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MAJOR ARTICLE

Staphylococcus aureus Bacteremia in Pediatric Patients: Uncovering a Rural Health Challenge

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Background. *Staphylococcus aureus* bacteremia poses significant risk for morbidity and mortality. This may be exacerbated in rural populations facing unique health challenges.

Methods. To investigate factors influencing *S. aureus* bacteremia outcomes, we conducted a retrospective cohort study of children admitted to St. Louis Children's Hospital (SLCH) from 2011 to 2019. Exposures included rurality (defined by the Rural-Urban Continuum Code), Area Deprivation Index, and outside hospital (OSH) admission before SLCH admission. The primary outcome was treatment failure, a composite of 90-day all-cause mortality and hospital readmission.

Results. Of 251 patients, 69 (27%) were from rural areas; 28 (11%) were initially admitted to an OSH. Treatment failure occurred in 39 (16%) patients. Patients from rural areas were more likely to be infected with methicillin-resistant *S. aureus* (45%) vs urban children (29%; $P = .02$). Children initially admitted to an OSH, vs those presenting directly to SLCH, were more likely to require intensive care unit–level (ICU) care (57% vs 29%; $P = .002$), have an endovascular source of infection (32% vs 12%; $P = .004$), have a longer duration of illness before hospital presentation (4.1 vs 3.0 days; $P = .04$), and have delayed initiation of targeted antibiotic therapy (3.9 vs 2.6 days; $P = .01$). Multivariable analysis revealed rural residence (adjusted odds ratio [aOR], 2.3; 95% CI, 1.1–5.0), comorbidities (aOR, 2.9; 95% CI, 1.3–6.2), and ICU admission (aOR, 3.9; 95% CI, 1.9–8.3) as predictors of treatment failure.

Conclusions. Children from rural areas face barriers to specialized health care. These challenges may contribute to severe illness and worse outcomes among children with *S. aureus* bacteremia.

Keywords. Area Deprivation Index; bacteremia; rural health; Rural-Urban Continuum Code; *Staphylococcus aureus*.

Individuals living in underserved rural areas have been designated as a "health disparity population" by the National Institute on Minority Health and Health Disparities [1]. Adult residents of rural areas have worse health behaviors and health outcomes and access health services less frequently [2–4]. Mortality rates are higher among rural-dwelling individuals compared with their urban counterparts, even when controlling for poverty and age [2, 3]. A similar trend has been demonstrated in children; rural children have an annual mortality rate of 63 per 100 000 compared with 50 per 100 000 in urban children [2]. Alarmingly, the rural-urban disparity is growing, with the mortality gap increasing 5-fold from 1969 to 2009 [2]. The drivers of these poor outcomes are numerous and broad, including cultural, socioeconomic, and structural dynamics [5, 6]. Since 2010, more than 100 rural hospitals have closed [7]. Rural hospitals have fewer board-certified medical specialists and may lack on-site access to specialized diagnostic and therapeutic modalities, particularly for pediatric patients [8–10]. Despite these established health challenges, there is a paucity of research regarding the health outcomes of children in rural populations [11, 12].

Staphylococcus aureus bacteremia leads to significant morbidity and mortality in children. The rate of infection ranges from 1.5 to 3.5 per 1000 hospitalizations [13, 14]. Infection results in prolonged hospitalization, posing risk for complications; 10% of patients with *S. aureus* bacteremia develop septic emboli and metastatic infection [13, 14]. Additionally, these children have an increased risk of death, with mortality ranging from 2% to 15% [15–18]. Studies from Australia, the United Kingdom, and the United States demonstrate that infectious diseases (ID) consultation for *S. aureus* bacteremia improves management and outcomes; however, children residing in rural areas have limited access to pediatric ID subspecialists [4, 18–21]. As the impact of rural residence on pediatric *S. aureus* bacteremia outcomes is

Received 10 March 2023; editorial decision 25 May 2023; accepted 30 May 2023; published online 31 May 2023

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https://doi.org/10.1093/ofid/ofad296

unknown, we investigated the influence of rural residence and socioeconomic deprivation on outcomes in children with *S. aureus* bacteremia.

METHODS

Setting and Patients

This retrospective cohort study comprised 385 unique pediatric patients ranging from 0 to 24 years of age hospitalized with *S. aureus* bacteremia from January 2011 to December 2019 at St. Louis Children's Hospital (SLCH). SLCH is a 402-bed tertiary care hospital with ~13 000 admissions annually, serving patients from all 50 states and >80 countries, with a primary service region covering 6 states. Patients were either admitted directly to SLCH or admitted initially to an outside hospital (OSH; for a minimum of 24 hours) before being transferred to SLCH. Children with community-associated or community-onset health care-associated infections whose blood cultures were obtained within 48 hours of hospital admission (to an OSH or SLCH) and who were positive for *S. aureus* were eligible. Patients with hospital-onset infections were excluded (definitions provided in the Supplementary Data). Patients with positive blood cultures for which antibiotics were not prescribed (per provider notes and laboratory comments) were also excluded.

