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Evaluation of Organism profile and Antibiogram at Neonatal Intensive Care unit in a tertiary care Hospital

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Abstract: *Neonatal sepsis rate can determine the organism load in an Intensive care unit of Neonatology. It contributes 30% death in the developing country. It is of two types, Early onset and Late onset. Early detection by the clinical signs and symptoms followed by Microbiological detection of organism prevents the complications. Determination of organism profile at tertiary care set up is very much necessary for the characterization of them. Early clinical detection, followed by culture confirmation and use of proper antimicrobial agent can decrease the neonatal mortality and morbidity. Thus antibiogram of a set up is very important for the prevention of cross infection and control of the sepsis in a Neonatal setup. Continuous surveillance of the environment and also determination of choice of antimicrobial agent is very important to reduce the rate of Neonatal sepsis. Also determination of the First line, Second line and third line drug therapy according to the sensitivity pattern of the organism is also very important. Minimal drug resistance to multidrug resistance bacteria like, Klebsiella pneuminiae and Staphylococcus aureus are the main culprits. Other Gram negative bacteria like E.coli, Pseudomonas, Acinetobacter etc are also sometimes made the situation worse. We have mainly focused to determine an organism profile of a neonatal intensive care unit and also determined antimicrobial therapy of choice according to the sensitivity pattern of the organisms.*

Keywords: *Neonatal Sepsis, Anti-Bacterial Agents, Blood Culture, Cross infection, Asepsis*

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I. Introduction

Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection and bacteremia in the neonatal period. Neonatal sepsis is a major cause of mortality and neurodevelopmental impairment among neonates. It contributes to nearly 30 % of neonatal deaths in developing countries.[1] In the continent of Africa, Seventeen percent of neonatal deaths in sub Saharan Africa are attributed to neonatal sepsis as compared to only 6% of neonatal deaths are due to sepsis in high income countries. Neonatal sepsis, the major newborn killer in Ethiopia, accounts for more than one third of neonatal deaths. In Tigray region, neonatal sepsis is also a major cause of neonatal morbidity and deaths next to prematurity and birth asphyxia. It causes 24% of neonatal deaths with an incidence rate as high as 10% per 1000 live births.[2]

Furthermore, it is also associated with increased medical costs, prolonged hospital stay and potentially poor long-term neurodevelopmental outcomes. Surviving infants, approximately one-fourth of neonates, have significant neurological sequelae as a consequence of CNS involvement, septic shock or hypoxemia secondary to severe parenchymal lung disease despite prompt instigation of effective antibiotic therapy.[2]

Incidence rate of neonatal sepsis in developed countries ranged between 3-5 per 1,000 live births by CFR 10.3%. WHO (2007) reported the Case Fatality Rate (CFR) in the case of neonatal sepsis in the world is still high by 40%. Incidence rate of neonatal sepsis in Bangladesh in 2004 was 20-30 per 1,000 live births and CFR varies from 15-25%. [3] Neonatal sepsis is one of infectious diseases in newborns and it is a major problem that cannot be solved until today. In the last two decades, a remarkable progress has been shown on maternal and child deaths, but the neonatal health is a part of the 'unfinished agenda'. [2]

Definition: The term neonatal sepsis, refers to a clinical syndrome characterized by the blood stream infection of neonates and inflammatory response mounted by the neonate [1]

Classification

Based on the time of onset, neonatal sepsis has been traditionally classified as:

a. Early onset Neonatal sepsis (EOS), defined as onset of manifestations is within 72 hours of birth.

b. Late onset Neonatal sepsis (LOS) is defined as onset of manifestations after 72 hours of life.[1]

This classification helps in guiding the antibiotic therapy as it indicates the differences in the presumed mode of transmission and predominant organisms. EOS is mostly results due to vertical transmission of

organisms from mothers to infants during the antepartum and intrapartum period and LOS is attributed to the horizontal transmission of pathogens acquired during postnatal period from the hospital environment or from the community.[1] The organisms implicated in the development of neonatal sepsis vary from place to place.[1] Mortality rate in neonatal sepsis differs according to the type of organism involved. *Klebsiella spp*. and *Enterococcus spp* cause the highest mortality rate in neonatal sepsis. Spectrum of organisms which cause neonatal sepsis varies in different countries and sometimes changes from one center to another within the same country. Infections with multidrug-resistant organisms are also increasing in incidence.[4]

