Antibiotic susceptibility pattern of bacterial pathogens isolated in early onset neonatal sepsis

Jawad Khalid[1], Muhammad Sajid Mehmood[2], Irum Javed[3]

ABSTRACT

Objective: To determine the frequency of common pathogens causing early onset neonatal sepsis and pattern of antibiotic resistance of the isolated organism.
Study Design: Descriptive cross-sectional study.
Place and Duration: Neonatal Intensive Care Unit (NICU), Children Hospital, Pakistan Institute of Medical Sciences, Islamabad, from 1st June 2016 to 31st July 2017.
Methodology: The neonates born between 34 to 40 weeks of gestation, who had history of fever, positive C-reactive protein (CRP) and prolonged rupture of membranes i.e. more than 18 hours, with two or more signs and symptoms of neonatal sepsis like poor feeding, lethargy, hypothermia, tachypnea, tachycardia or sclerema were included in the study. Blood sample for blood culture was collected from every enrolled newborn. The culture pattern and sensitivity to various groups of antibiotics was assessed.
Results: Amongst total of 195 neonates the mean age of neonates was 1.91 (± 0.81) days. Klebsiella was the commonest pathogen isolated in 67% of blood culture specimens. Ampicillin showed 88% resistance for Klebsiella, 100% resistance for Pseudomonas, and 93% resistance for Staphylococcus aureus. Vancomycin showed 58% resistance for Klebsiella, 67% resistance for Pseudomonas, and 37% resistance for Staphylococcus aureus.
Conclusion: The commonest organism isolated on blood culture in neonates with early onset septicaemia was Klebsiella. Most of the antibiotics are resistant, however, imipenem and vancomycin have better sensitivity profile against these organisms.
Keywords: Neonate, Early onset sepsis, Blood culture, Culture pattern, Antibiotics, Sensitivity, Pathogen resistance.

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INTRODUCTION

Infections are the major culprits in causing neonatal and infant morbidity and mortality. In the past decade, the research in this field of neonatology and immunology has advanced substantially, from the understanding of the immunology and biology of pregnancy and early life. It is estimated that 2% of babies are infected in-utero. Neonatal infections are unique and it is deducted from various studies that 10 % of neonates get infected in first month of life[1]. Neonatal sepsis is categorized by bacteraemia and clinical signs and symptoms triggered by micro-organisms and their toxic metabolites.[2,3]. The foetus is sheltered in-vitro from bacterial contact by the placenta and membranes[4]. The infected babies' present symptoms at birth, suggesting that bacterial colonization may take place before birth. Listeria monocytogenes and few other bacteria cause transplacental contagions via the mother's bloodstream[5]. The competence of the neonatal immune system, prematurity, and maternal immunological factors determine severity of the disease[6]. Factors like inoculum size, virulence of the infecting organism, innate immune system and transplacental maternal antibodies will determine the severity of disease[7]. Ingestion or aspiration of bacteria in the amniotic fluid lead to congenital pneumonia and systemic infection[8].

Early onset neonatal sepsis is defined as an infant, who develop clinical signs of neonatal sepsis within 72 hours of life[9]. Earlier the onset bacterial infection greater is risk of morbidity and death. Early onset (within 72 hours of life) neonatal sepsis is

1. Consultant of Paedriatics, DHQ Hospital Kotli, AJK
2. Associate Professor of Physiology, Frontier Medical and Dental College, Abbottabad.
3. Senior Registrar of Paedriatrics, Poonch Medical College, Rawalakot, AJK

Correspondence:
Muhammad Sajid Mehmood
Associate Professor of Physiology,
Frontier Medical and Dental College, Abbottabad.
Email: drsaji111@gmail.com

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mostly acquired from maternal genital tract, whereas late onset sepsis (after 72 hours till 28 days of life) is environmental in origin, either iatrogenic or community acquired[10]. It is estimated from statistics of World Health Organization (WHO) that approximately 5 million neonatal deaths each year occurs due to sepsis. Neonatal mortality burdens one-third of all child deaths per annum in the world[11-13]. It is predictable that approximately 1.6 million of neonatal deaths are triggered by neonatal infections each year. Neonatal mortality due to neonatal sepsis varies from 20% to 50% depending upon the type of microorganism involved. The disease burden is highest with enterococcus and gram negative bacteria. The spectrum of microorganism isolated in neonatal sepsis differ amongst developing and developed nations[14,15].

