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High Burden of Bloodstream Infections Associated With Antimicrobial Resistance and Mortality in the Neonatal Intensive Care Unit in Pune, India

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(See the Editorial Commentary by Hamer and Coffin on pages 281–2.)

Background. Antimicrobial resistance (AMR) is a growing threat to newborns in low- and middle-income countries (LMIC).

Methods. We performed a prospective cohort study in 3 tertiary neonatal intensive care units (NICUs) in Pune, India, to describe the epidemiology of neonatal bloodstream infections (BSIs). All neonates admitted to the NICU were enrolled. The primary outcome was BSI, defined as positive blood culture. Early-onset BSI was defined as BSI on day of life (DOL) 0–2 and late-onset BSI on DOL 3 or later.

Results. From 1 May 2017 until 30 April 2018, 4073 neonates were enrolled. Among at-risk neonates, 55 (1.6%) developed early-onset BSI and 176 (5.5%) developed late-onset BSI. The majority of BSIs were caused by gram-negative bacteria (GNB; 58%); among GNB, 61 (45%) were resistant to carbapenems. *Klebsiella* spp. (n = 53, 23%) were the most common cause of BSI. Compared with neonates without BSI, all-cause mortality was higher among neonates with early-onset BSI (31% vs 10%, *P* < .001) and late-onset BSI (24% vs 7%, *P* < .001). Non–low-birth-weight neonates with late-onset BSI had the greatest excess in mortality (22% vs 3%, *P* < .001).

Conclusions. In our cohort, neonatal BSIs were most commonly caused by GNB, with a high prevalence of AMR, and were associated with high mortality, even in term neonates. Effective interventions are urgently needed to reduce the burden of BSI and death due to AMR GNB in hospitalized neonates in LMIC.

Keywords. neonatal sepsis; antimicrobial resistance; neonatal intensive care unit; low- and middle-income countries.

Of 2.5 million babies who die within the first 4 weeks of life every year, 23% are estimated to die due to infectious causes, including sepsis and pneumonia [1]. Progress in neonatal survival has not kept pace with global reductions in child mortality, and neonatal deaths now account for 47% of deaths in children aged <5 years [1, 2]. In regions with the highest neonatal mortality, infections are responsible for up to 50% of neonatal deaths [1].

Facility delivery is promoted in many low- and middle-income countries (LMIC) to ensure access to emergency obstetric care and to decrease neonatal mortality. Low- and middle-income countries (LMIC) healthcare facilities increasingly provide care for premature and sick neonates in neonatal intensive care units (NICUs) [3–6]. Similar trends are seen in India, a lower-middle-income country where facility births have risen from 39% (2005–2006) to 79% (2015–2016) and neonatal mortality is high at 23 per 1000 live births in 2018 [1, 7, 8].

Hospitalized neonates are especially vulnerable to invasive infections, including bloodstream infections (BSIs), due to such factors as an immature immune system, poor skin integrity, need for life-sustaining invasive procedures, and prolonged hospital stays [9–11]. Data on the epidemiology of BSI in LMIC NICUs are scarce and often limited to outbreak investigations [12–18]. A 2019 review of neonatal sepsis in South Asia reported widespread antimicrobial resistance (AMR) and predominance of gram-negative infections, which are associated with significantly greater morbidity and mortality and have limited treatment options in neonates [19–22]. While AMR is a global crisis, India is particularly affected, with resistance to third-generation cephalosporins exceeding 70% for common gram-negative bacteria (GNB), as well as widespread carbapenem resistance in up to 70% of *Acinetobacter baumannii* and more than half of *Klebsiella pneumoniae* isolates [23].

There are scant data on the epidemiology of neonatal sepsis and associated prevalence of AMR in LMIC, especially in NICU populations. It is critical to better understand the local, regional, and global epidemiology of neonatal sepsis and AMR among hospitalized neonates in order to guide future prevention efforts and policies.

METHODS

Study Design and Population

We conducted a prospective cohort study from 1 May 2017 until 30 April 2018 in neonates admitted to the NICU at 3 tertiary care centers in Pune, India: Byramjee Jeejeebhoy Government Medical College (BJGMC) & Sassoon Hospital, Dr. D. Y. Patil Medical College, Hospital and Research Centre, and King Edward Memorial (KEM) Hospital. All neonates admitted to the NICU were enrolled and followed until discharge, transfer, or death. This minimal-risk study did not require consent and was approved by the Johns Hopkins Medicine Institutional Review Board, site ethics committees, and the Indian Health Ministry's Screening Committee.

Study Sites

BJGMC is a government medical college affiliated with Sassoon Hospital that has a 60-bed NICU. Dr D. Y. Patil Medical College is a private medical college and has a 26-bed NICU. KEM Hospital is a nongovernmental facility run by a charitable trust and has a 46-bed NICU. All participant NICUs have an open ward structure and admit inborn and outborn neonates. All hospitals have an active infection control committee. Prior to study initiation, the study team assessed microbiology laboratory capacity at all sites by. Site microbiology laboratories are accredited by the Indian National Accreditation Board for Testing & Calibration Laboratories and perform routine microbiology tests, including organism identification and antimicrobial susceptibility testing (AST). Automated methods include use of VITEK for organism identification and AST; manual methods include organism identification by agar plate and biochemical workup and AST by disk diffusion methods.

