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Original Article

Paediatrics Section

Drug Utilization Pattern of Antimicrobials in Neonatal Sepsis in a Tertiary Care Teaching Hospital, India

NARENDRA BEHERA, JAYANTI PRAVA BEHERA

ABSTRACT

Introduction: Neonatal sepsis is a major cause of neonatal mortality and treated with antibiotics. The antibiotic susceptibility pattern varies from place to place at any point of time. Antimicrobial resistance, a burning problem globally, is due to irrational use of antibiotics. Drug utilization study is a strong tool for evaluating rational use of antibiotics.

Aim: To evaluate the antimicrobial use pattern, to identify problems associated with rational drug utilization and to know the clinical outcomes of neonates under treatment with various antimicrobial regimens in neonatal sepsis. Also to suggest any steps can be taken for possible improvement in rational antimicrobials use in this condition.

Materials and Methods: This was a descriptive observational study conducted from June, 2015 to September, 2016 in a Tertiary Care Teaching Hospital, Odisha, India. The consecutive neonatal sepsis cases, admitted to SNCU, Paediatrics Department, were included. The protocol was approved by IEC and written informed consents were obtained from the parents/guardians prior to the study. Total 204 diagnosed, screen positive neonatal sepsis cases of 0 -28 weeks old and both the sexes were enrolled. Demographic data like age, sex, place of delivery, gestational age and birth weight and antibiotic use data as per WHO guide line for drug utilization study were recorded in a case record form. The categorical data were expressed in percentage and mortality data was analyzed using GraphPad Prism ver.0.7 by Chi square test and $p<0.05$ was considered as significant.

Results: EONS (Early Onset of Neonatal Sepsis) was more than LONS (Late Onset of Neonatal Sepsis). Neonatal sepsis predominantly affected male babies. Preterm, LBW (Low Birth Weight), home delivery and NVD (Normal Vaginal Delivery) cases were more associated this condition. All of them received empirical antibiotics such as ampicillin/cefotaxime combined with amikacin/gentamicin from EDL (Essential Drug List) and prescribed almost rationally. Though cure rate was good, the death percentage was quite alarming.

Conclusion: The empirical antibiotics were given to all cases of neonatal sepsis, selected from EDL. Though, in this study group the antibiotic use pattern found rational, death rate was still high. So further study regarding risk factors associated and awareness about preventive measures will be required.

Keywords: Antimicrobial resistance, Empiric antibiotics therapy, Preterm babies, Susceptibility pattern

INTRODUCTION

Neonatal sepsis is a clinical syndrome presented with symptoms of infection that may or may not associated with bacteraemia during the first month of life. It includes different systemic infections like septicaemia, menigitis, pneumonia, arthritis and urinary tract infections [1]. In this condition blood infection occurs with neonates below 90 days old. EONS occurs within first week of life whereas LONS occurs after 1st week and prior to 3rd month of life [2]. It was estimated about four million neonatal deaths occurs globally each year and more than one third of which contributed by severe infection. A quarter (around 1 million) deaths were caused only by neonatal sepsis or pneumonia [3]. About 45% of deaths among children under five were newborns in 2015 [4]. The two categories of neonatal sepsis like EONS and LONS comprises of 85% and 5% respectively [5].

The mortality due to neonatal sepsis can be preventable by early diagnosis and using antimicrobial agent rationally. In addition aggressive supportive care is necessary [1].

