

# Changing Pattern of Bacteriological Profile, Antimicrobial Resistance and Mortality in Neonatal Sepsis in a Developing Country: A Retrospective Study

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## ABSTRACT

**Introduction:** Neonatal sepsis is one of the major contributors of mortality and morbidity among neonates. Irrational and overuse of antibiotics have led to an increase in antimicrobial resistance. This study was undertaken to investigate the bacteriological profile, antimicrobial resistance and predictors of mortality among blood culture-positive cases of neonatal sepsis.

**Methods:** Demographic and bacteriological data were collected from electronic and manual case records. Automated BACTEC 9050 system using Peds Plus Vial was used for blood culture. Multidrug resistance was defined as a resistance to any three of five antibiotic classes like aminoglycoside, carbapenem, extended spectrum cephalosporins, fluoroquinolones and piperacillin.

**Results:** Among 7180 admitted neonates, 433 (6.03%) were blood culture positive with early onset sepsis (EOS) in 50.1% of cases. Gram negative bacteria was the causative organism in 371 (85.7%) babies with klebsiella being the commonest pathogen (43.6%). The pathogen mix of early onset and late onset sepsis was similar and 90% of gram negative isolates were resistant to penicillin group. Multi drug resistance (MDR) was found in 51.2% of the gram negative organisms. EOS (Odds ratio 1.99; 95% confidence interval, 1.29-3.05) and MDR (Odds ratio 2.07; 95% confidence interval, 1.77-4.12) were independently associated with neonatal death due to sepsis.

**Conclusions:** Gram-negative pathogens, specifically klebsiella accounted for a huge burden of neonatal sepsis. EOS and MDR were found to be independent predictors of death due to such sepsis. This study calls for multicentric studies on early onset neonatal infection and its relationship with pathogenic maternal flora.

**Keywords:** Klebsiella; Mortality; Multi-drug resistance; Newborn; Sepsis



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## INTRODUCTION

Neonatal sepsis remains the major cause of mortality and morbidity among neonates worldwide despite great advances in neonatal care. In India, the incidence of neonatal sepsis is 30/1000 live births.<sup>1,2</sup> Neonatal sepsis alone contributes to 19% of all neonatal deaths in India which increases to 50% in case of culture-proven sepsis.<sup>3</sup>

Overuse of empirical broad spectrum antibiotics has increased the incidence of multi drug resistance (MDR).<sup>4</sup> In a recent multi-center Indian cohort study from North India,<sup>5</sup> gram -negative organisms contributed to two third of isolates that showed a high degree of antimicrobial resistance to antibiotics like extended spectrum cephalosporins and carbapenems. Almost similar picture has been drawn in another retrospective study from Delhi, India.<sup>6</sup>

In India, a country with diverse demographics and heterogeneous level of neonatal care, bacterial isolates at NICUs and their antimicrobial sensitivity may differ in relation to different places and population and also with secular change. However, there is paucity of long term collaborative national data for bacteriological isolates of neonatal sepsis. This study was undertaken to investigate the distribution of bacteriological isolates and antimicrobial susceptibility patterns and mortality among blood culture positive cases of neonatal sepsis from a level III NICU of a large tertiary-care hospital in eastern India from 2014-2019. In reference to the earlier reports of neonatal sepsis from the same NICU in previous decade,<sup>7,8</sup> this study will also pave the way to determine the trend of bacterial isolates of neonatal sepsis and their antibiotic resistance over the years, which is yet to be documented in India.

## METHODS

Demographic and bacteriological data were collected from electronic and manual case records. Automated BACTEC 9050 system using Peds Plus Vial was used for blood culture. Multidrug resistance was defined as a resistance to any three of five antibiotic classes like aminoglycoside, carbapenem, extended spectrum cephalosporins, fluoroquinolones and piperacillin.

