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Outcomes of Febrile Events in Pediatric Patients with Sickle Cell Anemia

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Abstract

Background: Limited evidence exists to create institutional admission criteria guidelines for febrile sickle cell patients. In addition, evidence is lacking to understand readmission rates for febrile sickle cell patients discharged from the Emergency Department (ED) or hospital.

Procedures: We conducted a 16 year retrospective study of bacteremia outcomes for febrile sickle cell patients. Risk variables analyzed included fever (either 39.5°C or 40°C), abnormal WBC (>30,000 or <5,000/mcl), tachycardia and hypotension, or “ill appearing”. Fourteen day readmission rates were analyzed to determine outcomes for febrile sickle cell patients discharged from the ED or discharged within 72 hours.

Results: Bacteremia was identified in 17 (2.6%) of 653 febrile events that presented to the ED. “Ill appearing” patients had a 8.5 fold increased odds of being diagnosed with bacteremia. Models using white blood cell count, “ill appearing”, and hypotension have the highest sensitivity and specificity (AUC >0.75). Among 427 patients discharged from the ED or within 72 hours of hospitalization, only 10 (2.3%) were readmitted for a new sickle cell complication.

Conclusions: Institutions can develop admission criteria based on white blood cell count, hypotension, and “ill appearance”. Persistently febrile, well appearing patient can be discharged at 48 hours with minimal risk for new complications.

Keywords

Sickle Cell Anemia; Outcomes; Infection; Bacteremia; Fever

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Drs. Sirigaddi, Aban, Jantz, Bhatia designed and coordinated data collection, carried out initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Introduction

Infants and toddlers with sickle cell anemia (SCA) are at high risk for morbidity and mortality from infection by encapsulated bacteria, especially *Streptococcus pneumoniae*. [1,2] With the benefit of penicillin prophylaxis and development of efficacious vaccines against strains of pneumococcus, bacteremia and premature mortality incidence has markedly decreased in children with SCA. [3–6] Nonetheless, patients with SCA remain at high risk for infection and require an immediate evaluation of each febrile episode that includes blood cultures and initiation of empiric antibiotics. [7] This concern for infection-related morbidity and mortality directs hospitalization of many febrile pediatric SCA patients until blood cultures are negative for bacteria.

Historically, decision to admit SCA patients for a febrile episode were based on physician acumen, age of patient, maximum temperature, or change in hematologic laboratory values from baseline.[8] In an attempt to validate criteria for admission for febrile SCA patients, a randomized trial of outpatient therapy vs. inpatient therapy was conducted among “low-risk” participants. [9] Patients were excluded from randomization in this study if they met “high-risk” criteria which included: 1) seriously ill-appearing, 2) abnormal blood pressure or poor capillary refill, 3) temperature $>40^{\circ}\text{C}$, 4) white blood cell (WBC) >30 or $<5 \times 10^9/\text{L}$, 5) platelet count $<100 \times 10^9/\text{L}$, 6) history of pneumococcal infection, or 7) other SCA complications requiring hospitalization. Among these “high-risk” participants that were not randomized, 8% of febrile events were associated with bacteremia, while none of the “low-risk” randomized participants developed bacteremia. A modified version of this “high-risk” definition was also evaluated in a large retrospective review, which provided additional evidence that “lower risk” patients as compared to the “high-risk” patients presenting to the emergency department (ED) can be safely managed in the outpatient setting. [10] Recently, the 2014 NIH expert panel on the management of sickle cell disease suggests that all SCA patients with a temperature 103.1°F (39.5°C) and who are ill-appearing should be admitted to the hospital for observation and intravenous antibiotics.[7] Importantly, this statement from the NIH reflects a consensus opinion of their expert panel due to a lack of high quality literature in this field. These two risk definitions differ in their recommendations for admission (Wilimas “high risk” fever admission criteria[9]: including temperature of 40°C , ill appearance, abnormal vital signs or laboratory results vs NIH expert panel fever admission criteria[7]: 39.5°C and ill appearance) and therefore warrant further investigation regarding outcomes for febrile SCA patients.

