Research Article

Frequency of bacteriological agents of early onset sepsis and their antibiotic susceptibility pattern in neonatal intensive care units of University of Lahore teaching hospital & affiliated hospitals, Lahore.

Amna Ilyas[1], Muhammad Awais[2], Alishba Rasool[3], Saima Batool[4], Muhammad Naveed [5], Ayesha Zafar[6]

[1,4-6] *University of Lahore teaching Hospital, Lahore* [2-3] *King Edward Medical University, Lahore*

Abstract

Background: In developing countries, early-onset sepsis (EOS) persists as a major cause of neonatal morbidity and mortality.

Objectives: This study aimed to find out the frequency of bacteriological agents causing early onset sepsis, their antibiotic sensitivity and resistance patterns.

Methods: This cross-sectional study enrolled 84 neonates having early-onset sepsis from the neonatal intensive care units of University of Lahore teaching hospital and affiliated hospitals. Blood culture isolates were evaluated for antibiotic sensitivity and resistance. Chi-square test was used to assess the association between organism and antibiotic sensitivity or resistance, keeping p-value <0.05 as significant.

Results: Of the included 84 neonates, males were 59.5% and preterm neonates were 76.2%. Most common isolates were Klebsiella species (35.7%) and Escherichia coli (29.8%). Highest resistance was found for amoxicillin-clavulanic acid, 73 out of 76 isolates (96.1%) and ceftriaxone, 80 out of 84 isolates (95.2%), while lowest resistance was found for meropenem, 9 out of 73 isolates (12.3%) and imipenem 10 out of 73 isolates (13.7%). Sensitivity of linezolid was 100% (n=11) for Staphylococcus aureus and sensitivity of colistin was found in 69 out of 73 isolates (94.5%). Resistance and sensitivity patterns showed significant associations (p<0.05) along with sociodemographic variables.

Conclusion: Gram-negative bacteria were most commonly involved in EOS among neonates with high resistance to frequently prescribed antibiotics. Those antibiotics having highest sensitivity like carbapenems and colistin should be considered for empirical treatment. Antimicrobial stewardship programs are urgently required to counter the highest resistance to antibiotics.

Keywords: Neonates, Early-Onset Sepsis, Antibiotic Resistance,

Corresponding Authors: Muhammad Awais **Email:** awaisgill68@gmail.com

Received: 05-03-2025 | **Accepted:** 25-11-2025

Introduction

Early onset sepsis (EOS) is defined as an onset of symptoms of systemic infection within first 72 hours after birth which are proven by a positive blood or cerebrospinal fluid culture [1]. Pakistan has a highest neonatal mortality rale of 42 per 1000 live births in South Asia [2]. EOS is an important cause of neonatal morbidity and mortality especially in low- and middle-income countries (LMlCs) [3]. The global incidence of neonatal sepsis is estimated to be 2824 cases per 100,000 live births, among them the greater contribution is of EOS cases & from LMlCs [4]. Transmission is through transplacental, hematogenous spread or vertical ascending transmission from mother to neonate due to maternal gut microorganism colonization that may occur in utero or mostly during labor and delivery [5]. Both maternal and neonatal risk factors can contribute to develop EOS which includes low birth weight neonates, low gestational age, chorioamnionitis, premature rupture of membranes, prolonged labor, spontaneous delivery, maternal history of UTI/sexually transmitted infections (STl), maternal colonization of GBS & history of previous infant with GBS [6].

