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Neonatal outcomes associated with antimicrobial resistance: A retrospective cross-sectional study

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ABSTRACT

Neonatal sepsis (NS) is a leading cause of morbidity and mortality requiring immediate admission and prolonged neonatal intensive care unit (NICU) stay. This study attempts to identify factors associated with NS and its outcomes. A total of 186 NS cases records (January 2017 to September 2019) were analyzed retrospectively. Multiple logistic regression and linear regression were employed to determine the factors associated with mortality, length of NICU stay, and treatment cost with a significance level of $p \leq 0.05$. The mean neonatal age was 6.8 ± 9.5 days. Culture reports identified *Klebsiella pneumonia* (69%) as the major pathogen. Forty-four percent of neonates died, of whom 57% and 44% suffered early-onset sepsis and late-onset sepsis respectively. Logistic regression showed that mortality was significantly associated with platelet count (OR = 0.998; 95% CI =0.996–1.000) and very low birth weight (LBW) (OR = 2.427; 95% CI = 1.103–5.342). Linear regression showed that the number of definitive antibiotics used was associated with prolonged length of NICU stay. Also, length of NICU stay, number of definitive antibiotics, seizures, and heart disease, were significantly associated with overall cost. Mortality was higher with early-onset of sepsis than with late-onset of sepsis. The study could help policymakers and clinical practitioners to develop and implement targeted interventions that potentially reduce the global prevalence of NS.

INTRODUCTION

Neonatal sepsis (NS) is a blood infection in newborns less than 28 days old. There is no internationally recognized unified definition for NS. Currently, employed definitions vary (McGovern *et al*., 2020). Based on the time of presentation of sepsis after birth, NS is classified into early-onset sepsis (EOS): ‘occurring within 72 hours, and late-onset sepsis (LOS): occurring after 72 hours (Singh *et al*., 2022). Risk factors such as premature membrane rupture, very low birth weight (VLBW), prematurity, invasive medical procedures, poor intra- and postpartum hygiene, maternal pyrexia, and prolonged neonatal intensive care unit (NICU) stay are critically associated with both EOS and LOS (Leal *et al*., 2012). Many studies have shown a preponderance of Gram-negative bacteria (GNB) in EOS and Gram-positive bacteria (GPB) in LOS (Hornik *et al*., 2012). Global Burden of Disease study report (2016–17) mentions a global incidence of 1.3 million cases of NS per year with more than two hundred thousand sepsis-attributable deaths (Fleischmann *et al*., 2021).

World Health Organization (WHO) reported 2.4 million neonatal deaths globally, with one-third and three-fourths of mortality on the day of birth and within the first week of birth, respectively (WHO, 2020). Centre for Disease Dynamics, Economics and Policy (CDDEP), USA, reported that in 2019,

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sepsis caused nearly 1 million neonatal deaths globally within the first 4 weeks of life, of which 190,000 deaths were in India (CDDEP, 2012). NS, especially in VLBW populations, is significantly associated with increased complications of prematurity and adverse neurodevelopmental outcomes, which underscore the need for immediate diagnosis of NS and the commencement of antibiotic therapy. Antibiotics usage in NICUs is widespread, and numerous studies from high-income countries and low-income and middle-income countries (LMICs) have reported that 74% to 94% of neonates with negative blood cultures received antibiotics for suspected sepsis (Dadgostar, 2019; Thomson *et al*., 2021). The unnecessary administration of empiric antibiotics is an independent risk factor for the rapid emergence of antimicrobial resistance (AMR) and is associated with increased long-term morbidity and mortality. Thirty percent of NS deaths are due to AMR (Hayes *et al*., 2021; Shelar, 2019).

AMR is a global problem, which is particularly challenging in developing countries like India (Murthy *et al*., 2019; Singh *et al*., 2022). Among GNBs, cephalosporin resistance rates ranged from 26% to 84%, and carbapenem resistance rates ranged from 0% to 81%. The percentage of GPBs resistant to glycopeptides ranged from 0% to 45% (Li *et al*., 2020).

Due to increasing healthcare expenses globally, pharmacoeconomic considerations, including the cost of illness and the cost-effectiveness of health interventions, have become crucial for developing and implementing health policies (Fenny *et al*., 2020; Gastmeier *et al*., 2004). In India, neonatal intensive care is among the most expensive components of pediatric care. The per-capita income of an Indian parent is only $1,920, making NS a catastrophic financial burden (Prinja *et al*., 2013; The World Bank, 2021). Among the very few publications on the costs of NS in India, a systematic review estimated the cost of treatment for NS per patient in India and the United States as $55 and $129,632, respectively (Salman *et al*., 2020). The paucity of investigations on AMR patterns, mortality, and the cost of NS in India creates an urgent need to increase epidemiological studies for implementing targeted interventions. This study aims to assess the antibiogram and evaluate factors associated with the length of NICU stay, mortality, and the costs incurred due to NS.

MATERIALS AND METHOD

Our study included case records of neonates clinically diagnosed with NS between January 2017 and September 2019. Only neonates with culture-positive bacteria were included. Culture sensitivity reports were retrospectively collected from the Laboratory Information Service software maintained by the hospital. Fungal or viral sepsis and incomplete records were excluded. Demographic details of neonates [gender, GA (gestational age), birth weight, and morbidities] were collected from case records. The study also classified EOS and LOS based on the National Institute for Health and Care Excellence guidelines (Cortese *et al*., 2016).

Statistical analysis

Patient demography, susceptibility patterns of bacterial isolates, and cost are indicated in percentages, mean (±SD), and median (±IQR) values. The skewed data sets were transformed to log data for statistical analysis. To study the impact of neonatal and maternal variables on the length of NICU stay and cost, we performed a multiple linear regression analysis using the backward selection method (to avoid multicollinearity between the variables) with $p < 0.05$ considered statistically significant. Multicollinearity between independent variables was determined by Tolerance (T) values (significant if $T < 0.1$). Variance inflation factor above five was considered significant. We tested the correlation between cost and clinically significant neonatal variables using 'Pearson's correlation (two-tailed) (Ananya19b, 2021). We also performed binomial logistic regression using the backward stepwise (likelihood ratio) method to determine the association between risk factors, mortality, and LOS/EOS (Schober *et al*., 2018). All statistical analyses were carried out using the SPSS 28.0 package (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY).

RESULTS

Between 2017–18 and 2018–19, the number of neonates admitted to the NICU was 3,818 and 3,856, respectively. The overall incidence of sepsis was between 9% and 10%, of which bacterial sepsis occurred in only 2.4% of cases annually. Of the 186 cases of NS, 57% were males. Cesarean section (C-section) and vaginal birth constituted 68% and 32%, respectively. The neonatal mortality rate (NMR) was 44%. The demographic details are presented in Table 1.