As economic stressors are placed on healthcare systems to ensure appropriate admission criteria and length of hospitalization, it is vital that additional research explore outcomes of febrile SCA patients and attempt to more accurately define “risk” categories for admission and appropriate length of hospitalization for patients that have been admitted for fever. The current study was undertaken to address the limitations in the field of having two differing admission criteria for febrile SCA events. Accordingly, we used retrospectively abstracted data from a single institution in patients with SCA that presented to the ED with fever over a 16 year period to compare the level of concordance between the two published admission criteria and, if needed, to consider modification of these criteria with the eventual goal of developing novel admission criteria.[7,9] Second, we evaluated the impact of hospitalization

of febrile patients on preventing new SCA complications by comparing fourteen-day readmission rates among febrile patients initially discharged from the ED versus febrile patients admitted to the hospital and discharged within 72 hours. This study can inform decision making for admission criteria and hospitalization length in febrile pediatric SCA patients.

METHODS

Study Population.

We conducted a retrospective study of the electronic medical records of individuals with SCA patients (HbSS or SB⁰ thalassemia) who were <18 years old that presented to the Children's of Alabama ED with a temperature $\geq 101.0^{\circ}\text{F}$ from October 1999 to June 2016. This study was approved by the University of Alabama at Birmingham Institutional Review Board. As the primary objective of this study was to determine outcomes of fever in the ED at Children's of Alabama, this study excluded patients that presented afebrile to our outpatient clinic but developed fever in our clinic, most often during a blood transfusion through a central venous line. Second, we excluded patients from our rural-based satellite clinics that initially presented to a local ED with fever and subsequently transferred to our inpatient unit. [11] Third, we excluded patients with a subjective fever at home and a temperature $<101.0^{\circ}\text{F}$ throughout their ED visit. Finally, we excluded afebrile patients admitted for other sickle cell complications but developed fever during an admission.

Laboratory and Clinical Investigations.

The emergency department standard of care for sickle cell patients presenting to the ED with a temperature $\geq 101.0^{\circ}\text{F}$ is to obtain a complete blood count and blood cultures prior to receiving a dose of antibiotics; a chest X-ray is obtained for febrile patients with any concern for a respiratory illness. We abstracted details regarding age, vital signs, peripheral blood counts, and the radiologist's interpretation of the chest x-ray. We reviewed ED provider physical examination or clinical statements to identify patients that were clinically ill. The statements categorized as "ill" in this study included "ill" (n=40), "uncomfortable" (n=5), "chills" (n=3), "lethargic" (n=1), or "seizure" (n=1). Finally, we recorded all blood culture results obtained during the ED visit and hospitalization to identify cases with bacteremia and time from admission to blood culture positivity. Clinical practice guideline mandates admission for patients with acute chest syndrome; therefore, *a priori* we decided to exclude 122 patients admitted with fever and an abnormal chest x-ray.

Outcomes.

The primary outcomes of interest, bacteremia identified from a blood culture, was categorized as "yes" or "no". We excluded bacteremia cases that were determined to be a contaminant by the inpatient team. The risk variables for fever admission criteria identified from the literature and extracted for this analysis included: temperature (fever categorized from the admission criteria literature as either $\geq 39.5^{\circ}\text{C}$ or $\geq 40^{\circ}\text{C}$), WBC (abnormal categorized as >30 or $<5 \times 10^9/\text{L}$), heart rate and blood pressure (tachycardia and hypotension definitions were based on the age-specific 2015 Pediatric Advanced Life

Support guidelines). We determined sensitivity, specificity, and positive predictive value for these risk variables for the primary outcome of bacteremia.

We acknowledge that this study represents the experience from a single institution where there has not been a consistent admission practice for febrile SCA events over the 16 year period. However, this heterogeneity in practice has allowed us to examine the bacteremia outcomes using differing risk variables for admission from the literature and explore novel admission criteria. We created a “high risk” category, using a modified version of the Wilimas definition, defined by having at least one abnormal risk variable (temperature 40°C , tachycardia by age, hypotension, WBC (>30.0 or $<5.0 \times 10^9/\text{L}$). Second, we created a category for patients that met admission criteria based on the NIH consensus of a temperature 39.5°C) and ill appearance.