As per the WHO definition,drug utilization is “The marketing, distribution, prescription and use of the drug in a society, with special emphasis on the resulting medical, social and economic consequences”. Very less information is available regarding the extent and pattern of antibiotic drug use in perinatal period. In practice, the antimicrobials selected for a particular condition basing on local antimicrobial use policy. The duration of therapy is decided on the culture sensitivity report and clinical symptoms

by the treating physician [6]. Normally, antimicrobial treatment for a case of sepsis is predicted with general principles for appropriate use of drugs and information gathered from other populations instead of evidence based therapy for the specific individual [7]. There is no appropriate universally accepted guide line for empiric use of antimicrobials presently for management of sepsis [5,8]. Sepsis screening tests are done to decide whether healthy looking neonate of high risk group do not need AMAs or antimicrobial treatment discontinued safely [9]. Neonates are vulnerable to adverse consequences of drug use due to their immature organ system. So the cares to be taken to use the drugs as minimum number as possible [7]. Studies reported the unnecessary, injudicious, or excessive use of antibiotics, led to antibiotics resistance, which is a major public health concern globally. Some studies have demonstrated that resistance is directly associated with selection and use of inappropriate antimicrobials [9]. Improved guidelines for antibiotic treatment in sepsis neonatorum from institutional aetiology and microbial sensitivity should be encouraged.

MATERIALS AND METHODS

This descriptive observational study was carried out in SNCU of Paediatric Department of MKCG MCH, Berhampur, Odisha, India, from June 2015 to September 2016. This protocol was approved by of the Institutional Ethics Committee.

Inclusion Criteria: Diagnosed cases of neonatal sepsis as per the IMNCI criteria, screen positive cases, new born with 0-28 days of age group, both female and male sexes were included in this study.

Exclusion Criteria: The parents/guardians of the neonate who did not give their written consent in an inform consent form were excluded. The patients more than 28 days old, did not satisfy sepsis screening, of AIDS infected mother, healthy baby, septicaemia due to viral or fungal infection, congenital abnormality, physiological jaundice, premature baby without sepsis, hypoxic ischemic encephalopathy and metabolic disorders without sepsis were not included in this study.

Study Procedure: Total 204 sepsis screen positive cases were enrolled in this study. Written informed consent was obtained from the parents/guardians. Data were collected in a predesigned case record form, from hospital record like serial number, age, sex, birth weight, gestational age, antibiotics used were recorded. In culture positive cases causative microorganism isolated also noted. The antimicrobials use data such as selection of drug, dosage form and route of administration, duration were collected as per WHO guide line for drug utilization study.The patients were followed-up daily during the hospital stay to collect the data about change in antibiotic and also about outcomes in terms of cured, LAMA (Leave Against Medical Advice) or died.

STATISTICAL ANALYSIS

The categorical data were expressed in percentages and some data analysed by Chi-square tested by GraphPad Prism version.7.

RESULTS

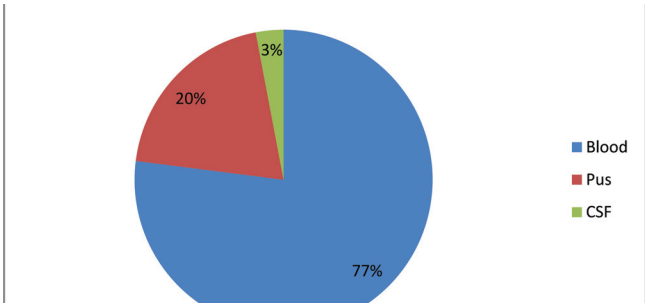
In this study population, the occurrence of EONS was more common (62%) than LONS. Higher male prevalence (73.5%) was found compared to that of females. Home delivery (61%) and NVD (79%) were more prone to neonatal sepsis than that of institutional delivery and caesarean section respectively. Preterm (74.5%) and LBW (63%) babies were more associated with neonatal sepsis [Table/Fig-1]. Blood culture was positive in 77% of cases out of total 157 culture positive cases [Table/Fig-2].

Staphylococcus aureus (49%) was the commonest microorganism isolated among different cultures followed by *Klebsiella pneumonia* (27%), *E.coli* (11%) in EONS cases. Whereas, in less number of cases, microorganisms like *Streptococcus pneumonia* (3%), *Enterococcus* (5%), *Proteus* (3%) and *Pseudomonas* (2%) were involved in this condition. [Table/Fig-3a]. As it was observed in [Table/Fig-3b] *E.coli* (32%) leads the list of organisms causing LONS followed by *Staphylococcus aureus* (28%), *Klebsiella pneumonia* (22%), *Enterococcus* (9%), *Pseudomonas* (3%), *Proteus* (5%) and *Staphylococcus epidermidis* (1%).