Culture sensitivity tests

Culture sensitivity tests showed that 78% of neonates were infected with GNBs, while 22% were infected GPBs. EOS was associated with 43% and 15% GNBs and GPBs, respectively. Thirty-four percent of GNBs and 8% of GPBs were associated with LOS. *Klebsiella pneumoniae* 55% (n = 129) was the most abundant, followed by *E. coli* 17% (n = 40), *Acinetobacter* spp. 14% (n = 34) and *Enterobacter cloacae* 9% (n = 21). Among different strains, extensively drug-resistant/Pandrug-resistant (XDR/PDR) strains of *Klebsiella pneumonia* (56%) were higher followed by *E. coli* (18%) and *Acinetobacter* spp. (15%). However, multidrug-resistant (MDR) strains of *E. coli* (80%) were higher followed by *Enterococcus* spp. (75%). *Enterobacter cloacae* (47%) and *K. pneumoniae* (33%) (Fig. 1).

Empirical antibiotics were administered to 31% (n = 58) of patients. Commonly used antibiotics were ampicillin (20%), followed by amikacin (19%), piperacillin-tazobactam (15%), etc. Sixty-nine percent (n = 128) of the patients received definitive therapy (either continuing the empirical treatment or changing antibiotics based on the culture sensitivity test). The most frequently prescribed antibiotics in the definitive therapy category were amikacin (91%), followed by piperacillin-tazobactam (69%) (Table 2). Results of the antimicrobial susceptibility testing are depicted in the supplementary file (Supplementary Figs. S1–S5). The risk factors associated with EOS is mentioned in Table 3.

Mortality

Eighty-one (44%) neonates died, of whom 57% had EOS. Binomial logistic regression using a backward stepwise method (likelihood ratio) showed that septic shock ($p < 0.027$) and platelet count ($p < 0.001$) were significantly associated with

Table 1. Demographic features of the sample population (Total $N = 186$).

Patient characteristics	
Age (days) (Mean ± SD)	6.8 ± 9.5
Birth weight (g) (Median ± IQR)	1975 ± 1550
Sex, *n*(%)	
Female	80(43)
Male	106(56)
Maternal parity *n* (%)	
Primigravida	90(48)
Multigravida	75(40)
Unknown	21(11)
GA *n*(%)	
Post term (>42 weeks)	1 (1)
Term (37–41 weeks)	68(37)
Preterm (<37 weeks)	117 (63)
Neonatal growth outcome, *n* (%)	
LGA	7(4)
AGA	140(75)
SGA	42(23)
Mode of delivery, *n* (%)	
Vaginal delivery	60(32)
C-section delivery	126(68)
APGAR score (Mean ± SD)	
At 1 minute	7.3 ± 2.1
At 5 minutes	8.4 ± 1.2
Length of NICU stay (days) (Mean ± SD)	17.5 ± 21
NS *n*(%)	
EOS	110(59)
LOS	76(41)
Culture	
GNBs	138(74)
GPBs	48(26)
Neonatal morbidities *n* (%)	
Bradycardia	73(39)
Apnoea	44(24)
RDS	75(40)
Meningitis	21(11)
Metabolic acidosis	46(25)
Hyperbilirubinemia	43(23)
Overall mortality	81(44%)
Number of days to death (Median ± IQR)	17 (± 19)

SD = Standard Deviation; IQR = Interquartile range; GA = Gestational age; LGA = Large for gestational age; AGA = Accurate for gestational age; SGA = Small for gestational age; APGAR = Appearance, pulse, grimace, activity and respiration; NS = Neonatal sepsis; EOS = Early-onset sepsis; LOS = late-onset sepsis; GNBs = Gram-negative bacterias; GPBs = Gram-positive bacterias; RDS = Respiratory distress.

mortality (Table 5). Mechanical ventilation (MV) was associated with 75% of neonatal mortality. Other risk factors associated with mortality are shown in Table 4.

Length of NICU stay

Small gestational age (SGA) ($p < 0.02$), LBW ($p < 0.036$), intrauterine growth restriction (IUGR) ($p < 0.013$), heart disease ($p < 0.049$), vasopressor ($p < 0.001$), surfactants ($p < 0.006$), EOS ($p < 0.001$), LOS ($p < 0.014$), persistent pulmonary hypertension of the neonates (PPHN) ($p < 0.001$), and the number of definitive antibiotics administered per patient ($p < 0.001$) were significantly associated with the length of NICU stay (Table 6). A residual scatter plot indicates that the linear model for length of stay fits the data well (Supplementary Fig. S6).

Cost of NS

The median antibiotic cost and the median length of NICU stay cost for LOS were twice and thrice that of the EOS, respectively. The median cost for LOS is double the total cost of EOS (Table 7). The antibiotic cost constitutes 6% and 2% of the total drug and total costs, respectively. Antibiotic costs and the overall treatment cost for extremely low birth weight (ELBW) were higher and were closely followed by VLBW and LBW.

Multivariate linear regression analysis shows that overall treatment cost increased significantly with an increase in the NICU stay ($p < 0.001$). Co-morbidities further increased the length of NICU stay. Heart disease ($p < 0.001$), seizures ($p < 0.001$), respiratory syncytial virus (RSV) infection ($p < 0.004$), anemia ($p < 0.051$), and peritonitis ($p < 0.046$) were significantly associated with the total cost (Table 8). A residual scatter plot showed that the linear model for the cost of the length of NICU stay fits the data well (Fig. 2).

DISCUSSION

NS remains a serious clinical concern in neonatology, with high morbidity and mortality rate, particularly in LMICs such as India, especially with the rapid emergence of AMR. This study shows that the incidence of bacterial sepsis in 2.4% of live births for two consecutive years. The Burden of Antibiotic Resistance in Neonates from Developing Societies study has shown the incidence of bacterial sepsis as 0.04% (Milton *et al*., 2022). Two different studies from the USA reported the incidence of bacterial sepsis from the Indian sub-continent as 40.1 per 1,000 live births and 6.7 per 1,000 live births respectively (Panigrahi *et al*., 2017; Sundaram *et al*., 2009). The extremely low rate of NS in our hospital's NICU demonstrates the effectiveness of our infection control policies and the maintenance of an aseptic atmosphere while performing any invasive procedures.

This study assessed the demographics and antibiogram of all the neonates. The mean neonatal age was 6.8 ± 9.5 days, predominantly males ($n = 106$; 56%). GNBs (74%) outnumbered GPBs (26%). *Klebsiella pneumoniae* 55% ($n = 129$) was the most abundant, followed by *E. coli* 17% ($n = 40$), *Acinetobacter* spp. 14% ($n = 34$) and *E. cloacae* 9% ($n = 21$). *Klebsiella pneumoniae* constituted a high proportion of XDR/PDR (56%) and MDR (33%) strains highly resistant to ampicillin (99%), cefotaxime (84%), cefuroxime (84%), cefepime (82%) and moderately resistant toward meropenem (74%), piperacillin-tazobactam (73%), and cefoperazone (72%). A study from Pakistan reported a mean neonatal age of 11.41 ± 6.76 days, predominantly affecting females (57.6%), with culture sensitivity reports of *K. pneumoniae* (34.1%) followed by *Staphylococcus aureus* (31.7%), *E. coli* (19.5%), and coagulase-negative *Staphylococci* (12.2%) (Liyakat

