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Pediatric *Staphylococcus aureus* Bacteremia: Clinical Spectrum and Predictors of Poor Outcome

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Background. *Staphylococcus aureus* is a common cause of bacteremia, yet the epidemiology and predictors of poor outcome remain inadequately defined in childhood.

Methods. ISAIAH (Invasive *Staphylococcus aureus* Infections and Hospitalizations in children) is a prospective, cross-sectional study of *S. aureus* bacteremia (SAB) in children hospitalized in Australia and New Zealand over 24 months (2017–2018).

Results. Overall, 552 SABs were identified (incidence 4.4/100 000/year). Indigenous children, those from lower socioeconomic areas and neonates were overrepresented. Although 90-day mortality was infrequent, one-third experienced the composite of: length of stay >30 days (26%), intensive care unit admission (20%), relapse (4%), or death (3%). Predictors of mortality included prematurity (adjusted odds ratio [aOR],16.8; 95% confidence interval [CI], 1.6–296.9), multifocal infection (aOR, 22.6; CI, 1.4–498.5), necrotizing pneumonia (aOR, 38.9; CI, 1.7–1754.6), multiorgan dysfunction (aOR, 26.5; CI, 4.1–268.8), and empiric vancomycin (aOR, 15.7; CI, 1.6–434.4); while infectious diseases (ID) consultation (aOR, 0.07; CI .004–.9) was protective. Neither MRSA nor vancomycin trough targets impacted survival; however, empiric vancomycin was associated with nephrotoxicity (OR, 3.1; 95% CI 1.3–8.1).

Conclusions. High SAB incidence was demonstrated and for the first time in a pediatric setting, necrotizing pneumonia and multifocal infection were predictors of mortality, while ID consultation was protective. The need to reevaluate pediatric vancomycin trough targets and limit unnecessary empiric vancomycin exposure to reduce poor outcomes and nephrotoxicity is highlighted. One in 3 children experienced considerable SAB morbidity; therefore, pediatric inclusion in future SAB comparator trials is paramount to improve outcomes.

Keywords. bacteremia; mortality; outcomes; pediatrics; *Staphylococcus aureus*.

Staphylococcus aureus frequently causes childhood bacteremia and is the most common cause of sepsis requiring pediatric intensive care unit (ICU) admission [1, 2]. It is a principal reason for infectious diseases (ID) consultation [3]. Despite this, the epidemiology and predictors of poor outcomes in children remain inadequately defined.

Fowler et al revolutionized *S. aureus* bacteremia (SAB) adult treatment recommendations by identifying clinical factors associated with complicated disease and mortality [4]. To date, a large, prospective, pediatric SAB dataset with robust outcomes has not been established. Our objectives in this study were to provide a deeper understanding of the SAB clinical phenotype in children, identify pediatric-specific markers for severe disease, and establish risk factors for poor outcomes.

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METHODS

ISAIAH (Invasive *Staphylococcus aureus* Infections and Hospitalizations in children) is a prospective, multicenter, cross-sectional study of pediatric SAB in Australia and New Zealand. Tertiary (n = 8) and secondary (n = 3) pediatric hospitals and neonatal ICUs (NICUs; n = 10) were included. The aims were to identify host, pathogen, and treatment factors predictive of the primary outcome, 90-day all-cause mortality, and a composite outcome (defined a priori as 90-day all-cause mortality, 90-day relapse, ICU admission, or length of stay [LOS] >30 days).

Children aged ≤18 years with a positive blood culture for *S. aureus* who presented to study hospital sites were eligible for inclusion and identified using site microbiology or ID services over 24 months (2017–2018). Children with SAB who were transferred from peripheral hospitals to study sites were also included. Polymicrobial bacteremias were excluded.

Information on demographics, comorbidities, infection focus, investigations, disease severity, treatment, and patient outcomes were prospectively collected from the hospital, laboratory, and radiology records into an electronic database [5]. Antibiotic agent(s), route, and duration, as well as initial vancomycin dose, frequency, and vancomycin trough level obtained within 3 days of commencing were also recorded.

Hospital- and community-onset SAB was defined as a positive blood culture(s) collected >48 hours or ≤48 hours after presentation, respectively. A healthcare-associated SAB definition was adapted from the National Healthcare Safety Network Centres for Disease Control and Prevention definitions (Supplementary Materials 1) [6]. Multifocal disease was classified as clinical or radiological evidence of infection in more than 1 noncontiguous site. Indigenous ethnicity (Aboriginal or Torres Strait Islander, hereafter referred to as Aboriginal in Australia or Māori or Pacific peoples in New Zealand) was verified through routinely collected self-identification at hospital admission.

All time points were calculated from the date of index SAB sampling (day 1), including peak C-reactive protein (CRP), days of fever, and bacteremia (informed by date of first and last SAB). Multiorgan dysfunction was defined as 2 or more of the following: alanine aminotransferase ≥5 times the upper limit of normal (ULN), creatinine ≥2 times the ULN, positive pressure ventilation, or hemodynamic instability requiring inotropic support [7]. Nephrotoxicity was defined as creatinine ≥2 times the ULN in week 1. Antibiotic treatment was defined as empiric (prior to susceptibility results) or targeted (susceptibility results known). Combination therapy was defined as simultaneous receipt of ≥2 antibiotics for ≥24 hours. Empiric antibiotics were deemed appropriate by site investigators if in vitro susceptibility was demonstrated for beta lactams (methicillin-susceptible *S. aureus* [MSSA]) and vancomycin, daptomycin, ceftaroline, or linezolid (methicillin-resistant *S. aureus* [MRSA]) [8]; antibiotic(s) were administered ≤48 hours from index SAB.

Multiple positive SAB cultures within 14 days were considered a single SAB episode. Relapse was defined as repeat *S. aureus* sterile site culture(s) or hospital representation 15–90 days post-SAB and deemed by site investigators to relate to the initial SAB. Seven-, 30-, and 90-day attributable and 7-, 30-, 90-, and 365-day all-cause mortality were collected for in-hospital deaths. Laboratories used standard commercial blood culture systems (BACTEC, BD Diagnostics), bacterial identification (matrix-assisted laser desorption/ionization time-of-flight; Bruker Daltonics, Bremen, Germany), and semiautomated susceptibility platforms (Vitek 2, bioMérieux, France, or BD Phoenix, BD), with minimum inhibitory concentration breakpoints from Clinical and Laboratory Standards Institute M100 [9] or the European Committee on Antimicrobial Susceptibility Testing [10].