In India gram negative organisms predominate in both early and late onset sepsis. In the recently conducted DeNIS study, the most frequently isolated organisms among inborn cohort were Acinetobacter spp followed by Klebsiella. Among outborn cohort Klebsiella was the most common pathogen isolated. Fungal isolates were responsible for one -fourth of systemic infections.[1] This distinction based on age is of value in presumptive identification of predominant organism. Early-onset sepsis is acquired during fetal life, delivery, or at the nursery. Group B *Streptococcus*, *Escherichia coli*, or *Listeria monocytogenes* happen to be the most common organism. Late-onset sepsis is most commonly caused by coagulase negative Staphylococci (CONS), *Staphylococcus aureus, Escherichia coli, Klebsiella spp*, and *Pseudomonas aeruginosa* and is usually acquired in the neonatal intensive care unit (NICU) or the community.[4]

Blood culture should be done in all suspected cases before initiating antimicrobial therapy.[1] The volume of blood inoculated and amount of culture medium used for culture plays an important role in the yield of blood culture. Usually one-mL of blood should be inoculated for a blood culture bottle containing 5-10 mL of culture medium. Recently introduced BACTEC or BACT/ ALERT culture system can detect bacterial growth within 12-24 hours.[1]

The choice of antimicrobial drug for an infant with suspected sepsis depends upon the predominant pathogen and antibiotic sensitivity pattern of the given hospital and hence there cannot be a universal recommendation that can be used in all settings. The decision to initiate antibiotic therapy depends on the results of septic screen and the clinical findings present in the baby, the following the major indications for stating antibiotic therapy. [1] Indeed, strategies that can prevent and treat neonates with sepsis are essential to accelerate the progress of newborn survival. [2]

II. Aims and Objectives

The Aim of the present study are to determine the organism profile and to determine the proper antibiotic profile of our tertiary level Neonatal Intensive Care set up to diminish the incidence of the Neonatal sepsis.

III. Material and Methods

The study was conducted at the Microbiology Research Laboratory of Department of Neonatology in a tertiary care super specialty Hospital of Kolkata, West Bengal, India. It was a retrospective cross sectional study involving review of patients' laboratory records and files. Neonates were admitted in this department were being screened for clinically suspected Neonatal Sepsis and blood culture was done by automated blood culture system. Convenience selection of positive blood culture reports was employed. Neonates admitted between the periods 1st January 2017 to 31st December 2018 with reports showing bacterial growth from blood culture specimen were included. Growth of contaminants due to improper aseptic techniques during blood specimen collection was excluded and Blood culture was done by Automated Blood Culture system with BD BACTEC FX 40. The antibiotic susceptibility testing was done by Kirby Bauer method according to Standard CLSI guidelines.

IV. Results

During the study period 2188 blood samples from clinically suspected cases of neonatal septicaemia were obtained, out of which Blood culture was positive in 237 cases, positivity rate being 10.8 %. The most common organism amongst Gram positive isolates was *Staphylococcus aureus* and amongst Gram negative isolates *Klebsiella pneumoniae* (Table 1).

Table-1: Details result of Blood culture:

Details of Blood Culture	Results
Total blood culture done	2188
Blood culture positive	237 (10.8%)
Gram positive cocci (GPC)	81 (34.17%)
Gram negative bacilli (GNB)	156 (65.83%)
Candida	30

As illustrated in **Table-1** below there was a preponderance of gram negative organisms (n=156) 65.8% over gram positive organisms (n=81) 34.17%.

Candida was detected in 30 cases which are mostly out born babies and were not analyzed in this study. Speciation was not possible due to lack of infrastructure and all the Candida was isolated either from outborn babies or also with long term antibiotic therapy. Here the discussions were limited with the Gram negative and Gram positive organisms.

Table-2: Showing the details organism profile (n=237):

NAME OF ORGANISM	NUMBER OF ISOLATES	PERCENTAGE
CONS	52	21.94
COAG POS STAPH	60	25.32
KLEBSIELLA PNEUMONIAE	76	32
E COLI	17	7.17
ACINETOBACTER SP	15	6.33
PSEUDOMONAS AU	15	6.33
SERRATIA SP	2	0.84
TOTAL	237	100

Table-2 is showing the details organism profile isolated from blood culture. In details, in the predominance of GNB, Klebsiella pnemoniae (32%) was the principle organism followed by E.coli (7.17%), Acinetobacter (6.33%), Pseudomonas aeruginosa (6.33%) and also Serratia species (0.84%). In the Gram positive cocci population Coagulase Positive Staphylococcus aureus (25.32%) is the predominant organism. CoNS(Coagulase negative Staphylococcus) in our set up also contribute 21.94% of the blood culture positive sepsis.

