgery, and the remaining classified as low-risk. The odds ratio for development of acute chest syndrome in moderate- and high-risk procedure categories was 2.97 (95% CI, 1.30 to 6.81). Equivalent outcomes were also seen in a cohort study of children receiving simple *versus* exchange transfusion prior to tonsillectomy and/or adenoidectomy.[6]

More recently the TAPS trial (Transfusion Alternatives Perioperatively in Sickle Cell Disease) assessed 67 patients with HbSS or HbS-beta 0-thalassemia who had been randomized to receive no pre-operative transfusion or to be transfused to a target pre-operative hemoglobin of 100 g/L.[7] Patients in the transfusion group who had pre-transfusion hemoglobin <90 g/L had simple "top-up" transfusion, whereas those with hemoglobin ≥90 g/L received partial manual-exchange transfusion, targeting HbS level <60%. Exclusion criteria included: baseline hemoglobin <65 g/L, recent transfusion (within 3 months), history of acute chest syndrome within 6 months, any history of intubation and mechanical ventilation for treatment of acute chest syndrome, oxygen saturation <90%, current renal dialysis or history of stroke in children. In the study population, 13 (39%) patients in the no-transfusion group had clinically important complications, compared with five (15%) in the pre-operative-transfusion group (P=0.023), giving an OR of 3.8 (95% CI, 1.2 to 12.2, P=0.027). Of these complications, there were 10 (30%) serious adverse events in the non-transfusion group versus one (3%) in the transfusion group. Most events in this category were episodes of acute chest syndrome. Duration of hospital stay and readmission rates did not differ between study groups. Over 80% of patients in this study were scheduled for a moderate-risk procedure.

Low-risk surgeries

In a natural history study of 1,079 procedures performed in 717 patients with SCD, peri-operative transfusion in patients with HbSS undergoing low-risk procedures was associated with a lower rate of SCD-related post-operative complications (4.8% vs. 12.9% without transfusion).[1] Subsequent prospective observational studies in patients with SCD, however, have suggested that prophylactic transfusion is not required prior to low-risk procedures.[8-10] Given the lack of consensus from observational studies, and the fact that low-risk procedures accounted for a small proportion of patients enrolled in the Preoperative Transfusion in Sickle Cell Disease Study and TAPS trials (results outlined above), pre-operative transfusion may still be considered in patients with major comorbidities or history of severe sickle cell disease phenotype.

High-risk surgeries

No major studies have formally assessed transfusion strategies in high-risk surgeries. Expert opinion suggests that a pre-operative exchange transfusion be considered in most SCD patients, based on the complexity and/or duration of high-risk procedures.

Peri-operative Supportive Care

In addition to prophylactic transfusion, attentive peri-operative care is important, including: pre-operative anesthesiology consultation and hydration, intra-operative monitoring of cardiorespiratory paraemeters, and post-operative monitoring with administration of supplemental oxygen and intravenous hydration.

It is prudent to keep several units of crossmatched RBCs on hold, depending on the surgical risk of bleeding, because of the high prevalence of RBC alloantibodies in the SCD population.

To prevent dehydration, careful attention must be paid to volume status, with the patient receiving intravenous hydration while NPO (pre-, intra- and post-operatively). Selection of isotonic fluids will minimize the risk of RBC dehydration with hypertonic solutions and the risk of hyponatremia with hypotonic solutions.

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2. CONTRACEPTION, PRE-CONCEPTION COUNSELING, AND PREGNANCY

Principles

- To facilitate effective, safe contraception for individuals with SCD who are aiming to prevent conception.
- To provide appropriate pre-conception hemoglobinopathy screening and genetic counseling for individuals with SCD and their partners.
- To educate women with SCD about the maternal and fetal risks associated with pregnancy, and to optimize timing of pregnancy with disease stability.
- To provide comprehensive, multidisciplinary medical care for women with SCD during pregnancy, labour, and the post-partum period.

Recommendations

Contraception

- For women with SCD who wish to prevent pregnancy, contraception — including barrier methods, intra-uterine device, and progesterone-only hormonal contraception — may be considered. Progesterone-only contraception is effective, and may be associated with reduced sickle pain.

Pre-conception Counseling

- Men and women with SCD should be counseled about the genetic inheritance of SCD, and the availability of partner genetic screening and counseling prior to planning conception.
- Women planning or considering pregnancy should receive counseling about the known fetal and maternal risks. Pre-conception medical status should be optimized, including immunization and folic acid supplementation. Hydroxyurea and chelation therapy should be discontinued prior to conception.

Pregnancy

- During pregnancy, women should be followed by a multi-disciplinary obstetrical team knowledgeable in the care of SCD, with input from maternal-fetal-medicine, hematology, neonatology, and anesthesia.
- NSAIDs should be avoided in the first and third trimesters, but can be used judiciously between 12 and 28 weeks gestational age.
- Opiate use should be optimized to effectively control pain. Neonates with chronic in utero opioid exposure should be monitored and managed for opioid withdrawal.

Labour and Delivery

- Delivery should take place in an expert centre, with availability of fetal and maternal monitoring, and attention to maternal hydration, warmth, and adequate analgesia.

Post-partum

- Post-partum VTE prophylaxis should be offered for women with any additional risk factors (e.g., history of prior VTE, Caesarean section, or reduced post-partum mobility).

Contraception

For women with sickle cell disease (SCD) who wish to prevent pregnancy, contraception — including barrier methods, an intra-uterine device (IUD), and progesterone-only hormonal contraception — may be considered. Progesterone-only contraception is effective, and may be associated with reduced sickle pain.[1-3] There is no clear evidence of harm with combined oral contraception.[4] An IUD is an effective method of long-term contraception. There is no evidence of harm with an IUD, and no theoretical concerns with IUD use.[4] Progesterone-based IUD is being used increasingly in some centres, but has not been investigated in SCD.[5]

Elements of Pre-conception Consultation

a) Genetic Counseling

Patients with SCD who are planning a pregnancy should be aware of the inheritability of SCD. Partners should undergo hemoglobinopathy testing, prior to pregnancy when possible, to determine fetal risk of clinical disease; any positive partner testing must be followed by detailed genetic counseling for the couple as to the potential risk and probability of conceiving an affected fetus. Pre-implantation genetic diagnosis may be considered in relevant circumstances.[6]

b) Maternal and Fetal Risk Assessment

Women with sickle cell disease who are considering pregnancy should receive careful counseling about the maternal and fetal risks associated with pregnancy. Thorough sickle cell and obstetric history should be obtained. Regular medications must be reviewed. A detailed physical examination should be performed, with recording of pre-pregnancy weight and height, as well as splenic size.

Pregnancy is associated with increased incidence of pain episodes, infection, pulmonary complications, venous thromboembolism (VTE), antepartum bleeding, and hospitalization in women with SCD.[8-11,18] Women with SCD are also at an increased risk of pre-eclampsia.[8,11,12] Because of this, pregnancy should be timed during a time of relative disease stability.

