Bacteremia Risk and Outpatient Management of Febrile Patients With Sickle Cell Disease

WHAT'S KNOWN ON THIS SUBJECT: Before the introduction of conjugate pneumococcal vaccines and routine penicillin prophylaxis, febrile patients with sickle cell disease were known to have a 3% to 5% risk of bacteremia. Consequently, hospitalization rates for febrile episodes are >70%.

WHAT THIS STUDY ADDS: We observed no mortality or morbidity among those managed completely as outpatients, and bacteremia occurred in <1%. Physicians should strongly consider outpatient management of febrile children with sickle cell disease if there are no other indications for admission.

BACKGROUND AND OBJECTIVES: Previous studies have indicated that febrile children with sickle cell disease (SCD) had a 3% to 5% risk of being bacteremic due to compromised immune function. The introduction of routine penicillin prophylaxis and conjugate vaccines may have lowered the risk of bacteremia. Our goals were to determine the rate of bacteremia among children with SCD per febrile episode and to estimate the safety of outpatient management among these febrile SCD patients.

METHODS: This 18-year retrospective cohort study included febrile SCD patients who presented to Boston Children’s Hospital between 1993 and 2010.

RESULTS: A total of 1118 febrile episodes were evaluated. Nine blood specimens had growth of a pathogen in culture (0.8%; 95% confidence interval: 0.3%–1.3%). Of the 466 febrile patients initially managed as outpatients, 3 were bacteremic (0.6%). All 3 received intravenous ceftriaxone at the initial outpatient visit and returned when contacted after growth of bacteria was detected in the blood culture. Upon return to the hospital, none were “ill appearing,” required supportive care, or were admitted to an ICU.

CONCLUSIONS: Our rate of bacteremia among febrile children with SCD is much lower than previous estimates, and there was no associated morbidity or mortality among the patients managed as outpatients. A well-appearing febrile child with SCD may be managed as an outpatient after blood is obtained for bacterial culture and parenteral antibiotics are administered, provided there are no other reasons for admission and the patient is able to return promptly for worsening condition or for growth of a pathogen from their blood culture.

Patient safety and outcomes in the healthcare setting can be significantly improved by the implementation of best practices and evidence-based guidelines. This study highlights the importance of considering outpatient management for febrile children with sickle cell disease, provided there are no other indications for admission. The study findings support the potential for reducing hospitalization rates while ensuring patient safety.
Sickle cell disease (SCD) refers to a group of autosomal recessive genetic blood disorders that result in the formation of abnormal hemoglobin S within erythrocytes. Patients with SCD have compromised splenic function that increases both the rate of bacteremia among these children and the subsequent risk of a rapid progression to sepsis, septic shock, and death.

Previous investigators have reported febrile children with SCD to have a 3% to 5% risk of bacteremia. 

Young age, homozygous SS SCD, elevated temperature, and elevated white blood cell (WBC) count have been associated with an increased likelihood of bacterial infection.

Changes in clinical practice over the past 3 decades include the universal screening of newborns for SCD, the routine use of penicillin prophylaxis for children with SCD under the age of 5 years, and the routine use of conjugate pneumococcal and Haemophilus influenzae type b vaccines. These practice changes have resulted in a substantial decrease in mortality due to sepsis.

Recommendations for the clinical management of patients with SCD have been published by the National Heart, Blood, and Lung Institute (NHBLI). This publication includes recommendations for the management of febrile episodes among children with SCD. These recommendations state that temperatures >38.5°C should be considered an emergency and patients should seek immediate medical attention for laboratory evaluation and empirical antimicrobial therapy. Two studies documented high rates of admission of 70% and 77% in 1990 and 2005–2006, respectively, for febrile SCD patients. The safety of outpatient management has not been well studied.

The primary objectives of this study were to determine the rate of bacteremia per febrile episode among SCD patients presenting to the emergency department (ED) and the safety of outpatient management of febrile patients with SCD.

METHODS

This was a retrospective cohort study of febrile patients with SCD presenting to the ED of Boston Children’s Hospital (BCH) between January 1, 1993, and December 31, 2010. BCH is an urban, tertiary care pediatric hospital with an annual ED volume of 50,000 to 60,000.