Ampicillin + amikacin/gentamicin were the preferred choices for empirical antibiotic therapy both in EONS (46%) and LONS (58%). The other commonly use antibiotic regimen was cefotaxime+gentamicim/amikacin i.e., 33%) and 28% in EONS and LONS respectively. Three antibiotics combination like cefotaxime + ampicillin + gentamicin/amikacin, used only in 25% of cases of EONS and 14% of LONS, which was reserved for

Type of Sepsis	No. of Cases	% of Cases
Early onset sepsis	126	62
Late onset sepsis	78	38
Male	150	73.5
Female	54	26.5
Institutional	80	39
Home	124	61
Normal Vaginal	161	79
Caesarean Section	33	16
Preterm	152	74.5
Term	52	25.5
LBW	128	63
Normal Body Weight	76	37

[Table/Fig-1]: Demographic characteristics of Neonatal Sepsis. (n = 204), data expressed in number and percentage



[Table/Fig-2]: Distribution of culture positive cases in neonatal sepsis.
(n=157), data expressed in percentage

Type of Microorganism	No. of Cases	% of Cases
Staphylococcus aureus	62	49
Klebsiella pneumonia	34	27
E.coli	14	11
Enterococcus	6	5
Proteus	4	3
Streptococcus pneumoniae	4	3
Pseudomonas aerogenosa	2	1.5

[Table/Fig-3a]: Microorganism isolated from different culture in early onset sepsis (n=126).

Microorganisms	No. of Cases	% of Cases
Staphylococcus aureus	22	28
Klebsiella pneumonia	17	22
E.coli	25	32
Enterococcus	7	9
Proteus	4	5
Pseudomonas	2	3
Staphylococcus epidermidis	1	1

[Table/Fig-3b]: Microorganisms causing late onset sepsis (n=78).

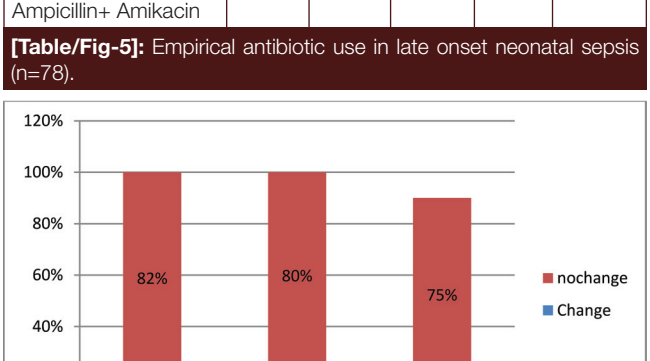
some specific conditions like meningitis. The antibiotics were used intravenously in all cases and prescribed from EDL without a single in generic name [Table/Fig-4,5]. Antibiotics which were used empirically, changed to pipperacillin + tazobactum with amikacin or three drug regimen like cefotaxime + ampicillin + amikacin/ gentamicin or vancomycin + amikacinin few instances as per the finding of culture sensitivity report. It was observed only with 20% of cases of EONS and 15% cases of LONS [Table/Fig-6]. Rest of the patients continued as prescribed before even if culture sensitivity was different. The antibiotic prescribed per prescription were either 2 or 3 /or 4 in all cases of EONS and LONS empirically. Their average number of antibiotics per encounter was 2.4 in both EONS and LONS [Table/Fig-7]. There was significantly more cured percentage in both EONS (68%) and LONS (80%) individually. But death percentage was significantly more associated with EONS (20%) compared with LONS i.e., 10 % [Table/Fig-8].