Data Sources

Neonates admitted to the NICU were identified by regular review of the admission register. Study staff performed prospective review of neonates' medical records, including baseline demographic and clinical characteristics and daily clinical and microbiology data. All laboratory studies were obtained at the discretion of the clinical teams.

Study Outcomes

The primary outcome of interest was BSI, defined as a blood culture positive for a known neonatal pathogen. Blood cultures positive for well-described contaminants were not considered BSIs. Early-onset BSI was defined as BSI occurring day of life (DOL) 0 through DOL 2, where DOL 0 is the day of birth. Late-onset BSI was defined as BSI occurring on or after DOL 3. Only first episodes of early-onset BSI and late-onset BSI were included. Secondary outcomes of interest included pathogen distribution, AMR among GNB, and all-cause mortality.

Study Cohort Definitions

All neonates admitted to the NICU were enrolled in this prospective cohort study. Neonates included in the early cohort were considered at risk for early-onset BSI by presence in the NICU during the risk period, DOL 0 through DOL 2. Neonates included in the late cohort were considered at risk for late-onset BSI by presence in the NICU during the risk period, DOL 3 or later. Neonates could be included in both cohorts. Neonates admitted to the NICU discharged home or transferred to the nursery or postpartum ward on the same day as admission were excluded from analysis.

Statistical Analyses

Descriptive analysis was performed to characterize the study population. The incidence of early-onset BSI was described as the proportion of neonates who experienced early-onset BSI among neonates in the early cohort. The incidence of late-onset BSI was described as the proportion of neonates who experienced late-onset BSI among those in the late cohort. Incidence density of late-onset BSI was expressed as the number of BSI cases per 1000 patient-days among neonates included in the late cohort; only patient-days at risk for late-onset BSI were included. All-cause mortality was expressed as a proportion of neonates deceased among admitted neonates. The Pearson χ^2 test was used to evaluate group differences in mortality. The association between variables of interest and risk of early and late-onset BSI was explored using univariate and multivariable logistic regression with multiple imputation for missing data in the adjusted model. Statistical analyses were performed using Stata version 15.0 (Stata Corp., College Station, TX).

RESULTS

During the study period, 4619 neonates were enrolled (Figure 1). Neonates discharged or transferred on the same day as NICU admission (n = 546) were excluded from analysis. An additional 94 neonates were excluded due to insufficient data. The remaining 4073 neonates served as the early and late cohort. The early cohort (n = 3341) excluded neonates admitted on DOL 3 or later (n = 732). The late cohort (n = 3178) excluded all neonates who exited the NICU before DOL 3 (n = 895). The 2 cohorts were quite similar, with a substantial proportion of inborn and low birth weight (LBW, <2500 g at birth) neonates (Table 1). Of 4073 neonates included in this study, 226 (5.5%) experienced at least 1 episode of BSI. There were 55 cases of early-onset BSI (1.6%; 95% confidence interval [CI], 1.2–2.1; Table 2). The incidence was highest in lower birth
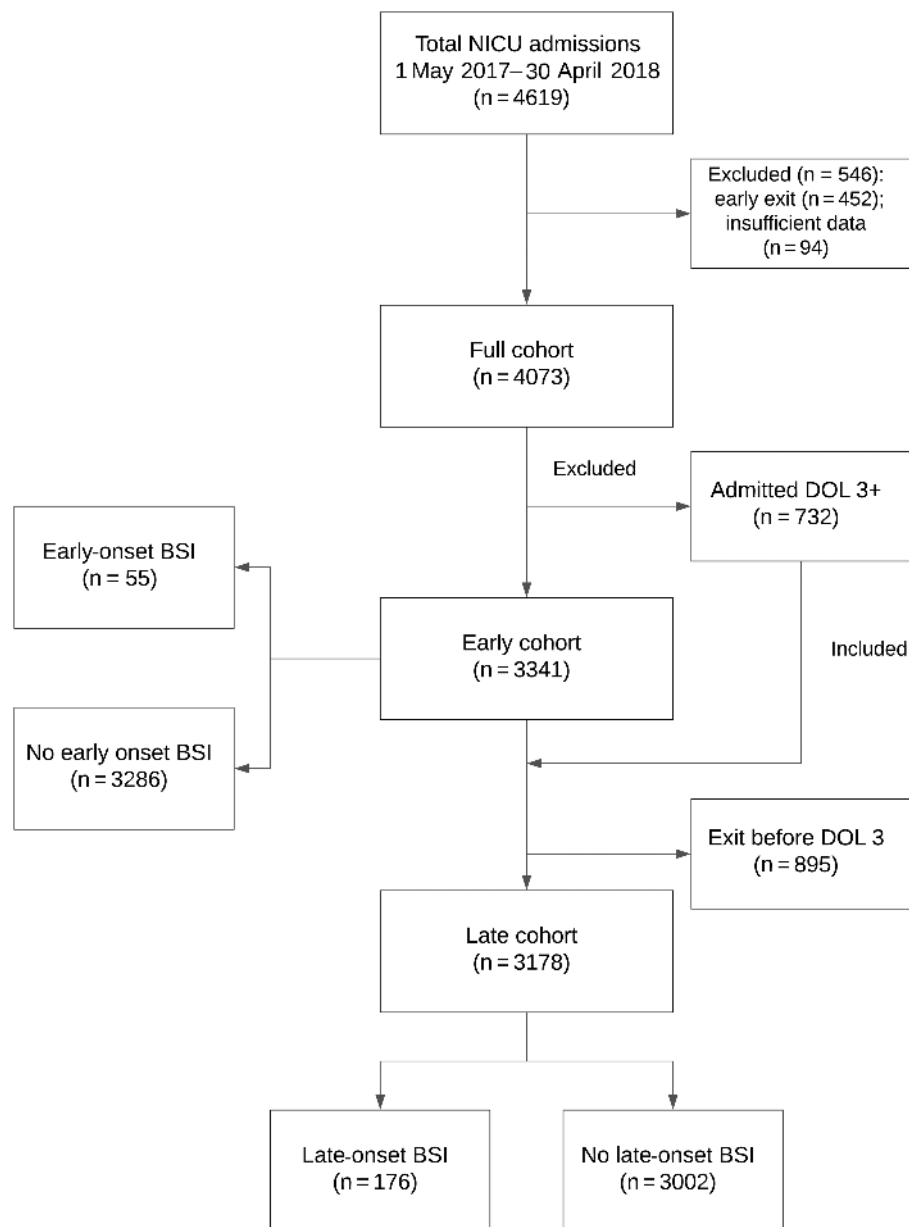
Figure 1. Study flow diagram. Neonates included in the early cohort were considered at risk for experiencing the outcome of early-onset BSI by their presence in the NICU during the risk period, DOL 0 through DOL 2. Neonates not at risk for early-onset BSI, those admitted on or after DOL 3, were excluded from the early cohort. Neonates included in the late cohort were considered at risk for experiencing the outcome of late-onset BSI by their presence in the NICU during the risk period, DOL 3 or later. Neonates not at risk for late-onset BSI, those who exited the NICU before DOL 3, were excluded from the late cohort. *Early exit, discharge (n = 26), or transfer to ward (n = 426) on same calendar day as admission. **Insufficient data, no birth weight or admission weight. Abbreviations: BSI, bloodstream infection; DOL, day of life; NICU, neonatal intensive care unit.