Annual population SAB incidence was calculated by age, country, ethnicity, socioeconomic status (SES), and rural residence using national census statistics for children aged ≤14 years [11, 12]. SES was assigned according to postal code–derived national census decile-rank scales of income, the New Zealand index of deprivation (NZiDep) [13], and the Australian socioeconomic index for areas (SEIFA) [14]. NZiDep was inverted to align with the Australian SEIFA score. Australian urban residence was defined as children residing in regions with a population >100 000, determined from postal code–derived population census data [14].

Statistical analyses were performed using R version 3.6.3 (R Core Team, 2020). The χ^2 test or Fisher exact test was used to compare categorical variables and the Student *t* test or Mann-Whitney *U* test was used to compare continuous variables. Potentially significant covariates were considered a priori (age, sex, country, number of surgeries performed for SAB management, device removal, and MRSA), and those with a *P* value <.1 on univariate analysis were included in the multivariable regression model. Pairwise correlation coefficients were examined between variables before inclusion in the multivariable model to avoid collinearity. Stepwise backward elimination was performed, and *P* values <.05 considered statistically significant. Model performance was assessed using the C-statistic for discrimination and the Hosmer-Lemeshow test for calibration. Ethics approval was obtained from each hospital.

RESULTS

Epidemiology and Clinical Characteristics

A total of 552 SAB patient episodes were identified (Figure 1), with an annual incidence of 4.4/100 000 (95% confidence interval [CI], 2.2–8.8); Australia, 4.1/100 000 (95% CI, 2.2–8.8);

New Zealand, 6.4/100 000 (95% CI, 3.4–11.7). The median age was 6.3 years (interquartile range [IQR], 1.0–11.3), with a male (342 of 552, 62%) predominance (Table 1).

Elevated SAB incidence was observed among Indigenous children (8.1/100 000; 95% CI, 4.8–14.4), particularly NZ Pacific children 15.2/100 000 (95% CI, 9.9–23.5) compared with other New Zealand children (incidence rate ratio, 3.0/100 000; 95% CI, 1.1–9.2), neonates (6.6/100 000; 95% CI, 3.4–11.7), and those residing in low SES areas (5.5/100 000; 95% CI, 2.8–10.2; Supplementary Materials 3).

MSSA bacteremia (465 of 552, 84%) was the dominant antibiotic susceptibility phenotype, accounting for 78% (363 of 465) of community-onset infections. The main preceding factors included furuncles (32 of 552, 6%), skin trauma (19 of 552, 3%), and influenza (14 of 552, 3%; Table 2). Underlying comorbidities (232 of 552, 42%) included immunosuppression (83 of 552, 15%), congenital heart disease (48 of 552, 9%), and prematurity (48 of 552, 9%), of which most (22 of 48, 46%) were extremely premature (<28 weeks; Table 2). Healthcare-associated SAB (159 of 528, 30%) occurred more frequently in neonates compared with older children (odds ratio [OR], 3.7; 95% CI, 1.9–7.2), particularly premature neonates (<37 weeks' gestation; 24 of 48, 50%) with device-related infections (15 of 24, 62%; Figure 2).

Focus of Infection, Investigation, and Disease Severity

Most children who were hospitalized (542 of 552, 98%) had at least 1 radiological investigation (502 of 552, 90%), follow-up blood culture (539 of 552, 98%), and an ID consultation (478 of 552, 87%). The most frequent foci of SAB were osteoarticular (273 of 552, 49%), device-related (123 of 552, 22%), deep soft-tissue infection (122 of 552, 22%), and skin and soft tissue infection (83 of 552, 15%; Table 3). Two-thirds had a single focus, while 16% (87 of 552) had multifocal disease (pulmonary and bone most common; 35 of 87, 40%). Multifocal disease was associated with endocarditis (OR, 12.3; 95% CI, 5.7–27.7) and MRSA bacteremia (OR, 2.6; 95% CI, 1.5–4.4). No focus was evident in 14% (78 of 552), more frequently among infants vs older children (OR, 4.4; 95% CI, 2.7–7.3), despite imaging (62 of 78, 79%) and follow-up blood culture(s) (76 of 78, 97%). Surgical source control occurred in nearly half (234 of 552, 42%). In device-related infections, central vascular line–related focus predominated (106 of 123, 86%), and the majority (88 of 123, 71%) had line removal after a median of 3 days (IQR, 2–5; Tables 3 and 4).

Children spent a median of 4 days with a fever (IQR, 2–7) and 1 day (IQR, 1–3) with bacteremia. CRP peaked on day 2 (IQR, 1–3) with a median of 117 mg/L (IQR, 47–205). Those with MRSA bacteremia had a higher median peak CRP of

