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Healthcare-associated Infections in Very Low Birth–weight Infants in a South African Neonatal Unit

Disease Burden, Associated Factors and Short-term Outcomes

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Background: Infection is a leading cause of death among very low birth–weight (VLBW) infants in resource-limited settings.

Methods: We performed a retrospective review of healthcare-associated infection (HAI) episodes among VLBW infants from January 1, 2016, to December 31, 2017. The epidemiology, causative organisms and short-term outcomes were analyzed. Logistic regression was used to investigate for factors associated with development of HAI.

Results: During the study period, 715 VLBW infants with suspected HAI were investigated, including 162/715 (22.7%) proven and 158/715 (22.1%) presumed HAI. Of the proven infections, 99/162 (61.1%) contained at least one Gram-negative organism per blood culture; 84/162 (51.9%) single Gram-negative organisms and 15/162 (9.3%) polymicrobial growth. Independent factors associated with development of any HAI included low gestational age, small for gestational age, indwelling central venous catheter and invasive ventilation. Compared with infants in whom HAI had been excluded, infants with HAI were more likely to be diagnosed with necrotizing enterocolitis (5.6% vs. 23.1%; $P < 0.001$) and bronchopulmonary dysplasia (1.0% vs. 4.4%; $P = 0.007$). Infants with any HAI also had a longer hospital stay [44 (25–65) vs. 38 (26–53) days; $P < 0.001$] and increased mortality [90/320 (28.1%) vs. 21/395 (5.3%); $P < 0.001$] compared with infants who did not develop HAI episodes.

Conclusions: Proven and presumed HAI are a major contributor to neonatal morbidity and mortality; further research is urgently needed to better understand potential targets for prevention and treatment of HAI in resource-limited neonatal units.

Keywords: neonate, low birth–weight, healthcare-associated infection, sepsis, Africa, outcome

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Infection is a leading cause of morbidity and mortality during the first 4 weeks of life—the neonatal period—worldwide.[1,2] It is estimated that as many as 22 neonates per 1000 live births develop infection, with 11%–19% infection-associated mortality.[3] Preterm and very low birth–weight infants (VLBW; <1 500 g) are particularly vulnerable to acquisition of neonatal healthcare-associated infection (HAI; infections occurring after 72 hours of admission), as they have altered innate and adaptive immune responses and long hospital stays.[4] HAI prevalence rates vary from 10% to 30% among VLBW infants, exceeding that observed in term infants 2- to 5-fold.[5] Furthermore, HAI is associated with adverse short- and long-term outcomes, such as death or neurodevelopmental impairment.[5,6]

Despite the substantial HAI burden encountered in VLBW infants, the pathogenesis of HAI is poorly understood and the knowledge of factors associated with HAI is limited.[7] A further challenge is the lack of a consensus definition for neonatal HAI, making it difficult to compare the burden and impact of HAI in different settings, especially in Africa.[8] Diagnosis of neonatal HAI traditionally relies on microbiological culture-based organism identification, but blood culture yields are often low (5–10%) and prone to contamination by skin commensals.[9,10] In many low-middle income countries, access to microbiology laboratories is limited, leading to an increased reliance on adjunctive tests, such as the C-reactive protein (CRP), to make the diagnosis of presumed or culture-negative HAI.[11,12] Very few neonatal units have reported prevalence estimates for presumed HAI, likely leading to an underappreciation of the true infection burden, antimicrobial prescription rates and adverse outcomes. The National Institute of Child Health and Human Development Neonatal Research Network and a large Chinese study both recently reported that preterm infants with presumed (culture-negative) HAI had higher rates of complications, higher risk of neurodevelopmental impairment and increased mortality compared with those with no HAI.[13,14]

In South Africa, there is limited data relating to neonatal HAI, and there are no known publications referring to presumed HAI. The objectives of this study were to describe the disease burden of proven and presumed HAI at a tertiary neonatal center in South Africa, and to describe the factors associated with any HAI and the short-term outcomes of these in VLBW infants with HAI compared with those in whom the diagnosis of HAI had been excluded.