Patient Consent

This study was approved by the Washington University institutional review board with waiver of informed consent.

Data Collection

Electronic medical record review was performed to collect demographic and clinical factors that may be associated with *S. aureus* bacteremia and outcomes (Supplementary Data). Administration of targeted antibiotic therapy was based on *S. aureus* susceptibility: cefazolin, nafcillin, or oxacillin for methicillin-susceptible *S. aureus* (MSSA) and vancomycin, ceftaroline, or daptomycin for methicillin-resistant *S. aureus* (MRSA). Sufficient antibiotic therapy was defined as treatment with an antibiotic with potential antistaphylococcal activity, though not targeted (eg, clindamycin for MRSA or ceftriaxone for MSSA). Study data were managed with REDCap [22, 23].

Exposures and Outcomes

The primary objective of this study was to evaluate the impact of rural residence on clinical outcomes in pediatric patients with *S. aureus* bacteremia. The primary outcome was treatment failure, defined as a composite of all-cause 90-day mortality and 90-day hospital readmission in patients diagnosed with *S. aureus* bacteremia, congruent with other research in this area [24]. Secondary outcomes included length of hospitalization, length of bacteremia, and endovascular focus of infection. Exposures included rurality, primary admission to an OSH before transfer to SLCH, and Area Deprivation Index (ADI), as described below.

Rural-Urban Continuum Code

The first exposure evaluated in this study was the Rural-Urban Continuum Code (RUCC). The RUCC is a validated definition of rurality used by the US Department of Agriculture (USDA), which considers the population size as well as nearness to an urban center (Table 1). The RUCC ranges from 1 to 9, where 1 is the most urban and 9 is the most rural. The traditional rural/urban cutoff is between 3 and 4, with codes 1–3 considered urban and codes 4–9 considered rural [25].

Outside Hospital Admission

The second exposure evaluated was primary admission to an OSH before transfer to SLCH. A child was determined to have their primary admission at an OSH if they were admitted to any outlying hospital for a minimum of 24 hours before transfer to SLCH.

Area Deprivation Index

The third exposure evaluated was the ADI [26]. The ADI uses 9-digit zip codes corresponding to census block groups, allowing for the characterization of deprivation in small tracts with similar demographic and geographic features. This methodology uses a composite of variables (eg, education, employment, income, housing quality) to give a rank-based score quantifying disadvantage. As SLCH serves a multistate region in the Midwestern United States, our study used the national percentile, which assigns 1 as the least disadvantaged and 100 as the most disadvantaged [26]. We categorized percentiles into quartiles: Quartile 1 reflects the least disadvantaged 25% of the nation (ie, ADI 1–25), while quartile 4 represents the most disadvantaged 25% of the nation (ie, ADI 76–100).

Statistical Analysis

Descriptive statistics characterized the study population. Means and standard deviations were computed for data that were normally distributed; medians and interquartile ranges (IQRs) were computed for non–normally distributed data.

Table 1. Rural-Urban Continuum Code (RUCC)

Code	Description
1	Counties in metropolitan areas of 1 million population or more
2	Counties in metropolitan areas of 250 000 to 1 million population
3	Counties in metropolitan areas of fewer than 250 000 population[a]
4	Urban population of 20 000 or more, adjacent to a metropolitan area
5	Urban population of 20 000 or more, not adjacent to a metropolitan area
6	Urban population of 2500 to 19 999, adjacent to a metropolitan area
7	Urban population of 2500 to 19 999, not adjacent to a metropolitan area
8	Completely rural or less than 2500 urban population, adjacent to a metropolitan area
9	Completely rural or less than 2500 urban population, not adjacent to a metropolitan area

United States Department of Agriculture Economic Research Service, Rural-Urban Continuum Codes 2019 [25].

[a]The common cutoff for rural and urban is between RUCC 3 and RUCC 4.

Categorical variables were compared using chi-square analysis; continuous variables were analyzed using either independent-sample *t* tests or Mann-Whitney *U* tests. *P* values of ≤.05 were considered significant. Backward stepwise logistic regression was performed to analyze factors associated with treatment failure. Variables were initially selected based on statistical significance in univariate analysis, demographics, and expert input (Supplementary Data). At each step, variables were retained based on *P* values <.05. All statistical analyses were performed in SPSS, version 27, for Windows (IBM SPSS, Chicago, IL, USA).

