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MULTI DRUG RESISTANCE SEPSIS IN NEONATES AND THEIR ANTIBIOTIC SENSITIVITY

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Abstract:
Introduction: *- Neonatal sepsis remains a serious problem in any neonatal intensive care unit (NICU). Bacterial organisms have developed increased resistance to commonly used antibiotics. The aim of our study was to determine the multidrug resistance sepsis in neonates and their antibiotic sensitivity*
Subject & methods: *This single centre cross sectional study was conducted from the May 2020 to Nov 2020 in pediatric department, Ziauddin University Hospital, Karachi. All patients who fulfilled the inclusion criteria were included in the study. After ethical approval and informed and written consent, multiple sets of blood cultures were sent and antibiotic sensitivities were then assessed on the bacterial isolate to reach the outcome i-e frequency of multidrug resistance.*
Results: *- Total of 185 neonates admitted in neonatal units with sepsis were included. 72 neonates (38.9%) were males & 113 (61.1%) were females with the mean age of 13.810±7.865 days. The Multidrug resistance (MDR) was seen in 90 neonates (48.6%).*
Conclusion: *There is an alarming increase in frequency multidrug resistance to the commonly used antibiotics, it increases with the increase in age of neonate and predominant in female gender.*
Keywords: *Sepsis, Multidrug Resistance, Neonates, Antibiotic Sensitivity*

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INTRODUCTION:

Neonatal sepsis (NS) is a significant contributor of mortality and morbidity in the newborn. It is estimated that globally 4million newborns die yearly with one-third of the deaths caused by infections. Various conditions contribute to high neonatal mortality especially in Sub-Saharan Africa of which neonatal sepsis accounts for approximately 26%. In 2008, 22, 672 deaths were estimated to have occurred among neonates in Ghana with neonatal sepsis causing 4923 deaths (21.7%). Neonatal sepsis refers to a clinical syndrome that is marked by signs and symptoms of infection in the first 28 days of life, with or without isolation of a pathogen. A normal fetus is sterile until shortly before birth since placenta and amniotic sac serve as effective protection against infection. However, at birth, the newborn is exposed to the microbial environment. NS can be categorized as early onset sepsis (EOS) and late onset sepsis (LOS). EOS is defined as onset of signs and symptoms of infection within 72 h of life and may be associated with pathogen isolation or not. In the LOS, signs and symptoms present after 72 h of life and categorization of EOS and LOS is to show the varying causes and pathophysiology of common isolates related to the time of onset of the condition. It is also crucial in prevention and treatment due to aetiological variation.

Some maternal and neonatal factors have been identified to predispose a neonate to sepsis. In a study on neonatal sepsis conducted in 2013 in China, maternal age›35; mother with affixed occupation; mother of urban residence; caesarean section delivery; and parity were found to influence early onset neonatal sepsis in a univariate analysis. The prevalence of culture positive sepsis was 17.3% of the 150 suspected cases. A total of 26 different pathogens were isolated, of which gram-positive organisms had a preponderance of 18 (69%) over gram negative organisms 8 (31%). *Staphylococcus epidermidis* was the most common 14 (53.8%) isolate identified. Coagulase negative staphylococci (CONS) was the most common causative LONS, which reached to 43(40.6%) of total isolates, followed by Micrococcus, Enterobacter, Coagulase positive staphylococci (COPS), Candida, Shigella, E. coli, Bacillus, Citrobacter and Klebsiella, which reached to 13(12.3%), 11(10.4%), 10(9.4%), 7(6.6%), 5(4.7%), 5(4.7%), 4(3.8%),4(3.8%) and 4(3.8%), respectively.

Almost one-third of the admitted neonates (33.4%) were diagnosed as having neonatal sepsis, 32.25% of them culture-proven. Early/late onset sepsis was found in 35.4 and 64.6%, respectively. Gram-negative/gram-positive bacteria was found in 68 to 25.6%. Fungal infection was detected in 9% of the isolates. Escherichia coli was the main pathogen isolated in both early-onset sepsis (41.2%) and late-onset sepsis (24.5%). Overall, 77% of the isolates were multidrug-resistant (60% of gram-positive bacteria and 83.4% of gram-negative bacteria). In Ghana, resistance rate of 96.4%, and 96.4% to ampicillin, and penicillin respectively was reported [4]; We observed a lower resistance (25%) to ceftriaxone and gentamicin. In Mohsen et al[11] study Gram negative organisms were most resistant to ampicillins (100%), cephalosporins (93%–100%) and piperacillin-tazobactam (99%) with less resistance to aminoglycosides (36%–52%). Gram positive isolates were least resistant to vancomycin (18%). Multidrug resistance was detected in 92 (38%) cultures, mainly among gram negative isolates (78/92).