## RESULTS

During the study period, a total of 7180 babies were admitted in the NICU of which 1977 babies were treated for suspected neonatal sepsis. Blood culture was positive in 661 samples. Excluding fungal growth and growth of contaminants, a total of 455 blood culture samples were positive in 433 babies (6.03%) who were eligible for the study. The culture positivity rate of suspected sepsis was 21.9% (433 among 1977 babies). Table 1 showed the baseline characteristics of the study participants. Proportion of inborn and out born babies was almost equal among culture positive babies. EOS occurred in 50.1% (217) of the study infants.

### Bacteriological profile

Frequency of various bacterial isolates is depicted in table 2. Gram-negative bacteria caused neonatal sepsis in 371 babies (85.7%) and of them 260 (60%) belonged to the family Enterobacteriaceae. *Klebsiella pneumoniae* was the foremost infectious agent with 189 cases (43.6%) followed by *Escherichia coli* in 63 (14.5%), *Acinetobacter* spp in 52 (12.0 %) and *Pseudomonas aeruginosa* in 59 (13.6 %) cases. Gram-positive cocci were found in 62 (14.3%) cases.

### Early onset versus late onset sepsis

There were equal share of EOS and LOS (table 2). *Klebsiella pneumoniae* was predominant in both early and late infection. However, the incidence of *Staphylococcus aureus* sepsis was higher in LOS than EOS (17.1 % versus 8.3%,  $p < 0.005$ ).

### Mortality proportion and case fatality of different organisms

The CFR was 35.3% (153) among culture positive babies and mortality was significantly more in EOS than LOS (43.8 % versus 26.6%,  $p = 0.01$ ) (Tables 1 and 2). *Klebsiella pneumoniae* caused highest number of deaths (80, 52.3%). Gram positive pathogens (*Staphylococcus aureus* and *Enterococcus* spp.) were responsible for only five (3.3 %) deaths. *Klebsiella pneumoniae* and *Escherichia coli* sepsis carried almost equal high CFR of 42 to 46% (Table 2). Overall the CFR was significantly higher in gram negative sepsis than gram positive sepsis (39.9% vs. 8.1%,  $p < 0.05$ ).

Table 1. Base line characteristics of the enrolled participants

Neonatal variable	value
Birth weight* , g	2000 (1285-2605)
≥ 2500 g	139 (32.10)
1500 - 2499 g	143 (33.02)
1000 - 1499 g	84 (19.39)
≤ 999 g	67 (15.47)
Small for gestational age	155 (35.79)
Gestation (weeks)	36 (32-38)
Sex	
Boy	263 (60.73)
Girl	170 (39.26)
Caesarean delivery	206 (47.57)
Type of admission	
Inborn	215 (49.65)
Outborn	218 ( 50.34)
Birth asphyxia	34 (7.85)
Types of Culture positive sepsis	
Early (EOS)	217 (50.11)
Late (LOS)	216 (49.89)
Neonatal death before discharge	153 (35.33)
EOS	95/217(43.78) p = 0.016
LOS	58 /216 (26.85)

<sup>a</sup> n (%)

\*Median (Inter quartile range)

### Antibiotic resistance

The antibiotic resistance pattern is shown in figure 1. Among gram-positive cocci, 85-90 % isolates were resistant to first line antibiotics like ampicillin - penicillin. Resistance to vancomycin and linezolid was seen in 15 - 25 % of cases. Gram negative organisms were found to be resistant to ampicillin in > 95% of cases, to extended spectrum cephalosporins in 75 - 80% of cases, to piperacillin-tazobactam in 55% of cases, to aminoglycosides in 50 - 60% of cases and to fluoroquinolones in 75% of cases. Resistance pattern of individual bacteria to various antibiotics is depicted in table 3. *Klebsiella pneumoniae* showed higher resistance to all cephalosporins (80%), ampicillin (90%) and fluoroquinolones (70%) but less resistance to piperacillin - tazobactam (64%), aminoglycosides (55-60%), carbapenems (30%) and colistin (9.5%). *Escherichia coli* expressed higher resistance to

colistin (15%). *Pseudomonas aeruginosa* showed less resistance to piperacillin - tazobactam (15%) and ceftazidime (33%). But *acinetobacter* spp showed higher resistance to all antibiotics (> 70%) except carbapenems (50-60%) and colistin (38%). *Serratia* spp was found resistant to fluoroquinolones, ampicillin and amoxicillin. Enterococci spp was resistant to vancomycin in 14% of cases and linezolid in 57% of cases.