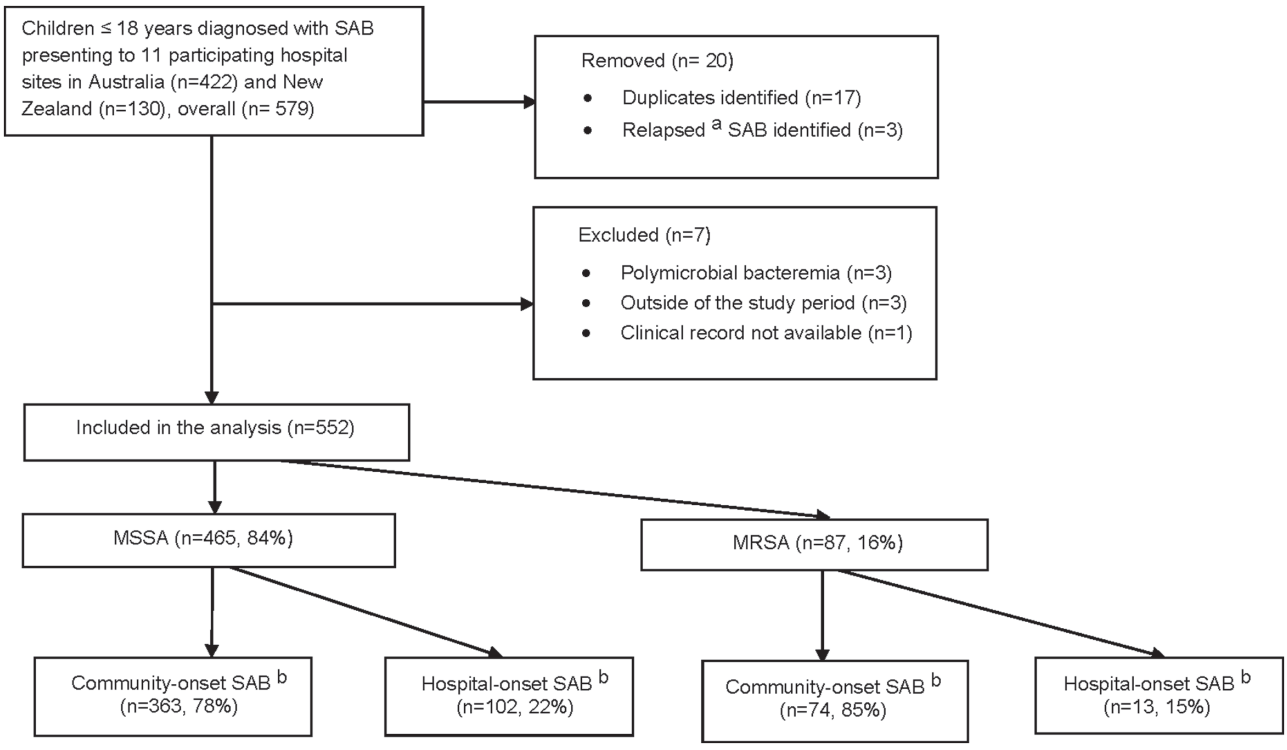

Figure 1. Study participant flow chart. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; SAB, *S. aureus* bacteremia. [a] Relapse defined as any hospital representation or *Staphylococcus aureus* sterile site culture identified >14 and ≤90 days from index blood culture that was deemed by the infectious diseases clinical site investigator to be related to the initial SAB episode. [b] Hospital- and community-onset *S. aureus* bacteremias were those collected >48 hours or ≤48 hours after hospital presentation, respectively.

Table 1. Baseline Characteristics of Children Aged ≤18 Years Diagnosed With *Staphylococcus aureus* Bacteremia Across 11 Pediatric Hospitals in Australia and New Zealand: 2017–2018

Baseline Characteristic	Total, n (%)	MSSA, n (%)	MRSA, n (%)	*P* Value (MRSA vs MSSA)
Pediatric SAB	552	465 (84) [a]	87 (16) [b]	-
Age, median (interquartile range), years	6.3 (1.0–11.3)	6.3 (0.9–11.3)	5.9 (2.1–10.9)	.522
Female	210 (38)	175 (38)	35 (40)	.725
Ethnicity				
Aboriginal and Torres Strait Islander in Australia SAB	51/356 (14)	24/296 (8)	27/60 (45)	<.0001***
Māori + Pacific children in NZ SAB	76/129 (59)	60/107 (56)	16/22 (73)	.141
Location				
Australia	422 (76)	357 (77)	65 (75)	.686
New Zealand	130 (24)	108 (23)	22 (25)	.686
Resides in a rural location (Australia)	113/417 (27)	85/352 (24)	28/65 (43)	.001**
Transferred from a peripheral hospital	148/548 (27)	115/461 (25)	33/87 (38)	.012*
Hospital admission for SAB	546 (99)	461 (99)	85 (98)	.424
Classification				
Hospital-onset	115 (21)	102 (22)	13 (15)	.141
Community-onset	437 (79)	363 (78)	74 (85)	.141
Healthcare-associated	159/528 (30)	138/442 (31)	21/86 (24)	.195
Device	126/528 (24)	107/442 (24)	19/86 (22)	.690
Surgery	37/528 (7)	34/442 (8)	3/86 (3)	.101
Neutropenia	27/528 (5)	24/442 (5)	3/86 (3)	.422

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; SAB, *S. aureus* bacteremia.

[a]Penicillin-susceptible *S. aureus* n = 49/465 (10%) (11 beta-lactamase negative out of 16 results available).

[b]Multiresistant MRSA *n = 3*/87 (0.4%).

* *P* < .05, ** *P* < .01, *** *P* < .001.

Table 2. Baseline Comorbidities and Preceding Factors for Children Aged ≤18 Years Diagnosed with *Staphylococcus aureus* Bacteremia Across 11 Pediatric Hospitals in Australia and New Zealand: 2017–2018

Baseline Characteristic	Total, n (%)	MSSA, n (%)	MRSA, n (%)	*P* Value (MRSA vs MSSA)
Pediatric SAB	552	465 (84)	87 (16)	-
Comorbidities	232 (42)	201 (43)	31 (36)	.225
Immune compromise	83 (15)	70 (15)	13 (15)	1
Hematological malignancy	32 (6)	27 (6)	5 (6)	1
Solid organ transplant	30 (5)	26 (6)	4 (6)	1
Other				
Congenital heart disease	48 (9)	45 (10)	3 (3)	.035*
Premature (<37 weeks)	48 (9)	40/433 (9)	8/81 (10)	.871
Extreme prematurity <28 weeks	22 (4)	19 (5)	3 (4)	.701
Moderate prematurity 28 to <32 weeks	13 (2)	10 (2)	3 (4)	.272
Prematurity 32 to <37 weeks	13 (2)	11 (2)	2 (2)	1
Eczema	42 (8)	35 (7)	7 (8)	.740
Genetic syndrome	15 (3)	12 (3)	3 (3)	1
Chronic neurological disorder	9 (2)	9 (2)	0 (0)	.184
Chronic renal disease	7 (1)	6 (1)	1 (1)	1
Chronic lung disease	15 (3)	14 (3)	1 (1)	.289
Chronic liver/gastrointestinal disease	15 (3)	12 (3)	3 (3)	1
Preceding factors	61 (11)	36 (8)	25 (29)	<.0001***
Furuncle(s)	32 (6)	19 (4)	13 (15)	.0001***
Skin trauma	19 (3)	11 (2)	8 (9)	.0006***
Influenza	14 (2)	9 (2)	5 (6)	.0325*

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; SAB, *S. aureus* bacteremia.

* *P* < .05, *** *P* < .001.

187 mg/L (IQR, 68–267, *P* = .0001), longer duration of fever (median of 5 days: IQR, 3–11; *P* = .0002), and bacteremia (median of 2 days: IQR, 1–3; *P* = .04) than those with MSSA bacteremia.