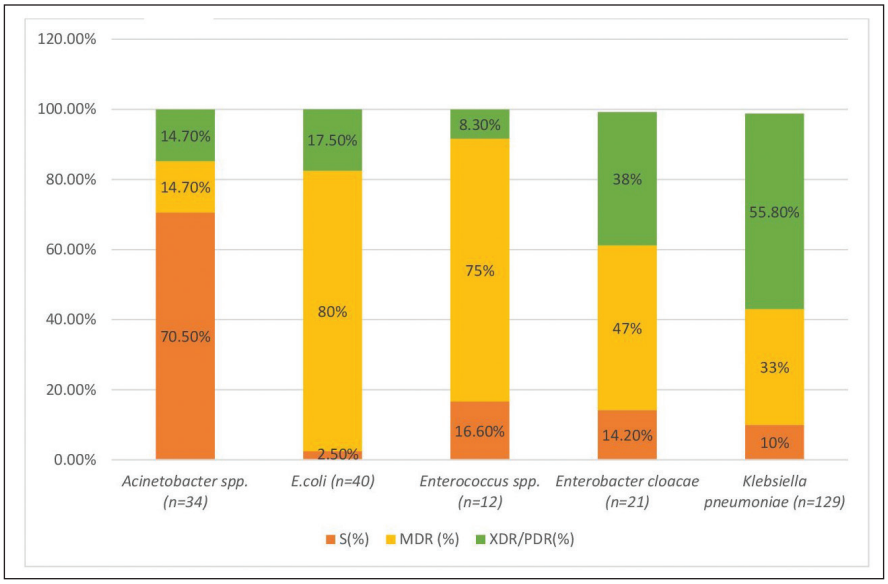

Figure 1. MDR, PDR, and sensitive strains of different GNBs (%), and GPBs (%) found in the study.

Table 2. Antibiotics used in neonates [values in percentages (%)].

Antibiotics	AMP	AMK	PIP-TAZ	CFP-SUL	METZ	CFLX	COL
Empirical therapy	20	19	15	1	2	0	0
Definitive therapy	6	91	69	20	10	14	10

AMP = Ampicillin; AMK = Amikacin; PIP-TAZ = Piperacillin-tazobactam; CFP-SUL = Cefoperazone-sulbactum; METZ = Metronidazole; CFLX = Ciprofloxacin; COL = Colistin.

Table 3. Risk factors associated with EOS.

Attributes	OR	95% CI		*p*-value
		Lower bound	Upper bound	
NICU stay(days)	0.948	0.925	0.971	<0.001
CPAP	0.367	0.159	0.848	0.019
Number of empirical antibiotics per patient	0.357	0.23	0.556	<0.001
Vasopressor	0.232	0.089	0.607	0.003
Constant	43.21	-	-	<0.001

OR = Odds ratio; EOS = Early onset of sepsis; CPAP = Continuous positive airway pressure; CI = Confidence interval.

et al., 2021). *Klebsiella pneumoniae* is the most frequent cause of outbreaks in NICU leading to significant morbidity and mortality. In our study, MDR [Beta (β) = 1.882, 95% CI 2.708–15.923, $p < 0.0001$ and XDR/PDR] (β = 1.101, 95% CI 1.354–6.684, $p < 0.007$) strains of *K. pneumoniae* was highly associated with LOS unadjusted with all other study variables. Similarly susceptible (β = 1.236, 95% CI 0.089-0.953, $p < 0.041$) and MDR (β = 1.905, 95% CI 0.024–0.928, $p < 0.041$) strains of *Acinetobacter* spp. and, MDR (β = 2.085, 95% CI 0.049–0.953, $p < 0.0001$) and XDR/PDR (β = 1.340, 95% CI 0.119–0.953, $p < 0.003$) strains of *K. pneumoniae* were highly associated with EOS unadjusted with all other variables respectively. According to the Lancet report, *K. pneumoniae* was responsible for the majority of NS and mortality (124,000 deaths in 2019) (Dall, 2022). MDR strains frequently emerge in intensive care unit (ICU) settings as a result of prolonged and excessive usage of multiple antibiotics. The lack of specific signs and symptoms makes it extremely difficult to diagnose and treat sepsis. Lengthy turnaround times for laboratory diagnoses force continued empirical antibiotics until suspected sepsis is ruled out. The rise of MDR and XDR bacteria restricts available treatment alternatives, hindering effective therapy. Ampicillin combined with amikacin is the first-line empirical treatment in our NICU. A third-generation cephalosporin and piperacillin-tazobactam is the second line of treatment if there is no improvement. Until blood culture results are received, carbapenems are used as a last resort (Hassuna *et al*., 2020). In our study, a combination of ampicillin (20%) and amikacin (19%) was preferred as the first-line agent for NS. However, most isolates were resistant to ampicillin, shifting definitive therapy choices to piperacillin-tazobactam (69%) and amikacin (91%). Third-generation cephalosporins such as cefoperazone-sulbactam and fluoroquinolones such as ciprofloxacin were infrequently used. When the isolates (e.g., XDR/PDR strains of *K. pneumoniae*) were found resistant to most of the antibiotics, colistin and carbapenems were prescribed as a last resort. Our hospital consistently prescribed doses of antibiotics recommended by Micromedex NeoFax Essentials guidelines (Micormedex NeoFax Essentials, 2014).

Table 4. Risk factors associated with mortality.

Neonatal variables	Neonatal mortality (%)
C-section delivery	68
SGA	25
MV	75
Thrombocytopenia	65
Anaemia	50
Bradycardia	43
Desaturation	49
RDS	36
LBW	32
VLBW	19
ELBW	36
EOS	57
Pre-term	63
Term	36

SGA = Small for gestational age; LBW = low birth weight; VLBW = very low birth weight; ELBW = extremely low birth weight; EOS = Early onset of sepsis; RDS = Respiratory distress.

Table 5. Association between neonatal variables and mortality.

Neonatal or maternal variables	OR	95% CI		*p*-value
		Lower bound	Upper bound	
Hypotension	12.876	1.380	120.135	0.025
PPHN	5.986	1.295	27.670	0.022
CPAP	2.427	1.103	5.342	0.028
VLWB	0.998	0.996	1.000	0.029
Platelets	0.998	0.996	1.000	0.029
C-section delivery	0.277	0.113	0.679	0.005
Constant	0.640			0.313

OR = Odds ratio; CI = Confidence interval; VLBW = Very low birth weight; CPAP = Continuous positive airway pressure; PPHN = Persistent pulmonary Hypertension in neonates.

Table 6. Association between neonatal variables and NICU length of stay.

Variables	Standardise beta (β)	*p*-value	95% CI	
			Lower bound	Upper bound
(Constant)		<0.001	0.43	1.326
EOS	0.442	0.001	−0.599	−0.145
LOS	0.332	0.014	−0.5	−0.056
Number of definitive antibiotics per patient	0.244	<0.001	0.056	0.097
Surfactants	0.14	0.006	0.035	0.207
PPHN	0.103	0.001	0.06	0.234
IUGR	0.082	0.013	0.022	0.183
Heart disease	0.066	0.049	0.001	0.254
SGA	−0.081	0.02	−0.148	−0.013
ELBW	−0.079	0.016	−0.145	−0.015
LBW	−0.145	0.036	0	0
Vasopressor	−0.17	<0.001	−0.215	−0.081

CI = Confidence Interval; SGA = Small for gestational age; LBW = Low Birth Weight; ELBW = Extremely Low Birth Weight; IUGR = Intrauterine growth retardation; EOS = Early-onset sepsis; LOS = Late-onset sepsis; PPHN = Persistent Pulmonary Hypertension in neonates; Adjusted R square = 0.87.