MATERIAL AND METHODS

This study was conducted after approval from CPSP. The neonates with sepsis as per operational definition who was admitted in neonatal unit in the department of Pediatric Medicine, Ziauddin University Hospital Karachi and fulfilled the inclusion criteria was included in the study. Patient demographics and clinical history regarding above mentioned symptoms were taken by the principal investigator. Inform consent was taken for each patient. Laboratory investigations will be done. Presence of sepsis was confirmed with blood sample demonstration as per operational definition. A minimum of 10 ml of blood was drawn and injected into two or more "blood bottles" with specific media for aerobic and anaerobic organisms. A common medium used for anaerobes is thiogly collate broth. The blood is collected using aseptic technique. This requires that both the tops of the culture bottles and the venipuncture site of the patient are cleaned prior to collection by swabbing with 70% isopropyl alcohol (povidone and left to dry before venipuncture).

To maximize the diagnostic yield of blood cultures, multiple sets of cultures (each set consisting of aerobic and anaerobic vials filled with 3–10 mL) may be ordered by medical staff. A common protocol used in US hospitals includes the following:

- Set 1 = left antecubital fossa at 0 minutes

- Set 2 = right antecubital fossa at 30 minutes
- Set 3 = left or right antecubital fossa at 90 minutes

Ordering multiple sets of cultures increases the probability of discovering a pathogenic organism in the blood and reduces the probability of having a positive culture due to skin contaminants.

After inoculating the culture vials, advisably with new needles and not the ones used for venipuncture, the vials are sent to the clinical pathology microbiology department. Here the bottles are entered into a blood culture machine, which incubates the specimens at body temperature. The blood culture instrument reports positive blood cultures (cultures with bacteria present, thus indicating the patient is "bacteremic"). Most cultures are monitored for five days, after which negative vials are removed. If a vial is positive, a microbiologist performed a Gram stain on the blood for a rapid, general identification of the bacteria and to assess the multi dug resistant as per operational definition, which the microbiologist reported to the attending physician of the bacteremic patient. The blood was also sub-cultured or "subbed" onto agar plates to isolate the pathogenic organism for culture and susceptibility testing, which takes up to three days. This culture and sensitivity (C&S) process identifies the species of bacteria. Antibiotic sensitivities were then assessed on the bacterial isolate to inform clinicians with respect to appropriate antibiotics for treatment. The microbiological results were confirmed by the senior microbiologist of experience more than 5 years. The effect modifiers and biasness were controlled by strictly following the inclusion and exclusion criteria

STATISTICAL ANALYSIS

Patients' data was compiled and analyzed through statistical package for Social Sciences (SPSS) Version 22. Frequency and percentage were computed for qualitative variables like gender, organism isolated on blood culture and sensitivity pattern of organism (Sensitive/Resistant), multidrug resistance (yes/no). Mean ± SD was calculated for quantitative variable i.e. age, weight, height, fever, total leukocyte count (TLC). The stratification was done on gender, age, weight, height, fever, total leukocyte count (TLC) and organism isolated on blood culture to see the effect of these modifiers on outcome using Chi-square test. $P \leq 0.05$ was considered as significant.

RESULTS:

A total of 185 neonates admitted in neonatal units with sepsis were selected to conduct this study. The mean age was 13.810±7.865 days. The distribution of age is presented in Graph-I. The descriptive statistics of age is presented in Table-1. The mean weight was 3.806±0.679 kg. The descriptive statistics of weight is presented in Table-1. The mean height was 48.648±5.065 cm. The descriptive statistics of height is presented in Table-1. The mean fever was 99.9492±1.730 (ºF), as shown in Table-1. The mean total leukocyte count was 10.409±5.382 (c/m^3), as shown in Table-1. In our study 72 neonates (38.9%) were males & 113 neonates (61.1%) were females (as shown in Table-2). The organisms on blood culture were E. coli in 78(42.2%), Staphylococcus in 71(38.4%), & Klesbsella pneumonia in 36(19.5%) babies, as shown in Table-3. The sensitivity to drugs Ciprofloxacin was sensitive in 126(68.1%) & resistant in 59(31.9%), Co Amoxiclav was sensitive in 126(68.1%) & resistant in 59(31.9%), Sulbactum Cefoperazone was sensitive in 164(88.6%) & resistant in 21(11.4%), Tazobactum was sensitive in 173(93.5%) & resistant in 12(6.5%), Amikacin was sensitive in 170(91.9%) & resistant in 12(6.5%), Imipenum was sensitive in 173(93.5%), Nitrofurantoin was sensitive in 174(94.1%) & resistant in 11(5.9%) babies, as shown in Table-4. The Multidrug resistance (MDR) was seen in 90 neonates (48.6%), as shown in Table-5.

The frequencies of age groups, gender, weight, height, fever, total leukocyte count & organism on blood culture were calculated according to multidrug resistance and sensitivity to drugs. The results are presented in Table-2 & Table-3 respectively. In our study multidrug resistance was significantly associated with gender but was not significantly associated with age, weight, height, fever, total leukocyte count and organism on blood culture with P-value of .0016, 0.955, 0.582, 0.691, 0.713, 0.611 & 0.907 respectively.

Graph-I Frequency distribution of Age (years)

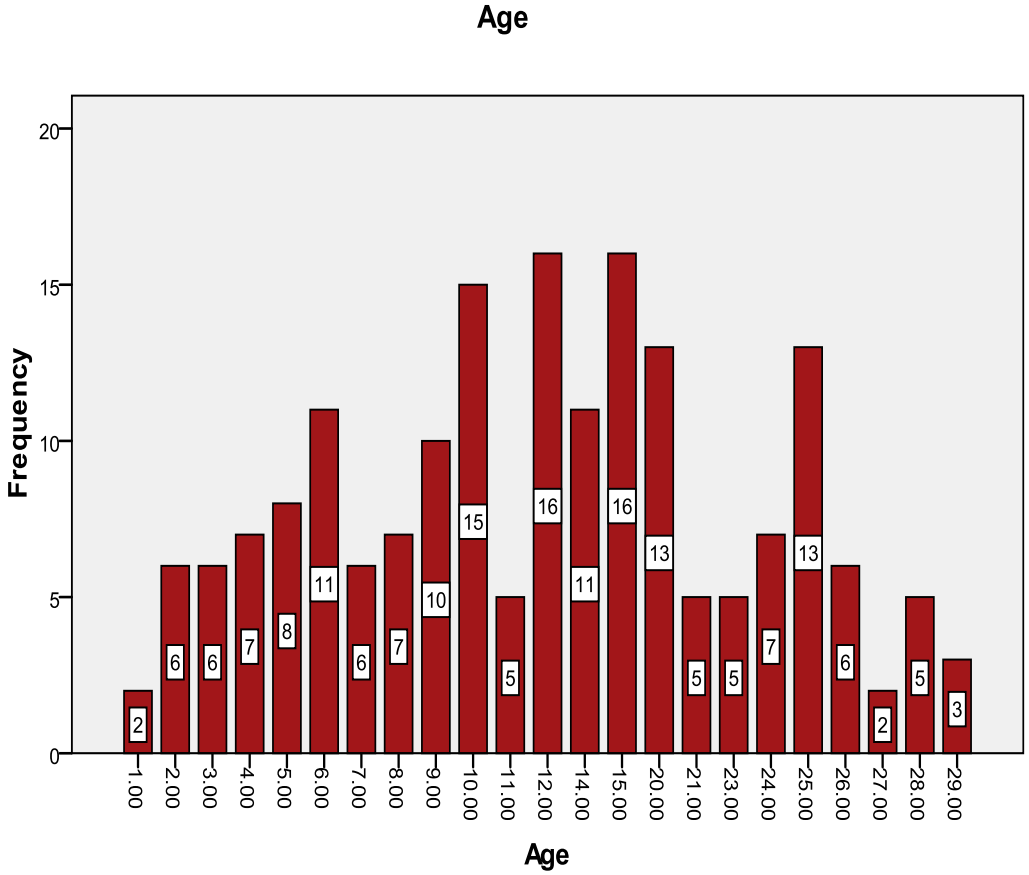

TABLE – 1

Descriptive statistics of age, Weight (Kg), Height (cm), Fever, Total leukocyte count (c/m^3), gender, Organism on blood culture, Sensitivity to Drugs, Multidrug resistance (n=185)