RESULTS

A total of 385 unique pediatric patients with *S. aureus* bacteremia were identified. We excluded 29 due to having a blood culture deemed to be a contaminant and 105 with hospital-onset infections. Therefore, 251 patients were included in this study. Within this cohort, 148 (59%) children had a community-associated infection, while 103 (41%) had a health care–associated, community-onset infection. Patients were predominantly White (67%) and male (62%) (Table 2). Patients were more frequently diagnosed with MSSA bacteremia (66%) than MRSA bacteremia (34%). The median distance from the patients' homes to SLCH (IQR) was 31 (0–131) miles, and the median distance to an infectious diseases specialist (IQR) was 23 (0–104) miles. Twenty-eight children were diagnosed with bacteremia without an identified source (11%), while 223 (89%) had an additional source of infection including skin and soft tissue, pulmonary, musculoskeletal, endovascular, and hardware- and central line–associated infections. Of note, for children with central line–associated infections, the median time to removal of their infected central line (IQR) was 6 (2–36) days. Overall, 39 (16%) children experienced treatment failure within 90 days of initial hospital admission: 29 patients were readmitted within 90 days, and 12 died.

Rural vs Urban

Of 251 patients, 69 (27%) lived in an area designated as rural by the RUCC (Table 2). Patients from rural areas were predominantly White (88%) compared with urban children (58% White; $P \leq .001$). Age and sex did not differ significantly between the groups. Significant comorbidities (eg, malignancy, congenital heart disease, cystic fibrosis, and bowel abnormalities) were present similarly between urban-dwelling (47%) and rural-dwelling (49%) children. Fifteen rural children (22%) initially presented to an OSH, while 54 (78%) presented directly to SLCH. In comparison, 13 (7%) urban children presented initially to an OSH, and 169 (93%) presented directly to SLCH ($P = .001$). Of the rural children who presented directly to SLCH, 27 of 54 (50%) had a significant comorbidity. Children from rural areas were more likely to present with MRSA infection (45%) compared with urban children (29%, $P = .02$). The median distance rural patients traveled to SLCH (IQR) was 119 (80–161) miles, compared with 19 (10–40) miles traveled by urban patients. The median distance to a pediatric infectious diseases physician (IQR) was 105 (73–155) miles for rural children and 15 (7–28) miles for urban children. Endovascular infection was diagnosed in 23% of rural children compared with 11% of urban children ($P = .01$). Treatment failure was significantly higher among rural children (23%) compared with urban children (13%; $P = .04$).

Primary OSH Admission vs Entire Admission at SLCH

Twenty-eight (11%) of 251 children were admitted to an OSH (for at least 24 hours) before being transferred to SLCH. These OSHs ranged from small community hospitals with limited pediatric resources (23 patients) to medium-sized academic institutions with access to pediatric infectious diseases specialists (5 patients). These children spent an average (SD) of 2.9 (1.7) days at the OSH before transfer to SLCH (Table 3). Of the 28 children initially admitted to an OSH, 15 (54%) were from rural areas. Children initially presenting to an OSH did not differ significantly in age, sex, or race compared with children admitted to SLCH for the entirety of their hospitalization. Patients who were initially admitted to an OSH had a significantly higher incidence of MRSA infection (57%) vs those initially admitted to SLCH (30%; $P = .005$). Patients transferred from an OSH lived significantly farther from SLCH than children presenting directly to SLCH (median [IQR], 134 [33–235] miles vs 27 [0–113] miles, respectively; $P < .001$) or to pediatric infectious diseases specialists (116 [2–230] miles vs 21 [0–82] miles, respectively; $P < .001$). Children who were transferred had a significantly higher incidence of endovascular infection (32%) compared with those presenting directly to SLCH (12%; $P = .004$) and were significantly more likely to require ICU-level care (57% vs 29%, respectively; $P = .002$), ventilator support (43% vs 15%; $P \leq .001$), and inotropic support (29% vs 11%; $P = .01$). These patients also had a significantly longer mean duration of symptoms [SD] before initial hospitalization (4.1 [3.1] days) compared with children initially presenting to SLCH (3 [2.7] days; $P = .04$). The median time to infectious diseases consultation (IQR) was 4 (3–6) days for children initially admitted to an OSH and 2 (1–4) for children presenting directly to SLCH ($P = .002$). Optimal antibiotic management was also delayed for children first admitted to an OSH. The mean number of days to sufficient antibiotic therapy (SD) was 2.6 (2.9) days for children transferred from an OSH and 1.5 (2) days for children initially admitted to SLCH ($P = .01$). The mean number of days to targeted antibiotic therapy (SD) was 3.9 (2.8) days for children transferred from an OSH and 2.6 (2.4) days for children initially admitted to SLCH ($P = .01$). Children initially admitted to an OSH had a longer total duration of bacteremia (mean [SD], 3.6 [2.7] days) than children first

Table 2. Patient Characteristics by Rural vs Urban Residence (per Rural-Urban Continuum Code Classification)