Understanding resistance patterns require continuous surveillance of antimicrobial susceptibility. India is at the epicenter of this expanding public health hazard, with various levels of government and healthcare organizations undertaking AMR action plans. Kerala (2018) was one of the first Indian states to establish policies and prioritize activities to address AMR hazards, followed by Madhya Pradesh and New Delhi (2020). However, ensuring the state-wide execution of an AMR action plan needs collaborative and committed efforts from healthcare professionals from both private and public sectors (Chandra *et al*., 2022; Singh *et al*., 2021). Neonatologists must be familiar with the bacteriological profile and the local geographic susceptibility patterns to reduce the morbidity and mortality associated with NS.

NS predisposes neonates to an increased risk of mortality or morbidity, especially by MDR organisms. The incidence (59%) and mortality (57%) were higher for EOS than LOS, similar to the results of a systematic review from Germany (Fleischmann *et al*., 2021). Preterm babies are more susceptible to infection in early life. However, appropriate care and rational antibiotic prescriptions could prevent LOS or mortality. While we found that LOS accounted for 43% of the total cases (n = 76), Taiwan reported 23% in a similar study (Tsai *et al*., 2014).

This study showed that mortality was significantly associated with hypotension, presence of PPHN, C-section delivery, and neonates receiving continuous positive airway pressure (CPAP). CPAP has been shown to reduce fatality risk by 48%. Costly surfactants and MV reduce fatality risk by 50%, and fewer days of NICU stay. However, prolonged use of CPAP has been reported to cause sepsis (possibly from inappropriate handling or lack of knowledge on CPAP administration, especially in LMICs) which is an independent factor for neonatal mortality (Dewez *et al*., 2018; Duke, 2014; Thukral *et al*., 2016).

We also checked the association between bacterial isolates and mortality. However, with or without adjustment for age, preterm, term, LBW, VLBW, and ELBW, there was no significant association between bacterial isolates and mortality.

C-section deliveries increased by more than twice as much as vaginal deliveries between 2017 and 2019 in our hospital. The C-section delivery had higher mortality than vaginal delivery and was significantly associated [OR = 0.277 (95% CI 0.113 to 0.679), $p < 0.005$] with mortality. A study from India reported C-section delivery was positively associated with neonatal mortality [OR 1.19 (95% CI 1.02 to 1.39), $p < 0.001$] (Gondwe *et al*., 2020). In our study, neonates born via C-section were more likely to require NICU admission, oxygen supplementation, ventilatory support for respiratory distress syndrome (RDS), desaturation, and PPHN than those born via vaginal delivery, which may have

Table 7. Median costs incurred (in $) due to NS.

Neonatal variables	Antibiotics cost	Total drug cost	Other costs	NICU stay cost	Total cost
NS	14 (4–33)	303 (154–618)	643 (334–1,116)	51 (24–106)	1,006 (571–2,040)
EOS	10 (3–24)	181 (99–383)	491 (258–720)	31 (16–75)	761 (443–1,250)
LOS	19 (9–47)	530 (303–1,065)	1,057 (560–1,539)	67 (37–156)	1,761 (958–2,618)
LBW	14 (4–31)	309 (158–559)	655 (407–1,043)	47 (24–110)	988 (614–1,678)
VLBW	12 (4–33)	303 (179–709)	656 (415–1,509)	58 (26–161)	963 (684–2,756)
ELBW	15 (7–35)	537 (379–1,128)	1,203 (557–1,499)	94 (37–165)	2,287 (1,244–2,504)

NS = Neonatal sepsis; LBW = low birth weight; VLBW = Very low birth weight; ELBW = extremely low birth weight; Median Costs, with the interquartile range given in brackets. Total other cost includes material costs and other hospital services. (Current exchange rate: United States Dollar ($) 1 = 76.32 Indian national rupee: EOS = Early-onset of sepsis; LOS = late-onset of sepsis.

Table 8. Association between neonatal variables and total cost.

Variable	Standardised beta (β)	*p*-value	95% CI	
			Lower bound	Upper bound
(Constant)		<0.001	4.261	4.942
NICU stay (in days)	0.508	<0.001	0.009	0.012
Number of definitive antibiotics used per patient	0.336	<0.001	0.08	0.128
PPHN	0.172	<0.001	0.137	0.345
Term	0.164	0.003	0.05	0.229
Heart disease	0.162	<0.001	0.175	0.438
Meropenem (Definitive)	0.125	<0.001	0.313	1.069
APGAR 5minutes	0.123	0.002	0.004	0.019
Seizures	0.123	<0.001	0.055	0.203
Vasopressor	0.1	0.022	0.012	0.159
Peripheral line	0.082	0.017	0.034	0.344
Anaemia	0.075	0.051	0	0.123
Peritonitis	0.07	0.046	0.003	0.349
Neutropenia	−0.065	0.051	−0.003	0
Ampicillin cloxacillin (Definitive)	−0.07	0.034	−0.243	−0.01
Ceftriaxone (Definitive)	−0.072	0.037	−0.143	−0.005
Linezolid (Definitive)	−0.096	0.004	−0.513	−0.102
Ampicillin cloxacillin (Empirical)	−0.118	<0.001	−0.728	−0.196
EOS	−0.12	0.003	−0.165	−0.034
AGA	−0.235	0.024	−0.417	−0.029
LBW	−0.276	<0.001	0	0

AGA = Appropriate for gestational age; LBW = Low Birth Weight; APGAR=Appearance, pulse, grimace, activity and respiration; EOS = Early onset of sepsis; APGAR = Appearance, pulse, grimace, activity and respiration; Adjusted R square = 0.824.

progressed to severe respiratory failure and resulted in death. For newborns delivered via C-section without experiencing labor, respiratory morbidity caused by failure to remove fetal lung fluid is common and can be challenging. Numerous studies have shown that respiratory morbidity such as RDS, transient tachypnea, and PPHN has led to the need for supplemental oxygen (extracorporeal membrane oxygenation) or death (Kamath *et al*., 2009). The C-section rate in India, which may influence neonatal outcomes, appears to be influenced by a combination of socioeconomic, medical, and maternal factors. Worldwide, the rate of C-section deliveries has been rising rapidly, accounting for more than half of births today. Data from more than 150 countries suggest that 5% to 10% of C-section delivery rates accounted for the lowest neonatal and maternal mortality rates. When cesarean delivery rates exceeded 10%, mortality rates seemed to stabilize, suggesting that more cesarean deliveries do not reduce mortality. WHO advises that the national cesarean delivery rate should not exceed 15% (Boerma *et al*., 2018; Ye *et al*., 2016). India's National Family Health Survey for 2015–2016, reported that cesarean deliveries are rising and account for 17.2% of all births, with a massive gap between rural (12.9%) and urban (28.3%) households (Gondwe *et al*., 2020).

