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MAJOR ARTICLE

Multidrug-Resistant Bacterial Infections Among Very Low Birthweight Infants With Late-Onset Sepsis in Johannesburg, South Africa

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Background. An estimated 2.4 million babies died within the first 28 days of life in 2020. The third leading cause of neonatal death continues to be neonatal sepsis. Sepsis-causing bacterial pathogens vary temporally and geographically and, with a rise in multidrug-resistant organisms (MDROs), pose a threat to the neonatal population.

Methods. This was a single-center, retrospective study of very low birth weight (VLBW) infants with late-onset sepsis (LOS) admitted to a neonatal unit in South Africa. We aimed to calculate the prevalence of multidrug-resistant (MDR) infections in this population. The data collected included demographic and clinical characteristics, length of hospital stay, risk factors for MDRO and mortality, and microbiology results. Logistic regression was used to assess the association between prespecified risk factors with MDR infections and mortality.

Results. Of 2570 VLBW infants admitted, 34% had LOS, of which 33% was caused by MDROs. Infection with *Acinetobacter* spp., *Pseudomonas* spp., extended-spectrum beta-lactamase *Klebsiella* spp., or *Escherichia coli* was associated with the highest mortality in the LOS cohort. Infants with congenital infections (adjusted odds ratio [aOR], 5.13; 95% CI, 1.19–22.02; $P = .028$) or a history of necrotizing enterocolitis (aOR, 2.17; 95% CI, 1.05–4.49; $P = .037$) were at significantly higher risk for MDR infections.

Conclusions. More than one-third of LOS cases in VLBW infants were caused by MDROs in this study. MDR infections cause substantial neonatal mortality. Antimicrobial stewardship programs, infection control protocols, and ongoing surveillance are needed to prevent further emergence and spread of MDR infections worldwide.

Keywords. neonatal sepsis; sub-Saharan Africa; very low birthweigth infants.

Despite significant progress in decreasing global childhood mortality rates in the last 3 decades, the progress in decreasing neonatal mortality rates (NMRs) has plateaued. In 2020 alone, 2.4 million babies died within the first month of life [1, 2]. Disparities in NMRs exist across regions and countries, with Sub-Saharan Africa and Southeast Asia accounting for 79% of the total burden of neonatal deaths [2, 3]. In South Africa, for example, the neonatal mortality rate in 2018 was 11 deaths for every 1000 live births, compared with 3.5 deaths for every 1000 live births in the United States [4]. Furthermore, reported NMRs in low- to middle-income countries (LMICs) are likely inaccurate. South African databases and global agencies report neonatal death rates; however, these estimates are variable, which highlights the need for more accurate methods, such as additional estimation techniques [5, 6].

Among neonates, sepsis continues to be the third leading cause of global mortality, preceded by prematurity and intrapartum-related events [7]. These top 3 global causes of neonatal death have remained the same for decades. Rhoda et al. reported causes of neonatal death in South Africa from the years 2012 to 2016 and estimated that ~13% of all neonatal deaths among babies weighing >1 kg were due to infection [5]. The bacterial pathogens responsible for such infections change, both geographically and temporally [8]. Although epidemiological data from low- to middle-income countries (LMICs) are insufficient at this time, we have strong evidence to suggest that different causative organisms exist among developed and developing countries [9, 10]. As the microbiological patterns change with time, this ongoing phenomenon gives rise to pathogens resistant to first-line antibiotic therapy, impacting morbidity and mortality of neonates today and in the future.

The emergence of multidrug-resistant (MDR) infections that began in the mid-1990s has now become an urgent matter. The World Health Organization (WHO) has claimed antimicrobial resistance (AMR) as one of the top 10 global public health

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threats facing humanity [11]. A major challenge to addressing AMR is understanding the true burden, especially in regions where data and surveillance are limited [12]. In a South African neonatal unit, Ballot et al. reviewed multidrug-resistant *Enterobacterales* (MDRE) and found an increasing number of MDRE isolates between 2013 and 2015 and the emergence of carbapenem-resistant *Enterobacterales* [13]. Many neonatal intensive care units (NICUs) across other LMICs experienced a similar emergence of resistant pathogens; therefore, interventions to help delay the emergence and outbreaks of resistant pathogens are a pressing matter [14–16]. Infection prevention and surveillance of neonatal sepsis are crucial to conserve the efficacy of currently used antibiotics and delay the progression of AMR [17–19]. Furthermore, identifying risk factors for the development of antimicrobial-resistant infections among neonates, specifically the very low birthweight (VLBW) infant population, will help us in our effort to prevent significant morbidity and mortality. Additionally, epidemiological studies in LMICs are crucial in estimating the impact AMR has on NMRs and reducing existing disparities [20].

