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Position Statement

Acute complications in children with sickle cell disease: Prevention and management

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ABSTRACT

Sickle cell disease (SCD) is a chronic, multi-system disease that requires comprehensive care. The sickling of red blood cells leads to hemolysis and vascular occlusion. Complications include hemolytic anemia, pain syndromes, and organ damage. Patterns of immigration and an increase in newborn screening mean that paediatric health care providers across Canada, in small and large centres alike, need to be knowledgeable about SCD. This statement focuses on principles of prevention, advocacy, and the rapid treatment of common acute complications. Guidance includes the current status of newborn screening, recommendations for immunizations and antibiotic prophylaxis, and an introduction to hydroxyurea, a medication that reduces both morbidity and mortality in children with SCD. Case vignettes demonstrate principles of care for common acute complications of SCD: vaso-occlusive episodes (VOE), acute chest syndrome (ACS), fever, splenic sequestration, aplastic crises, and stroke. Finally, principles of blood transfusion are highlighted, along with indications for both straight and exchange blood transfusions.

KEYWORDS: *Hemolytic anemia*; *Hemoglobinopathy*; *Hydroxyurea*; *Newborn screening*.

Sickle cell disease (SCD) is the world's most common human genetic disease, and it affects at least 5,000 individuals in Canada (1). This chronic, multi-system disease is best managed with comprehensive care, including prevention, anticipatory guidance, and the prompt diagnosis and treatment of acute complications. With evolving patterns of immigration, SCD care is no longer limited to Canada's largest cities. For example, there has been a 3.5-fold increase in paediatric hemoglobinopathy patients in northern Alberta over the last decade (2). Recent administrative data from Ontario reveal patients with SCD residing in every health region, with one-third aged 14 or less (3). Also, as newborn screening (NBS) programs across the country increasingly include SCD, more SCD patients requiring early disease-specific care are being identified. Both trends require first-line care providers to be more knowledgeable about SCD and to manage cases collaboratively with centres of expertise. This position statement provides health care practitioners (HCPs) with the information they need to deliver evidence-based, timely care for children with SCD who experience acute complications. It also highlights principles of patient advocacy, and strategies to prevent complications from developing.

SCD can be caused by homozygosity (i.e., possessing two identical alleles for the sickle beta-globin gene [HbS]), or by heterozygosity (possessing two different alleles for HbS and another beta-globin variant, most commonly beta-thalassemia or hemoglobin C) (4). While phenotypic severity varies among patients, acute management principles are consistent. Children who have only one sickle beta-globin gene (with one normal beta-globin gene) have the sickle cell trait, but they do not usually exhibit clinical manifestations or require disease-specific care, apart from genetic counselling.

SCD's clinical manifestations are caused by the complex pathophysiology of deformed and fragile sickle red cells. Complications can arise from three main sources (5): hemolytic anemia; pain syndromes (most commonly resulting from vaso-occlusion and ischemia-reperfusion injuries); and major organ complications due to hemolysis, vaso-occlusion or vasculopathy, or a combination of both. While prevention, treatment strategies, and comprehensive care have significantly decreased mortality in children with SCD, complications continue to cause significant morbidity.

This statement cannot address all the complications related to SCD but will focus on the most common presentations. Readers are directed to the Canadian Haemoglobinopathy Association (CANHAEM) consensus statement (https://www.canhaem.org/wp-content/uploads/2018/05/Sickle-Cell-Consensus.pdf) for more information.

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PREVENTION AND ADVOCACY

All affected children should be referred to a SCD clinic. SCD clinics can help bridge distance and other barriers to care by supporting a family's primary HCP and using video or telephone consultations. Preventive and supportive strategies should be offered, as outlined below.

Newborn screening

SCD was part of NBS in seven provinces and two territories in 2021. Its inclusion has not only helped reduce SCD-related infant mortality rates (6), but allows for earlier referral, parent education, preventive strategies, and genetic counselling (1).

Immunizations

While the routine Canadian vaccination schedule includes partial immunization against pneumococcal disease and immunization against meningococcal type C bacterial infection, it is imperative that children with SCD receive enhanced vaccination against these encapsulated bacteria. Specifically, children with SCD should receive the 13-valent pneumococcal conjugate *and* polysaccharide vaccines against *Streptococcus pneumoniae*, and both conjugated quadrivalent meningococcal (A, C, W, Y) *and* serogroup B vaccines targeting *Neisseria meningitidis*. Further, an extra booster dose against *Haemophilus influenzae* type B (Hib), immunization against hepatitis A and B, and annual influenza vaccines are all recommended. In the context of travel, vaccination against *Salmonella typhi* and malaria prophylaxis should be offered (1,7).

