Original Article

Bacteriological profiles and antibiotic susceptibility of neonatal sepsis in a university hospital of Northern India

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Abstract

Context: Knowledge of epidemiology of bacterial isolates and their anti-biograms in hospital settings is necessary for prompt empirical anti-microbial therapy of neonatal sepsis. **Aims:** To study risk factors, bacteriological profiles, and anti-biograms of blood culture isolates of both early and late onset neonatal sepsis. **Settings and Design:** It is a prospective observational study conducted from January 2020 till July 2021 at our tertiary care center. **Material and Methods:** Neonates (0–28 days) admitted to this neonatal intensive care unit clinically suspected with sepsis were subjected to blood cultures, and the isolates were identified both biochemically and by the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry system. Antibiotic susceptibility testing (AST) was performed as per CLSI guidelines. **Statistical Analysis:** Chi-square test was used. **Results:** Out of 280 suspected cases of neonatal sepsis, 43 (15.3%) cases showed positive blood culture. Of these, the majority (30, 69.8%) had late-onset neonatal sepsis. Major pre-disposing risk factors were pre-term birth and a low birth weight (26, 60.5%). Gram-negative bacteria and Gram-positive bacteria were isolated in 25 (58.1%) and 18 (41.9%) blood cultures, respectively. *Klebsiella pneumoniae* (37.5%) was the most predominant pathogen in both early-onset (23.1%) and late-onset (46.7%) sepsis. Coagulase negative Staphylococcus (34.8%) was the second most common organism and was more common in late onset (23.2%) neonatal sepsis. A high level of antibiotic resistance was noted in *Klebsiella pneumoniae* isolates, even to amikacin (76.5%) and carbapenems (66.7%). **Conclusion:** Increased resistance in bacterial isolates of neonatal sepsis emphasizes the need of AST of bacterial isolates for proper antibiotic administration.

Keywords: Antibiotic susceptibility, bacteriological profile, neonatal sepsis

Introduction

Distribution of microorganisms causing neonatal sepsis changes over time and varies from region to region.[1,2] Emergence of multi-drug-resistant bacteria imposes further challenges in its treatment.[3,4] Prevalence of local bacterial isolates, their anti-biograms, and correlation with clinical profiles can guide the primary care physicians in identifying the possible risk factors of neonatal sepsis, initiation of prompt empirical anti-microbial therapy, and timely referral to higher speciality centers. Therefore, we aimed to study the onset, bacteriological profile, risk factors (sex, age, birth weight, gestational age), anti-biograms, and outcome of neonatal sepsis in an intensive care unit (ICU) of our tertiary center.

Material and Methods

This is a prospective observational study conducted from January 2020 till July 2021 in the Microbiology laboratory of a university hospital. This study was a part of an intramural project, and ethical clearance was obtained from institutional ethics

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committee (PGI/BE/1561/2021). All neonates (0–28 days) suspected of having neonatal sepsis and admitted in the neonatal intensive care unit (NICU) of our hospital during the study period were included. Written informed consent was obtained from parents. Neonates were suspected of sepsis if they presented with one of the following signs or symptoms: fever (≥38.0°C), hypothermia (≤36.5°C), convulsions, lethargy, poor feeding, respiratory distress, vomiting, bulging fontanels, jaundice, and umbilical pus infections. Neonates whose parents declined to give informed consent were excluded.

Early onset and late onset of sepsis were defined as infection within the first 72 h of life and > 72 h of life, respectively.[2,5,6] All neonates born before 37 completed weeks of gestation were classified as pre-term, and those born between 37 and 42 weeks of gestation were classified as term.[7] Demographic and clinical data plus laboratory parameters were filled for each patient on a pre-designed study proforma.

During the study period, blood culture was performed for all neonates suspected of clinical sepsis. All the blood cultures were performed on an automated blood culture System (Becton Dickinson Diagnostics, USA). After the bottles were flagged positive, Gram stain was performed from the broth for preliminary identification of the type of organisms isolated. Sub-cultures were made in blood agar and MacConkey agar and incubated at 37°C for 18–24 h. The grown bacteria were identified by colony morphology, Gram stain, and bio-chemical tests.[8] The culture was reported sterile if there was no growth in 5 days. Species identifications of all isolates were confirmed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) using a Biotyper system according to the manufacturer's recommendations (VITEK MS, bioMérieux, U.S.A.).