We identified patients from the registry of the BCH Comprehensive Sickle Cell Clinic with homozygous sickle cell anemia (SS), sickle-hemoglobin C disease, sickle-β-thalassemia, or sickle-β-thalassemia. Their medical records were then reviewed to identify all ED encounters. ED episodes were included if patients were <21 years of age; had a temperature >38.5°C in the ED, at home, or at a transferring facility; and had blood obtained for bacterial culture. Febrile ED episodes were excluded if patients received any antibiotic treatment other than baseline oral antibiotic prophylaxis before evaluation, the ED records were not available, or there was a previous ED evaluation for fever within the previous 7 days. Subjects presenting with temperatures between 38.0°C and 38.5°C were assessed only for their rate of bacteremia. For follow-up, we reviewed the ED, inpatient, and clinic medical records for events after the febrile episode to assess for any mortality or morbidity.

A single investigator (X.L.G.) abstracted historical, clinical, laboratory, radiologic, management, and outcome data. If there were discrepancies in documentation of historical or examination variables between physicians, we used the documentation of the most senior physician.

The first 50 episodes were coreviewed by a second investigator (M.N.B.). Six percent of all episodes were blindly reviewed by the senior investigator (M.N.B.) for the variables “ill appearing,” “supportive care,” and “chest radiograph reading” for interrater reliability. Institutional review board approval of the study was obtained.

Definitions and Outcome Measures

The following bacteria were defined as pathogens: Streptococcus pneumoniae, salmonella species, Staphylococcus aureus, Neisseria meningitidis, Escherichia coli, H influenzae type b, Streptococcus agalactiae, Streptococcus bovis, Streptococcus pyogenes, Streptococcus MG-intermedius, Listeria monocytogenes, and Citrobacter species.

The following bacteria were defined as contaminants: non–aureus staphylococci, Streptococcus viridans, Acinetobacter species, Bacillus species, Corynebacterium species, Micrococcus species, non-meningitidis neisseria species, otherwise unidentified non-enteric Gram-negative rods, and unidentified α-hemolytic streptococci.

For patients with growth of bacteria in culture of blood that were defined as contaminants, the record was reviewed to determine whether the treating clinicians administered parenteral antibiotic therapy with coverage for the identified organism for ≥4 days, and these cases were reviewed by an infectious disease specialist (M.B.H.) blinded to their outcome for possible reclassification.

Vital sign measurements were the initial vital signs obtained during the BCH or referring hospital visit.

A patient was defined as ill appearing if the ED physician used one of the following terms to describe the patient: “ill appearing,” “toxic,” “limp,” “unresponsive,” “gray,” “cyanotic,” “apnea,” “weak cry,” “poorly perfused,” “grunting,” “listless,” “lethargic,” or “irritable.” If a single term such as “slightly irritable,” “mildly irritable,” or “low grade sepsis” was used to describe the patient, the record was reviewed and reviewed as ill appearing. For patients with growth of bacteria in culture of blood that were defined as contaminants, the record was reviewed to determine whether the treating clinicians administered parenteral antibiotic therapy with coverage for the identified organism for ≥4 days, and these cases were reviewed by an infectious disease specialist (M.B.H.) blinded to their outcome for possible reclassification.
“cranky,” “fussy,” “mottled,” “slightly delayed capillary refill,” “tired,” or “sleepy” was used, the patient was not categorized as ill appearing. Examination findings suggesting acute pain or respiratory distress alone would not categorize the patient as ill appearing. For instance, patients described as “moaning with leg pain, responds to pain medication” or “moderate respiratory distress and wheezing” would not be categorized as ill appearing due to these words alone.

ED supportive care was defined as follows: oxygen therapy for hemoglobin oxygen saturations of <95%, administration of >1 inhaled β-adrenergic agonist, administration of ≥40 cc/kg of intravenous 0.9% saline, >1 dose of parenteral opiates, blood transfusion, or surgical intervention.

Chest radiographs were categorized as “infiltrate,” “possible infiltrate,” or “no infiltrate.”

Patients were categorized as eligible for outpatient management according to the NHBLI guidelines if they met the following conditions: not admitted to an ICU, no supportive care in the ED, not ill appearing, no reported history of bacterial sepsis, temperature <40°C, no infiltrate on chest radiograph if obtained, WBC <30,000/μL and >5000/μL, platelets >100,000/μL, and hemoglobin >5 g/dL.

We defined morbidity as any decline from the patient’s baseline functioning documented at discharge.

Statistical Analysis

To determine the difference between the means of normally distributed variables, t tests were used. Differences in the medians of continuous variables not normally distributed were compared by the Mann-Whitney U test. The χ2 test was used for the evaluation of categorical variables; Yates correction for continuity was applied to any 2 × 2 contingency table, and Fisher’s exact test was used if any cells had a value <5. A P value <.05 was considered significant. Variables that were significantly associated with bacteremia in the univariate analysis had sensitivity, specificity, and likelihood ratios (LRs) calculated.

