ORIGINAL ARTICLE

Neonatal Sepsis by Gram negative bacteria and antibiotics susceptibility pattern at a tertiary care Paediatric Hospital in Pakistan

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ABSTRACT

Background: Neonatal sepsis has become a leading contributor to mortality and morbidity among neonates in developing countries with recent surge in infections with multidrug resistant Gram-negative bacteria. Aim of this study was **t**o find out the spectrum of Gram-negative organisms and their antimicrobial susceptibility pattern in neonatal sepsis.

Material and Methods: This is a cross-sectional study conducted in the Department of Microbiology, University of Child Health Sciences, The Children's Hospital, Lahore from September to December 2023. A total of 374 blood culture samples received from neonatal unit were incubated at 37 °C for upto 7 days and sub cultured on blood and MacConkey agar after observing signs of growth. Bacterial isolates were identified by standard microbiological techniques. Antimicrobial testing was done by Kirby-Bauer disc diffusion method. Data was analyzed with descriptive statistics using SPSS 23.0.

Results: Out of 374 neonates, males were predominant (n=238, 63.6%). Eighty-seven (23.3%) cultures were positive for Gram negative bacilli which comprised of 29.9% *Klebsiella pneumoniae*, 23% *Acinetobacter baumannii*, 17.2% *Enterobacter* spp., 8.1% *Serratia marcescens*, 10.4% *Pseudomonas* spp., 4.6% *Escherichia coli*, 3.4% *Pantoea* spp., 2.3% *Burkholderia cepacia* and 1.1% *Stenotrophomonas maltophilia*. High resistance to multiple groups of antibiotics including β-lactams, β-lactam combinations, cephalosporins and aminoglycosides was observed among majority of the isolates.

Conclusion: In this study, *Klebsiella pneumoniae* were the most common isolates in neonatal sepsis. High antibiotics resistance is an alarming situation. Antimicrobial stewardship is required to develop appropriate guidelines for empiric antimicrobial use.

Keywords: Neonatal sepsis, Gram negative bacteria, Antimicrobial resistance, Antimicrobial stewardship

BACKGROUND

Neonatal sepsis has been declared as a global concern by the World Health Organization (WHO)[1]. Sepsis is a leading contributor to mortality and morbidity of neonatal age group. In developed countries, it contributes 13-15 deaths per 1000 live births while in low-middle income countries it contributes to 30-50 deaths per 1000 live births. In Pakistan, sepsis contributes to approx. 23 deaths per 1000 live births[2]. According to reports on the disease burden of neonatal sepsis in terms of mortality in Pakistan, 1-4 babies per 1000 live births die from neonatal sepsis each year.[3] Neonatal sepsis refers to a systemic infection of newborns younger than 28 days old. According to the time of presentation: Early onset sepsis (EOS) occurs at or before 72 h of life and Late onset sepsis (LOS) occurs after 72 h up to 28 days of life with possible risk factors such as compromised health care practices and overuse of maternal antibiotics[3,4]. The gold standard in the diagnosis of neonatal sepsis is blood culture, in which low positivity rates account for real management challenge[5,6]. Although the main cause of sepsis is unknown in about one- half of cases, the most common pathogens for sepsis and septic shock are Gram- positive bacteria like *Staphylococcus aureus (S. aureus)* and Coagulase-negative *Staphylococci (CONS*) followed by Gram-negatives including *Escherichia coli* (*E. coli*),

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Klebsiella pneumoniae (K. pneumoniae), Enterobacter spp., *Acinetobacter baumannii (A. baumannii)*, and *Pseudomonas* spp.[7,8] In recent studies, about 39-64% of the cases of neonatal sepsis were caused by Gram-negative organisms and *Klebsiella* spp., *Serratia marcescens (S. marcescens), E. coli, Enterobacter* spp., and *A. baumannii* were the most commonly isolated organisms.[9,10] *E. coli* was the most frequently isolated organism in EOS with a ratio of 2:1 in developing countries[11]. Most of the isolates show antimicrobial resistance towards first line treatment of sepsis recommended by WHO.[12] Early identification and treatment of neonatal sepsis is always challenging, so the antibiotics are given empirically to prevent the severe consequences.[6] A significant burden is placed on developing countries due to the inappropriate use of broad-spectrum antibiotics without testing, which increases the number of multidrug resistant pathogens in neonatal units. WHO has declared antibiotic resistance as a major health issue[13]. With such high rates of antibiotic-resistant organisms, less antibiotics options are available. Hence, proper institutional guidelines regarding the local prevalence of pathogens and their antimicrobial profiles are needed. The results of this study aim to provide bacterial spectrum and susceptibility pattern of pathogens causing neonatal sepsis with special reference to gram-negative bacilli. This will ultimately help us in devising appropriate management strategies regarding empiric antimicrobial treatment.