It was aspired in Millennium Development Goal-4 to reduce under-5 mortality near to 30 child deaths per 1000 live births by year 2015. However, neonatal deaths share approximately 41% of all deaths in children below 5 years of age worldwide. Pakistan is one of the five countries contributing 49% (4.294 million) of child deaths and has one of the highest neonatal mortality of 53/1000 live births[8]. Approximately, two-third neonatal deaths across the globe are contributed by just ten countries and unluckily, Pakistan ranks at third position with a share of 7%[16] A cohort study conducted in Pakistan revealed that 45% of all neonatal deaths occurred within 48 hours of birth and 73% within 1st week of delivery[17]. Information regarding antimicrobial resistance among the bacterial infections in masses is essential for developing appropriate management strategies. Hospital-based statistics show alarming rates of resistance to Ampicillin and Gentamicin among common pathogens causing neonatal sepsis. WHO recommended Ampicillin and Gentamicin combination is no longer effective in the management of neonatal sepsis in newborns. Pathogens instigating neonatal infections and their antibiotic resistance may change over time and differ between countries[18]. Hence, it is essential to monitor the epidemiology of neonatal infections in order to apprise local government and clinicians.

The purpose of this study was to look for common pathogens involved in neonatal sepsis and the resistance pattern of causative organism in our population, so that new appropriate antibiotic regimen could be selected for the neonates in accordance to susceptibility of isolated organism. It can also prevent misuse and reduce the resistance of effective antibiotics against common pathogens. To encourage the stake holders to carry out large scale studies at local, national and international levels to find the most common pathogens involved and the drugs resistant and sensitive against these pathogens. The objective of the study was to determine the major pathogens involved in neonatal sepsis and their response to various drugs. To determine the drugs sensitive and resistant against these pathogens. So, this study was conducted with an objective to determine the frequency of common pathogens causing early onset neonatal sepsis and pattern of antibiotic resistance of the isolated organism.

METHODOLOGY

This descriptive cross-sectional study was conducted at Neonatal Intensive Care Unit (NICU), Children Hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad from 1st June 2016 to 30th June 2017. All neonates with suspected sepsis admitted were screened for enrolment. Those who fulfilled inclusion criteria were enrolled in this study. A convenience, non-probability, sampling technique was chosen.

All neonates, with informed consent, admitted in neonatal intensive care unit immediately after birth till 72 hours of life born by spontaneous vertex delivery or caesarean section between 34 to 40 weeks of gestation fulfilling any two of following criteria. Antenatal history of one of the following: fever, positive C-reactive protein and prolonged rupture of membranes > 18 hours of life. Two or more signs and symptoms of neonatal sepsis like poor feeding, lethargy, hypothermia (axillary temperature less than 36.5°C) tachypnoea (respiratory rate > 60), tachycardia (>160) or sclerema. Positive C- reactive protein of neonate (>10mg/dl). Total leukocyte count > 20,000 or < 5000 or platelet count < 50,000. Neonates with congenital anomalies. Neonates with surgical intervention done for any cause. Neonates with hypoxic ischemic encephalopathy. Neonates with gestational age < 34 weeks of age. Neonates with very low birth weight < 1.5 kg. Neonates already receiving antibiotics.

Informed consent was taken from parents for inclusion in the study. All neonates with clinically proven sepsis fulfilling diagnostic criteria were enrolled in the study. Specimen of 3 ml of blood was collected aseptically for each of the enrolled neonate. The blood sample obtained was inoculated directly into the blood culture bottles of Bactec-9240. The inoculated bottles were transported immediately to pathology laboratory, children hospital, PIMS and incubated at 37 ℃ in Bactec-9240 machine which is a continuous monitoring blood culture system.

On having positive cultures, the specimen was inoculated on Blood agar, MacConkey agar and incubated in the incubators at 37 ℃ +/-3 for a period of 18-24 hours. As growth on these agar plates grows, they were further identified by standard methods i.e. colony morphology, gram stain and other biochemical test. For gram positives catalase, coagulase and DNase were performed. For gram negatives API 20 E which is an analytical profile index of biochemical test for gram negative bacteria. The organism isolated were then tested on *Mueller Hinton Agar* for susceptibility testing of antibiotics (Ampicillin, Amoxicillin, Amikacin, Tobramycin, Cefotaxime, Ceftazidime, Ceftriaxone, Imipenem, Ofloxacin, Ciprofloxacin, Vancomycin) by standard *Kirby-Bauer* method. The panel of gram positive and gram-negative organism were tested as per CLSI (Clinical laboratory standard institute).

Different variables as per objective such as age, birth weight, gender, antenatal care, postnatal signs and symptoms, bacterial pathogen, sensitivity, were recorded personally by researchers in a performa for analysis.

