The Professional Medical Journal
www.theprofesional.com

DOI: 10.29309/TPMJ/18.4719

ORIGINAL PROF-4719

NEONATAL SEPSIS;

FREQUENCY OF VARIOUS BACTERIA AND THEIR ANTIBIOTIC SENSITIVITY IN NEONATAL SEPSIS

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Article received on:
22/05/2018
Accepted for publication:
17/08/2018
Received after proof reading:
06/11/2018

ABSTRACT… Objectives: To study the frequency of different types of bacteria causing sepsis in neonates, their sensitivity and resistance to various antibiotics in common practice at a tertiary care hospital. **Study Design:** Prospective cross-sectional study. **Stetting and Duration of study:** The study was conducted in Neonatal unit, Lady Reading Hospital, Peshawar, Pakistan from January to October 2017 (10 months duration). **Material and Methods:** Blood culture positive neonatal sepsis patients admitted to the Nursery C, LRH during 10 months were analyzed for bacteria and their sensitivity/ resistance pattern. **Results:** During study period total 115 blood culture proven neonatal sepsis causes were found. Only 3 pathogens were isolated, where E. Coli was the most frequent organism found in 85 cases. Staphylococcus aureus (25Cases) was the second frequently occurring organism while Klebsiella spp. was the third pathogen causing sepsis in my study (7 cases). Amikacin (88% sensitive against E. Coli), vancomycin (100% sensitive against Staphylococcus aureus) were found most sensitive than commonly used antibiotics. As the organisms were mostly resistant to ampicillin (76.23%) Amoxicillin (82.48%), Cefotaxime (93.75%) and Ceftriaxone (66.29%), Ceftazidime was comparatively less resistant (55.80%). **Conclusion:** E. Coli was found to be the major cause for neonatal sepsis followed by Staphylococcus aureus in admitted neonates at Lady Reading Hospital. An alarming increase in the resistance pattern of empirically used antibiotics was observed. So, there is dire need for continuous monitoring/ surveillance of this alarming resistance of commonly used drugs. Moreover, an effective infections control program is needed to limit the spread of resistant strains of these pathogens.

Key words: Antibiotics Sensitivity, Bacterial Isolates, Bacterial Resistance, Neonatal Sepsis.

Article Citation: Hussain M, Aurakzai AA, Irshad M, Ihsan Ullah. Neonatal sepsis; frequency of various bacteria and their antibiotic sensitivity in neonatal sepsis. Professional Med J 2018; 25(11):1683-1688. **DOI:**10.29309/TPMJ/18.4719

INRODUCTION

Neonatal sepsis refers to systemic inflammatory response syndrome secondary to infection occurring within the neonatal period, (the first 28 days of life for a term baby, and up to 4 weeks beyond the expected date of delivery in a preterm baby).[1] The incidence of neonatal sepsis is 1 to 8 cases per 1000 live births; amongst which meningitis occur in 1 out of 6 septic neonates.[2] Neonatal sepsis as compared to the neonates who have no sepsis, not only had increased morbidity but their mortality is very high and their length of hospital stay are prolonged.[3] In developing countries about 1.6 million neonates die every year due to infections.[4] About 7% of the world neonatal deaths occur in Pakistan.[5] Amongst which 33% deaths occur due to infection.[6] Sepsis is the most common cause of death in very low birth weight neonate[2], while low and very low birth weight neonates make up about 25% of the sepsis population in paediatrics.[1]

Prompt treatment with appropriate empirical antibiotics should be initiated for suspected neonatal sepsis.[7] Though there are no definition randomized controlled trials to adopt the best empirical antibiotic regimens for the newborn, narrow-spectrum antibiotics should be used and only when significant infections are likely.[1,2] Early use of appropriate empirical antibiotics reduces not only the emergence of commonly used drug resistant pathogens but also minimize the morbidity and mortality from neonatal sepsis.[8]

The appropriate empirical regimen for neonatal sepsis should be based on optimum knowledge of the causative agents and their antibiotic resistance in that area.[3] Yearly identification of the causative pathogens and their antibiotic resistance in a neonatal unit helps in selection of the appropriate empirical therapy.[9] Though most of the pathogens causing sepsis in neonates remain sensitive to the new antibiotics, emergence of resistance strains is always predicted. That's why continuous surveillance is required to monitor the changing epidemiology of organisms, antibiotic sensitivity and antibiotic use needed to overcome the emerging resistance to conventional antibiotics.[10]

Limited data is available in KP-Pakistan on neonatal sepsis and the antibiotic susceptibility. We tried to provide a local data on pattern of microorganism and their antibiotics susceptibility, causing neonatal sepsis. This will help in decreasing mortality from neonatal sepsis through development of local, evidence based clinical guidelines.

