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CLINICAL RESEARCH ARTICLE

The impact of infectious diseases consultation for children with *Staphylococcus aureus* bacteremia

Kyle J. Whittington[1]✉, Yinjiao Ma[2], Anne M. Butler[2], Patrick G. Hogan[1], Faria Ahmed[1], JessieAnn Flowers[1], Grace Milburn[1], John J. Morelli[1], Jason G. Newland[1] and Stephanie A. Fritz[1]✉

BACKGROUND: Despite clear benefit of improved outcomes in adults, the impact of infectious diseases (ID) consultation for *Staphylococcus aureus* bacteremia in children remains understudied.
METHODS: To assess the impact of pediatric ID consultation on management and outcomes, we conducted a cohort study of children with *S. aureus* bacteremia at St. Louis Children's Hospital from 2011 to 2018. We assessed adherence to six established quality-of-care indicators (QCIs). We applied propensity score methodology to examine the impact of ID consultation on risk of treatment failure, a composite of all-cause mortality or hospital readmission within 90 days.
RESULTS: Of 306 patients with *S. aureus* bacteremia, 193 (63%) received ID consultation. ID consultation was associated with increased adherence to all QCIs, including proof-of-cure blood cultures, indicated laboratory studies, echocardiography, source control, targeted antibiotic therapy, and antibiotic duration. Obtaining proof-of-cure blood cultures and all indicated laboratory studies were associated with improved outcomes. In propensity score-weighted analyses, risk of treatment failure was similar among patients who did and did not receive ID consultation. However, the number of events was small and risk estimates were imprecise.
CONCLUSIONS: For children with *S. aureus* bacteremia, ID consultation improved adherence to QCIs, some of which were associated with improved clinical outcomes.

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IMPACT:

- In children with *Staphylococcus aureus* bacteremia, consultation by an infectious diseases (ID) physician improved adherence to established quality-of-care indicators (QCIs).
- The current literature regarding ID consultation in pediatric *S. aureus* bacteremia is sparse. Three prior international studies demonstrated improved quality of care with ID consultation, though results were disparate regarding clinical outcomes.
- This article impacts the current literature by strengthening the evidence that ID consultation in children improves adherence to QCIs, and demonstrates that adherence to QCIs improves clinical outcomes.

BACKGROUND

Staphylococcus aureus bacteremia is a serious illness with potential for adverse outcomes. The rate of this infection in children ranges from 1.5 to 3.5 per 1000 hospitalizations.[1,2] Among pediatric patients, *S. aureus* bacteremia poses risk for significant morbidity, including metastatic infection and prolonged hospitalization.[1,2] Moreover, the mortality incidence in children with *S. aureus* bacteremia ranges from 2 to 6%,[1,3–5] and is as high as 15% in patients with cardiac conditions.[6]

Despite the morbidity and mortality associated with pediatric *S. aureus* bacteremia, factors driving outcomes remain understudied. In contrast, modifiable risk factors are better understood for adults with *S. aureus* bacteremia, for whom fatality rates range from 15 to 25%.[7–9] An important factor impacting outcomes in adults with *S. aureus* bacteremia is consultation by an infectious diseases (ID) specialist, which is associated with a 50% reduction in morbidity and mortality.[7,8,10,11] In adult populations, thorough diagnostic evaluation, targeted antibiotic treatment, and an appropriate length of antibiotic therapy have been demonstrated to improve clinical outcomes for patients with *S. aureus* bacteremia.[7,9,11,12] Hence, several transdisciplinary, multinational groups of clinicians have derived quality-of-care measures for the management of *S. aureus* bacteremia. These quality-of-care measures focus on diagnostics, monitoring, and treatment and are associated with improved outcomes (Table 1).[11,13] In adult patients, ID consultation confers a greater likelihood of management adhering to these quality-of-care indicators (QCIs).[7,9,11,12]

In the pediatric population, data are lacking regarding the best management strategies for children with *S. aureus* bacteremia, including the impact of ID consultation. Two single-institution

[1]Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA. [2]Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA. ✉email: wkyle@wustl.edu; fritz.s@wustl.edu

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Table 1. Quality-of-care indicator definitions.

Quality-of-care indicator	Definition
Proof-of-cure blood culture	Documentation of two negative blood cultures following a positive blood culture[13]
Indicated labs	Receipt of indicated labs at any time including CBC, CMP, ESR, and CRP for all patients; vancomycin trough and creatinine for children who received 3 doses or 2 days of vancomycin
Echocardiogram	Performance of echocardiogram in patients with structural heart anomalies or complicated bacteremia[a]
Source control	A composite of surgical procedure to remove the source of infection (e.g., osteomyelitis) or removal of infected central venous catheter or instrumentation[b] [16]
Targeted antibiotic therapy	The use of vancomycin, ceftaroline, or daptomycin for children diagnosed with MRSA infection and cefazolin, oxacillin, or nafcillin for children diagnosed with MSSA infection[13,18]
Duration of targeted antibiotics	Duration of therapy for a minimum of 14 days for children with a primary diagnosis of bacteremia or in cases for which a source could not be identified[13,16]

QCI quality-of-care indicator, *CBC* complete blood count, *CMP* comprehensive metabolic panel, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-susceptible *S. aureus*.