Variable	Total (n = 251), No. (%)	Rural (n = 69), No. (%)	Urban (n = 182), No. (%)	*P*
Age, mean (SD), y	7.9 (±5.5)	8.0 (±5.3)	7.8 (±5.6)	.76
Sex				
Female	94 (38)	22 (32)	72 (40)	.26
Male	157 (62)	47 (68)	110 (60)	
Race				
White	167 (67)	61 (88)	106 (58)	<.001
African American and "other" races[a]	84 (33)	8 (12)	74 (42)	
Staphylococcal susceptibility				
MRSA	84 (34)	31 (45)	53 (29)	.02
MSSA	167 (66)	38 (55)	129 (71)	
Initial admission to SLCH vs OSH				
SLCH	223 (89)	54 (78)	169 (93)	.001
OSH	28 (11)	15 (22)	13 (7)	
Distances				
Distance from patient's home to SLCH, median (IQR), mi	31 (11–112)	119 (80–161)	19 (10–40)	<.001
Distance from patient's home to nearest pediatric ID specialist, median (IQR), mi	23 (10–92)	105 (73–155)	15 (7–28)	<.001
Infection entity[b]				
Bacteremia without focus	28 (11)	6 (9)	22 (12)	.45
Central line–associated infection	42 (17)	10 (15)	32 (18)	.56
Musculoskeletal infection	122 (49)	38 (55)	84 (46)	.21
Endovascular focus	36 (14)	16 (23)	20 (11)	.01
Pulmonary infection	31 (12)	8 (12)	23 (13)	.82
Skin and soft tissue infection[c]	36 (14)	13 (19)	23 (13)	.21
Other diagnosis (urinary tract infection/pyelonephritis, gastrointestinal tract, central nervous system)	29 (12)	6 (9)	23 (13)	.38
Severity of illness				
Duration of symptoms before initial hospitalization, mean (SD), d	3.14 (±2.8)	3.4 (±2.6)	3.1 (±2.8)	.38
Complicated bacteremia (≥3 d)[d]	176 (70)	52 (75)	124 (68)	.26
Required a surgical procedure	109 (43)	32 (46)	77 (43)	.56
Time to surgical debridement (osteomyelitis only, n = 77), mean (SD), d	5.2 (±3.9)	4.8 (±3.9)	5.5 (±4)	.52
ICU admission	80 (32)	22 (32)	58 (32)	.99
Required ventilator support	46 (18)	15 (22)	31 (17)	.39
Required inotropic support	33 (13)	10 (15)	23 (13)	.70
Presence of instrumentation at infection site	33 (13)	5 (7)	28 (15)	.09
Comorbidities[e]	120 (48)	34 (49)	86 (47)	.78
Structural heart condition	15 (6)	7 (10)	8 (4)	.09
Cystic fibrosis	6 (2)	3 (4)	3 (2)	.20
Malignancy	11 (4)	5 (7)	6 (3)	.20
Outcomes				
Duration of bacteremia, mean (SD), d	2.6 (±2.3)	2.7 (±2)	2.6 (±2.4)	.67
Duration of hospitalization (including stay at OSH), mean (SD), d	13 (±26)	11 (±9)	14 (±30)	.47
Musculoskeletal infection complications (n = 122)[f]	25 (20)	18 (21)	7 (18)	.70
Treatment failure[g]	39 (16)	16 (23)	23 (13)	.04
90-d mortality	12 (5)	5 (7)	7 (4)	.26
90-d readmission	29 (12)	12 (17)	17 (9)	.08

Means and SDs were computed for data that were normally distributed; medians and interquartile ranges were computed for non–normally distributed data.

Abbreviations: ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; OSH, outside hospital; SLCH, St. Louis Children's Hospital.

[a]African American 74, Asian 5, biracial 2, Pacific Islander 1, Native American 1, other not specified 1.

[b]Categories are not mutually exclusive (eg, a patient could have skin infection, pneumonia, and osteomyelitis); *P* value of chi-square analysis is 1 entity vs all other entities.

[c]Including infections resulting from skin breakdown (eg, burns).

[d]Complicated bacteremia was defined as the patient having 1 or more of these factors: duration of bacteremia >3 days, fever >72 hours, metastatic disease, or endocarditis.

[e]Comorbidities include severe prematurity, congenital anomalies, malignancy, cystic fibrosis, structural heart conditions, etc.

[f]Musculoskeletal infection complications included chronic osteomyelitis, pathologic fracture, chronic pain or limp, and leg length discrepancy.

[g]Treatment failure: a composite of 90-day all-cause mortality and 90-day all-cause hospital readmission.

Table 3. Characteristics of Patients Admitted Initially to an Outside Hospital vs St. Louis Children's Hospital