MATERIAL AND METHODS

The study was conducted from January 2017 to October 2017 at Neonatal unit/Nursery "C" of MTI-Lady Reading Hospital, Peshawar. After approval from hospital research and ethical board, only the blood culture positive consecutive neonatal sepsis cases admitted to our unit were included. While the blood culture negative suspected sepsis cases and premature neonates were excluded from study. Blood sample (5ml) of all the full-term neonates admitted with clinical sepsis were sent to laboratory for culture and sensitivity. Blood culture reports were developed into positive and negative cases and only blood culture positive cases were included. All cultures done from the same laboratory using standard bottle for inoculation and incubated for 5 days. As per microbiologist report sub culture was done on MacConkey Agar, Chocolate Agar and Blood Agar while incubated at 37^{0}c aerobiology. Gram staining and other biochemical serological tests were performed to identify organisms. The detected organisms were subjected to various antibiotics for their susceptibility using Kirby Baur Disc diffusion technique. Isolated with intermediate resistance were included as sensitive. The data was analyzed through SPSS version 22 and frequency/percentages were calculated for qualitative variable.

RESULTS

A total of 15 blood culture proven of neonatal sepsis were found during this 10 months study. Late onset sepsis (LOS) was found in 81 (70.43%) cases, while early onset neonatal sepsis (EOS) in 34 (29.57%). Of these 66 (57.39%) were male and 49 (42.6%) were female. Amongst the bacterial isolates Gram negative bacteria was more frequently found in 84 (73.04%) than Gram positive bacteria, 31 (26.96%). The most frequently identified bacteria were E. Coli, 71 (61.74%) followed by Staphylococcus aureus and Klebsiella spp. i.e. 31 (26.96%) and 13 (11.30%) respectively.

According to this study the empirical therapy currently in use at neonatal unit of Medical Teaching Institution, Lady Reading Hospital i.e. Ampicillin & Cefotaxime were found resistant in most the cases of neonatal sepsis i.e. 87.50% and 86.12% respectively. While Ceftazidim was comparatively less resistant 65.61%. other commonly used antibiotics are also proven resistant like Gentamicin 54.44%, Tobramycin 40,20%, Amoxicillin 90.40%, and Ceftriaxone 88.76%. The less commonly used antibiotics like Imipenem and Quinolones were showing variable pattern of susceptibility, like Imipenem was resistant in 33.96% while Ciprofloxacin & Ofloxacin were resistant in 36.66% & 52.73% respectively. Amikacin was the most sensitive against E. Coli 96.70%, Vancomycin was most sensitive against Staphylococcus aureus 100% and Imipenem and Quinolones were the most sensitive against Klebseilla spp. in 74% & 80% respectively.

DISCUSSION

Despite advances in diagnosis and management of neonatal sepsis in recent years, it is still a leading cause of mortality and morbidity in the newborn.[1]

No			Number of Patients	Percentage
1	Gender	Male Female	66 49	57.39% 42.6%
2	Types of Sepsis	Early Onset Sepsis Late Onset Sepsis	34 81	29.57% 70.43%

Table-I. Percentage of gender & type of sepsis (Total n = 115)

No			Number of Cases	Percentage
1	Group of Causative Bacteria	Gram Positive Gram Negative	31 84	26.96% 73.04%
2	Causative Bacteria	Staph aureus E. Coli Klebseilla	31 71 13	26.96% 61.74% 11.30%

Table-II. Bacterial groups & various bacteria found (Total cases = 115)

No	Bacteria	Most Sensitive Antiobiotic	Sensitivity	Most Resistant Antibiotic	Resistance
1.	Escherichia Coli	i. Amikacin ii. Imipenem iii. Tobramycin iv. Ceftazidime v. Ciprofloxacin	96.7% 80% 70% 49.26% 41.2%	i. Cefotaxime ii. Amoxicillin iii. Ceftriaxone iv. Ampicillin v. Gentamycin	96% 94% 94% 93.1% 60%
2.	Staph Aureus	i. Vancomycin ii. Ciprofloxacin	100% 69.6%	i. Cefotaxime ii. Ampicillin iii. Amoxicillin iv. Ceftriaxone v. Imipenem	80% 77.1% 77% 74.3% 74.2%
3.	Klebsiella	i. Imipenem ii. Ofloxacin iii. Ciprofloxacin iv. Amikacin v. Gentamycin	92.3% 86.5% 79.2% 74.4% 51.1%	i. Amoxicillin ii. Ceftriaxone iii. Ampicillin iv. Cefotaxime v. Ceftazidime	100% 98% 92.3% 82.36% 70.5%

Table-III. Sensitivity pattern of isolated pathogens (Total number = 115)

The indirect indices of sepsis like total white blood cell count, absolute neutrophil count, C-reactive protein level, procalcitonin level and levels of a variety of inflammatory cytokines are non-specific and are not adequately sensitive to confirm or exclude sepsis. Blood culture is the gold standard for diagnosis of sepsis.[11] In this study of 115 blood culture positive sepsis cases 66 (57.39%) were male and 49 (42.6%) were female. Male to female ratio 1.3:1 which is consistent with study from Dow University Karachi.[12,15]

Our study described that late onset sepsis (LOS), 70.43% occur more commonly than early onset sepsis (EOS), 29.57%. This is similar to the studies from Latin America[16], Malaysia[17] and Saudi Arabia.[18] This study found Gram negative pathogens in 73.04% as compared to Gram positive isolates 26.96%, which is in conformity to similar studies from Karachi[15,19,20], Peshawar[22], India[23] and Bangladesh.[24]

While in contrast to this study Gram positive organisms were predominately found causing neonatal sepsis in studies from Karachi[12,25] and Nigeria.[26] This may be due to the changing pattern of bacterial pathogen causing neonatal sepsis in different geographical areas.