Poor feeding, temperature instability, lethargy, vomiting & tachypnea are common but non-specific signs of EOS; and the complications that may arise are disseminated intravascular coagulation, respiratory failure, septic shock, meningitis, cardiac failure, renal failure, liver dysfunction and hypoglycemia [7]. Many microorganisms are known to

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https://doi.org/10.21649/jspark.v4i4.741
2959-5940/

cause EOS & they vary across regions, between health facilities of same region and even within the same facility. A recent study conducted in Pakistan showed that the most common organisms responsible for causing EOS are Klebsiella (36.5%) followed by Escherichia coli (28.54/a), Staphylococcus aureus (15.4%), Citrobacter species (9.6%), Pseudomonas aeruginosa (5.8%) & Enterobacter species (1.9%). In this study gram positive organisms are mostly sensitive to meropenem (100%), linezolid (87.5%), vancomycin (77.B%), clarithromycin (7 5%) and oxacillin (75%); while the gram negative organisms are mostly sensitive to imipenem (97.5%), Cefoperazone + sulbactam (82.9%), Piperacillin + Tazobactam (82.6%), levofloxacin (71.8%) & amikacin (61%) [8]. Other organisms responsible for causing EOS are Group B Streptococcus, Coagulase negative streptococci (CONS), Haemophilus influenzae, Listeria monocytogenes & Enterococci [9]. Risk is higher in males than females [10]. According to a study from Nepal estimated prevalence of EOS is 62.5% among neonates [11].

The incidence of EOS is increasing & antibiotic resistance is also increasing day by day owing to the extensive & inappropriate use of antibiotics during the recent past, which becomes a public health problem worldwide. To treat EOS effectively, updated knowledge about the pathogens of EOS & antibiotic susceptibility is mandatory. So, this study is aimed to find out the frequency of bacteriological agents causing early onset sepsis, their antibiotic sensitivity and resistance patterns. Due to growing antibiotic resistance phenomenon, keeping track of antibiotic resistance pattern is necessary to improve guidelines for empirical antibiotic therapy.

Methods

This cross-sectional study was conducted from April to December 2024 after obtaining the ethical approval from research evaluation unit of college of physicians and surgeons Pakistan having reference No. CPSP/REU/PED-2021-3025-6698. 84 neonates were included in the study by non-Probability consecutive sampling technique after calculating the sample size from 5% margin of error, 95% confidence interval and 5.9% expected frequency of pseudomonas aeruginosa. [8] The included neonates were taken from Neonatal intensive care units of University of Lahore teaching hospital, Lahore & affiliated hospitals (Nawaz Sharif Social Security Hospital, Al Khidmat Trust Hospital & Social Security Hospital Kot Lakhpat). The neonates enrolled in the study were from both genders and both the term and preterm neonates who were having signs of early-onset sepsis like poor feeding, temperature instability, lethargy, vomiting & tachypnea, along with an evidence of positive blood culture within first three days of life. In addition, Maternal history of Preterm premature rupture of membranes (PPROM) & UTI/STl were also included. Those neonates were excluded who were given antibiotics before the blood sample was taken. Those bacteria were considered resistant and sensitive to antibiotic if the zone of inhibition was less than 18mm and greater than 18mm respectively. [12] After obtaining the informed consent from guardians/parents of the participants, predesigned proforma was filled comprising of sociodemographic details and information regarding the gestational age and presenting complaints. 1-3ml of blood was drawn from the peripheral vein or artery and send to microbiology laboratory of the hospital in a blood culture bottle after labeling for blood culture and sensitivity.

The antibiotics which were studied for sensitivity and resistance were Amoxicillin+clavulanic acid , Piperacillin+tazobactam, Cefoperazone+sulbactam, Vancomycin, Teicoplanin, Cefepime, Ceftazidime, Cefotaxime, Ceftriaxone, Imipenem, Meropenem, Ciprofloxacin, Amikacin, Gentamicin, Colistin, Linezolid, Ampicillin, Clotrimazole, Flucloxacillin, Fusidic acid, Tetracycline, Clindamycin, Cefuroxime and Trimethoprim/sulfamethoxazole. Then after receiving the reports the data was entered on the Proforma that which organism was isolated from the culture, and it was resistant & sensitive to which antibiotic/s. All the information & details regarding the patients were kept confidential.