Variable		**MEAN±SD**
Age		13.810±7.865
Weight (Kg)		3.806±0.679
Height (cm)		48.648±5.065
Fever		99.9492±1.730
Total leuckocyte count (c/m^3)		10.409±5.382
Gender	**FREQUENCY (n)**	**PERCENTAGE (%)**
Male	72	38.9%
Female	113	61.1%
Total	**185**	**100%**
Organism on blood culture	**FREQUENCY (n)**	**PERCENTAGE (%)**
E.coli	78	42.2%
Staphylococcus	71	38.4%
Klesbsella pneumonia	36	19.5%
TOTAL	**185**	**100%**
Sensitivity to Drugs	**FREQUENCY (n)**	**PERCENTAGE (%)**
Ciprofloxacin	**Frequency (n)**	**Percentage (%)**
Sensitive	126	68.1%
Resistant	59	31.9%
Total	185	100%

Co AMOXICLAV	Frequency (n)	Percentage (%)
Sensitive	126	68.1%
Resistant	59	31.9%
Total	185	100%
Sulbactum cefoperazone	**Frequency (n)**	**Percentage (%)**
Sensitive	164	88.6%
Resistant	21	11.4%
Total	185	100%
Tazobactum	**Frequency (n)**	**Percentage (%)**
Sensitive	173	93.5%
Resistant	12	6.5%
Total	185	100%
Amikacin	**Frequency (n)**	**Percentage (%)**
Sensitive	170	91.9%
Resistant	15	8.1%
Total	185	100%
Imipenum	**Frequency (n)**	**Percentage (%)**
Sensitive	185	100%
Resistant	0	0
Total	185	100%
Nitrofurantoin	**Frequency (n)**	**Percentage (%)**
Sensitive	174	94.1%
Resistant	11	5.9%
Total	185	100%
Polymyxin	**Frequency (n)**	**Percentage (%)**
Sensitive	127	68.6%
Resistant	58	31.4%
Total	185	100%
Multidrug resistance (MDR)	**Frequency (n)**	**Percentage (%)**
Yes	90	48.6%
No	95	51.4%
Total	185	100%

TABLE – 2
Multidrug resistance (MDR) according to age, gender, weight (n=185)

Varible	**Multidrug resistance (MDR)**			**P-value**
Age	**Yes** (n=90)	**No** (n=95)	**TOTAL**	
1-15	**61(34.1%)**	**65(36.4%)**	**126(70.5%)**	**0.955**
16-29	**29(14.5%)**	**30(15%)**	**59(29.5%)**	
Total	**90(48.6%)**	**95(51.4%)**	**185(100%)**	
Gender	**Yes** (n=90)	**No** (n=95)	**Total**	**0.016**
Male	**43(23.2%)**	**29(15.7%)**	**72(38.9%)**	
Female	**47(25.4%)**	**66(35.7%)**	**113(61.1%)**	
Total	**90(48.6%)**	**95(51.4%)**	**185(100%)**	
Weight (kg)	**Yes** (n=90)	**No** (n=95)	**Total**	**0.582**
2.5-4.3	**67(36.2%)**	**74(40%)**	**141(76.2%)**	
4.4-6	**23(12.4%)**	**21(11.4%)**	**44(23.8%)**	
TOTAL	**90(48.6%)**	**95(51.4%)**	**185(100%)**	

TABLE – 3: Multidrug resistance (MDR) according to height, fever and Total leukocyte count (n=185)

Height (cm)	Vitamin D Deficiency			P-value
40-50	Yes (n=90)	No (n=95)	Total	
51-60	64(34.6%)	65(35.1%)	129(69.7%)	0.691
Total	26(14.1%)	30(16.2%)	56(30.3%)	
Fever (^{o}F)	Yes (n=90)	No (n=95)	Total	0.713
97-101	17(9.2%)	20(10.8%)	37(20%)	
102-105	73(39.5%)	75(40.5%)	148(80%)	
Total	90(48.6%)	95(51.4%)	185(100%)	
Total leukocyte count (c/m^3)	Yes (n=90)	No (n=95)	Total	0.611
2.1-12.6	46(24.9%)	45(24.3%)	91(49.2%)	
12.61-23	44(23.8%)	50(27%)	94(50.8%)	
Total	90(48.6%)	95(51.4%)	185(100%)	