weight neonates, with 4.3% (95% CI, 1.9–8.3) of extremely LBW (ELBW, <1000 g) experiencing early-onset BSI. Late-onset BSI was more common than early-onset BSI; 176 neonates (5.7%, 95% CI, 4.9–6.5) experienced at least 1 episode of late-onset BSI (Table 1). Late-onset BSI was more common in neonates with lower birth weight, with 18.6% (95% CI, 12.6–25.9) of ELBW neonates and 10.0% (95% CI, 7.8–12.6) of very LBW (VLBW, 1000 g–1499 g) neonates developing late-onset BSI. The late-onset BSI rate per 1000 patient-days was 6.6 (95% CI, 5.6–7.6);

comparable rates were seen in ELBW, VLBW, and LBW neonates. The BSI rate was highest among neonates with a birth weight of 2500 g or greater, at 8.9 per 1000 patient-days (95% CI, 6.0–12.6).

The range of BSI occurrence was DOL 0 through DOL 110. The highest risk period for BSI was the first 2 weeks of life; 84.4% of infections occurred in the first 2 weeks (Figure 2). Five neonates experienced both early-onset BSI and late-onset BSI. One neonate had 2 blood cultures positive for *Staphylococcus*

Table 1. Baseline Clinical and Demographic Characteristics of Neonates at Risk for Early- and Late-onset Bloodstream Infection

Characteristic	Early Cohort (n = 3341)	Late Cohort (n = 3178)
Maternal age, median (interquartile range), y	25 (22–28)	25 (22–28)
Male, n (%)	1791 (54)	1703 (54)
Gestational age, mean (SD), wk	34.9 (3.7)	34.9 (3.7)
Preterm, <37 weeks' gestation, n (%)	1899 (64)	1807 (64)
Birth weight, mean (SD), g	1996 (702)	2005 (693)
Low birth weight, n (%)	2421 (72)	2313 (73)
Multiple gestation, n (%)	398 (12)	354 (11)
Inborn, n (%)	3115 (93)	2780 (87)
Cesarean delivery, n (%)	1335 (44)	1352 (46)
Positive-pressure ventilation at delivery, n (%)	691 (24)	573 (20)
Mechanical ventilation on admission, n (%)	368 (12)	341 (11)
Central line on admission, n (%)	256 (9)	240 (8)
Pressors on admission, n (%)	393 (13)	370 (12)
Antibiotics on admission, n (%)	1221 (41)	1333 (45)

Baseline clinical and demographic characteristics for early and late cohorts. Note that early and late cohorts overlap. A total of 2446 neonates (60% of full cohort of 4073 neonates) were included in both early and late cohorts; please see Figure 1. Select characteristics not available for all neonates in cohort; percentages calculated based on denominator of neonates with known characteristic.

Abbreviation: SD, standard deviation.

aureus on DOL 1 and DOL 4; these cultures were considered a single case of early-onset BSI.

GNB accounted for 53% of early-onset BSI and 60% of late-onset BSI. *Klebsiella* spp. (n = 53, 23%), *Acinetobacter* spp. (n = 30, 13%), and *Citrobacter* spp. (n = 25, 11%) were the 3 most common GNB identified (Table 3). Among GNB, 61 (45%) isolates were resistant to carbapenems. Gram-positive organisms were responsible for 47% of early-onset BSI and 29% of late-onset BSI; coagulase-negative *Staphylococcus* (CONS) and *S. aureus* were the most frequently identified gram-positive organisms. Among late-onset BSI, *Candida* spp. were identified in 11% of cases. There were no early-onset fungal BSI cases.