This study aims to estimate the prevalence of MDR infections in VLBW infants with late-onset sepsis (LOS) in the NICU at the Charlotte Maxeke Academic Hospital in Johannesburg, South Africa. Additionally, we aim to identify risk factors associated with MDR infections and increased mortality and to identify the distribution of bacterial pathogens and their associated mortality rate in infants with LOS.

METHODS

Study Design and Patients

In this single-center, retrospective cohort study, we identified VLBW infants admitted to the NICU at Charlotte Maxeke Academic Hospital in Johannesburg, South Africa, between January 2015 and December 2020. Infants with a birth weight between 401 and 1500 g and a gestational age >22 weeks who were admitted within 48 hours of birth were included. We identified infants with LOS (n = 869) and those with multidrug-resistant organisms (MDROs), as defined below. All infants with positive blood and cerebrospinal fluid (CSF) cultures meeting MDRO definitions were included. Infants with an isolated positive urine and/or respiratory culture were excluded unless a concomitant blood and/or CSF infection was detected. Patients with >1 episode of LOS were classified as infants with MDRO if that patient had at least 1 bacterial isolate that met criteria as MDRO in any 1 episode of LOS. If a patient cultured the same pathogen repeatedly, the bacterial pathogen was only included in the data analysis a single time.

Data Collection

We analyzed data collected from an existing neonatal database created in Research Electronic Data Capture (REDCap) and hosted by the University of Witwatersrand [21]. The data collected included maternal/neonatal demographic and clinical characteristics, length of stay, risk factors for MDRO and mortality, microbiology results, and all-cause mortality.

Definitions

Infants classified as "outborn" were born at home or at a different facility and referred to the Charlotte Maxeke Hospital NICU. Early-onset sepsis (EOS) was defined as culture-proven sepsis within 72 hours of life. Late-onset sepsis (LOS) was defined as a single positive blood or CSF culture after 72 hours of life, including infants with coagulase-negative *Staphylococcus* (CoNS) spp. Bacterial isolates classified as MDRO included methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacterales*, extended-spectrum beta-lactamase (ESBL)–producing *Klebsiella* species, or any gram-negative bacterium with nonsusceptibility to at least 1 antimicrobial drug in 3 or more classes. Further, patients were subclassified into 2 groups: (1) MDRO infants with at least 1 bacterial isolate that met criteria for MDRO and (2) non-MDRO infants with bacterial isolates that did not meet criteria for MDRO. Necrotizing enterocolitis (NEC) was defined as modified Bell's stage 2 or 3 [22]. Congenital infection was defined as a child infected at birth with 1 of the following: *Toxoplasma gondii*, *Rubella*, *Treponema pallidum* (syphilis), cytomegalovirus, herpes simplex, Zika, parvovirus b19, or varicella zoster. Mortality was defined as all-cause mortality during hospitalization.

Statistical Analysis

Categorical data, presented by frequency tables and percentages, were compared using Pearson's chi-square test. Continuous variables, presented in terms of medians and interquartile ranges (IQRs), were compared between groups using the Mann-Whitney *U* test.

We used univariate logistic regression analysis to assess the risk factors associated with mortality in the LOS cohort and to compare baseline variables between MDRO and non-MDRO patients within the LOS cohort. We then used multivariate logistic regression to investigate the risk factors associated with LOS caused by MDRO, adjusted for birthweight, gestational age, sex, and length of stay in the NICU. Variables included in the final model were prespecified and selected based on clinical knowledge and literature review. Odds ratios (ORs) and 95% CIs were calculated. A P value <.05 was interpreted as statistically significant. All statistical analyses were performed using Stata (version 16.1; StataCorp LLC, College Station, TX, USA).

Patient Consent

This study did not require patient consent and was reviewed and approved by the Human Research Ethics Committee of

the University of the Witwatersrand and the Institutional Review Board of Vanderbilt University Medical Center.

