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Original Article

Bacteriological Profile and Antibiotic Susceptibility Pattern of Isolates in Neonatal Sepsis

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ABSTRACT

Sepsis in newborns is a serious medical condition having a high mortality. Pakistan and other developing countries have a high burden of neonatal sepsis. **Objectives:** To determine the bacterial spectrum and antibiotic activity pattern in neonatal sepsis. **Methods:** This retrospective cross-sectional research was performed at the Pediatrics Unit of Ziauddin University Hospital Karachi from 1st June 2022 till 1st December 2022. A total of 120 medical records of neonates admitted with the clinical suspicion of sepsis were reviewed. Non-probability convenience sampling technique was used. Data regarding clinical characteristics of neonates, type of bacteria isolated and antibiotic susceptibility results were recorded. SPSS version 20 was used for statistical analysis. The results were written as frequencies / percentages. **Results:** Neonatal sepsis was suspected in 120 newborns but blood culture-proven infection was present in 32 (13.3%) neonates with 23(71.8%) having early -onset sepsis. The mean age on admission was 7.61±3.61 days. Acinetobacter was the commonest bacteria implicated in sepsis followed by Klebsiella ,Burkholderia and Serratia. The mortality rate in study population was 8.3%.Mortality was highest in Klebsiella sepsis. None of the bacterial species were sensitive to ampicillin while Acinetobacter and Burkholderia species responded to colistin ,polymyxin and meropenem but showed resistance to imipenem. **Conclusion:** Early-onset neonatal sepsis has a high prevalence especially with gram -negative bacteria. Antimicrobial resistance to first line empiric therapy is common.

INTRODUCTION

Neonatal sepsis is a medical disorder which typically has an early presentation in life. It shows specific clinical manifestations and is recognized as one of the prime reasons of illness and death in newborns worldwide [1]. Sepsis in the first month of life is grouped as early onset sepsis (EOS) if occurring before 72 hours of life and late onset sepsis (LOS) if after. EOS is caused mainly by bacterial organisms acquired intrauterine and at birth from the maternal reproductive tract whereas late onset sepsis results from infection acquired after birth from the home or hospital environment. It is challenging to confirm sepsis in newborns on the basis of mere clinical presentation as clinical signs can be generalized and non-specific. It is defined clinically or bacteriologically, either by positive blood or body fluid culture. Despite the advancement in medical management of infections in newborn , blood culture is still the mainstay of investigation [2]. World Health Organization (WHO) has reported that throughout the world , the annual death rate in newborns is 1.6 million and 40% of these happen in growing countries [3]. In Pakistan, sepsis is the principal contributor of an extremely high neonatal mortality rate, attributing to 17.2% of newborn deaths [4]. The type of pathogens causing neonatal sepsis exhibits dissimilarity in not only different countries but even within medical facilities as particular bacteria transition and exhibit variability in occurrence. Developing countries have sepsis caused predominantly by gram-negative organisms such as Klebsiella pneumoniae and Escherichia coli , whereas in high income countries Group B streptococci and other gram-positive bacteria

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predominantly cause neonatal infection [5].Therefore, the bacteriological profile varies significantly based on the geographical location. The bacterial isolates causing infection in newborns shows variation from time to time in the same setting. A majority of neonatal deaths can be prevented by early institution of suitable antibiotics according to the local sensitivity pattern [6]. In this era of widespread antibiotic use , multi-drug resistant (MDR) organisms are a constant challenge to treat especially in low and middle income set up. Bacteria implicated in late onset sepsis have been observed to be resistant to antibiotics to a greater extent as compared to those producing early-onset sepsis [7]. Nosocomial infection is acquired during hospitalization and is contracted by a patient at least 48 hours after being admitted. In developing countries Burkholderia cepacian ,Acinetobacter baumannii, Klebsiella pneumoniae , Pseudomonas aeruginosa and Serratia marcescens have been found to be implicated in a majority of these infections. Insensitivity to antibiotics is defined as development of unresponsiveness to at least one or more antimicrobial medications as per recommendations [8]. Development of clinical guidelines for judicious use of antimicrobials is imperative. Unresponsiveness of microorganisms to penicillin and third generation cephalosporins suggests the need to re-assess guidance for empiric treatment in infected newborns. Hospital policies to limit spread of disease and training of medical staff regarding the importance of measures such as frequent hand sanitization needs to be emphasized. It has been observed , that in the past decade or so resistance to ampicillin and aminoglycosides has emerged as evidenced by research data, therefore it is important that treatment should be administered according to the local sensitivity pattern and correct dose and duration of antibiotics given [9]. This study was thus , conducted with the aim of determining the pattern of various bacteria and their responsiveness to antimicrobials in sepsis during neonatal period and in the conditions prevailing locally. It emphasizes the need for identifying the culture and drug susceptibility pattern of locally prevalent microorganisms , judicious use of empiric therapy and the requirement for constant surveillance.