Statistical analyses were conducted by using Statistical Program for the Social Sciences, version 19.1.1 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

RESULTS

Subjects

During the 18-year study period, 627 SCD patients had 2088 ED encounters for fever, and 1118 met the study criteria (Fig 1). Clinical and laboratory characteristics for the study patients are shown in Table 1. Thirty-eight patients met criteria for ill appearing, which was associated with increased rates of supportive care, hospital admission, and ICU level admission (P < .01).

Rate and Description of Bacteremic Episodes

Cultures of blood obtained during 9 of 1118 (0.8%; 95% confidence interval [CI]: 0.3%–1.3%) febrile episodes grew a pathogen. Of the 9 episodes, none of the patients were ill appearing or required supportive care while in the ED nor did any morbidity or mortality occur. Table 2 provides a summary of bacteremic episodes.

Both cases of S pneumoniae bacteremia occurred after the introduction of the heptavalent pneumococcal conjugated vaccine. One patient was fully immunized. The other patient had received 1 of 2 recommended 23-valent pneumococcal polysaccharide vaccinations and...
1 of 2 recommended heptavalent pneumococcal conjugated vaccinations. The pneumococcal serotypes were 15A and 15C, both were nonvaccine serotypes and both were susceptible to penicillin.

Bacteria defined as contaminants were recovered during 4 febrile SCD patient visits for which the treating clinicians administered >4 days of parenteral antibiotic therapy. The organisms were *S viridans* (2 patients), *Neisseria sicca*, and non—meningitidis neisseriae species not further identified. None of these patients were recorded as ill appearing in the ED or required ICU care. No morbidity or mortality occurred.

A parenteral antibiotic was administered during the initial evaluation for 1101 (98%) of the episodes. Ceftriaxone was most commonly administered and accounted for 958 (87%) of the administered antibiotics. No patients had allergic reactions requiring ICU admission, and there were no cases of ceftriaxone-induced hemolysis.

### Outpatient Versus Inpatient Management

Six hundred fifty-two (58%) febrile episodes were managed with admission to the hospital from the initial ED visit and 466 (42%) were managed as outpatients. Table 3 describes the characteristics of these patients. Follow-up was obtained for 457 patients, 62 (13%) subsequently returned for reevaluation and were admitted initially as outpatients.

Of the 652 patients with febrile episodes admitted to the hospital at the initial evaluation, 6 (0.9%) had growth of a pathogen in blood culture. None of the 6 bacteremic patients were described as ill appearing or required supportive care in the ED. One patient, who was tachycardic and transiently hypotensive in the ED, was later transferred from the floor to the ICU for persistent hypotension and required vasopressor support but did not require respiratory support. Her blood culture grew *S pneumoniae*. She recovered fully.

Of the 466 febrile patients initially managed as outpatients, 3 were bacteremic (0.6%). All 3 received intravenous ceftriaxone before initial ED discharge. All returned when contacted to return after growth of bacteria was detected in blood. None of the 3 patients were ill appearing on return, required supportive care in the ED, or were admitted to an ICU.

Of the 466 managed initially as outpatients, 62 (13%) subsequently returned for reevaluation and were admitted to the hospital within 14 days of the initial febrile encounter. Their median length of stay was 2 days (interquartile range [IQR]: 1–3). Three patients were called back because of growth from their blood culture. All 3 were stable in the ED and admitted to a non-ICU floor for initiation of parenteral antibiotics. Repeat blood cultures did not grow a pathogen for 2 patients and 1 patient’s repeat blood culture grew *E coli* that was sensitive to ceftriaxone. In the ED, this patient was afebrile with stable vital signs, documented as well appearing, and remained stable as an

### TABLE 1 Clinical and Laboratory Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
<th>n (%)</th>
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<td>Gender, n (%)</td>
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<tr>
<td>Male</td>
<td>652</td>
<td>(58)</td>
</tr>
<tr>
<td>Female</td>
<td>466</td>
<td>(42)</td>
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<td>Sickle phenotype, n (%)</td>
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<tr>
<td>SS</td>
<td>827</td>
<td>(74)</td>
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<tr>
<td>SC</td>
<td>205</td>
<td>(18)</td>
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<td>Sβ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54</td>
<td>(5)</td>
</tr>
<tr>
<td>Sβ&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>(3)</td>
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<td>Immunization status (ED note), n (%)</td>
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<td>Not documented</td>
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<td>(9)</td>
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<td>(97)</td>
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<td>Not documented</td>
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<td>Triage temperature, °C</td>
<td>38.6</td>
<td>± 1.0</td>
</tr>
<tr>
<td>WBC count, 10&lt;sup&gt;3&lt;/sup&gt;/L</td>
<td>16.5</td>
<td>± 0.3</td>
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<td>Chest radiograph, n (%)</td>
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<td>Infiltrate</td>
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<td>(10)</td>
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<td>Possible infiltrate</td>
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<td>(56)</td>
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<tr>
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<td>Supportive care, n (%)</td>
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<td>No</td>
<td>894</td>
<td>(80)</td>
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</table>