Fetal risks include intrauterine growth restriction, fetal anemia due to maternal alloantibodies, premature labour and delivery, and stillbirth.[8,9,10,12,13] There is an increased rate of cesarean section for pregnant women with SCD.[11] As a result of higher rates of maternal and fetal complications, women with SCD should be followed closely in a high-risk obstetric unit knowledgeable in the care of SCD.

c) Hydroxyurea discontinuation

Discontinuation of hydroxyurea prior to conception is advised, due to evidence of teratogenicity in animals. Although retrospective observational data of women who received hydroxyurea during pregnancy suggests no specific adverse outcomes in fetal life, infancy, or childhood,[14,17] more robust prospective and long-term data are still needed to confidently recommend continuation of hydroxyurea in pregnant SCD patients.

d) Chelation Therapy Discontinuation

Chelation therapy should be discontinued during pregnancy. In cases of critical iron overload, deferoxamine can be used safely in the second and third trimesters, and while breastfeeding.

e) Analgesia

Analgesics should be reviewed. Non-steroidal anti-inflammatory drugs (NSAIDs) are best avoided during the first and third trimesters, as they have been linked with an increased risk of miscarriage in the former and premature closure of the fetal ductus arteriosus in the later. Judicious use of NSAIDS between 12 and 28 weeks of gestation, however, can be a useful adjunct in attaining pain control. Women requiring analgesia for sickle pain should be prescribed opioids in doses sufficient to manage pain. Following delivery, a pediatric consultation should be obtained for infants with *in utero* opioid exposure to observe for and manage neonatal opioid dependency and withdrawal.

f) Folic Acid

Supplementation with folic acid 5 mg daily is recommended prior to conception and throughout pregnancy, in view of the ongoing background hemolysis, which increases the risk of folate deficiency.[15] From the fetal perspective, folic-acid supplementation is particularly essential during the time of neural-tube closure, which corresponds to the first four weeks of gestation.

g) Laboratory and Screening Evaluations

Initial comprehensive laboratory testing must be obtained, and should include complete blood count with reticulocyte count, hemoglobin electrophoresis to determine baseline sickle hemoglobin percentage (HbS%), serum ferritin levels, liver and kidney function, blood group, and antibody screen, red blood cell phenotype (if not obtained in the past), and serology for human immunodeficiency virus (HIV), hepatitis B and hepatitis C.

Screening for end-organ complications should include a retinal exam, echocardiography to rule out pulmonary hypertension and ventricular dysfunction, and pulmonary function testing in patients with respiratory symptoms.

h) Immunizations and Chronic Infection

Many women with SCD undergo auto-splenectomy, and are therefore at risk of infection with encapsulated organisms. As such, immunizations against haemophilus influenza type B, pneumococcus, and meningococcus should be up to date. Additionally, patients should be immunized against hepatitis B virus. Yearly influenza vaccines should be encouraged.

Management in Pregnancy

a) Principles of Care

Pregnant women with SCD should be followed closely in a high-risk obstetric unit knowledgeable in the care of SCD. **Any relevant counseling, clinical assessment or testing that was not completed prior to conception should be performed early in pregnancy** (e.g., baseline hemoglobin and hemolytic screen; blood group and screening for RBC alloantibodies; testing for iron overload; assessment of renal and liver function; echocardiography; and retinal exam) *(see section above entitled "Elements of Pre-Conception Consultation")*

b) Maternal Laboratory Monitoring

Regular monitoring of hemoglobin levels should be initiated.

Asymptomatic urinary-tract infections (UTIs) are common in pregnancy, and may precipitate sickle cell crisis. A UTI can also evolve into pyelonephritis, which is associated with an increased risk of pre-term labour. Because of this, consideration should be given to collection of monthly mid-stream urine samples for analysis and treatment as appropriate.

c) Fetal Monitoring

If exposure to teratogenic medication has taken place early in gestation, an early anatomy ultrasound around 15 weeks, and a level II anatomy ultrasound between 18 and 20 weeks gestational age are recommended.

In view of the higher risk of adverse fetal outcomes, a number of which may be placentally mediated, placental assessment in the form of placental biochemistry as well as ultrasound evaluation of the placenta, including uterine artery Doppler, may be considered. In the late second and third trimesters, serial ultrasounds for fetal growth and well being, including assessment of fetal Doppler, amniotic fluid volume, and biophysical profile, are strongly recommended.

d) Role of Red Cell Transfusions

Routine use of prophylactic red blood cell transfusion in pregnancy is not advised. A randomized controlled trial of prophylactic transfusion versus on-demand transfusion in pregnant women with sickle cell anemia (HbSS) was associated with reduced painful episodes, but there was no significant difference in fetal outcome, at the expense of a four-fold increase in the number of red cell units transfused.[16] Indications for transfusion in pregnancy may include: acute chest syndrome, recurrent pain episodes, symptomatic anemia, or placentally mediated intrauterine growth restriction. Exchange transfusion may be considered in place of simple transfusion.

Labour and Delivery

Delivery should take place in an expert centre, with availability of relevant maternal and fetal monitoring. Spontaneous labour can be awaited, with an aim for vaginal delivery. Caesarean sections should be reserved for the usual obstetric indications. Maternal hydration should be emphasized, either via the oral or intravenous route, as should maintenance of maternal warmth and comfort, including adequate pain relief and supplemental oxygen, as required.

Postpartum Care

Following delivery, a pediatric assessment should be available for infants with *in utero* opioid exposure, to observe for and manage neonatal opioid dependency and withdrawal. This can be facilitated through an antenatal Pediatric consultation in the third trimester, or via consultation of the Pediatric service at the time of delivery, depending on local practice.

Post-partum venous thromboembolism (VTE) prophylaxis may be considered for all women with SCD, and should be offered to patients with additional risk factors (e.g., history of VTE, Caesarean section, or reduced post-partum mobility).

Contraception and plans for future pregnancies should be discussed. Resumption of pre-pregnancy medication must be re-evaluated.

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3. NEWBORN SCREENING

Principles

- To ensure early detection of children with sickle cell disease through newborn screening.
- To enable the prompt introduction of secondary prevention strategies and parental education for affected infants with sickle cell disease.
- To provide genetic counseling facilities for affected families.

Recommendations

- Health-care providers and policy makers should advocate for the availability of universal newborn screening for SCD throughout Canada. Hemoglobinopathy screening should be integrated within existing newborn screening programs for other inherited disorders.
- Prior to the implementation of universal hemoglobinopathy screening, appropriate procedures need to be developed for documentation, result notification, and clinical follow-up.
- With the implementation of universal hemoglobinopathy screening, there must be a clear policy regarding heterozygous carrier notification. Asymptomatic carriers do not need to be referred to a hematologist.
- A clear protocol should be implemented to enable familial counseling for affected infants and asymptomatic carriers, which will facilitate the discussion of sibling testing, recurrence risk, reproductive options, and prenatal diagnosis.
- Affected newborns should be referred immediately to a comprehensive SCD program and/or to a pediatric hematologist.
- Penicillin prophylaxis should be initiated prior to the age of 2 months.

Background

Newborn screening is an important public-health strategy in the management of sickle cell disease (SCD). Although newborns with SCD are clinically asymptomatic due to the predominance of fetal hemoglobin, early identification of newborns with SCD allows for early introduction of critical interventions that reduce SCD-related morbidity and mortality.

