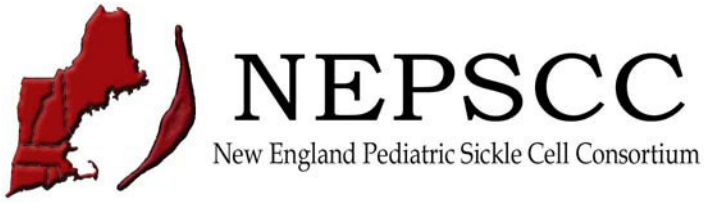
New England Pediatric Sickle Cell Consortium



Initial Evaluation and Management of Fever in Pediatric Patients with Sickle Cell Disease

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Disclaimer Statement:
This clinical practice guideline provides clinicians and organizations a framework for the management of febrile events in children with sickle cell disease. It is not intended to be used as a single reference or to replace clinical judgement. The ultimate decision regarding the care of any patient should be made by their treating clinicians and be based upon that individual patient presentation. Other guidelines are available to reference including publications by the National Heart, Lung, and Blood Institute, American Society of Hematology, and Centers for Disease Control and Prevention. This working group performed a thorough systematic review of these guidelines and the published literature on this topic as of April X, 2020. There are no financial disclosures regarding the development of this guideline, beyond those identified by the NEPSCC as a whole. Any individual conflicts of interest are listed below. The strength of these recommendations relies on the quality of the existing evidence, the consensus opinion of experts, and the decades of success using standardized fever management plans to reduce morbidity and mortality for children with sickle cell disease.

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FEVER

Inclusion Criteria:

Children and adolescents > 2 months of age with sickle cell disease (SCD) (Hb S with any variant Hb or with a beta thalassemia)

- Fever > 38.5º C/101.3º F

I. INTRODUCTION

Children and adolescents with SCD are prone to invasive infections caused by encapsulated bacteria (i.e., meningococcal, pneumococcal, and Hemophilus influenza in particular) and are at high risk of fulminant disease, including life-threatening sepsis, with these organisms[1-3]. A constellation of factors, most notably splenic hypofiltration, along with numerous other impairments of immune function create a predisposition to infectious complications that contributes to significant morbidity and mortality[4].

Evidence of spleen dysfunction is noted within the first year of life for those with SCD[5, 6]. The current standard of care is to presume acquired functional asplenia and impaired immune function and to maintain diligent surveillance for infectious complications, beginning at the time of diagnosis, which is most often in the first month of life (identified by newborn screening) in high resource countries.

Due to standardized fever management including prophylactic penicillin (PCN)[7, 8], targeted immunizations, and aggressive empiric drug therapy, *Streptococcus pneumoniae* (pneumococcal) sepsis is no longer the leading cause of death in children with SCD[9-11]. Continued vigilance and management of fever is crucial, however, in order to prevent bacterial sepsis and to continue to prevent early childhood morbidity and mortality[12, 13].

Standard infection precautions**:**

1. ***Oral PCN prophylaxis*** should be administered until age five in all children with SCD (HbSS and HbSβ^0). In children less than three years of age, administer 125 mg po BID and for children greater than three years administer 250 mg po BID[14, 15]. The NHLBI supports the use of oral PCN prophylaxis as a strong recommendation with moderate quality evidence. In 2014 NHLBI's revised guidelines[14] further recognized that data for use of oral PCN prophylaxis in Hb SC and Hb S beta plus thalassemia is lacking and suggested treatment could be deferred in those genotypes. In the event of PCN allergy, erythromycin ethylsuccinate 250mg po BID. The PROPS II study in 1995[16] showed no benefit to continuing PCN prophylaxis beyond age 5 years, as long as the child has a non-surgically removed spleen, no prior history of infection from an encapsulated organism (pneumococcal or meningococcal)[17] and is up to date with immunizations. The AAP policy statement [18] in 2014 recommends that once adequate vaccinations are administered then PCN prophylaxis can be safely discontinued in children with SCD after age five years. The ideal time to discontinue prophylaxis in patients who are surgically asplenic remains controversial[19]. In recent years, discontinuation of PCN before age 5 years has been under consideration, following the development of drug resistant micro-organisms, as well as the apparent preservation of splenic function owing to early initiation of therapy with hydroxyurea. A Cochrane review from 2017 concluded future research is needed to determine the proper age to discontinue[20].
2. ***Maintaining updated immunization status*** is strongly recommended based on NHLBI consensus panel and the Advisory Committee for Immunization Practices (ACIP)[21, 22]. Specific attention should be made to the recommendations for pneumococcal, meningococcal A, meningococcal B, H flu, and seasonal influenza vaccines for persons with hemoglobinopathies or functional asplenia[23]. See the *Comprehensive Care Guidelines and SCD specific immunization guidelines* for specific vaccine recommendations.
3. ***A strong recommendation should be made to seek urgent medical evaluation for fever greater than 38.5º C/101.3º F***. Parents and caregivers of children with SCD should be educated

to monitor for fever. This discussion should begin at the time of diagnosis of SCD and be reiterated at routine surveillance visits with both hematology and primary care teams. The goal of rapid triage and parenteral antibiotic coverage for acute febrile event is to reduce the occurrence of overwhelming sepsis. Empiric antibiotic administration is necessary to reduce both mortality and morbidity. Even those patients compliant with antibiotic prophylaxis or greater than 5 years of age should be considered high-risk for bacteremia. Children with an obvious source of infection (otitis, gastroenteritis) should still receive full evaluation and empiric antibiotic coverage as appropriate.