All data was entered in SPSS version-24 for analysis. Frequency and percentages were calculated for qualitative variables like age, gender, EOS, microorganisms, sensitive strain, resistance strain & multi drug resistant strain, and were presented through charts and tables. Clinical characteristics of study participants such as TLC Count, Neutrophil Count, Lymphocyte Count, Hemoglobin level, Platelet Count and CRP Levels were presented as mean and standard deviation. The chi-square test was used to evaluate the association between organisms and antibiotic sensitivity or resistance. Confounders like age, gender & gestational age were controlled through stratification. Post stratification chi-square test was applied. P-value <0.05 was considered significant.

Results

Out of 84 included neonates, majority of the neonates were males 50(59.5%), while females were 34(40.5%). Preterm neonates were 64(76.2%) and term neonates were 20 (23.8%). Neonates were divided into three groups on the basis of their age into day 1(56%), day 2(23.8%) and day 3 (20.2%) neonates. The sociodemographic characteristics of study participants are given in table 1.Hematological profile of the study participants showed marked differences. The mean hemoglobin level, platelet count, neutrophil count, lymphocyte count, TLC count and CRP concentrations were 13.9 g/dL (SD ± 2.2), 196,345/ µL (SD ± 102,042), 64.6% (SD ± 12.2), 30.1% (SD ± 11.1) and 15,452 cells/µL (SD ± 5353) and 15.8 mg/dL (SD ± 20.7) respectively. The detailed hematological characteristics of study participants are given in table 2. Blood culture of the 84 included neonates showed that klebsiella species 30(35.7%) were the most common isolates followed by E.coli 25(29.8%), Staphylococcus aureus 11(13.1%), Citrobacter species 10(11.9%) and Pseudomonas aeruginosa 8(9.5%).

The resistance patterns showed that ceftriaxone and

Table 1: *Sociodemographic Characteristics of Study Participants*

Variable	Category	Frequency (n)	Percent (%)
Age (Days)	Day 1	47	56
	Day 2	20	23.8
	Day 3	17	20.2
Gender	Male	50	59.5
	Female	34	40.5
Gestational Age (Weeks)	Week 28	3	3.6
	Week 29	2	2.4
	Week 30	9	10.7
	Week 31	3	3.6
	Week 32	11	13.1
	Week 33	10	11.9
	Week 34	9	10.7
	Week 35	6	7.1
	Week 36	11	13.1
	Week 37	11	13.1
	Week 38	9	10.7
Gestational Age (Term/Preterm)	Term	20	23.8
	Preterm	64	76.2

amoxicillin-clavulanic acid were the most resistant antibiotics as it was observed in 80 out of 84 isolates (95.2%, p = 0.0001) and 73 out of 76 isolates (96.1%, p = 0.0002) respectively. Significant association was found for resistance to ciprofloxacin among preterm neonates (p=0.016). However, significantly lower resistance was found for carbapenems as it was observed in 10 out of 73 isolates (13.7%, p = 0.035) for imipenem and 9 out of 73 isolates (12.3%, p = 0.028) for meropenem. Linezolid was 100% sensitive for Staphylococcus aureus (n=11, p < 0.0001). Sensitivity to colistin and amikacin was observed for 69 out of 73 isolates (94.5% , p = 0.004) and 64 out of 84 isolates (76.2%, p = 0.015) respectively. Antibiotic sensitivity and resistance patterns of bacterial isolates are given in table 3.

Significantly higher resistance was found in males (p = 0.011) as compared to females for (p = 0.065) for

Table 2: *Hematological Characteristics of Study Participants*

Variable	Mean (± SD)	Minimum	Maximum
TLC Count (cells/mm³)	15452.38 (± 5353.54)	2,000.00	28000
Neutrophil Count (%)	64.57 (± 12.17)	26.00	80.00
Lymphocyte Count (%)	30.14 (± 11.13)	12.00	70
Hemoglobin (g/dl)	13.89 (± 2.23)	9.00	18.00
Platelet Count (cells/mm³)	196345.24 (± 102042.57)	17,000.00	480000
CRP Levels (mg/dl)	15.85 (± 20.73)	1.00	150.00
CRP Positivity **Positive 59 (70.2%)** **Negative 24(28.6%)** **Missing data 1 (1.2%)**			

amoxicillin-clavulanic acid and cefotaxime resistance was comparatively more pronounced in males ($p = 0.014$). However, ciprofloxacin resistance was not statistically significant in in females ($p = 0.083$).

