Epidemiology of Methicillin-Resistant *Staphylococcus aureus* Bacteremia in Children

Rana F. Hamdy, MD, MPH, MSCE,[a] Alice J. Hsu, PharmD,[b] Chris Stockmann, PhD,[c,†] Jared A. Olson, PharmD,[d] Matthew Bryan, PhD,[e,f] Adam L. Hersh, MD, PhD,[c] Pranita D. Tamma, MD, MS,[g] Jeffrey S. Gerber, MD, PhD[e,f]

abstract

BACKGROUND: Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is associated with high rates of treatment failure in adults. The epidemiology, clinical outcomes, and risk factors for treatment failure associated with MRSA bacteremia in children are poorly understood.

METHODS: Multicenter, retrospective cohort study of children ≤18 years hospitalized with MRSA bacteremia across 3 tertiary care children's hospitals from 2007 to 2014. Treatment failure was defined as persistent bacteremia >3 days, recurrence of bacteremia within 30 days, or attributable 30-day mortality. Potential risk factors for treatment failure, including the site of infection, vancomycin trough concentration, critical illness, and need for source control, were collected via manual chart review and evaluated using multivariable logistic regression.

RESULTS: Of 232 episodes of MRSA bacteremia, 72 (31%) experienced treatment failure and 23% developed complications, whereas 5 (2%) died within 30 days. Multivariable analysis of 174 children treated with vancomycin with steady-state vancomycin concentrations obtained found that catheter-related infections (odds ratio [OR], 0.36; 95% confidence interval [CI]: 0.13–0.94) and endovascular infections (OR, 4.35; 95% CI: 1.07–17.7) were associated with lower and higher odds of treatment failure, respectively, whereas a first vancomycin serum trough concentration <10 μg/mL was not associated with treatment failure (OR, 1.34; 95% CI, 0.49–3.66). Each additional day of bacteremia was associated with a 50% (95% CI: 26%–79%) increased odds of bacteremia-related complications.

CONCLUSIONS: Hospitalized children with MRSA bacteremia frequently suffered treatment failure and complications, but mortality was low. The odds of bacteremia-related complications increased with each additional day of bacteremia, emphasizing the importance of achieving rapid sterilization.

[a]*Department of Pediatrics, Children's National Health System, Washington, DC;* [b]*Department of Pharmacy, The Johns Hopkins Hospital, Baltimore, Maryland;* [c]*Department of Pediatrics, University of Utah, Salt Lake City, Utah;* [d]*Department of Pharmacy, Primary Children's Hospital, Salt Lake City, Utah;* [e]*Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania;* [f]*Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and* [g]*Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland*

Dr Hamdy conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection at 1 site, analyzed the data, drafted the initial manuscript, and approved the final manuscript as submitted; Dr Hsu participated in study design, designed the data collection instruments, coordinated and supervised data collection at 1 site, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Stockmann participated in study design, reviewed and revised the manuscript, and approved a close-to-final manuscript; Dr Olson participated in study design, coordinated data collection at

WHAT'S KNOWN ON THIS SUBJECT: In adults, methicillin-resistant *Staphylococcus aureus* bacteremia is associated with high morbidity and mortality. In adults, higher vancomycin trough correlates with better clinical outcomes, and these adult data have been used to guide therapeutic management in children.

WHAT THIS STUDY ADDS: Children with methicillin-resistant *Staphylococcus aureus* bacteremia frequently suffered complications, but mortality was low. Initial vancomycin trough concentrations were not associated with treatment failure. The odds of bacteremia-related complications increased with each additional day of bacteremia, emphasizing the importance of achieving rapid sterilization.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is associated with substantial morbidity and mortality in adults. Risk factors for treatment failure associated with MRSA bacteremia in adults include lower vancomycin serum concentrations,[1,2] retained central venous catheters,[3] hospital-onset infection,[4] pneumonia,[4] and endocarditis,[4] but these associations have not been shown in children. For example, the most prevalent anatomic sites of *S aureus* infection associated with bacteremia differ; adults more commonly present with MRSA endocarditis, whereas children more commonly present with bone and joint infections.[5–8] Antibiotic susceptibility patterns of MRSA also differ. Although the minimum inhibitory concentration (MIC) to vancomycin has increased over time in adults,[9] this trend has not been consistently observed in children.[10,11] Furthermore, the pharmacokinetics of vancomycin, the antibiotic recommended as first-line for treatment of MRSA bacteremia,[12] differ between adults and children.

To address these knowledge gaps, the objectives of this study were to characterize the clinical epidemiology of MRSA bacteremia in children and identify risk factors associated with treatment failure in these children.