Decreased platelet count (thrombocytopenia) has been associated with neonatal mortality. Thrombocytopenia in NS

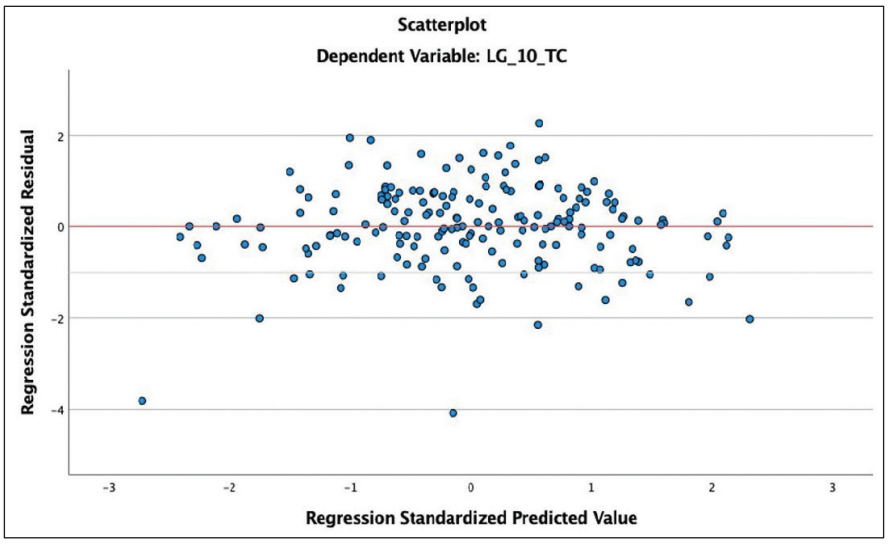

Figure 2. Scatterplot overall cost and neonatal variable-predicted value (X-axis) versus residual value (Y-axis).

increases mortality risk nearly four-fold. The bacterial infection triggers thrombocytopenia, severe sepsis, and disseminated intravascular coagulation, leading to death. Both thrombocytopenia and bacterial infections are independent risk factors for mortality (Ree *et al*., 2017). The global NMR (within the first 28 days of life) in 2020 was 17 deaths per 1,000 live births (UNICEF, 2021). NMR in India, per 1,000 live births, fell drastically from 84.32 in 1970 to 16 (2017) 23 (2018), 21 (2019), and 20 (2020). India plans to reduce this to 12 per 1,000 live births by 2030 (Bora and Saikia, 2018). NMR in Karnataka in 2018 was 16 per 1000 live births which is much higher than other South Indian states such as Kerala (2020; 3.4 per live births) and Tamil Nādu (2019); 11 per 1000 live births (Ahuja, 2021; Bhaskar, 2021; Bora and Saikia, 2018). A study from Haryana, India, reported that district-to-district variation for life expectancy at birth was highest for the Udupi district in Karnataka and lowest for Kargil in Jammu and Kashmir (Kesarvani, 2015).

The major causes of neonatal mortality in India are prematurity, birth asphyxia or injury, and infections. Efforts toward decreasing mortality from birth asphyxia, preterm births, and LBW have been met with varied success. The incidence of NS and mortality in our hospital (the only tertiary care hospital within the Udupi district) is very low, suggesting that the standard of care given by the NICU, effectiveness of home-based neonatal care, better socioeconomic circumstances, and new governmental health schemes such as National Rural Health Mission have enhanced the health of rural and underserved communities (Bang *et al*., 1999). A study from Gadchiroli, India, showed that the decline in the incidence of NS and associated mortality results from the effective implementation of government-run programs and the standard of care given by both private and public hospitals (Bang *et al*., 2021). Madhya Pradesh, an Indian state with one of the highest NMR, also improved significantly (59 in 2,000 *vs.* 35 in 2018) because of substantial progress in maternal and child health interventions at the government level (Maternal and Neonatal Health in Madhya Pradesh, 2022.).

This study has also demonstrated a significant positive correlation between length of NICU stay and neonatal clinical variables such as EOS ($p < 0.001$) and LOS ($p < 0.114$), followed by the number of definitive antibiotics per patient ($p < 0.001$), PPHN (0.001) and IUGR ($p < 0.013$) and heart disease ($p < 0.049$). A study from Eritrea showed that GA, birth weight <2,000 g, SGA, and pneumonia were associated with an increase in the length of NICU stay (Shah *et al*., 2012). Multiple reports suggest that morbidities such as heart disease, IUGR, PPHN, EOS, and LOS are associated with a prolonged NICU stay, in agreement with our results, suggesting the need for extensive clinical monitoring while recovering from NS (Liyakat *et al*., 2021; Niknajad *et al*., 2012; Pokhrel *et al*., 2018; Shrestha *et al*., 2007). Anticipating the length of NICU stay or time to discharge would help resource allocation, planning, treatment quality, research, and medical practice. LBW, followed by SGA and ELBW, are negatively correlated with the length of NICU stay, possibly because early deaths reduced the median length of NICU stay (Niknajad *et al*., 2012).

We have shown that the median overall cost of treating NS was $1,006 (571–2040), higher than other LMICs. Antibiotic cost constitutes 6% and 2% of the total drug and overall treatment costs, respectively. The overall treatment cost for managing NS was higher in ELBW ($2,287) group and was least for VLBW ($963) group. A study from the USA reported the overall treatment cost for the management of LOS in ELBW is more than $20,000 compared to VLBW ($2,994) (Johnson *et al*., 2013). Prolonged antibiotic administration in the 1st week of life or suspected NS increases morbidity and mortality, necrotizing enterocolitis (NEC), compromises gut microbiota, escalates AMR, separates the mother and child, and increases healthcare costs (Boverman *et al*., 2022). A retrospective study from the US showed that every additional day on antibiotics increases the risk of developing NS, NEC, or fatality by 24%, increasing the healthcare cost (Cantey *et al*., 2018). AMR also increases healthcare costs disastrously. According to the CDC in 2013, AMR alone may increase hospital bills for treating bacterial infections by approximately $1,400 in the US, possibly raising annual healthcare expenditures by more than $2 billion. Many estimates suggest that by 2050, the global cost of AMR might be between $300 billion and more than $1

trillion yearly. AMR's immediate financial impact on healthcare includes high costs of expensive and extended treatments and increased resource usage (Dadgostar, 2019).

This study showed that overall treatment costs were significantly associated with anemia ($p < 0.051$), presence of peripheral line ($p < 0.017$), seizures ($p < 0.001$), and heart disease ($p < 0.001$). Overall, treatment cost was lower in EOS because cost decreases when appropriate treatment is received early. A study from Nepal showed that the median cost for NS was $111.7 (69.8–155.5) (Shrestha *et al*., 2007). A multicentric study from Mozambique and South Africa showed that the median overall cost of treatment was $ 75.12 [IQR, 149.43–386.12] and $653.62 (543.33–827.53), respectively (Aerts *et al*., 2022). Our study is the first to evaluate the factors responsible for the higher cost in India. Based on a few LMICs studies, the median hospitalization costs in our study appear higher than in previous reports. The cost of treatment depends on inter-country variations in resource unit costs, length of NICU stay, availability of standard care within the hospital, and willingness to pay. LMICs such as India, with a high burden of infection and low resources settings, the cost of treatment is generally above the affordable range. The average Indian per capita income stands at $1,947 (2020–21), making insurance a prominent social need. India's healthcare expenditure is below $15, with the bulk of the cost of therapy met by out-of-pocket payments (IANS, 2021).