[a]Complicated bacteremia is defined as the patient having one or more of these factors: duration of bacteremia ≥3 days, fever >72 h, metastatic disease, or endocarditis.[13]

[b]Instrumentation includes prosthetic heart valve, prosthetic cardiac shut or patch, implantable cardiac defibrillator, ventricular assist device, spinal or other orthopedic hardware, ventricular shunt, baclofen pump, or dialysis catheter.

studies of children with *S. aureus* bacteremia conducted in Australia ($n = 100$) and the United Kingdom ($n = 63$) evaluated the impact of ID consultation.[4,14] Both studies demonstrated that ID consultation was associated with improved diagnostics, laboratory monitoring, and targeted antibiotic therapy; the larger study demonstrated reduced mortality in children receiving ID consultation.[4,14] An additional multicenter study, also conducted in Australia, provided further evidence that ID consultation was associated with reduced mortality.[15] While these results suggest there are multiple benefits from ID consultation, these studies may have limited generalizability due to innate differences in geography, epidemiology, and medical systems.

The objective of this study was to investigate the impact of ID consultation on adherence to six established QCIs in US children with *S. aureus* bacteremia. We also sought to estimate the effect of ID consultation on treatment failure, defined as a composite of all-cause mortality or hospital readmission within 90 days. Importantly, we used propensity score methodology (underutilized in prior studies) in the treatment failure analysis to account for potential confounding by severity of illness and other important factors.

METHODS

Setting and patients

We conducted a cohort study comprised of 306 patients aged 0–24 years with *S. aureus* bacteremia hospitalized at St. Louis Children's Hospital (SLCH), a 402-bed tertiary care center, from January 2011 to May 2018. Children with one or more blood cultures positive for *S. aureus* for which antibiotic treatment was administered were eligible. Patients with positive blood cultures for which antibiotics were not prescribed (per provider notes and laboratory comments) were excluded. In August 2016, SLCH instituted a formal handshake stewardship antibiotic stewardship program. This study was approved by the Washington University institutional review board.

Data collection

Electronic medical records were reviewed to abstract demographic and clinical factors including primary clinical service; ID consultation; clinical diagnosis; blood culture results; *S. aureus* susceptibility (methicillin-susceptible or -resistant); location of infection onset (community or hospital); antibiotic administration; vital signs; imaging and laboratory studies; presence of a central venous catheter or instrumentation; surgical procedures for source control; ICU admission; ventilator, inotropic, or extracorporeal membrane oxygenation support; and outcomes.

Exposures and outcomes

Exposures. The primary exposure was the receipt of timely ID consultation, defined as a formal ID consultation within 6 days of collection of the initial positive blood culture. In clinical practice, the large majority of ID consultations occur within this 6-day time period. Our secondary exposure was the receipt of targeted antibiotic therapy (i.e., the antibiotic administered while the patient was bacteremic). The definition of targeted therapy was dependent on *S. aureus* susceptibility: for MSSA, targeted therapy included cefazolin, nafcillin, or oxacillin. For MRSA, targeted therapy included vancomycin, ceftaroline, or daptomycin.[16,17]

Outcomes. We assessed the adherence to six factors previously established as QCIs in patients diagnosed with *S. aureus* bacteremia (Table 1) to test the hypothesis that ID consultation would improve adherence to these QCIs.[11,13] We also tested the hypothesis that ID consultation is associated with improved clinical outcomes in pediatric patients with *S. aureus* bacteremia. Specifically, we used the clinical outcome of treatment failure, defined as a composite of 90-day all-cause mortality or 90-day all-cause hospital readmission. In addition, we tested whether exposure to targeted antibiotic therapy, based on *S. aureus* susceptibility, reduced treatment failure.

Other definitions

Blood culture proof-of-cure was defined as two consecutive negative blood cultures following a positive blood culture.[3] Complicated bacteremia was defined as the duration of bacteremia ≥3 days, fever >72 h, metastatic disease (defined as a deep, distal, or secondary[17] infection, anatomically unrelated to the primary site of infection), or endocarditis.[17] Source control was defined as a composite of surgical intervention, central venous catheter removal, or instrumentation removal, when applicable. Community infection was defined as a positive blood culture for *S. aureus* obtained within the first 48 h of hospital admission (see Supplementary methods for further detail).

Statistical analysis

We compared the distribution of adherence to QCIs and treatment failure by exposure groups. Differences were assessed using χ^2 tests for categorical variables, and independent sample *t*-tests or Mann–Whitney *U* tests for continuous variables. Differences in proportions of ID consultation by year of hospital admission were performed using χ^2 for trend analysis. *P* values ≤0.05 were considered significant.

To examine the relationship between ID consultation and treatment failure, we used Cox proportional hazards models to estimate unadjusted and propensity score-weighted hazard ratios (HRs). Standardized mortality ratio (SMR) weights were calculated from a propensity score using multivariable logistic regression, where the propensity score represented the probability that a patient received ID consultation versus no ID consultation, accounting for baseline covariates selected a priori based on expert knowledge (age, race, sex, primary service, year of admission, staphylococcal susceptibility, infection entity, and targeted antibiotic therapy, Supplementary Table 1).

We used similar methods to examine the relationship between receipt of targeted antibiotic therapy and treatment failure. Specifically, SMR weights

were calculated from two separate propensity scores representing the probability that targeted antibiotic therapy was initiated (1) −1 to 2 days in relation to the index date (defined here as the date the first positive blood culture was drawn) versus 3–6 days from the index date; or (2) −1 to 2 days versus no initiation of targeted antibiotic therapy between 0 and 6 days from the index date, accounting for baseline covariates (age, race, sex, primary service, year of admission, ID consult performed, comorbidities, infection entity, and infection onset).