To evaluate new SCD complications that developed in febrile patients, we compared 14-day readmission rates among patients with febrile events either initially discharged from the ED or from the hospital within 72 hours of their admission. We made an *a priori* decision that re-admissions after 14 days from the initial presentation to the ED may not be attributable to the initial febrile event. All patients admitted to the hospital received intravenous antibiotics until 48 hour cultures were negative; we could not determine if patients discharged from the ED filled an oral antibiotic prescription if it was prescribed by the ED physician.

Statistical Analysis.

Each febrile event was deemed to be an independent event. Descriptive statistics (means/standard deviation) were calculated and compared using t-test. Logistic regression was used to model the odds of bacteremia. Sensitivity, specificity, and positive predictive values were computed from contingency tables with bacteremia as outcome and current admission criteria (Yes/No) as risk factor. Using the same set of admission criteria variables (temperature, white blood cell count, ill appearance, and abnormal vital signs), we explored and compared different cut-offs for admission criteria by computing the area under the receiving operating characteristic curve (AUC) and reported those models with an AUC at least 0.75. Analyses were performed in JMP12 (Cary, NC) or SAS v. 4.0 (Cary, NC).

RESULTS

We identified 653 febrile events in 155 patients with SCA (HbSS or SB⁰ thalassemia) that presented to the Children’s of Alabama ED with fever and a normal chest x-ray. The median number of febrile events per patient was 3 (range, 1–9). Eighty-two (53%) of the patients were male. The median age for febrile events was 2 years (range, 0.1–17 years). Five hundred and eight (78%) febrile events resulted in a hospitalization. The admission rate for febrile sickle cell patients declined over time: 1999–2004 (97% admitted), 2004 to 2008 (94% admitted), 2009 to 2012 (72%) admitted, and 2012 to 2016 (60% admitted, $p<0.0001$). The median length of inpatient admission was 3 days (range, 1–22 days). Clinical and laboratory variables for all febrile events are presented in Table 1.

All Febrile Events

Bacteremia was identified in 17 (2.6%) of the 653 febrile events that presented to the ED (Table 1). The positive predictive values, sensitivities, and specificities for bacteremia by categorical variables are presented in Table 2. Multivariable analysis (Table 3) revealed that “ill-appearing” phenotype was associated with an 8.5-fold increased odds of being diagnosed with bacteremia (95% CI, 2.9–25.3, $p<0.0001$). Presence of tachycardia by age was associated with a 3.7-fold increased odds of bacteremia, although this association did not reach statistical significance ($p=0.09$). Abnormal white count and abnormal BP were associated with a 2.4-fold odds of bacteremia, the association for these variables also did not reach statistical significance. In Figure 1, we show the receiver operating characteristics that included the following characteristics: the modified Wilimas “high-risk” criteria of ill-appearing, abnormal vital signs abnormal WBC, or high temperature ($T>40^{\circ}\text{C}$), yielding an area under the curve (AUC) of 0.67. The NIH criteria of $T>39.5^{\circ}\text{C}$ and ill-appearing was associated with an AUC of 0.58. As neither of these models achieved an AUC >0.75 , we also present two new admission criteria models identified from using differing combination of variables in our cohort that allowed for an AUC >0.75 . The first model includes admitting a patient with one of the following variables: “ill” appearing, hypotension, or $\text{WBC} > 30 \times 10^9/\text{L}$, while the second model includes “ill” appearing, hypotension, or $\text{WBC} > 20 \times 10^9/\text{L}$. The sensitivity, specificity, and positive predictive values for these two new admission criteria models are presented in Table 2.