In a report of the first 10 years of a neonatal hemoglobinopathy-screening program in California, Vichinsky *et al* demonstrated an overall mortality rate of 1.8% for infants with neonatally diagnosed SCD compared with an 8% mortality rate among infants who were diagnosed after 3 months of age.[1] Newborn screening allows for the identification of affected families, and provides an opportunity for parental education about the signs and symptoms of infections, splenic sequestration, and other complications of SCD. Newborn screening also provides an entry point for genetic counseling programs.[2,3] Universal screening of all newborns is preferable to selective screening because it has been estimated that as many as 20% of high-risk individuals will be missed with selective screening alone.[4]

In 2006, Ontario was the first province in Canada to implement universal newborn screening for the detection of SCD. The carrier frequency of the sickle gene is cited at 1 in 10 among the African-American population in the United States. The Canadian Task Force on Preventive Health Care (CTFPHC) estimates that this frequency may be higher in Canada.[5] In Canada, the black population is composed largely of individuals of Caribbean and African origin where carrier rates are 10% to 14% and 20% to 25%, respectively. Between 95 and 100 babies with SCD are born in Canada each year, with approximately 60 of these infants in Ontario alone.

Newborn screening can be performed using cord blood or a capillary blood sample from a neonatal heel prick. Initial screening should be performed prior to any blood transfusions. Infants who require emergent transfusions for other clinical indications should have testing done 3 months after the transfusion.

Screening methods include high performance liquid chromatography (HPLC), isoelectric focusing, and hemoglobin electrophoresis. Enzyme-linked immunsorbent assay (ELISA) techniques to detect sickle hemoglobin (HbS) and hemoglobin C (HbC) have also been used.[6] A sickle solubility test is inappropriate in the newborn period,

and should not be performed. With positive newborn screening results, either DNA studies and/or testing of both parents should be done to confirm the results.

Interpretation of newborn screening results

Hemoglobins identified by neonatal screening are generally reported by level of expression or in order of quantity. For instance, a normal infant will show HbFA because, at birth, more fetal hemoglobin (HbF) is present than normal adult hemoglobin (HbA).

Sickle disorder	Neonatal screening result
SS	FS
S beta thal°	FS
S beta thal+	FSA / FS
S-HPFH	FS
SC	FSC

Neonatal screening for SCD may also identify non-sickle hemoglobinopathies such as beta thalassemia major, hemoglobin H disease, hemoglobin E disease or hemoglobin C disease. Several other hemoglobin variants may also be detected through newborn screening, such as alpha globin variants; the majority of these are of no clinical consequence.[7]

Carriers of the sickle gene and other hemoglobinopathies are also identified through newborn screening. These patients are usually clinically asymptomatic, but the information may be useful for purposes of genetic counseling. With the implementation of universal hemoglobinopathy screening, there must be a clear policy regarding the notification of asymptomatic carriers.

Carrier state	Neonatal screening result
Sickle cell trait (HbAS)	FAS
Hemoglobin C (HbC) carrier	FAC
Hemoglobin E (HbE) carrier	FAE

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4. IMMUNIZATIONS AND ANTIMICROBIAL PROPHYLAXIS

Principles

- To reduce the incidence of bacteremia and associated complications due to *S. pneumoniae, N. meningitides,* and *H. influenzae B* among children with sickle cell disease (SCD).
- To prevent hepatitis B, seasonal influenza, and *S. typhi* infections among children and adults with SCD.

Recommendations

1. General

- Advocate for universal newborn screening to ensure early identification of children with SCD.
- Antimicrobial prophylaxis should be given to all children with SCD.
- In addition to routine immunizations, children with SCD should receive additional vaccinations to reduce their risk of *S. pneumoniae, N. meningitidis,* hepatitis B, and seasonal influenza infections.

2. Antimicrobial Prophylaxis

- Penicillin V Potassium (VK) is the first-line choice for antimicrobial prophylaxis for children with SCD. Amoxicillin is an effective alternative in situations where penicillin VK is not available.
- The dose given is dependent on the patient's age. Tablets are preferable to suspension formulations due to their longer shelf life, and they may be crushed for younger children.

Age	Dose of Penicilin VK
≥2 months to 3 years)	125 mg twice daily
≥3 years	250 mg twice daily

- Patients with a penicillin allergy may be placed on the equivalent dose of oral cotrimoxazole or erythromycin.
- All children with SCD should receive antimicrobial prophylaxis from age 2 months to at least 5 years.
- Children with SCD who have had previous invasive pneumococcal disease such as pneumonia, septicemia, or meningitis, those whose immunizations are not up-to-date, and those who have had a surgical splenectomy should continue on penicillin prophylaxis indefinitely. Indefinite prophylaxis should also be considered for children with inconsistent compliance with antimicrobial prophylaxis.
- Patients and families must receive adequate education about the importance of antimicrobial prophylaxis to ensure compliance. They must also be counseled to seek medical attention immediately if children with SCD develop fever, regardless of oral antibiotic status.
- Special consideration should be made for continuing antimicrobial prophylaxis for individuals with SCD who have undergone hematopoietic stem-cell transplantation, solid organ transplantation, and/or have human immunodeficiency virus (HIV) infection. An Infectious Disease specialist may be consulted for these circumstances.

3. Immunizations

Children with SCD should receive all routine childhood immunizations as recommended by the current Canadian Immunization Guide.

S. pneumoniae

- ***Pneumococcal conjugate vaccine:*** Pneu-C-13 (PCV13) vaccine is the product of choice. Infants with SCD should receive three doses of PCV13 at least 8 weeks apart beginning at 2 months of age and followed by a booster at 12 to 15 months of age.

- Infants 7 to 11 months of age who have not been previously immunized against *S. pneumoniae* should receive two PCV13 doses at least 8 weeks apart and a third dose after 12 months of age, at least 8 weeks after the second dose.
- Children between 12 and 23 months of age who have not been previously immunized against *S. pneumoniae* should receive two doses of PCV13 at least 8 weeks apart.
- Children aged 24 months and over who have not been previously immunized against *S. pneumoniae* require only one dose of PCV13.
- Children who have received complete, age-appropriate vaccination with Pneu-C-7 or Pneu-C-10 (i.e., 0 doses of PCV13) should receive a single dose of PCV13 at least 8 weeks after previous PCV.
- Immunization with PCV after age-appropriate childhood vaccination is not necessary.

- ***Pneumococcal polysaccharide vaccine*** (PPV23) should initially be given at 24 months of age. PPV23 should not be administered sooner than 8 weeks after PCV13.
  - PPV23 should be re-administered to children ≥24 months of age once after the initial immunization. The interval between PPV23 immunizations will depend on the child's age at the initial immunization.
  - <11 years of age at the initial immunization: A single re-immunization with PPV23 vaccine 3 years after the initial immunization is recommended.
  - ≥11 years of age at the initial immunization: Re-immunization should take place 5 years after the initial immunization with PPV23 vaccine.
  - No more than two lifetime doses of PPV23 should be administered.
- For individuals ≥24 months of age who have not received PCV13 or PPV23, PCV13 should be given first.