Antibiotic prophylaxis

Daily prophylactic penicillin VK or amoxicillin should be prescribed for all children with SCD from 2 months to 5 years of age. Duration of prophylaxis may be extended for children who have had a surgical splenectomy or a history of invasive bacterial infections, or whose immunizations are not up to date. Cotrimoxazole or erythromycin are alternatives in cases of penicillin allergy (1,7).

Hydroxyurea

High quality studies have shown that hydroxyurea use can significantly reduce risk for acute chest syndrome (ACS), vaso-occlusive episodes (VOE), transfusions, hospitalization, and mortality (8–11). Treatment risks and benefits should be discussed with families and the medication offered to all children ≥9 months of age. Hydroxyurea is now standard of care for all patients with HbSS and HbSB^0 thalassemia. While experience with paediatric HbSC patients is limited, hydroxyurea should be considered for symptomatic cases. Dosing and monitoring protocols are outlined in the CANHAEM consensus statement (1,4). Hydroxyurea is usually held if patients become cytopenic, a scenario which should be discussed with a consulting hematologist.

CASE-BASED VIGNETTES

The following cases demonstrate principles of management for the most common acute SCD complications (1). (See also Table 1.)

Vaso-occlusive episodes

Danielle, a 6-year-old girl with SCD, presents to the emergency department (ED) with a 2-day history of leg pain. She was given acetaminophen and ibuprofen at home but continues to rate her pain 9/10. On exam, she has diffuse leg tenderness without erythema, edema, or fever, and her vital signs are normal. She receives a working diagnosis of a VOE.

Pain evaluation should be prompt and non-SCD-related etiologies considered. Pain management (Table 2) is initiated within 30 to 60 minutes of arrival, with a dose of intranasal (IN) fentanyl, followed by a dose of oral morphine. IN fentanyl can be administered quickly and has a rapid onset of action (12,13). In this setting of SCD with VOE, fentanyl significantly reduces the time needed to provide the first opiate dose and the number of intravenous (IV) line insertions (13). After a minimum observation period of 2 to 3 hours, children who achieve pain control with oral opiates may be managed as outpatients. Parents should receive a clear, written plan of treatment and follow-up (1,14).

When Danielle's pain proves intractable, a morphine bolus is administered, with subsequent escalation to a morphine infusion with intermittent bolus doses or patient-controlled analgesia (PCA). Because Danielle's pain is difficult to control, she is admitted to hospital. The following principles of pain management apply:

- Prescribe round-the-clock acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) to be administered alongside opioids and conjunctively with psychological supports and physical comfort measures (e.g., distraction, heat packs) (15). Cold packs are not applied because, due to vasoconstriction, they will worsen the VOE and can injure tissue.
- Order PEG 3350 to prevent opioid-related constipation.
- Encourage oral hydration. Administer IV fluids to reach a total fluid intake (TFI) equivalent to maintenance volumes but not beyond, to avoid over-hydrating. Hyperhydration has been associated with increased risk for ACS.
- Promote incentive spirometry in cases of chest, back, or abdominal pain, and encourage a seated posture and walking as soon as possible to mitigate risk for pulmonary complications.
- Ensure that oxygen saturations are at least 95%. Provided that target is met, supplemental oxygen is not recommended as routine practice due to theoretical risk for hypoventilation leading to ACS.
- When Danielle's pain is under control, the next step is to wean the opioid infusion and transition to regular oral dosing. Educate her parents regarding pain medication at home and provide adequate doses to manage her VOE over several days following hospital discharge. Routine follow-up includes updating this child's pain management plan.

Acute chest syndrome

Two days into Danielle's admission for VOE, she develops respiratory distress, along with fever, cough, and chest pain. A chest x-ray (CXR) reveals a right lower lobe infiltrate. She is diagnosed with ACS.