This study has a few limitations: The results are based on a single center. The small sample size may limit the extrapolation of results to the general population. We could not estimate the indirect costs. Thirdly, we did not collect data on family income, working parents'/caregivers' salaries, time away from work, travel expenses, or caregivers' living costs, which limited the estimated expenditures and out-of-pocket expenses, with long-term economic consequences for poorer households seeking care in private hospitals.

CONCLUSION

Sepsis in neonates is often fatal. *Klebsiella pneumoniae* was the predominant organism isolated from samples, with a high incidence of XDR/PDR isolates. EOS was associated with higher mortality rates than LOS. NICU length of stay increases with morbidities in neonates. Septic shock and platelet count were significantly associated with mortality. The median total cost for LOS is twice that of EOS. The total cost of treatment was significantly associated with the onset of EOS, length of NICU stay, presence of peripheral line, and heart disease in neonates. Clinical data being scarce in India, such studies could help frame informed policy decisions toward developing and implementing targeted interventions to reduce the burden of NS within and outside India.

AUTHOR CONTRIBUTIONS

Sl. No	Author	Contribution
1	P C	Involved in the conception and designing of the study. Also involved in the statistical analysis and interpretation and drafting of the article.
2	F I	Involved in the conception and designing of the study. Also involved in the statistical analysis and interpretation and drafting of the article.
3	U MK	Involved in drafting and revising the manuscript for its intellectual content.
4	J P	Involved in revising the manuscript for its intellectual content.
5	PA S	Involved in revising the manuscript for its intellectual content.
6	E AS	Involved in the statistical analysis and interpretation.
7	R V	Involved in revising the manuscript for its intellectual content.
8	SR M	Involved in revising the manuscript for its intellectual content.
9	L E SL	Involved in conception and designing, revising the manuscript for its intellectual content, and the final approval of the version to be published.

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There is no financial assistance from any of the organizations in conducting the study.

CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study was approved by the institutional ethics committee (IEC: 81/2020) and registered at the Clinical Trial Registry India (CTRI identifier: CTRI/2020/06/025920).

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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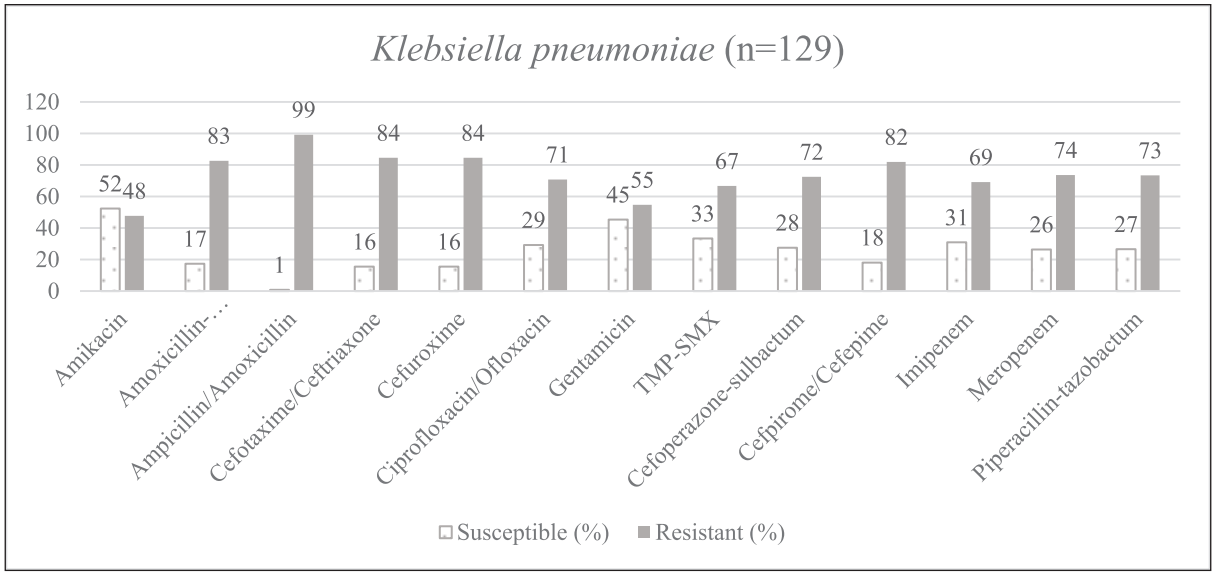
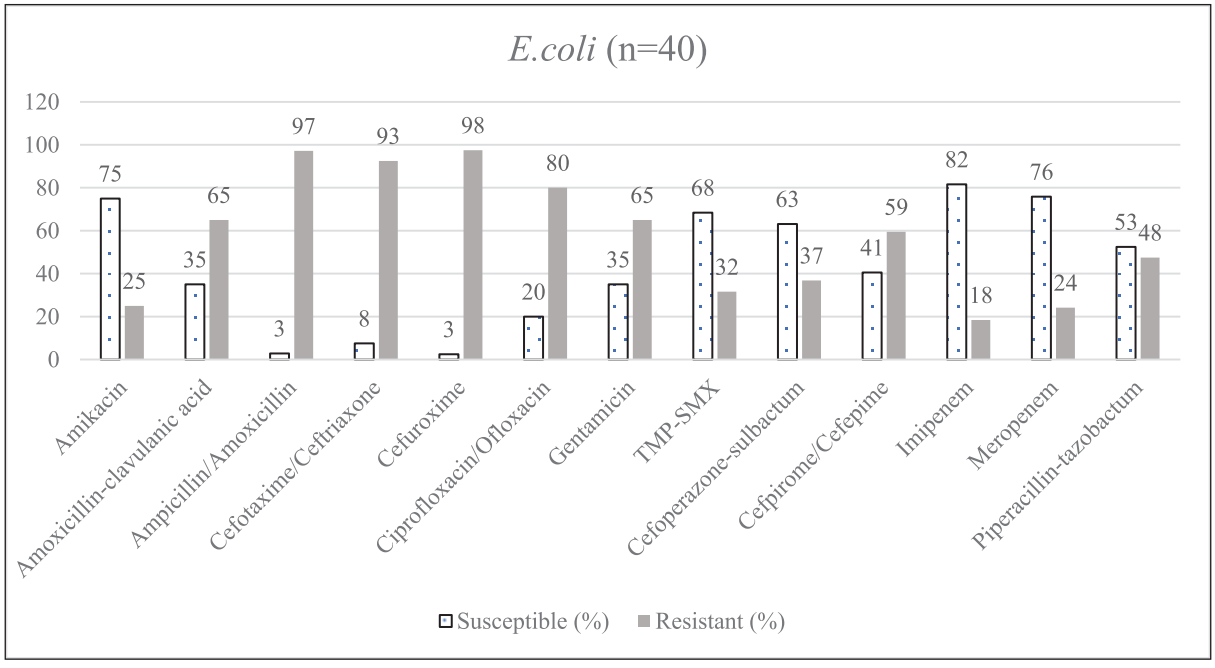
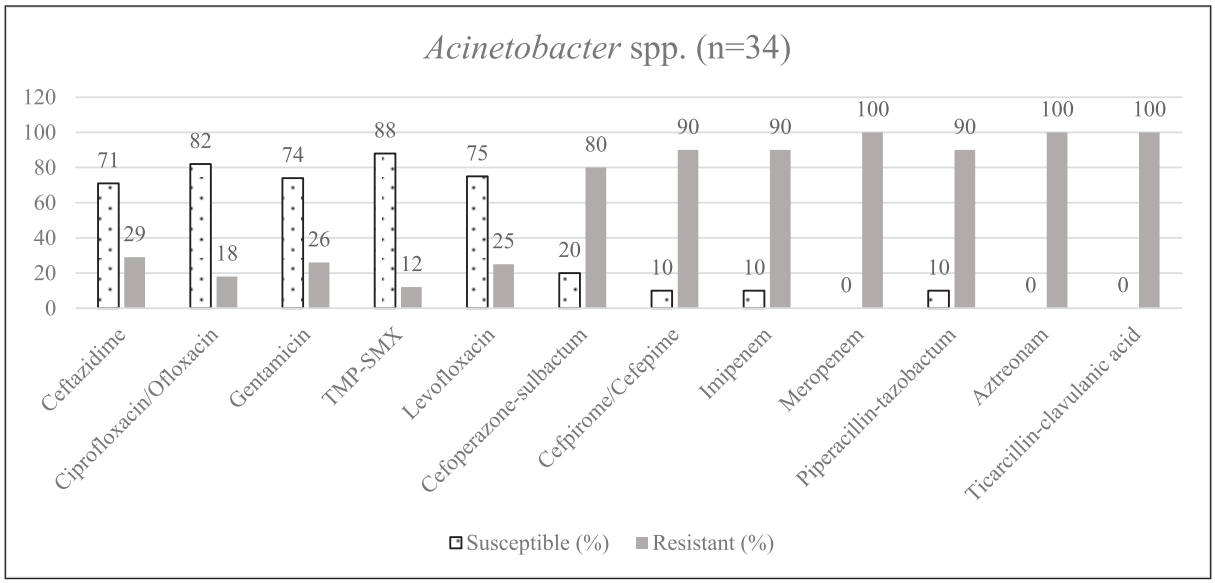
SUPPLEMENTARY MATERIAL