N. meningitidis

- Children between 2 and 11 months of age should receive 2 or 3 doses of Menveo™ given 8 weeks apart, with another dose between 12 and 23 months of age (at least 8 weeks from the previous dose), and booster doses as below.
- Children between 12 to 23 months of age should be given 2 doses of Menveo™ at least 8 weeks apart and booster doses as below.
- Children and adults 24 months of age and older should receive 2 doses of any of the Men-C-ACYW-135 vaccines at least 8 weeks apart, followed by booster doses as below.
- Booster doses of Men-C-ACYW-135 vaccines are recommended every 3 to 5 years for those vaccinated at 6 years of age and younger, and every 5 years for those vaccinated at 7 years of age and older.
- Bexsero® (4CMenB) has been recently approved for serogroup B vaccination in Canada. The recommended dosing schedule according to the manufacturer is as follows:[24]
  - Infants should receive 3 doses of the vaccine at 2, 4, and 6 months of age. A booster should be administered between 12 and 23 months of age.
  - Infants between 6 and 11 months of age who have not received Bexsero® should receive 2 doses of the vaccine ≥2 months apart. A booster should be administered between 12 and 23 months of age, and 2 months or more from the preceding dose.
  - Children between 12 and 23 months of age should receive 2 doses of the vaccine at least 2 months apart. A booster dose should be administered between 12 and 23 months after the primary series.
  - Children between 2 and 10 years of age should receive 2 doses of the vaccine at least 2 months apart. The need for a booster dose after this primary series has not been established.
  - Patients >10 to 17 years of age should receive 2 doses of the vaccine at least 1 month apart. The need for a booster dose after this primary series has not been established.

H. influenza B (Hib)

- The recommended vaccination schedule for Hib is a primary series of 3 doses given at age 2, 4, and 6 months with a booster dose at age 18 months.
- All patients 5 years of age or older who never received Hib immunization or missed one or more doses should receive one dose. Some experts recommend one additional dose of Hib vaccine for all asplenic patients over 5 years of age, even if previously fully immunized.
- Children with asplenia who present with life-threatening Hib infections should receive a Hib vaccine, as the infection itself does not confer lifelong protection.

Other immunizations

- Children with SCD who are 6 months of age or older should receive the seasonal influenza vaccine each year to decrease the risk of the superimposed bacterial infections that are associated with influenza infections.
- All asplenic patients travelling to less developed areas of the world may be at risk of Salmonella infection, and should receive *Salmonella typhi* immunization.
- Children with SCD should be offered hepatitis A vaccination during infancy, according to the routine immunization schedule.
- In provinces where hepatitis B vaccine is not administered during infancy, children with SCD should receive the hepatitis B vaccination during infancy or as soon as they are identified to have SCD. The vaccine should be administered 0, 1, and 6 months apart, between ages 0 and 12 months.

Background

Children with sickle cell disease (SCD) require the same routine immunizations for vaccine preventable diseases, which are given to well children without SCD. Patients with SCD, however, are at high risk of fatal septicemia caused by polysaccharide-encapsulated organisms such as *Streptococcus pneumoniae* (Pneumococcus), *Neisseria meningitidis* (Meningococcus) and *Hemophilus influenzae* type B (Hib). An important reason for the increased predisposition to infection is the splenic dysfunction that occurs in SCD. Functional asplenia occurs in 94% of patients with sickle cell anemia (HbSS) SCD by the age of 5 years.

In the era before antimicrobial prophylaxis and routine immunization, the highest rates of bacteremia in SCD were seen in children less than 2 years old, with *Streptococcus pneumoniae* being the predominant pathogen.[1] At that time, patients with SCD had a 12.5% risk of developing septicemia or meningitis. In those with homozygous sickle cell anemia (HbSS), the risk increased to 15.2%.[2] Case-fatality ratios for sepsis and meningitis were 35% and 10%, respectively. Disease complications due to *S. pneumoniae* occurred almost exclusively among children with HbSS disease who were under the age of 5 years.

Patients with SCD are also at an increased risk of contracting blood-borne infections such as hepatitis B and C, as they may receive multiple red blood cell transfusions (see Part II: *Transfusion*).

Preventive strategies for reducing the risk of infection include patient and family education, antibiotic prophylaxis, empiric antibiotic use for febrile episodes, and immunizations.

Streptococcus pneumoniae

Pneumococcal polysaccharide vaccines (PPV) were licensed in North America over 30 years ago. A 23-valent vaccine (Pneu-P-23) is currently available, and has been shown to increase antibody levels and reduce the incidence of invasive pneumococcal disease (IPD) in older children and adults with SCD. Its efficacy is limited in children less than 2 years of age due to poor immunogenicity.[3] Prevnar-7 is a pneumococcal conjugate vaccine that contains seven capsular polysaccharide antigens from the bacterium Streptococcus pneumoniae. It is effective against pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, and may have cross-reactivity against other serotypes, such as 6A.

More recently, the Prevnar-13 pneumococcal conjugate vaccine (PCV) has been released, and induces immunity against thirteen pneumococcal antigens. It expands upon the antigenicity of Prevnar-7 to include serotypes 1, 3, 5, 7F, 19A, and 23F. Unlike the 23-valent pneumococcal vaccine, pneumococcal conjugate vaccines elicit T cell-dependent immune responses, which result in enhanced immunogenicity among young children, including infants with SCD.[3-5] In 2007, Halasa *et al* reported a 93.4% decrease in invasive pneumococcal disease (IPD) among SCD patients aged less than 5 years following introduction of the PCV.[6] Rates of IPD also decreased among children with SCD who were aged ≥5 years, but the difference was not statistically significant (161 cases per 100,000 person-years during the pre-PCV period to 99 cases per 100,000 person-years during the post-PCV period; *P*=0.36). In a 2008 study on the efficacy of the PCV in children with SCD in a metropolitan U.S city, a 68% reduction in IPD was noted after PCV licensure.[7] Patients with SCD who are aged 2 years and older have higher antibody concentrations when given a combined schedule of both 7-valent PCV and 23-valent vaccines.[8]

The efficacy of prophylactic penicillin in preventing IPD was clearly demonstrated in the penicillin prophylaxis study (PROPS 1), which was terminated 8 months early.[9] Children with SCD who were younger than 3 years of age were enrolled in the study and randomized to receive either oral Penicillin V or placebo, twice daily. After an average of 15 months of follow up, there was an 84% reduction in infection rates, and there were no deaths from pneumococcal septicemia in the penicillin group compared with the placebo group. In 1995, the PROPS 2 trial evaluated the effect of discontinuing penicillin prophylaxis at age 5 years in children with SCD.[10] The authors concluded that children with SCD without prior severe pneumococcal disease and who had not had a splenectomy could safely stop penicillin prophylaxis at age 5 years. It is important to note, however, that, since the 1990s, there has been a marked increase in the worldwide prevalence of penicillin-resistant pneumococci. In Canada, it has been estimated that approximately 8% of *S. pneumoniae* isolates have decreased in their susceptibility to penicillin.[11] Another caveat is that it is unclear whether the risk of bacteremia is the same or increased for surgically splenectomized individuals with SCD compared with those individuals with functional asplenia alone. There are no studies that have evaluated the optimal duration of penicillin prophylaxis in surgically splenectomized patients with SCD.