In the early cohort, the median length of stay was 4 days (interquartile range [IQR], 2–11), and 343 neonates (10%) died. The median gestational age among neonates with BSI who died was 31 weeks (IQR, 29–35). Mortality was higher in early cohort neonates with BSI compared with those without BSI (31% vs 10%, $P < .001$). ELBW neonates had an overall mortality of 57%. Among ELBW neonates with BSI (n = 8), 75% died, whereas 56% of ELBW neonates without BSI died ($P = .287$; Figure 3A). Among VLBW and LBW neonates, mortality was higher among neonates with BSI (VLBW neonates: 44% vs 16%, $P = .020$; LBW neonates: 26% vs 6%, $P < .001$). Among neonates with birth weight of 2500 g or greater, all-cause mortality was 4%; there were no deaths among the 12 neonates in this birth weight stratum with early-onset BSI.

In the late cohort, the median length of stay was 6 days (IQR, 3–12) and 245 neonates (8%) died. The median gestational age among neonates with BSI who died was 32 weeks (IQR, 29–34). All-cause mortality was higher among neonates with late-onset BSI (23% vs 7%, $P < .001$). There was no difference in all-cause mortality among ELBW neonates with and without late-onset BSI (37% vs 40%; $P = .789$; Figure 3B). In the 3 other birth weight strata, there was an increase in mortality among neonates with late-onset BSI; VLBW mortality 22% vs 12% ($P = .022$), LBW mortality 19% vs 4% ($P < .001$), and mortality among neonates with birth weight of 2500 g or greater 23% vs 3% ($P < .001$).

Among key baseline clinical and demographic characteristics, pressors on admission and antibiotics on admission were associated with an increased risk of early-onset BSI in the

Table 2. Bloodstream Infection Incidence by Birth Weight Strata, Early and Late Cohorts

Birth Weight Stratum	Early Cohort BSI Cases as a Proportion of NICU Admissions[a] (n = 3341)	Late Cohort BSI Cases as a Proportion of NICU Admissions[a] (n = 3178)	Late Cohort BSI Rate per 1000 Patient-days[b] (n = 3178)
Extremely low birth weight (<1000 g)	8/185 = 4.3% (1.9–8.3)	27/145 = 18.6% (12.6–25.9)	6.0 (4.0–8.7)
Very low birth weight (1000 g–1499 g)	9/635 = 1.4% (0.7–2.7)	64/641 = 10.0% (7.8–12.6)	5.9 (4.6–7.6)
Low birth weight (1500 g–2499 g)	27/1601 = 1.7% (1.1–2.4)	54/1527 = 3.5% (2.7–4.6)	6.7 (5.0–8.7)
2500 g+	11/920 = 1.2% (0.6–2.1)	31/865 = 3.6% (2.5–5.0)	8.9 (6.0–12.6)
Total	55/3341 = 1.6% (1.2–2.1)	176/3178 = 5.5% (4.8–6.4)	6.6 (5.6–7.6)

[a]Incidence expressed in number of cases divided by number of NICU admissions, % (95% confidence interval).

[b]Late cohort incidence density is expressed as the BSI rate per 1000 patient-days and takes into account patient-days during at-risk period or any days in the NICU occurring on or after day of life 3 (95% confidence interval).

Abbreviations: BSI, bloodstream infection; NICU, neonatal intensive care unit.
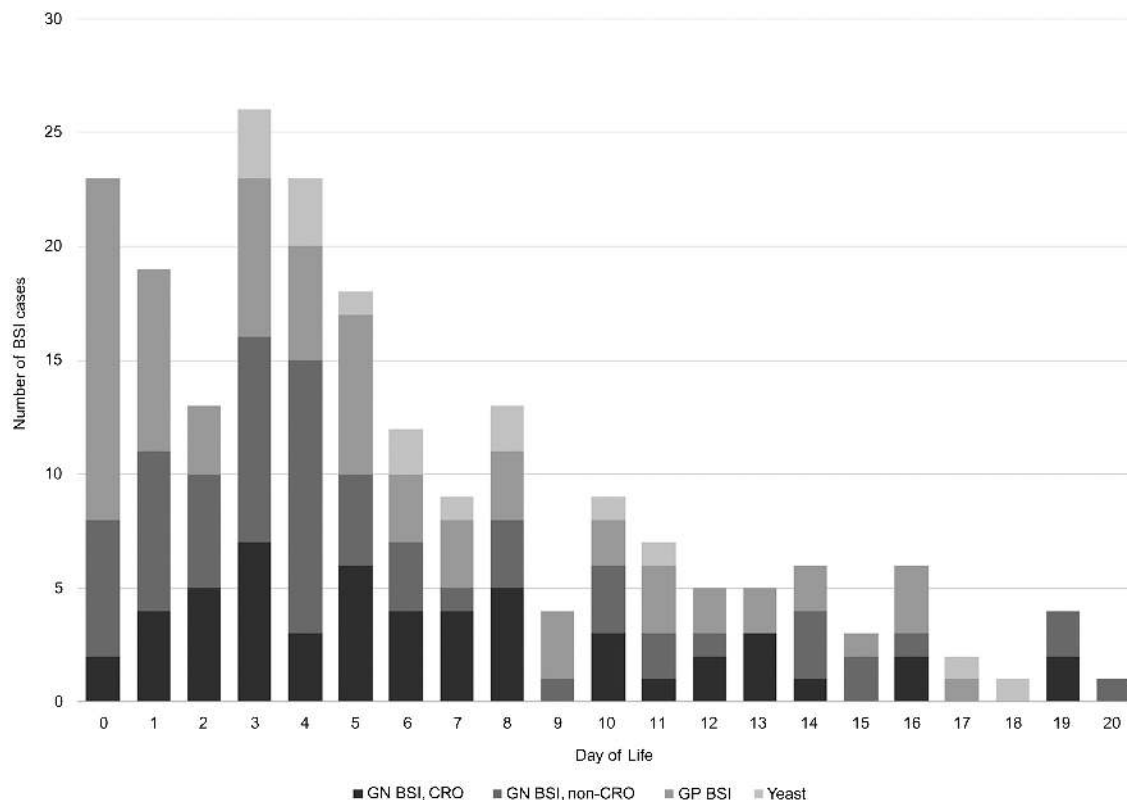
Figure 2. Distribution of BSIs by day of life (DOL). BSI cases by DOL on which blood culture was obtained. Day of birth is DOL 0. Early-onset BSI cases (n = 55) occurred on DOL 0–2, whereas late-onset BSI cases (n = 176) occurred on DOL 3 or later. Figure is censored at DOL 20; 92% (n = 212) of BSIs occurred during the first 3 weeks of life. Abbreviations: BSI, bloodstream infection; CRO, carbapenem-resistant organism; GN, gram-negative; GP, gram-positive.