METHODS

This cross-sectional retrospective took place at Pediatric Unit of Ziauddin University , Karachi for six months i.e. 1st June 2022 till 1st December 2022. Medical records of All neonates admitted with suspected sepsis ,and also those with a positive blood culture result were included. Electronic medical records were accessed and data recorded. Newborns with congenital malformations , laboratory evidence of inborn error of metabolism and those with a history of perinatal hypoxic insult were excluded to control effect modifiers and bias in results. Data was recorded on a pre-designed structured proforma by two pediatric residents and it was pilot tested for clarity. For sample size estimation , WHO sample size calculator with confidence level taken as 95% and desired precision as 6% and approximate population estimation (frequency of neonatal sepsis as 13% from research studies) , the largest sample size calculated was 120 cases. Approval from the Ethical review committee was sought (reference code : 5870822RMPED). Blood samples of approximately 5 ml of venous blood was drawn from the neonates using aseptic technique and injected into BACTEC® PEDS Plus (Becton Dickinson, Towson, MD) culture media bottle after ensuring aseptic measures. In the laboratory , BACTEC 9050 automated blood culture instrument was added to BACTEC bottle, using fluorescent technology. The positive vials were cultured on special media by inoculating the culture broth on blood, chocolate and MacConkey agar plates. These were then incubated in an incubator at 37°C in a chocolate plate. The culture vials were observed daily for bacterial growth. The pure bacterial isolates are obtained using subculture technique and later the organisms are identified using standard microbiological methods such as studies of colony morphology, Gram-staining and biochemical characteristics (triple sugar iron, catalase, urease, citrate ,oxidase coagulase tests). Blood culture bottles wherein there was no evidence of any bacterial growth after 5 days of incubation (growth on MacConkey/blood agar) were labelled as negative after a verifying subculture. Antimicrobial sensitivity was tested using Muller Hinton Agar by the Kirby Bauer Disc diffusion technique according to Clinical Laboratory Standards Institute (CLSI) guidelines 2017. Antibiotic discs containing ampicillin, aztreonam, carbapenems ,ceftazidime, ceftriaxone, ciprofloxacin, clindamycin, colistin, co-trimoxazole, gentamicin, ceftazidime, clindamycin, colistin , levofloxacin , piperacillin/tazobactam , polymyxin, teicoplanin, vancomycin was obtained and used according to the manufacturer's instructions. The zone of inhibition was decided employing the CLSI recommendations , and the antibiotics were marked accordingly as “sensitive“, “intermediate“ or “resistance“ [10]. For admitted newborns ,history findings and thorough physical examination were recorded. Data were recorded with regards to gestational age , gender ,weight ,type of sepsis ,mode of delivery , blood culture and antibiotic sensitivity result. Analyses of data was done through SPSS version 20.0. Mean and standard deviation were used to denote continuous variables. Measurement data that was qualitative was expressed as frequencies and percentages. Effect

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modifiers were controlled through stratification of data to see the effects of these outcome variables using chi-square and p-value was considered significant if <0.05'

RESULTS

Out of a total of 240 neonates were admitted during the study period , in 120 neonates there was a clinical suspicion of sepsis but only 32 neonates had a positive blood culture result i.e. the prevalence of neonatal sepsis was 13.3 %. Table 1. shows the clinical characteristics of the study population. The male to female ratio was 1.5: 1 as 72 were males and 48 females. The mean age of the study population on admission was 7.61±3.61 days. The mean birth weight was 2.78 ± 3.07 kg. Majority of neonates i.e. 23 (71.8%) had early onset sepsis. The frequency of gram-negative bacteria was 27 (84.3%) was much higher than gram-positive organisms which was 5(15.6%).

Table 1: Characteristics of study population

Variable	N (%)
Gender	
Male	72 (60%)
Female	48 (40%)
Age (Days)	7.50±8.4
Weight (Kg)	2.78±3.07
Occipitofrontal Circumference (CM)	33.88±4.9
Gestational Age (Weeks)	
Pre-Term	53 (44.2%)
Term	67 (55.8%)
Mode Of Delivery	
SVD	39 (32.5%)
C-Section	81 (67.5%)
Maternal Antenatal Visits	
Regular	110 (91.7%)
Irregular	10 (8.3%)
Onset Of Sepsis	
Early Onset	88 (73.3%)
Late Onset	32 (26.7%)

Among gram-negative isolates, Acinetobacter baumannii was the predominant organism being isolated in 12 (37.5%), followed by Pseudomonas aeruginosa in 6(18.75%), Burkholderia cepacia in 3(9.4%) and Serratia Marcescens in 3 (9.4%).Table 2 shows the distribution of bacterial isolates in blood culture of the study population. It was noted that among the gram-positive isolates, streptococcus pneumoniae (12.5%) and staphylococcus aureus 1 (3.1%) were the commonest organisms isolated. Table 2 shows the bacterial spectrum of blood culture isolates.