METHODS

Setting and Participants

All patients <19 years of age hospitalized at center A, a 520-bed children's hospital in Philadelphia, Pennsylvania; center B, a 205-bed children's center in Baltimore, Maryland; or center C, a 289-bed children's hospital in Salt Lake City, Utah, between January 1, 2007 and November 17, 2014 with a blood culture positive for MRSA were evaluated for inclusion in the study. Patients with polymicrobial bloodstream infections or transferred from another institution with incomplete laboratory or drug administration data were excluded. For subjects with >1 episode of MRSA bacteremia, only the first episode was included. The primary analysis was limited to children treated with vancomycin for at least 2 days within 48 hours of onset of bacteremia and with a steady-state vancomycin concentration obtained within the first 3 days of therapy.

Microbiologic Methods

Blood isolates growing *S aureus* resistant to oxacillin (MIC ≥4 μg/mL) or cefoxitin (≥8 μg/mL) were included in our cohort. Clinical samples were processed at the microbiology laboratories of each participating institution according to standard operating procedures. Automated instruments were used at each participating institution's clinical microbiology laboratory for pathogen identification and antibiotic susceptibility testing: centers A and C used the Vitek 2 system (bioMérieux), and center B used the BD Phoenix Automated System (BD Diagnostics).

Data Collection

Laboratory databases were used to identify all MRSA blood cultures during the study period. All clinical data were extracted from the electronic health records through structured chart review.

Data abstracted through chart review included: (1) demographic information; (2) presence of underlying comorbidities, defined as any of the following present before the onset of bacteremia: clinically significant heart disease, end-stage renal disease, end-stage liver disease, diabetes, immunosuppressive therapy or >14 days of systemic steroid use, primary immunodeficiency, neutropenia (absolute neutrophil count <500 cells/mm^3), HIV infection, solid organ transplant, receipt of chemotherapy within previous 6 months, hematopoietic stem cell transplantation within 1 year, chronic lung disease, intestinal failure, neuromuscular disease, burn, or eczema; (3) critical illness, defined as vasopressor use within 48 hours of the onset of MRSA bacteremia; (4) anatomic site of infection, categorized by the study investigator using predetermined definitions: catheter-related as defined by the National Healthcare Safety Network,[13] skin and soft tissue, musculoskeletal (osteomyelitis, septic arthritis, or pyomyositis), endovascular (including endocarditis defined as ≥2 positive cultures >12 hours apart and endocardial involvement or suppurative thrombophlebitis defined as inflammation involving a vascular site, or an intraluminal thrombus), pneumonia, or other; (5) community-onset (bacteremia from culture obtained <48 hours after admission) versus hospital-onset; (6) surgical intervention for source control, categorized as: none performed, performed within 3 days of bacteremia onset, performed beyond 3 days of bacteremia onset; (7) removal of catheter, categorized into: not removed, removed within 3 days of bacteremia onset, removed beyond 3 days of bacteremia onset; (8) initial vancomycin steady-state trough, defined as vancomycin serum concentration drawn within 3 days of initiating vancomycin therapy, having received at least 2 doses at the same dose within 2 hours of the scheduled administration time and drawn within 1 hour before the next dose; (9) antibiotic treatment data from the hospital medication administration record; and (10) MRSA susceptibility data, including vancomycin MIC. Time to the first anti-MRSA antibiotic was defined as the number of days between the first positive blood culture and the first dose of an anti-MRSA antibiotic to which the isolate was susceptible. This study was approved by the institutional review boards of all 3 participating institutions.

Study Outcomes

The primary outcome was treatment failure, a composite outcome defined by any 1 of the following: (1) MRSA-attributable mortality within 30 days (when blood culture was positive for MRSA at the time of death, MRSA infection was listed in the medical record as cause of death, or death occurred within 14 days of the first day of MRSA bacteremia without an alternate explanation as determined by the study investigators); (2) recurrence of bacteremia within 30 days (when a new blood culture was positive for MRSA within 30 days of discontinuing antibiotic therapy and separated by at least 7 days from the last positive blood culture for MRSA, with documentation of at least 1 negative blood culture in the interim time period); or (3) persistence of bacteremia for >3 days from the first positive culture. It is the practice of the 3 participating facilities to obtain daily blood cultures for patients with MRSA bacteremia. Because the definition of persistent bacteremia has been inconsistent in the adult literature (ranging from 3–7 days)[1,12,14] and anecdotal experience across centers suggested that the mean duration of bacteremia would be shorter in children than in adults, persistent bacteremia was defined a priori as bacteremia continuing for >3 days, but secondary analyses were repeated using 5 and 7 days.

