

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

**AUTHORS:** Marc N. Baskin, MD,<sup>a,b</sup> Xin Lyn Goh, BMedSc,<sup>c</sup> Matthew M. Heeney, MD,<sup>b,d</sup> and Marvin B. Harper, MD<sup>a,b,e</sup>

Divisions of <sup>a</sup>Emergency Medicine, <sup>b</sup>Hematology/Oncology, and <sup>c</sup>Infectious Diseases Department of Medicine, Boston Children's Hospital, Boston, Massachusetts; <sup>d</sup>Department of Pediatrics, Harvard Medical School, Boston, Massachusetts; and <sup>e</sup>Faculty of Medicine, Dentistry, and Health Sciences, University of Melbourne, Melbourne, Australia

## KEY WORDS

sickle cell disease, fever, bacteremia, ambulatory care

## ABBREVIATIONS

BCH—Boston Children's Hospital

CI—confidence interval

ED—emergency department

IQR—interquartile range

LR—likelihood ratio

NHBLI—National Heart, Blood, and Lung Institute

SCD—sickle cell disease

WBC—white blood cell

Dr Baskin conceptualized and designed the study, designed data collection instruments, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted; Ms Goh assisted in the study design and in developing data collection instruments, collected the data, assisted in analyses, and helped draft the manuscript; Dr Heeney assisted in the study design and patient identification, critically revised the manuscript, and approved the final manuscript as submitted; and Dr Harper assisted in the study design, developed procedures for data collections, provided infection disease consultation, critically revised the manuscript, and approved the final manuscript as submitted.

[www.pediatrics.org/cgi/doi/10.1542/peds.2012-2139](http://www.pediatrics.org/cgi/doi/10.1542/peds.2012-2139)

doi:10.1542/peds.2012-2139

Accepted for publication Feb 6, 2013

Address correspondence to Marc N. Baskin, MD, Division of Emergency Medicine, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail: [marc.baskin@childrens.harvard.edu](mailto:marc.baskin@childrens.harvard.edu)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2013 by the American Academy of Pediatrics

**FINANCIAL DISCLOSURE:** *The authors have indicated they have no financial relationships relevant to this article to disclose.*

**FUNDING:** No external funding.



**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.

## abstract

FREE

**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. *Pediatrics* 2013;131:1035–1041

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.<sup>1–7</sup> Young age, homozygous SS SCD, elevated temperature, and elevated white blood cell (WBC) count have been associated with an increased likelihood of bacterial infection.<sup>2,6,8,9</sup>

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.<sup>10</sup>

Recommendations for the clinical management of patients with SCD have been published by the National Heart, Blood, and Lung Institute (NHBLI).<sup>11</sup> This publication includes recommendations for the management of febrile episodes among children with SCD. These recommendations state that temperatures  $>38.5^{\circ}\text{C}$  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.<sup>12,13</sup> 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- $\beta^0$ -thalassemia, or sickle- $\beta^+$ -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  $>38.5^{\circ}\text{C}$  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  $38.0^{\circ}\text{C}$  and  $38.5^{\circ}\text{C}$  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  $\alpha$ -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  $\geq 4$  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,"

“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  $\beta$ -adrenergic agonist, administration of  $\geq 40$  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  $<40^\circ\text{C}$ , no infiltrate on chest radiograph if obtained, WBC  $<30\,000/\mu\text{L}$  and  $>5000/\mu\text{L}$ , platelets  $>100\,000/\mu\text{L}$ , 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  $\chi^2$  test was used for the evaluation of categorical variables; Yates correction for continuity was applied to any  $2 \times 2$  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.

$\kappa$  Statistics were calculated for the variables “ill appearing,” “supportive care,” and “chest radiograph reading” to assess interrater reliability.

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

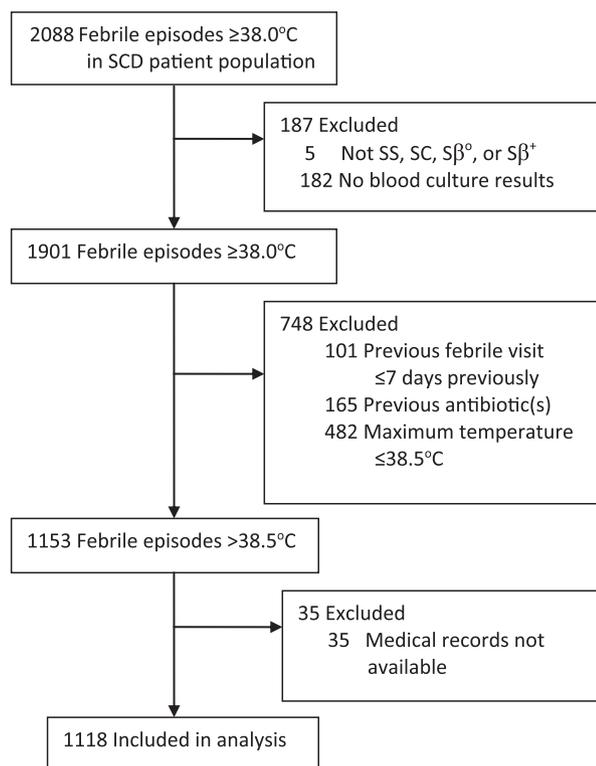
During the 18-year study period, 627 SCD patients had 2088 ED encounters for fever, and 1118 met the study criteria (Fig 1). Clinical and laboratory characteristics for the study patients are