Table 2: Bacteriological profile in blood culture - positive neonates

Gram Negative	Total n=32	Early-onset sepsis	Late-onset sepsis
		N (%)	N (%)
Escherichia coli	1		1(100%)
Burkholderia cepacia	3	2 (66.7%)	1(33.3%)
Serratia marcescens	3	2 (66.7%)	1(33.3%)
Klebsiella pneumoniae	2	2 (100%)	
Pseudomonas aeruginosa	6	5 (83.3%)	1(16.7%)
Acinetobacter baumannii	12	9 (75%)	3 (25%)
Gram positive			
Staphylococcus aureus	1		1(100%)
Streptococcus pneumoniae	4	3 (75%)	1(25%)

The overall mortality rate was 8.3% in the study population as 10 neonates expired. All the neonates who expired had gram-negative sepsis while no mortality was observed in sepsis with gram -positive organisms (p-value 0.04).Klebsiella pneumoniae sepsis had the highest mortality as out of the 10 expiries 7(70%) were infected with this organism whereas it was 3 (30%) had Acinetobacter baumannii infection. It was noted that 12 (44.4%)neonates with sepsis from gram -negative bacteria required invasive ventilation while those with gram-positive sepsis did not require ventilator support (p-value 0.0001).

Table 3: Association(cross tabulation) between gram staining and different factors

Variable		Gram staining				Chi-square value	p-value
		Negative(24)		Positive(3)			
		%	n	%	n		
Sepsis onset	Early	74.1	20	60	3	0.792	0.373
	Late	25.9	7	40	2		
Neonatal outcome	Discharged	63	17	100	5	11.23	0.004
	Expired	37	10	0	0		
Ventilation support provided	Yes	44.4	12	0	0	36.175	0·0001

The bacterial isolates from blood culture of the study population showed a variable pattern of antibiotics sensitivity. All species of gram- negative microorganisms causing neonatal sepsis in our study were sensitive to Meropenem. However ,colistin was effective against all gram -negative bacteria except Burkholderia cepacia and Escherichia coli. The results of antibiotic sensitivity pattern for both Gram -negative and Gram-positive bacteria are shown in Table 4.

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Table 4: Antibiotic sensitivity pattern of the isolate

Antibiotics	Gram negative organism						Gram positive organism	
	Escherichia coli (1/100%)	Burkholderia Cepacia (3/100%)	Serratia marcescens (3/100%)	Klebsiella pneumoniae (2/100%)	Pseudomonas aeruginosa (6/100%)	Acinetobacter baumannii (12/100%)	Staphylococcus Aureus (1/100%)	Streptococcus Pneumoniae (4/100%)
Ampicillin								
Co-trimoxazole		3(100%)				12(100%)		4(100%)
Ciprofloxacin				2(100%)	6(100%)		1(100%)	
Colistin			3(100%)	2(100%)	6(100%)	12(100%)		4(100%)
Ceftriaxone						12(100%)		4(100%)
Ceftazidime		3(100%)	3(100%)		6(100%)			
Gentamicin	1(100%)	3(100%)					1(100%)	
Imipenem/ meropenem	1(100%)	3(100%)	3(100%)	1(50%)	6(100%)	3(25%)		
Levofloxacin		3(100%)						4(100%)
Vancomycin						12(100%)	1(100%)	4(100%)
Clindamycin		3(100%)	3(100%)	2(100%)	6(100%)		1(100%)	4(100%)
Piperacillin tazobactam	1(100%)							
Teicoplanin							1(100%)	
Polymyxin			3(100%)	2(100%)	6(100%)	12(100%)		4(100%)