Hemophilus influenzae type B (Hib)

H. influenzae is a gram-negative coccobacillus, which may be encapsulated or non-encapsulated. Encapsulated (or typeable) strains of *H. influenzae* are grouped into six different serotypes ("a" through "f") according to their polysaccharide capsule. Encapsulated strains are more likely to cause invasive disease while non-encapsulated strains usually cause milder infections. Hib is the most pathogenic of all *H. influenzae* strains, and caused 95% of invasive disease prior to the implementation of routine immunization programs.[12] Risk factors for Hib include splenic dysfunction, antibody deficiency, Inuit descent, exposure to group child care, and cochlear implantation.[12]

Hib is most prevalent in children between 2 months to 2 years of age, and occurs worldwide. In young children, Hib can cause bacterial meningitis, pneumonia, and other serious invasive infections. In countries where Hib conjugate vaccines are widely used, invasive Hib disease in children has been virtually eradicated.[13] The clinical efficacy of Hib vaccines is high, and has been estimated to be between 95% and 100%. In Canada, Hib is given routinely to all children during their primary immunization schedule.[14] Since 1988, when Hib vaccines were introduced in Canada, the overall incidence of reported Hib-related disease has decreased by 94%.[12] In Canada, there are three forms of Hib vaccines currently available. Act-HIB® is a Hib-tetanus toxoid conjugate vaccine. Pediacel® contains diphtheria and tetanus toxoids and acellular pertussis vaccine combined with inactivated poliomyelitis vaccine and Hib conjugate vaccine. Infarix hexa™ is an adsorbed vaccine containing acellular pertussis, diphtheria and tetanus toxoids, recombinant hepatitis B, inactivated poliomyelitis, and conjugated Hib vaccine.

Children with SCD under 9 years of age have a four-fold increased risk of Hib septicemia compared with children without SCD.[15] The Cooperative Study of Sickle Cell Disease (CSSCD) in the United States reported a 20% mortality from Hib bacteremia.[16] Fortunately, the Hib conjugate vaccine has been demonstrated to be highly immunogenic in infants and children with SCD.[17] In Canada, the recommendations for Hib immunization among children with SCD are the same as those for individuals with hyposplenism or asplenia (see Immunizations section below).[12]

Neisseria meningitidis

Virtually all forms of invasive meningococcal disease are caused by *N. meningitidis* serotypes A, B, C, Y, and W-135.[18] Invasive meningococcal infections usually present with an acute febrile illness and rapid development

of symptoms related to meningitis and/or septicemia. Meningococcemia is most often characterized by a non-blanching petechial or purpuric rash and hemodynamic collapse, which carries a high fatality rate. Among children with SCD, fatal *N. meningitidis* infections are most classically associated with disseminated intravascular coagulation (DIC).[18] Adrenal hemorrhage and adrenal venous thrombosis have also been described with severe meningococcal infections.[19]

Men-C-C and Men-C-ACYW-135 vaccines are highly effective, but due to waning immunity, a booster immunization is required during the second year of life if these meningococcal vaccines are administered during infancy.[20,21] In Canada, three monovalent conjugate meningococcal vaccines (Men-C-C) are currently in use: Meningitec®, Menjugate® and NeisVac-C®. Menactra® and Menveo™ are quadrivalent conjugate meningococcal vaccines against *N. meningitidis* serogroups A, C, Y, and W-135. Menomune is the only quadrivalent polysaccharide meningococcal vaccine (Men-P-ACYW-135) that is available for use in Canada.

According to data from the Public Health Agency of Canada, *N. meningitidis* serogroup B caused >50% of invasive meningococcal disease cases between 2002 and 2011, and is now the most prevalent serogroup in Canada.[22] In December 2013, Bexsero® (4CMenB) vaccine was approved by Health Canada for immunization against *N. meningitidis* serotype B.

Individuals who have the highest risk of invasive meningococcal disease include patients with hyposplenism or asplenia (e.g., individuals with SCD); congenital deficiencies in primary antibodies, properdin, factor D, or complement; individuals with more than one episode of invasive meningococcal disease; patients who are prescribed eculizumab; and individuals who work with *N. meningitidis*.[23] Anyone who falls into these categories should be offered immunizations against serotypes A, B, C, Y, and W-135 when available (see table below).

Suggested Immunizations for Individuals with Sickle Cell Disease (in addition to routine immunization schedule)

S. pneumoniae		
All patients aged 2 to 11 months	PCV13	3 doses ≥8 weeks apart + additional dose between 12 to 15 months
7-11 months of age, unvaccinated	PCV13	2 doses ≥8 weeks apart + additional dose after 12 months of age, ≥8 weeks after the second dose
12-23 months of age, unvaccinated	PCV13	2 doses ≥8 weeks apart
≥24 months of age, unvaccinated	PCV13	1 dose
Unvaccinated children who have received complete vaccination with Pneu-C-7 or Pneu-C-10	PCV13	1 dose
All patients ≥24 months of age	PPV23	1 dose ≥8 weeks after PCV13
Booster		
<11 years of age at the initial immunization	PPV23	1 dose 3 years after the initial immunization with PPV23
≥11 years of age at the initial immunization	PPV23	1 dose 5 years after the initial immunization with PPV23
N. meningitidis		
All patients aged 2-11 months	Menveo™ Bexsero®	2 or 3 doses ≥8 weeks apart + additional dose between 12-23 months ≥8 weeks from previous dose
12-23 months of age, unvaccinated	Menveo™	2 doses ≥8 weeks apart
	Bexsero®	2 doses ≥8 weeks apart+ additional dose 12-23 months from previous dose
≥24 months of age, unvaccinated	Men-C-ACYW-135*	2 doses ≥8 weeks apart
2-10 years of age	Bexsero®	2 doses ≥8 weeks apart
>10-17 years of age	Bexsero®	2 doses ≥4 weeks apart

Booster		
<7 years of age at the initial immunization	Men-C-ACYW-135*	Every 3 to 5 years
≥7 years of age at the initial immunization	Men-C-ACYW-135*	Every 5 years
H. influenzae B		
All patients	Primary series (see Canadian Immunization Guide).	
All patients ≥5 years of age	Consider single booster dose of conjugated Hib vaccine.	
Hepatitis B		
All patients	Hepatitis B vaccine	0, 1 and 6 months apart between age 0-12 months
Hepatitis A		
All patients	Hepatitis vaccine	See Canadian Immunization Guide
Influenza		
Children aged 6 months to <9 years receiving seasonal influenza vaccine for the first time	Seasonal vaccine	2 doses ≥4 weeks apart
All patients ≥9 years of age	Seasonal vaccine	1 dose annually

* Menveo™ or Menactra®

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5. NUTRITIONAL MANAGEMENT

Principles

- Children and adults with SCD have higher metabolic expenditure and are at higher risk of malnutrition, poor growth and micronutrient deficiencies.
- Early referral to a registered dietician and close monitoring of growth is essential for early detection of malnutrition and nutritional deficiencies.