Secondary outcomes included (1) readmission within 30 days of hospital discharge attributable to MRSA bacteremia; (2) development of sequelae from MRSA bacteremia, including septic emboli or new thrombus, metastatic focus of infection, or endocarditis; and (3) progression of infection, such as an increase in abscess size or the need for repeat surgical intervention.

Statistical Analysis

A multivariable logistic regression model for the probability of treatment failure was built incorporating random effects to account for correlation across institutions, including the following a priori selected variables: catheter-related infection, endovascular infection, first steady-state vancomycin serum trough concentration (<10 or ≥10 μg/mL), source control intervention performed (not needed, performed within 3 days, performed beyond 3 days from the first positive blood culture), and critical illness (vasopressor use within 48 hours).

Post hoc analyses included variables that were associated with treatment failure in univariable analyses with a *P* value <.10 in addition to the a priori selected variables that were associated with treatment failure in primary analyses (critical illness, catheter-related bloodstream infection, and endovascular infection). To explore and quantify the effect of the duration of bacteremia on the development of sequelae and hematogenous complications, a secondary analysis was performed by using these complications as the outcome of interest and duration of bacteremia (continuous) as the exposure of interest, adjusting for the variables included in the primary analysis with the institution included as a fixed effect. Data were analyzed by using Stata, version 13.1 (Stata Corp, College Station, TX).

RESULTS

Study Cohort

A total of 278 episodes of MRSA bacteremia were identified across 3 hospitals. Of these, 232 met study inclusion criteria and were included in the cohort, and 205 were treated with vancomycin, 174 of which had a steady-state vancomycin concentration obtained within the first 3 days of therapy (Fig 1). Baseline characteristics of the cohort are described in Table 1.

Clinical and Microbiologic Characteristics

Of the 232 included patients, the median age was 5.3 years (interquartile range [IQR]: 1.2–10.9), 121 (52.2%) had an underlying comorbid condition, 50 (21.6%) had a hospital-onset infection, and 22 (9.5%) required vasopressors within 48 hours of bacteremia onset. The primary sources of infection were as follows: osteomyelitis (72, 31%), catheter-related (52, 22.4%), skin and soft tissue infection

TABLE 1 Baseline Characteristics of Children with MRSA Bacteremia

	N = 232
Institution	
A	110 (47.4)
B	65 (28.0)
C	57 (24.6)
Age, median, y (IQR)	5 (1.2–10.9)
Girl	98 (42.2)
Hispanic ethnicity	24 (10.3)
African American race	86 (37.1)
Public insurance	103 (44.4)
Comorbid medical conditions (any)	121 (52.2)
Hospital-onset infection	50 (21.6)
Indwelling device present at baseline	
None	148 (63.8)
Central venous catheter	57 (24.6)
Other indwelling device	27 (11.6)
Vasopressor use within 48 h	22 (9.5)
Primary source of infection	
Catheter-related bloodstream infection	52 (22.4)
Musculoskeletal	
Osteomyelitis[a]	72 (31.0)
Septic arthritis	11 (4.7)
Pyomyositis	6 (2.6)
Orthopedic hardware	5 (2.2)
Skin/soft tissue infection	36 (15.5)
Endovascular	
Suppurative thrombophlebitis	7 (3.0)
Endocarditis	4 (1.7)
Pneumonia	21 (9.0)
Central nervous system	6 (2.6)
Intraabdominal	1 (0.4)
No source identified	11 (4.7)
Vancomycin MIC for MRSA isolate	
MIC ≤ 1 μg/mL	198 (85)
MIC = 2 μg/mL	17 (7.3)
Unknown	17 (7.3)

Data are presented as *n* (%) unless otherwise noted.

[a] Among the 72 patients with the primary source of infection identified as osteomyelitis, 22 (31%) also had septic arthritis at the time of presentation.

(36, 15.5%), pneumonia (21, 9%), septic arthritis (11, 4.7%), endovascular infection (11, 4.7%), and no source identified (11, 4.7%) (Table 1). Among the 52 patients with catheter-related infections, 20 of 52 (38.5%) underwent removal of the catheter within ≤3 days, 16 of 52 (30.8%) underwent removal of the catheter beyond 3 days, and 16 (30.8%) had their catheters retained.

Among the 205 patients who received vancomycin within the first 48 hours, 65 (32%) received an additional anti-MRSA antibiotic within the first 48 hours to which the isolate was known to be susceptible: 62 received clindamycin, 2 received linezolid, and 1 received doxycycline. The median initial vancomycin steady-state trough was 6.9 μg/mL (IQR: 4.4–10.3); 59 (33.9%) had an initial vancomycin trough <5 μg/mL, 69 (39.7%) had a trough between 5 and <10 μg/mL, 29 (16.7%) had a trough between 10 and <15 μg/mL, and 17 (9.8%) had a vancomycin trough ≥15 μg/mL. Only 17 (8%) MRSA isolates had an MIC >1 μg/mL.