MATERIAL AND METHODS

This cross-sectional observational study was conducted at the Department of Microbiology, University of Child Health Sciences, The Children's Hospital, Lahore. After approval from Institutional Review Board (IRB letter no. 1262/SAHS dated 05/10/2023), blood culture samples from admitted neonates with suspicion of sepsis from nursery ICU were taken in compliance with the Helsinki declaration during September to December 2023. A total of 374 neonates including 160 cases with primary diagnosis of sepsis and 214 cases with other diseases as primary diagnosis and whose blood cultures had Gram negative bacteria (GNB) were included in this study. While samples from patients with history of antibiotic intake and those with yield of Gram-positive bacteria were excluded. For Blood cultures, about 1-3 ml of venous blood was collected under aseptic conditions in a Brain Heart Broth (BHI) broth of blood culture medium followed by incubation at 35–37° C $\pm 2^0$ and routine inspection for signs of microbial growth. Blood culture bottles, which showed no microbial growth after 48 hours were re-incubated upto 7 days, before labelling it as negative. Blood culture samples with signs of bacterial growth were sub cultured on commercially prepared Blood Agar and MacConkey agar (Oxoid, UK) using strict aseptic technique and incubated at 37°C in ambient air. For bacterial growth, plates were examined after 24 h of incubation. Bacterial growths were analyzed by the morphology of bacterial colonies, fermentation of lactose, odor, pattern of growth and Gram-staining. Gram negative bacterial isolates were identified by conventional biochemical tests. For the identification of *Enterobacteriaceae* and non-*Enterobacteriaceae*, Analytical profile index API-20E and API NE (Biomerieux, France) were used respectively.

Antimicrobial susceptibility of the isolates was evaluated using the Kirby-Bauer disk diffusion, following the guidelines of Clinical and Laboratory Standards Institute (CLSI) 2023[14]. Four to five isolated colonies with similar morphology were suspended in sterile saline solution adjusted to the turbidity equivalent to 0.5 McFarland standard and uniformly spread on the entire 90 mm Muller Hinton Agar (MHA) plates. Commercially available antibiotic discs from Oxoid (UK) were applied on the plates and were incubated at 35±1°C for 16-20 h. Gram- negative bacilli were tested against antibiotics including beta lactam drugs, such as amoxicillin/clavulanic acid, piperacillin/tazobactam, cefoperazone/sulbactam, cefotaxime, ceftriaxone, ceftazidime, cefepime, meropenem, aminoglycosides such as amikacin and tobramycin. Interpretation of zone of inhibitions was done according to CLSI guidelines 2023. Susceptibility results were reported as sensitive (S), Intermediate (I) or resistant (R) for clinical interpretation.

The data was analyzed by Statistical Package for the Social Sciences (SPSS V-23). Continuous variables such as age was described as mean ± SD, whereas categorical variables were analyzed with descriptive statistics and presented in frequencies and percentages. The Chi-Square test was used to determine statistically significant association among different variables. A p-

value of <0.05 was considered statistically significant between categorical variables.

RESULTS

Between September 2023 and December 2023, 374 blood cultures were received in the Microbiology laboratory from the Nursery unit. Of these, 160 (42.7%) were clinical suspects of sepsis, while 214 (57.2%) were with primary diagnosis of other diseases. Among other diseases 77(20.5%) had a primary diagnosis of bronchopneumonia, and 137 (36.9%) had other systemic infections. Out of the 374 blood cultures, 87 (23.3%) had GNB yield. Among total number of patients, male-to-female ratio was 1.73 consisting of 238 (63.6%) males and 136 (36.4%) females. The mean age of the neonates was 5 days, with an age range from 1 to 15 days. EOS accounted for 52(59.6%) cases, and LOS accounted for 35 (40.4%) of all positive cultures for GNB (Figure-I).