DISCUSSION:

About five million neonatal deaths occur worldwide every year, 98% of which occur in developing countries, particularly Asia and Africa. Infections such as tetanus, pneumonia, septicaemia, meningitis, and diarrhea account for 30–50% of neonatal deaths in developing countries. Neonatal sepsis is a life-threatening emergency and any delay in treatment may result in death. The spectrum of organisms causing neonatal sepsis in Rahman et al study is similar to that reported for other neonatal units in developing countries, with Gram negative organisms being responsible for most cases, particularly early onset. Almost 70% of episodes of neonatal sepsis in our unit are caused by Gram negative organisms, with *E coli* being the most common (36.6%) and *Pseudomonas* the second most common (22.4%). A similar pattern has been reported for the Children's Hospital, Lahore. In that series, Gram negative organisms were responsible for almost 80% of episodes of neonatal sepsis, with *E coli* being the most common (45.8%) followed by *Klebsiella* (17.2%) and *Pseudomonas* (16.2%). Bhutta and Yusuf reported that *Klebsiella* was the most common cause of neonatal sepsis in Karachi, Pakistan. Joshi *et al*, from India, reported Gram negative sepsis in 67.2% of their cases, with *Pseudomonas aeruginosa* being the most common organism (38.3%) followed by *Klebsiella* (30.4%) and *E coli* (15.6%). Similar patterns have been reported in Trinidad and Southern Israel.

In our study the Multidrug resistance (MDR) was seen in 90 neonates (48.6%), as compare to Awad et al study, 77% of the isolates were multidrug-resistant (60% of gram-positive bacteria and 83.4% of gram-negative bacteria). In Ghana et al resistance rate of 96.4%, and 96.4% to ampicillin, and penicillin respectively was reported; Aku et al observed a lower resistance (25%) to ceftriaxone and gentamicin. In Mohsen et al study Gram negative organisms were most resistant to ampicillins (100%), cephalosporins (93%–100%) and piperacillin-tazobactam (99%) with less resistance to aminoglycosides (36%–52%). Gram positive isolates were least resistant to vancomycin (18%). Multidrug resistance was detected in 92 (38%) cultures, mainly among gram negative isolates (78/92). The data of Anwer *et al* from Karachi show 80% resistance to ampicillin but only 11–13% resistance to cefotaxime and 0–10% resistance to amikacin. Bhutta *et al* from Karachi also reported a high degree of resistance to ampicillin and gentamicin among Gram negative organisms.

Emerging multiple drug resistance has also been reported in other parts of the world. The data of Orrett and Shurland[17] from Trinidad show 85% of *S aureus* are resistant to ampicillin, and *Pseudomonas* had 76.6% resistance to ceftazidime and 72.1% resistance to gentamicin. The study of Joshi *et al* from India shows a predominance of Gram negative bacteraemia (67.2%) in their series, which had 25–75% resistance to cephalosporins, 68–78% resistance to piperacillin, and 23–69% resistance to gentamicin. Antibiotic resistance is increasing worldwide and has become a serious health problem in hospitals and the community. Infection with resistant organisms has been associated with treatment failure, higher morbidity and mortality, and increased costs. This has necessitated the

development, implementation, and evaluation of policies on the use of antibiotics. Prudent use of antibiotics and antibacterial must be promoted to maintain the balanced microbial environment in which we live. Routine bacterial surveillance and study of their resistance patterns must be an essential component of neonatal care. A knowledge of these patterns is essential when local policies on the use of antibiotics are being devised. The limitation of our study was single center study, smaller sample size. Further studies with larger sample sizes are required.

STUDY LIMITATION

The limitation of our study was single center study, smaller sample size. Further studies with larger sample sizes are required.

CONCLUSION:

There is an alarming increase in frequency multidrug resistance to the commonly used antibiotics, it increases with the increase in age of neonate and predominant in female gender.

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