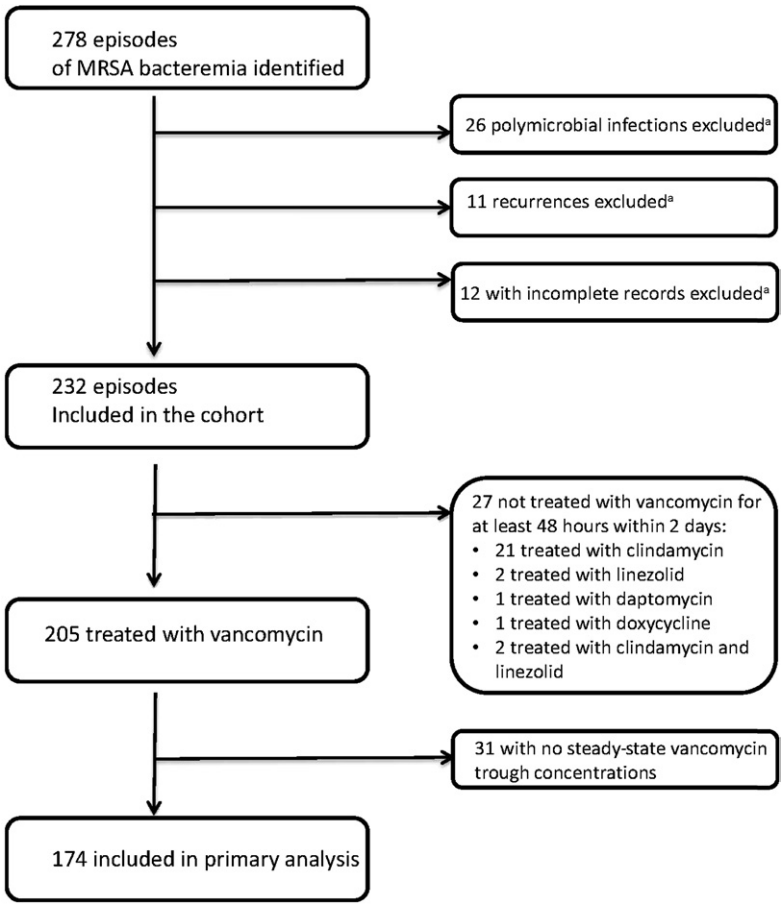

FIGURE 1
Flow diagram of children with MRSA bacteremia. [a] Not mutually exclusive.

Clinical Outcomes

Overall, 72 (31%) children experienced treatment failure: 64 (27.6%) had persistent bacteremia >3 days, 7 (3%) had recurrence of bacteremia within 30 days of discontinuing anti-MRSA therapy, and 5 (2.2%) died due to MRSA bacteremia. The median duration of bacteremia was 2 days (IQR: 1–4 days) (Fig 2); 30 of the 232 patients (12.9%) had persistent bacteremia >5 days, and 24 (10.3%) had persistent bacteremia >7 days. Progression of infection occurred in 17 cases (7.3%), and hematogenous complications or sequelae occurred in 54 (23.3%), including septic emboli or thrombus in 28 (12.1%) and metastatic focus of infection in 19 (8.2%). Readmission within 30 days that was attributable to MRSA bacteremia occurred for 11 (4.7%) children (Table 2).

Of the 5 patients who died, 1 was at center B and died 3 days after onset of bacteremia, with the primary source of infection identified as being catheter-related, and the remaining 4 patients were at center A with pneumonia identified as the primary infection and death occurring 7, 8, 9, and 11 days from bacteremia onset.

The proportion of patients who experienced treatment failure ranged from 21.1% to 38.2% across institutions, whereas the distribution of the anatomic site of infection, the proportion with hospital-onset infections, the frequency and timing of source control intervention, and the proportion who were critically ill were similar across institutions.

Of the 19 patients with persistent bacteremia beyond 7 days, all were treated initially with vancomycin and 17 received at least 1 additional antibiotic, including clindamycin (10), gentamicin (8), rifampin (7), linezolid (5), doxycycline (1), and trimethoprim-sulfamethoxazole (1). Two of these patients died, both with pneumonia as the primary source of infection (1 received linezolid and gentamicin and the other received vancomycin plus rifampin).