RESULTS

A total of 2780 VLBW infants were admitted to the Charlotte Maxeke NICU during the study period (Table 1). Two hundred ten infants (7.5%) did not meet inclusion criteria and were excluded from the study (gestational age <22 weeks n = 7 and transferred to outside facility n = 203). Of the 2570 VLBW infants who were included, the median maternal age was 29 years. Of the mothers, 1927 (75%) attended at least 1 antenatal care visit before delivery. Approximately 30% (n = 780) of mothers had known HIV infection, of whom ~93% were receiving antiretroviral therapy. Maternal hypertension was also common (26%).

Among the infants enrolled, 52% were female. The median birth weight was 1100 g, and the median length of time in the NICU was 28 days. Approximately 34% (n = 869) were characterized as having LOS, with a prevalence of 287 (33%) LOS cases caused by MDROs. The prevalence of LOS caused by MDROs in the entire cohort was ~11%. A total of 872 (34%) VLBW infants died during their hospitalization, compared with 119 (41%) among the infants with LOS caused by MDROs.

Table 1. Maternal and Neonatal Characteristics

Total (n = 2570)	No. (%)
Maternal characteristics	
Maternal age, median [IQR], y	29 [24–33]
Antenatal care	
Yes	1927 (75)
No	512 (19.9)
Unknown	131 (5.1)
Chorioamnionitis	68 (2.6)
Maternal hypertension (chronic or PIH)	673 (26.2)
Maternal HIV infection	780 (30.4)
Maternal antiretroviral therapy	728 (93.3)
Maternal syphilis (RPR positive)	51 (2)
Maternal tuberculosis	21 (<1)
Maternal diabetes	32 (1.2)
Prenatal steroids	695 (27)
Neonatal characteristics	
Sex	
Male	1225 (47.7)
Female	1345 (52.3)
Gestational age, median [IQR], wk	29 [27–30]
Birth weight, median [IQR], g	1100 [900–1300]
Total days in NICU, median [IQR]	28 [11–47]
Place of birth	
Inborn	2122 (82.6)
Outborn[a]	440 (17.2)
Major birth defect	57 (2.2)
Congenital HIV	19 (<1)
Congenital Infection	45 (1.8)
LOS	869 (33.8)
LOS caused by MDRO	287 (33)
Death	872 (34)

Abbreviations: CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; IQR, interquartile range; LOS, late-onset sepsis; MDRO, multidrug-resistant organism; NICU, neonatal intensive care unit; PIH, pregnancy induced hypertension; RPR, rapid plasma reagent.

[a]Children classified as "outborn" were born at home or a different facility and referred and admitted to CMJAH.

Types of Pathogens

A total of 1305 bacterial pathogens were isolated from 869 patients classified as LOS; 313 (36%) were gram-positive bacteria, 273 (31.4%) gram-negative bacteria, 190 (21.9%) polymicrobial, and 93 (10.7%) other bacteria (Figure 1). The most common bacterial isolate was CoNS (333/1305; 25.5%), followed by *Klebsiella* spp. (274/1305; 21%), *Acinetobacter* spp. (158/1305; 12%), and MRSA (130/1305; 10%). The most common bacterial isolates causing polymicrobial infections were CoNS (121/190; 64%), *Klebsiella* spp. (118/190; 62%), and MRSA (61/190; 32%). The 2 most common bacterial isolates categorized as "other bacteria" were *Serratia* spp. (29/133; 22%) and extremely drug-resistant (XDR) *Acinetobacter baumannii* (25/133; 19%).

Among the LOS cohort, the highest mortality occurred among patients infected with gram-negative bacteria. *Acinetobacter* spp., *Pseudomonas* spp., ESBL *Klebsiella* spp., and *Escherichia coli* were the pathogens with the highest mortality, at 53%, 45%, 43%, and 42%, respectively (Figure 2).

Two hundred eighty-seven (33%) of the 869 patients with LOS had MDRO infections. The pathogen distribution in the MDRO subgroup consisted of 69 (24.1%) gram-positive bacteria, 102 (35.5%) gram-negative bacteria, 115 (40.1%) polymicrobial infections, and 1 (0.3%) other bacterium (Figure 1).