Antibiotic Treatment

Most children (489 of 539, 91%) commenced appropriate empiric antibiotic therapy. The majority received empiric beta lactams (516 of 536, 93%), principally flucloxacillin (362 of 536, 66%); half (269 of 536, 49%) received empiric vancomycin-containing regimens combined with a beta lactam in 98% (263 of 269). Eighty-four percent (449 of 536) received 1 antibiotic for targeted therapy, with favored MSSA bacteremia regimens including intravenous (IV) flucloxacillin (305 of 452, 67%) or IV cefazolin (55 of 452, 12%). Children with MRSA bacteremia were more likely to receive combination targeted therapy (OR, 3.89; 95% CI, .06–.19) than those with MSSA bacteremia, most commonly with vancomycin and clindamycin (20 of 85, 24%; Table 4).

For empiric vancomycin dosed at 60 mg/kg/day 4 times a day, only 10% (11 of 108) achieved initial vancomycin troughs of 15–20 mg/L. Those who received empiric vancomycin developed nephrotoxicity more frequently (23 of 269, 9%) than those who did not (8 of 259, 3%; OR, 3.1; 95% CI, 1.3–8.1). Approximately half of children received oral antibiotics following their IV course (303 of 543, 56%) for whom the median duration of IV therapy was 11 days (IQR, 8–20), followed by oral therapy for 23 days (IQR, 14–35). Median total duration of therapy was 26 days (IQR, 15–45) and was longer for MRSA bacteremia (39 days; IQR, 18–48) compared with MSSA bacteremia (23 days; IQR, 15–44; *P* = .0005). Longer median total duration of therapy was also observed for multifocal SAB (43 days; IQR, 26–49) compared with nonmultifocal SAB (20 days; IQR, 14–43; *P* =< .0001).

Outcome and Predictors of Mortality

Median LOS for SAB was 15 days (IQR, 9–31) and longer for MRSA bacteremia (22 days; IQR, 14–35; *P* = .001). Relapse occurred in 4% (21 of 531) after a median of 45 days (IQR, 38–71). Seven-day, 30-day, 90-day, and 12-month all-cause mortalities were 1% (5 of 546), 2% (13 of 546), 3% (14 of 542), and 4% (23 of 542), respectively. Death occurred after a median of 21 days

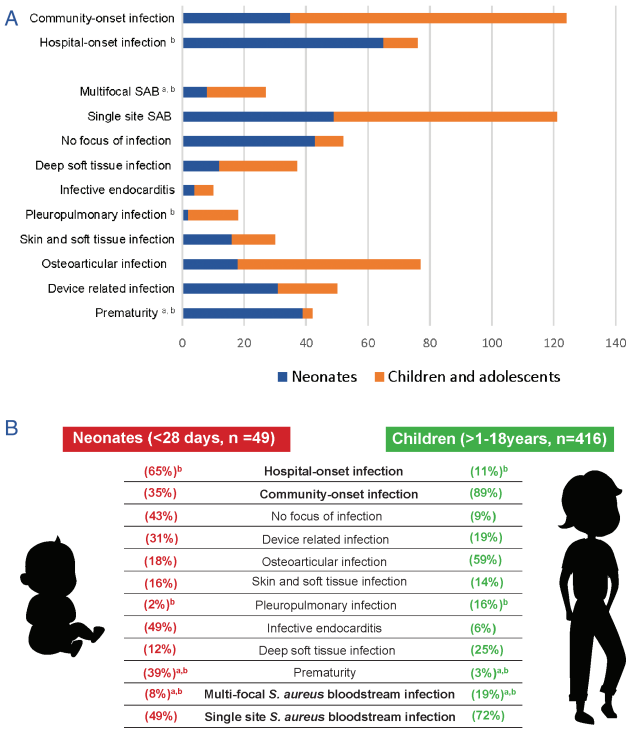

Figure 2. *A,* Site and onset of *Staphylococcus aureus* bacteremia infection in neonates and children. Abbreviation: SAB, *Staphylococcus aureus* bacteremia. [a] Independent variables associated with mortality in children on multivariable logistic regression modeling. [b] Independent variables associated with the composite of 90-day all-cause mortality, 90-day relapse, intensive care unit (ICU) admission, or length of stay >30 days in children on multivariable logistic regression modelling. *B,* Site and onset of *S. aureus* bacteremia infection in neonates and children.

(IQR, 9–164). One in 3 children (186 of 503, 36%) experienced the composite outcome of 90-day all-cause mortality (14 of 542, 3%), relapse (21 of 531, 4%), ICU admission (111 of 550, 20%), or LOS >30 days (140 of 530, 26%).

Significant predictors of 90-day all-cause mortality included prematurity (aOR, 16.8; 95% CI, 1.6–296.9; $P = .03$), multifocal infection (aOR, 22.6; 95% CI, 1.4–498.5; $P = .03$), necrotizing pneumonia (aOR, 38.9; 95% CI, 1.7–1754.6; $P = .03$), multiorgan dysfunction (aOR, 26.5; 95% CI, 4.1–268.8; $P = .001$), and empiric vancomycin therapy (aOR, 15.7; 95% CI, 1.6–434.4; $P = .04$; Table 5). Initial vancomycin troughs of <15 mg/L (OR, 0.6; 95% CI, .1–4.2; $P = .5$) and MRSA (aOR, 0.4; 95% CI, .04–3.3; $P = .4$) were not predictive of mortality in children. Factors associated with a mortality reduction included ID consultation (aOR, 0.07; 95% CI, .004–.9; $P = .05$), an osteoarticular focus (aOR, 0.01; 95% CI, .0002–.4; $P = .03$), and country of origin, Australia compared with New Zealand (aOR, 0.1; 95% CI, .01–.6; $P = .02$). No variables were predictive of 90-day relapse, although less frequent relapse was observed in those who received empiric beta-lactam therapy (aOR, 0.17; 95% CI, .03–1.3; $P = .05$; Supplementary Materials 2).

A peak CRP >200 mg/L by day 3 was predictive of the composite outcome (aOR, 2.9; 95% CI, 1.5–6.1; $P = .002$). Congruent with mortality predictors, prematurity (aOR, 4.4; 95% CI, 1.5–14.1; $P = .008$), pneumonia (aOR, 2.7; 95% CI, 1.1–7.1; $P = .04$), and empiric vancomycin (aOR, 2.0; 95% CI, 1.0–4.1; $P = .05$) were independent risk factors for this composite outcome. The presence of congenital heart disease (aOR, 6.2; 95% CI, 1.7–27.6; $P = .009$), age ≤1 year (aOR, 2.3; 95% CI, 1.1–4.8; $P = .03$), ≥3 surgeries for SAB management (aOR, 5.5; 95% CI, 2.1–14.8; $P = .0006$), increasing days of *S. aureus* bacteremia (aOR,1.2; 95% CI, 1.0–1.4; $P = .04$), and hospital-onset SAB (aOR, 6.6; 95% CI, 2.9–15.5; $P =< .0001$) were also predictive (Table 6).