Risk Factors for Treatment Failure: Primary Analysis

In univariable analyses, African American race, critical illness, musculoskeletal infection, and endovascular infection were associated with higher odds of treatment failure, whereas comorbid conditions, central venous catheter, and lack of an identified source of infection were associated with lower

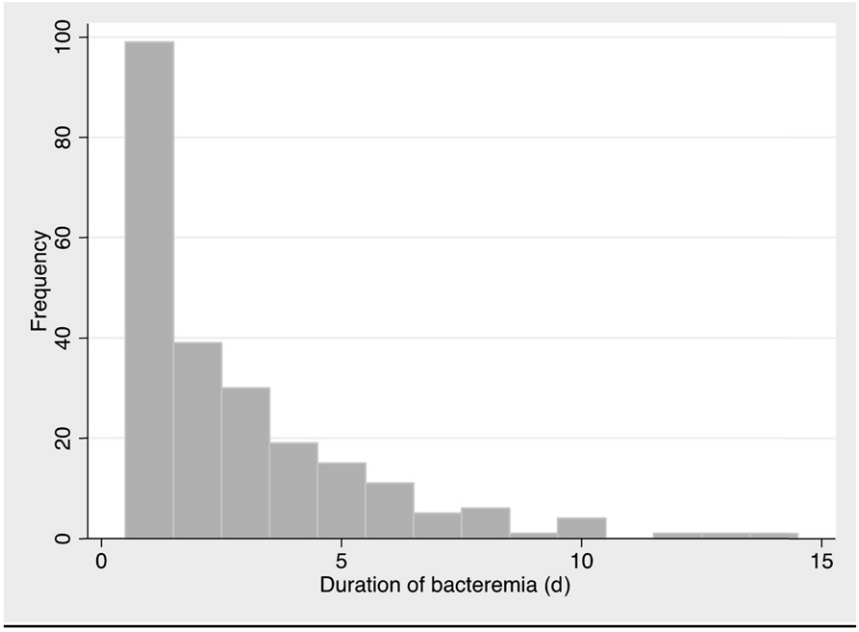

FIGURE 2
Distribution of the duration of MRSA bacteremia.

odds of treatment failure (Table 3). In the primary multivariable analysis limited to the 174 patients treated with vancomycin and with a steady-state vancomycin trough obtained, endovascular infection (odds ratio [OR], 4.63; 95% confidence interval [CI]: 0.83–25.7) and critical illness (OR, 2.99, 95% CI: 0.94–9.44) were associated with an increased odds of treatment failure, whereas catheter-related infection (OR, 0.36; 95% CI: 0.13–0.94) was associated with lower odds of treatment failure (Table 4). An initial vancomycin trough ≤10 μg/mL was not associated with treatment failure (OR, 1.34, 95% CI: 0.49–3.66).

TABLE 2 Clinical Outcomes of Children with MRSA Bacteremia

	Entire Cohort (*N* = 232)	Treated With Vancomycin and With Steady-State Trough (*n* = 174)	Treated With Vancomycin but No Steady-State Trough (*n* = 31)	Not Treated With Vancomycin (*n* = 27)
Treatment failure	72 (31.0)	60 (34.5)	9 (29.0)	3 (11.1)
Attributable mortality within 30 d	5 (2.2)	2 (1.2)	3 (9.7)	0 (0)
Duration of bacteremia, median, d (IQR)	2 (1–4)	2 (1–4)	2 (1–3)	1 (1–3)
Persistent bacteremia >3 d	64 (27.6)	54 (31.0)	7 (22.6)	3 (11.1)
Persistent bacteremia >5 d	30 (12.9)	26 (14.9)	3 (9.7)	1 (3.7)
Persistent bacteremia >7 d	24 (10.3)	16 (9.2)	2 (6.5)	1 (3.7)
Recurrence of bacteremia	7 (3.0)	6 (3.5)	1 (3.2)	0 (0)
Attributable readmission within 30 d	11 (4.7)	10 (5.7)	1 (3.2)	0 (0)
Duration of fever, median, d (IQR)	3 (2–7)	3.5 (2–8)	3 (2–6)	4 (1–6)
Any sequelae	54 (23.3)	43 (24.7)	9 (29.0)	2 (7.4)
Progression of infection	17 (7.3)	14 (8.1)	1 (3.2)	2 (7.4)
Septic emboli/thrombus	17 (7.4)	15 (8.6)	2 (6.5)	0 (0)
Metastatic focus of infection	16 (6.9)	12 (6.9)	5 (16.1)	0 (0)
Other[a]	3 (1.3)	3 (1.7)	2 (6.5)	2 (7.4)

Data are presented as *n* (%) unless otherwise noted.
[a] Other sequelae include development of stroke, need for amputation, or need for extracorporeal membranous oxygenation.

Risk Factors for Treatment Failure: Secondary Analyses

Because criteria for treatment failure of MRSA bacteremia has not been established in children, secondary analyses were performed with modifications of the primary outcome, including redefining persistent bacteremia as >5 days or >7 days, as well as including progression/sequelae of infection as part of the composite definition of treatment failure. These modifications to the outcome definition did not change the effect size of the clinical variables associated with treatment failure, nor did a secondary analysis that excluded the 17 neonates from the cohort.