Recommendations

Nutrition

- At each medical visit, a nutrition-focused physical examination should be performed to screen for the presence of nutrient deficiencies.
- Referral to a Registered Dietitian is essential for nutrition screening and assessment, which should include an ascertainment of malnutrition risk, an assessment for possible weight loss and nutrient deficiencies, and education and planning for the management of nutritional concerns.
- A stress factor of 1.3 to 1.5 should be added to standard basic metabolic rate/resting energy expenditure equations for age to account for increased metabolic rates in individuals with SCD.
- Protein energy estimations should exceed the standard recommended dietary allowance intakes for age by adding a stress factor range of 1.5 to 1.7 to protein calculations.

Growth Monitoring

- Serial growth measurements should be performed to capture both acute changes and long-term growth velocity.
- Recumbent length for infants should be measured supine until 24 months of age; head circumference should be measured serially until an infant reaches at least 36 months of age, as brain development in chronic malnutrition can be critically altered during this important phase of growth.[9]
- Age-appropriate growth charts should be used to identify suitable trajectories in growth in infants, children, and adolescents, and identify suboptimal growth.
- Mid-arm circumference or skinfold measurement should be conducted during dietician assessments to assess changes in muscle mass and identify potential muscle wasting with assessment based on reference population data.
- There are no evidence-based guidelines for the frequency of bone density monitoring in SCD, but dual-energy X-ray absorptiometry (DXA) assessments should be considered to evaluate for deviations in bone mineral density compared with reference data.[10]

Monitoring for Micronutrient Deficiencies

- A 24-hour dietary food recall should be undertaken to assess dietary intake of vitamin D compared with age-based requirements.
- Request serum 2-OH vitamin D levels bi-annually to identify whether vitamin D insufficiency/deficiency exists and to provide vitamin D supplementation as necessary.
- Serum zinc levels should be measured annually and analyzed for potential deficiency.
- Annual serum levels of vitamin B6, vitamin B12, and folate to be conducted to screen for deficiency.
- Daily supplementation should be considered with a complete age-appropriate multivitamin containing vitamins B6, B12, folic acid, a minimum of 400 International Units vitamin D, and zinc.

Background

There are several nutritional considerations that are necessary for the assessment of patients with sickle cell disease (SCD). It is well established in the scientific literature that individuals with SCD have higher resting energy expenditure rates. This can be attributed to greater hematopoiesis due to the shorter half-life of erythrocytes, increases in cardiac output, febrile episodes associated with frequent acute crises, frequent infections, increased protein turnover, acute and chronic inflammation, and elevated substrate utilization for growth and development, particularly in the pediatric population.

Adequate energy and protein intake are paramount to favor utilization of nutrients obtained via dietary intake versus breakdown of body stores. There are no standard equations that exist to account for elevated resting energy expenditure. Individuals with SCD can require 13% to 15% more energy than standard resting energy expenditure estimations to account for their increased energy expenditure.[1,2]

Increased protein turnover and catabolism are further consequences of the effects of SCD. Individuals with SCD have an elevated consumption of the amino acid arginine, which is particularly needed for the synthesis of nitric oxide and cysteine.[3] Vaso-occlusive crises require effective nitric-oxide production to promote vasodilation. Inherent to SCD is the lysis of sickle-shaped red blood cells resulting in cell damage; this cell breakage increases the rate of protein catabolism, and promotes reactive oxygen species.

Growth Monitoring

Delayed and ineffective growth is a crucial area of consideration when working with pediatric patients with SCD. There are many reasons to account for the lack of adequate growth in this population. Firstly, fatigue and anorexia commonly accompany acute painful crises and febrile illnesses. Pain and febrile episodes may also drive up energy expenditure and concurrently release pro-inflammatory cytokines and mediators, which can down-regulate appetite, reducing the effective ingestion of nutrients. Children admitted to hospital for acute crises or illness may not adapt well to changes in environment, and, therefore, may reduce their energy intake.[5] There may also be cultural food preferences that limit appropriate dietary intake. Lastly, frequent hemolysis demands that adequate energy and protein is ingested to rebuild healthy cells. When unavailable in the diet, nutrients within body stores will be broken down and utilized to achieve the building blocks necessary for red blood cell synthesis.

Individuals with suboptimal height- and BMI-for-age velocities and trajectories may be at risk for deficits in cognitive potential and brain growth.[6] Linear growth is correlated with long-term nutrition status, which means that chronic malnutrition may be present in those individuals with suboptimal linear growth.[7] Moreover, there is evidence that demonstrates a decline in adequate dietary intake with increasing age, which reaches its nadir during adolescence.[8] Lactose intolerance and reduced affinity for vitamin D and calcium-rich milk products may decrease the absorption of bone-building nutrients, especially during important phases of growth.

Monitoring for Micronutrient Deficiencies

There are several micronutrients that require special attention in relation to SCD. Vitamin D plays a crucial role in bone health, but also has an important function in immunity. Vitamin D is obtained via dietary intake and sunlight exposure. Most Canadians will not be able to gain adequate vitamin D concentrations necessary to convert to active vitamin D, due to sunlight constraints from October through April. Moreover, melanin concentrations in the skin are higher in individuals of African descent, which further limits vitamin D absorption via sunlight.

Foods that are rich in vitamin D include cod liver oil, salmon, tuna, mackerel, egg yolk, beef liver, mammalian milk, and orange juice fortified with vitamin D.[11] Many people affected with SCD have poor total energy intake, limiting intake of food sources rich in vitamin D. Individuals with SCD generally have a reduced tolerance of outdoor physical activity, which also decreases their exposure to sunlight and further reduces vitamin D intake.[12,13] It is important to monitor serum 2-OH vitamin D levels periodically.

Zinc is directly associated with growth and development, particularly sexual maturation and linear growth. Delayed wound healing and impaired immune function are devastating consequences of zinc deficiency, which can be frequently seen in individuals with SCD.[14] Zinc has also been studied with regard to rates of infection and chronic inflammation. Individuals with SCD have high rates of both infection and inflammation due to vaso-occlusion, hemolysis, and resultant organ damage. As an antioxidant, zinc is a component of superoxide

dismutase, which is known to inhibit pro-inflammatory cascades and thereby reduce reactive oxygen species activity and oxidative stress. As a component of thymulin, zinc is incorporated into hormones that assist in differentiating and maturing T-cells, and also is incorporated into immune cells that exert macrophagic-monocytic activity.[15] Zinc supplementation has been shown to help reduce the frequency of pain crises and rates of infection in those receiving supplementation.[16]

Folate, an essential B vitamin, is vital for DNA, RNA, and protein synthesis. It is a widely accepted practice to supplement patients with SCD with 1 to 5 mg of folic acid daily to ensure adequate folate supply for erythrocyte production.[17] Since folate requires the co-factors vitamin B6 (pyridoxine) and vitamin B12 (cobalamin) to promote synthesis of red blood cells, it would be prudent to evaluate serum levels of patients with SCD to screen annually for deficiencies in folate, vitamin B6, and vitamin B12. Deficiency of vitamin B6 is rare, since it is found in a wide variety of foods; however, those who do not consume meat products over time can become deficient in vitamin B12.[18]

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6. HEMATOPOIETIC STEM CELL TRANSPLANTATION

Principles

- Providers, patients, and families should be informed about the role of HSCT in the treatment of sickle cell disease based on current scientific evidence.
- For every patient with sickle cell disease, the benefits and risks of HSCT should be carefully weighed within the context of his or her individual disease severity and age. The criteria for eligibility continue to evolve and should be updated regularly.
- Following HSCT, close follow-up is indicated to monitor for acute and long-term complications of HSCT and sickle cell disease.