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



**FIGURE 1**

Flow diagram of the study population. SC, sickle-hemoglobin C disease; SS, homozygous sickle cell anemia;  $S\beta^0$ , sickle- $\beta^0$ -thalassemia;  $S\beta^+$ , sickle- $\beta^+$ -thalassemia.

1 of 2 recommended heptavalent pneumococcal conjugated vaccinations. The pneumococcal serotypes were 15A and 15C; both were nonvaccine

**TABLE 1** Clinical and Laboratory Characteristics

Characteristics	Value (n=1118)
Gender, n (%)	
Male	652 (58)
Female	466 (42)
Sickle phenotype, n (%)	
SS	827 (74)
SC	205 (18)
Sβ <sup>+</sup>	54 (5)
Sβ <sup>o</sup>	32 (3)
Age (IQR), y	4.3 (1.7–9.4)
Antibiotic prophylaxis, n (%)	
Yes	816 (73)
No	275 (25)
Not documented	27 (2)
Immunization status (ED note), n (%)	
Up to date	869 (79)
Not up to date	19 (2)
Not documented	230 (20)
Immunization status (SCD clinic notes), n (%)	
Up to date	679 (61)
Not up to date	342 (31)
Not documented	97 (9)
Ill appearing, n (%)	
Yes	38 (3)
No	1070 (97)
Not documented	10 (1)
Triage temperature, ± SD, °C	38.6 ± 1.0
WBC count, ± SD, 10 <sup>9</sup> /L	16.5 ± 8.3
Chest radiograph, n (%)	
Infiltrate	112 (10)
Possible infiltrate	52 (5)
No infiltrate	629 (56)
Not performed	325 (29)
Supportive care, n (%)	
Yes	224 (20)
No	894 (80)

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

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 of 466 (98.1%) of the patients managed 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 2** Characteristics of Bacteremic Episodes

Organism	Date of Visit	SCD Type	Age, y	Initial Temperature	WBC, 10 <sup>9</sup> /L	Admitted to Hospital
<i>Salmonella</i>	March 1993	SC	1.1	39.6	16.18	Yes
<i>Salmonella</i>	September 1995	SS	19.3	39.4	30.63	Yes
<i>Salmonella</i>	September 1996	SC	13.3	39.8	9.09	Yes
<i>Salmonella</i>	November 2002	SC	9.5	39.9	11.30	Yes
<i>Streptococcus pneumoniae</i>	May 2003	SS	13.1	39.3	12.48	Yes
<i>Streptococcus pneumoniae</i>	February 2009	SS	7.4	39.0	26.98	Yes
<i>Escherichia coli</i>	August 1998	SS	3.7	40.1	24.64	No
<i>Escherichia coli</i>	July 2001	SS	1.4	38.9	17.76	No
<i>Staphylococcus aureus</i>	December 2009	Sβ <sup>o</sup>	20.2	39.0	5.36	No

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

**TABLE 3** Characteristics of Inpatients and Outpatients

Characteristics	Outpatients (n = 466)	Inpatients (n = 652)	P Value
Gender, n (%)			.11
Male	256 (55)	396 (61)	
Female	210 (45)	256 (39)	
Median age (IQR), y	3.9 (1.7–7.9)	4.6 (1.7–10.7)	.03
Hemoglobinopathy, n (%)			<.01
SS	325 (69)	502 (77)	
SC	100 (22)	105 (16)	
Sβ <sup>0</sup>	32 (7)	22 (3)	
Sβ <sup>+</sup>	9 (2)	23 (4)	
Antibiotic prophylaxis, n (%)			.10
Yes	328 (70)	488 (75)	
No	127 (27)	148 (23)	
Ill appearing, n (%)			<.01
Yes	0 (0)	29 (4)	
No	463 (100)	616 (96)	
Triage temperature, ± SD, °C	38.4 ± 0.9	38.7 ± 1.0	<.01
WBC count (IQR), 10 <sup>9</sup> /L	13.2 (9.7–18.0)	16.8 (11.8–22.6)	<.01
Chest radiograph, n (%)			<.01
No infiltrate	266 (97)	362 (70)	
Infiltrate or possible infiltrate	8 (3)	157 (30)	
Supportive care, n (%)			<.01
Yes	22 (5)	202 (31)	
No	444 (95)	450 (69)	