Table 1. Summary of recommendations

Acute complication of SCD	Principles for management
VOE	- Evaluate pain with appropriate tools - Initiate analgesia within 30–60 minutes - Use pharmacologic, psychologic, and physical pain management. Avoid cold packs. - Administer acetaminophen and a NSAID regularly, in conjunction with opioids - Avoid over-hydration and promote incentive spirometryto prevent ACS - Consider other SCD complications (e.g., splenic sequestration, cholecystitis if abdominal pain), and differential diagnosis (e.g., avascular necrosis, osteomyelitis, septic arthritis if articular pain) - At discharge, provide appropriate prescriptions and education, and ensure follow-up
ACS	- Admit to hospital - Maintain oxygen saturation ≥95% - Avoid over-hydration and promote incentive spirometry - Initiate broad-spectrum antibiotics - Crossmatch for possible transfusion or ExT in severe cases (consult with hematology and intensive care)
Fever	- Draw blood culture and administer broad-spectrum antibiotics within 30 minutes of presentation, independent of focus for fever (do not delay antibiotics if blood culture is not yet drawn) - Treat influenza, if suspected - Consider serious bacterial infection, including osteomyelitis - Consider outpatient management for low-risk patients (Table 3)
Splenic sequestration	- Highest risk before age 5 (prior to auto-splenectomy) - Teach parents to palpate their child's spleen and document spleen size at each visit - Strong indication for simple RBC transfusion - Discuss indication for splenectomy or chronic transfusion with a paediatric hematologist
Aplastic crisis	- Heralded by signs of anemia and low reticulocyte count - Parvovirus B19 is most common etiologic agent - Strong indication for simple RBC transfusion - Immunity conferred
Stroke	- Annual TCD ultrasounds (age 2–16) to identify high-risk patients - Maintain high index of suspicion, evaluate with CT scan +/- MRI - In children, AIS is more common than hemorrhagic, but either may occur - Indication for ExT - Strong evidence for chronic transfusions for primary and secondary prevention

ACS Acute chest syndrome; AIS Acute ischemic stroke; ExT Exchange transfusion; NSAID Non-steroidal anti-inflammatory drug; RBC Red blood cell; SCD Sickle cell disease; TCD Transcranial Doppler; VOE Vaso-occlusive episode

ACS is defined as a new pulmonary infiltrate in the presence of fever and respiratory signs or symptoms. ACS can be caused by infection, pulmonary infarction, or fat embolism. Because these causes are difficult to differentiate, management principles are the same for all. Up to one-half of paediatric patients with ACS present during a hospital admission, most commonly for VOE. VOE patients should always be monitored for signs of ACS, as morbidity and mortality may result from this complication. ACS investigation and management should be prompt and orderly.

- First, Danielle receives oxygen therapy to maintain a saturation of at least 95% (1).
- Along with her CXR, appropriate investigations include a blood culture, CBC, reticulocyte count, and crossmatch. Consider a nasopharyngeal (NP) swab and *Mycoplasma pneumoniae* PCR for infectious etiology.
- Do not wait for test results before initiating empiric therapy, which includes a broad-spectrum third-generation cephalosporin for typical bacterial organisms and a macrolide to cover for *Mycoplasma pneumoniae*. (The latter can be discontinued if Danielle's PCR test is negative.)
- If Danielle clinically deteriorates, consult with hematology, broaden antibiotic coverage and, based on clinical severity, consider a simple or exchange transfusion (ExT). Anticipate the possible need for transfer to an intensive care unit.

Fever

Jared, a 3-year-old boy with SCD, presents to the ED with a sore throat and a temperature of 39.0°C. He is alert and nontoxic, has enlarged erythematous tonsils, but no other apparent focus of infection. His mother assures you that she administers his prophylactic antibiotics daily, and that his immunizations are up to date.

Functional asplenia renders children with SCD particularly at risk for invasive bacterial infections, such as sepsis, meningitis, or osteomyelitis. Consequently, all febrile episodes (defined as an oral temperature ≥38.0°C or a rectal temperature ≥38.5°C) in these children warrant a CBC, reticulocyte count, bilirubin, blood culture, and a type and screen if they are unwell.

- Within 30 minutes of arrival, Jared has had blood work drawn and an IV (or IM) third-generation cephalosporin

Table 2. Dosing of pain medications for acute vaso-occlusive episodes in children with SCD