MATERIALS AND METHODS

Study Design and Setting

We conducted a retrospective review of HAI episodes among VLBW infants at Tygerberg Hospital, South Africa, between January 1, 2016, and December 31, 2017. Tygerberg hospital is a 1384-bed tertiary hospital in the Western Cape, South Africa. The obstetric-neonatal service manages approximately 8000 high-risk deliveries (37% low birth–weight, <2500 g) and 3000 neonatal admissions annually.[15] The 132-bed neonatal unit includes a 12-bed neonatal intensive care unit, 3 high-dependency wards and 1 kangaroo mother care ward. Because of limited

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neonatal intensive care unit beds, neonates with a gestational age of less than 27 weeks and a birth weight of less than 800 g are managed on the neonatal wards. Noninvasive ventilation and surfactant administration are practiced on the wards.[16] Data on VLBW infants admitted in the neonatal unit were extracted from admission records. Using the National Health Laboratory Service Trakcare Results viewer, and the Tygerberg Hospital Enterprise Content Management electronic patient records, any VLBW infant undergoing investigation for suspected infection after 72 hours of admission was identified. Only the first suspected infection episode that was investigated was included in the analysis. Data were captured using REDCap, a secure online electronic data capture tool hosted at Stellenbosch University.[17,18]

Investigation and Management of Suspected Neonatal Hospital-acquired Infection

Neonatal HAI is usually clinically suspected based on signs of possible infection, for example, tachypnea, tachycardia, temperature or glucose instability, mottled skin. Based on these clinical symptoms and signs, and at the discretion of the attending clinician, a single blood culture is aseptically collected, as well as a CRP and a complete blood count, and empiric antimicrobials initiated.

Study Definitions

HAI episodes occurring after 72 hours of admission to the neonatal unit were classified into 3 categories[19]:

1. Proven HAI: Positive blood culture. Organisms were classified using the United States Centers for Disease Control (CDC) list of pathogens and contaminants.[20] Repeat blood cultures isolating the same pathogen within 10 days of the original specimen were considered to represent a single episode of infection. Patients who isolated coagulase-negative staphylococci from 2 separate blood cultures taken 24–48 hours apart, or from a single positive blood culture combined with a serum CRP ≥ 10 mg/L and clinical features suggestive of infection, were included in the analysis. All other contaminants were grouped in the HAI excluded category.
2. Presumed HAI: Clinical signs and symptoms of infection, such as respiratory distress, apnea, tachycardia, abdominal distention, temperature instability, lethargy and vomiting; in the presence of a CRP ≥ 10 mg/L and a negative blood culture, where antibiotic treatment was continued for ≥5 days.
3. Excluded HAI: Clinical signs and symptoms of infection, such as respiratory distress, apnea, tachycardia, abdominal distention, temperature instability, lethargy and vomiting; in the presence of a CRP ≤ 10 mg/L and a negative blood culture, where antibiotic treatment was discontinued within 48–72 hours based on local treatment guidelines.

Small for gestational age (SGA) was defined as birth weight for gestational age below the 10th centile.[21] Invasive ventilation included any form of ventilation through an endotracheal tube. Central venous catheters (CVC) were included as a variable when present at the time of investigation for infection, or present in the 48 hours before the investigation. The diagnosis of bronchopulmonary dysplasia was based on the Vermont Oxford Network algorithm of supplemental oxygen requirement at 36 weeks postmenstrual age.[22] Patent ductus arteriosus was diagnosed according to the Vermont Oxford Network definition which incorporates a combination of Doppler echocardiogram and clinical criteria.[22] Severe intraventricular hemorrhage (sIVH) was defined as grades III and IV hemorrhage according to the grading method described by Papile et al.[23] Cystic periventricular leukomalacia (cPVL) was diagnosed according to the grading system by de Vries et al.[24] Necrotizing enterocolitis was classified according to the VON criteria which incorporates features from Bell staging.[22]

Statistical Analysis and Ethics Approval

Statistical analysis was performed using IBM SSPS Statistics for Macintosh, Version 27.0 using an α level of 0.05 with a corresponding 95% confidence interval, for descriptive statistics. For normally distributed continuous variables, means and standard deviations were calculated. Medians and interquartile ranges (IQR) were used for non-normally distributed continuous data. For categorical variables the χ^2 or Fisher's exact test were used. Variables with a P value <0.1 on univariate analysis were included in logistic regression analysis. Independent t-tests and one-way analysis of variance was used to compare continuous variables with normal distributions.

