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ORIGINAL RESEARCH ARTICLE

Trend of bacteriological profile and antibiotics sensitivity pattern in neonates with late onset sepsis

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ABSTRACT

Background: Neonatal sepsis is a major cause of morbidity and mortality in low- and middle-income countries (LMICs). It is categorized as early onset sepsis (EOS, ≤72 hours) and late onset sepsis (LOS, >72 hours). The World Health Organization (WHO) has emphasized antibiotic stewardship. In LMICs, antibiograms are crucial where sepsis significantly contributes to neonatal deaths.

Objective: To analyze trends in bacteriological profile and antibiotics sensitivity in neonates with Late Onset Sepsis (LOS).

Methods: This was a 10-year retrospective study of culture-proven LOS cases. Demographics, isolate types, and sensitivity patterns were recorded. Multidrug-resistant (MDR) gram-negative isolates were defined as resistance to ≥3 of 5 antibiotic classes: extended-spectrum cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, and piperacillin-tazobactam.

Results: Among 14,336 NICU admissions (2010–2019), 6092 (42.5%) were evaluated for sepsis, and 647 (10.6%) had culture-positive LOS. Gram-negative organisms comprised 488 (75.3%) isolates—*Klebsiella* (35.3%), *E. coli* (13.3%), and *Acinetobacter* (10.5%) were most common. Gram-positive isolates (24.7%) included *S. aureus* (9.4%), coagulase-negative staphylococci (10.5%), and *Enterococcus* (4.8%). High MDR rates were observed in *Klebsiella* (56.3%), *E. coli* (56.9%), and *Acinetobacter* (86.8%). Methicillin resistance was seen in 77.3% of *S. aureus* and 74.2% of *Enterococcus*.

Conclusions: Alarming antimicrobial resistance in both gram-negative and gram-positive organisms calls for urgent attention. Antibiotic stewardship and regular antibiogram surveillance are essential to develop effective hospital policies.

INTRODUCTION

Neonatal sepsis is a leading cause of morbidity and mortality in low- and middle-income countries (LMICs). Globally, 2.5 million neonates die annually, with over a quarter of these deaths occurring in India.[1] The National Neonatal Perinatal Database (NNPD) of India reported an incidence of blood culture-proven sepsis of 8.5 per 1,000 live births during 2002–2003.[2] A community-based rural study found culture-confirmed neonatal sepsis at 6.7 per 1,000 live births.[3] Neonatal care improvements have reduced the Neonatal Mortality Rate (NMR) from 38 to 23 per 1,000 live births between 2000 and 2017.[4]

Neonatal sepsis is classified as early-onset sepsis (EOS) if occurring within 72 hours of life, and late-onset sepsis (LOS) if after 72 hours.[5] In developed countries, gram-positive organisms predominate in both EOS and LOS,[6,22] whereas in LMICs, gram-negative bacteria account for two-thirds of isolates.[7]

The rise of resistant pathogens over the last two decades is mainly attributed to uncontrolled antibiotic use. The DeNIS multicentric study reported high antimicrobial resistance among neonatal pathogens.[7,21] In response, the World Health Organization (WHO) emphasized antibiotic stewardship,[8] and the Indian Council of Medical Research (ICMR) launched the Antibiotic Stewardship, Prevention of Infection & Control (ASPIC) program.[9,19]

Since bacterial profiles and resistance patterns vary regionally, regular review of antibiograms guides antibiotic policies[18,20]. In LMICs, antibiograms are crucial due to the high neonatal mortality burden from sepsis. This study aimed to evaluate pathogen trends and antibiotic resistance in neonates admitted to a NICU in western India.

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METHODS

A retrospective study was conducted in neonates admitted in tertiary care NICU of Pune, India over a period of January 2010 to December 2019. Patients were identified from the local database of the hospital for discharge summaries. Ethical approval was waived by the local ethical committee due to retrospective nature of the study. For the robustness of the data, it was cross verified with the departmental annual audit data for culture proven sepsis as well as with the records from the microbiology database.

Data was collected from the patient file records for culture proven late onset sepsis after permission of Hospital and Head of Neonatology Department. It was analyzed for demographic characteristics, morbidities during hospital stay and various outcomes in neonates.