Of the 87 GNB, *K. pneumoniae* (26/87, 29.9%) was the most common isolate causing sepsis. Out of culture proven cases, 16(61.5%) were from EOS category and 10 (38.4%) from LOS category with a P-value of 0.7 which shows no significant correlation of isolated bacteria with onset of sepsis (Fig. 1). Other significant GNBs were *A. baumannii (*20/87, 23.0%), *Enterobacter* spp. (15/87, 17.2%), *Pseudomonas* spp. (9/87, 10.4%), *S. marcescens* (7/87, 8.1%), *E. coli* (4/87,4.6), *Pantoea* spp. (3/87, 3.4%), *Burkholderia cepacia (B. cepacia)* (2/87, 2.3%) and *Stenotrophomonas maltophilia (S. maltophilia)* (1/87, 1.1%) (Table-I**)**. *K. pneumoniae* strains exhibited resistance to all antibiotics with only 20% of the strains were sensitive to levofloxacin and 15% showed susceptibility to meropenem, amikacin, tobramycin, ciprofloxacin and piperacillin/ tazobactam.

Enterobacter spp. was 100% resistant to cephalosporins and 13.3% exhibited sensitivity to ciprofloxacin and 66.6% to levofloxacin. Approximately,55% of *A. baumannii* were susceptible to cefoperazone/sulbactam, 45% to tobramycin, 25% to ciprofloxacin and levofloxacin, 15% to meropenem and piperacillin/tazobactam, (10%) to amikacin and ceftazidime whereas (100%) resistance to cefepime was also seen. *E. coli* exhibited 100% resistance to all β- lactam antibiotics and aminoglycosides while 50% susceptibility to ciprofloxacin and moxifloxacin. *B. cepacia* were 100% sensitive to levofloxacin and chloramphenicol while 50% to meropenem and ceftazidime. *S. marcescens* were 100% resistant to all applied antibiotics. *Pseudomonas* spp. had 66% sensitivity to amikacin and tobramycin while 44% to cefepime, sulbactam/ cefoperazone, piperacillin/ tazobactam, meropenem and 55% to ceftazidime. There was one isolate of *S. maltophilia* which was sensitive to levofloxacin only. *Pantoea* spp. exhibited 77% sensitivity to meropenem and cefepime while 100% sensitivity to aminoglycosides and piperacillin/ tazobactam **(**Table-II).

Table-I: Distribution of isolated bacteria according to sepsis onset (N=87).

Isolated Organisms	n (%)	Early onset n (%)	Late onset n (%)	p-value
Klebsiella pneumoniae	26(29.9)	16(61.5)	10(38.4)	0.68
Acinetobacter baumannii	20(23.0)	14(70.0)	6(30.0)	0.68
***Enterobacter* spp.**	15(17.2)	9(60.0)	6(40.0)	1.00
Serratia marcescens	7(8.1)	2(28.6)	5(71.4)	0.10
***Pseudomonas* spp.**	9(10.4)	5(55.6)	4(44.4)	0.80
Escherichia coli	4(4.6)	2(50.0)	2(50)	0.68
***Pantoea* spp.**	3(3.4)	1(22.2)	2(77.7)	0.30
Burkholderia cepacia	2(2.3)	2(100.0)	0(0)	0.20
Stenotrophomonas maltophilia	1(1.1)	1(100.0)	0(0)	0.40
Total	87	52(59.8)	35(40.2)	0.40

* P-value < 0.05 is significant

Table-II: Antimicrobial susceptibility pattern of gram-negative bacteria isolated from blood cultures of septic neonates.