Variable	Total (n = 251), No. (%)	OSH (n = 28), No. (%)	SLCH (n = 223), No. (%)	*P*
Age, mean (SD), y	7.9 (±5.5)	9.2 (±5.9)	7.7 (±5.5)	.17
Sex				
Female	94 (38)	14 (50)	80 (26)	.15
Male	157 (62)	14 (50)	143 (64)	
Race				
White	167 (67)	22 (79)	143 (64)	.13
African American and "other" races[a]	84 (33)	6 (21)	80 (36)	
Staphylococcal susceptibility				
MRSA	84 (34)	16 (57)	68 (30)	.005
MSSA	167 (66)	12 (43)	155 (70)	
Rural vs urban residence				
Rural	69 (28)	15 (54)	54 (24)	.001
Urban	182 (72)	13 (46)	169 (76)	
Distances				
Distance from patient's home to SLCH, median (IQR), mi	31 (11–112)	134 (33–235)	27 (0–113)	<.001
Distance from patient's home to nearest pediatric ID specialist, median (IQR), mi	23 (10–92)	116 (2–230)	21 (0–82)	<.001
Infection entity[b]				
Bacteremia without focus	28 (11)	4 (14)	24 (11)	.58
Central line–associated infection	42 (17)	2 (7)	40 (18)	.15
Musculoskeletal infection	122 (49)	14 (50)	108 (48)	.88
Endovascular focus	36 (14)	9 (32)	27 (12)	.004
Pulmonary infection	31 (12)	6 (21)	25 (11)	.12
Skin and soft tissue infection[c]	36 (14)	4 (14)	32 (14)	.99
Other diagnosis (urinary tract infection/pyelonephritis, gastrointestinal tract, central nervous system)	29 (12)	4 (14)	25 (11)	.63
Severity of illness				
Duration of symptoms before initial hospitalization, mean (SD), d	3.1 (±2.8)	4.1 (±3.1)	3.0 (±2.7)	.04
Complicated bacteremia (≥3 d)[d]	176 (70)	22 (79)	154 (69)	.30
Required surgical procedure	109 (43)	13 (46)	96 (43)	.73
Time to surgical debridement (osteomyelitis only, n = 77), mean (SD), d	5.2 (±3.9)	7.6 (±5.5)	4.8 (±3.6)	.09
ICU admission	80 (32)	16 (57)	64 (29)	.002
Required ventilator support	46 (18)	12 (43)	34 (15)	<.001
Required inotropic support	33 (13)	8 (29)	25 (11)	.01
Presence of instrumentation at infection site	33 (13)	6 (21)	27 (12)	.17
Comorbidities[e]	120 (48)	12 (43)	108 (48)	.58
Structural heart condition	15 (6)	2 (7)	13 (6)	.78
Cystic fibrosis	6 (2)	1 (4)	5 (2)	.70
Malignancy	11 (4)	0 (0)	11 (5)	.20
Diagnostics				
Echocardiogram (any)	46 (18)	7 (25)	39 (18)	.33
Echocardiogram (following 3 positive cultures)	35 (34)	12 (39)	23 (32)	.54
Time to echocardiogram, median (IQR), d	3 (2–6)	5.5 (2–14)	3 (2–4)	.04
All appropriate labs[f]	112 (45)	15 (54)	97 (44)	.31
Blood culture proof of cure[g]	234 (93)	27 (96)	207 (93)	.47
Time to obtain radiology study (osteomyelitis only, n = 77), mean (SD), d	3 (±3.2)	3.77 (±3.4)	2.9 (±3.1)	.34
Outcomes				
ID consult obtained	182 (73)	24 (86)	158 (71)	.10
Time to ID consultation, median (IQR), d	2 (1–4)	4 (3–6)	2 (1–4)	.002
Empiric antibiotic therapy sufficient for any *S. aureus* type (includes OSH)	188 (75)	19 (68)	169 (76)	.36
Days to empiric antibiotic therapy sufficient for any *S. aureus* type, mean (SD) (n = 188)	1.6 (±2)	2.3 (±2.2)	1.5 (±1.9)	.06
Empiric antibiotic therapy sufficient for MSSA (includes OSH)	239 (95)	27 (96)	212 (95)	.75
Days to empiric antibiotic therapy sufficient for MSSA, mean (SD) (n = 239)	1.5 (±1.9)	2.1 (±2.1)	1.5 (±1.9)	.10
Days to initiating sufficient antibiotic therapy (including OSH), mean (SD)[h]	1.7 (±2.2)	2.6 (±2.9)	1.5 (±2)	.01
Days treated with sufficient antibiotics for *S. aureus* bacteremia,[h] mean (SD)	38 (±52)	35 (±27)	38 (±54)	.72
Received targeted antibiotic therapy[i]	221 (88)	26 (93)	195 (87)	.41

Table 3. Continued

Variable	Total (n = 251), No. (%)	OSH (n = 28), No. (%)	SLCH (n = 223), No. (%)	*P*
Days to targeted antibiotic therapy, mean (SD) (n = 221)	2.8 (±2.4)	3.9 (±2.8)	2.6 (±2.4)	.01
Duration of bacteremia, median (SD), d	2.6 (±2.3)	3.6 (±2.7)	2.5 (±2.2)	.02
Duration of hospitalization, median (IQR), d	8 (5–14)	13 (7–21)	7 (5–13)	.03
Treatment failure[j]	39 (16)	5 (18)	34 (15)	.72
90-d mortality	12 (5)	1 (4)	11 (5)	.75
90-d readmission	29 (12)	4 (14)	25 (11)	.63

Means and SDs were computed for data that were normally distributed; medians and interquartile ranges were computed for non–normally distributed data.