We identified pneumococcal bacteremia during six (0.9%) febrile events (Table 1). Three pneumococcal events occurred in 2014 and one event occurred in 1999, 2005, and 2008. Febrile events with pneumococcal bacteremia had significantly higher WBC (25.8 vs $16.5 \times 10^9/\text{L}$, $p=0.001$) when compared with those without bacteremia. No statistically significant differences were found for febrile events with and without any pneumococcal bacteremia for initial ED temperature ($p=0.2$), age ($p=0.8$), heart rate ($p=0.2$), systolic blood pressure ($p=0.9$), diastolic blood pressure ($p=0.5$), hemoglobin ($p=0.5$), or platelet count ($p=0.9$).

Time to positive blood culture and length of stay

The median time to the first positive blood culture was 18 hours (range, 8–85 hours). *Streptococcus pneumoniae* infections were identified at a mean of 16 hours (range 9–24 hours) (Table 4). The one patient with a positive blood culture identified after 48 hours grew *Bordetella holmesii* at 85 hours of incubation. This patient was clinically stable and discharged from the hospital after 48 hours, but re-admitted two days later with the positive blood culture. The median length of hospitalization among patients admitted with bacteremia was 8.0 days (range: 2 to 22 days) which was longer than the admission length of febrile events ($n=496$) not associated with bacteremia (median: 3 days, $p<0.0001$).

Febrile Admission Events that Progressed to Acute Chest Syndrome

We identified ten patients that presented to the ED with a fever and a negative CXR on admission that were subsequently identified with an infiltrate on CXR during the hospitalization and diagnosed with ACS. Nine of the ten patients (90%) required oxygen in the ED and were admitted with a concern for ACS despite having an initial negative CXR. One additional patient did not develop respiratory distress until 42 hours of hospitalization

and subsequently diagnosed with acute chest syndrome based on a new infiltrate on chest CXR.

Fourteen Day Readmission for patients discharged from ED or within 72 hours of initial hospitalization

Despite admitting 78% of the 653 febrile events at our institution, five of 145 patients (3.4%) initially discharged from the ED were subsequently identified with bacteremia and re-admitted to the hospital. (Supplemental Table S1). We also identified an additional 26 readmission events within 14 days of the initial ED febrile visit (6%) among 287 febrile events discharged from the hospital within 72 hours or 140 febrile events initially discharged from the ED. Sixteen readmission events were due to persistent fever, five for pain, two for ACS, and one each for aplastic crisis, croup, and osteomyelitis. No statistically-significant difference was noted for the 14-day readmission rate among 14 (4.9%) of 287 hospital discharged febrile events as compared to 12 (8.6%) of 140 ED discharged febrile events ($p=0.2$). When analyzing the association between initial ED variables and 14-day readmission events, we could not identify statistically-significant differences for 14-day readmission between events that required a readmission ($n=26$) as compared to events that were not readmitted ($n=401$) including: age (3.4 vs 3.2 years, $p=0.7$), initial ED temperature (39.2 vs 39.2°C, $p=0.7$), initial ED heart rate (142 vs 143 beats per minute, $p=0.9$), initial SBP (114 vs 115 mmHg, $p=0.9$), initial DBP (66 vs 63 mmHg, $p=0.2$), or initial WBC (14.6 vs $16.1 \times 10^9/L$, $p=0.3$).

We identified two patients that were diagnosed with ACS within fourteen days of their initial febrile event. One patient was admitted for fever, cough, rhinorrhea, and subsequently diagnosed with influenza. The patient did not have respiratory distress during the hospitalization and was discharged after 48 hours of receiving Tamiflu. The patient returned eight days later with increased work of breathing and was diagnosed with ACS. The second febrile patient was discharge from the ED with fever and a negative CXR but developed ACS eleven days after that febrile event.