SMR weights were computed from propensity scores, equal to 1 for children in the reference group and equal to the propensity odds (i.e., propensity score/[1 − propensity score]) for children in the other group. SMR weights allowed us to standardize the covariate distribution in each comparator cohort to that in the reference cohort. Thus, under the assumption of no unmeasured confounding, our exposure comparisons would be unconfounded with respect to their effect on the outcome.

We calculated absolute standardized mean differences of baseline covariates in the unweighted and SMR-weighted populations to determine whether weighting the population reduced imbalances of observed covariates and made the treatment groups more exchangeable (defined by absolute standardized mean difference <0.10; Supplementary Tables 2 and 3).[18] We used robust variance estimators to calculate 95% confidence intervals (CIs). We verified the proportional hazards assumption with an interaction term between (log) time and treatment. In the analysis comparing patients with and without timely ID consultation, patients categorized as no timely ID consultation (i.e., no ID consultation within 6 days of collection of the initial positive blood culture) were censored upon receipt of late ID consultation (i.e., ID consultation occurring 7 days or more after blood draw). In the analysis comparing patients for whom targeted antibiotic therapy was initiated −1 to 2 days versus no antibiotic therapy, patients were censored upon receipt of antibiotics after day 2.

RESULTS

Of 306 patients hospitalized with *S. aureus* bacteremia from January 2011 to May 2018, 193 (63%) received ID consultation. The median time from the date of collection of the initial positive blood culture to ID consultation was 3 days for patients receiving ID consultation (interquartile range [IQR] 0, 3). Patient sex and race did not differ between patients who did or did not receive ID consultation (Table 2); however, children receiving ID consultation were older (mean 7.3 ± 5.9 years) compared to those not receiving consultation (5.3 ± 6.3 years; $P = 0.005$). Seventy-three percent of children receiving ID consultation had a community-onset infection compared to 58% without ID consultation ($P = 0.005$). While 84% of patients in the general pediatric and surgery services received ID consultation, this was less frequent for children in the PICU (63%), NICU (43%), and in the hematology/oncology service (20%; $P = 0.001$).

The proportion of patients with *S. aureus* bacteremia who received ID consultation increased between 2011 and 2018 from 50 to 90% (χ^2 for trend, $P = 0.001$, Fig. 1). ID consultation was more likely for patients with musculoskeletal infection (93%) and endovascular foci (94%) and less likely for patients with central venous catheter-associated infections (46%) and in cases of *S. aureus* bacteremia with no identifiable source (33%). Of the children receiving ID consultation, 72% were diagnosed with complicated bacteremia versus 36% of those without ID consultation ($P < 0.001$); 49% of the ID consultation group had underlying conditions versus 87% of those without ID consultation ($P < 0.001$; Table 2).

Children receiving ID consultation were more likely to have fulfilled all 6 QCIs when compared to the group without ID consultation (Fig. 2a), including proof-of-cure blood cultures (95% with consultation versus 84% without; $P = 0.002$), all indicated laboratory studies (46% versus 8%; $P < 0.001$ [Fig. 2b]), echocardiography when indicated (e.g., structural heart anomalies or complicated bacteremia; 32% versus 15%, $P = 0.03$), source control when indicated (e.g., removal of infected central venous catheter or instrumentation; 57% versus 28%; $P < 0.001$), targeted antibiotic therapy (92 versus 71%; $P < 0.001$), and appropriate duration of targeted antibiotic therapy (evaluated in patients with bacteremia without a focus, median [IQR] 14 days [2–16] versus 9 [5–23], $P = 0.004$ [Table 2]). We also assessed the relationship between QCI fulfillment and treatment outcomes (Table 3). Treatment success was associated with proof-of-cure blood cultures (93% versus 87% in those with treatment failure, $P = 0.05$) and obtaining all indicated laboratory studies (39% versus 20% in failure; $P = 0.001$).

Patients receiving ID consultation were more likely to receive targeted antibiotic therapy (92%) compared to those without ID consultation (71%; $P < 0.001$, Fig. 2a). The composite outcome of treatment failure was significantly higher in patients not receiving ID consultation (46%) compared to those receiving consultation (31%). When performing propensity score analysis our unweighted, crude model reflected an increased HR (1.56; 95% CI 1.03–2.38) for children who did not receive consultation.

Univariate analysis of factors associated with treatment failure demonstrated no significant difference in demographic factors or *S. aureus* susceptibility (Table 3). Patients with treatment failure were more likely to have hospital-onset infection (40%, versus 29% of those with treatment success; $P = 0.05$), central venous catheter-associated infections (31% versus 20%; $P = 0.03$), underlying conditions (87% versus 50%; $P < 0.001$), and to require ICU-level care (63% versus 43%; $P = 0.001$).

Propensity score-weighted analysis

We observed similar weighted risks of treatment failure between children who did, versus those who did not, receive ID consultation (HR, 1.03; 95% CI 0.69–1.53) after accounting for age, race, year of admission, sex, staphylococcal susceptibility, infection entity, targeted antibiotic therapy, and primary service (Table 4). In considering the timing of initiation of targeted antibiotic therapy, we accounted for age, sex, race, ID consultation, primary service, comorbidities, infection onset, infection entity, and year of admission. Similar weighted risks of treatment failure were observed between patients for whom targeted antibiotic therapy was initiated −1 to 2 days in relation to the index date (date the first positive blood culture was collected) and those for whom targeted therapy was initiated 3–6 days after the index date (HR, 1.05; 95% CI 0.59–1.87). However, the number of events was small and risk estimates were imprecise.