The Stellenbosch University Health Research Ethics Committee and the Tygerberg Hospital management reviewed and approved the study protocol (N18/09/099).

RESULTS

Epidemiology

During the study period, 715 VLBW infants (44.4% of the total neonatal unit admissions of 1609) were investigated for clinically suspected HAI after 72 hours of admission, and 162/715 (22.7%) were diagnosed with proven HAI and 158/715 (22.1%) with presumed HAI. A third of the infants diagnosed with proven HAI died (34.0%; 55/162), and 22.2% (35/158) of those with presumed HAI died. The all-cause in-hospital mortality rate for all VLBW infants during this period was 16.0% (unpublished data). During the study period, the incidence of proven HAI and presumed HAI among VLBW infants was 3.3/1000 and 3.2/1000 inpatient days, respectively.

Pathogen Distribution

The majority (99/162, 61.1%) of proven HAI episodes were caused by Gram-negative organisms [84/162 (51.9%) single Gram-negative organisms and 15/162 (9.3%) with polymicrobial growth] (Table 1). Single Gram-positive organisms accounted for 34.6% (56/162). *S. aureus* and *A. baumannii* were the most common organisms, contributing 18.5% (30/162) and 14.8% (24/162), respectively. Onset of proven HAI occurred at a median of 9 days (IQR 6–13). There was a significant difference between the age in days at onset of infection by pathogen type: Gram-negative infections [7 days, IQR 5–10]; Gram-positive infections [11 days, IQR 7–18]; and polymicrobial infections [10 days, IQR 6–13], $P = 0.003$).

Antimicrobial resistance was common, with methicillin-resistance present in 73.3% (22/30) of *S. aureus* isolates. Among *Klebsiella* spp., 73.9% (17/23) produced extended-spectrum β-lactamase, 83.3% (20/24) of *A. baumannii* were carbapenem resistant and 65.0% (13/20) of *S. marcescens* produced inducible β-lactamases. There were no fungal organisms cultured during the first episode of infection, and polymicrobial growth was documented in 13.6% (22/162).

Factors Associated With Proven, Presumed and Any HAI

When comparing VLBW infants without HAI to VLBW infants who developed proven HAI, lower gestational age and lower birth weight, invasive ventilation and the presence of an indwelling CVC were found to be significant (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E789). After logistic regression analysis, only ventilation and CVC remained independent risk

TABLE 1. Etiology of Proven HAI in VLBW Infants (n = 162)

Organism	Number (%)		Median Age at Onset (d, IQR)		Crude Mortality by Causative Pathogen (%)	
Gram-negative organisms	**84**	**(51.9)**	**7**	**(5–10)**	**33**	**(39.3)**
A. baumannii	24	(14.8)	5	(4–6)	11	(45.8)
Klebsiella spp.	23	(14.2)	8	(6–10)	8	(34.8)
S. marcescens	20	(12.3)	7	(5–10)	7	(35.0)
E. coli	7	(4.3)	16	(9–26)	2	(28.6)
Other*	10	(6.2)	7	(5–15)	5	(50.0)
Gram-positive organisms	**56**	**(34.6)**	**11**	**(7–18)**	**13**	**(23.2)**
S. aureus	30	(18.5)	10	(7–16)	8	(26.7)
Enterococcus spp.	10	(6.1)	11	(7–13)	4	(40.0)
CoNS	9	(5.6)	15	(11–33)	0	(0.0)
S. agalactiae	7	(4.3)	28	(13–32)	1	(14.3)
Polymicrobial growth	**22**	**(13.6)**	**10**	**(5–18)**	**9**	**(40.9)**
Gram-negative only	6	(27.3%)	4	(4–8)	6	(100.0)
Gram-positive only	7	(31.8%)	11	(5–32)	2	(28.6)
Mixed growth	9	(40.9%)	12	(10–21)	1	(11.1)
Total	**162**	**(100.0)**	**9**	**(6–13)**	**55**	**(34.0)**

*Other: *E. cloacae* (n = 3, *P. aeruginosa* (n = 2), *P. mirabilis* (n = 2), unspecified other (n = 3).
CoNS indicates coagulase-negative staphylococci; HAI, healthcare-associated infection; IQR, interquartile range; VLBW, very low birth weight.