Antibiotic sensitivity was analyzed by the Kirby–Bauer disk diffusion method, and minimum inhibitory concentrations (MICs) were determined using the E-test method as per Clinical Laboratory Standards Institute recommendations (CLSI), 2020.[9] For bio-chemical tests and antibiotics sensitivity tests, the following reference strains were used for quality control: *E. coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC27853, *Staphylococcus aureus* ATCC25923, and *Enterococcus faecalis* ATCC 29212. The sensitivity of particular isolates to each tested antibiotic was calculated by the number of isolates susceptible divided by the total number of isolates and expressed as a percentage.

Neonates were treated as per the decision of the neonatologist depending upon their clinical conditions and antibiotic susceptibility profile of the isolated organism. All neonates were followed till discharge or death.

Statistical analysis

Statistical tests were performed using Statistical Package for the Social Sciences (IBM-SPSS) software (Version 25) for descriptive statistics. The significance among percentages was calculated with the Chi-square test, and a P value of < 0.05 was considered statistically significant.

Results

During the study period, 280 blood samples were collected from the clinically suspected cases of neonatal sepsis admitted in the NICU. Among them, positive blood cultures were obtained for 43 neonates (15.3%). Of these, 26 (60.5%) were from pre-term neonates and 17 (39.5%) were from term neonates. Twenty-six (60.5%) neonates were with a low birth weight, and 17 (39.5%) were with a normal birth weight [Table 1]. There were 23 (53.5%) male and 20 (46.5%) female, with the male to female ratio of 1.2:1 [Table 1]. Twenty-five (58.1%) had sepsis with Gram-negative bacteria and 18 (41.9%) were with Gram-positive bacteria with a ratio of Gram-negative organisms to Gram-positive organisms of 1.4:1 [Table 2]. The most common isolated Gram-negative bacteria were *Klebsiella pneumoniae* (17, 39.5%), followed by *Enterobacter spp.* (2, 4.6%), *Pseudomonas aeruginosa* (2, 4.6%), *Acinetobacter baumannii* (2, 4.6%), *Serratia marcescens* (1, 2.3%), and *Escherichia coli* (1, 2.3%) [Table 2/Figure1]. Coagulase negative *Staphylococcus aureus* (CONS) were the most isolated prevalent Gram-positive bacteria (6.3%) [Table 2/Figure 1]. Among neonates with sepsis, 13 patients (30.2%) had early onset and 30 patients (69.8%) had late-onset neonatal sepsis [Table 1]. *Klebsiella pneumoniae* (37.5%) was the most common pathogen in both early-onset (23.1%) and late-onset (46.7%) sepsis. CONS (34.8%) was the second most common organism and was more common in late-onset (23.2%) neonatal sepsis. *Enterococcus spp.* was isolated from 3 (7%) cases of late-onset neonatal sepsis. The mean duration of NICU stay was 11 days (7–18 days), and the total leucocyte count (TLC) was de-ranged in both early (17.4 ± 7.6) and late (18.8 ± 6.2) neonatal sepsis. The mortality was 9 (20.9%) in this study [Table 1].

A high level of antibiotic resistance was noted in *Klebsiella pneumoniae* isolates showing variable susceptibility to carbapenems (7, 41.2%), amikacin (5, 29.4%), and cefoperazone-salbactum (4, 23.5%), followed by three isolates being susceptible to ciprofloxacin (17.6%), ceftriaxone (17.6%), and ceftazidime (17.6%). Both the *Enterobacter* isolates were susceptible to carbapenems (100%), whereas only one was susceptible to amikacin, ciprofloxacin, ceftriaxone, and ceftazidime. The one *Escherichia coli* isolated was resistant to amikacin, ciprofloxacin, cefoperazone-salbactum, and carbapenems and was only susceptible to colistin. One isolate of *Serratia marcescens* was susceptible to amikacin, ciprofloxacin, cefoperazone-salbactum, and carbapenems. Both the isolates of *Acinetobacter baumannii* were resistant to carbapenem, ceftriaxone, ciprofloxacin, ceftazidime, and amikacin and were only susceptible to colistin. Both the *Pseudomonas aeruginosa* isolates were susceptible to amikacin, aztreonam, ciprofloxacin, piperacillin-tazobactum, and carbapenem with one isolate being susceptible to ceftazidime, ceftriaxone, and cefoperazone-salbactum [Table 3]. All the 15 CONS were susceptible to linezolid, vancomycin, and teicoplanin