Data Analysis: Software SPSS version-20 used for analysis. The descriptive analysis was carried out and reported as mean with standard deviation and median for continuous variable. Similarly, for categorical variables frequencies and percentages were calculated. Further, the comparisons of bacterial

pathogens with age and gender were also performed using Chi-square test and p-value was reported. The level of significance was considered as 5%.

RESULTS

Amongst total of 195 neonates the mean age of neonates was 1.91 (± 0.81) days. Out of 195 neonates with sepsis, 73 (38%) neonates were one day old, 67 (34%) were 2 days old and 55 (28%) were 3 days old. In our sample 132 (68%) were baby boys and 63 (32%) were baby girls. Out of 195 neonates with sepsis, 73 (38%) neonates were one day old, 67 (34%) were 2 days old and 55 (28%) were 3 days old. In the enrolled sample, 73 (37%) neonates were hypothermic and 122 (63%) were of normal temperature. In the current study, 69 (35%) had poor feeding and 126 (65%) had normal feeding. Out of 195 enrolled neonates, 61 (31%) were lethargic while 134 (69%) were not lethargic at the time of enrolment. Tachycardia was noted in 96 (49%)of total sample. Sclerema was noticed in 89 (46%) and 54(28%) had positive C-reactive protein (CRP). The minimum value of total leukocyte count was 2000 and maximum was 67000 mm^3/dL.