Medication	Dosing	Daily dose limit	Notes
Acetaminophen	10 to 15 mg/kg/dose (maximum 650 mg to 1 g/dose) by mouth every 4–6 h	75 mg/kg/day or 4 g/day (whichever is less)	Administer 'round the clock'. Contraindicated in severe hepatic impairment.
NSAID by mouth: Ibuprofen or naproxen	Ibuprofen: 10 mg/kg/dose (maximum 400 mg to 600 mg/dose) by mouth every 6–8 h Naproxen: 5 to 7 mg/kg/dose (maximum 250 mg to 500 mg/dose) by mouth every 8–12 h	Ibuprofen: 40 mg/kg/day or 2400 mg/day Naproxen: 1 g/day	Administer "round the clock". Contraindicated with impaired renal function or GI bleeding. Choose oral or IV NSAID, not both.
NSAID IV: Ketorolac	0.5 mg/kg/dose IV every 6–8 h	<16 years: 15 mg/dose ≥16 years: 30 mg/dose	Administer "round the clock". Caution with impaired renal function or GI bleeding. Limit therapy to 48 h Choose oral or IV NSAID, not both.
Fentanyl	1 to 2 mcg/kg/dose intranasal (maximum 100 mcg/dose)	Use x 1 to 2 doses (maximum 100 mcg total) until alternative mode of analgesia is administered. Use fentanyl 50 mcg/mL for a maximum of 1 mL/nostril.	Use for patients above 1 year of age. Divide dose between both nostrils to maximize absorption.
Morphine by mouth	0.2 to 0.5 mg/kg/dose by mouth every 4–6 h (maximum 15 mg/dose)		Start at lower end in opioid-naive patients
Morphine IV (intermittent dosing)	0.1 mg/kg/dose IV (maximum 7.5 mg/dose) over 5 minutes, repeat up to every 3 h	May add 0.05 mg/kg (maximum 5 mg) hourly as needed	Consider lower doses in opioid-naive patients If pain is insufficiently controlled with intermittent morphine dosing, consider initiating a morphine infusion or patient-controlled analgesia (PCA). Consultation with paediatric hematology is recommended. If patient is intolerant or allergic to morphine, liaise with paediatric hematology for alternative analgesia options.

GI Gastrointestinal; IV Intravenous; NSAID Non-steroidal anti-inflammatory drug.
Adapted from reference (15).

(e.g., ceftriaxone or cefotaxime) administered (16). Levofloxacin could be substituted in settings of significant beta-lactam allergy, and vancomycin added if he were clinically unstable. Being mindful of rare but potentially fatal ceftriaxone-induced hemolytic reactions, you observe Jared for 2 hours following administration of this antibiotic (17).

- Investigating the source of his fever should include a CXR, with further work-up as clinically indicated, without delaying antibiotic administration. Consider seasonal influenza (via NP swab) and treat appropriately (18).
- Children who meet low-risk criteria may be discharged home, following receipt of ceftriaxone, with daily follow-up to ensure clinical stability and negative cultures (Table 3).
- Jared is hospitalized because his WBC is 3.9×10^9/L, with leukocytosis and leukopenia being risk factors for sepsis (Table 3 [1]). He receives broad-spectrum antibiotics until the blood culture is negative. Subsequent narrowing or discontinuation depend on focus of infection and clinical status. After 36 hours, Jared's blood culture remained negative and he has improved clinically. Jared is discharged home, and you instruct his mother to resume his prophylactic antibiotics.

Splenic sequestration

Six months later, Jared returns to the ED with pallor and abdominal pain. He is tachycardic, with normal blood pressure, and has a palpable spleen at 7 cm below the costal margin (normal for him is 1 cm). Jared's mother, who was taught to palpate the spleen in clinic, fortunately noticed his enlarged spleen at home. Labs reveal a Hb 52 g/L (baseline 90 g/L), reticulocytosis, and mild thrombocytopenia, all consistent with a diagnosis of splenic sequestration.

- Splenic sequestration is a potentially fatal complication of SCD. It more commonly occurs before age 5 but can happen at any age, particularly in children with HbSC and $HbSB^{Thal+}$. Jared is transfused with 10 mL/kg of packed RBCs. Blood transfusion volume is cautious in splenic se-

Table 3. Low-risk criteria for SCD and fever

Well-appearing, hemodynamically stable
Fever <40°C
Age ≥6 months
WBC 5 to 30 × 10^9/L, platelet count ≥100 × 10^9/L and not significantly lower than baseline, Hb ≥60 g/L and not >20 g/L lower than baseline (admit when baseline is unknown)
No respiratory distress or CXR abnormality
No clinical findings suggestive of meningitis, osteomyelitis, septic arthritis, ACS, splenic sequestration
No history of pneumococcal sepsis or meningitis
No significant pain or dehydration
Initial visit for the episode
Safe for discharge, ability for close follow-up

ACS Acute chest syndrome; CXR Chest x-ray; Hb Hemoglobin; WBC White blood cell.
Data drawn from reference (1).

questration, beginning with 5 mL/kg to 10 mL/kg, because sequestered blood can recirculate rapidly following transfusion, increasing risk for hyperviscosity.
- Jared's Hb is monitored closely to ensure that it does not rise to >100 g/L to 110 g/L.
- Options for secondary prevention, including elective splenectomy or chronic transfusion therapy, are discussed with hematology when sequestration episodes reoccur.