TABLE 2. Factors Associated With Proven, Presumed and Any HAI

Risk Factor	Proven HAI*			Presumed HAI*			Any HAI*		
	OR	(95% CI)	*P*	OR	(95% CI)	*P*	OR	(95% CI)	*P*
Gestational age (wks), median (IQR)	0.934	(0.827–1.056)	0.275	0.745	(0.660–0.841)	<0.001	0.861	(0.755–0.981)	0.025
Birth weight (g), median (IQR)	1.000	(0.999–1.001)	0.928				0.999	(0.998–1.001)	0.305
Small for gestational age, n (%)				5.041	(2.556–9.940)	<0.001	2.269	(1.190–4.328)	0.013
Delivery outside of tertiary facility, n (%)				1.232	(0.600–2.529)	0.570	1.365	(0.757–2.460)	0.301
Central venous catheter, n (%)	8.400	(4.305–16.390)	<0.001	3.491	(1.695–7.189)	0.001	5.379	(2.903–9.967)	<0.001
Invasive ventilation, n (%)	3.704	(2.181–6.291)	<0.001	6.119	(3.505–10.684)	<0.001	4.679	(2.943–7.440)	<0.001

*Only factors with $P < 0.1$ on univariate analysis included in logistic regression analysis.
CI indicates confidence intervals; HAI, healthcare-associated infection; IQR, interquartile range; OR, odds ratio.

factors (Table 2). VLBW infants with a CVC and invasive ventilation were 8.4 and 3.7 times more likely to have proven HAI.

Compared with VLBW infants without HAI, those who developed presumed HAI were characterized by lower gestational age and SGA, delivery outside of a tertiary facility, invasive ventilation and the presence of an indwelling CVC (Table, Supplemental Digital Content 2, http://links.lww.com/INF/E790). After logistic regression analysis all but delivery outside of tertiary facility remained independent risk factors (Table 2). SGA, CVC and invasive ventilation were associated with a 5.0-, 3.5- and 6.1-times increased likelihood of being diagnosed with presumed HAI.

When combining presumed and proven HAI (any HAI) and comparing it to VLBW without HAI, lower gestational age, lower birth weight, SGA, delivery outside of a tertiary facility, invasive ventilation and the presence of an indwelling CVC reached significance on the univariate analysis (Table, Supplemental Digital Content 3, http://links.lww.com/INF/E791). Lower gestational age, SGA, CVC and invasive ventilation remained independent factors associated with any HAI after logistic regression analysis (Table 2). VLBW infants with SGA, CVC and invasive ventilation were found to be 2.3, 5.4 and 4.7 times more likely to be diagnosed with any HAI.

Short-term Outcomes

All comorbidities, except for severe intraventricular hemorrhage, occurred more frequently in VLBW infants with any HAI, compared with those without HAI (Table 3). Those with any HAI also had a longer hospital stay [44 (25–65) days vs. 38 (26–53) days; $P < 0.001$] and increased mortality [90/320 (28.1%) vs. 21/395 (5.3%); $P < 0.001$]. Gram-negative HAI tended to have a shorter hospital stay [29 (10–50) days vs. 52 (28–72) days; $P < 0.001$] and higher mortality [33/84 (39.3%) vs. 13/56 (16.1%); $P = 0.035$] than those with Gram-positive HAI.

DISCUSSION

HAI, both proven and presumed, contributes substantially to morbidity and mortality among VLBW infants at this tertiary neonatal unit in South Africa.

The main strength of this study is the inclusion of presumed HAI in our analysis. The prevalence of presumed HAI among VLBW infants has not been well described and can therefore not be compared with other facilities and countries. We included a large sample of VLBW infants investigated for suspected HAI with robust laboratory investigation for infection using CRP, complete blood count and blood culture. The retrospective nature of this study was a major limitation. This was also a single-center study at a tertiary referral hospital, and subsequently, the results may not be generalizable to other facilities in low-middle income countries.

The incidence of proven and presumed HAI of 3.3/1000 and 3.2/1000 in-patient days, respectively, is equal to the previously published rate of 3.3/1000 in-patient days for the period of 2014–2018, for the same neonatal unit at Tygerberg hospital (term infants included; proven HAI).[25] However, our study only included the first episode of proven HAI, and if all proven HAI among VLBW for the study period were to be included, the incidence will likely be much higher.

