Bloodstream Infections among Neonates Admitted to Neonatal Intensive Care Units in Pune, India

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Abstract

Background: Facility-based births are increasing in low resource settings and the number of Neonatal Intensive Care Units (NICUs) is growing to accommodate neonates requiring intensive care. Neonates admitted to the NICU are at high risk of infection, and antimicrobial resistance (AMR) is increasing among neonatal infections, including in India.

Objective: To describe the epidemiology of culture-confirmed bloodstream infections (BSI) in neonates admitted to the NICU in three hospitals in Pune, India

Design/Methods: Prospective cohort study of all neonates admitted to the NICU. Clinical and demographic characteristics were collected at baseline, and daily clinical characteristics were collected until discharge, transfer, or death. Blood culture results were reviewed for pathogens isolated and antibiotic susceptibility testing.

Results: From May 1, 2017, until April 1, 2018, 4280 neonates were enrolled. Mean gestational age was 35 weeks, mean birth weight was 2078 grams, 89% were inborn, and 43% were delivered via C-section. On NICU admission, 10% required mechanical ventilation, 12% required pressors, and 41% received antibiotics. 1157 (27%) neonates had at least one blood culture, of which 222 (19%) had at least one positive blood culture. Late-onset BSI (≥3 days of life) (n=147) were more common than early-onset BSI (<3 days of life) (n=75). Among 239 blood culture isolates, organism distribution included Gram-negatives (GN) (n=135), Gram-positives (n=78), and *Candida* spp. (n=24). Two positive cultures were not identified. Predominant organisms were *Klebsiella pneumoniae* (n=55), *Acinetobacter* spp. (n=29), coagulase-negative *Staphylococcus* (n=25), and *Staphylococcus aureus* (n=18). Among GN isolates, resistance to third generation cephalosporins was pervasive (94% of *Klebsiella* spp., 67% of *Escherichia* spp., 85% of *Acinetobacter* spp.). Carbapenem resistance was found in 50% of *Klebsiella* spp., 50% of *Escherichia* spp., and 50% of *Acinetobacter* spp. High rates of AMR were seen in both early- and late-onset GN infections; third generation cephalosporin resistance was seen in 76% and 87% and carbapenem resistance in 58% and 48%, respectively. The BSI rate was 7.0 (95% CI 6.0-7.8) per 1000 patient-days. The all-cause mortality was 8% of admitted neonates (n=354). Among neonates with BSI, 60 (28%) did not survive to NICU discharge.

Conclusions: Among neonates admitted to the NICU in Pune, India, BSI were most commonly associated with GN pathogens. AMR was ubiquitous among early- and late-onset GN BSI, and neonates with bacteremia had a high risk of mortality.

Background

- While tremendous gains have been made in reducing under-5 mortality in low and middle income countries (LMICs), progress in reducing neonatal mortality has been significantly slower.[1]
- In regions with the highest neonatal mortality rates, infections account for 30-50% of deaths.[2]
- In 2016, the neonatal mortality rate in India was 25 per 1000 live births, and over 30% of neonatal deaths were due to infectious causes.[2]
- The number of NICUs in LMICs, including in India, is growing to accommodate neonates requiring intensive care.[3,4]
- In low resource settings, neonatal sepsis is more likely to be caused by Gram-negative pathogens, and antimicrobial resistance is common.[5]
- Understanding the local epidemiology of neonatal sepsis is paramount in developing locally appropriate infection prevention and control interventions.

Methods

We conducted a prospective cohort study from May 1, 2017, until April 1, 2018, in neonates admitted to the NICU at three tertiary care centers, Byramjee-Jeejeebhoy Government Medical College, DY Patil Medical College, and King Edward Memorial Hospital in Pune, India. All neonates admitted to the NICU were enrolled and followed until discharge, transfer, or death. Demographic and clinical characteristics were collected at baseline, and daily clinical and microbiology data were collected prospectively for the duration of the NICU stay. The primary outcome of interest was the incidence of culture-confirmed BSI; secondary outcomes included all-cause mortality. This study was approved by the Johns Hopkins Medicine Institutional Review Board and participant site Ethics Committees.