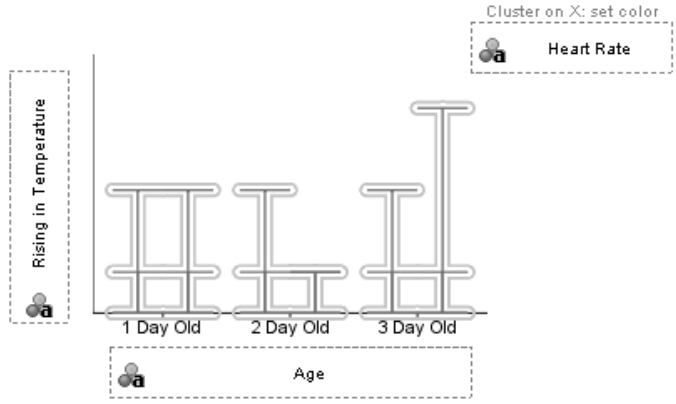

Figure-1: Relationship of Age of Neonate with Heart Rate and Temperature

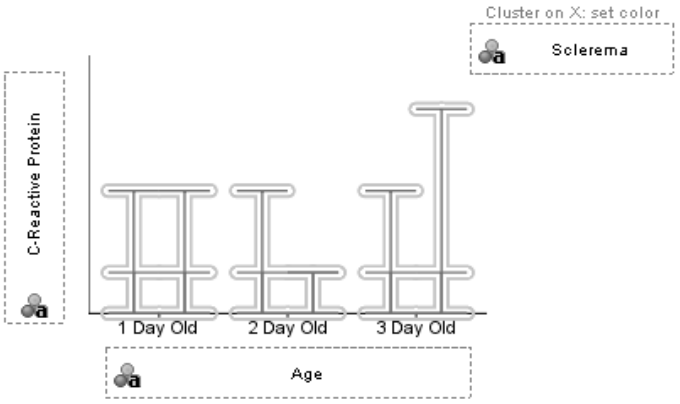

Figure-2: Relationship of Age of Neonate with CRP and Sclerema

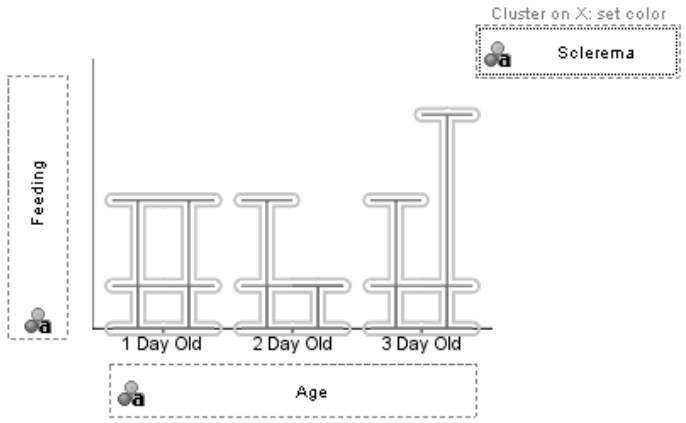

Figure-3: Relationship of Age of Neonate with feeding and Sclerema

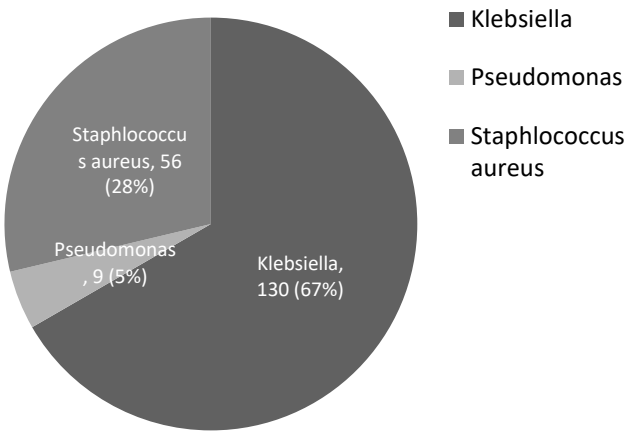

Figure-4: Frequency of bacterial pathogens isolated in blood culture of all the enrolled neonates (N = 195)

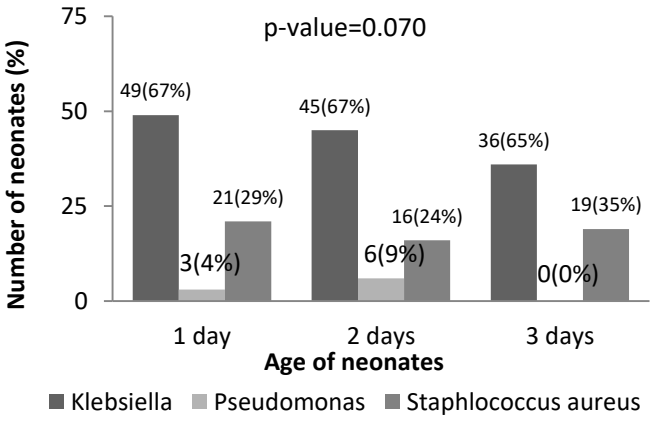

Figure-5: Presence of bacterial pathogens in blood culture by age of all the enrolled neonates (N = 195)

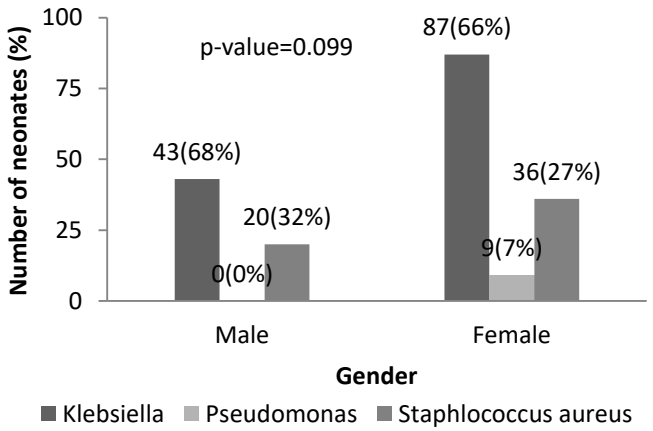

Figure-6: Presence of bacterial pathogens in blood culture by gender of all the enrolled neonates (N = 195)

The findings of bacterial pathogens identified in blood cultures are presented in Figure-1.

The findings of antibiotic resistance pattern of different bacterial pathogens are shown in Table-I. The findings of antibiotic resistance pattern of different bacterial pathogens are shown in Figure-3. However, these differences were not statistically significant (p-value=0.070). The findings of bacterial pathogens by gender of all the enrolled neonates are presented in graph-IV. These differences were also not statistically significant (p-value=0.099).

DISCUSSION

In Pakistan neonatal mortality reported as 68% of infant mortality. As seen in other studies, our study depicts that most cases are reported within 48 hours of birth. In most of the cases clinical features of early neonatal sepsis are reported in day two of life[2]. There were more cases of female reported in our set up which is similar to study of Makkar et al.[19] and in contradiction to study carried out at Ayub Teaching Hospital, Abbottabad[1] and study by Binet et al.[20] This can only be by chance as randomization was not done. Moreover, cultural norms regarding gender may also play some role[21,22]. Most of the cases were norm-thermic which is similar to other studies[23,24]. Early neonatal sepsis was related to raised serum CRP levels in approximately 40% of neonates which is consistent with other studies[25]. Early onset neonatal sepsis is usually caused by bacterial pathogens such as Group B Streptococcus, E-Coli, Klebsiella, Listeria or other Gram-negative organisms. These pathogens are usually acquired from the maternal genitourinary tract[26].