The type of organisms grown and its sensitivity pattern were noted. Antimicrobial susceptibility pattern was classified as susceptible, intermediate, resistant, or not tested for each individual antibiotic. The Gram-negative pathogens' resistance profiles were categorized based on resistance to various antimicrobial classes namely, (i) extended-spectrum cephalosporins (any two of ceftazidime, ceftriaxone, or cefotaxime), (ii) aminoglycosides (any one of gentamicin or amikacin), (iii) carbapenem (meropenem), (iv)fluoroquinolone (ciprofloxacin), and (v) piperacillin and tazobactam. If resistance to any three of the five specified classes were detected, the pathogen was labeled multidrug resistant (MDR).

Descriptive statistics and frequency distributions of all variables of interest were reported as proportion for categorical variables and as mean (SD) for continuous variables. Data was analyzed using a chi square test or Fisher's exact test as applicable for categorical variables and student t-test for continuous variables. All statistical analysis was performed using IBM SPSS Statistics version 20.0.

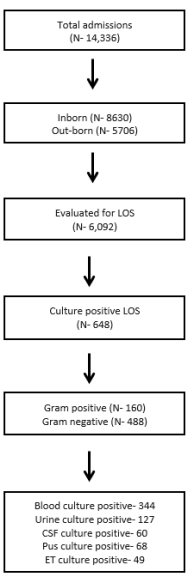

Figure 1: Flow chart of study patients

RESULTS

Of 14,336 neonates admitted in NICU between 1st January 2010 to 31st December 2019, 8630 (60.2%) were inborn and 5706 (39.8%) were out-born referrals. Of all admissions, 6092 (42.5%) neonates were evaluated and 648 (10.6%) neonates were diagnosed as culture positive LOS. Gram negative organisms were isolated from 488 (75.3%) cases and gram positive from 160 (24.7%) cases. Blood culture was positive in 344 (53%) cases, urine culture in 127 (19.6%) cases, CSF culture in 60 (9.3%) cases, pus culture in 68 (10.5%) cases, Endotracheal Tube culture in 49 (7.6%) cases (Fig.1).

Table 1 shows the baseline characteristics of study participants. Approximately, 56.3% (365) were males. Extremely Low Birth Weight (ELBW) neonates were most commonly affected 30% (195) followed by 24% (155) Very Low Birth Weight (VLBW) and 22.5% (146) Low Birth Weight (LBW) neonates. Mean gestational age was 33 (27-39) weeks. Of all, 20.4% (132) were Small for Gestational Age (SGA) neonates.

Neonatal morbidities noted were Hemodynamically significant Patent Ductus Arteriosus (HsPDA) 9.6% (62), Ventilator Associated Pneumonia (VAP) 5.5% (36), NecrotizingEnterocolitis (NEC) 6.2% (40), Respiratory Distress Syndrome (RDS) requiring surfactant 36.3% (235), Interventricular Hemorrhage (IVH) Grade III or IV 6.8% (44), Retinopathy of Prematurity (ROP) 1.9% (12), Hypoxic Ischemic Encephalopathy (HIE) of any grade 12% (78) and Broncho Pulmonary Dysplasia (BPD) 8.3% (54), respectively. Overall, mortality among culture positive LOS neonates was 23.4% (152).

Table 1: Demographic characteristics of patients (n- 648)

Characteristics of patients	Frequency (%)
Outborn	272 (42%)
Inborn	376 (58%)
Birth weight, gm	
a) ≥2500 gm	152 (23.5%)
b) 1500-2499 gm	146 (22.5%)
c) 1000-1499 gm	155 (24%)
d) ≤999 gm	195 (30%)
Gestational age, weeks	33 (27-39 weeks)
Term neonates	174 (26.8%)
Preterm neonates	474 (73.2%)
Small for Gestational Age (SGA)	132 (20.4%)
Sex	
Male	365 (56.3%)
Female	283 (43.7%)
a) Interventions Central line	
Umbilical arterial line	188 (29%)
Umbilical venous line	272 (42%)
b) Peripheral Inserted Central Catheter	119 (18.4%)
c) Vasopressor	339 (52.3%)
d) Surfactant	128 (19.8%)
e) CPAP	301 (46.5%)
f) Mechanical ventilation	286 (44.1%)
Neonatal Morbidities	

a) HsPDA	62 (9.6%)
b) VAP	36 (5.5%)
c) NEC (Stage III)	40 (6.2%)
d) RDS (Requiring surfactant)	235 (36.3%)
e) IVH (Grade III or IV)	44 (6.8%)
f) ROP (Requiring LASER)	12 (1.9%)
g) HIE (Any stage)	78 (12%)
h) BPD	54 (8.3%)
Neonatal death	152 (23.4%)

Table 2 shows the distribution of pathogens. Of the total of 648 culture positive cases, about 24.7% were gram positive and 75.3% were gram negative organisms. The predominant gram positive pathogens were *Staphylococcus aureus, Coagulase-negative Staphylococcus* and *Enterococcus* spp. in that order. The predominant gram negative organisms were *Klebsiella, E. coli, Acinetobacter, Enterobacter, Serratia, Pseudomonas, Elizabethkingia* and *Burkholderia*.

