## 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 *Part III, section 4 – Immunizations and Antimicrobial Prophylaxis*).
- 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 x$10^9$/L), thrombocytopenia (platelet count <100 x$10^9$/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 3 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 sickle cell disease (HbS$\beta^0$) 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.[7] Viral and bacterial respiratory infections may trigger acute chest syndrome, which is another serious and potentially fatal complication in these patients.[8]

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,[9,10] the protection is not complete, and serious bacteremia does occur.[11] 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.[11, 12]

Considering the potential serious complications of infection in patients with SCD, urgent administration of antibiotics for febrile patients with SCD is critical.[13] 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.[14] 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.[15]

In patients with SCD and fever, the prescribed antibiotic must be effective against common pathogenic bacteria in SCD.[13] 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.[15]

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