Antibiotics	No. of Cases	% of Cases	IV Route	EDL	Generic Name
Ampicillin + Amikacin/ Gentamicin	58	46	100%	100%	0%
Cefotaxime + Gentamicin/Amikacin	41	33	100%	100%	0%
Cefotaxime + Ampicillin+ Amikacin/ Gentamicin	27	25	100%	100%	0%

[Table/Fig-4]: Empirical antibiotic used in early onset neonatal sepsis (n=126).

Antibiotic	No. of Cases	% of Cases	I V Route	EDL	Generic Name
Ampicillin + Amikacin/ Gentamicin	45	58	100%	100%	0%
Cefotaxime + Gentamicin/ Amikacin	22	28	100%	100%	0%
Cefotaxime + Ampicillin+ Amikacin	11	14	100%	100%	0%

[Table/Fig-5]: Empirical antibiotic use in late onset neonatal sepsis (n=78).



[Table/Fig-6]: Change in antibiotic on culture and sensitivity report.

DISCUSSION

Incidence of early onset neonatal sepsis cases were more than late onset type of neonatal sepsis but not statistically different. Our finding corroborates with other study conducted in a Tertiary Care Hospital of Tanzania [10].

Male preponderance over female babies found in this study, was in accordance with the other similar type of studies [11-13]. The majority of neonatal sepsis cases were home deliveries in comparison to institutional delivery. This result corroborates with the finding of Gogia et al., [14]. Normal vaginal delivery cases were more associated with neonatal sepsis in comparison to caesarean section deliveries. Similar result found by other study from Raipur, India [15]. Many researchers had postulated that maternal genital tract as the source of infection in neonatal sepsis especially EONS [16]. Preterm babies were more affected by neonatal sepsisin comparison with term babies [1]. This observation may be due to low immunity of preterm babies.

No. of Antibiotics	EONS (n=126)		LONS (n=78)	
	No. of Encounters	%	No. of Encounters	%
2	84	67	44	56
3	26	20.5	31	40
4	16	12.5	3	4
Average	2.4		2.4	

[Table/Fig-7]: The number of antibiotics prescribed per encounter.

Outcome	EONS (n=126)	LONS (n=78)
Cured and discharged	68%†	80%†
Deteriorated/LAMA	12%	10%
Died	20% ‡	10%

[Table/Fig-8]: Treatment outcome of neonatal sepsis cases.
N=204, LAMA (Leave against medical advice), Chi –square test, † indicates p <0.05 (Cured Vs Deteriorated/LAMA and Died), ‡ indicates p <0.05 (Died EONS Vs Died LONS)

Newborns with low birth weight were more associated with neonatal sepsis than normal birth weight which corroborates with the findings [6]. Another Indian study reported that LBW is significantly associated with neonatal death [17].

As a method to ascertain infection and to isolate the causative organism, blood culture was performed in all cases as a routine investigation. This practise is in tune with the AIIMS-NICU protocol 2014 [1].The samples sent for culture were blood, pus,and CSF as per clinical signs and symptoms. In this study blood samples exhibited bacterial growth in higher percentage of cases i.e., 77 % cases than that of pus and CSF culture [18]. The causative organisms in EONS were *Staphylococcus aureus* (49%), *Klebsiella pneumonia* (27%), *E.coli* (11%) followed by *Enterococcus, Proteus*, *Streptococcus pneumonia* and *Pseudomonas* in this present study [19]. This result differs from other study report that *Klebsiella pneumonia* is predominant microorganism followed by *E.coli* and *Pseudomonas* [20]. In case of LONS also the predominant etiological agents were *E.coli* (32%), *Staphylococcus aureus* (28%), *Klebsiella pneumonia* (22%) [21]. The incidence of infections due to *E.coli* was higher than EONS. *Pseudomonas* and *Staphylococcus epidermidis* were isolated in few cases which indicates towards hospital acquired infection.