Abbreviations: CBC, complete blood count; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; OSH, outside hospital; SLCH, St. Louis Children's Hospital.

[a]African American 74, Asian 5, biracial 2, Pacific Islander 1, Native American 1, other not specified 1.

[b]Categories are not mutually exclusive (eg, a patient could have skin infection, pneumonia, and osteomyelitis); *P* value of chi-square analysis is 1 entity vs all other entities.

[c]Including infections resulting from skin breakdown (eg, burns).

[d]Complicated bacteremia was defined as the patient having 1 or more of these factors: duration of bacteremia >3 days, fever >72 hours, metastatic disease, or endocarditis.

[e]Comorbidities include severe prematurity, congenital anomalies, malignancy, cystic fibrosis, structural heart problems, etc.

[f]Appropriate labs includes CBC, ESR, and CRP for all patients and vancomycin trough and creatinine for children who received 3 doses or 2 days of vancomycin.

[g]Proof of cure is 2 consecutive negative cultures following a positive culture.

[h]Sufficient therapy: antibiotic therapy with antisstaphylococcal activity, but not targeted therapy.

[i]Targeted therapy: antibiotic therapy based on *S. aureus* susceptibility. For MSSA, targeted therapy includes cefazolin, nafcillin, and oxacillin. For MRSA, targeted therapy includes vancomycin, ceftaroline, and daptomycin.

[j]Treatment failure: a composite of 90-day all-cause mortality and 90-day all-cause hospital readmission.

admitted to SLCH (mean [SD], 2.5 [2.2] days; $P = .02$) and a longer total duration of hospitalization (median length of stay [IQR], 13 [7–21] days vs 7 [5–13] days, respectively; $P = .03$). Overall, treatment failure was similar between children transferred from an OSH and those initially admitted to SLCH (18% and 15%, respectively).

Area Deprivation Index

Of the 251 patients included in the study, 15 (6%) resided in ADI quartile 1 (ie, the least disadvantaged 25%), 51 (20%) in quartile 2, 70 (28%) in quartile 3, and 115 (46%) in quartile 4 (ie, the most disadvantaged) (Table 4). Of the 69 rural children per RUCC designation, 46 (66%) resided in an area classified as ADI quartile 4, while 38% of urban children resided in quartile 4 ($P \leq .001$). None of the children residing in rural areas were categorized into quartile 1. Children living in more disadvantaged areas were more likely to be diagnosed with MRSA, while children living in more advantaged areas were more likely to be diagnosed with MSSA. The MRSA incidence increased across quartiles: 8% in quartile 1, 25% in quartile 2, 27% in quartile 3, and 40% in quartile 4 ($P = .007$). ADI was not associated with treatment failure.

Multivariable Logistic Regression Analysis

In the multivariable model (Table 5), treatment failure was associated with rural residence (adjusted odds ratio [aOR], 2.3; 95% CI, 1.1–5.0), comorbidities (aOR, 2.9; 95% CI, 1.3–6.2), and need for ICU admission (aOR, 3.9; 95% CI, 1.9–8.3).

DISCUSSION

Pediatric *S. aureus* bacteremia is a serious infection that can lead to significant morbidity and mortality. Rural health systems face many challenges, particularly for patients needing a higher level of medical care. These challenges include a paucity of resources to provide specialized care, including lack of access to subspecialists and inability to perform specialized diagnostic and imaging studies or surgical procedures. This is especially true for pediatric patients and may lead to a delay in diagnosis and ultimately delayed treatment [4, 10, 27–31]. Thus, patients residing in rural areas who present to a local hospital may require transfer to larger tertiary care centers for the management of invasive infections. This study aimed to determine the impact of rural residence and admission to an OSH before transfer to SLCH on the clinical outcomes of children with *S. aureus* bacteremia. Importantly, we found that children residing in rural areas were more likely to experience treatment failure. Additionally, even when controlling for comorbidities, we found that primary admission to an OSH was correlated with a higher level of acuity upon admission to SLCH. Lastly, we determined that children with *S. aureus* bacteremia living in rural areas and areas with higher levels of deprivation had a higher incidence of MRSA infection. These findings underscore the urgent need to address the significant health disparities faced by children residing in rural areas to ultimately improve child health.