To additionally explore these associations, a post hoc analysis was performed by including variables that were associated with treatment failure in univariable analyses (critical illness, endovascular, catheter-related infection, and treatment with an additional anti-MRSA antibiotic in the first 48 hours) in addition to the a priori determined variables from the primary analysis (musculoskeletal infection and race). Because the presence of a catheter and the presence of comorbid conditions were highly correlated with catheter-related bloodstream infection, these variables were not included in the post hoc analysis despite showing an association with treatment failure in univariable analysis. This analysis found endovascular infection (OR, 4.45, 95% CI: 1.09–18.2), musculoskeletal infection (OR, 2.4, 95% CI: 1.08–5.16), and critical illness (OR, 2.77, 95% CI: 1.02–7.5) to be associated with increased odds of treatment failure.

Finally, a multivariable logistic regression model examined the association between duration of bacteremia and the composite outcome of death or development of a complication (progression

of infection, metastatic focus of infection, or septic emboli), controlling for catheter-related infection, endovascular infection, surgical intervention for source control, critical illness, and institution. In this model, every 1-day increase in the duration of bacteremia was associated with a 50% increase in the odds of developing a complication (95% CI: 26%–79%). The unadjusted association between the duration of bacteremia and the development of complications or death is displayed in Fig 3.

DISCUSSION

This study explored the epidemiology and outcomes of MRSA bacteremia and examined the risk factors associated with treatment failure in children across 3 tertiary care children's hospitals. Musculoskeletal infections, endovascular infections, and critical illness were associated with an increased risk of treatment failure. Initial vancomycin trough and vancomycin MIC were not associated with treatment failure. For each additional day of MRSA bacteremia, the risk of developing complications increased by 50%.

In this cohort of hospitalized children with MRSA bacteremia, 78% of infections were community-onset, and the primary sources of infection were osteomyelitis (31%), catheter-related bloodstream infections (22%), and skin and soft tissue infections (16%), whereas endocarditis was an infrequent diagnosis (2%). The median observed duration of MRSA bacteremia in this cohort was 2 days, and only 10% persisted beyond 7 days. This finding is in contrast to the epidemiology of MRSA bacteremia in adults, in whom bacteremia is more frequently attributed to catheter-related infections (31%–36%),[7,15] endovascular infections (13%–15%),[7,8] or an unknown source (15%–20%),[7,8,15] and the

TABLE 3 Univariable Analyses of Risk Factors Associated With Treatment Failure Among Children With MRSA Bacteremia

	Treatment Failure *n/N* (%)	OR (95% CI)	*P*
Institution			.06
A	42/110 (38.2)	Ref	
B	18/65 (27.1)	0.65 (0.32–1.2)	
C	12/57 (21.1)	0.61 (0.21–0.91)	
Sex			.33
Girl	27/98 (27.6)	Ref	
Boy	45/134 (31.0)	1.33 (0.75–2.35)	
Race			.07
Non–African American	38/142 (26.8)	Ref	
African American	33/86 (38.4)	1.7 (0.96–3.01)	
Ethnicity			.14
Non-Hispanic	52/163 (31.9)	Ref	
Hispanic	4/24 (16.7)	0.43 (0.14–1.31)	
Insurance			.35
Private or self-pay	43/127 (33.9)	Ref	
Public	29/103 (28.2)	0.76 (0.44–1.35)	
Epidemiological category			.23
Community-onset	60/182 (33.0)	Ref	
Hospital-onset	12/50 (24.0)	0.64 (0.31–1.32)	
Comorbid condition at baseline			.03
None	42/111 (37.8)	Ref	
Yes (any)	30/121 (25.8)	0.54 (0.31–0.95)	
Indwelling device			.03
None	55/148 (37.2)	Ref	
Central venous catheter	11/57 (19.3)	0.40 (0.19–0.84)	
Other indwelling device	6/27 (22.2)	0.48 (0.18–1.27)	
Primary source			.003
Catheter-related[a]	10/52 (19.2)	Ref	
Musculoskeletal[b]	36/83 (43.4)	3.21 (1.42–7.27)	
Skin/soft tissue	9/42 (21.4)	1.15 (0.42–3.14)	
Pneumonia	7/21 (33.3)	2.1 (0.67–6.56)	
Endovascular[a]	7/11 (63.6)	7.35 (1.80–30.1)	
No source	1/11 (9.1)	0.42 (0.05–3.67)	
Other	2/12 (16.7)	0.84 (0.15–4.45)	
Time until anti-MRSA antibiotic			.84
0–1 d	68/218 (31.2)	Ref	
≥2 d	4/14 (28.6)	0.88 (0.27–2.91)	
Treated with vancomycin plus additional anti-MRSA antibiotic in the first 48 h			.02
No (vancomycin alone)	32/119 (27)	Ref	
Yes	37/86 (43)	2.05 (1.14–3.70)	
Critical illness[a]			.06
No	62/212 (29.5)	Ref	
Yes	10/20 (50.0)	2.42 (0.96–6.10)	
Initial vancomycin dose			.56
<50 mg/kg/d	41/117 (35.0)	Ref	
≥50 mg/kg/d	20/65 (30.8)	0.82 (0.43–1.58)	
First vancomycin serum trough[a,c]			.72
<5 μg/mL	22/58 (37.9)	Ref	
5 to <10 μg/mL	25/69 (36.2)	0.94 (0.46–1.92)	
10 to <15 μg/mL	9/28 (32.1)	0.81 (0.34–1.97)	
≥15 μg/mL	4/17 (23.5)	0.71 (0.24–2.09)	
Vancomycin MIC[d]			.24
MIC ≤ 1 μg/mL	62/198 (31.3)	Ref	
MIC = 2 μg/mL	3/17 (17.7)	0.47	
Source control intervention[a]			
None needed	13/46 (28.3)	Ref	.85
Within 3 d	29/95 (30.5)	1.11 (0.51–2.42)	
Delayed (>3 d)	30/91 (33.0)	1.25 (0.57–2.71)	