TABLE 3. Short-term Outcomes of VLBW Infants

	HAI Excluded	Any HAI	Proven HAI	Presumed HAI
n	395	320	162	158
Length of hospital stay (d), median (IQR)	38 (26–53)	44 (25–65)*	37 (15–57)	53 (33–70)†
Severe IVH, n (%)	14 (3.5)	18 (5.6)	12 (7.4)	6(3.8)
Cystic PVL, n (%)	11 (2.8)	37 (11.6)*	20 (12.3)*	17 (10.8)
NEC, n (%)	22 (5.6)	74(23.1)*	24 (17.9)*	50 (31.6)†
PDA, n (%)	37 (9.4)	60 (18.8)*	29(17.9)*	31 (19.6)
BPD, n (%)	4 (1.0)	14 (4.4)*	5 (3.1)	9 (5.7)
Mortality, n (%)	21 (5.3)	90 (28.1)*	55 (34.0)*	35 (22.2)†

*Compared with HAI excluded, $P < 0.05$.

†Compared with proven HAI.

BPD indicates bronchopulmonary dysplasia; HAI, healthcare-associated infection; IQR, interquartile range; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; VLBW, very low birth weight.

The overall period prevalence of proven HAI among VLBW infants at our hospital (162/1609; 10.1%) is higher than that reported in China (4.4%),[26] similar to proven HAI prevalence in Singapore (12.9%),[27] but markedly lower than those reported in other resource-limited settings such as Bangladesh (53.2%),[28] Brazil (34%)[29] and Egypt (21.5%).[30] Kenya and Nigeria have reported proven HAI prevalence of 16.9% and 52.5%, respectively, but this included neonates of all birth weight and gestational age categories, and these studies were performed more than 20 years ago.[31,32] It is difficult to compare the prevalence of proven HAI with other units in Africa, as there is a paucity of data on VLBW infants, as well as differences in definitions used to classify proven HAI (72 hours vs. 7 days).[8]

The majority of proven HAI was caused by antimicrobial-resistant Gram-negative organisms, with infection onset earlier than Gram-positive organisms, and associated with a higher risk of mortality. The predominance of Gram-negative pathogens is in keeping with reports from Ethiopia,[33] Nigeria[34] and Johannesburg (South Africa).[35] However, it is in contrast to reports from Tanzania,[36] where Gram-positive organisms, specifically *Staphylococcus aureus*, predominated, and to reports form high-income countries, where coagulase-negative staphylococci predominated..[37] Interestingly, there has been a recent report of increases in Gram-negative infections in Utrecht, Netherlands.[38]

Lower gestational age and lower birth weight has been found to be inversely related to an increased risk of infection by several authors.[5,39,40] Although not consistently found to be an independently associated with HAI in our analysis, it should continue to be considered a major associated factor based on clinical experience and previous publications. Our findings confirmed that the presence of a CVC poses a significant risk of HAI, as has been described in previous publications.[39,41–43] Invasive ventilation has also been associated with an increased risk of HAI,[40] but can also be used as an indication of the severity of the underlying illness.

Human immunodeficiency virus (HIV) exposure was not statistically associated with the presence or absence of HAI, which is in contrast with previous publications. Kabwe et al[44] found decreased odds of proven HAI in Zambian babies born to mothers with HIV; and in a recent study in Johannesburg, South Africa, it was found that babies born to mothers with HIV but not living with HIV had a 1.4-fold increased odds of developing HAI.[45]

The higher incidence of cPVL, NEC, patent ductus arteriosus and bronchopulmonary dysplasia among infants with any HAI episode is not surprising and in keeping with the increased HAI associated risk described by several authors, especially in neonates with multiple episodes of infection.[46,47]

The all-cause mortality in the VLBW admission cohort over the 2-year period was 16.0% (unpublished data). This is higher than the mortality reported from high-income settings, for example, Germany (9.9%)[48] and Israel (13.8%),[49] and markedly lower than that reported from other African neonatal units [Johannesburg (26.6%),[50] Limpopo (22.6%)[51] and Malawi (58%)[52]]. Gram-negative infections are associated with a higher risk of death,[36,53] and our findings were consistent with this finding as the mortality of single and polymicrobial Gram-negative infections was 40.4% (40/99). The shorter hospital stay observed among VLBW infants with Gram-negative HAI compared with Gram-positive HAI in this study is most likely caused by the higher mortality rate experienced by those with Gram-negative HAI.