Antibiotic susceptibility testing was done according to standard CLSI guidelines for the all isolates. Amongst the GNB, majority of the Klebsiella showed multidrug resistance or only sensitive to colistin, isolated till December 2017. Also other Gram negative Bacteria also showed multidrug resistance in the same manner. From Jan 2018 onwards the number of incidence of the multidrug resistance and only colistin sensitive bacteria were diminished, along with Klebsiella pneumoniae (only 18 % of the total isolates of 2018). The Staphylococcus aureus initially also shown multidrug resistance type isolated in the year 2017 (65% of the isolates of 2017), but later on it was diminished to 25% of the total isolates of 2018.

From our observation according to the antibiotic susceptibility pattern, as most of the Isolates in the early part of the study (2017), the Colistin was the only drug in most of the pan-resistant isolates amongst GNB. In case of GPC, mainly Staph. aureus, Vancomycin was the best solution. Later, we have taken some measures in infection control to diminish the nosocomial infection and cross infection, from the early part of 2018, the organisms both GNB and Staph aerues , were found sensitive to Piperacillin-Tazobactum and Amoxycillin-Clavulinic acid combinations respectively. Few percentages (23% of the 2018 isolates) of the GNBs were found to be sensitive to Meropenem and very rarely (2-3% of the 2018 isolates) we found pan-resistant or only Colistin sensitive. Sixty seven percent of the 2018 isolates of Staphylococcus aureus showed sensitive to Amoxy-Clav combinations and rest of the organisms were either linezolid (27%) sensitive. Very few of them are MRSAs and were Vancomycin sensitive. CONS were found to be sensitive to almost all antibiotics in our set up.

The second most common organism E.coli was 100% sensitive to Meropenem and Colistin. Sensitivity of 50% was seen with Amikacin, Gentamycin and only 33.33% to Netilmycin. These isolates were 100% resistant to Ofloxacin. About 13.88% of K. pneumoniae and E. coli were extended spectrum beta-lactamase (ESBL) producers. Pseudomonas and Acinetobacter isolates were 100% sensitive to piperacillin tazobactum and colistin, 75% sensitive to imipenem and 50% to meropenem. Most common gram positive isolate which was CONS, were highly (100%) sensitive to vancomycin and linezolid. 75% were sensitive to netilmycin and amikacin. 50% of CONS isolates were sensitive to meropenem and amoxyclav.

Fungal sepsis, mostly from the outborn neonates showed more or less uniform sensitivity pattern in which all were 100% sensitive to amphotericin-B, fluconazole, voriconazole and flucytosin. Figure 1 below illustrates most common sensitivity pattern of Gram negative isolates.

Table 3: Analysis of culture positive sepsis cases:

Characteristic	Value
LOS (%)	67.7%
EOS (%)	32.3%

The percentage of incidence of LOS was higher in the 2017 culture positive cases, but in the later part in 2018 it was diminished and the LOS and EOS were almost same. There was no statistically significant difference in antibiotic therapy between early onset sepsis and late onset sepsis.

V. Discussion

Despite of growing knowledge about adverse outcome associated with use of antimicrobials in neonates, Anti microbial agents (AMAs) are one of the most commonly used drugs in Neonatal Intensive Care Units. Antibiotic stewardship programme is the most important tool minimizes this problem.

Neonatal sepsis is a major cause of morbidity worldwide and one of the three primary causes of 2.7 million deaths every year. Over 600,000 of these deaths are attributed to infections alone (United nations) and 99% of these deaths take place in developing country settings. Among the 6.9 million neonatal sepsis burden, South Asia accounts for 3.5 million cases per year. India, with its 1.2 billion population, claims a large proportion of this disease burden.[5]

Infections are the single largest cause of neonatal deaths globally. *Klebsiella pneumoniae* and *Staphylococcus aureus* were the two most common organisms isolated.(3) In our set we have seen the similar picture. In the year 2017 we had observed a higher incidence of Nosocomial and cross infection many routes especially by hand to hand transmission. But from the January 2018, we had taken several surveillance in the Neonatal care unit to evaluate the route of transmission and measures taken by barrier nursing, proper hand wash, separate instrumentation for the each baby, which leads to diminished incidence of Neonatal sepsis for both EOS and LOS.

Clinical features of sepsis are nonspecific in neonates and a high index of suspicion is required for timely diagnosis. Although blood culture is the gold standard for the diagnosis of sepsis, culture reports would be available only after 48-72 hours.[6]

Gram-negative sepsis predominates with Klebsiella being the most frequent gram negative isolate and *S. aureus* the gram-positive one. Kuruvilla et al reported similar isolates in his study in 1998. [6] In the present study we had seen a similar organism profile.