Table 1: Distribution of culture-proven septic neonates according to onset of sepsis, gestational age, birth weight, sex, and mortality

Category	Total number of cases (%)	*GA (weeks)		Weight (grams)		§TLC (1000/µl) [Mean±||SD]	Mortality
		Term >37	Pre-term <37	†AGA >2500	‡SGA <2500		
Early onset	13 (30.2%)	5 (11.6%)	8 (18.6%)	4 (9.3%)	9 (20.9%)	17.4±7.6	4 (9.3%)
Late onset	30 (69.8%)	12 (27.9%)	18 (41.8%)	13 (30.2%)	17 (39.5%)	18.8±6.2	5 (11.6%)
Total	43 (100%)	17 (39.5%)	26 (60.5%)	17 (39.5%)	26 (60.5%)	-	9 (20.9%)

*GA: Gestational age; †AGA: Appropriate for gestational age; ‡SGA: Small for gestational age; §TLC: Total leucocyte count; ||SD: Standard deviation

Table 2: Type and number of bacterial isolates in neonates with sepsis based on the sepsis onset and mortality

Microorganism	No. of isolates, *n* (%)		*P*
	Early onset *n* (%)	Late onset *n* (%)	
K.pneumoniae	3 (23.1%)	14 (46.7%)	0.0002
Enterobacter	1 (7.7%)	1 (3.3%)	1.0000
E. coli	1 (7.7%)	0	0.3173
Serratia	0	1 (100%)	0.3173
Acinetobacter	2 (15.4%)	0	0.0833
Pseudomonas	1 (7.7%)	1 (3.3%)	1.0000
CoNS	5 (38.5%)	10 (33.3%)	0.0671
Enterococcus	0	3 (10%)	0.0253
Total	13	30	-

and variably susceptible to other tested drugs [Table 4]. All three *Enterococcus* isolates were susceptible to linezolid, followed by two isolates being susceptible to doxycycline, vancomycin, and teicoplanin [Table 4].