Table 3 shows the resistance pattern of predominant organisms against antimicrobial agents. Most of the pathogens showed antimicrobial resistance to not only common antibiotics but also to reserve antibiotics such as carbapenems and extended spectrum penicillins. Majority of Gram negative organisms were multidrug resistant (*Klebsiella*- 56.3%, *E.coli*- 5.9% and *Acinetobacter*- 86.8%). Antimicrobial resistance was also very high among gram positive organisms, 77.3% *Staphylococcus aureus* and 74.2% of *Enterococcus* were methicillin resistant. Vancomycin resistance was also seen among 5.3% *Staphylococcus aureus* and 19.4% of *Enterococcus*.

Table 2: Distribution of microorganisms

Microorganisms	Number of isolates (n = 648)
Gram negative	
Klebsiella spp.	229 (35.3%)
E. coli	86 (13.3%)
Acinetobacter	68 (10.5%)
Enterobacter	27 (4.2%)
Serratia	25 (3.8%)
Pseudomonas	19 (3%)
Elizabethkingia	10 (1.5%)
Burkholderia spp.	8 (1.2%)
Others	16 (2.5%)
Gram positive	
Staphylococcus aureus	61 (9.4%)
MRCONS	68 (10.5%)
Enterococcus	31 (4.8%)

Table 3: Antimicrobial resistance among common organisms

Pathogens	Antimicrobial class	Resistance
Gram negative		
Klebsiella (N-229)	Extended Spectrum Cephalosporins	180/229 (78.6%)
	Carbapenems	117/229 (51.0%)
	Aminoglycosides	102/229 (44.5%)
	MDR	129/229 (56.3%)
E. coli (N- 86)	Extended Spectrum Cephalosporins	78/86 (90.7%)
	Carbapenems	19/86 (22.0%)
	Aminoglycosides	43/86 (50.0%)
	MDR	49/86 (56.9%)
Acinetobacter (N- 68)	Extended spectrum Cephalosporins	59/68 (86.8%)
	Carbapenems	51/68 (75.0%)
	Aminoglycosides	55/68 (80.9%)
	MDR	59/68 (86.8%)
Gram positive		
Staphylococcus aureus (N- 75)	Methicillin	58/75 (77.3%)
	Vancomycin	4/75 (5.3%)
Enterococcus (N- 31)	Methicillin	23/31 (74.2%)
	Vancomycin	6/31 (19.4%)

Table 4: Change in trend of bacteria causing late onset sepsis over last 10 years

Bacteria	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Klebsiella	18	21	26	35	26	34	12	14	19	24
E.coli	8	4	4	2	16	6	7	14	15	10
Acinetobacter	4	7	16	10	7	5	6	4	6	3
S. aureus	6	5	8	7	5	5	8	7	6	4
MRCONS	7	9	3	4	10	7	8	7	8	5
Enterococcus	1	2	2	3	7	4	3	2	5	2

Table 4 shows the trend of common organisms over a period of 10 years. *Klebsiella* and *E. coli* remained the most common organisms over the years. *Acinetobacter* cases increased in 2012-2013 but after improving infection control measures their number showed a decreasing trend. Trend of other common organisms like *Staphylococcus aureus*, Methicillin Resistant Coagulase Negative *Staphylococcus* (MRCONS) and *Enterococcus* remained same over the years (Fig.2).