Escherichia Coli was the most common bacteria found in our study, 61.74%. Which is consistent with studies from Karachi[15], Lahore[21] and Multan.[27] The other pathogens were Staphylococcus aureus, 26.9% and Klebseilla pneumonia in 11.3%. The difference in occurrence of various bacterial pathogens amongst different centers in

Pakistan like Staph aureus is the most frequently found followed by Pseudomonas aeruginosa & E. Coli in a study from Karachi[12] while Enterobacter was found the most common pathogen from Islamabad.[28] Outside Pakistan, Klebseilla spp. was most common in Bangladesh[24], Pseudomonas in India[23] and Enterobacter in Iran.[29] This confirms the difference in occurrence of various pathogens in different geographical areas.

Like previous studies from Peshawar[21,30], Lahore[21] and Karachi[19], Listeria and Group B Streptococcus (GBS) were not isolated in this study. Which is in contrast to the study from West.[31] This may be due to the presence of low virulence strains of these organisms here.

Our study revealed that most of the commonly used antibiotics are highly resistant. Like Ampicillin and Amoxicillin over all resistance rates were 87.50% and 90.4% respectively in this study. Ampicillin showed high resistance i.e 93%, 79% and 77.1% to E. Coli Klebseilla spp. and Staph aureus respectively which is consistent with a local study by Waseem et al[32] and a Nigerian study by Alwoniyi et al.[33]

Third generation Cephalosporins were also found highly resistant against both Gram positive and Gram-negative bacteria. Cefotaxime, the most important empirical therapy drug in LRH was found resistant in 86.2%. The high resistance to cefotaxime is supported by Waseem et al[32], Rehman S et al[21] and others.[13,19,27,28] Ceftriaxone and Ceftazidime were also found resistant in considerable degree, 66.9% and 63.61% respectively. This emerging resistance to cephalosporin is supported by Rao MS[12], Shaw et al.[13] Because of the limited options for treating cephalosporin resistant pathogens, this rising pattern of resistance is going to be a huge challenge in choosing empirical/ antimicrobial therapy.

Aminoglycosides showed variable pattern of resistance ranging from as high resistance as 54.4% in case of Gentamycin to as low as 14.97% in case of Amikacin. While Tobramycin was found to be resistant in 40.2% cases in our study. This is supported by studies from Karachi[12,20] and Islamabad.[28] However, in contrast study conducted in 2007[34] reported high resistance for aminoglycosides which was then supported by another study in 2011.[21]

Amongst quinolones only Ciprofloxacin and Ofloxacin were tested in our study, showing good sensitivity to Klebseilla spp. i.e. 79.2% & 86.5% respectively, while high resistance found against E. Coli 70.5% (Ofloxacin) and 58.8% (Ciprofloxacin). This is in contrast to other studies[12,28,30] showing high sensitivity to most pathogens. This difference in sensitivity pattern may be due to indiscriminate use of antibiotics.

Vancomycin was found sensitive against 100% cases of Staph aureus which is consistent with Shaw et al.[13]

Imipenem was resistant in 20%, 7.65% and 74.2% of E. Coli, Klebseilla spp. and Staph aureus respectively in our study. This is in contrast to a study by Shaw et al[33], from Nigeria.

CONCLUSION

It is concluded that E. Coli is the most common cause of neonatal sepsis in patients admitted to LRH. The bacterial isolate varies in its occurrence and antimicrobial sensitivity geographically. Most of the empirical regimens/ commonly using antibiotics like Ampicillin, Amoxicillin, Cefotaxime and Gentamycin are highly resistant against both Gram positive and Gram-negative pathogens causing neonatal sepsis. That's why further multi culture studies in other hospitals of Peshawar rest of the country are crucial for the bacterial surveillance and their antibiotic sensitivity pattern for considering new treatment protocols. To reduce the high morbidity & mortality from neonatal sepsis, inclusion of Amikacin in the empirical antibiotic therapy proposed. Moreover, judicial use of antibiotics with accurate dosage and duration, adopting latest guidelines and continuous monitoring of this antibiotic resistance pattern are essential to control the emergence of the resistant strains of these bacteria.

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Motivation is what gets you started,
Habit is what keeps you going.

– Unknown –

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Muhammad Hussain	Data collection, Manuscript writing and intellectual concept of the article.	
2	Ahmad Ali Aurakzai	Methodology, Data analysis and results.	
3	Mohammad Irshad	Abstract, discussion, conclusion and references writing.	
4	Ihsan Ullah	Data analysis, review as pathologist, final proof reading and correction.	