The diagnosis of presumed HAI is controversial: There are many conditions that mimic infections in the neonate, and there are noninfectious causes of raised inflammatory markers like CRP. However, negative blood cultures may not necessarily indicate the absence of a blood stream infection, as obtaining adequate inoculum volumes (≥1 mL of blood) in VLBW infants is challenging.[54] Subsequently, it is important to describe this group of patients, as often they receive antimicrobial therapy for periods of 5 days or longer. In the era of increasing antimicrobial resistance, further research into this group is essential to guide appropriate antimicrobial stewardship, especially in neonatal units where access to microbiological services is limited. Additionally, neonates with presumed HAI are at higher risk of adverse neurological outcomes,[13,14] highlighting the importance of further research to identify possible areas of intervention to improve outcomes.

The WHO published "Every newborn: an action plan to end preventable deaths," to reach the target of 10 or less neonatal deaths per 1000 live births by 2035[55] and the United Nations have developed Sustained Development Goals, including goal number 3, which aims to reduce neonatal mortality to at least as low as 12 per 1000 live births by 2030.[56] As HAI remain a major contributor to neonatal mortality, the prevention there-of is paramount to reducing neonatal mortality. However, the lack of a consensus definition and the limited data pertaining to risk factors and accurate diagnosis, especially related to presumed infections, is a challenge that will need to be addressed urgently.

CONCLUSION

Healthcare-associated infections, albeit proven or presumed, remains a major contributor to neonatal morbidity and mortality in South Africa, and further research is urgently needed to improve neonatal outcomes.

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Erratum

Early Transition to Oral Antimicrobial Therapy Among Children With *Staphylococcus aureus* Bacteremia and Acute Hematogenous Osteomyelitis: ERRATUM

In the article, "Early Transition to Oral Antimicrobial Therapy Among Children with Staphylococcus aureus Bacteremia and Acute Hematogenous Osteomyelitis" that appeared on pages 690–695 of the September 2022 issue of *The Pediatric Infectious Disease Journal*, was originally published, inadvertently omitting Table 4, which can be found below.

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Sanchez MJ, Patel K, Lindsay EA, et al. Early transition to oral antimicrobial therapy among children with staphylococcus aureus bacteremia and acute hematogenous osteomyelitis. *Pediatr Infect Dis J*. 2020;41: 690–695.

TABLE 4. Comparison of Severity of Illness Cohorts Based on Short- and Intermediate-term Outcome Measures

	Mild (0–3)	Moderate (4–7)	Severe (8–10)	P
Inpatient hospital LOS (d), median (IQR)	4.8 (3.8–5.8)	7.4 (5.6–10.7)	16.4 (11.5–24.4)	<0.001
ICU LOS (d), median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	2.0 (0.0–7.3)	<0.001
Bacteremia (d), median (IQR)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	4.0 (2.0–6.0)	<0.001
Duration of IV Abx (d), median (IQR)	3.6 (3.0–5.4)	6.5 (4.6–10.5)	14.3 (11.0–29.8)	<0.001
Total Abx duration (d), median (IQR)	34.5 (30.9–45.6)	44.7 (34.3–67.6)	60.7 (44.6–130.4)	<0.001
Readmission, n (%)	6 (7.5)	2 (2.0)	18 (26.5)	<0.001
Treatment failure*, n (%)	0 (0.0)	5 (5.1)	10 (14.7)	<0.001

*Treatment failure is defined as recurrence of infection requiring additional Abx therapy or surgery after discharge, chronic osteomyelitis or recrudescence of bacteremia.
ABX indicates antibiotics; ANOVA, analysis of variance; ICU, intensive care unit; IV, intravenous; IQR, interquartile range.
P value is based on 1-way ANOVA followed by Tukey test for multiple comparisons. Nonparametric testing was conducted with the Kruskal-Wallis method for 3 group comparisons. *P* value is based on Fisher exact test.