Aplastic crisis

Kya, who is 13 months old with SCD, presents with fever and fatigue. Hb is 40 g/L, with reticulocyte count of zero. You send a blood culture and initiate ceftriaxone, request serology for parvovirus B19, and transfuse Kya with RBC 10 mL/kg to 15 mL/kg.

- Similar to other inherited hemolytic anemias, children with SCD are prone to aplastic crises secondary to parvovirus B19 ('fifth disease') (4), which infects erythroid precursors in the bone marrow. Signs and symptoms are secondary to severe anemia, typically associated with an inappropriately low reticulocyte count, mild thrombocytopenia and leukopenia.
- As more than one transfusion may be required, Kya is closely monitored until her reticulocytes begin to rise.
- You reassure Kya's family that, due to development of immunity against parvovirus B19, recurrences rarely occur.

Stroke

At age 5, Kya re-presents in your ED with right-sided weakness and decreased level of consciousness. The most recent of her annual transcranial Doppler (TCD) assessments was abnormal (cerebral blood flow velocities >200 cm/second [19]), and she was due to begin a prophylactic blood transfusion program known to be highly effective for both primary and secondary stroke prevention (20). Brain imaging confirms a diagnosis of acute ischemic stroke (AIS).

SCD is the most common cause of paediatric stroke, with children between 2 and 9 years of age being at highest risk. They typically present with ischemic stroke, a consequence of vasculopathy development. Children aged 2 to 16 years with SCD should be screened annually for vasculopathies using TCD. (There is no evidence to support TCD screening beyond 16 years of age.)

- Immediate management of stroke requires oxygen to maintain saturations ≥95%, IV hydration not exceeding a maintenance rate, and stat head imaging. A CT scan is ordered as a first-line diagnostic tool, but in cases of clinical suspicion for stroke and a negative CT scan, MRI with MR angiogram is indicated.
- Kya is admitted to the ICU for an ExT, with the aim of decreasing her HbS level to <30%.
- Kya's care is being provided in close collaboration with a paediatric hematologist and neurologist.

Kya's stat CT scan confirms a left middle cerebral artery AIS. She has persistent mild right-sided deficits, and her follow-up will include comprehensive rehabilitation services, a chronic transfusion program to prevent stroke recurrence, and collaborative management with a specialized centre.

PRINCIPLES OF TRANSFUSION

Along with chronic anemia, individuals with SCD have a high blood viscosity. Providing a blood transfusion in this context will further increase viscosity, raising risk for vascular complications. Also, compared with other transfusion patients, those with SCD are at increased risk for alloimmunization (1). Clinicians must weigh the benefits and risks of blood transfusions in paediatric SCD patients. When a transfusion is indicated, liaising with the blood bank to optimize phenotypic matching and reduce risk for alloantibody development and other transfusion reactions is essential.

Transfusions are considered for individuals with acute anemia and complications of SCD. Knowing a patient's baseline Hb and examining the reticulocyte count alongside the CBC are instrumental in decision-making. Decisions to transfuse should be guided both by a child's clinical status and the clinical context. In all situations, setting the post-transfusion target Hb to <100 g/L mitigates risk for hyperviscosity (4).

Clinical scenarios where the strength of recommendation is highest for providing a simple transfusion include acute splenic sequestration with severe anemia, and aplastic episodes (1,4). Simple transfusion may also be considered in cases of severe anemia, when

the Hb is ≥20 g/L below patient baseline or <60 g/L when the baseline is unknown (4). Simple transfusion may also be administered to manage severely symptomatic ACS (1,4). Importantly, transfusion is not indicated for uncomplicated painful crisis.

ExT, where the recipient's blood is removed during the donor infusion, should always be carried out in consultation with a paediatric hematologist. The advantage of ExT over simple transfusion for ACS remains debatable, but ExT remains the preferred option in SCD patients with stroke (1,4).

Finally, to prepare for surgical procedures involving general anesthesia, transfusions have been shown to reduce postsurgical risk for ACS and severe VOE. Be sure to liaise with the nearest paediatric hematologist to optimize peri-operative care.

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