DISCUSSION

ID consultation has been demonstrated to be an important part of the management of adults and children with *S. aureus* bacteremia. This study is the first to demonstrate that ID consultation resulted in a greater likelihood of adherence to multinational derived QCIs leading to appropriate diagnostics, monitoring, and treatment, factors that have been associated with fewer rehospitalizations and deaths.[11,13]

We also estimated the effect of ID consultation on the risk of treatment failure while accounting for potential confounding variables such as the severity of illness, through the use of propensity score analysis. Crude results showed modest benefit of ID consultation; however, weighted results did not demonstrate that ID consultation was associated with decreased treatment failure. Effect estimates for these analyses were imprecise given the small numbers of events in our single-institution study. Furthermore, this study included both community-onset and hospital-onset infections which may differ in their potential for adverse outcomes. Future multicenter studies are needed to investigate this research question.

Although QCIs have not been ascertained for pediatric patients, we adapted 6 QCIs established for the adult population derived by Hadano et al. to assess diagnostic evaluation and treatment practices performed among children with *S. aureus* bacteremia.[11] In a multicenter study of children with *S. aureus* bacteremia, each day of bacteremia was associated with 50% increased odds of

Table 2. Patient characteristics by receipt of infectious diseases consultation.

Variable	Total, $N = 306$ (%)	No ID consult, $N = 113$ (%)	ID consult, $N = 193$ (%)	*P*
Age, years, median (IQR)	4.5 (0, 16)	2.6 (0, 13)	6.7 (0, 17)	<0.001
Sex[a]				
Female	122 (40)	42 (37)	80 (42)	0.46
Male	184 (60)	71 (63)	113 (58)	
Race[a]				
White	204 (67)	71 (63)	133 (69)	0.29
African American and "Other" races[b]	102 (33)	42 (37)	60 (31)	
Staphylococcal susceptibility				
MRSA	105 (34)	32 (28)	73 (38)	0.09
MSSA	201 (66)	81 (72)	120 (62)	
Infection onset				
Community	206 (67)	65 (58)	141 (73)	0.005
Hospital	100 (33)	48 (42)	52 (27)	
Primary service				
General medicine and surgery	117	19 (17)	98 (51)	<0.001
PICU	73	27 (24)	46 (24)	
NICU	49	28 (25)	21 (11)	
Hematology/oncology	35	28 (25)	7 (3)	
Other medicine specialties[c]	32	11(9)	21 (11)	
Infection entity[d]				
Bacteremia without focus	51 (17)	34 (30)	17 (9)	<0.001
Central-line-associated infection	71 (23)	39 (35)	32 (17)	<0.001
Musculoskeletal infection	99 (32)	7 (6)	92 (48)	<0.001
Endovascular focus	32 (11)	2 (2)	30 (16)	<0.001
Pulmonary infection	46 (15)	18 (16)	28 (15)	0.74
Skin and soft tissue infection[e]	37 (12)	13 (12)	24 (12)	0.81
Other diagnosis (urinary tract infection/pyelonephritis, gastro-intestinal sources, central nervous system sources)	38 (12)	7 (6)	31 (16)	0.01
Severity of illness				
Underlying condition[f]	193 (63)	98 (87)	95 (49)	<0.001
Complicated bacteremia[g]	179 (59)	41 (36)	138 (72)	<0.001
Instrumentation at infection site	43 (14)	12 (11)	31 (16)	0.19
ICU admission	153 (50)	59 (52)	94 (48)	0.55
Required ventilator support	106 (35)	46 (41)	60 (31)	0.09
Required inotropic support	64 (21)	22 (20)	42 (22)	0.63
Other outcomes				
Duration of targeted antibiotics for bacteremia without focus, days, median (IQR) ($N = 51$)	10 (3, 17)	9 (2, 16)	14 (5, 23)	0.004
Time to targeted antibiotic therapy[h], median, days (IQR), $N = 257$	1 (0, 2)	2 (0, 4)	1 (0, 2)	0.27
Length of hospital admission, median, days (IQR)	12 (0, 39)	14 (0, 62)	12 (0, 35)	0.50
Duration of bacteremia, median, days (IQR)	1 (1, 3)	1 (1, 2)	2 (1, 5)	<0.001
Death attributable to *S. aureus* bacteremia	6 (2)	4 (4)	2 (1)	0.41

ID infectious diseases, *SD* standard deviation, *IQR* interquartile range, *NICU* neonatal intensive care unit, *PICU* pediatric intensive care unit, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-susceptible *S. aureus*.

[a]Sex and race $N = 298$ due to 8 patients who were evaluated for multiple instances of *S. aureus* bacteremia.

[b]Other races include Asian, American Indian, biracial, and "Other, Not Specified".

[c]Other medicine specialties include cardiology, gastroenterology, infectious diseases (classified as ID consult group), neurology, nephrology, and pulmonology.

[d]Categories are not mutually exclusive (e.g., a patient could have skin infection, pneumonia, and osteomyelitis); *P* value of χ^2 analysis is one entity vs all other entities.

[e]Including infections resulting from skin breakdown (e.g., burns).

[f]Underlying conditions include: severe prematurity, congenital anomalies, malignancy, or cystic fibrosis.

[g]Complicated bacteremia defined as the patient having one or more of these factors: duration of bacteremia ≥3 days, fever >72 h, metastatic disease, or endocarditis.