Antibiotics	*Klebsiella pneumoniae* (n=26)	*Enterobacter* spp. (n=15)	*Acinetobacter baumannii* (n=20)	*Escherichia coli* (n= 4)	*Burkholderia cepacia* (n=2)	*Stenotrophomonas maltophilia* (n=1)	*Pseudomonas* spp. (n=9)	*Serratia marcescens* (n=6)	*Pantoea* spp. (n=3)
	(frequency of antibiotic sensitive isolates(n) / %)								
Co-amoxiclav	1 (4)	*IR	-	0 (0)	-	*IR	*IR	*IR	-
Cefuroxime	1 (4)	0 (0)	-	0 (0)	-	-	*IR	*IR	-
Cefotaxime	2 (8)	0 (0)	-	0 (0)	-	-	-	0 (0)	-
Ceftazidime	2 (8)	0 (0)	2 (10)	0 (0)	1 (50)	0 (0)	5 (55)	0 (0)	0 (0)
Ceftriaxone	2 (8)	0 (0)	-	0 (0)	-	-	*IR	0 (0)	-
Cefepime	2(8)	1 (6.6)	0 (0)	0 (0)	-	-	4 (44)	0 (0)	2 (66.6)
Meropenem	4 (15.3)	2 (13.3)	3 (15)	0 (0)	1 (50)	0 (0)	4 (4)	0 (0)	2 (66.6)
Amikacin	4 (15.3)	1 (6.6)	2 (10)	0 (0)	-	-	6 (66)	0 (0)	0 (0)
Tobramycin	4 (15.3)	1 (6.6)	9 (45)	0 (0)	-	-	6 (66)	0 (0)	0 (0)
Ciprofloxacin	4 (15.3)	2 (13.3)	5 (25)	2 (50)	-	-	7 (77)	0 (0)	0 (0)
Levofloxacin	5 (20)	10 (66.6)	5 (25)	2 (50)	-	1 (100)	7 (77)	0 (0)	0 (0)
Cefoperazone/ sulbactam	1 (4)	1 (6.6)	11 (55)	0 (0)	-	-	4 (44)	0 (0)	-
Piperacillin/ tazobactam	4 (15.3)	0 (0)	3 (15)	0 (0)	-	-	4 (44)	0 (0)	0 (0)
Chloramphenicol	-	-	-	-	2 (100)	-	-	-	-

IR= Intrinsically Resistant

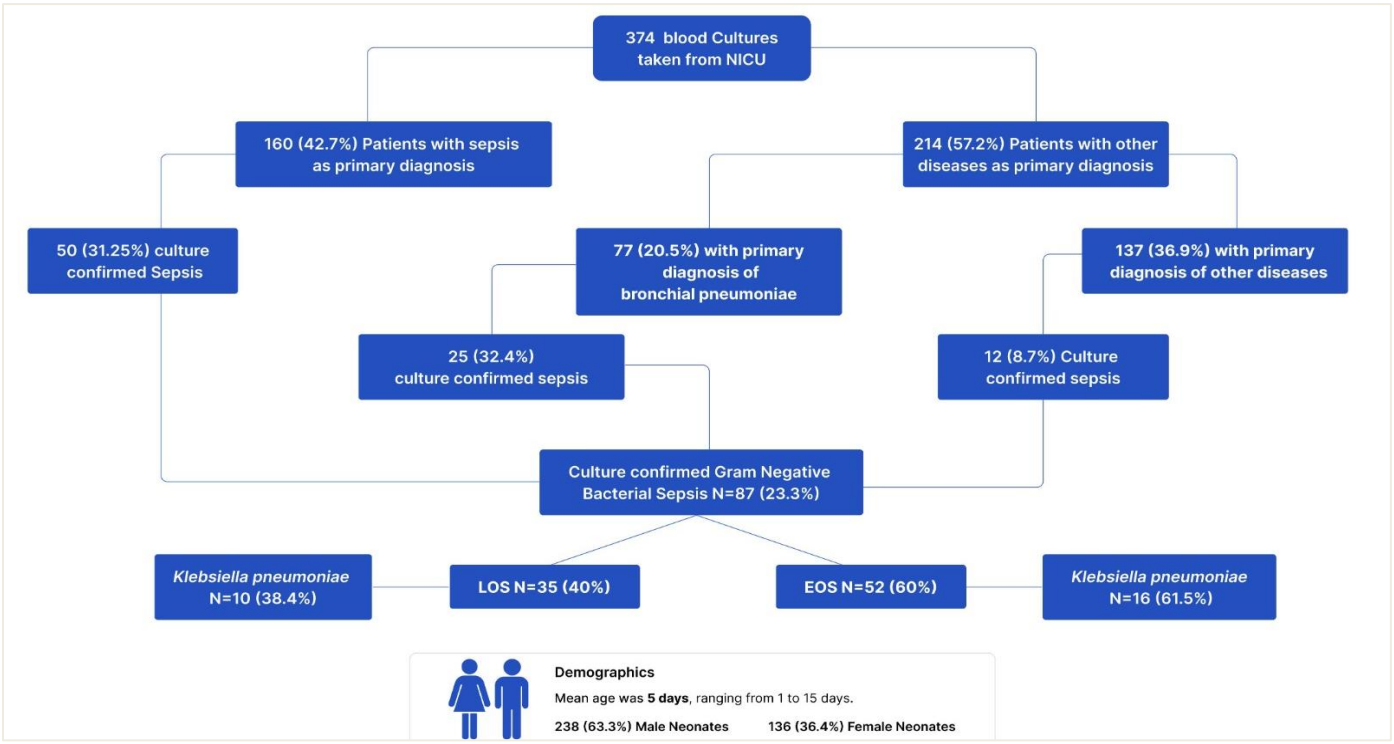

Figure-I: Frequency distribution of blood cultures according to onset of sepsis.