### Multi drug resistance

MDR in cases of gram negative organism is depicted in table 2. Individually *klebsiella pneumoniae* topped the list of MDR organisms with 93 (48.9%) cases but the proportion of MDR was highest in *acinetobacter* spp (71.1%) followed by *escherichia coli* (57%), *klebsiella pneumoniae* (49.4%) and *pseudomonas* spp (37.3%) and the overall MDR proportion was 51.2% among gram negative bacteria. The CFR of MDR positive sepsis was 46.3% (88 / 190).

### The trend of bacteriological isolates

The trend of blood culture positive sepsis cases over the years is shown in table 4. *Klebsiella pneumoniae* was the commonest isolate in early years (2014 - 2017) but was outnumbered by *escherichia coli* and *pseudomonas aeruginosa* in subsequent years (2018 - 2019). The proportion of MDR showed similar trend over the years (45% - 60%).

### Mortality risk factors

Prematurity, LBW, infection with MDR organisms and early onset sepsis were significantly associated with increased risk of mortality as found in univariate analysis (Table 5). In multiple logistic regression modelling, only EOS (OR 1.99, 95 % CI 1.29 - 3.05) and MDR infection (OR 2.07 , 95% CI 1.77 - 4.12) were found as independent predictors of mortality in culture positive sepsis.

## DISCUSSION

Our study has presented the epidemiology of neonatal sepsis and its causative bacterial organisms from a single center NICU of Eastern India dealing with more than 7000 admitted newborn over half a decade.

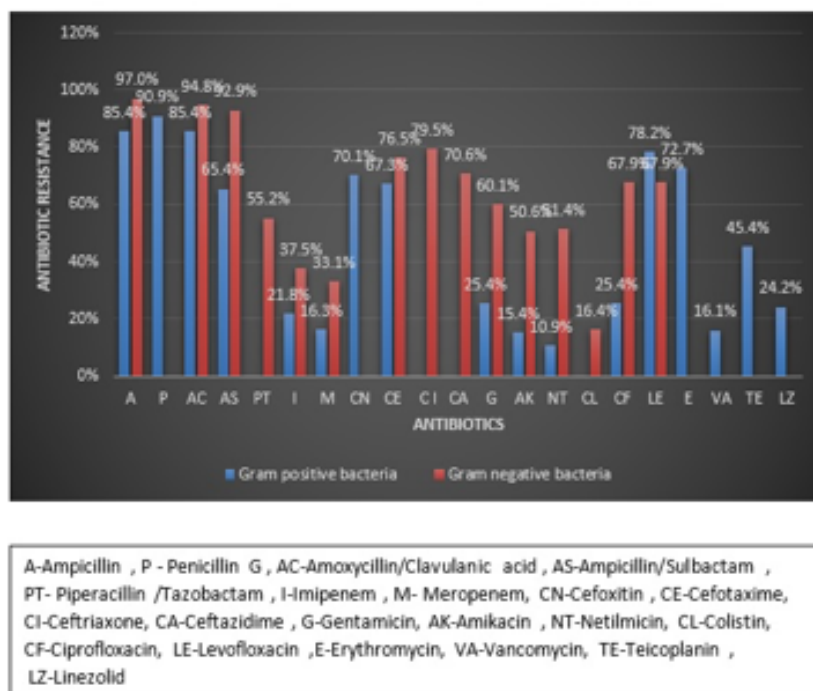
**Table 2.** Bacterial pathogens of neonatal sepsis, distribution, MDR and associated mortality