[h]Time to targeted therapy was calculated from the date of the collection of the initial positive blood culture to the date of the first dose of targeted antimicrobial therapy.

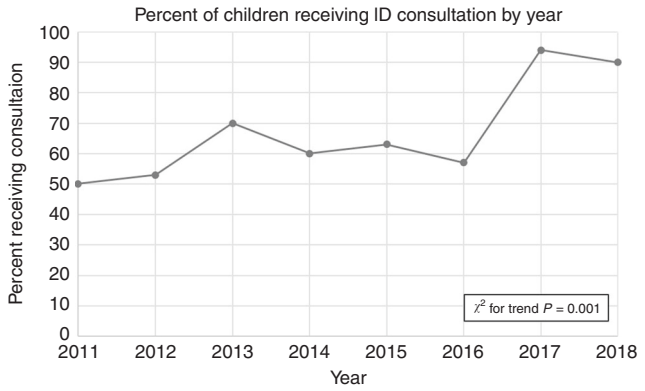

Fig. 1 Children with *Staphylococcus aureus* bacteremia receiving pediatric infectious diseases consultation by the year. The year 2018 includes only January through May. A formal handshake antibiotic stewardship program was initiated in August 2016.

sequelae, including hematogenous complications or metastatic foci.[19] Thus, obtaining daily blood cultures to monitor response to antibiotic therapy, and ultimately demonstrating clearance of bacteremia, is imperative to reduce this risk. Moreover, as prolonged bacteremia may reflect endocarditis or another focus of infection, investigation of the source of prolonged bacteremia, including echocardiogram or other imaging, is necessary to ensure sources are identified and controlled. In the present study, the length of bacteremia in patients receiving ID consultation was longer than in children without ID consultation, which may be reflective of a delay in further diagnostic evaluation until consultation was requested. Children receiving ID consultation were more likely to undergo the indicated monitoring laboratory studies as well as proof-of-cure blood cultures, echocardiography, source control, and targeted antibiotic therapy. Proof-of-cure blood cultures and monitoring laboratory studies were, in turn, associated with a reduction in treatment failure.

ID consultation has been demonstrated to improve morbidity and mortality among adult patients with *S. aureus* bacteremia.[7]