Mortality Risk Factors

We assessed the risk factors for all-cause mortality in this cohort of VLBW infants with LOS (Table 2). Univariate logistic regression revealed a 12% lower likelihood of death for each 1-week increase in gestational age (OR, 0.88; 95% CI, 0.82–0.94; $P = .001$) and a roughly 20% lower likelihood of death for each 100-g increase in birthweight (OR, 0.81; 95% CI, 0.75–0.87; $P = .001$). VLBW infants who received respiratory support at 36 weeks had a 74% lower likelihood of mortality (OR, 0.26; 95% CI, 0.18–0.37; $P = .001$). Infants with LOS who required mechanical ventilation during their hospitalization had a nearly 3.5-fold higher likelihood of death (OR, 3.56; 95% CI, 2.67–4.75; $P \leq .001$), while those diagnosed with a congenital infection had a roughly 4-fold higher likelihood of death (OR, 4.29; 95% CI, 1.10–16.7; $P = .036$). Infants with LOS who had a prior episode of EOS were 1.58 times more likely to die, though this was not statistically significant (OR, 1.58; 95% CI, 0.92–2.70; $P = .094$).

MDRO Risk Factors

Among the cohort of infants with LOS, we compared infants with MDRO infections with those with non-MDRO infections

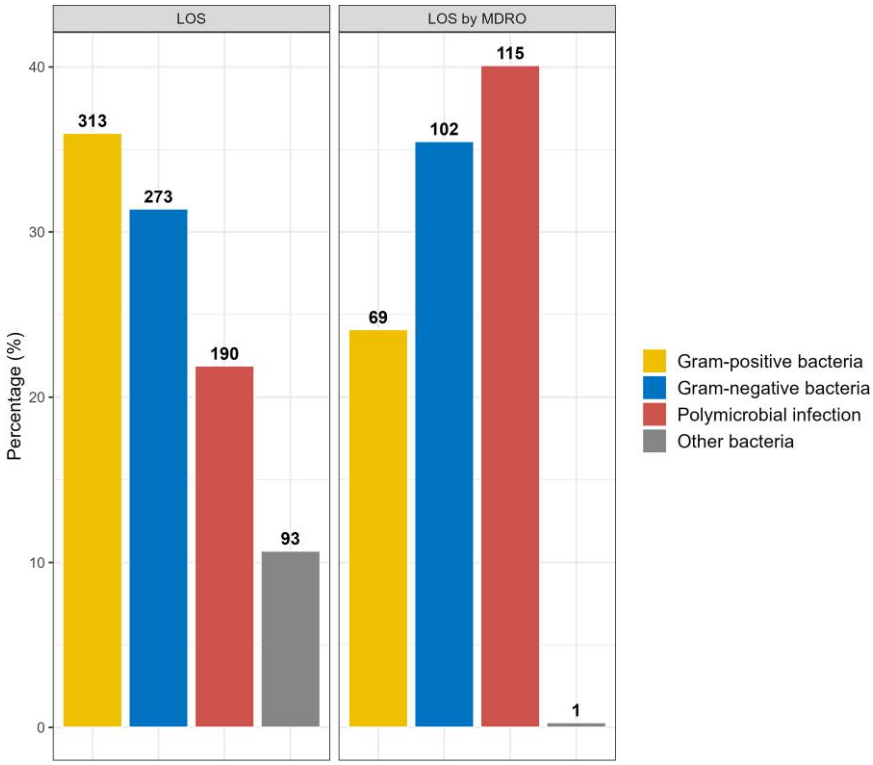

Figure 1. Pathogen distribution in LOS and MDRO groups. Abbreviations: LOS, late-onset sepsis; MDRO, multidrug-resistant organism.

(Table 3). Infants in the MDRO group had a longer median length of stay (48 days) compared with the non-MDRO group (43 days; $P = .004$). The proportion of infants who died before discharge was higher in the MDRO group when compared with the non-MDRO group, 41% and 34%, respectively ($P = .036$). The MDRO group had more infants with the following diagnoses: patent ductus arteriosus (25%; $P = .01$), respiratory support at 36 weeks (37%; $P < .001$), and NEC (27%; $P < .001$). There was a higher proportion of infants with EOS and fungal sepsis in the MDRO group, though neither was statistically significant (7% vs 6% and 22% vs 16%, respectively).