DISCUSSION

Neonatal sepsis has become a major concern worldwide due to increasing mortality and morbidity among neonates. In our study, 87 neonates were confirmed as having sepsis on blood culture due to Gram negative rods. There were 58 (66.6%) male babies and 29 (33.3%) female babies with ratio of 2:1 which is consistent with previous studies conducted at Kharadar hospital, Karachi and at CMH, Sialkot.[2,14]

In this study, frequency of neonatal sepsis due to Gram negative bacilli was 23.3%, which is quite

similar to 29.9% reported in NUMS, Rawalpindi.[16] In Pakistan region, high prevalence of neonatal sepsis has also been reported from Peshawar.[17] A study conducted in India reported 68% neonatal sepsis by Gram negative organisms,[18] whereas another study conducted in Cairo reported 31.7% culture positive sepsis cases caused by both Gram positive and Gram-negative bacteria, out of which more than 50% were Gram negative rods.[19] Similar to other studies, *K. pneumoniae* (29.9%) were the most common cause of sepsis in our setting.[19, 20] A previous study from this center has also reported *K. pneumoniae* to be a major pathogen of neonatal sepsis[21]. Another study carried out at a tertiary care hospital of Pakistan mentioned *E. coli* and *K. pneumoniae* as predominant organisms among GNB causing sepsis.[14] A study conducted in Rawalpindi ranked *E. coli* at the top among GNB causing sepsis in neonates.[16]

In this study, 68% were proven cases of EOS, similar to previously reported from Patan hospital, Nepal in 2017 where 78.3% cases were EOS.[22] *K. pneumoniae* has been reported the predominant organism in both EOS and LOS, as reported in the study from Cairo.[19] Like our study, *K. pneumoniae* were mentioned as the most common isolated pathogen which showed resistance only to penicllins and cephalosporins in China.[23] Other major isolates identified in our study were *A. baumannii* (23.0%), *Enterobacter* spp. (7.2%) while *E. coli* was (4.6%), *S. marcescens* (6.9%) and *Pseudomonas* spp. (5.7%). Another gram-negative isolate found in this study was *Pantoea* spp. (3.4%) which is very rare pathogen to be isolated and could have been acquired from the environment. A case series in India has also documented *Pantoea* spp. as an unusual pathogen in the etiology of neonatal sepsis.[24]

The results of our study indicate an alarming rise in Gram-negative sepsis caused by carbapenem-resistant organisms in neonates. This, combined with limited access to new antibiotics, highlights the importance of infection prevention and control measures to limit the spread of these organisms, as well as antibiotic stewardship to prevent the emergence of resistant strains.

LIMITATIONS

Not all blood cultures were drawn in automated culture bottles which have affected the yield of positive blood cultures.

CONCLUSION

Bacterial spectrum and microbial pattern are showing considerable variation with *K. pneumoniae* being the most common organism in both EOS and LOS cases. Low susceptibility was reported to antibiotics such as ß-lactams and aminoglycosides. Continuous monitoring of local data will help in determining the causative agents and antimicrobial patterns which will assist in minimizing morbidity and mortality by revising appropriate institutional guidelines.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHORS CONTRIBUTION

Shamsa Javed: Conception of the work, manuscript writing, data acquisition, analysis, or interpretation, accountable for all aspects of the work

Naima Mehdi1: Research designing and supervision, Drafting the work, revisions, final approval of the version to be published, accountable for all aspects of the work

Nadia Majeed: Design of the work, revisions, final approval of the version to be published, final approval of the version to be published, accountable for all aspects of the work

Anum Tahir: Data acquisition, analysis, or interpretation, final approval of the version to be published, accountable for all aspects of the work

Nazia Akber Mir: Drafting the work or revising it critically for important intellectual content, final

approval of the version to be published, accountable for all aspects of the work

Humera Javed: Research designing and supervision**,** Drafting the work or revising it critically, final approval of the version to be published, accountable for all aspects of the work

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