Our models demonstrated that treatment failure was more than twice as likely among children residing in rural areas

Table 4. Factors Associated With Area Deprivation Index

Variable	Total (n = 251), No. (%)	ADI 1 (n = 15), No. (%)	ADI 2 (n = 51), No. (%)	ADI 3 (n = 70), No. (%)	ADI 4 (n = 115), No. (%)	*P*
Race						
White	167 (100)	13 (8)	34 (21)	52 (32)	65 (39)	.02
African American and other races[a]	84 (100)	2 (2)	16 (19)	18 (21)	50 (58)	
Staphylococcal susceptibility						
MRSA	84 (100)	2 (2)	9 (11)	25 (30)	48 (57)	.007
MSSA	167 (100)	13 (8)	42 (25)	45 (27)	67 (40)	
Patient resides >70 mi from a pediatric infectious disease physician						
Yes	77 (100)	1 (1)	8 (10)	26 (34)	42 (55)	.005
No	174 (100)	14 (8)	43 (25)	44 (25)	73 (42)	
Rural vs urban residence						
Rural	69 (100)	0 (0)	4 (6)	19 (28)	46 (66)	<.001
Urban	182 (100)	15 (8)	47 (26)	51 (28)	69 (38)	
Outcomes						
Treatment failure	39 (100)	2 (5)	6 (15)	15 (39)	16 (41)	.44
90-d mortality	12 (5)	0 (0)	3 (6)	5 (7)	4 (4)	.54
90-d readmission	29 (12)	2 (13)	4 (8)	10 (14)	13 (11)	.74

ADI percentiles were categorized into quartiles: Quartile 1 reflects the least disadvantaged 25% of the nation (ie, ADI 1–25), while quartile 4 represents the most disadvantaged 25% of the nation (ie, ADI 76–100).

Abbreviations: ADI, Area Deprivation Index; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

[a]Other races: African American 74, Asian 5, biracial 2, Pacific Islander 1, Native American 1, other not specified 1.

Table 5. Factors Associated With Treatment Failure, Multivariable Logistic Regression Model

Covariate	aOR (95% CI)
Residence	
Rural	2.3 (1.1–5.0)
Urban	Ref
Age, y[a]	0.9 (0.9–1.0)
Comorbidities[b]	
Yes	2.9 (1.3–6.2)
No	Ref
Intensive care unit admission	
Yes	3.9 (1.9–8.3)
No	Ref

Hosmer Lemeshow test = 0.92; Nagelkerke R^2 = 0.194 (the model explains nearly 20% of the variation of the outcome). Other variables that were included but did not remain in the final model included race, sex, endovascular focus of infection, duration of symptoms before initial hospitalization, antibiotic susceptibility (MSSA vs MRSA), and initial admission to an OSH.

Abbreviations: aOR, adjusted odds ratio; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

[a]aOR represents each year of age increase.

[b]Comorbidities include severe prematurity, congenital anomalies, malignancy, cystic fibrosis, or structural heart problem.

compared with urban-dwelling children. This finding was independent of initial presentation to an OSH, suggesting that the factors driving the association between rurality and treatment failure are multifactorial. These factors likely include underlying systemic issues of disadvantage, more so than where one presents for care. This aligns with prior studies demonstrating that children with cancer living in rural areas had worse survival outcomes [32]. Moreover, half of the children residing in rural areas presented directly to SLCH for care. Of these children presenting directly to SLCH, half had underlying comorbidities, including malignancy or cystic fibrosis, which placed them at increased risk for severe infection. Importantly, these children have an established relationship with subspecialists at the academic medical center. In prior studies, given concerns regarding lack of local resources, parents of children with complex health needs have described a desire to present directly to the specialty care center, even for emergent care, rather than seeking care from a local hospital [31].

Our analysis demonstrated that patients who were transferred to SLCH after initial admission to an OSH had a higher acuity of illness, frequently requiring ICU admission, as well as a higher incidence of endovascular infection. These children also had a more prolonged illness before presenting for medical care, presenting a full day after the onset of illness. This delayed presentation has been previously described among rural populations in Australia and the United States and is likely attributable to access to care, lack of specialists, and social and economic factors (eg, missed time from work, disruption to family routine, poverty, and transportation) [4, 31, 33, 34]. Furthermore, these children had a delay in the management of their *S. aureus* bacteremia, including a longer time from hospital admission to diagnostic studies and initiation of targeted antibiotics. As many of the OSH did not have an infectious diseases specialist, infectious diseases consultation, which has been demonstrated to improve the quality of care and patient outcomes, was also delayed [18–21]. Overall, delays in diagnostic evaluation and treatment likely contributed to prolonged bacteremia, a predisposing factor for the development of

endovascular or metastatic infection, and hence a longer duration of hospitalization [13, 14, 20]. These delays highlight the need for partnerships between community hospitals and tertiary care centers to avoid these undesirable outcomes.