adjusted model (Table 4). We performed a sensitivity analysis of neonates with complete data for variables of interest, which showed the same associations. Additionally, outborn status (adjusted odds ratio [aOR], 2.06; *P* = .040) and respiratory support on admission (aOR, 2.06; *P* = .039) were associated with early-onset BSI risk. Outborn status, any respiratory support on admission, central line on admission, and antibiotics on admission were associated with risk of late-onset BSI in the adjusted model (Table 5). A sensitivity analysis of neonates with complete data for variables of interest showed similar associations.

DISCUSSION

This prospective cohort study highlights the burden of neonatal sepsis among hospitalized neonates in India, a lower-middle-income country with widespread AMR and nearly a quarter of global neonatal deaths annually [1, 19]. In our cohort, 1.6% of neonates experienced early-onset BSI and 5.5% experienced late-onset BSI. BSIs were caused predominately by GNB, with 23% of BSIs caused by *K. pneumoniae* alone and an additional 24% caused by *Acinetobacter* spp. and *Citrobacter* spp. Alarmingly, AMR was pervasive, including to broad-spectrum antibiotics such carbapenems, limiting therapeutic options for clinicians caring for these neonates. Nearly one-third of early cohort neonates and one-quarter of late cohort neonates with

BSIs died, highlighting the toll of infections in these vulnerable hospitalized neonates. It is imperative to note that the majority of neonates who developed BSIs and died in our cohort were moderate to late preterm neonates who had already survived the first 3 days of life, the highest risk period for neonatal death [2]. These are not neonates who are likely to develop life-threatening complications of prematurity such as severe respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. Without BSIs, these neonates are likely to survive to hospital discharge and go home with their families. This cannot be overstated—the bulk of neonatal deaths due to infections in LMIC occur in neonates who would otherwise likely survive and thrive as children.

BSI incidence in our cohort is difficult to compare to incidence from most studies reporting infection rates among hospitalized neonates in LMIC, as rates are frequently reported as a function of live births, not NICU admissions [19, 24]. However, the 2016 Delhi Neonatal Infection Study, a prospective cohort study in 3 tertiary care NICUs in Delhi, India, did report an incidence of culture-positive sepsis of 6.2%, strikingly similar to our overall incidence, though this study included only inborn neonates [25]. Importantly, the majority of cases were early-onset, whereas the converse is true in our population.

Table 3.   Pathogen Distribution for Early- and Late-onset Bloodstream Infections