Significant resistance to Cefoperazone+sulbactam was observed in day 1 neonates ($p = 0.026$), however, day 2 and day 3 neonates showed no significant differences ($p > 0.05$).

Preterm neonates showed statistically significant resistance to amoxicillin+clavulanic acid ($p = 0.002$) and ciprofloxacin ($p = 0.016$), while no significant difference was noted in term neonates ($p = 0.085$).

Table 3: *Frequency of Antibiotic Resistance & Sensitive in Study Participants*

Sr. No	Antibiotic	Sensitive N(%)	Resistant N(%)	Total Tested
1	Amoxicillin+clavulanic acid	3(3.9%)	73(96.1%)	76
2	Piperacillin+tazobactam	9(42.9%)	12(57.1%)	21
3	Cefoperazone+sulbactam	45(61.6%)	28(38.4%)	73
4	Vancomycin	9(81.8%)	2(18.2%)	11
5	Teicoplanin	8(72.7%)	3(27.3%)	11
6	Cefepime	12(18.5%)	53(81.5%)	65
7	Ceftazidime	14(32.6%)	29(67.4%)	43

8	Cefotaxime	18(24.7%)	55(75.3%)	73
9	Ceftriaxone	4(4.8%)	80(95.2%)	84
10	Imipenem	63(86.3%)	10(13.7%)	73
11	Meropenem	64(87.7%)	9(12.3%)	73
12	Ciprofloxacin	49(58.3%)	35(41.7%)	84
13	Amikacin	64(76.2%)	20(23.8%)	84
14	Gentamicin	59(70.2%)	25(29.8%)	84
15	Colistin	69(94.5%)	4(5.5%)	73
16	Linezolid	11(100%)	0(0%)	11
17	Ampicillin	5(8.5%)	54(91.5%)	59
18	Clotrimazole	9(81.8%)	2(18.2%)	11
19	Flucloxacillin	7(63.6%)	4(36.4%)	11
20	Fusidic acid	1(9.1%)	10(90.9%)	11
21	Tetracycline	2(18.2%)	9(81.8%)	11
22	Clindamycin	3(27.3%)	8(72.7%)	11
23	Cefuroxime	32(38.1%)	52(61.9%)	84
24	Trimethoprim/sulfamethoxazole	30(73%)	43(58.9%)	73

Discussion

This study was conducted to identify the bacteriological agents of early onset sepsis in neonates, which revealed that klebsiella species (35.7%) and Escherichia coli (29.8%) were the most common isolated organisms. Highest resistance was found for amoxicillin-clavulanic acid, 73 out of 76 isolates (96.1%) and ceftriaxone, 80 out of 84 isolates (95.2%), while lowest resistance was found for meropenem, 9 out of 73 isolates (12.3%) and imipenem 10 out of 73 isolates (13.7%). Sensitivity of linezolid was 100% (n=11) for Staphylococcus aureus and sensitivity of colistin was found in 69 out of 73 isolates (94.5%). Resistance and sensitivity patterns showed significant associations ($p<0.05$) along with sociodemographic variables. Preterm male neonates showed higher resistance to certain antibiotics, as demonstrated by amoxicillin-clavulanic acid ($p = 0.002$ and $p = 0.011$, respectively).