Organism	No of cases (% of total cases)	EOS (% of total EOS cases)	LOS (% of total LOS cases)	Death (case fatality ratio)	MDR (% of total MDR cases)	Death among MDR (Case fatality ratio)
Gram negative bacteria	371 (85.7)	197 (90.7)	174 (80.5)	148 (39.9)	-	
Klebsiella pneumoniae	189 (43.6)	99 (45.6)	90 (41.7)	80 (42.3)	93 (48.9)	44/93 (47.3)
Escherichia coli	63 (14.5)	32 (14.7)	31 (14.4)	29 (46.0)	36 (18.9)	20/36 (55.5)
Proteus mirabilis	2 (0.4)	1 (0.5)	19 (8.8)	1 (50.0)	1 (0.5)	0 /1 (0)
Serratia marcescens	5 (1.1)	3 (1.3)	2 (0.9)	1 (20.0)	0 (0)	0/0 (0)
Enterobacter cloacae/cloacae complex	1 (0.2)	0	1 (0.5)	0	1 (0.5)	0/1 (0)
Acinetobacter baumannii / baumannii complex	52 (12.0)	26 (12.0)	26 (12.0)	20 (38.5)	37 (19.5)	18/37 (48.6)
Pseudomonas aeruginosa	59 (13.6)	36 (16.6)	23(10.6)	17 (28.8)	22 (11.6)	6/22 (27.3)
Gram positive bacteria	62 (14.3)	20 (9.2)	42 (19.4)	5 (8.1)	-	
Staphylococcus aureus	55 (12.7)	18 (8.3)	37 (17.1)	2 (3.6)	-	
Enterococcus spp.	7 (1.6)	2 (0.9)	5 (2.3)	3 (42.9)	-	
Total	433	217	216	153 (35.3)	190	88/190 (46.3)

The predominance of *klebsiella pneumoniae* as the causative organism in all types of neonatal sepsis in our study matched with the results of the studies from various parts of India, ie Chennai, Rajasthan, Karnataka and Delhi<sup>6,11-13</sup> but differed strikingly from the results of the DeNis study<sup>5</sup> which reported acinetobacter spp as the predominant organism. Interestingly, previous reports from Punjab, Himachal Pradesh and Kerala<sup>14-17</sup> showed staphylococcus aureus as the main pathogen which is also less common in our study. Systematic analysis by Le Doare and colleagues<sup>18</sup> that included results from eleven neonatal units from developing countries also showed *Klebsiella pneumoniae* to be the predominant pathogen. Hence, *klebsiella pneumoniae* may be regarded as the new emerging threat in neonatal sepsis in developing countries.

Two earlier reports from the same unit during 2007 to 2014 had also shown acinetobacter spp as the

most common causal organism even before the result of the DeNis study was published.<sup>5,7,8</sup> The present study represents the subsequent era of the same unit from 2014-2019. The authors of the previous reports found that more resistant non-fermenting gram-negative bacteria (NFGNB) dominated the causative organisms of neonatal sepsis including certain rare organisms. Now in the same unit, acinetobacter spp (12%) has been outnumbered by klebsiella pneumoniae (43.6%) and escherichia coli (14.5%). The present-day incidence of acinetobacter spp and pseudomonas spp (NFGNB) sepsis is less (12 - 13%) than the previous report from the same NICU (23.6%) in 2014.<sup>8</sup> One organism or a group of organisms may be replaced over a period of time in critical areas like NICU which was also reflected in a previous study by Roy et al.<sup>2</sup> This could be the result of continuous quality control initiatives for prevention of infection and implementation of



**Figure 1.** Antimicrobial resistance among gram-positive and gram-negative isolates

antimicrobial stewardship program adopted since 2012 with a target of zero tolerance to sepsis.