Discussion

Neonatal sepsis causes significant morbidity and mortality among neonates worldwide[10,11] and is a major cause of mortality in developing countries such as India. World Health Organization has estimated that 1.6 million deaths occur globally every year because of neonatal infections and 40% of all neonatal deaths occur in developing countries.[12] In India, the incidence of blood culture-proven sepsis was reported as 8.5 per 1,000 live births for the year 2002–2003 by the National Neonatal Perinatal Database.[13] In the present study, the blood culture positivity rate was 15.3%, which is in accordance with previous studies performed in India where the culture positivity ranged from 16% to 54%.[11,14-18] Although bacteria are the most common agents causing neonatal sepsis, it can also be caused by organisms other than bacteria such as enterovirus, adenovirus, coxsackievirus, rubella virus, Candida species, and Toxoplasma species.[19] Therefore, only a proportion of the blood culture from cases with clinical sepsis will be positive for pathogenic organisms. Collection of blood samples after administration of empirical antibiotics can also result in poor isolation of the bacterial pathogens in culture. Culture positivity was higher in males compared to females, which is in agreement with previous studies.[16,20] The prevalence of positive blood culture was found to be higher in late onset of sepsis compared to early onset of sepsis, which is in concordance with the previous studies.[21,22] Prolonged use of an invasive ventilator and catheter, failure of early breast feeding, longer use of parenteral nutrition, hospitalization, surgery, cardio-vascular diseases, and respiratory infections lead to late onset of sepsis among neonates.[23,24] Highly positive blood cultures (60.5%) were observed in low-birth-weight neonates, signifying that low birth weight is a strong neonatal risk factor that leads to neonatal sepsis.[20] This study showed higher infection among pre-term neonates (60.5%) compared to term neonates (39.5%). Pre-mature birth and low birth weight are the major pre-disposing factors of infection in these neonates. Threefold to tenfold higher incidence of infections is seen in pre-term neonates in comparison to full-term normal birth weight infants.[25] Because of a difference in mode of infection, the bacteriological profile of early-onset sepsis differs from that of late-onset sepsis.[26] Early-onset neonatal sepsis is acquired trans-placentally or during passage of the baby through a colonized birth canal.[19] *Klebsiella pneumoniae* was the most common agent implicated in early-onset sepsis, and Group B Streptococcus was not isolated from any neonate in our study. Group B Streptococcus was considered as an important agent associated with early- onset sepsis, but the recent studies are showing a decreasing trend in the incidence of this pathogen.[27] Late-onset neonatal sepsis is usually acquired from the care giving environment, and CONS, *Escherichia coli,* and *Klebsiella species* are the common agents involved.[19] The common etiological agents of late-onset sepsis in the present study were *Klebsiella pneumoniae* and CONS. An increasing trend of CONS isolation was observed in an epidemiological study performed to observe the long-term trends in the agents causing neonatal sepsis.[27] The majority of the *Klebsiella pneumoniae* isolates of the present study were resistant to all the tested antibiotics, which is similar to a study where 50–100% of the *Klebsiella pneumoniae* isolates were observed to be resistant to commonly used antibiotics, especially gentamicin and the second- and third-generation cephalosporins.[28,29] Another study from North India reported a 30–80% resistance to third-generation cephalosporins in Gram-negative isolates.[9] The present study shows increasing resistance in other Gram-negative bacilli and Gram-positive cocci, thus emphasizing the need of antibiotic susceptibility testing for proper antibiotic administration.

There is still a lack of data on the incidence of neonatal sepsis in different age groups in various regions of developing countries. The current study highlights the importance of primary care physicians in counseling and providing the basic antenatal care which can reduce low-birth-weight and pre-term births and

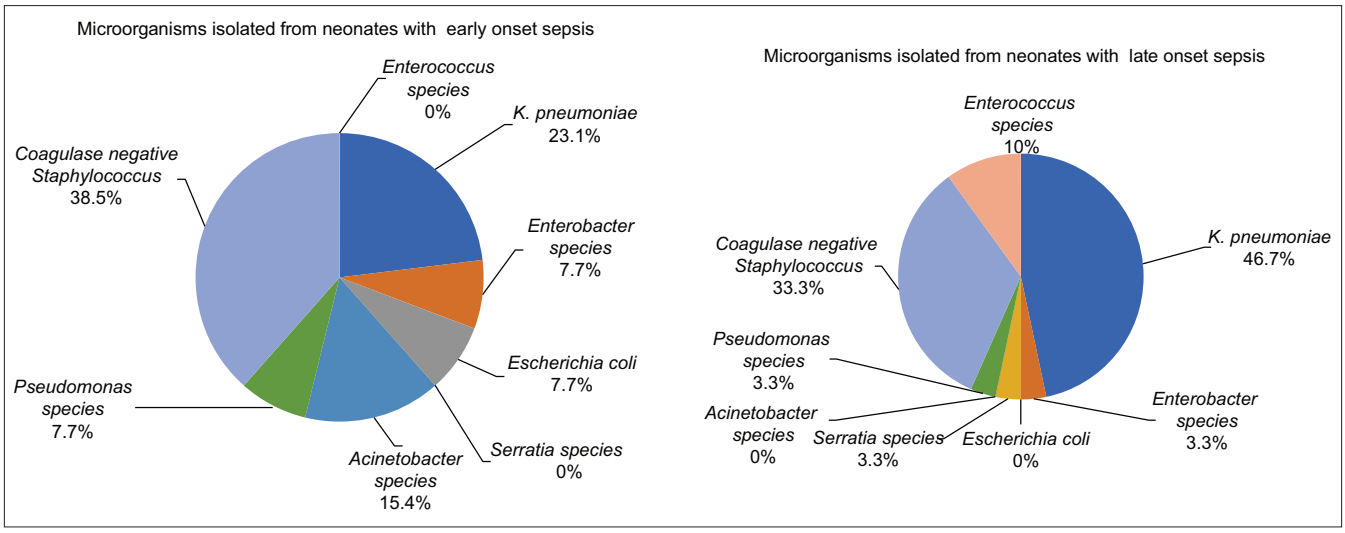

Figure 1: Distribution of microorganisms among the neonates who developed sepsis (N = 43)