DISCUSSION

There is a high prevalence of sepsis in the newborn period as well as an alarmingly high resistance to antibiotic therapy partly due to inadequate surveillance systems. Usage of empiric antibiotic therapy is usually required to be initiated early ,as blood culture results take 48 to 72 hours to get. Insensitivity to first- and second-line antibiotics has led to the use of carbapenems as the initial empirical therapy in developing countries. The bacteriological spectrum and antibiotic sensitivity patterns exhibit variance among countries depending on socioeconomic and environmental factors. To improve quality of patient care ,hospital policies should be formulated to promote rational administration of antibiotics especially in the intensive care units [11]. Our study reports a 13.3% rate of culture-proven sepsis in newborns ,in contrast to that reported by Salah *et al* and Al-Shamahy *et al* in Yemen ,wherein the culture -positivity rate of 77.4% and 57% was reported respectively [12, 13]. In concert with our results, in a similar study from Rawalpindi by Ahmed M *et al* the prevalence of culture-proven sepsis in newborns was noted to be 11.3 % whereas other studies from Pakistan by Anwar *et a*l and Malik *et al* have reported a very high prevalence of 42% and 62.5% respectively [14-16]. However, in a study on neonatal sepsis from India by Roy *et al* culture-positivity rate of 26% was reported [17]. Other studies report considerable disparity in prevalence of culture proven sepsis in newborns as evidenced by a prevalence rate of 49.5% observed by Shehab-El Din *et al* from Egypt, 24% was reported in a study from Tanzania and 12.1% from Nepal [18-20]. These differences in the prevalence of neonatal sepsis across different geographical regions could be as a result of various elements involved , such as different socioeconomic conditions and dissimilarity in sampling methods. In advanced countries, neonatal sepsis in a large majority of cases is caused by gram-positive bacteria (58-70.2%) [21]. In the present study , gram-negative bacteria were the most prevalent organisms implicated in both early onset and late onset sepsis. This finding is in concordance with findings of research studies conducted earlier in other growing countries. Macharashvili *et al* in a study from Georgia ,stated that gram-negative bacteria were responsible for 78% of neonatal sepsis cases, with Klebsiella pneumoniae accounting for 37% and Escherichia coli 11% of the cases [22]. Acinetobacter baumannii is a causative organism for a majority of nosocomial infections globally. An Indian study by Kamath *et al* observed Klebsiella pneumoniae species to be most commonly responsible for neonatal sepsis ,being present in16.4%, and Acinetobacter baumannii in 10% of their study population [23]. Similarly, we also found an alarmingly high rate of sepsis with Acinetobacter baumannii in our study , indicating the need to implement strict infection control measures to decrease nosocomial infection. Similar to our findings , Yusef *et al*, found Acinetobacter baumannii (27%) to be the commonest bacteria isolated followed by Klebsiella pneumoniae (22%) [24]. In our study both colistin and polymyxin were found to be effective against all cases of neonatal sepsis with Acinetobacter baumannii and Klebsiella pneumoniae whereas in 75% of Acinetobacter baumannii and 50% of Klebsiella pneumoniae isolates , carbapenem resistance was observed. In concert with our findings, a study from India reported that 93.68 % of Acinetobacter baumannii isolates showed carbapenem resistance and a very high mortality of 59% was observed with Acinetobacter baumannii infection [25]. The use of co-trimoxazole is not very common these days but we found it

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to be quite effective against Burkholderia cepacia. Being a cheaper drug, it would offer the advantage of cost - effectiveness in nosocomial infections caused by unusual organisms such as Acinetobacter baumannii and Burkholderia cepacia [23]. We report an overall mortality rate of 8.3% for neonatal sepsis and it was significantly related to sepsis with gram -negative organisms. In our study ,Acinetobacter baumannii infection was implicated in 30% of the expiries whereas 70% mortality was due to Klebsiella pneumoniae sepsis. Yusef *et al* have reported similar findings [24]. In the present study , Pseudomonas was isolated in 6 blood culture samples out of a total of 32 culture positive samples(18.8%), this suggests the need to control hospital-acquired infection. In concert with the findings of Vinodkumar *et al* ,we observed Pseudomonas aeruginosa isolates to be mostly resistant to aminoglycosides which is a cost effective antibiotic [26]. However ,they were sensitive to expensive therapy such as colistin and ceftazidime. In the present study we observed that ampicillin was not effective against any type of bacteria though it should be empiric first line therapy in neonatal sepsis along with aminoglycosides. This antimicrobial resistance and increase in the prevalence of nosocomial infection in under developed countries is worrisome and can be explained by the irrational use of antibiotics ,lack of antibiotic stewardship programs, self-medication and malpractice by physicians [27].

CONCLUSIONS

There is a high prevalence of early-onset neonatal sepsis with gram-negative bacteria. Acinetobacter and Pseudomonas contribute to a high mortality and were the commonest bacteria isolated indicating a need to control nosocomial infection. Bacterial insensitivity to ampicillin as empiric therapy is worrisome and calls for strict implementation of antibiotic stewardship programs to rationalize the administration of antimicrobials.

Conflicts of Interest

The authors declare no conflict of interest

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