In multivariate logistic regression, we assessed prespecified maternal and neonatal risk factors that are associated with LOS caused by MDRO infections (Table 4). When adjusted for birth weight, gestational age, sex, and length of NICU stay, only congenital infection (aOR, 5.13; 95% CI, 1.19–22.02; $P = .028$) and prior history of NEC (aOR, 2.17; 95% CI, 1.05–4.49; $P = .037$) were significantly associated with being diagnosed with an MDRO infection.

DISCUSSION

In this study, we found that VLBW infants admitted to a representative NICU in South Africa had a significantly high mortality rate of 34%. One-third of the VLBW infants with LOS were infected with an MDRO. South African studies have shown increasing AMR rates and AMR's impact on morbidity and mortality across NICUs [13, 23, 24].

Gram-positive bacteria were the most common LOS isolates, and this was largely due to isolation of CoNS affecting 25% of all infants with LOS. Despite the possibility of blood culture contamination with skin commensal flora, VLBW infants contribute disproportionately to CoNS-related mortality, in contrast to full-term infants who usually suffer milder symptoms [25, 26]. If CoNS isolates were excluded from the analysis, *Acinetobacter* spp. were the leading cause of LOS in this cohort. Extensively resistant *Acinetobacter* arising in NICUs worldwide is now one of the WHO's top priorities for research and development of new antibiotics. Several studies have identified risk factors associated with extensively drug-resistant *Acinetobacter baumannii* infections (XDRABIs) in neonatal units. *A. baumannii* is a difficult pathogen to eradicate once present in a hospital setting given its ability to form strong biofilms [27]. Perovic et al. reported >4800 cases of *A. baumannii* from 2017 to 2019, with the majority (60%) of cases from Gauteng province and 41% occurring in infants [28]. Length of stay, use of antimicrobials (specifically glycopeptides and aminoglycosides), mechanical ventilation, use of total parenteral nutrition (TPN), and the presence of central venous access have been identified as independent risk factors for XDRABIs