DISCUSSION

This study highlights that bacteremia, including pneumococcal bacteremia, is a rare yet serious outcome for febrile SCA patients. We identified a prevalence of bacteremia(17 cases (2.6%)) in febrile children with a normal chest x-ray at our emergency department that was similar to the 3–4% identified in the earlier studies of bacteremia but higher than other recent publications.[8–10,12] The prevalence of bacteremia in patients with SCA is still higher than the 0.4–0.9% prevalence identified among young pediatric patients presenting to the ED with fever.[13–15] The modified “high” risk model (Temp $\geq 40^\circ\text{C}$, abnormal WBC, ill appearing, tachycardia by age) had a higher AUC than the NIH model but neither models obtained a value >0.75 . We developed several models and identified two novel admission criteria models with an appropriate AUC; the model using ill appearing, hypotension, and $\text{WBC} > 30 \times 10^9/L$ had the highest AUC. In comparison to other models based on WBC, this model with a $\text{WBC} > 30 \times 10^9/L$ allows for the lowest hospitalization rate (17% of admissions for febrile ED visits) but also had the lowest sensitivity of 71% among those

tested with AUC >0.75. In comparison, using a WBC >20 × 10⁹/L increases the sensitivity to 88% but more than doubles the hospitalization rate. Finally, using a “high risk” model that includes tachycardia by age would increase the sensitivity to 94% but requires almost 60% of febrile SCA patients to be admitted. Institutions may consider temperature in their fever guidelines but only 4 (23%) of our bacteremia cases had a temperature >40°C and 6 (35%) had a temperature >39.5°C. This data demonstrates that it is difficult to develop admission criteria for SCD based on fever.

The leading organism for bacteremia remained *Streptococcus pneumoniae* despite implementing vaccination and penicillin prophylaxis policies.[16] (Supplemental Table S2) These data further demonstrate that bacteremia will be identified within 48 hours for the overwhelming majority of febrile SCA patients. The one patient in our cohort identified with bacteremia after 48 hours grew *Bordetella holmesii*, a rare gram negative bacteria that has been identified as a slow growing bacteria in patients with asplenia.[17] Two prior studies identified that mean time to a positive blood culture in SCA febrile patients was 17–23 hours and that 96% of cases would be identified within 48 hours.[16,18]

For SCA patients that remain febrile at 48 hours but are well-appearing and have negative blood cultures, a potential concern for discharge among clinicians may be the risk for patient progression to an additional sickle cell complication after discharge including development of ACS. Among the ten febrile patients with a normal CXR in the ED that developed ACS during their hospitalization, nine required oxygen on admission and therefore were already being monitored or treated for ACS. The one patient that did not require oxygen or have an infiltrate in the ED, developed an oxygen requirement on hospital day two and was diagnosed with ACS based on an abnormal CXR on day three. Therefore, prior to 48-hour discharge for a well-appearing but persistently febrile patient, clinicians should perform an additional history and physical examination at the time of discharge to confirm that the patient has developed no new signs or symptoms concerning for early ACS. In our analysis of the 14-day follow-up, we identified two patients who developed ACS within 14 days of their initial ED visit for fever. One patient admitted for influenza, a known risk factor for ACS, discharged home but eight days later developed worsening respiratory symptoms and admitted for ACS. The second patient developed ACS 11 days later. It is difficult to determine if additional inpatient therapy for the initial fever would have prevented either of these two episodes of ACS. Therefore, discharge instructions for well-appearing febrile patients must include specific education to return to the ED with any new onset cough or respiratory symptoms. Finally, our data suggest that febrile patients discharged from the ED have a low incidence of developing new SCA complications and the rate of events is similar to febrile patients admitted for <72 hours. The majority of the readmission events in our cohort were due to persistent fever (62%) but a few patients (2%) did have new SCA complications. Therefore, we suggest that patients who are not ill-appearing or in respiratory distress after 48 hours of inpatient hospitalization can be discharged from the hospital without a significant increased risk for new SCA complications.