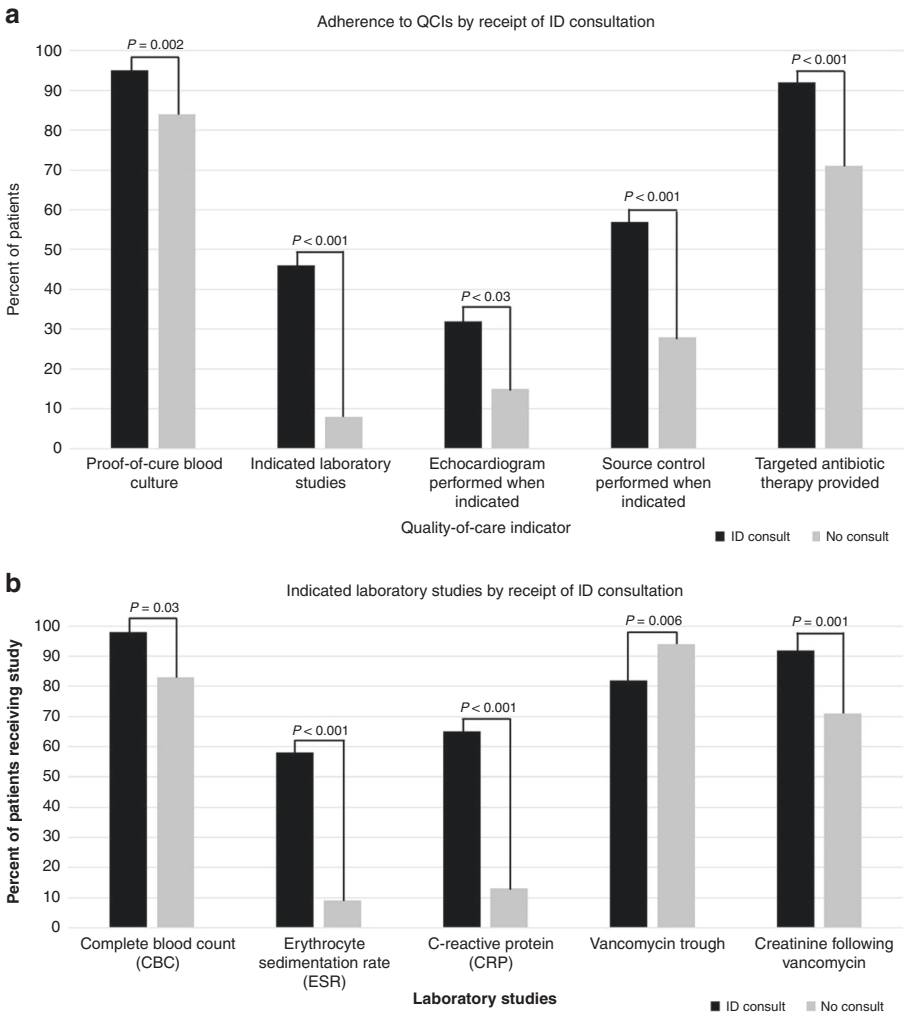

Fig. 2 ID consultation results in QCI fulfillment. a Adherence to quality care indicators by receipt of pediatric infectious diseases consultation. **b** Individual indicated laboratory studies by receipt of pediatric infectious diseases consultation. ID infectious diseases, QCI quality-of-care indicators. Proof-of-cure was considered two negative blood cultures following a positive blood culture. The indicated laboratory studies included CBC, ESR, and CRP for all patients and vancomycin trough and creatinine for children who received at least 3 doses, or 2 days, of vancomycin ($N = 248$). An echocardiogram was indicated if the patient had complicated bacteremia (defined as the duration of bacteremia ≥3 days, fever >72 h, metastatic disease, or endocarditis) or presence of structural heart condition ($N = 174$). Source control was a composite of a surgical procedure to debride the source of infection (e.g., osteomyelitis) or removal of an infected central venous catheter or instrumentation ($N = 172$). Targeted antibiotic therapy was defined for MSSA as nafcillin, oxacillin, or cefazolin and for MRSA bacteremia as vancomycin, ceftaroline, or daptomycin.

Table 3. Adherence to quality-of-care indicators and other measures by treatment success.

Quality-of-care indicators	Total, $N = 306$ (%)	Treatment success, $N = 195$ (%)	Treatment failure, $N = 111$ (%)	P
Proof-of-cure blood culture[a]	278 (91)	182 (93)	96 (87)	0.05
Indicated laboratory studies[b]	97 (32)	75 (39)	22 (20)	0.001
CBC	294 (96)	188 (97)	106 (96)	0.69
ESR	122 (40)	96 (49)	26 (23)	<0.001
CRP	140 (46)	107 (55)	33 (30)	<0.001
Vancomycin trough[c]	214 (86)	124 (82)	90 (93)	0.02
Creatinine following vancomycin[c]	215 (87)	128 (85)	87 (90)	0.27
Echocardiogram performed when indicated[d]	49 (28)	29 (25)	20 (33)	0.30
Source control performed when indicated[e]	84 (48)	56 (51)	28 (44)	0.39
Targeted antibiotic therapy[f]	257 (84)	164 (84)	93 (84)	0.94
Duration of targeted antibiotics for bacteremia without focus, median, (IQR) ($N = 51$)	10 (3, 17)	10 (4, 16)	8.5 (0, 21)	0.83
Other factors				
Age, years, median (IQR)	4.5 (0, 16)	5.1 (0, 16)	3.4 (0, 14)	0.91
Sex[g]				
Female	122 (40)	80 (41)	42 (38)	0.58
Male	184 (60)	115 (59)	69 (62)	
Race[g]				
White	204 (67)	134 (69)	70 (63)	0.33
African American and "Other" races[h]	102 (33)	61 (31)	41 (37)	
Staphylococcal susceptibility				
MRSA	105 (34)	61 (31)	44 (40)	0.14
MSSA	201 (66)	134 (69)	67 (60)	
Infection onset				
Community	206 (67)	139 (71)	67 (60)	0.05
Hospital	100 (33)	56 (29)	44 (40)	
Infection entity[i]				
Bacteremia without focus	51 (17)	25 (13)	26 (23)	0.17
Central-line-associated infection	72 (24)	38 (20)	34 (31)	0.03
Musculoskeletal infection	99 (32)	85 (44)	14 (13)	<0.001
Endovascular focus	32 (11)	20 (10)	12 (11)	0.88
Pulmonary infection	47 (15)	26 (13)	21 (27)	0.19
Skin and soft tissue infection[j]	37 (12)	24 (12)	13 (12)	0.88
Other diagnosis (urinary tract infection/pyelonephritis, gastrointestinal sources, central nervous system sources)	38 (12)	25 (13)	13 (12)	0.98
Severity of illness				
Time to consult median, days, (IQR)	1 (0, 3)	1 (0, 3)	1 (0, 4)	0.51
Underlying condition[k]	193 (63)	97 (50)	96 (87)	<0.001
Complicated bacteremia[l]	179 (59)	118 (61)	61 (55)	0.34
Instrumentation in place at infection site	43 (14)	19 (10)	24 (22)	0.004
ICU admission	153 (50)	83 (43)	70 (63)	0.001
Required ventilator support	106 (35)	55 (28)	51 (46)	0.002
Required inotropic support	64 (21)	31 (16)	33 (30)	0.004

IQR interquartile range, *NICU* neonatal intensive care unit, *PICU* pediatric intensive care unit, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-susceptible *S. aureus*.

[a]Proof of cure is two negative blood cultures following a positive blood culture.

[b]Indicated laboratory studies include CBC, ESR, CRP, for all patients and vancomycin trough and creatinine for children who received 3 doses or 2 days of vancomycin.

[c]Following a minimum of 3 doses of vancomycin, $N = 248$.

[d]Echocardiogram indicated if complicated bacteremia (defined as the patient having one or more of these factors: duration of bacteremia ≥3 days, fever >72 h, metastatic disease, or endocarditis) or presence of structural heart condition, $N = 174$.

[e]Source control is a composite of surgical procedure to remove the source of infection (e.g., osteomyelitis) or removal of infected central venous catheter or instrumentation, $N = 172$.

[f]Targeted therapy is defined as nafcillin, oxacillin, or cefazolin for children with MSSA bacteremia and vancomycin, ceftaroline, or daptomycin for children with MRSA bacteremia.

[g]Sex and race $N = 298$ due to 8 patients who were evaluated for multiple instances of *S. aureus* bacteremia.

[h]Other races include Asian, American Indian, biracial, and "Other, Not Specified".