Incidence of EOS and LOS were almost equal in the present study, which is in sharp contrast with the reports published from other Asian countries,<sup>19,20</sup> as well as those from developed countries where most infection are late onset in NICU.<sup>21</sup> Our data is somewhat consistent with the recent report published from Delhi where EOS was more than LOS and the pathogen mix of EOS and LOS was almost similar with the predominance of gram negative organism.<sup>6</sup> In a large referral unit like ours the predominance of in-utero transfer of sick pregnant mothers and heavy load of high-risk delivery increases the likelihood of perinatal and early onset infection among NICU babies.

Resistance to reserve drugs like colistin and carbapenems were found in 16-35% cases. Third generation cephalosporins have already been ineffective with documented resistance in 75 - 80% of cases. In view of resistance to more than 90% of gram negative isolates and 85 - 90% of gram positive isolates; ampicillin as the first line antibiotic needs revision. In the present study, the

incidence of MDR was already 50% among gram negative organisms. The observation was quite similar to a few reports published from North India.<sup>14,16,22</sup> Hence judicious use of empirical antibiotics based on local isolates and antibiotic sensitivity pattern should be made mandatory in neonatal units. Based on a review of 11,471 blood cultures from developing countries in South-East Asia, Zaidi et al<sup>23</sup> have recommended imipenem and amikacin regimen for initial treatment of suspected sepsis. However, considering an increase in the proportion of acinetobacter spp, use of carbapenem group of drugs also needs restriction as the antibacterial armamentarium is extremely limited at present.

The case fatality was higher in case of gram negative organisms and even higher in MDR strains. High load of antimicrobial resistance may be the cause behind this. Contrary to previous reports,<sup>5,7,8</sup> the isolation of more resistant and fatal acinetobacter spp was less in our study. The CFR of culture positive sepsis in developed countries is higher in case of LOS.<sup>21</sup> But in the present study death was significantly higher in EOS like which was similar to other reports from developing

Table 3. Antimicrobial resistance of all bacterial isolates to various antibiotics

	Ampicillin	Penicillin G	Ampicillin-sulbactam	Piperacillin-Tazobactam	Amoxicillin – Clavulanic acid	Cefotaxime	Ceftriaxone	Ceftazidime	Cefoxitin	Imipenem	Meropenem	Genetamicin	Amikacin	Netilmicin	Ciprofloxacin	Levofloxacin	Erythromycin	Colistin	Vancomycin	Linezolid	Teicoplanin
Klebsiella pneumoniae* N = 1890	182 (96.3)	NT	120 (64.5)	179 (94.7)	152 (80.4)	158 (83.6)	145 (76.7)	NT	59 (31.2)	61 (32.2)	119 (62.9)	107 (56.6)	108 (57.1)	133 (70.3)	131 (69.3)	NT	18 (9.5)	NT	NT	NT	
Escherichia coli* N = 636	55 (87.3)	NT	35 (55.5)	60 (95.2)	53 (84.1)	54 (85.7)	52 (82.5)	NT	23 (36.5)	19 (30.1)	36 (57.1)	24 (38.0)	23 (36.5)	44 (69.8)	45 (71.4)	NT	10 (15.8)	NT	NT	NT	
Enterobacter cloacae/cloacae complex* N = 1	1 (100)	NT	0 (0)	1 (100)	1 (100)	1 (100)	1 (100)	NT	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	NT	0 (0)	NT	NT	NT	
Serratia marcescens* n = 5	5 (100)	NT	0 (0)	5 (100)	0 (0)	4 (80)	0 (0)	NT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NT	2 (40)	NT	NT	NT	
Proteus mirabilis* n = 2	1 (50)	NT	1 (50)	2 (100)	1 (50)	1 (50)	1 (50)	NT	1 (50)	0 (0)	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)	NT	0 (0)	NT	NT	NT	
Acinetobacter baumannii/ baumannii complex* n = 52	47 (90.4)	NT	40 (76.9)	50 (96.2)	42 (80.8)	45 (86.5)	43 (82.7)	NT	32 (61.5)	26 (50)	40 (76.9)	38 (73.0)	31 (59.6)	41 (78.8)	41 (78.8)	NT	8 (15.3)	NT	NT	NT	
Pseudomonas aureginosa* N = 592	54 (91.5)	NT	9 (15.2)	57 (96.6)	35 (59.3)	32 (54.2)	20 (33.9)	NT	24 (40.7)	16 (27.1)	27 (45.7)	18 (30.5)	28 (47.4)	33 (55.9)	33 (55.9)	NT	23 (38.9)	NT	NT	NT	
Staphylococcus aureus* N = 554	47 (85.4)	50 (90.8)	36 (65.4)	NT	47 (85.4)	37 (67.2)	NT	NT	39 (70.9)	12 (21.8)	9 (16.3)	14 (25.4)	9 (16.3)	6 (10.9)	14 (25.4)	43 (78.2)	40 (75.6)	NT	14 (25.4)	11 (20)	25 (45.4)
Enterococci spp* n = 7	NT	6 (85.7)	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	1 (14.3)	4 (57.1)	NT	