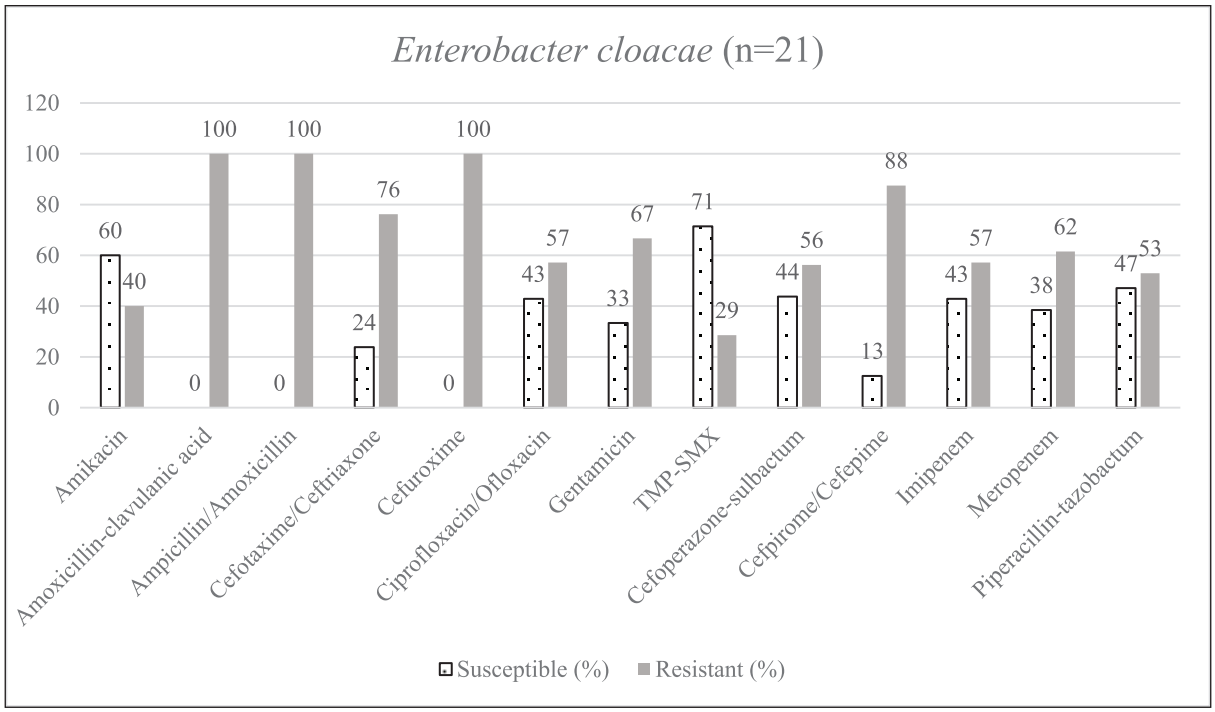
Supplementary Figure S1. AST of *K. pneumoniae*.



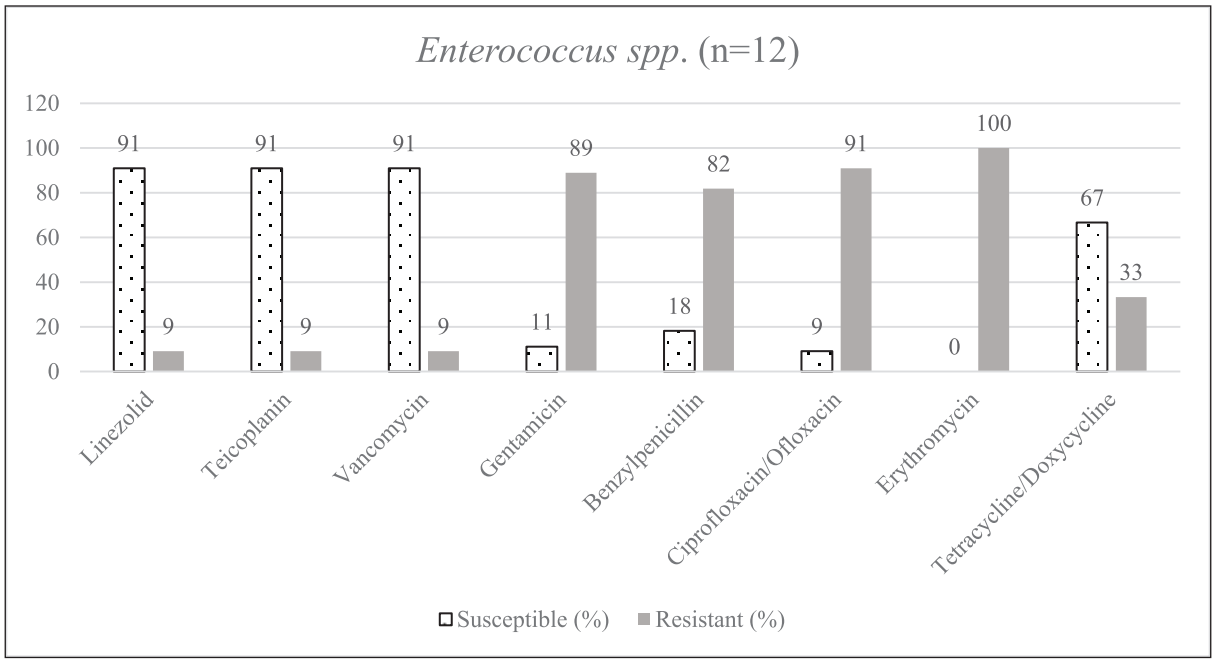
Supplementary Figure S2. AST of *E.coli.*