Recommendations

- Information regarding HSCT should be part of the counseling process of patients and families with sickle cell disease. Any potentially eligible patients for HSCT should be referred for consultation at a specialist centre where HSCT is available.
- HSCT should be performed in accordance with the specialist centre's guidelines, and should align with evidence-based recommendations from major sickle cell disease transplant centres.
- During the transplant period, and in the long term, a comprehensive sickle cell team must closely follow patients who undergo HSCT in consultation with any other relevant sub-specialties.
- HLA-typing and storage of umbilical cord blood should be considered for siblings of patients with sickle cell disease. HLA typing may be coordinated with pre-natal diagnostic techniques (such as chorionic villus sampling, amniocentesis or pre-implantation genetic diagnosis) to determine if the fetus is affected with sickle cell disease. Ethical concerns regarding the use of pre-implantation genetic diagnosis (PIGD) must be addressed.
- Male patients should be referred for sperm banking prior to HSCT. Consider ovarian cryopreservation for female patients with sickle cell disease who undergo HSCT.[4]
- Develop a protocol for the prevention of neurological complications following HSCT, which may include the use of anticonvulsant prophylaxis during treatment with cyclosporine.
- There must be a close liaison with the blood bank to individualize red cell and platelet transfusion needs.
- After HSCT, patients should be followed in long-term, multidisciplinary follow-up clinics to ensure early detection of complications such as infertility, growth failure, and chronic graft-versus-host disease.
- More research is needed to guide the development of non-myeloablative conditioning regimens that have reduced toxicity but allow sufficient donor engraftment to provide significant clinical benefit.[2,5]

Background

Hematopoietic stem-cell transplantation (HSCT) is currently the only curative therapy for patients with sickle cell disease. Donor stem cells used for HSCT come from donors with either hemoglobin AA (normal) or AS (sickle trait) to promote a successful transplant and a clinically asymptomatic patient. Successful HSCT has been found to improve sickle cell vasculopathy, splenic and pulmonary function, and to stabilize sickle cell-related neurological complications.[1,2] Excellent outcomes have been reported following matched sibling donor transplants with an overall survival of greater than 90% and event-free survival of greater than 80%.[1,3] Some patients with stable mixed donor and recipient chimerism have also been reported to have substantial clinical benefits.

The decision to have a patient with sickle cell disease undergo HSCT is one that should be considered carefully. The risk of toxicity and potential mortality from HSCT must be balanced against the morbidity of sickle cell disease-related complications. Long-term complications following HSCT such as gonadal failure (particularly among females) and chronic graft-versus-host disease must also be considered.[1] The timing in HSCT is very challenging. Ideally, HSCT should be performed once the disease has been identified as having a moderate to severe phenotype, but prior to the occurrence of end-organ damage from sickle cell disease.

One of the major limitations in performing HSCT in patients with sickle cell disease is the lack of suitable human leukocyte antigen (HLA)-matched sibling donors.[4,7] Less than 14% of patients with sickle cell disease have an unaffected matched sibling donor. Unrelated donor HSCT and haploidentical HSCT are considered experimental.

Proposed indications for HSCT in patients with sickle cell disease include patients aged less than 16 years with at least one of the following: stroke or a CNS event lasting longer than 24 hours, impaired neuropsychological function with abnormal cerebral MRI scan, recurrent acute chest syndrome with multiple hospitalizations or previous exchange transfusions, recurrent severe vaso-occlusive pain or priapism, sickle nephropathy, stage I or II sickle lung disease, bilateral proliferative retinopathy and major visual impairment, osteonecrosis of multiple joints, and red cell alloimmunization during long-term transfusion therapy.[7,8]

Patients with sickle cell disease undergoing HSCT also have special considerations. An increased risk of acute neurologic complications (e.g., due to cyclosporine toxicity) such as seizures and intracranial hemorrhage has been reported at a median of about one month following HSCT.[5,6] Patients with sickle cell disease undergoing HSCT are also more likely to have a red blood cell alloimmunization and iron overload compared with the general population of children with sickle cell disease due to numerous red cell transfusions prior to HSCT.[9]

Future directions for HSCT in the treatment of sickle cell disease include the use of alternative sources of stem cells (such as matched unrelated donors, umbilical cord blood, and haploidentical donation) and measures to reduce toxicity of current HSCT conditioning regimens.[10] Non-myeloablative (or reduced intensity conditioning) allogenic-HSCT in children and adult patients with sickle cell disease has enabled stable mixed hematopoietic chimerism with promising results, and reduced HSCT-associated morbidity and mortality.[11] These alternative approaches are currently under investigation.

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7. TRANSITION OF CARE IN ADOLESCENCE

Principles

- Transitioning from pediatric to adult care is a challenging phase for patients with sickle cell disease, their caregivers and their health care providers.
- Effective transition from pediatric to adult medical care is a longitudinal process that relies on developmentally appropriate education and transfer of responsibility from the health care provider to the patient.
- Pediatric and adult sickle cell disease care providers should collaborate to develop an effective transition model for their patients and to monitor sickle cell disease-related outcomes after transfer to adult care.

Recommendations

Patient Education and Preparation

- Transition should not be left until an adolescent reaches 18 years of age, and should be started from a young age.
- There is no specific age to begin transitioning patients with SCD. Responsibility for medical care should be gradually shifted from the health provider to the caregiver(s), and finally to the young adult in a developmentally appropriate fashion.
- Pediatric health-care providers should provide patients and families with developmentally appropriate resources about SCD complications and management.
- Patients and caregivers should be evaluated for their transition readiness at various time points prior to being transferred to adult care.
- Pediatric sickle cell clinics should adopt specific education and assessment tools for transitioning SCD patients and their caregivers to adult care.

Planning and Implementation of the Transfer to Adult Care

- Pediatric and adult SCD care providers should communicate at least annually about patients between 17 and 18 years who are to be transferred within the calendar year.
- Prior to transfer to an adult facility, the pediatric health care providers should send a concise but complete summary to the receiving adult health care providers. At a minimum, this summary should include information about SCD-related complications, investigations and treatments. The content of this summary should be agreed upon by both the pediatric and adult health care providers to ensure effective communication.
- Adult health care providers should be educated about developmentally appropriate approaches for caring for newly transferred patients.
- The transferred youth and their caregivers should have an opportunity to meet the adult health care team, and to visit their facility prior to their initial appointment.
- After transfer, the patient's first appointment at the adult facility should occur within the interval within which they would have normally been seen at their pediatric facility.
- Pediatric and adult SCD care providers should collaborate to identify quality indicators for monitoring SCD-related outcomes after transfer to adult care.