SC, sickle-hemoglobin C disease; SS, homozygous sickle cell anemia; Sβ<sup>0</sup>, sickle-β<sup>0</sup>-thalassemia; Sβ<sup>+</sup>, sickle-β<sup>+</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  $\geq 39.0^{\circ}\text{C}$  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  $< 39.0^{\circ}\text{C}$  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  $38.0^{\circ}\text{C}$  and  $38.5^{\circ}\text{C}$  were not included in the study for analysis except to assess for the rate of bacteremia. Of the 482 cultures of blood that were obtained from SCD patients with temperatures between  $38.0^{\circ}\text{C}$  and  $38.5^{\circ}\text{C}$ , 1 culture (0.2%; 95% CI: 0.0%–0.6%) grew a pathogen. This 17-year-old patient presented to the ED limping, with hip pain and a temperature of  $38.1^{\circ}\text{C}$ , was not ill appearing, and was described as tender on his left iliac crest. His WBC was  $13.4 \times 10^9/\text{L}$  with 58% neutrophils. Clinical osteomyelitis was diagnosed in the ED. His culture of blood grew *S aureus*, and he fully recovered with antibiotic treatment.

### 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.

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  $\kappa$  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).

### DISCUSSION

Our 0.8% (95% CI: 0.3–1.3) rate of bacteremia is much lower than that in previous studies published between 1975 and 2002, which reported rates of 3% to 5%.<sup>2–7</sup> The low rate of bacteremia in our study may be due to increased quality of SCD medical care over the past 25 years, which includes the use of universal newborn screening for early

identification, provision of parental education, use of daily antibiotic prophylaxis, and the introduction of routine vaccination with conjugated *H influenzae* type b and pneumococcal vaccines.<sup>3,10,14–16</sup> Our cohort had a high self-reported rate of antibiotic prophylaxis (73%) and up-to-date vaccination rates (79%). This rate is higher than rates reported in previous studies, which had prophylaxis rates of 20% to 30% and vaccination rates ranging from 15% to 45%.<sup>16–19</sup> These practice changes may partially account for the lower rates of bacteremia seen in our study. The validity of our low rate of bacteremia is supported by a recent Canadian study that found no episodes of bacteremia in 180 SCD patients with a fever  $\geq 38^{\circ}\text{C}$  during 2005 and 2006.<sup>13</sup> Two previous studies had 70% and 77% hospital admission rates in 1990 and 2005–2006, respectively, for febrile SCD patients.<sup>12,13</sup> In our cohort overall, 58% of all febrile SCD patients were admitted and 44% of febrile SCD patients who met NHBLI guidelines for outpatient management were admitted. All patients in our cohort fully recovered. No morbidity or mortality was found among our 1118 febrile episodes. The low rate of bacteremia combined with the absence of adverse outcomes supports the safety of outpatient management of febrile patients with SCD. Inpatient management may be limited to patients with additional reasons for admission such as acute chest syndrome, acute pain crisis, dehydration, hypoxemia, or signs of sepsis that require inpatient level of supportive care and monitoring. For non-ill-appearing children presenting to the ED with a fever  $>38.5^{\circ}\text{C}$ , physicians should strongly consider outpatient management after blood for culture is drawn and parenteral 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.

Our data identified a triage temperature of  $<39.0^{\circ}\text{C}$  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  $39^{\circ}\text{C}$  could be substituted for the temperature of  $38.5^{\circ}\text{C}$ , but this would need confirmation with additional data.

The NHBLI recommends that patients with a temperature  $>38.5^{\circ}\text{C}$  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  $\leq 38.5^{\circ}\text{C}$ . Of the 482 cultures of blood obtained from children with temperatures between  $38.0^{\circ}\text{C}$  and  $38.5^{\circ}\text{C}$ , 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  $\leq 38.5^{\circ}\text{C}$  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 al<sup>20</sup> reported that among febrile patients with SCD,  $\sim 90\%$  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.