The study findings are consistent with worldwide trends for neonatal sepsis, where klebsiella species are the most frequent pathogens. A study conducted by Dutta M et al in 2021 also found that the most common organism in neonates suffering from EOS is Klebsiella with high resistance to aminoglycosides and cephalosporins. [13] Another study from India published in 2022 confirmed similar trends that managing EOS is a major challenge by carbapenem for Gram-negative organisms. [14] A study conducted in Pakistan in 2021 also align with the study findings where they concluded that first line antibiotics such as amoxicillin-clavulanic acid and ceftriaxone had

a limited efficacy against Gram-negative organisms.[15]

Notably, a study from European countries published in 2023 revealed higher susceptibility of pathogens to cephalosporins as compared to carbapenems which may be due to different resistance and antibiotic prescribing practices between two regions [16]. This variation can be explained by strict follow of antimicrobial stewardship programs as well as decreased use of carbapenems in European countries than South Asia.

In addition, a systematic review published in 2021 gives findings from low- and middle-income countries (LMICs), which supports this study's results of high frequency of Klebsiella and E. coli in EOS. This systematic review made evident the extensive irrational use of antibiotics and fragile infection control measures which leads to this trend. [17] Another study from Bangladesh came with the consistent results where Klebsiella accounted for 40% cases of EOS having high MDR gram negative bacteria with high resistance to third generation cephalosporins and better sensitivity to aminoglycosides and colistin. [18]

Contrarily, a 2020 study from United States of America reported lower resistance of Gram-negative organisms, which can be explained by rigorous regulation of strict antibiotic policies and good surveillance system in developed countries who have well established healthcare system. [19] Another study in sub-Saharan Africa in 2023 reported similar resistance patterns but emphasized the role of under-resourced healthcare systems in exacerbating MDR pathogens.[20]

This study's observation of 100% sensitivity to linezolid and high sensitivity to colistin aligns with findings from multiple reports published in 2023, which identified these antibiotics as reliable treatment options for MDR pathogens in neonatal EOS. [21,22]

The variations in the resistance and sensitivity patterns of EOS organisms in different countries and settings can be explained by different healthcare infrastructures, alignment with antimicrobial stewardship practices, over the counter antibiotic availability and pathogen epidemiology. [23,24]

Finally, confounding variables such as maternal antibiotic use during pregnancy or delivery were not assessed, which could influence the observed resistance patterns.

This study has certain limitations such as small sample size of only 84 neonates may subject to limit its generalizability to other settings. This study may be non-representative of study population due to selection bias encountered by non-probability consecutive sampling technique. In addition, this study had focused on limited antibiotics and pathogens which did not capture all the resistance patterns for all the pathogens. Most importantly , this study did not account for the maternal antibiotic use during antepartum or intrapartum period which have the potential to alter the resistance pattern in neonates.

Conclusion

This study findings demonstrate that Klebsiella species (35.7%) and Escherichia coli (29.8%) are the most common organisms in neonates causing EOS with marked resistance to first line antibiotics like ceftriaxone (95.2%) and amoxicillin-clavulanic acid (96.1%). Resistance to carbapenems was the lowest, imipenem and meropenem had resistance rates of 13.7% and 12.7% respectively. Staphylococcus aureus was 100% sensitive to linezolid. While 94.5% and 76.2% of bacterial isolates were sensitive to colistin and amikacin. Resistance patterns were significantly influenced by sociodemographic factors like gender, gestational age and age at onset of symptoms.

Future longitudinal studies are needed to keep track of resistance patterns for EOS causing organisms in neonates. Non-conventional treatment strategies should be investigated for their efficacy especially for preterm neonates. In addition, more studies are needed to find the association of maternal health and antenatal antibiotic use with neonatal sepsis.

These measures will aid in improving neonatal outcomes while curbing the alarming rise in antibiotic resistance in EOS cases. All of these measures can help in better neonatal outcomes along with suppressing the sharp rise in antibiotic resistance in neonatal sepsis.

Conflict of interest: Authors declare no conflict of interest.
Funding source: No funding was obtained for this study.
Ethical Approval: Obtained from the institutional review board of University of Lahore
Authors' Contributions:
AI.MA, AR: Involved in conceptualization of study and writing original draft.
AI, SB, MN: Involved in data curation, formal analysis and final review & editing
AI,AZ: Involvedin design ofstudy and finalreview &editing.

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