When performing a retrospective review, several limitations are worth noting. First, as ED medical records from outside hospitals are not consistently included in our hospital’s medical records, we excluded febrile events from an outside hospital and transferred to our

inpatient unit. We also excluded patients that developed a fever during an outpatient clinic visit. The additional bacteremia events identified, most commonly among chronic transfusion patients with line infections that initially presented to our clinic without fever, may have increased our outcome numbers but were not appropriate for the primary outcome of this study which focused on febrile events that presented to the ED. Next, among events with tachycardia defined by age-specific general pediatric sepsis heart rates, we were unable to differentiate outcomes by resolved versus persistent tachycardia after initial anti-pyretic therapy due to limitations in charting of time of anti-pyretic therapy administration. While future studies could evaluate bacteremia outcomes by response to anti-pyretic therapy, we did identify four bacteremic patients that had resolved fever or tachycardia in the ED with anti-pyretic therapy and initially discharged home. Also, this manuscript did not include pediatric patients with HbSC or HbSB+ thalassemia as they may have a lower incidence of bacteremia than patients with HbSS or HbSB0 thalassemia.[1] Next, we could not accurately determine adherence to penicillin prophylaxis or vaccination history for this retrospective review. Finally, we did not include current SCD therapy, prior co-morbidities, or presence of a central venous line as risk factors for fever requiring admission. We acknowledge that these potential risk factors for bacteremia should be considered when individualizing admission plans; however, these potential risk factors are not included in prior febrile SCA admission criteria literature or NIH guidelines and therefore were not included in this analysis.

The lower prevalence of bacteremia in this era of antibiotic prophylaxis and vaccination hindered our ability to develop an admission criteria model that included all high-risk variables. However, institutions can utilize these data to develop institutional guidelines for febrile SCA admissions. Admitted patients with persistent fever but who are otherwise well appearing and with good oxygenation and a negative CXR can be considered for early discharge after 48–72 hours as these patients demonstrated a low likelihood of developing new SCA complications in our study. Also, patients stable for discharge from the ED did not demonstrate a high prevalence of new SCA complications in the next 14 days. Individual institutions should consider their comfort with “risk” for bacteremia when developing inpatient admission and discharge criteria based on health outcomes, and health economics. Our data suggest using a model that includes ill appearance, abnormal BP, and a WBC between $20\text{--}30 \times 10^9/\text{L}$, however ultimately the decision to admit febrile SCD patients relies on clinical judgement and local institutional policies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation Key:

SCA	Sickle Cell Anemia
ED	Emergency Department
CXR	Chest X-ray
WBC	White Blood Cell

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Figure 1.
Receiver Operator Curves to Predict Bacteremia

Table 1
Laboratory and Clinical Variables in Sickle Cell Anemia Patients with Febrile Events Evaluated in the Emergency Department

Continuous Variables	All patients (n=653)	Patients with Bacteremia (n=17)	Patients without Bacteremia (n=636)	p-value	Patients with Pneumococcus (n=6)	Patients without Pneumococcus (n=647)	p-value
	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age (years)	3.2 (3.2)	5.1 (3.5)	3.2 (3.1)	0.02	3.6 (2.4)	3.3 (3.2)	0.8
Temperature (°F)	102.4 (0.9)	102.7 (1.2)	102.6 (0.9)	0.5	103.0 (1.2)	102.6 (0.9)	0.2
Heart Rate (beats per minute)	144 (22.8)	148 (19.4)	144 (22.9)	0.5	158 (20.8)	144 (22.8)	0.2
Systolic Blood Pressure (mmHg)	115 (13.7)	119(14.5)	115 (13.7)	0.2	115(8.9)	115 (13.7)	0.9
Diastolic Blood Pressure (mmHg)	64 (10.0)	62 (11.9)	64 (9.9)	0.6	67 (9.2)	64 (10.0)	0.5
White Blood Cell x 10 ⁹ /L	16.6 (8.1)	24.3 (9.1)	16.4 (8.1)	<0.0001	25.8 (11.5)	16.5 (8.1)	0.005
Hemoglobin g/dL	8.3 (1.6)	7.6 (1.1)	8.3 (1.6)	0.07	7.9 (0.8)	8.3 (1.6)	0.5
Platelet Count x 10 ⁹ /L	348 (146)	451 (181)	345 (143)	0.003	340 (127)	348 (146)	0.9