[i]Categories are not mutually exclusive (e.g., a patient could have skin infection, pneumonia, and osteomyelitis); *P* value of χ^2 analysis is one entity vs all other entities.

[j]Including infections resulting from skin breakdown (e.g., burns).

[k]Underlying conditions include: severe prematurity, congenital anomalies, malignancy, or cystic fibrosis.

[l]Complicated bacteremia defined as the patient having one or more of these factors: duration of bacteremia ≥3 days, fever >72 h, metastatic disease, or endocarditis.

Table 4. Propensity score-weighted hazard ratio estimates for composite outcome of 90-day hospital readmission or mortality.

Exposure group	*N*	Number of events	Crude HR (95% CI)	Weighted hazard ratio
ID consultation model[a]	292	88		
Consultation	182		1.00 (reference)	1.00 (reference)
No consultation	110		1.56 (1.03–2.38)	1.03 (0.69–1.53)
Antibiotic therapy model[b]	232	62		
Early targeted therapy −1 to 2[c] days	183		1.00 (reference)	1.00 (reference)
No targeted therapy	49		1.22 (0.70–2.21)	0.81 (0.40–1.63)
Timing of targeted antibiotic therapy model[b]	241	72		
Early targeted therapy −1 to 2[c] days	183		1.00 (reference)	1.00 (reference)
Late targeted therapy 3 to 6[c] days	58		1.68 (1.03–2.74)	1.05 (0.59–1.87)

[a]Analyses accounted for age, race, sex, primary service, year of admission, staphylococcal susceptibility, infection entity, and targeted antibiotic therapy.
[b]Analyses accounted for age, race, sex, primary service, year of admission, ID consult performed, comorbidities, infection entity, and infection onset.
[c]In relation to index date.

Three prior studies, two in Australia and one in the United Kingdom, evaluated the impact of ID consultation for pediatric patients with *S. aureus* bacteremia.[4,14,15] Despite differences in healthcare systems, cohort size, study design, and statistical methodology, there are common findings among these studies and the present study. ID consultation was less frequent among patients cared for by ICU services as well as the hematology/oncology service. Moreover, patients with hospital-onset infections and those with central-line-associated infections were also less likely to receive ID consultation. Lastly, patients not receiving ID consultation were more likely to be diagnosed with bacteremia without source, potentially reflecting an incomplete diagnostic workup. Across studies, ID consultation improved diagnostic evaluation and management, including echocardiography and proof-of-cure blood cultures, identified focus of infection and/or optimized source control, and improved choice and duration of directed antibiotic therapy. Among both Australian cohorts, children receiving ID consultation had a reduced mortality or had a higher likelihood of cure, defined as the absence of death or documented bacteremia relapse at 30 days. Importantly, in the present study, children who were diagnosed with hospital-onset infections, needed ICU-level care, had a central venous catheter-associated infection, and had underlying conditions (e.g., malignancy) were all more likely to suffer treatment failure, highlighting the need for collaboration between ID and other subspecialty services.

Among pediatric patients, mortality due to *S. aureus* bacteremia is fortunately uncommon; in the present cohort, only six deaths (2%) were attributable to *S. aureus* bacteremia. Thus, specifying appropriate outcome measures is an important consideration when evaluating the impact of a component of care, such as ID consultation. As reflected in this study, QCIs may represent the best markers of improved care. Indeed, patients with proof-of-cure blood cultures and monitoring laboratory studies had a decreased likelihood of treatment failure. To our knowledge, these findings are unique and bring to light the value of monitoring objective labs in critically ill children. In particular, patients for whom CRP and ESR were measured had improved outcomes. Monitoring these objective inflammatory markers may signal the need for further source control or other intervention, and may guide antibiotic management, which may in turn contribute to better outcomes.

The present investigation used propensity score modeling in an attempt to control for the severity of illness and thus minimize potential confounding bias. We undertook this method with the hypothesis that ID physicians were more likely to be consulted for children with higher severity of illness, a factor that may be associated with an increased likelihood of treatment failure. Although our unadjusted analysis demonstrated benefit with ID consultation, our propensity score analysis demonstrated a similar incidence of treatment failure between groups. However, our analyses are complicated by several issues. The non-randomized nature of the exposure allows for the possibility of unmeasured confounders, such as those related to the severity of illness, due in part to the complex nature of the study with a variety of human elements, which may have biased the results to the null.

Given the potential consequences of *S. aureus* bacteremia, measures to improve management, and thus outcomes, are urgently needed. Lloyd et. al. conducted a quasi-experimental study to assess an electronic health record Best Practice Advisory (BPA) that recommended ID consultation and targeted antibiotic therapy (based on MRSA or MSSA) for all patients with *S. aureus* bacteremia.[20] One year following BPA implementation, 100% of patients with *S. aureus* bacteremia received ID consultation. Moreover, time to targeted antibiotic therapy significantly decreased following the intervention. Previous studies have demonstrated that the implementation of antimicrobial stewardship programs (ASPs) increases ID consultation.[21] Indeed, at our institution, a formal ASP was implemented in August of 2016, after which over 90% of children with *S. aureus* bacteremia received ID consultation. Lastly, additional measures to implement quality care measures and evidence-based practices include institutional clinical practice guidelines and standardized order sets. These interventions can be especially valuable in rural and other underserved areas where access to specialists is limited.[22]

This large pediatric study quantifying the impact of ID consultation for patients with *S. aureus* bacteremia is unique in its use of propensity score methodology to account for clinical and demographic differences (e.g., severity of illness) between exposure groups. This study also has several limitations. While this is a large pediatric cohort, our sample size ($N = 306$) was smaller than optimal for propensity score methodology, resulting in imprecise effect estimates, demonstrated by the wide CIs. Data from adult studies, several pediatric studies, and now this study, support ID consultation. A mortality benefit in these prior studies and an improvement in recognized quality indicators for optimal outcomes support ID consultations for children with *S. aureus* bacteremia. Additional analyses are needed that incorporate larger patient populations to further support these recommendations. Furthermore, our single-center study may not be fully generalizable regarding clinical practice and patient outcomes.