II. EVALUATION: RAPID TRIAGE, ASSESSMENT AND LABORATORY STUDIES

DO NOT DELAY ANTIBIOTICS. GIVE IMMEDIATELY AFTER OBTAINING BLOOD CULTURES, NO LONGER THAN 1 HOUR AFTER PRESENTATION TO ED/CLINIC

1. As soon as possible, upon arrival to an ER or urgent treatment center, the patient's vital signs should be measured, including temperature, heart rate, respiratory rate, blood pressure and room air pulse oximetry.
2. Obtain a history of the present illness including date and time of the onset of fever and any associated symptoms. Specifically inquire about the use of antipyretics (i.e. acetaminophen or NSAIDs) prior to arrival and document the name, dose and time of administration of the medication.
3. Review past medical history and particularly inquire about a history of acute chest syndrome, asthma or prior h/o of bacteremia/sepsis as these are associated with increased risk of sequelae.
4. Perform a physical examination with focus on signs of sepsis i.e. lethargy, altered mental status, poor peripheral perfusion, or increased work of breathing.
5. Review current medications and medication allergies.
6. If the child meets fever criteria (i.e. temp > 38.5ºC/101.3ºF), then place a peripheral IV or access a central venous access device if present. At a minimum, collect a CBC with differential, reticulocyte count, and blood culture. If the patient has a central line, then blood cultures must be drawn off this line and a peripheral culture should also be considered[24]. If the patient has a dual lumen catheter for erythrocytapheresis then two cultures should be collected, one from the draw line and one from the return line. Obtain a urinalysis and urine culture from all males <6 months and females <2 years if there are any symptoms suggestive of a UTI or there is no focus of infection and concern for a possible UTI (past history of UTIs).
7. Additional diagnostic testing should be added as needed when other symptoms are present.

SYMPTOMS	TESTING TO CONSIDER
Vomiting, diarrhea, and/or poor oral intake	Electrolytes, metabolic panel, stool studies, influenza testing.
Nasal congestion, sore throat, cough	Respiratory viral panel, throat culture, chest X-ray
Pallor, tachycardia	Parvovirus, type and screen
Neurologic findings	LP, PT/PTT/INR, D-dimer
Dysuria	Urinalysis, urine culture
Risk of pregnancy	HCG

III. MANAGEMENT: PARENTERAL ANTIBIOTICS & OTHER THERAPEUTIC INTERVENTIONS

Time to administration of antibiotics is a national quality indicator endorsed by Agency for Heallth Care Research and Quality (AHRQ[25]. The optimal time to administer antibiotics is within 60 minutes from arrival at triage.

All patients require parenteral antibiotic coverage for the first 24 hours.

Administer Ceftriaxone as a single dose of 50 mg/kg IV (may use IM if no IV access) to a max of 2 grams/day per institutional guidelines.

For patients allergic to Ceftriaxone, then IV clindamycin 10 mg/kg every six to eight hours (maximum daily dose 2.7 g for children; 4.8 g for adults) can be used, or an oral fluoroquinolone such as levofloxacin 10mg/kg.dose every 12 to 24 hours (maximum dose 750mg/day).

If acute chest syndrome is suspected (i.e. new infiltrate on CXR or new signs indicative of a pulmonary process), then add a macrolide (azithromycin) S*ee Acute Chest Syndrome Guidelines* for evaluation and management of this condition.

If CNS or meningitis is suspected then vancomycin 15 mg/kg IV (maximum dose 1 g) should be administered, in addition to ceftriaxone, with consideration for the role of a lumbar puncture before antibiotics are provided, as long as this does not delay antibiotic therapy.

If a central line is present, then administer antibiotic directly into the line and not peripherally. If it is a double lumen catheter alternate antibiotic administration between the two lumens.