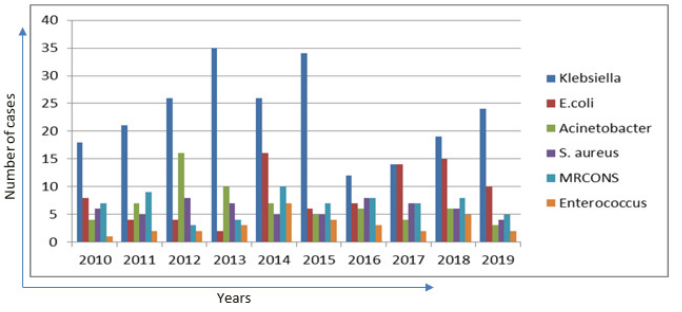

Figure 2: Change in trend of pathogens causing Late Onset Sepsis (LOS)

DISCUSSION

In our study, majority of neonates were low birth weight or preterm. About 40% were out-born referrals from other centers. We found a predominance of gram negative organisms 69.1% which is much higher than DeNIS study[7] but similar to Thapa S et al.[10] Among culture positive cases, 272 (42%) were out-born with 234 (86%) had gram negative sepsis. Of 648 neonates, 30% (195) were ELBW and 24% (155) were VLBW neonates. Neonatal comorbidities like HsPDA, VAP, NEC, RDS, IVH, ROP, HIE and BPD were frequent.

The NNPD network involving 10 leading out-born units in India reported a prevalence of about 40% .[2] DeNIS study reported a prevalence of 55% among the enrolled neonates.[7] In this study, we found neonatal sepsis in 42.5% of all neonates admitted in NICU. Culture positive rates are also variable among various studies conducted in Low and Middle Income Countries LMICs. In India, DeNIS study reported culture proven sepsis in 13.1% neonates,[7] Thapa S et al reported a culture positivity rate of 10.8% in Nepal[10] which is quite similar to our study (10.6%). Mudzikati et al. in 2015 reported a prevalence of culture positive neonatal sepsis 9.8% in Botswana (Southern Africa).[11] Blood and CSF culture positivity rate in our study was similar to Turhan et al. except for urine culture positivity rate which was more in our study.[12] The variation in culture positivity rate of neonatal septicemia might be due to differences in population characteristics, prior antibiotic administration before sample collection, and infection with anaerobes, viral or fungal pathogens, and effective control in spread of nosocomial infection.

Bacteriological profile revealed high prevalence of gram-negative bacteria (75.3%) with predominance of *Klebsiella, E.coli* and *Acinetobacter* which was similar to DeNIS study.[7] *Klebsiella* was also reported as one the most common gram-negative organism from other studies.[13-15] Among gram positive isolates, *Staphylococcus aureus* (9.4%) and MRCONS (10.5%) were the predominant organisms which are common causes of hospital acquired infections.[16]

We have identified significantly high resistance to antibiotics, including reserve antibiotics in both gram-positive and gram-negative isolates. *Acinetobacter* was the most resistant among gram negative organisms, with 86.8% isolates showed multidrug and extensive resistance which was similar to DeNIS study.[7] Gram positive organisms also showed high degree of resistance to penicillin group. Some degree of resistance to vancomycin was also noted among MRCONS and *Enterococcus* species.

In our study, we reported significantly high mortality rate (nearly one fourth) among neonates with culture positive sepsis. This could be because of high rate of sepsis among vulnerable premature neonates, prolonged requirement of ventilatory support, central intravenous and arterial lines, longer duration of NICU stay and high rate of antibiotic resistance.

This study is one of the largest from India with data collected over a period of ten years. Bandopadhyay et al conducted a similar retrospective study with a sample size of 183 neonates and a duration of 24 months in terms of sample size and duration.[17] However, our study has several limitations. First, our study was a single center retrospective study and 40 % babies suffering from LOS were referred to our center, which limits the applicability of the results. Second, we have not collected data on EOS because of the low yields on blood culture in EOS in our center.

CONCLUSION

This study describes the bacteriological profile of neonates with late onset sepsis in a tertiary care NICU in western India. We observed a high rate of gram-negative sepsis especially in low-birth-weight babies. There was an alarming rate of antimicrobial resistance among both gram negative and gram-positive organisms which needs urgent attention. There is a great need of antibiotic stewardship and periodic study of antibiograms to formulate hospital policies to curb antibiotic resistance.

CONFLICT OF INTEREST: None

FINANCIAL DISCLOSURE: None

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AUTHORS CONTRIBUTION: Concept and design: LKS; data collection and statistical analysis: LKS; writing of the manuscript: LKS; monitoring and supervising the research finalizing the manuscript: LKS, PP, SS, NB, PS; and all authors read and agreed with the contents of the final manuscript.

AVAILABILITY OF DATA AND MATERIALS: The datasets used and analyzed for the study are available from the corresponding author upon reasonable request

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