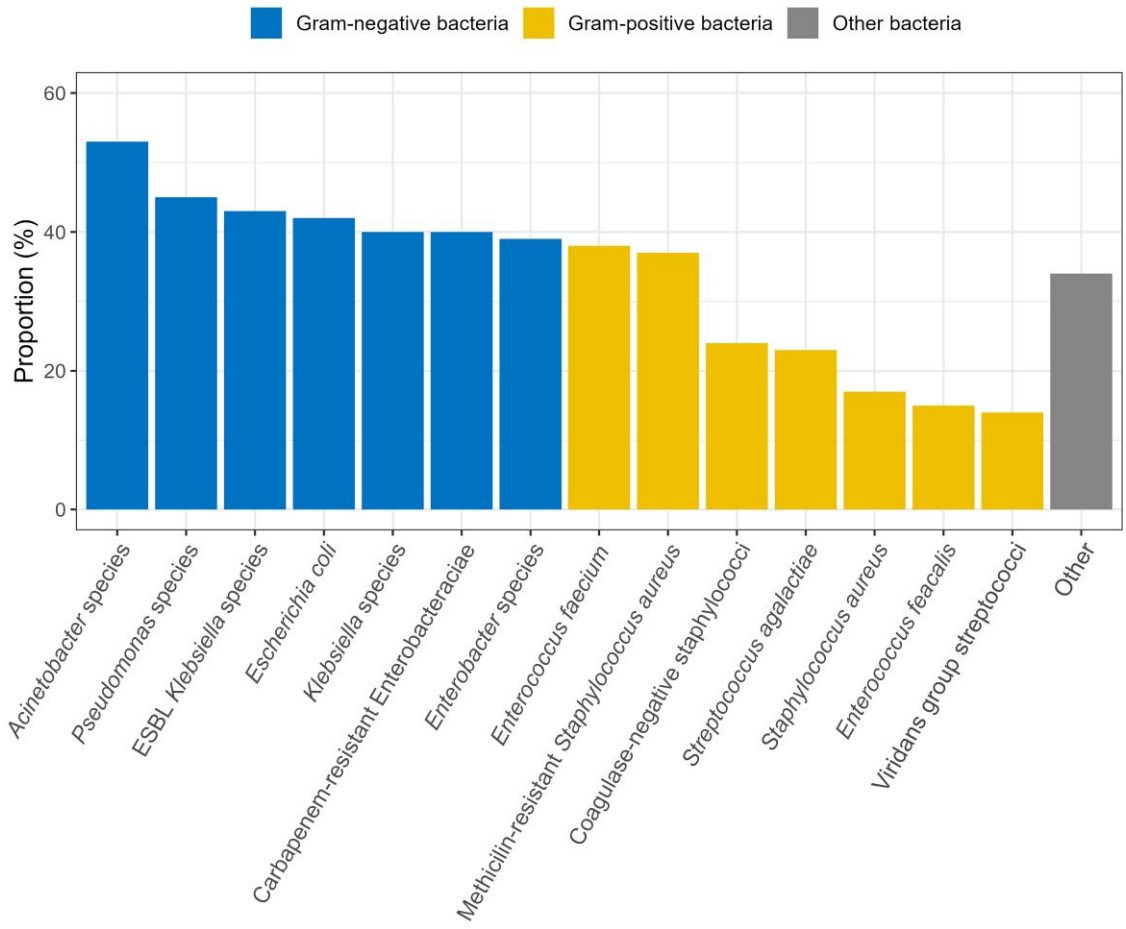

Figure 2. Proportion of deaths in LOS by isolated bacterial pathogens. Abbreviations: ESBL, extended-spectrum beta-lactamase; LOS, late-onset sepsis.

Table 2. Neonatal Risk Factors and Mortality in LOS Cohort

	OR	95% CI	*P* Value
Gestational age (per 1-wk increase)	0.88	[0.82–0.94]	<.001
Birth weight (per 100-g increase)	0.81	[0.75–0.87]	<.001
Sex			
Female	1.0	[0.76–1.32]	.979
Male	1.0	[0.76–1.32]	.979
Resuscitation in delivery room	0.89	[0.62–1.28]	.545
Respiratory support after initial resuscitation	2.86	[0.33–24.6]	.338
Respiratory support at 36 wk	0.26	[0.18–0.37]	<.001
Early-onset sepsis	1.58	[0.92–2.70]	.094
Mechanical ventilation	3.56	[2.67–4.75]	<.001
Maternal chorioamnionitis	0.96	[0.42–2.20]	.933
Maternal HIV	1.12	[0.83–1.50]	.468
Congenital HIV	1.35	[0.30–6.1]	.693
Congenital infection[a]	4.29	[1.10–16.7]	.036
Fungal sepsis	1.05	[0.73–1.50]	.791

Abbreviations: LOS, late-onset sepsis; OR, odds ratio.

[a]Toxoplasmosis (*Toxoplasma gondii*), rubella virus, syphilis (*Treponema pallidum*), cytomegalovirus, herpes simplex, parvovirus B19, Zika virus, varicella zoster virus.

[29–31]. Although gram-positive bacteria were most commonly isolated in this cohort of VLBWs with LOS, the highest mortality occurred with gram-negative infections, which is consistent with other studies [32]. When we studied the subpopulation of infants with MDR infections, polymicrobial infections were the most common, followed by gram-negative bacteria and, third, gram-positive bacteria. The distribution of pathogens was different among the subgroup with MDR infections when compared with the LOS cohort. The main pathogens responsible for LOS at any given institution can change with time, allowing for the emergence of dangerous MDROs. Establishing infection control protocols, antimicrobial stewardship programs, and ongoing surveillance are key components to combatting the threat these MDROs pose on VLBW infants.

When we studied prespecified risk factors associated with mortality among the LOS cohort, the younger, smaller infants and those requiring mechanical ventilation had a higher risk