Table 3. Baseline Investigations and Source of Infection for Children Aged ≤18 Years Diagnosed With *Staphylococcus aureus* Bacteremia from 11 Pediatric Hospitals in Australia and New Zealand: 2017–2018

Baseline Characteristic	Total, n (%)	MSSA, n (%)	MRSA, n (%)	*P* Value (MRSA vs MSSA)
Pediatric SAB	552	465 (84)	87 (16)	-
Investigations for SAB				
Follow-up blood culture	539 (98)	453 (97)	86 (99)	.289
Any imaging performed	502 (90)	419 (90)	83 (95)	.139
Number of images performed (median, interquartile range)	3 (2–5)	3 (2–4)	4 (2–6.5)	.0001***
Skeletal imaging	341 (62)	278 (60)	63 (72)	.034*
Echocardiogram	269 (49)	211 (45)	58 (67)	.0002***
Source of infection				
Osteoarticular	273 (49)	230 (49)	43 (49)	1
Device-related	123 (22)	103 (22)	20 (22)	1
Central vascular catheter	106 (86)	88 (85)	18 (90)	.559
Orthopedic device	6 (5)	5 (5)	1 (5)	1
Cardiac device	6 (5)	6 (6)	0 (0)	.263
Peripheral intravenous cannular	5 (4)	4 (4)	1 (5)	.838
Deep soft tissue infection	122 (22)	97 (21)	25 (29)	.1
Skin and soft tissue infection	83 (15)	64 (14)	19 (22)	.057
Pleuropulmonary	80 (14)	56 (12)	24 (27)	.0003***
No focus	78 (14)	71 (15)	7 (8)	.083
Endovascular	37 (7)	23 (5)	14 (16)	.0002***
Infective endocarditis	31 (6)	22 (5)	9 (10)	.067
Other	14 (2)	8 (2)	6 (7)	.009**
Central nervous system	13 (2)	8 (2)	5 (6)	.032*
Gastrointestinal	6 (1)	6 (1)	0 (0)	.349
Renal	5 (1)	3 (1)	2 (2)	.424
Foci of infection				
No focus	78 (14)	71 15)	7 (8)	.083
Single site focus	387 (70)	332 (71)	55 (63)	.136
Multifocal disease	87 (16)	62 (13)	25 (29)	.0002***

*** $P < .001$; ** $P < .01$; * $P < .05$
Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; SAB, *S. aureus* bacteremia.

Table 4. Severity, Management, and Outcome of Children Aged ≤18 Years Diagnosed With *Staphylococcus aureus* Bacteremia from 11 Pediatric Hospitals in Australia and New Zealand: 2017–2018

Baseline Characteristic	Total, n (%)	MSSA, n (%)	MRSA, n (%)	*P* Value (MRSA vs MSSA)
Pediatric SAB	552	465 (84)	87 (16)	-
Severity				
Intensive care unit admission for SAB	111/550 (20)	86/463 (18)	25/87 (29)	.0181*
Positive pressure ventilation	68/550 (12)	49/464 (10)	19/87 (22)	.0015**
Inotropic requirement	47/550 (9)	35/462 (7)	12/87 (14)	.0284*
Alanine transferase > 5 times upper limit of normal	26/512 (5)	20/430 (5)	6/82 (7)	.4600
Creatinine > 2 times upper limit of normal	32/541 (6)	22/455 (5)	10/86 (12)	.0130*
Multiorgan dysfunction, [a]	43/512 (8)	31/430 (7)	12/82 (15)	.0161*
Days febrile, median (IQR), n = 471	4 (2–7)	4 (2–6)	5 (3–11)	.0002***
Days of SAB, median (IQR), n = 552	1 (1–3)	1 (1–3)	2 (1–3)	.0403 *
Peak C-reactive protein ≤7 days from SAB, median (IQR), mg/L, n = 503	117 (47–205), day 2 (1–3)	104 (43–192), day 2 (1–3)	187 (68–267), day 2 (1–4)	.0001***
SAB management				
Empiric antibiotic treatment				
Combination antibiotics	375/535 (70)	303/452 (67)	72/83 (87)	.0005***
Any antibiotic susceptible	510/535 (95)	444/452 (99)	66/83 (78)	<.0001***
Appropriate antibiotics [b]	500/535 (94)	434/452 (93)	66/83 (78)	<.0001***
Targeted antibiotic treatment				
Number of different targeted antibiotics, median (IQR)	2 (1–2)	2 (1–3)	2 (2–3)	<.0001***
Combination antibiotics	87/536 (16)	53/453 (12)	34/83 (41)	<.0001***
Length intravenous antibiotic(s), median (IQR) length of antibiotics in days	15 (10–28)	15 (9–15)	19 (12–37)	.019*
Length oral antibiotic(s), median (IQR)	23 (14–35)	22 (14–35)	28 (14–42)	.008**
Total length of antibiotic(s), median (IQR)	26 (15–45)	23 (15–44)	39 (18–48)	.0005***
Poor antibiotic adherence	16/497 (3)	11/421 (3)	5/76 (7)	.086
History of antibiotic allergy	36/547 (7)	33/460 (7)	3/87 (3)	.161
Vancomycin trough <15 mg/L	138/179 (77)	84/111 (76)	54/68 (79)	.644
Vancomycin trough 15–20 mg/L	24/179 (13)	17/111 (15)	7/68 (10)	.337
Surgical source control performed	234/550 (42)	185/463 (40)	49/87 (56)	.0057**
Number of surgeries, median (IQR), n = 550	0 (0–1)	0 (0–1)	1 (0–2)	.0008**
Device removal	88/123 (71)	73/104 (70)	15/19 (79)	.427
Infectious diseases consult	474/545 (87)	391/458 (84)	83/87 (95)	.0072**
Hospital-in-the-home usage	164/546 (30)	143/461 (31)	21/85 (25)	.268
Length of stay, median (IQR), days, n = 530	15 (9–31)	13 (9–30)	21 (12.5–37.5)	.001**
Outcome				
30-day all-cause mortality	13/546 (2.4)	10/461 (2.2)	3/85 (3.5)	.472
90-day all-cause mortality	14/542 (2.6)	11/458 (2.4)	3/84 (3.6)	.524
12-month all-cause mortality	23/542 (4.2)	18/458 (4)	5/84 (6)	.407
Day of death from SAB, median (IQR), n = 542	21 (9.5–164)	22 (12–140)	21 (6–227)	.912
Relapse within 90 days	21/531 (3.9)	18/450 (4.0)	3/81 (3.7)	.899
Day of relapse from SAB, median (IQR), n = 530	45 (38–71)	52 (41–76)	19 (16.5–29)	.024*
Composite outcome, [c]	186/503 (87)	141/417 (34)	45/86 (52)	.002**

Abbreviations: IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; SAB, *S. aureus* bacteremia.