In conclusion, we found that ID consultation improved diagnostics, monitoring, and treatment, which were associated with improved outcomes in pediatric patients with *S. aureus* bacteremia. Additional strategies such as improved collaboration between subspecialty teams and development of multispecialty

clinical practice guidelines can improve clinical management of patients with *S. aureus* bacteremia, limit complications, and minimize morbidity and mortality.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Hamdy, R. F., Dona, D., Jacobs, M. B. & Gerber, J. S. Risk factors for complications in children with *Staphylococcus aureus* bacteremia. *J. Pediatrics* **208**, 214–220.e2 (2019).
2. Kumarachandran, G., Johnson, J. K., Shirley, D. A., Graffunder, E. & Heil, E. L. Predictors of adverse outcomes in children with *Staphylococcus aureus* bacteremia. *J. Pediatr. Pharm. Ther.* **22**, 218–226 (2017).
3. Cardenas-Comfort C, Kaplan SL, Vallejo JG, McNeil JC. Follow-up blood cultures in children with *Staphylococcus aureus* bacteremia. *Pediatrics* **146**, e20201821 (2020).
4. Duguid RC, Al Reesi M, Bartlett AW, Palasanthiran P, McMullan BJ. Impact of infectious diseases consultation on management and outcome of *Staphylococcus aureus* bacteremia in children. *J. Pediatric Infect. Dis. Soc.* **10**, 569–575 (2021).
5. Iwamoto, M. et al. Trends in invasive methicillin-resistant *Staphylococcus aureus* infections. *Pediatrics* **132**, e817–e824 (2013).
6. Friedland, I. R., du Plessis, J. & Cilliers, A. Cardiac complications in children with *Staphylococcus aureus* bacteremia. *J. Pediatr.* **127**, 746–748 (1995).
7. Vogel, M. et al. Infectious disease consultation for *Staphylococcus aureus* bacteremia – a systematic review and meta-analysis. *J. Infect.* **72**, 19–28 (2016).
8. Tissot, F. et al. Mandatory infectious diseases consultation for MRSA bacteremia is associated with reduced mortality. *J. Infect.* **69**, 226–234 (2014).
9. Borde, J. P. et al. Adherence to an antibiotic stewardship bundle targeting *Staphylococcus aureus* blood stream infections at a 200-bed community hospital. *Infection* **42**, 713–719 (2014).
10. Schmitt, S. et al. Infectious diseases specialty intervention is associated with decreased mortality and lower healthcare costs. *Clin. Infect. Dis.* **58**, 22–28 (2014).
11. Hadano, Y. et al. Reduction of 30-day death rates from *Staphylococcus aureus* bacteremia by mandatory infectious diseases consultation: comparative study interventions with and without an infectious disease specialist. *Int J. Infect. Dis.* **103**, 308–315 (2021).
12. Fries, B. L. et al. Infectious diseases consultation and the management of *Staphylococcus aureus* bacteremia. *Clin. Infect. Dis.* **58**, 598–599 (2014).
13. Ten Oever, J. et al. Development of quality indicators for the management of *Staphylococcus aureus* bacteraemia. *J. Antimicrob. Chemother.* **74**, 3344–3351 (2019).
14. Saunderson, R. B. et al. Impact of infectious diseases consultation on the management of *Staphylococcus aureus* bacteraemia in children. *BMJ Open* **4**, e004659 (2014).
15. Campbell, A. J. et al. Pediatric *Staphylococcus aureus* bacteremia: clinical spectrum and predictors of poor outcome. *Clin. Infect. Dis.* **74**, 604–613 (2022).
16. Liu, C. et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin. Infect. Dis.* **52**, e18–e55 (2011).
17. McMullan, B. J. et al. Clinical management of *Staphylococcus aureus* bacteremia in neonates, children, and adolescents. *Pediatrics* **146**, e20200134 (2020).
18. Yang, D. & Dalton, J. E. A unified approach to measuring the effect size between two groups using SAS. In: *SAS Global Forum* (Orlando FL, 2012).
19. Hamdy, R. F. et al. Epidemiology of methicillin-resistant *Staphylococcus aureus* bacteremia in children. *Pediatrics* **139**, e20170183 (2017).
20. Lloyd, E. C. et al. Impact of a Best Practice Advisory for pediatric patients with *Staphylococcus aureus* bacteremia. *J. Pediatric Infect. Dis. Soc.* **10**, 282–288 (2021).
21. Messacar, K. et al. A handshake from antimicrobial stewardship opens doors for infectious disease consultations. *Clin. Infect. Dis.* **64**, 1449–1452 (2017).
22. Mayer, M. L. Disparities in geographic access to pediatric subspecialty care. *Matern Child Health J.* **12**, 624–632 (2008).

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Kyle J. Whittington or Stephanie A. Fritz.

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