In view of the fact that neonatal sepsis has a rapid progression and high mortality rate due to severe systemic infections like meningitis and pneumonia, empiric antimicrobial therapy was initiated immediately after hospitalization. Ampicillin + aminoglycoside i.e., amikacin or gentamicin was the preferred combination for empirical antibiotic therapy both in EONS and LONS. Cephalosporin's like cefotaxime with an aminoglycoside was the second most preferred antimicrobial combination in both type of cases. Three drug regimens of cefotaxime + Ampicillin + aminoglycoside was opted only in few number of cases in this study. The choice of third generation cephalosporin to include in drug regimen may be because of their lack of dose related toxicity and their ability to reach adequate serum and CSF concentrations [6]. Cloxacillin was given only in small number of late onset sepsis cases, possibly due to signs suggesting staphylococcal infection. The empirical antibiotics were selected, was similar with the practice by AIIMS-NICU protocol for the management of sepsis in Newborn 2014 [1]. All the antibiotics were given intravenously and chosen from EDL for Children, Government of Odisha. No antibiotics prescribed in generic name.

In this study, upon arrival of culture and sensitivity reports, a decision was made on the course of antibiotics i.e., whether to continue with the ongoing regimen (because of improving patient condition) or to opt for a regimen as suggested by the sensitivity report. There was a change in the antimicrobial regimen in 18% cases only including both EONS and LONS. In some cases ampicillin was replaced by reserve antibiotics like piperacillin with tazobactum when it was not responding. The problem of resistance was even bigger in cases of LONS which were mostly hospital acquired infections. Here, in this study it was found that there was development of resistance to most of the first line drug like ampicillin, cefotaxime, ceftriaxone and cloxacillin. In cases of resistance amikacin/gentamicin were replaced by netilmicin and in few cases ampicillin was replaced by vancomycin.

It was found that in maximum cases, 2-3 antibiotics prescribed per prescription. Our study showed lesser number of antibiotics prescribed per prescription in comparison to other studies [22,23]. More percentage of cases significantly cured in comparison to LAMA and death with medical management in both the types of neonatal sepsis individually. But the death percentage was significantly higher with EONS than LONS [24] among all cases of neonatal sepsis of this study.

LIMITATION

The data were not compared between the inborn and outborn cases. This is a short term study with small sample size. It can be suggested large term study with large sample size can produce better information in this regard.

CONCLUSION

To sum up, all though this study had a small sample size it gave us an overall pattern of antimicrobial drug use profile in patients of neonatal sepsis in a Tertiary Care SNCU. This study also intended to be a step in the broader evaluation of safety and efficacy of drug prescription in SNCU. Neonates are a very vulnerable group due to immaturity of their body functions and great care needs to be taken to use the minimum number of drugs. Data reported in this study about microbiological profile of this population and utilization pattern of antibiotics for neonatal sepsis cases will be helpful in establishing priority

agendas for future drug studies. Rational use of antibiotic prevents antimicrobial resistance. Though, it was found in this study, antibiotic utilization pattern as per the guide line made by other population, in this centre there is no standard treatment guide line of its own as per the local microbiological profile. Neonatal drug utilization is a dynamic process and the reported use of drugs changes periodically. Our report can enable the treating physicians to encourage for creating specific priorities for developing an antibiotic use guideline for specifically neonates which is the most vulnerable population.

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AUTHOR(S):

1. Dr. Narendra Behera
2. Dr. Jayanti Prava Behera

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Paediatrics, MKCG Medical College, Berhampur, Odisha, India.
2. Associate Professor, Department of Pharmacology, MKCG Medical College, Berhampur, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE

CORRESPONDING AUTHOR:

Dr. Jayanti Prava Behera,
Associate Professor, Department of Pharmacology,
Or No. 4R/11, MKCG Medical College Campus,
Berhampur-760004, Odisha, India.
E-mail: pravabeherajayanti@yahoo.co.in
naribehera@yahoo.co.in

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