Table 3. Neonatal Characteristics and Risk Factors by MDRO Status

Variables	MDRO (n = 287), No. (%)	Non-MDRO (n = 582), No. (%)	*P* Value
Clinical characteristics			
Sex			
Male	138 (32)	296 (68)	.592
Female	149 (34)	286 (66)	…
Gestational age, median [IQR], wk	28.5 [27–30]	28 [27–30]	.267
Birth weight, median [IQR], g	1020 [890–1230]	1070 [905–1230]	.227
Length of stay, median [IQR], d	48 [25–70]	43 [20–62]	.004
Death before discharge	119 (41)	199 (34)	.036
Risk factors			
Respiratory distress syndrome	262 (91)	536 (92)	.652
Patent ductus arteriosus	71 (25)	101 (18)	.010
Ibuprofen treatment	28/71 (39)	31/101 (31)	.015
PDA ligation	–	2/101 (2)	–
Respiratory support at 36 wk	107 (37)	139 (24)	<.001
Steroids for chronic lung disease	89 (33)	161 (30)	.315
Necrotizing enterocolitis (stage 2 or 3)	78 (27)	98 (17)	<.001
NEC surgery	33/78 (42)	32/98 (33)	.002
Congenital HIV (positive birth PCR)	4 (1.6)	3 (0.6)	.177
Early-onset sepsis	21 (7)	37 (6)	.574
Fungal sepsis	62 (22)	94 (16)	.056
Any surgery	47 (16)	65 (11)	.031

Abbreviations: IQR, interquartile range; MDRO, multidrug-resistant organism; NEC, necrotizing enterocolitis; PCR, polymerase chain reaction; PDA, patent ductus arteriosus.

Table 4. Maternal/Neonatal Risk Factors Associated With LOS Caused by MDRO

	aOR	95% CI	*P* Value
Maternal chorioamnionitis	0.76	[0.07–7.84]	.817
Maternal HIV	1.02	[0.56–1.85]	.952
Respiratory distress syndrome	1.59	[0.43–5.90]	.491
Mechanical ventilation	0.89	[0.50–1.59]	.705
Respiratory support at 36 wk	1.27	[0.691–2.35]	.438
Early-onset sepsis	0.54	[0.16–1.91]	.343
Fungal sepsis	0.76	[0.35–1.66]	.497
Congenital infection	5.13	[1.19–22.02]	.028
Necrotizing enterocolitis	2.17	[1.05–4.49]	.037
Patent ductus arteriosus	0.90	[0.44–1.85]	.782

Abbreviations: aOR, adjusted odds ratio (adjusted for birth weight, gestational age, sex, length of hospital stay); LOS, late-onset sepsis; MDRO, multidrug-resistant organism.

of mortality, as expected. Interestingly, infants requiring respiratory support at 36 weeks postmenstrual age (PMA) were significantly less likely to die. Further analysis revealed that most infants who died within this cohort were <36 weeks PMA, meaning that the infants who reached 36 weeks were more likely to survive to discharge. Among the subgroup of infants with MDRO infections, infants with congenital infections and those with a history of NEC were associated with development of an MDRO infection. Infants with congenital infections and NEC are usually exposed to prolonged antimicrobial therapy that can last several weeks. Prolonged antimicrobial therapy can lead to increasing rates of NEC [33], antimicrobial resistance, altered intestinal microbiome, and mortality in premature infants.

This study had several limitations as it was conducted at a single center. The available data were limited and did not include patient information on important risk factors associated with LOS such as central vascular access and antimicrobial exposure. Additionally, we did not describe the susceptibility patterns for all isolates. All CoNS isolates were included in the study given that the data-collecting method was not robust enough to differentiate a contaminant from CoNS-related sepsis. Lastly, paper charts were used for data collection at the time of discharge; therefore, temporal information was not available to conduct a time-to-event analysis for bacterial pathogens and the outcome of mortality. For example, if a patient had >1 episode of LOS with >1 bacterial pathogen isolated, we could not determine which bacterial pathogen was associated with the outcome of interest, mortality.

In conclusion, our study showed that LOS caused by MDROs is a serious challenge in NICUs of developing countries. More than one-third of VLBW infants with LOS had at least 1 MDRO isolated from a blood or CSF culture. From our data, we conclude that gram-negative isolates have the highest burden of mortality in this patient population, which coincides with previous studies. Antimicrobial stewardship programs, infection control protocols, ongoing surveillance, rapid diagnostic tests, and novel treating agents for MDROs are crucial. Research efforts should prioritize the development of new antibiotics and should include the neonatal population in the dosing evaluations needed for these efforts to impact the MDRO burden among these infants. Additionally, the implementation of electronic medical records, electronic prescribing, and adaptation of standardized and comprehensive reporting in LMICs would help monitor the burden of LOS and MDR infections.

Supplementary Data

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

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

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