SC, sickle-hemoglobin C disease; SS, homozygous sickle cell anemia; Sβ<sup>a</sup>, sickle-β<sup>a</sup>-thalassemia; Sβ<sup>b</sup>, sickle-β<sup>b</sup>-thalassemia.

### TABLE 2 Characteristics of Bacteremic Episodes

<table>
<thead>
<tr>
<th>Organism</th>
<th>Date of Visit</th>
<th>SCD Type</th>
<th>Age, y</th>
<th>Initial Temperature, °C</th>
<th>WBC, 10&lt;sup&gt;9&lt;/sup&gt;/L</th>
<th>Admitted to Hospital</th>
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<tbody>
<tr>
<td>Salmonella</td>
<td>March 1993</td>
<td>SC</td>
<td>1.1</td>
<td>39.6</td>
<td>16.18</td>
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<td>39.4</td>
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<td>15.3</td>
<td>39.8</td>
<td>9.08</td>
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<td>Salmonella</td>
<td>November 2002</td>
<td>SC</td>
<td>9.5</td>
<td>39.9</td>
<td>11.50</td>
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<tr>
<td>Streptococcus pneumonia</td>
<td>May 2003</td>
<td>SS</td>
<td>13.1</td>
<td>39.3</td>
<td>12.48</td>
<td>Yes</td>
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<tr>
<td>Streptococcus pneumonia</td>
<td>February 2009</td>
<td>SS</td>
<td>7.4</td>
<td>39.0</td>
<td>26.98</td>
<td>Yes</td>
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<td>Escherichia coli</td>
<td>August 1998</td>
<td>SS</td>
<td>3.7</td>
<td>40.1</td>
<td>24.64</td>
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<td>Escherichia coli</td>
<td>July 2001</td>
<td>SS</td>
<td>1.4</td>
<td>38.9</td>
<td>17.76</td>
<td>No</td>
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<tr>
<td>Staphylococcus aureus</td>
<td>December 2009</td>
<td>Sβ&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20.2</td>
<td>39.0</td>
<td>5.36</td>
<td>No</td>
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</table>

SC, sickle-hemoglobin C disease; SS, homozygous sickle cell anemia; Sβ<sup>a</sup>, sickle-β<sup>a</sup>-thalassemia.
inpatient without any complications. Two of the 62 return visits resulted in admission to the ICU. Neither of the ICU admissions was associated with infection; 1 patient returned 6 days after the febrile episode for control of hypertension and 1 returned 9 days after the febrile episode for parvovirus-induced aplastic crisis.

**Predictors of Bacteremia**

In univariate analysis, only triage temperature and percentage of neutrophils were significantly associated with bacteremia. A triage temperature ≥39.0°C has a sensitivity and specificity for growth of a pathogen from blood of 0.88 and 0.65, respectively, a positive LR of 2.5, and negative LR of 0.17. One of 721 (0.14%; 95% CI: 0.00%–0.77%) febrile episodes with a triage temperature <39.0°C resulted in growth of a pathogen from blood. The sensitivity and specificity of >80% neutrophils for growth of a pathogen from blood was 0.67 and 0.87, respectively. The positive LR was 5.2 and the negative LR was 0.38. Six of 147 (4%; 95% CI: 1%–7%) febrile episodes with percentage of neutrophils >80% had growth of a pathogen from blood.

Patients with temperatures between 38.0°C and 38.5°C were not included in the study for analysis except to assess the rate of bacteremia. Of the 482 cultures of blood that were obtained for the rate of bacteremia, 341 (56%) were initially managed as outpatients; 62 of 341 (18%) returned within 2 weeks requiring admission with a median length of stay of 2 days (IQR: 1–3), including 2 of 341 patients (0.6%) whose blood cultures revealed growth of a pathogen. Neither of these patients’ repeat blood cultures grew a pathogen. Of the 508 episodes that did not meet the NHBLI criteria for outpatient management, 127 (25%) were managed initially as outpatients; 23 of 127 (18%) returned within 2 weeks requiring admission with a median length of stay of 2 days (IQR: 1–3), including 1 of 127 patients (0.8%) whose blood culture revealed growth of a pathogen. This patient's repeat blood culture grew *E coli* sensitive to ceftriaxone when recalled to the ED. In the ED, this patient was afebrile with stable vital signs, documented as well appearing, and remained stable as an inpatient without any complications. There was no relationship between meeting NHBLI criteria for outpatient management and growing a pathogen from blood culture (*P* = .74).