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  $\kappa$  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  $>38.5^{\circ}\text{C}$  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 their blood culture grow a pathogen. We believe that febrile SCD patients managed as outpatients should have follow-up in 24 hours to

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

- West TB, West DW, Ohene-Frempong K. The presentation, frequency, and outcome of bacteremia among children with sickle cell disease and fever. *Pediatr Emerg Care*. 1994;10(3):141–143
- West DC, Andrada E, Azari R, Rangaswami AA, Kuppermann N. Predictors of bacteremia in febrile children with sickle cell disease. *J Pediatr Hematol Oncol*. 2002;24(4):279–283
- Wilimas JA, Flynn PM, Harris S, et al. A randomized study of outpatient treatment with ceftriaxone for selected febrile children with sickle cell disease. *N Engl J Med*. 1993;329(7):472–476
- Rogers ZR, Morrison RA, Vedro DA, Buchanan GR. Outpatient management of febrile illness in infants and young children with sickle cell anemia. *J Pediatr*. 1990;117(5):736–739
- Gaston MH, Verter JL, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia: a randomized trial. *N Engl J Med*. 1986;314(25):1593–1599
- McIntosh S, Rooks Y, Ritchey AK, Pearson HA. Fever in young children with sickle cell disease. *J Pediatr*. 1980;96(2):199–204
- Powars DR. Natural history of sickle cell disease—the first ten years. *Semin Hematol*. 1975;12(3):267–285
- Gill FM, Sleeper LA, Weiner SJ, et al; Co-operative Study of Sickle Cell Disease. Clinical events in the first decade in a cohort of infants with sickle cell disease. *Blood*. 1995;86(2):776–783
- Buchanan GR, Glader BE. Leukocyte counts in children with sickle cell disease: comparative values in the steady state, vaso-occlusive crisis, and bacterial infection. *Am J Dis Child*. 1978;132(4):396–398
- Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. *Blood*. 2010;115(17):3447–3452
- National Heart, Lung, and Blood Institute. *Division of Blood Diseases and Resources. The Management of Sickle Cell Disease*. 4th ed. Bethesda, MD: National Institute of Health; 2002
- Frush K, Ware RE, Kinney TR. Emergency department visits by children with sickle hemoglobinopathies: factors associated with hospital admission. *Pediatr Emerg Care*. 1995;11(1):9–12
- Rogovik AL, Friedman JN, Persaud J, Goldman RD. Bacterial blood cultures in children with sickle cell disease. *Am J Emerg Med*. 2010;28(4):511–514
- Benson JM, Therrell BL Jr. History and current status of newborn screening for hemoglobinopathies. *Semin Perinatol*. 2010;34(2):134–144
- Consensus conference. Newborn screening for sickle cell disease and other hemoglobinopathies. *JAMA*. 1987;258(9):1205–1209
- Halasa NB, Shankar SM, Talbot TR, et al. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of the pneumococcal conjugate vaccine. *Clin Infect Dis*. 2007;44(11):1428–1433
- Adamkiewicz TV, Silk BJ, Howgate J, et al. Effectiveness of the 7-valent pneumococcal conjugate vaccine in children with sickle cell disease in the first decade of life. *Pediatrics*. 2008;121(3):562–569
- Sox CM, Cooper WO, Koepsell TD, DiGiuseppe DL, Christakis DA. Provision of pneumococcal prophylaxis for publicly insured children with sickle cell disease. *JAMA*. 2003;290(8):1057–1061
- Vichinsky EP. Comprehensive care in sickle cell disease: its impact on morbidity and mortality. *Semin Hematol*. 1991;28(3):220–226
- Norris CF, Smith-Whitley K, McGowan KL. Positive blood cultures in sickle cell disease: time to positivity and clinical outcome. *J Pediatr Hematol Oncol*. 2003;25(5):390–395

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

Marc N. Baskin, Xin Lyn Goh, Matthew M. Heeney and Marvin B. Harper  
*Pediatrics* 2013;131;1035

DOI: 10.1542/peds.2012-2139 originally published online May 13, 2013;

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/131/6/1035">http://pediatrics.aappublications.org/content/131/6/1035</a>
<b>References</b>	This article cites 19 articles, 3 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/131/6/1035#BIBL">http://pediatrics.aappublications.org/content/131/6/1035#BIBL</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Allergy/Immunology</b> <a href="http://www.aappublications.org/cgi/collection/allergy:immunology_s_ub">http://www.aappublications.org/cgi/collection/allergy:immunology_s_ub</a> <b>Immunologic Disorders</b> <a href="http://www.aappublications.org/cgi/collection/immunologic_disorder_s_sub">http://www.aappublications.org/cgi/collection/immunologic_disorder_s_sub</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.aappublications.org/site/misc/Permissions.xhtml">http://www.aappublications.org/site/misc/Permissions.xhtml</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.aappublications.org/site/misc/reprints.xhtml">http://www.aappublications.org/site/misc/reprints.xhtml</a>

# American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



# PEDIATRICS<sup>®</sup>

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

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

*Pediatrics* 2013;131;1035

DOI: 10.1542/peds.2012-2139 originally published online May 13, 2013;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/131/6/1035>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN<sup>®</sup>