Table 2

Bacteremia and Pneumococcal Bacteremia by Risk Variables

All Febrile Patients without Acute Chest Syndrome	Admitted cases if variable used (% febrile cases admitted)	Bacteremia 17 cases			Pneumococcal bacteremia 6 cases		
		n (PPV)	n (Sensitivity)	n (Specificity)	n (PPV)	n (Sensitivity)	n (Specificity)
“High risk” Model. AUC=0.67							
Temp 40°C	57 (8.7)	4 (7.0)	4 (23.5)	583 (91.7)	2 (3.5)	2 (33.3)	592 (91.5)
Tachycardia [#]	320 (59.8)	14 (4.4)	14 (87.5)	213 (41.0)	4 (1.3)	4 (80)	214 (40.4)
Hypotension [@]	33 (6.7)	2 (6.1)	2 (12.5)	443 (93.5)	0 (0)	0 (0)	452 (93.2)
WBC >30 or <5 10 ⁹ /L	54 (8.2)	3 (5.6)	3 (17.7)	587 (92.0)	2 (3.7)	2 (33.3)	597 (92.0)
Ill appearing	50 (7.6)	7 (14.0)	7 (41.2)	593 (92.2)	3 (6.0)	3 (50.0)	600 (92.7)
“High risk” model: At least one of the above variables	387 (59.3)	16(4.1)	16 (94.1)	265 (41.6)	6 (1.5)	6 (100)	266 (41.1)
NIH 2014. AUC=0.58							
Temp 39.5°C	163 (25.0)	6(3.7)	6 (35.3)	479 (75.3)	4 (2.5)	4 (66.7)	488 (75.4)
Ill appearing	50 (7.6)	7 (14.0)	7 (41.2)	593 (92.2)	3 (6.0)	3 (50.0)	600 (92.7)
NIH model: Both of the above variables	17 (2.6)	3 (17.6)	3 (16.7)	621 (97.6)	2 (33.3)	2(11.1)	631 (97.5)
New Models with AUC >75%							
At least one of: Ill appearing, WBC>30, or Hypotension	112 (17.2)	12 (10.7)	12 (70.6)	536 (84.3)	4 (3.6)	4(66.7)	539 (83.3)
At least one of: Ill appearing, WBC>20, or Hypotension	244 (37.4)	15 (6.2)	15 (88.2)	407 (64.0)	5 (2.1)	5(83.3)	408 (63.1)

bacteremia (n=16) with heart rate recorded in EMR; pneumococcal bacteremia (n=5); febrile admissions (n=535)

@ bacteremia (n=16) with blood pressure recorded in EMR and 5 pneumococcal (n=5); febrile admissions (n=490)

PPV: Positive Predictive Value; Temp: Temperature; CXR: Chest X-ray; WBC: White Blood Cell Count

Table 3

Risk Factors Associated with Bacteremia

Variable	Odds Ratio	95% CI	p-value
Temperature			
<39.5°C	1.0		
39.5 °C	1.35	0.46–4.01	0.6
Abnormal heart rate			
No	1.0		
Yes	3.73	0.82–17.05	0.09
Ill-appearing			
No	1.0		
Yes	8.50	2.85–25.33	0.0001
Abnormal BP			
No	1.0		
Yes	2.42	0.48–12.23	0.3
White blood cell count			
Normal	1.0		
Abnormal	2.35	0.58–9.48	0.2

Table 4

Bacteremia Cases and Time to Positive Blood Culture

Organism	N	Median Hours to positive blood culture (Range)
<i>Streptococcus pneumoniae</i>	6	18 (9–46)
<i>Escherichia coli</i>	3	10 (8–12)
<i>Salmonella species</i>	3	21 (18–22)
<i>Bordetella holmesii</i>	1	85
<i>Staphylococcus aureus</i>	1	23
<i>Staphylococcus parasanguinis</i>	1	24
<i>Streptococcus pyogenes</i>	1	18
<i>Streptococcus viridans</i>	1	36