**Interrater Reliability**

Sixty-two (6%) charts were reviewed blindly by the senior author (M.N.B.) to assess interrater reliability. The κ for the variable ill appearing was 1.0, for chest radiograph reading was 0.7 (95% CI: 0.5–0.9), and for supportive care in the ED was 0.9 (95% CI: 0.7–1.0).

**NHBLI Guidelines for Outpatient Management**

Six hundred ten (55%) episodes met NHBLI criteria for outpatient management and 508 (45%) did not meet these criteria. Of the 610 episodes that met the NHBLI criteria for outpatient management, 341 (56%) were initially managed as outpatients; 62 of 341 (18%) returned within 2 weeks requiring admission with a median length of stay of 2 days (IQR: 1–3), including 2 of 341 patients (0.6%) whose blood cultures revealed growth of a pathogen. Neither of these patients’ repeat blood cultures grew a pathogen.
in a retrospective study, clinical data are limited to information that was available in the medical record. The ability to determine ill appearing from retrospective data can be difficult; however, our definition of ill appearing was associated with increased rates of supportive care and admission and ICU level admission, suggesting some validity as a useful variable. High x scores for the variables ill appearing, chest radiograph reading, and supportive care in the ED of 1.0, 0.7, and 0.9, respectively, suggest high interrater reliability. Of the 466 episodes managed as outpatients, 9 (1.9%) were lost to follow-up. Vaccination and antibiotic prophylaxis rates were based on self-report and may not reflect actual treatment adherence.

Our data were collected from a single ED at a tertiary care hospital and may not be generalizable to other institutions. Levels of adherence with vaccinations and prophylactic antibiotics and parental adherence with regard to bringing the child to medical attention for fever may vary at different institutions.

CONCLUSIONS

We found a low rate of bacteremia (0.8%) among acutely febrile patients with SCD and no associated morbidity or mortality associated with outpatient management. Physicians should strongly consider outpatient management for non–ill-appearing children with SCD and a temperature >38.5°C after blood for culture is drawn and empirical parenteral long-acting antibiotics administered, provided there are no other reasons for admission, the patient has at least 1 functioning telephone number, and the patient is able to promptly return to the ED should his or her culture of blood grow a pathogen.

The NHBLI recommends that patients with a temperature >38.5°C should have laboratory testing and empirical administration of long-acting parenteral antibiotics. In this study, many children had laboratory testing and were treated and even admitted with temperatures ≤38.5°C. Of the 482 cultures of blood obtained from children with temperatures between 38.0°C and 38.5°C, only 1 grew (0.2%; 95% CI: 0%–0.6%) a pathogen. This patient, a 17-year-old with a blood culture that grew S. aureus, had symptoms and signs of clinical osteomyelitis, which was the admitting diagnosis from the initial visit in the ED. Our extremely low rate of bacteremia for those with temperatures ≤38.5°C supports the NHBLI guidelines that state that these patients should not routinely have blood collected for culture.

Most febrile SCD patients managed as outpatients will not need a second dose of antibiotics if cultures are negative at follow-up. Norris et al19 reported that among febrile patients with SCD, ~90% of pathogens will be detected within 24 hours. Our care guideline recommends a single dose of parenteral ceftriaxone without additional outpatient antibiotics. A follow-up visit to assess the patient clinically is indicated to evaluate for other factors that might require admission, for example, acute pain crisis.

Our data identifi ed a triage temperature of <39.0°C to be a predictor for lack of bacteremia with a negative LR of 0.17 and a 0.14% rate of bacteremia. It is possible that moving the threshold to obtain a blood culture at 39°C could be substituted for the temperature of 38.5°C, but this would need confirmation with additional data.

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assess their clinical condition (eg, to check for possible dehydration, acute pain crisis, or acute chest syndrome) but that a second dose of antibiotics is not generally required because the vast majority of blood cultures grow within 24 hours. A temperature of 38.5°C should be used as a testing threshold to obtain blood for cultures.

REFERENCES


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Marc N. Baskin, Xin Lyn Goh, Matthew M. Heeney and Marvin B. Harper

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Bacteremia Risk and Outpatient Management of Febrile Patients With Sickle Cell Disease

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