Results

- From May 1, 2017, until April 1, 2018, 4280 neonates were enrolled at three sites.
- Mean gestational age was 35 weeks gestation, with a mean birth weight of 2078 grams.
- Most neonates were inborn (89%); C-section deliveries were common (43%) among neonates admitted to the NICU.
- Antibiotics were initiated on admission in 41% of neonates.
- Baseline clinical and demographic characteristics are summarized in Table 1.

Results

Table 1: Baseline clinical and demographic characteristics by site

	Site 1 (n=3002)	Site 2 (n=783)	Site 3 (n=495)	All sites (n=4280)
Maternal age in years, median (IQR)	23 (21-26)	28 (24-31)	24 (22-27)	25 (22-28)
Male, n (%)	1661 (55%)	407 (52%)	272 (55%)	2340 (55%)
Gestational age in weeks, mean (SD)	36 (3.6)	34 (3.8)	37 (2.8)	35 (3.7)
Birth weight in grams, mean (SD)	2131 (679)	1811 (718)	2227 (641)	2078 (696)
Low birth weight, n (%)	1774 (70%)	627 (82%)	317 (65%)	2718 (72%)
Multiple gestation, n (%)	208 (7%)	175 (22%)	32 (6%)	415 (10%)
Inborn, n (%)	2696 (90%)	716 (91%)	385 (78%)	3797 (89%)
C-section, n (%)	794 (32%)	553 (73%)	239 (50%)	1586 (43%)
PPV at delivery, n (%)	409 (20%)	186 (25%)	95 (20%)	690 (21%)
Mechanical ventilation on admission, n (%)*	191 (8%)	126 (17%)	50 (10%)	367 (10%)
Central line on admission, n (%)*	71 (3%)	93 (12%)	80 (16%)	244 (7%)
Pressors on admission, n (%)*	127 (6%)	79 (10%)	191 (39%)	397 (12%)
Antibiotics on admission, n (%)*	829 (38%)	394 (52%)	175 (36%)	1398 (41%)

Table 1 notes. *Data points not available for all enrolled neonates; PPV = positive pressure ventilation

- Among 4280 neonates, 1157 had at least one blood culture drawn over the course of NICU admission.
- Of 1157 neonates who had a blood culture, 222 (19%) had at least one positive blood culture.
- Characteristics of neonates with and without a positive blood culture during NICU admission are summarized in Table 2.

Table 2: Characteristics of neonates with and without positive blood culture

	No Positive Blood Culture (n=4054)	Positive Blood Culture (n=222)	P value
Male, n (%)	2229 (55%)	107 (48%)	0.17
Gestational age, mean (SD)	36 (4)	33 (4)	**<0.001**
Birth weight, mean (SD)	2102 (687)	1646 (699)	**<0.001**
Low birth weight, n (%)	2544 (71%)	173 (87%)	**<0.001**
Inborn, n (%)	3631 (90%)	162 (73%)	**<0.001**
C-section, n (%)	1489 (43%)	95 (44%)	0.83
PPV at birth, n (%)	627 (21%)	61 (29%)	**0.004**
Mechanical ventilation on admission, n (%)*	312 (9%)	55 (25%)	**<0.001**
Central line on admission, n (%)*	203 (6%)	41 (19%)	**<0.001**
Pressors on admission, n (%)*	344 (11%)	53 (24%)	**<0.001**
Antibiotics on admission, n (%)*	1228 (38%)	169 (77%)	**<0.001**

Table 2 notes. Excludes four neonates for whom microbiology data are pending. *Data points not available for all enrolled neonates; PPV = positive pressure ventilation

- BSI rates at participant sites varied from 4.8 per 1000 patient-days to 14.7 per 1000 patient-days.
- Among neonates with BSI, all-cause mortality was significantly higher, with a mortality of 28% (n=60).
- All-cause mortality was higher in neonates with early-onset BSI (32%) than in neonates with late-onset BSI (26%).
- BSI rates and mortality data are summarized in Table 3.