[a]Multiorgan dysfunction defined as ≥2 of the following: alanine aminotransferase ≥5 times the upper limit of normal, creatinine ≥2 times the upper limit of normal, positive pressure ventilation, or requiring inotropes for SAB.

[b]Any antibiotic administered testing susceptible using conventional laboratory methods AND commenced ≤2 day from index *S. aureus* bacteremia.

[c]Composite outcome defined as any of the following: 90-day all-cause mortality, 90-day relapse, intensive care unit admission, or length of stay >30 days.

* $P < .05$, ** $P < .01$, *** $P < .001$.

DISCUSSION

In one of the largest prospective cohorts of pediatric SAB to date, we report a high annual incidence affecting 4.4/100 000 children with increased burden among neonates, Indigenous children, and those from lower SES areas. We identified early markers of poor outcomes in children, including multifocal infection, CRP >200 mg/L, prematurity, and congenital heart disease.

Our reported incidence (4.4/100 000) is similar to the incidence from other high-income countries including Canada (5.9/100 000) [15] and Denmark (8.4/100 000) [16]. The lower incidence compared with the Australian and New Zealand 2007–2012 cohort (8.3/100 000) [17] likely reflects differences in methodology (postal code–adjusted incidence rates in the former, with unadjusted whole pediatric population incidence rates used here, and some variation in study sites), rather than a true decline. Overrepresentation of Indigenous children (8.1/100 000; 95% CI, 4.8–14.4) has been reported nationally and internationally [17, 18], which may be due to a disproportionate burden of socioeconomic disadvantage [18],

Table 5. Univariate and Multivariable Logistic Regression for Children Aged ≤18 Years Diagnosed With *Staphylococcus aureus* Bacteremia, Examining 90-Day All-Cause Mortality

		Univariate Analysis		Multivariable Logistic Regression	
Variable	n (%)	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Multiorgan dysfunction [a]	43/511 (8)	30.04 (9.28–115.62)	< 0.0001	26.54 (4.06–268.79)	.001 **
Osteoarticular focus	273/552 (49)	0.16 (0.02–0.60)	0.018	0.01 (.0002–0.41)	.028 *
Prematurity	48/514 (9)	5.79 (1.71–17.55)	0.002	16.79 (1.60–296.96)	.028*
Country, Australia	422/552 (76)	0.54 (0.18–1.81)	0.287	0.11 (0.01–0.65)	.018*
Multifocal SAB	87/552 (16)	3.07 (0.92–9.11)	0.049	22.64 (1.41–498.49)	.031*
Necrotizing pneumonia	13/552 (2)	14.13 (2.88–54.37)	0.0002	38.99 (1.67–1754.60)	.034*
Empirical antibiotics inclusive of vancomycin	269/549 (49)	11.43 (2.20–209.78)	0.017	15.70 (1.55–434.39)	.041*
Infectious diseases consult	474/545 (87)	0.36 (0.12–1.35)	0.094	0.07 (0.004–0.94)	.048*
Congenital heart disease	48/552 (9)	4.61 (1.22–14.44)	0.013	3.83 (0.36–35.67)	.233
≥2 comorbidities present	49/552 (9)	6.43 (1.90–19.51)	0.001	3.28 (0.39–30.15)	.267
Age, years [b]	6.3 (IQR 1.0–11.3)	0.99 (0.99–1.00)	0.274	1.00 (0.99–1.00)	.226
Male	342/552 (62)	1.10 (0.37–3.61)	0.869	2.41 (0.42–18.39)	.349
Number of surgeries for SAB management [b]	0 (IQR 0–1)	0.86 (0.46–1.24)	0.555	0.76 (0.28–1.36)	.474
Methicillin-resistant *Staphylococcus aureus*	87/552 (16)	1.50 (0.33–4.94)	0.537	0.41 (0.04–3.26)	.417
Pleuropulmonary focus [c]	80/552 (14)	8.58 (2.90–26.76)	0.0001	-	-
Empiric number antibiotics [b,c]	2 (IQR 1–3)	1.84 (1.15–2.92)	0.01	-	-
Empiric antibiotics inclusive of third-generation cephalosporin [c]	134/536 (25)	3.07 (0.94–9.98)	0.056	-	-
Pacific ethnicity (New Zealand) [d]	43/129 (33)	8.51 (1.21–169.51)	0.059	-	-
Chronic renal disease [d]	7/551 (1)	6.69 (0.34–43.28)	0.088	-	-
Aboriginal and Torres Strait Islander ethnicity (Australia)[e]	51/356 (14)	3.05 (0.63–11.98)	0.123	-	-
Targeted antibiotics inclusive of vancomycin [e]	85/539 (16)	2.07 (0.45–7.32)	0.29	-	-
Vancomycin trough <15 mg/L [e]	138/179 (8)	0.57 (0.11–4.23)	0.527	-	-
Device removal [e]	88/123 (71)	1.55 (0.34–5.21)	0.511		
Age <1 year [e]	136/552 (2)	1.22 (0.33–3.73)	0.736	-	-
Māori ethnicity (New Zealand)[e]	33/129 (26)	0.70 (0.04–4.97)	0.757	-	-
Age <28 days[e]	49/552 (9)	0.79 (0.04–4.09)	0.82	-	-

Multivariable logistic regression model adjusted for age, sex, location (by country), number of surgeries performed for SAB source control, and methicillin susceptibility. C-statistic: 0.969; Hosmer-Lemeshow goodness-of-fit test χ^2: 2.089; df: 8; *P* value: .978.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IQR, interquartile range; OR, odds ratio; SAB, *Staphylococcus aureus* bacteremia.

