

Guidelines for the Management of Fever in Sickle Cell Patients

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Background:

Invasive bacterial infection is a common cause of morbidity and mortality in children with sickle cell disease (SCD). Without appropriate intervention, 15-20% of children with SCD may die from invasive bacterial infections. Standard medical interventions to minimize risks include:

1. The use of prophylactic penicillin starting from the age of 2 months
2. Appropriate immunizations, especially with vaccines against encapsulated bacteria
3. Prompt intervention for fever in the emergency room with parenteral antibiotic therapy
4. Education of parents and health care providers regarding the serious risk of life threatening infections in this patient population.

Patients with SCD become functionally asplenic within the first few months of life. As a result, they are at risk for overwhelming sepsis, particularly due to encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae type B*, as well as *Neisseria meningitides*. Children with SCD are particularly susceptible to *S. pneumoniae* for several reasons. In addition to being functionally asplenic, children with sickle cell disease have a decreased IgG response to polysaccharide antigens compared to children who do not have SCD. Other organisms to consider are gram negative enteric bacteria and *Salmonella*. In children with SCD less than 6 years of age who develop invasive bacterial infections, 66% of such infections are caused by *S. pneumoniae*. In contrast, gram negative organisms tend to predominate for those children beyond 6 years of age.

The following guidelines were developed for those professionals who care for patients with sickle cell disease, either in an outpatient, inpatient or emergency room setting. They are modified from protocols developed by the Hospital for Sick Children (Toronto, ON), Children's Hospital and Medical Centre (Seattle, WA) and the US National Institute of Health (Bethesda, MD).

Initial Assessment:

Children with sickle cell disease who develop a fever need to be seen urgently in either the hematology clinic or the emergency room. The goal should be to have parenteral (IV/ IM) antibiotics administered within 30-60 minutes of arrival.

A fever is defined here as a temperature $\geq 38.5^{\circ}\text{C}$ orally, $\geq 38^{\circ}\text{C}$ under the arm or 39°C rectally. Other symptoms/signs which should prompt the consideration of sepsis are refusal to feed, irritability, lethargy.

Such children should be designated CTAS (Canadian Triage and Acuity Scale) Level 2 in the emergency room and immediately placed in an examination room. They will require:

- a full assessment, including a complete set of vital signs

- O₂ saturation check
- a full history and physical examination including attention to cardiorespiratory status (due to the potential for sepsis, severe anemia, pneumonia and/or acute chest syndrome), pallor, jaundice, size of the spleen and neurologic status.

Initial Investigations:

The following should be obtained with the initial intravenous placement:

- complete blood count with reticulocyte count
- group and screen (if appropriate)
- bilirubin (direct and unconjugated), AST, ALT, alk phos, lactate dehydrogenase
- C reactive protein
- blood cultures

Other investigations to consider:

- A blood gas may be indicated if there are significant respiratory concerns
- Urine testing (microscopy and culture) as appropriate

Parenteral Antibiotic Therapy:

Intravenous **Ceftriaxone 100 milligrams/kg/DOSE intravenous** (max 2 grams per dose) should be given as soon as possible, preferably after the blood culture but *within 60 minutes of presentation even if there is a problem in obtaining IV access or getting a blood culture.* Intramuscular preparations may be used if necessary.

The antibiotic should be given prior to obtaining other investigations such as a chest x-ray and one *should not wait for the results of blood work.* Parenteral antibiotics should be given even if there is a potential focus of infection such as otitis media or an upper respiratory tract infection.

If the child has an allergy precluding the use of ceftriaxone, one may use **Clindamycin 40 milligrams/kg/DAY intravenous divided q6-8h** (max 2.7 grams per day). *Please note that clindamycin does not cross the blood-brain barrier.*

If meningitis is suspected, or the child looks seriously unwell (i.e. septic), then **Vancomycin 60 milligrams/kg/DAY intravenous divided q6h** (max 4 grams per day) can be added.

Other Investigations:

- Chest X-ray
There should be a low threshold for obtaining a plain chest film. It should be ordered if the child has cough, chest pain, fever $\geq 40^{\circ}\text{C}$ or O₂ saturation below 96%.
- O₂ saturation monitoring
Continuous oxygen saturation monitoring if O₂ saturation <96%, otherwise spot O₂ saturation checks should be done every 4 to 6 hours. Oxygen supplementation should be used liberally if there are any signs of hypoxia.

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- Consider Mycoplasma serology if there are respiratory symptoms or chest x-ray changes.
- Cultures from other sites as indicated (urine, CSF etc).
- Investigations for other foci of infection as indicated (i.e. evaluation for osteomyelitis).

Ongoing Care in Emergency Department:

A low threshold for hospitalization should be maintained. The following are risk factors for invasive disease and should prompt admission to hospital (**please page the Hematology Fellow on-call through locating if any of these are noted**):

- Fever $\geq 40^{\circ}\text{C}$
- Child appears unwell/lethargic/irritable
- Age < 1 year
- Any respiratory distress
- Infiltrate on chest x-ray
- Supplemental O_2 to keep oxygen saturation $\geq 96\%$
- Previous episode of sepsis or meningitis
- Recently missed doses of penicillin prophylaxis
- Blood cell counts significantly different from baseline, or WBC count $> 30 \times 10^9/\text{L}$, Hemoglobin $< 60\text{g/L}$ or Platelet count $< 100 \times 10^9/\text{L}$
- Concerns regarding follow-up or compliance at home

Ongoing Inpatient Management:

Intravenous **Cefotaxime 200 milligrams/kg/DAY divided q8h** (maximum 8 grams/day).

If allergy precludes the use of cefotaxime, then intravenous **Clindamycin 40 milligrams/kg/DAY divided q6-8h** (maximum 2.7 grams/day)

Vancomycin 60 mg/kg/DAY intravenous divided q6h (maximum 4 grams/day) to be added if clinically indicated.

Children > 5 years with respiratory symptoms or children < 5 years with suspicion of Mycoplasma infection, add **Clarithromycin 15 mg/kg/daily orally divided every 12h** (maximum 1g/day).

Intravenous hydration fluids 1.5 times maintenance.

Ongoing Outpatient Management:

After observing the patient in the clinic or emergency department for at least 4 hours, and the child remains clinically well with no other high risk features (as previously listed), one may consider discharging the patient home. Such a child will have already received an initial dose of Ceftriaxone. Arrangements should be made for follow-up with the hematology team on the following day.

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If the child is seen in the emergency room during the weekday, then follow-up can be arranged by contacting either **Heather McCartney, Hemoglobinopathy Nurse Clinician (604-875-2345 ext 7103 or pgr 604-686-3551)** or the Hematology Fellow on service via the switchboard. Please notify the hematology team when such patients are discharged home.

On weekends, the Hematology Fellow on-call should be paged through the switchboard so the hematology team can be made aware of the patient. The family should be advised to contact **Heather McCartney, Hemoglobinopathy Nurse Clinician (604-875-2345 ext 7103 or pgr 604-686-3551)** on the next weekday morning to arrange for subsequent follow-up.