Organism	Early-onset BSI n = 55 n (%)	Early-onset CRO[a] n = 11 n (%)	Late-onset BSI n = 176 n (%)	Late-onset CRO[a] n = 50 n (%)	Total n = 231 n (%)	Total CRO[a] n = 61 n (%)
Gram-negative organisms	29 (53)	11 (38)	106 (60)	50 (51)	135 (58)	61 (45)
Klebsiella spp.	10 (18)	6 (67)	43 (24)	19 (45)	53 (23)	25 (48)
K. pneumoniae	10 (18)	6 (67)	42 (24)	18 (44)	52 (23)	24 (48)
Klebsiella spp., unspecified	0	…	1 (1)	1 (100)	1 (0)	1 (100)
Acinetobacter spp.	3 (5)	0	27 (15)	15 (63)	30 (13)	15 (56)
A. baumannii	1 (2)	0	11 (6)	9 (82)	12 (5)	9 (75)
Acinetobacter spp., unspecified	2 (4)	0	16 (9)	6 (46)	18 (8)	6 (40)
Citrobacter spp.	10 (18)	3 (33)	15 (9)	6 (43)	25 (11)	9 (39)
C. freundii	2 (4)	1 (50)	7 (4)	0	9 (4)	1 (13)
Citrobacter spp., unspecified	8 (15)	2 (29)	8 (5)	6 (75)	16 (7)	8 (53)
Escherichia spp.	3 (5)	1 (33)	5 (3)	3 (60)	8 (3)	4 (50)
E. coli	1 (2)	1 (100)	5 (3)	3 (60)	6 (3)	4 (67)
Escherichia spp.	2 (4)	0	0	…	2 (1)	0
Enterobacter spp.	0	…	5 (3)	2 (40)	5 (2)	2 (40)
E. cloacae			2 (1)	1 (50)	2 (1)	1 (50)
Enterobacter spp., unspecified			3 (2)	1 (33)	3 (1)	1 (33)
Pseudomonas spp.	0	…	3 (2)	1 (50)	3 (1)	1 (50)
P. aeruginosa			2 (1)	1 (50)	2 (1)	1 (50)
Pseudomonas spp., unspecified			1 (1)	…	1 (0)	…
Serratia spp.	0	…	3 (2)	1 (33)	3 (1)	1 (33)
S. marcescens			3 (2)	1 (33)	3 (1)	1 (33)
Elizabethkingia spp.	0	…	3 (2)	3 (100)	3 (1)	3 (100)
E. meningoseptica			3 (2)	3 (100)	3 (1)	3 (100)
Other gram-negative spp.	3 (5)	1 (33)	2 (1)	0	5 (2)	1 (25)
Gram-negative rod, non-fermenter	3 (5)	1 (33)	2 (1)	0	5 (2)	1 (25)
Gram-positive organisms	26 (47)	…	51 (29)	…	77 (33)	…
Staphylococcus spp.	22 (40)	…	40 (22)	…	62 (27)	…
Coagulase-negative *Staphylococcus*	7 (13)	…	18 (10)	…	25 (11)	…
S. aureus	8 (15)	…	10 (6)	…	18 (8)	…
Staphylococcus spp., unspecified	7 (12)	…	12 (7)	…	19 (8)	…
Enterococcus spp.	3 (5)	…	8 (4)	…	11 (5)	…
E. faecalis	1 (2)	…	1 (0)	…	2 (1)	…
E. faecium			1 (0)	…	1 (0)	…
Enterococcus spp., unspecified	2 (4)	…	6 (3)	…	8 (3)	…
Streptococcus spp.	1 (2)	…	3 (2)	…	4 (2)	…
Yeast	0	…	19 (11)	…	19 (8)	…
Candida spp.	0	…	19 (11)	…	19 (8)	…
C. albicans			2 (1)	…	2 (1)	…
Candida spp., unspecified			17 (10)	…	17 (7)	…

Unique bacterial and fungal isolates from neonates included in early and late cohorts. All dashes mean "not applicable." There are no missing data. For Gram-negative organisms, there were no early onset infections due to *Enterobacter, Pseudomonas, Serratia,* and *Elizabethkingia* (indicated by zero in the table). Therefore, the subcategories for each bacterial genus were left blank (example, *E. cloacae*). Additionally, the column "Early-onset CRO" included dashes for these organisms because carbapenem resistance is not applicable due to a particular organism. Under late-onset CRO, the dashes for *Escherichia* spp. and *Pseudomonas* spp, unspecified indicate testing was not done for carbapenem resistance. For Gram-positive organisms and yeast, the columns "Early-onset CRO" and "Late-onset CRO" are not applicable — dashes were used to indicate this.

[a]Percentage of carbapenem-resistant isolates is calculated using a denominator of number of isolates for which carbapenem resistance testing was performed.

Abbreviations: BSI, bloodstream infection; CRO, carbapenem-resistant organism.