Among our population of pediatric patients with *S. aureus* bacteremia, the incidence of MRSA, compared with MSSA, infection was higher among children from rural areas. Antibiotic overuse has been demonstrated to drive antimicrobial resistance. Two separate studies conducted using pediatric Medicaid claims data from Kentucky and West Virginia found that antibiotic prescription rates were highest among rural-dwelling children [35, 36]. Thus, antibiotic overuse could be a driver of the higher incidence of MRSA detected among children from rural areas in our study population. Moreover, previous research has attributed higher rates of MRSA infection to lower socioeconomic status and associated living conditions [16, 37–41]. Thus, the higher incidence of MRSA infection among rural children may also be attributable to living conditions associated with overall lower socioeconomic status. Indeed, a large proportion of our rural patients resided in areas within ADI quartile 4, the most "disadvantaged" group. Similar to the present study, in a study of children with cystic fibrosis in Alabama, rural residence was correlated with a higher level of deprivation, as determined by the ADI. Moreover, this study demonstrated that children living in deprived areas had a 2-fold increased risk for MRSA infection compared with those not living in deprived areas [39]. In sum, the finding of higher incidence of MRSA infection among children residing in rural areas can impact the treatment of children presenting with an illness for which *S. aureus* is a likely pathogen. Rural physicians, or physicians at tertiary medical centers caring for patients from rural areas, need to be aware that this patient population is at an increased risk for MRSA infection, and thus empiric antimicrobial therapy should include coverage for MRSA.

The strengths of this study include applying multiple approaches (including rurality, outlying hospital care, and socioeconomic deprivation) to understand factors driving treatment failure among children with *S. aureus* bacteremia. While previous studies of pediatric rural health disparities have been conducted among children with chronic conditions (eg, malignancy and cystic fibrosis), this study evaluated outcomes among children with acute infections [4, 31, 39].

Several limitations are also of note. The first is the use of the RUCC as our indicator of rurality. The RUCC is a rural classification used by the USDA Economic Research Service to characterize "trends in nonmetro areas that are related to population density and metro influence" [25]. While this indicator is a useful baseline method, it was not created with health care in mind. The ideal classification system would focus on access to health care (eg, hospitals, primary care physicians, subspecialists), considerations for pediatric patients (as an adult subspecialist may not be equipped to care for children), recreational facilities and parks, and healthy food options. The second limitation is the potential bias that children of a higher acuity were transferred to SLCH for care, and those experiencing less severe illness may have been successfully treated at their local community hospital. However, the infrastructure to conduct clinical outcomes research at community hospitals is limited, and we were not able to obtain data regarding the overall incidence of *S. aureus* bacteremia in children at these outlying hospitals. To fully understand the clinical characteristics and management of children with *S. aureus* bacteremia and associated outcomes, a prospective multicenter study comprising community hospitals and tertiary care centers is needed. Third, this study was conducted at a single center and thus may not be generalizable to other regions of the United States or the world, particularly countries with differing health systems. Fourth, as there is no consensus regarding outcomes across studies of pediatric *S. aureus* bacteremia, we selected the composite of all-cause 90-day mortality and 90-day hospital readmission as our primary outcome measure, an outcome used in adult studies [20, 24, 42]. As mortality is rare among children with *S. aureus* bacteremia, determining an alternative, more optimal, measure would be of great benefit to the field. Finally, the retrospective nature of this project limited our data analysis to existing documentation, which could be mitigated through a prospective, multicenter study.

CONCLUSIONS

This study revealed a collision of social determinants of health impacting rural children, including a willingness to access care, the threshold that families use to determine when to seek care, and the ability to access pediatric subspecialists, diagnostics, and treatment. These factors intermingle with a potentially life-threatening illness to create a complex medical scenario. Children with *S. aureus* bacteremia from rural or resource-deprived areas, as well as those admitted to outlying hospitals, are at risk for adverse outcomes. A contributing factor to the state of health in rural areas is lack of research funding; only 1% of the National Institutes of Health budget is allocated to rural health, although nearly 20% of the US population lives in these areas. Strategies to address health disparities among rural populations are desperately needed. Highlighted by the recent COVID-19 pandemic, telemedicine allows patients to seek care from hours away in their own homes, in their primary care provider's office, or at a local hospital [43]. This solution is by no means perfect, with limited exam capacity and rural areas that often lack access to quality broadband internet [44]. However, access to specialists through telemedicine is undeniably valuable and has been shown to be acceptable to patients [45–49]. To overcome rural health disparities, specialized physicians in large academic centers can take multiple actions. First, foster professional relationships with their rural

colleagues, allowing for phone or email consultation, opportunities for telemedicine consultation, and established referral partners. Second, develop clinical practice guidelines and educational opportunities with rural primary care physicians. Third, advocate for a nursing coordinator who can act as a liaison between local health care providers and specialists at the academic medical center [4]. These care coordinators can help to prevent delays in care, assist families in the challenges of navigating a large metropolitan health center, and ensure appropriate follow-up after hospital discharge, ultimately yielding improved health outcomes.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Financial support. This work was supported by the Children's Discovery Institute of Washington University and St. Louis Children's Hospital; National Institutes of Health (NIH)/National Center for Advancing Translational Sciences (grant numbers UL1-TR002345 and TL1-TR002344 to K.J.W.); and the Agency for Healthcare Research and Quality (AHRQ; grant number R01-HS024269 to S.A.F.).

Disclaimer. These funding sources had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or AHRQ.

Potential conflicts of interest. All authors: no reported conflicts.

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