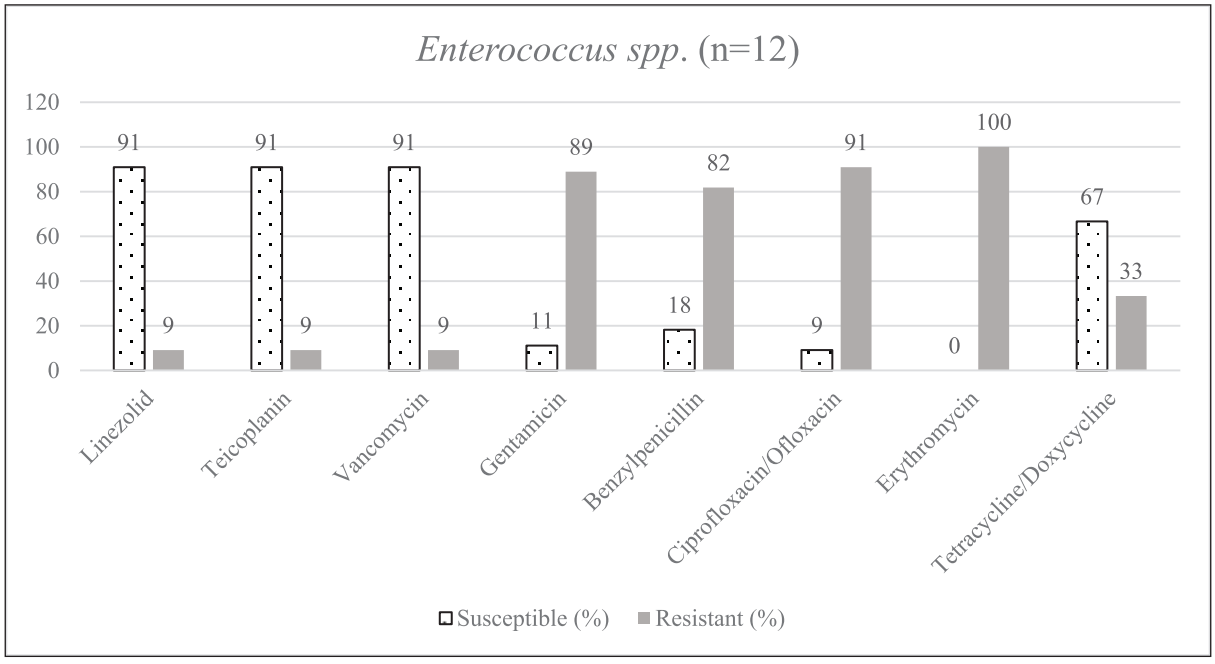
Supplementary Figure S3. AST of *Acinetobacter spp*.



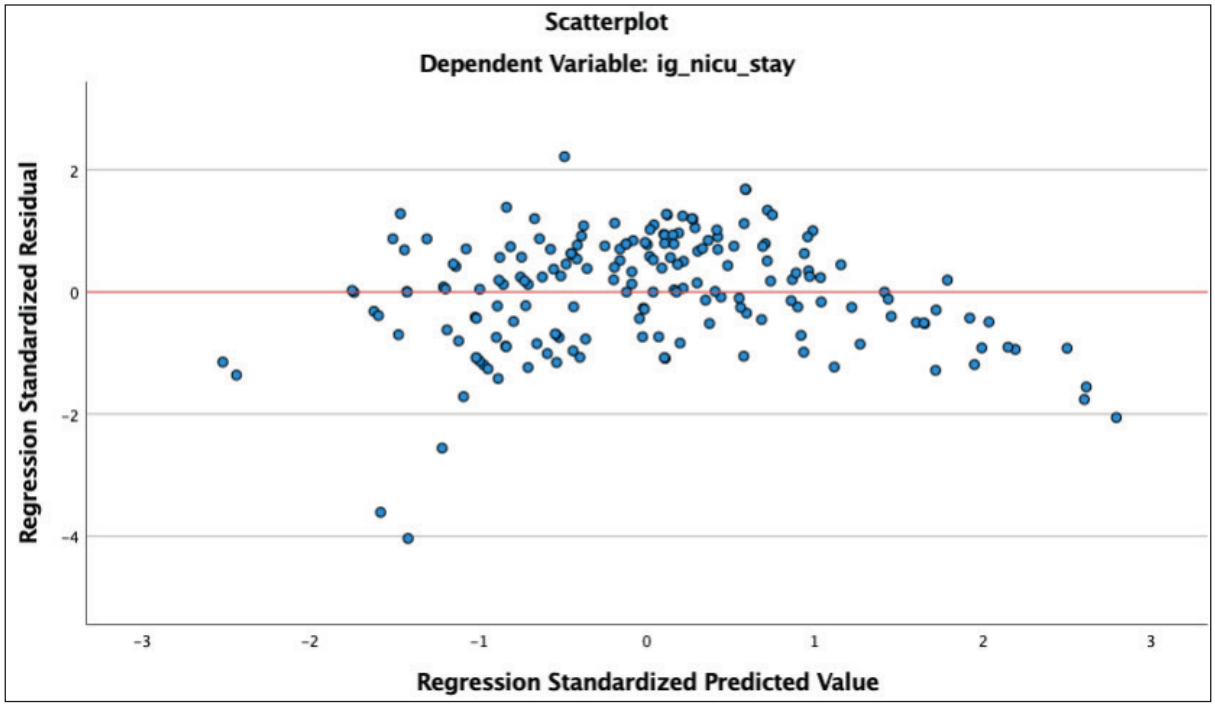
Supplementary Figure S4. AST of *E. cloacae.*



Supplementary Figure S5. AST of *Enterococcus spp.*



Supplementary Figure S5. AST of *Enterococcus spp.*



Supplementary Figure S6. Scatterplot NICU stay and neonatal attributes -predicted value (*X*-axis) versus residual value (*Y*-axis).