For the effective management of neonatal septicaemia cases, study of the bacteriological profile with their antibiotic susceptibility pattern plays a significant role. High positivity rates were also reported by Ako Nai *et al* (55%), Shaw *et al* (54.64%), Tallur *et al* (64%) and Karthikeyan *et al* (51%).(5) Our study showed incidence of *Staphylococcus aureus* was 25.32%, whereas Gram negatives bacteria were 65.83, amongst them Klebsiella were the most predominant(32%) .

Hammerberg *et al* had stated that if the venepuncture site had been carefully cleansed the growth of CONS in blood culture of specimens of premature neonates indicated bacteremia rather than skin contaminations in vast majority of cases. This view is also shared by Favre *et al* who concluded their study reporting that CONS bacteremia harbor a significant mortality and a single positive blood culture in the presence of signs of sepsis should be considered as clinically relevant.[7] But in our study though we had isolated a great percentage of CONS (21.94) , but no mortality or morbidity were reported in the outcome.

Sepsis is one of the main causes of neonatal morbidity and mortality. Nosocomial sepsis frequency and microorganism profiles vary widely from center to center and from country to country. The frequency of infections in NICUs varies from 6% to 25% in the United States and from 8% to 10% in Europe. There has been a wide variation in the growth positivity in India; a higher isolation rate of 52.63% was reported by Murty *et al.,* probably due to a low sample size.[4]

Klebsiella pneumonia and *Staphylococcus aureus* were the predominant isolates. *Klebsiella* and *Staphylococcus aureus* can survive in the environment for a relatively long time and fairly widely distributed in the hospital environment, and therefore, have the potential for being transmitted from the environment to the patients through practices that breach infection control measures. This emphasizes the need for the establishment of effective and functional infection control programs in hospitals. The most significant finding of this study was almost 80% of the *Klebsiella* isolates were resistant to commonly used antibiotics, especially gentamicin and the second and third generation cephalosporins. Screening for ESBL showed most of the *Klebsiella* isolates to be extended spectrum betalactamase (ESBL) producers. Antibiotic sensitivity testing of gram-negative bacteria showed high resistance to multiple drugs while imipenem is still the best for infections with multidrug-resistant gram-negative organism. Gram-positive bacteria responded very well to vancomycin. This situation is serious as these are the last line antibiotics available with us. If we continue using these, resistance will obviously emerge against these as well. To prevent, we should stress more upon preventive measures, so that minimum of our neonates develop sepsis. These preventive measures should focus on recognition of high-risk infant, strict asepsis during labor.[4]

So, in our study after observing the whole data regarding the organism profile, we found Klebsiella pneuminiae as the main culprit in our set up, followed by E.coli, Pseudomonas and Acinetobacter. Amongst the Gram positive cocci , Staphylococcus aureus is the most common organism. Regarding antimicrobial profile we have decided a protocol as follows:

In case of Gram negative bacteria, first line antibiotics should be Piperacillin – Tazobactum combination with/without Netilmycin, second line drug should be Ofloxacin and for very emergency and in multidrug resistant cases Meropenem and lastly Colistin can be used rarely. In case of Staph. aureus

Amoxycillin-Clauvulinic acid is the first line of choice, followed by Linezolid as second line, Vancomycin in case of MRSA as third line of antibiotic and Colistin is used very limited cases at the end. This protocol helps us immense to reduce the incidence of Neonatal Sepsis in our setup, reflected in the reduced Blood culture positivity rate to 3-4% as a whole.

VI. Conclusion

Multi-drug-resistant organisms were isolated from septicemia in neonates. Therefore, great caution is required in selection of antibiotic therapy. Strict infection control in neonatal units, hand washing along with regular surveillance of neonatal sepsis is required in order to bring about changes in risk factors and antibiotic susceptibility patterns.[4] Prolonged and inadverant use of antimicrobials is associated with adverse outcomes. Majority of AMAs usage is empirical and was based on sensitivity pattern of local prevalent flora, clinical response. Most of the organisms isolated from culture proven sepsis were observed to be multidrug resistant. Most common regimen used was a combination of piperacillin -tazobactam with aminoglycoside usually netilmycin. Use of reserve drug like colistin had limited application. The areas where unnecessary and prolonged use of AMAs can be reduced are the cases where sepsis has been ruled out and culture is negative at 48 hours. Timely de-escalation or discontinuation of antimicrobials in such cases may be considered which is one of the most important goal of antimicrobial stewardship programme. Antibiotic policy for each hospital should be framed and continuous prospective surveillance should be done. In the hospitals where such surveillance is not feasible, prospective audit and feedback may be one of the useful interventions for antibiotic stewardship programme in Neonatal Intensive care settings.

Contribution of the Authors:
RB: Compilation, PC: Compilation, editing and data analysis.

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