[a]Multiorgan dysfunction defined as ≥2 of the following: alanine aminotransferase ≥5 times the upper limit of normal, creatinine ≥2 times the upper limit of normal, positive pressure ventilation, or requiring inotropes for SAB.

[b]Continuous variable, reference is the lowest value.

[c]Variables contributing to collinearity in the model excluded from the model.

[d]Wide CIs (a small number of outcome events in the variable) excluded from the model.

[e]*P* value on univariate analysis ≥.1 excluded from the model.

* *P* < .05, ** *P* < .01.

as demonstrated in this cohort (Supplementary Materials 3). We conclude that SAB is the leading cause of pediatric bacteremia in Australia and New Zealand (with reported incidence of *Streptococcus pneumoniae*, 4.1/100 000; 95% CI, 2.2–8.8 [19]; group A *Streptococcus*, 2.7/100 000; 95% CI, 2.3–3.2 [20]; and *Neisseria meningitidis*, 0.9/100 000; 95% CI, .1–4.9 to 2.48/100 000; 95% CI 1.53–3.78) [21, 22]. Prioritization of further research into prevention strategies in the absence of an effective vaccine for SAB is needed.

The youngest children, particularly neonates (6.6/100 000; 95% CI, 3.4–11.7) had the highest SAB incidence, albeit lower than the incidence previously reported in the literature (13–124/100 000) [15, 23]. This comparatively lower incidence may relate to fewer NICUs included or improvements in intravascular catheter care bundle use in NICUs [24]. This study demonstrates that the degree of prematurity drives this early lifetime risk, with half (46%) of affected neonates born <28 weeks' gestation and prematurity was identified as a predictor of mortality and poor outcomes. This adds to the limited literature available on neonatal SAB [25] that largely focuses on MRSA [26] and neonatal *S. aureus* colonization risk factors [27]. With a predominance of neonatal healthcare-associated (49%) and device-related (31%) infections, our data support the importance of optimizing infection prevention measures in the NICU.

The 90-day mortality (3%) is congruent with that in the United Kingdom (2%) and the United States (2%) [28] while significantly lower than adult SAB (15%–20%) [29]. This is potentially associated with decreased pediatric comorbidities (42% children vs 85% adults) and lower infective endocarditis rates (6% children vs 12% adults) [29]. Lower mortality was confirmed in Australia (2%) compared with New Zealand (4%). Potential explanations include differences in clonal *S. aureus* virulence or host factor variations in genetic susceptibility to severe disease [17].

Table 6. Univariate and Multivariable Logistic Regression for Children Aged ≤18 Years Diagnosed With *Staphylococcus aureus* Bacteremia, Examining the Composite Outcome of 90-Day All-Cause Mortality, 90-Day Relapse, Intensive Care Unit Admission, or Length of Stay >30 Days

		Univariate Analysis		Multivariable Logistic Regression	
Variable	n (%)	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Hospital-onset SAB	115/552 (21)	9.51 (5.91–15.80)	<.0001	6.57 (2.88–15.47)	<.0001 ***
≥3 surgeries for SAB management	0 (IQR 0–1)	3.10 (1.71–5.77)	.0002	5.47 (2.08–14.80)	.0006***
Peak C-reactive protein >200 mg/L ≤7 days from SAB	121/470 (26)	2.81 (1.84–4.31)	<.0001	2.99 (1.47–6.15)	.002**
Empiric antibiotic(s) inclusive vancomycin	269/549 (49)	2.73 (1.90–3.93)	<.0001	2.01 (1.00–4.10)	.049*
Prematurity	48/514 (9)	7.48 (3.77–16.23)	<.0001	4.45 (1.53–14.06)	.008**
Congenital heart disease	48/552 (9)	9.74 (4.69–22.85)	<.0001	6.21 (1.66–27.63)	.009**
Pleuropulmonary focus	80/552 (14)	4.50 (2.73–7.60)	<.0001	2.74 (1.06–7.09)	.036*
Aged ≤1 year	136/552 (2)	3.28 (2.20–4.91)	<.0001	2.31 (1.09–4.85)	.027*
Number of days of SAB [a]	1 (IQR 1–3)	1.22 (1.12–1.34)	<.0001	1.21 (1.01–1.45)	.042*
Osteoarticular focus	273/552 (49)	0.42 (0.29–0.59)	<.0001	0.51 (0.23–1.09)	.083
Multifocal SAB	87/552 (16)	3.44 (2.15–5.58)	<.0001	2.08 (0.75–5.66)	.153
Immune compromise	83/547 (15)	1.65 (1.03–2.65)	.036	0.54 (0.18–1.54)	.258
Device removal	88/123 (71)	3.27 (2.00–5.41)	<.0001	1.68 (0.67–4.24)	.267
Infective endocarditis focus	31/552 (6)	7.57 (3.25–20.67)	<.0001	2.46 (0.52–13.69)	.275
Empiric antibiotics inclusive of a beta lactam	511/536 (95)	0.28 (0.11–0.63)	.003	0.79 (0.19–3.33)	.748
Location, Australia	422/552 (76)	0.86 (0.58–1.29)	.464	1.23 (0.58–2.63)	.594
Methicillin-resistant *Staphylococcus aureus*	87/552 (16)	1.56 (0.98–2.48)	.058	1.04 (0.45–2.34)	.926
Male	342/552 (62)	1.10 (0.77–1.57)	.602	1.01 (0.55–1.84)	.987
Aboriginal and Torres Strait Islander ethnicity (Australia) [b]	51/356 (14)	2.35 (1.29–4.32)	.006	2.06 (0.61–7.04)	.245
Rural residence (Australia) [b]	113/417 (27)	1.81 (1.17–2.81)	.008	1.21 (0.46–3.07)	.695
Empirical number of antibiotics [c]	2 (IQR 1–3)	2.10 (1.74–2.56)	<.0001	-	-
≥2 comorbidities [c]	49/552 (9)	4.21 (2.27–8.16)	<.0001	-	-
Aged <28 days [c]	49/552 (9)	4.21 (2.27–8.16)	<.0001		
Empiric antibiotics inclusive of third-generation cephalosporins [c]	134/536 (25)	2.63 (1.77–3.93)	<.0001	-	-
Device focus [c]	123/552 (22)	2.73 (1.81–4.12)	<.0001		
Days febrile [c]	4 (IQR 2–7)	1.05 (1.02–1.09)	.003	-	-
Targeted antibiotics inclusive of vancomycin [c]	85/539 (16)	1.99 (1.25–3.18)	.004	-	-
Vancomycin trough <15 mg/L [c]	138/179 (8)	0.39 (0.18–0.81)	.014	-	-
Empiric antibiotics inclusive of flucloxacillin [c]	362/536 (7)	0.67 (0.47–0.97)	.035	-	-
Māori ethnicity (New Zealand) [d]	33/129 (26)	0.54 (0.22–1.22)	.148	-	-
Pacific ethnicity (New Zealand) [d]	43/129 (33)	1.21 (0.57–2.54)	.613	-	-

Multivariable logistic regression model adjusted for age, sex, location (by country), source control (number of surgeries performed for SAB management and device removal and methicillin susceptibility. C-statistic: 0.887; Hosmer-Lemeshow goodness-of-fit test: χ^2: 6.015; df: 8; *P* value: .646.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IQR, interquartile range; OR, odds ratio; SAB, *S. aureus* bacteremia.