In our cohort, gram-negative pathogens predominated, including *Klebsiella* spp., *Citrobacter* spp., and *Acinetobacter* spp. These data are markedly different from the data from most high-income settings, including the United States, where group B *Streptococcus* continues to be the most common cause of early-onset sepsis and CONS is responsible for the greatest proportion of late-onset sepsis cases in hospitalized neonates [9, 26, 27]. *Escherichia coli* is an important gram-negative neonatal pathogen in high-income settings and was the second most common early-onset sepsis pathogen in a large US prospective cohort study [26]. Only a small proportion of BSIs in our cohort were caused by *E. coli*; key GNB in our population included *Klebsiella* spp., *Acinetobacter* spp., and *Citrobacter* spp. While reports of NICU outbreaks due to these pathogens in
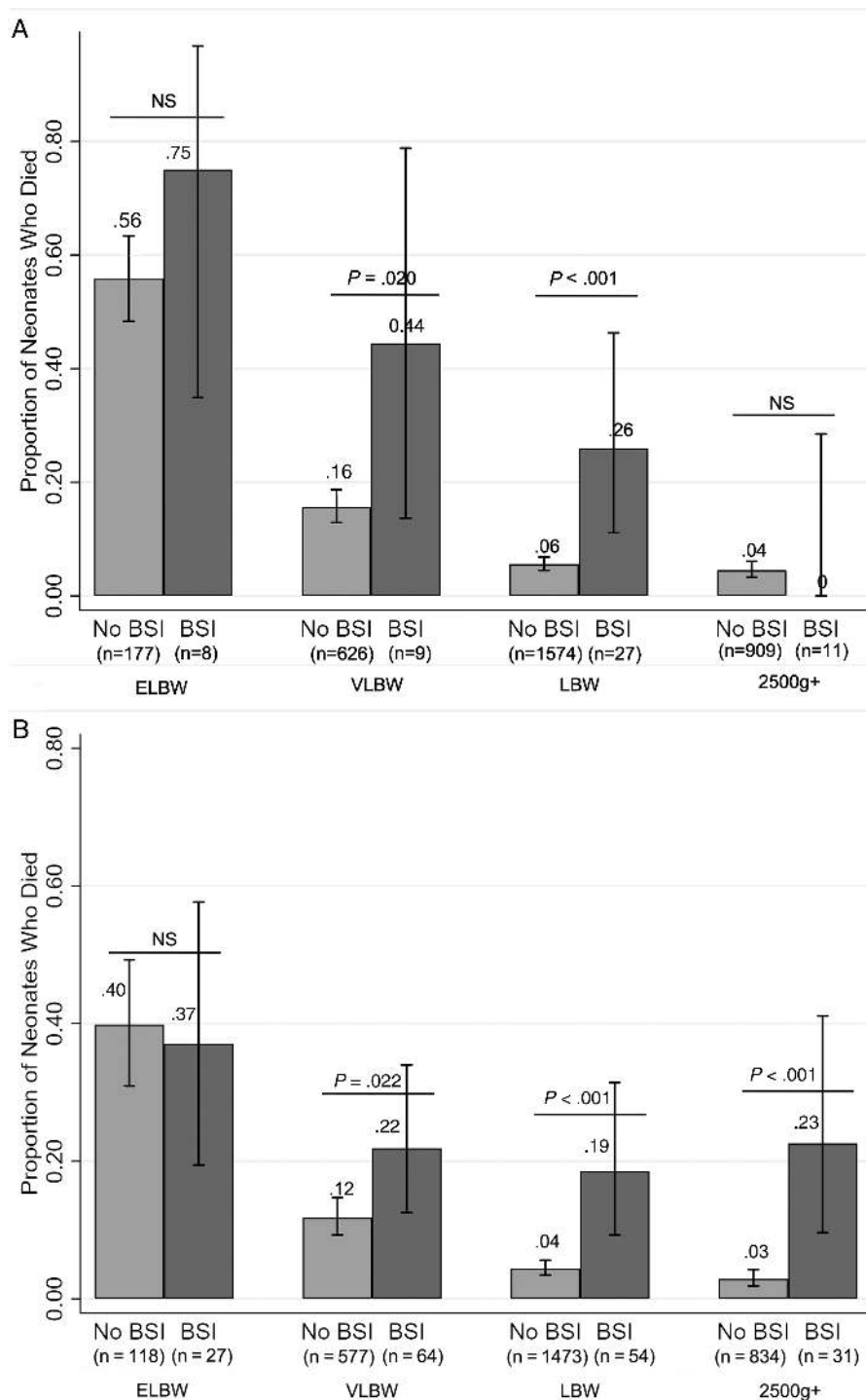
Figure 3. *A,* All-cause mortality by birth weight strata and early-onset BSI, early cohort. All-cause mortality among early cohort neonates, expressed as proportion of neonates deceased by birth weight strata with 95% confidence intervals (CIs); CI for neonates with birth weight ≥2500 g and BSI is a 1-sided 97.5% CI. *B,* All-cause mortality by birth weight strata and late-onset BSI, late cohort. All-cause mortality among late cohort neonates, expressed as proportion of neonates deceased by birth weight strata with 95% CIs. Abbreviations: BSI, bloodstream infection; ELBW, extremely low birth weight; LBW, low birth weight; NS, not significant; VLBW, very low birth weight.

high-income settings exist, the overall incidence of these infections is strikingly low compared with our study [12, 27–29].

In most LMIC studies, however, the pathogen distribution more closely mirrors our data. GNB, especially *Acinetobacter* spp. and *Klebsiella* spp., cause the overwhelming majority of neonatal sepsis in the NICU [19, 24, 25, 30–35]. However, important local, national, and regional differences exist, with gram-positive predominance reported in some LMIC NICUs [36–38]. Variations in pathogen distribution may reflect differences in the relative importance of potential reservoirs of

Table 4. Risk of Early-onset Bloodstream Infection by Baseline Clinical and Demographic Characteristics Among Neonates Included in the Early Cohort

Characteristic	Odds Ratio	95% CI	P Value	Adjusted Odds Ratio	95% CI	P Value
Male sex	0.77	.45–1.32	.343	0.71	.41–1.22	.209
Preterm, <37 weeks' gestation	1.62	.86–3.06	.136	1.23	.54–2.81	.616
Low birth weight	1.53	.79–2.97	.210	1.31	.54–3.17	.545
Multiple gestation	0.58	.21–1.60	.289	0.57	.20–1.63	.296
Outborn	2.40	1.12–5.13	**.025**	1.87	.84–4.15	.126
Cesarean delivery	0.69	.40–1.22	.203	0.81	.45–1.44	.468
Positive-pressure ventilation at delivery	2.28	1.31–3.96	**.004**	1.60	.87–2.95	.130
Any respiratory support on admission	4.54	2.13–9.67	**<.001**	2.20	.92–5.26	.074
Central line on admission	0.89	.40–2.00	.783	0.43	.16–1.17	.098
Pressors on admission	3.47	1.95–6.19	**<.001**	2.45	1.29–4.64	**.006**
Antibiotics on admission	3.69	2.02–6.74	**<.001**	2.00	1.00–3.98	**.049**

Logistic regression performed for select baseline characteristics in neonates included in the early cohort (n = 3341). Individual variables and their relationship with early-onset bloodstream infection (n = 55) were assessed using univariate logistic regression and multivariable logistic regression. Multiple imputation was used to account for missing data. P values <.05 were considered statistically significant and are in bold.
Abbreviation: CI, confidence interval.

transmission. While early-onset sepsis is classically thought to be due to vertical transmission and late-onset sepsis is primarily thought to be due to horizontal transmission, it is possible that these assumptions do not hold true in our cohort and in other LMIC settings. In our cohort, the overall similarity in pathogen distribution for both early- and late-onset sepsis may point to a single predominant reservoir of transmission, such as the hospital environment, with rapid colonization and subsequent infection of hospitalized neonates. However, it is also possible that maternal colonization in this setting may mirror environmental colonization and reflect an overall predominance of GNB. Such epidemiological differences should be carefully considered in designing interventions to prevent infections in hospitalized neonates in these settings.