Table 3: Bloodstream infection rates and mortality by site

	Site 1 (n = 3002)	Site 2 (n = 783)	Site 3 (n = 495)	Total (n = 4280)
BSI cases, n (%)	128 (4%)	46 (6%)	48 (10%)	222 (5%)
Total patient-days	20616	10896	3757	35269
BSI rate per 1000 patient-days (95% CI)	6.9 (5.7-7.8)	4.8 (3.3-5.9)	14.7 (10.8-18.7)	7.0 (6.0-7.8)
Neonates deceased, n (%)	253 (8%)	67 (9%)	34 (7%)	354 (8%)
Age in days at death, median (IQR)	5 (2-10)	4 (1-19)	7 (2-15)	5 (2-11)
Neonates deceased among neonates with BSI, n (% of neonates with BSI)	44 (35%)	12 (28%)	4 (8%)	60 (28%)
Age in days at death among neonates with BSI, median (IQR)	7 (5-17)	30 (12-60)	17 (9-42)	12 (6-22)

Table 3 notes. Mortality data excludes 19 neonates for whom disposition data are pending; BSI = bloodstream infection

Results

Table 4: Blood culture results by organism and onset

Organism	Early (n=52) n (%)	Late (n=187) n (%)	Total (n = 239) n (%)
Enterobacteriaceae			
Klebsiella spp.	9 (17)	46 (25)	55 (23)
Citrobacter spp.	10 (19)	15 (8)	25 (10)
Escherichia spp.	2 (4)	6 (3)	8 (3)
Enterobacter spp.	0	4 (2)	4 (2)
Serratia marcescens	0	3 (2)	3 (1)
Other Gram-negative organisms			
Acinetobacter spp.	3 (6)	26 (14)	29 (12)
GNR, non-fermenter species	3 (6)	2 (1)	5 (2)
Elizabethkingia meningoseptica	0	3 (2)	3 (1)
Pseudomonas aeruginosa	0	2 (1)	2 (1)
Brevundimonas diminuta	1 (2)	0	1 (0)
Gram-positive organisms			
Staphylococcus spp.	19 (37)	40 (22)	59 (25)
CONS	7 (13)	19 (10)	26 (11)
Staphylococcus aureus	7 (13)	11 (6)	18 (8)
Staphylococcus spp., unspecified	5 (10)	10 (5)	15 (6)
Enterococcus spp.	3 (6)	7 (4)	10 (4)
Streptococcus spp.	1 (2)	5 (3)	6 (3)
Bacillus spp.	0	2 (1)	2 (1)
Granulicatella spp.	0	1 (1)	1 (0)
Unknown	1 (2)	1 (1)	2 (1)
Yeast			
Candida spp.	0	24 (13)	24 (10)

Figure 1: Gram-negative BSI by site, onset, and drug susceptibility

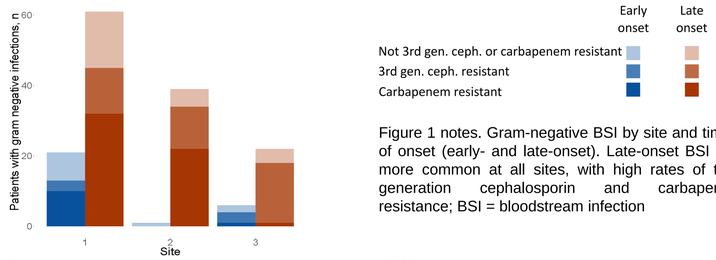

Figure 1 notes. Gram-negative BSI by site and timing of onset (early- and late-onset). Late-onset BSI was more common at all sites, with high rates of third generation cephalosporin and carbapenem resistance; BSI = bloodstream infection

- Gram-negative organisms exhibited high rates of AMR; resistance to third generation cephalosporins was seen in 94% of *Klebsiella* spp., 67% of *Escherichia* spp., and 85% of *Acinetobacter* spp. Carbapenem resistance was seen in 50% of *Klebsiella* spp., *Escherichia* spp., and *Acinetobacter* spp.
- Among early-onset GN infections, 76% of organisms were resistant to third generation cephalosporins and 58% were resistant to carbapenems. Among late-onset GN Infections, third generation cephalosporin resistance was seen in 87% and carbapenem resistance in 48%.

Conclusions

- Gram-negative infections predominated among neonates admitted to three NICUs at tertiary care centers in Pune, India; BSI were more likely among more preterm, smaller neonates.
- Rates of resistance to third generation cephalopsporins and carbapenems were high among early- and late-onset BSI.
- Neonates with BSI had high rates of mortality, and neonates with early-onset BSI had a higher risk of death than those with late-onset BSI.

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