Table 3: Antibiotic sensitivity pattern of the Gram-negative bacterial isolates

Antibiotic	Sensitivity pattern (*n*, %)					
	***K.pneumoniae* (*n*=17)**	***Enterobacter* (*n*=2)**	***E. coli* (*n*=1)**	***Serratia* (*n*=1)**	***Acinetobacter* (*n*=2)**	***Pseudomonas* (*n*=2)**
Amikacin	5 (29.4%)	1 (50%)	0	1 (100%)	0	2 (100%)
Cefatzidime	3 (17.6%)	1 (50%)	0	1 (100%)	0	1 (50%)
Ceftrioxone	3 (17.6%)	1 (50%)	0	1 (100%)	0	1 (50%)
Ciprofloxacin	3 (17.6%)	1 (50%)	0	1 (100%)	0	2 (100%)
Cefoperazone/Salbactum	4 (23.5%)	1 (50%)	0	1 (100%)	0	1 (50%)
Imipenem	7 (41.2%)	2 (100%)	0	1 (100%)	0	2 (100%)
Meropenem	7 (41.2%)	2 (100%)	0	1 (100%)	0	2 (100%)
Aztreonem	*NT	NT	NT	NT	NT	2 (100%)
Piperacillin/Tazobactum	NT	NT	NT	NT	NT	2 (100%)
Colistin	15 (88.2%)	2 (100%)	1 (100%)	1 (100%)	2 (100%)	2 (100%)

*NT: Not tested

Table 4: Antibiotic sensitivity pattern of the Gram-positive bacterial isolates

Antibiotic	Sensitivity pattern (*n*, %)			
	***S.haemolyticus* (*n*=3)**	***S.epidermidis* (*n*=8)**	***S.hominis* (*n*=4)**	***Enterococcus* (*n*=3)**
Amikacin	2 (66.7%)	3 (37.5%)	1 (25%)	1 (33.3%)
Clindamycin	0	0	0	NT
Erythromycin	0	1 (12.5%)	0	NT
Ampicillin	0	0	0	1 (33.3%)
Ampicillin/Salbactum	0	0	0	1 (33.3%)
Doxycycline	3	4 (50%)	2 (50%)	2 (66.7%)
Levofloxacin	0	6 (75%)	2 (50%)	1 (33.3%)
Vancomycin	3 (100%)	8 (100%)	4 (100%)	2 (66.7%)
Teicoplanin	3 (100%)	8 (100%)	4 (100%)	2 (66.7%)
Gentamicin	*NT	NT	NT	1 (33.3%)
Linezolid	NT	NT	NT	3 (100%)
Minocycline	NT	NT	NT	3 (100%)

*NT: Not tested

identifying the risk factors in neonates which may lead to neonatal sepsis and timely referral of such neonates to higher centers for treatment. Primary care physicians play a key role in preventing antibiotic resistance and using antibiotics judiciously. The blood culture positivity rate in our study was 15.3%, and *Klebsiella pneumoniae* was the most common agent causing both early-onset and late-onset sepsis, which is a cause of concern as most of time, this bug is resistant to antibiotics including carbapenems; therefore, antibiotic susceptibility testing is essential for proper antibiotic administration.

List of abbreviations

Abbreviation	Definition
NICU	Neonatal intensive care unit
MALDI	Matrix-assisted laser desorption/ionization
TOF MS	time-of-flight mass spectrometry
CONS	Coagulase negative Staphylococcus aureus
TLC	Total leucocyte count
GA	Gestational age
AGA	Appropriate for gestational age
SGA	Small for gestational age
AST	Antibiotic susceptibility testing
MIC	Minimum inhibitory concentration
CLSI	Clinical Laboratory Standards Institute
SPSS	Statistical Package for Social Sciences

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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