Among gram-negative BSI cases in our cohort, AMR was pervasive, including to third-generation cephalosporins and carbapenems. Our data must be considered within the broader context of widespread AMR in South Asia [19, 23, 25, 31, 32,

39–41]. These data highlight the challenges of caring for hospitalized neonates with suspected sepsis in regions of high AMR prevalence. While antimicrobial stewardship principles should be embraced to limit use of broad-spectrum antibiotics and reduce risk of future resistant infections, antibiotic selection at the time of suspected sepsis must be guided by local knowledge of resistance patterns. All too frequently, so-called last resort antibiotics such as polymyxins are used for empiric therapy in hospitalized neonates, with limited safety and pharmacokinetic/pharmacodynamic data [42].

Factors associated with increased risk of early-onset BSI included pressors and the need for respiratory support, reflective of clinical illness on admission. Outborn neonates were at greater risk of late-onset BSI, as were neonates who required any respiratory support, central line, and antibiotics on admission. In high-income settings, invasive devices and preceding antibiotic exposure have been identified as risk factors for nosocomial infections in neonates [9]. Understanding the role of

Table 5. Risk of Late-onset Bloodstream Infection by Baseline Clinical and Demographic Characteristics Among Neonates Included in the Late Cohort

Characteristic	Odds Ratio	95% CI	P Value	Adjusted Odds Ratio	95% CI	P Value
Male sex	0.84	.62–1.14	.256	0.80	.58–1.10	.164
Preterm, <37 weeks' gestation	2.83	1.84–4.35	**<.001**	1.52	.93–2.50	.095
Low birth weight	1.80	1.21–2.67	**.004**	1.21	.71–2.07	.483
Multiple gestation	1.35	.87–2.09	.185	1.07	.67–1.72	.773
Outborn	2.66	1.87–3.80	**<.001**	2.65	1.80–3.90	**<.001**
Cesarean delivery	0.96	.71–1.31	.802	1.02	.73–1.40	.925
Positive-pressure ventilation at delivery	1.41	.98–2.01	.064	0.85	.58–1.26	.422
Any respiratory support on admission	3.29	2.30–4.71	**<.001**	1.70	1.11–2.60	**.015**
Central line on admission	4.14	2.85–6.03	**<.001**	2.72	1.77–4.19	**<.001**
Pressors on admission	2.29	1.59–3.31	**<.001**	1.15	.76–1.76	.505
Antibiotics on admission	4.35	3.04–6.23	**<.001**	2.55	1.69–3.84	**<.001**

Logistic regression performed for select baseline characteristics in neonates included in the late cohort (n = 3178). Individual variables and their relationship with late-onset bloodstream infection (n = 176) were assessed using univariate logistic regression and multivariable logistic regression. Multiple imputation was used to account for missing data. P values <.05 were considered statistically significant and are in bold.
Abbreviation: CI, confidence interval.

such risk factors for late-onset BSI risk in India and other LMIC is essential for the development of effective NICU-based infection prevention strategies.

Strengths of this study include its prospective nature, enrollment of all neonates admitted to the NICU, and large sample size. The following limitations should be considered. First, blood cultures were obtained at the discretion of the clinical team. It is possible that BSI cases were missed, due to failure to obtain a blood culture prior to antibiotic initiation or inadequate blood volume obtained, a common issue in neonates. Outborn neonates may have received antibiotics prior to admission, limiting potential yield of blood cultures obtained. Second, it is not possible to ascertain whether CONS isolates represented true BSI or potential contaminants. CONS is known to be a neonatal pathogen, especially in late-onset BSI [9]. While diagnosis of CONS BSI usually relies on confirmation with a second blood culture, this practice is not routinely followed in resource-limited settings. We therefore considered all blood cultures positive for CONS as true cases of BSI. Finally, we did not standardize the laboratory workup of blood cultures obtained per clinical practice. While our laboratory capacity assessments confirmed that high-quality, accredited microbiology laboratories staffed by experienced medical microbiologists with external quality assurance mechanisms were in place, site differences in laboratory workup and reporting of results are possible.

This study adds to the evidence base that, in contrast to high-income countries, BSIs among hospitalized neonates in LMIC are predominately caused by GNB and AMR. Mortality is significantly increased among neonates with BSI, with marked increases especially in moderate to late preterm and term neonates. This points to the crucial need for infection prevention to improve the chance of survival in neonates who otherwise are likely to survive and thrive. As LMIC acquire increasing capacity to provide advanced care to preterm and sick neonates, hospital-onset sepsis due to AMR GNB will be a growing threat to neonatal survival in these settings. We must consider this a call to action to describe local epidemiology of infection and associated AMR, identify sources of transmission of these pathogens, and design and implement locally appropriate and cost-effective interventions to reduce infections and death in hospitalized neonates in LMIC.

Notes

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