Ref, reference.

TABLE 3 Continued

[a] Variables selected a priori for inclusion in multivariate logistic regression model.

[b] Including osteomyelitis, septic arthritis, and pyomyositis.

[c] A first serum trough of >10 μg/mL compared with <10 μg/mL was our a priori–determined cutoff that we hypothesized may convey risk for treatment failure.

[d] Excluding data unknown for 17 isolates; a sensitivity analysis assuming MIC <1 and then MIC >1 for the 17 unknown isolates also found no significant association between MIC and treatment failure.

TABLE 4 Multivariable Logistic Regression Analysis for Odds of Treatment Failure Among Children With MRSA Bacteremia (n = 174)

	OR (95% CI)	*P*
Catheter-related	0.36 (0.13–0.94)	.038
Endovascular	4.63 (0.83–25.7)	.08
Vancomycin trough <10 μg/mL	1.34 (0.49–3.66)	.56
Critical illness	2.99 (0.94–9.44)	.06
Source control intervention		
None needed	Ref	
Within 3 d	1.14 (0.47–2.8)	.77
Delayed >3 d	1.35 (0.51–3.59)	.55

Ref, reference.

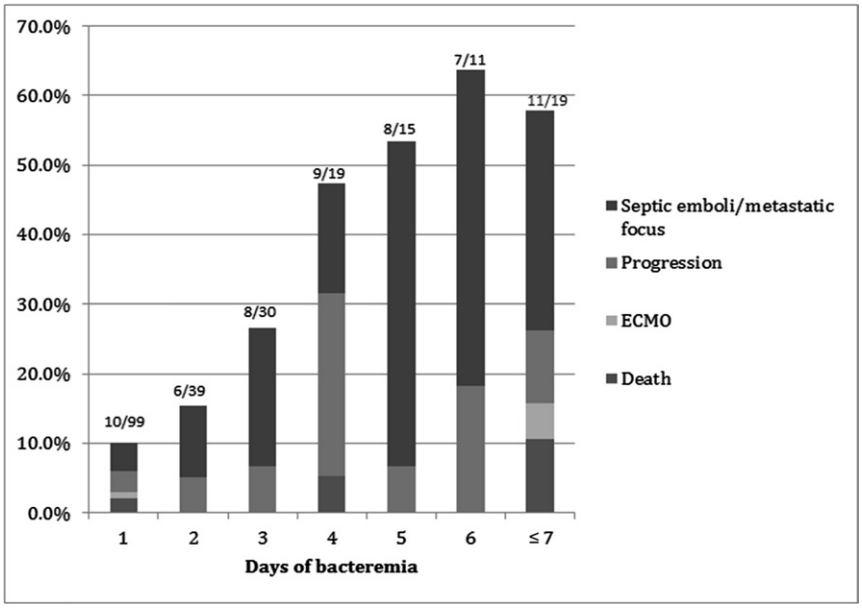

FIGURE 3
Proportion of children with complications or death, by duration of MRSA bacteremia. ECMO, extracorporeal membrane oxygenation.

durations of MRSA bacteremia are typically more prolonged (median duration of bacteremia is 8–9 days).[16] Differences in the epidemiology of MRSA bacteremia between children and adults emphasizes the need for dedicated pediatric studies to better understand the clinical characteristics and outcomes specific to children.