countries.<sup>5,6</sup> EOS and MDR were found to be independent predictors of mortality in the present study among culture positive sepsis. This might have had some relationship with the indiscriminate

use of antibiotics in mother resulting in a change of maternal microbiome. Preliminary reports of a multicentric study on the burden of antimicrobial resistance in neonatal sepsis in low socio-economic

**Table 4.** Year wise trend of bacterial isolates of culture positive sepsis

Year	2014	2015	2016	2017	2018	2019
Total admission	925	1392	1819	2208	2323	2649
Blood culture positive cases (%)	53 (5.72)	88 (6.31)	99 (5.44)	77 (3.48)	59 (2.53)	57 (2.15)
<i>Klebsiella pneumoniae</i>	25	59	54	34	6	11
<i>Escherichia coli</i>	12	11	10	9	9	12
<i>Proteus spp.</i>	1	0	1	0	0	0
<i>Serratia spp.</i>	1	0	2	1	1	0
<i>Enterobacter spp.</i>	0	1	0	0	0	0
<i>Acinetobacter spp.</i>	7	8	12	6	10	9
<i>Pseudomonas aeruginosa</i>	2	4	13	10	16	14
<i>Staphylococcus aureus</i>	3	4	6	17	17	8
<i>Enterococcus spp.</i>	2	1	1	0	0	3
MDR organism	32/53	37/88	39/99	37/77	17/59	28/57

countries also mentioned a significant role of similar maternal risk factors in developing EOS.<sup>24,25</sup> This burden of gram negative organism has increased as a result of very early horizontal transmission from delivery rooms and NICUs<sup>23,26</sup> or vertical transmission from the maternal genital tract colonized with these pathogens.<sup>25,27</sup> Hence infection control in delivery room and resuscitation area, eradication of maternal pathogenic flora and restriction on the indiscriminate use of antibiotics in expectant mothers might be the only sustainable measures to prevent this disaster.

Our study has explored the pertinent issue of neonatal sepsis in the resource limited set up. We have conducted our research in one of the largest NICUs of India with more than 7000 newborns over a half decade. This study has a bigger implication in Indian scenario where presently the neonatal care is going through the phase of rapid expansion with many level- II sick newborn care units. Despite being a large study, it does have limitations of being retrospective and single centric study. Similarly, we also have to acknowledge that molecular mechanism of resistance especially

extended-spectrum beta-lactamase and carbapenemases were not tested. This study calls for further multicentric, prospective studies on the burden of EOS and its relationship with of pathogenic maternal flora in view of significant case fatality observed in EOS.

## CONCLUSIONS

Gram negative pathogens and more specifically *klebsiella pneumonia* was the predominant organism of neonatal sepsis. EOS and MDR infection have been found to be two independent predictors of mortality in neonatal culture proven sepsis. There is an urgent need for revision of commonly used combination of ampicillin and gentamycin as empirical antibiotic therapy in view of a very high ampicillin resistance.

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