In areas with known high resistance to or the patient has a history of infection with resistant organisms, the dose of ceftriaxone should be increased to 75-100 mg/kg/d as per local infectious disease guidelines.
Other antibiotics should be prescribed, as appropriate, to add coverage for at least the 1st 24 hours. Possibilities include:

- Clindamycin
- Quinolones (Gatafloxacin, Levofloxacin)

IV. DISPOSITION

A. ***High Risk****:*

1. Emergency Room/Outpatient Disposition: Consider admission for inpatient management if **any** of the following high-risk criteria are present:

   Age < 6 months

   Constitutional Findings

   - Toxic appearance, concern for sepsis
   - Hypotension or poor perfusion
   - History of previous infection with resistant organism or encapsulated bacteria
   - Unable to maintain oral hydration

   New onset of abnormal neurological findings (See ASH Guidelines for prevention, diagnosis, and treatment of cerebrovascular disease in children and adults and NEPSCC Stroke CPG)

   Respiratory Findings (See NEPSCC Acute Chest Syndrome Guidelines)

   - New hypoxia (Room Air O2 sat > 3% points below baseline, or <92% if baseline not known)
   - New pulmonary infiltrate on CXR -
   - RAD exacerbation

   Hematological Findings

- Hct ≤18% or ≥ 5% points below baseline
- HEMOGLOBIN < 7g/dL or > 2 g below baseline

Other

- High risk for poor outpatient follow-up (i.e. High-risk social determinants of health - no or limited access to phone, transportation, food, or shelter; or overdue for routine healthcare).
- Inadequate immunization status
- Under age 5 years and not compliant with PCN
- Increase in spleen size suggestive of evolving splenic sequestration
- Multiple ED/Clinic visits in previous month(s)
- Unable to receive initial 24 hours of coverage from single dose of medication due to failed IV access, medication allergies or other reason

2. Inpatient Management [See individual institutional protocol for admission order set if written]

Ensure adequate parenteral antibiotic coverage for the 1st 24 hours. Hold oral antibiotic prophylaxis (PCN or equivalent) while on parenteral antibiotics. Patient does not necessarily need to remain in the hospital for the full 24 hours if clinically well and adequate antibiotic is administered.

If new CXR infiltrate add macrolide – (See NEPSCC *Acute Chest Syndrome Guidelines)*

Supportive care

- Correct fluid deficits, then administer IV + PO at 100-125% maintenance. Avoid over hydration, especially if signs or history of ACS, pulmonary hypertension, renal disease, severe hepatic iron overload or if administering RBC transfusion. Choice of IV fluid varies between institutions i.e. normal saline or D5 – ½ NS
- Administer oxygen only for documented hypoxemia or respiratory distress. Consider ABG for new hypoxemia.
- Treat other complications as appropriate (VOC, splenomegaly).
- Isolation precautions per institutional guidelines and as indicated if any concern of aplastic crisis (Parvovirus B19)
- Aggressive encouragement of ambulation and activities of daily living
- Incentive spirometry 10x / hour

If RBC transfusion is warranted based on significant drop in hemoglobin level from baseline, then avoid over-transfusion due to the risk of hyperviscosity which poses an increased risk for stroke and must be avoided. See RBC Transfusion Guidelines and ASH Transfusion Guidelines

Additional testing:

- CXR for any respiratory deterioration or drop on pulse oximetry
- Obtain CBC with differential and reticulocyte count Q24 hours throughout admission. Consider baseline electrolytes and Q3 days while on IV hydration to avoid hypo or hypernatremia/hypo or hyperkalemia.
- If fever recurs repeat blood culture only if unsure of CVL sterility or if clinical concern of ongoing sepsis.

If source identified, treat appropriately

- If blood culture positive for pneumococcus, obtain two-view CXR.
- If blood culture positive for salmonella species or staphylococcus aureus, obtain bone scan and further imaging as appropriate.
- If blood culture positive for staphylococcus non-aureus, and patient has indwelling CVL/port, add vancomycin and consider echocardiogram.
- If osteomyelitis is of concern (ongoing fever, persistent focal pain) consider Orthopedics consultation for invasive diagnostics.

On discharge complete full course of antibiotics for patients with positive blood culture or focus of infection (i.e. acute chest syndrome/pneumonia, osteomyelitis, strep throat)

B. ***Low Risk:*** Consider discharge home after receiving antibiotic, if no admission criteria are met[26].
ALL PATIENTS MUST BE OBSERVED PRIOR TO DISCHARGE FOR A MINIMUM OF ONE HOUR FOLLOWING ADMINISTRATION OF ANTIBIOTICS TO ENSURE CLINICAL STABILITY AND NO ACUTE ANTIBIOTIC SENSITIVITY.

Instruct to seek medical guidance or return immediately to emergency room for symptoms of worsening illness, including:

- Temperature > 39.4^0 C/103^0 F or if fevers persist after 48 hours
- Increased respiratory symptoms, difficulty breathing
- Dehydration - Reduced oral intake or increased fluid losses (i.e. emesis or diarrhea)
- Lethargy
- Pain
- Altered mental status

Provide instruction on use and dosages of antipyretics and need for PO fluids
Discharge with clear instructions for the next day's follow up either in ED, clinic or by phone
Identify practitioner to check all cultures at 24 hours

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