[a]Continuous variable, reference is the lowest value.

[b]Australian data only included for examining the variables Aboriginal and Torres Strait Islander ethnicity and rural residence (with location by country removed) in the multivariable logistical regression model.

[c]Variables contributing to collinearity in the model excluded from the model.

[d]*P* value on univariate analysis ≥.1 excluded from the model.

* *P* < .05, ** *P* < .01, *** *P* < .001.

Compared with previous Australian and New Zealand data (2007–2012), a decline in pediatric 30-day mortality was observed (5%–2%, *P* = .009) [17], with similar findings reported in adult SAB [29]. This is the only contemporary pediatric study to demonstrate this. Improvements are likely attributable to appropriate early antibiotic therapy, sepsis management [29], and ID consultation [30]. Indeed, an ID consult was frequent and protective against mortality in this study, similar to findings in adult SAB [30]. However, due to small numbers, the size of the effect remains uncertain. Despite improving mortality, one quarter of children required ICU admission and experienced LOS >30 days. Future comparator trials for children with SAB are critical to improve care and reduce prolonged hospitalizations.

This detailed dataset identified that MRSA bacteremia compared with MSSA bacteremia was associated with increased ICU admissions, more days with bacteremia, and longer LOS on bivariate analysis (Tables 3 and 4). Despite these differences, on multivariable regression, methicillin resistance was not associated with mortality, relapse, or poor outcomes in children. Our findings are consistent with those found in the global literature when examining children across ages (not just neonates) [31] and when MRSA bacteremia is predominantly community-acquired (in our study 85%) vs hospital-acquired [31-33]. This suggests that healthcare-associated *S. aureus* clonal virulence

factors may play a role in this mortality risk [31-33]. Recognition of both methicillin-resistant and methicillin-susceptible SAB as a cause of significant morbidity is critical to advancing approaches in prevention and treatment [16].

In this study, empiric vancomycin (given in combination with a beta lactam in 98% of children) predicted mortality and poor outcomes, even after adjusting for MRSA and disease severity. Increased risk of nephrotoxicity with empiric vancomycin, identified in this study, other pediatric cohorts [34], and a recent adult SAB randomized trial (CAMERA2) that reported increased nephrotoxicity and mortality with combination vancomycin/flucloxacillin therapy for MRSA bacteremia [35] may explain these findings. In addition, initial vancomycin troughs of less or greater than 15 mg/L did not result in improved survival overall or for MRSA bacteremia. These data highlight the need for reevaluation of pediatric vancomycin trough targets [36], particularly while vancomycin remains the standard of care for MRSA bacteremia [37]. It also supports the use of rapid diagnostics, coupled with antimicrobial stewardship [38] for SAB, to limit unnecessary vancomycin exposure in children and the potential harm associated with this.

Multifocal infection is a confirmed mortality risk in adult SAB (OR, 2.1–17.0) [4, 29] and a presumptive risk in children [28, 39]. This is the first pediatric cohort to demonstrate multifocal infection (16%) as a significant predictor of mortality (aOR, 22.6; 95% CI, 1.4–498.5; $P = .03$). In a Danish retrospective study, logistical regression models examining pediatric SAB mortality [16] used narrower definitions for multifocal SAB, excluding osteoarticular and pulmonary foci (most common in our study), which may explain differences in findings. SAB with pulmonary focus is an established predictor of mortality in adults [40] and children [17] and, specifically, in this cohort, necrotizing pneumonia (aOR, 38.9; 95% CI, 1.7–1754.6; $P = .03$). Previous case series of necrotizing pneumonia [41] describe high mortality; however, they are limited by selection bias and lack of adjustment for confounders. These data confirm the need for source-specific management of SAB and, with further validation, suggest the utility of multifocal disease as an outcome measure for future pediatric clinical trials.

Limitations of this study include some missing data as data were captured from multiple sources including medical records. However, the mortality end point, albeit infrequent, was well documented. Most children were cared for in tertiary pediatric hospitals, which may have introduced selection bias. Incidence is likely underestimated as not all secondary hospitals were included. To reduce data collection burden, the only antibiotic dose recorded was the initial vancomycin prescription; therefore, dose was not incorporated into the definition of appropriate empiric antibiotic therapy. We were not able to determine if empiric antibiotic choice impacted transfer to the ICU from an acute care setting given that data on ICU admission was collected as a binary variable. Relapse and death may be underestimated, with community, out-of-hospital, or private provider presentations or deaths not recorded, although this was estimated to be low. Models included adjustment for disease severity, using a definition of pediatric multiorgan dysfunction [7] that has not been rigorously externally validated and may not have accurately accounted for this. Despite this, our analysis of 552 pediatric SAB episodes provides an in-depth description of the clinical phenotype of severe disease and risk factors for poor outcome.

CONCLUSIONS

The incidence of SAB is confirmed to be the highest for invasive bacterial infections in children in the post-conjugate vaccine era. The most vulnerable at-risk populations include New Zealand-Pacific children, premature neonates, and those residing in lower socioeconomic areas. For the first time in a pediatric setting, we demonstrate that necrotizing pneumonia and multifocal infection were independent predictors of death, while ID consultation was protective. Given that MRSA and vancomycin trough levels did not impact on survival, further reevaluation of pediatric vancomycin trough targets is required. These data support the use of rapid diagnostics and antimicrobial stewardship for SAB to limit unnecessary vancomycin exposure in children and consequent nephrotoxicity. This contemporary analysis provides the foundation for a collaborative clinician network for future pediatric SAB randomized clinical trials given that 1 in 3 children experience SAB morbidity.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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