Background

With the evolution and improvement of comprehensive care for patients with sickle cell disease (SCD), there has been an increase in life expectancy, and an epidemiologic shift in the disease-related outcomes for this population.[1] In spite of better overall care for individuals with SCD, studies have shown that there is a sharp increase in disease-related mortality among young adults with SCD between 17 and 30 years of age, which is the time when most of these individuals would have been transferred to adult care.[1,2]

Although adolescents and young adults with SCD encounter developmental challenges similar to those of other youth with chronic health conditions, SCD poses unique barriers that must be considered during the transition process. Youth with SCD often come from different ethnocultural backgrounds from their health-care providers, which may influence their perceptions of their disease and health-care needs. Within certain cultural communities, there is also a social stigma that is often associated with SCD, which could make it difficult to provide support that is sensitive and relevant for a patient and their family.[3] There have been recent studies to evaluate the role and effectiveness of culturally sensitive interventions for adolescents with SCD and their families.[4] Furthermore, patients who have had prior neurological complications (e.g., silent or overt stroke) may have neurocognitive issues impacting on transition readiness.

Health-care transition is an important step in the lives of young people with pediatric-onset health conditions. Transfer to adult-centred care is an event, while transition is a process, one that involves preparing the young person and their family for this move, the transfer process, and negotiating with adult providers to accept these patients and provide developmentally appropriate care. Leaving the pediatric treatment centre and its medical team can be emotionally difficult for the patient, family and health care providers. Much of the early research in the field of transition was with young people with SCD,[5] who have a condition that will not disappear or be cured, have significant levels of treatment, and who may experience racism within society and even in the health-care system. SCD is a lifelong chronic condition, and the nature of the transfer to adult care can therefore have a significant impact on the entire lifespan in people with SCD.[6] Many organizations endorse transition planning in position statements, including the American Academy of Pediatrics and the Canadian Paediatric Society.[7,8]

There are many ways to approach the issue of transition from pediatric to adult care. We will examine it from three viewpoints – preparing adolescents and their families; practicalities of the transfer process; and recommendations for the adult system and its approach to young adults.

Preparation for Transfer

Many position statements have argued that transition should start at the time of diagnosis. If one thinks of self-management, knowledge of condition and self-advocacy as needed skills for transition, then it is clear that skill building can start at almost any age. In addition to this, parents require varying amounts of time to accustom themselves to the reality of transition to adult care. Starting early may help many of them adapt to the idea that their child will be leaving a pediatric facility at some point, and also give them hope that their child will survive and be able to manage adult responsibilities. One tool that can be used for this is the "Sickle Cell Timeline" from the Hospital for Sick Children, which has suggestions for parents to promote developmentally appropriate autonomy in the areas of social, education, self-care, and medical care from a young age.[9]

There are a number of theoretical models that can be used to underpin this movement from dependency to responsibility. One that is very helpful is the Shared Management Model developed by Keikhefer and Trahms in Seattle.[10] This model describes a gradual shift in responsibility for care from the health professional to the parent and then to the young person. For instance, in the case of patient "John" who has SCD, one can talk with families about "John's Health" as a corporation that starts off with the doctor as the CEO and the parents as customers. Parents naturally move into the role of a manager, and this is often where things stay, with the young person as a customer of the corporation. With transition preparation, the youth moves up into a manager role and the parent moves up in the organization too. Eventually, "John" ends up as the CEO of "John's Health," and the parents and health professionals are consultants. With this model, the child sees the parents taking an active role rather than being a passive consumer of health care, which is important role modeling for their future.

Self-efficacy is a belief that one can competently cope with a challenging situation. It is affected by life experience, the nature of parenting received, cultural influences, and locus of control. The pediatric system has often been seen as a culprit, "babying" patients and creating dependency, which can decrease a young person's ability to feel that they can cope with their condition and the adult health care system. Anything that we can do to help young people to increase their self-efficacy, by pointing out to them the times that they are effective in dealing with challenges (these don't have to be medical challenges), helping them identify how they have surmounted obstacles, and providing them with tools to effectively deal with their issues will help them in their confidence in moving into the adult system. In addition, it has been shown that those adults with SCD who have higher self-efficacy have lower reported pain severity and physical or psychological symptoms.[11]

Although young people need skills to navigate the adult world, these skills are less helpful if the youth does not have adequate information about SCD, about their own health history, and about the health-care system. Do not assume that children were listening (or able to understand) the explanations their parents have been given. There are many ways to impart this information, including small chunks of knowledge at medical appointments, education events, written materials, and electronic materials. Consider using youth-friendly materials such as comic books or videos of young adults sharing their knowledge and experience. A health passport is a useful pocket-sized tool to summarize important information related to the youth's SCD, which may serve as their personal resource about their condition.[12]

In addition to providing education and developmentally appropriate resources, it is important to evaluate the adolescent's and caregivers' readiness for transition through direct questioning and/or questionnaires. These readiness assessments will enable health-care providers and family members to attempt to bridge any knowledge gaps prior to transfer and, if this is not possible, to communicate these challenges to the adolescent's future health-care providers within the adult centre. There are validated generic and disease-specific tools that are available to assess transition readiness and self-efficacy, including the "Good 2 Go" readiness checklist, which is available through the Hospital for Sick Children.[13] These tools should be used to evaluate patient and caregiver knowledge and self-efficacy at several time points prior to transfer to adult care.

Transfer to Adult Care

Leaving the pediatric system is a major event for families and young people. They have come to know (and hopefully like) many of their health professionals, know their way around the building, and have friends they see at appointments. They may have heard horror stories about the adult system, and parents are especially worried that they will be left out of the care of their offspring. The actual process of transfer can have a huge impact on transition, with the quality of information shared, the experience of the last visit, attention paid to non-medical transitions, and the alleviation of parental, patient, and team anxiety about the process all being crucial.

A number of models have been developed for transfer clinics. All of the models recognize the day as a rite of passage for the family. In and of itself, this helps families leave the pediatric system with a feeling that they are graduating rather than being kicked out. Almost all transfer clinics involve the youth meeting all or part of their new health-care team. This clinic could take place at either the pediatric or adult facility. When both exist in the same building, there could even be a ritual walk between the two clinics. These clinics can involve small groups for discussion of transfer challenges, meetings with the new providers, creation of a portable medical summary, presentation of a graduation certificate, and even a party. When planning for the ultimate transfer from pediatric care, it is important that the patient's medical and psychosocial supports are maintained as much as possible following their transfer to the adult facility. In cases where certain resources are unavailable at the adult centre, it will be necessary to refer the patient and their caregivers to community specialists and/or services who may be able to provide these supports.

Although a number of different clinic models exist, it is fundamentally important that there is regular and clear communication between the pediatric and adult health-care teams. This will facilitate a complete transfer of patient information, and allow for ongoing evaluation and improvement of the transition process.

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