Similar to what has been observed in adults with MRSA bacteremia, 14% of children developed septic emboli or another metastatic focus of infection.[17,18] Each additional day of MRSA bacteremia was associated with a 50% increased odds of developing a complication. This association between the duration of bacteremia and the development of complications has been previously reported among adults with *S aureus* bacteremia[7] and provides important epidemiologic data that could inform decisions relating to the timing of additional imaging, such as echocardiograms, to identify metastatic foci.

Musculoskeletal infections and endovascular infections were associated with treatment failure, which might reflect the relatively higher burden of bacteria and/or decreased drug penetration into bone and endovascular infection sites. In studies of adults with MRSA bacteremia, endocarditis, pneumonia, and an unknown focus of infection have been associated with increased odds of treatment failure.[4,19] In the current study, catheter-related infections were associated with reduced odds of treatment failure. This finding is likely a reflection of these episodes being localized to the catheter and therefore potentially less invasive *S aureus* infections.

Vancomycin serum concentrations were not associated with treatment failure in our primary model that compared concentrations ≥10 μg/mL with <10 μg/mL. Although treatment failure was highest (37.9%) among those with a vancomycin trough concentration <5 μg/mL and lowest (23.5%) among those with a trough concentration ≥15 μg/mL, these differences were not statistically significant, potentially reflecting a lack of statistical power or the limitation of using trough concentrations as a surrogate for vancomycin exposure. Pharmacokinetic modeling studies have found that a trough of 7 to 10 μg/mL is associated with adequate vancomycin exposure for most pediatric patients,[20,21] and in 2 studies, analyses of smaller sample sizes of children with MRSA bacteremia (with 54 and 59 children, respectively) did not find a relationship between vancomycin MIC by automated methods or area under the curve/MIC ratio and clinical outcomes.[22,23] This finding raises questions about the necessity of routinely targeting higher trough concentrations (eg, 15 μg/mL, which is associated with an increased risk of

nephrotoxicity)[24] as is recommended for adults.[12] Additional studies focusing on of the association between vancomycin exposure and clinical outcomes in children are warranted.

This study has limitations. First, as a retrospective cohort study, the data rely on documentation from medical records and are subject to missing data. Misclassification of exposures and outcomes is a potential source of bias. To minimize potential misclassification, structured chart review was performed by using a standard data collection form across sites, with predefined definitions for each variable and adjudication by 2 pediatric infectious diseases physicians or pharmacists. Vancomycin exposure was measured by first steady-state serum trough only, which may not be the most accurate measure of vancomycin exposure[25] (although it is the current standard for therapeutic drug monitoring in most centers). Microbiologic methods depended on each institution's clinical microbiology laboratory for susceptibility testing, and although the automated platforms used by these institutions has shown >95% correlation in other studies,[26] they were not compared in this study. Vancomycin MICs determined by these methods may have underestimated the MIC determined by E-test, which some studies in adults have shown correlates more closely with outcomes.[27] The analysis of the association between the duration of bacteremia and the development of complications is subject to ascertainment bias, because prolonged bacteremia may have led to increased diagnostic imaging, which could have potentially inflated this association. Recognition of a thrombus after onset of bacteremia does not necessarily indicate that this finding was not present earlier. Furthermore, assessing cause and effect of this association is challenging, because prolonged bacteremia leading to complications and complications leading to prolonged bacteremia are both biologically plausible mechanisms. Finally, although this is the largest pediatric study of MRSA bacteremia to date, the sample size may have limited the power to detect associations where true differences exist, particularly in smaller subcategories of the analysis.

CONCLUSIONS

Although mortality among children with MRSA bacteremia was low (2%), nearly one-quarter of all patients experienced complications. Musculoskeletal infections and endovascular infections were associated with higher odds of treatment failure. The median duration of MRSA bacteremia among hospitalized children was 2 days, and each additional day of bacteremia increased the risk of complications substantially. Vancomycin trough concentrations or MICs were not associated with treatment failure. Future studies to determine the appropriate vancomycin dose, duration, and approach to therapeutic drug monitoring are warranted to optimize patient outcomes.

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ABBREVIATIONS

CI: confidence interval
IQR: interquartile range
MIC: minimum inhibitory concentration
MRSA: methicillin-resistant *Staphylococcus aureus*
OR: odds ratio

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Address correspondence to Rana F. Hamdy, MD, MPH, MSCE, Division of Infectious Diseases, Children's National Health System, 111 Michigan Ave NW, West Wing 3.5, Suite 100, Washington, DC 20008. E-mail: rhamdy@childrensnational.org

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