Amongst the neonates who admitted at the first day of their life, mostly Klebsiella (67%) and Staphylococcus aureus (23%) were isolated as compared to only 4%, Pseudomonas. Neonates admitted on 2nd day, Klebsiella was isolated in 67%, followed by Staphlococcus aureus (24%) and only 9% of Pseudomonas. Almost same pattern was noticed subsequently.

A study from Karachi Pakistan, aimed to study the bacterial pathogens causing neonatal sepsis and their sensitivity pattern so, guidelines can be prepared for empirical antibiotic therapy. The specimens of 520 was inoculated, which shows that organisms cultured are Staphylococcus aureus (30.7%), Klebsiella pneumoniae (34.4%), Acinetobacter baumannii (10.8%), Escherichia coli (10.4%), Enterobacter cloacae (8.5%), Citrobacter diversus (2.4%), Pseudomonas aeruginosa (1.9%) and group B Streptococcus (0.94%). On antibiotic sensitivity testing, 61.54% of Staphylococcus aureus isolates were found to be methicillin resistant. Susceptibility to the other common drugs was also quite low while 89.23% of these were susceptible to Amikacin and 100% to Vancomycin. More than 90% gram negative rods were resistant to Ampicillin and Cotrimoxazole. Resistance to Gentamicin was as high as 90.4% for Klebsiella pneumoniae; 60.87% for Acinetobacter baumannii. Resistance to the third generation Cephalosporins and the Quinolone tested (Ciprofloxacin) varied between 25-75%. Majority of the isolates were susceptible to Meropenem and Amikacin[27].

A study from Iran was carried out to determine the bacterial etiology and antibiotic sensitivity patterns of neonatal sepsis on 208 neonates which was divided into early onset sepsis (EOS, ≤5 days of age) and late onset sepsis (LOS, >5 days of age).

Study shows Escherichia coli was the most common organism followed by Klebsiella, Staphylococcus aureus (S. aureus). As for LOS, Coagulate-negative Staphylococci (CONS) were the most common organism followed by Enterococcus spp, S. aureus. The antibiogram on the isolated E. coli and Klebsiella spp revealed a greater combined sensitivity to Cefotaxime. Coagulate-negative Staphylococci and S. aureus had 100% and Entero- coccus spp 90% sensitivity to Vancomycin[28].

Another study from Egypt aimed to identify the frequency of bacterial isolates in early-onset neonatal sepsis (EONS) and their antimicrobial resistance pattern. Of 673 neonates screened, there were 138 positive blood cultures (20.5%) (confirmed EONS). Of the recovered isolates, 86.2% were gram-negative pathogens. *Klebsiella pneumoniae* (42.8%), *Enterobacter cloacae* (22.5%), and Escherichia coli (13.8%) were the commonest isolated organisms.

The most common gram-positive microorganism was Staphylococcus aureus accounting for only 12 isolates (8.7%). All Klebsiella isolates and 93% of Enterobacter isolates were resistant to Ampicillin. Gram-negative pathogens had the maximum overall sensitivity to Imipenem, Cefepime, and Ciprofloxacin; whereas, gram-positive isolates were most susceptible to Vancomycin, Imipenem, and Piperacillin[29].

Our findings regarding presence of bacterial pathogens in blood culture are comparable with the other studies conducted on neonatal sepsis and their sensitivity pattern[27,30]. The frequency of etiological agents and antibiotic sensitivity patterns were different from the studies conducted in India and Nepal[31-33]. This shows different virulence and prevalence of infective agents in various neonatal set-up which need regular data compilation and analysis to adapt better antibiotic regimens in various setup.

Generally, there was a trend of increasing resistance to commonly used antibiotics among nosocomial acquired gram-negative organisms[34]. However, in most of studies Imepenem, meropenum and aminoglycosides were effective, which is similar to the findings in our study.

CONCLUSION

The commonest organism isolated on blood culture in neonates with early onset septicaemia was Klebsiella. Most of the antibiotics are resistant, however, imipenem and vancomycin have better sensitivity profile against these organisms.

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Future Prospects: Our findings provide useful guidelines to neonatologists and paediatricians for the management of early onset of septicaemia in our clinical settings. However, there is a need to conduct a multicentre study in various parts of the country and internationally to know the exact pathogens and pattern of antibiotic resistance leading to early onset of septicaemia.

AUTHOR'S CONTRIBUTION

Khalid J: Conceived idea, Designed research methodology, Data collection, Final critical review of manuscript
Mehmood MS: Literature Search Manuscript writing, Data analysis, Manuscript final reading and approval.
Javed I: Data collection, final critical review of manuscript

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