

Original Article

**PATTERN OF ANTIBIOTICS UTILIZATION IN NEONATAL SEPTICEMIA: A CROSS-SECTIONAL STUDY FROM RURAL TERTIARY CARE HOSPITAL WESTERN MAHARASHTRA, INDIA**

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**ABSTRACT**

**Objective:** To assess the quantification of use of antibiotics and to find out empiric antibiotic regimen practiced for neonatal sepsis in rural tertiary health care centre.

**Methods:** A hospital, record based cross-sectional study was conducted in Neonatal Intensive Care Unit (NICU) at tertiary care hospital located in western Maharashtra, India. The study was planned during the year 2011-12 among 84 neonates with sepsis. Data were collected by using proforma includes demographic details, antibiotic prescriptions and relevant information.

**Results:** Among the total 84 neonates, max, 60.71% had a history of term delivery. The proportion of early and late onset of sepsis was 47.61% and 52.38% for which total 18 antibiotics were used of which max, 88.88% were injectables. Amikacin was used in max, 78.57% neonates followed by cefotaxime, 45.23% and ampicillin, 35.71% in single or combination form respectively. Amikacin was used for max; 929 d followed by cefotaxime, 523 d and ampicillin 331 d respectively. Antibiotics used in single, double and multiple regimens were 19.04%, 46.42% and 34.52% respectively. Empiric antibiotic regimens practiced were cefotaxim+amikacin and cefotaxim+ampicillin, of which max, 80% patients were treated with the cefotaxim+amikacin antibiotic regimen. Out of 84 neonates max, 70% were improved at the time of discharge.

**Conclusion:** Neonatal sepsis was well treated by cefotaxim+amikacin empirical injectable regimen with maximum survival.

**Keywords:** Antibiotic quantification, Empiric antibiotic regimen, Neonates, Sepsis

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**INTRODUCTION**

Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteraemia in the first month of life [1]. It is responsible for about 30-50% of the total neonatal deaths in developing countries and leading causes of neonatal mortality in India [2]. Neonatal sepsis is classified according to the time of onset of the disease as early onset of sepsis (EOS) and late onset of sepsis (LOS). EOS is defined as onset of sepsis in the first three days and is mostly the result of vertical transmission of bacteria from mothers to infants during the intrapartum period. LOS is defined as an infection occurring after 1 w of life is attributed to horizontal transmission of pathogens acquired post-natal (nosocomial or community) [3].

Organisms causing neonatal sepsis in developing countries are klebsiella, e. coli, pseudomonas, salmonella belonged to the gram-negative bacterial group, whereas staphylococcus aureus, coagulase-negative staphylococci are belonged to the gram-positive bacterial group [4, 5]. Since sepsis is a systemic inflammatory response to infection, isolation of bacteria from blood is considered the gold standard for the diagnosis of sepsis [6]. However, it takes 24 to 48 h for culture results. Therefore, non-culture-dependent methods need to be found out.

Repeated and prolonged courses of antibiotics exposure have resulted in an increase in the prevalence of hospital acquired, antibiotic resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin resistant enterococcus, etc [7]. Similarly, drug toxicity and cost of treatment is another issue raised especially when the patient is in NICU management. Evaluation of antibiotic use is, therefore, important since the prevalence of hospital-acquired antibiotic resistance in organisms is increasing in neonates [8]. The aim of present study was to assess the quantification of use of antibiotics and to find out empiric antibiotic regimen practiced for neonatal sepsis in rural tertiary health care centre.

**MATERIALS AND METHODS**

After obtaining permission from the Institutional Ethics Committee; Ref. No. KIMSDU/IEC/09/2011, the study was carried out in the NICU of Krishna Hospital and Medical Research Centre, a tertiary care hospital located in western Maharashtra, India. It was a retrospective, record-based type of epidemiological study. It includes assessment of case records of neonates admitted in paediatric NICU department and diagnosed with sepsis. A total of 84 neonates with a diagnosis of septicemia admitted and treated in NICU during a year of 1<sup>st</sup> Oct. 2011 to 30<sup>th</sup> Sept. 2012 were included and their records (case papers) viewed in the study.

**Inclusion criteria**

Neonates diagnosed as sepsis by the clinicians and admitted during our study period 1<sup>st</sup> Oct.2011 to 30<sup>th</sup> Sept 2012.

**Exclusion criteria**

Neonates who were discharged or transferred to other ward or hospital or died within 2 d of NICU stay were excluded from the study.

**Data collection**

The data were collected by investigator in NICU, Department of Pediatrics, according to pre-tested structured proforma from the case records of study subjects on the following variables;

Date of birth, weight at birth, gestational age, sex, diagnosis, outcome, and all antibiotic prescriptions (name, dose, frequency, and route of administration) were retrospectively recorded. Neonates were classified into the age of gestation in weeks at the time of birth. Once neonates have been discharged or transferred to other ward or hospital, no further data was collected. We did not get any data regarding drugs given to the mother.

**Statistical analysis**

Data so collected were entered into MS Excel 2007 and analyzed for descriptive statistics, frequency percentage and presented in the tabular and graphical form.

**RESULTS**

Total 84 neonates were enrolled in the study of which max, 60.71% delivered with full term pregnancy and 69.04% by normal vaginally.

The Mean (SD) weight (Kg.) and hospital stay (days) of neonates were 2.003±0.62 kg and 7.8±7.24 d respectively. The proportion of male patients was higher 71.42% than females (table 1).

Clinical presentation with which the neonates were presented to the hospital showed variation; we tabulated those complaints in table 2. Max, 25% neonates were admitted each for intrauterine growth retardation care (IUGR) and refusal to feed followed by fever 20.23%.

**Table 1: Demographic characteristics of neonates**

Study variables	Frequency (%)
Gestational age (weeks)	Preterm ( $\leq 37$ wks):33(39.28%) Full term ( $\geq 37$ wks): 51(60.71%)
Mode of delivery	Normal: 58 (69.04%) Cesarean: 26 (30.96%)
Weight (kg)	Minimum: 0.97 Maximum: 3.40 mean±SD: 2.003±0.6284
Hospital stay (days)	Minimum: 1 Maximum: 38 mean±SD: 7.8928±7.24
Gender	Male-60 (71.42%) Female-24 (28.58%)

**Table 2: Clinical presentation of neonates in frequency percentage**

Clinical presentation	Frequency (%)
Intra-uterine growth retardation care (IUGR)	21(25%)
Refusal to feed	21(25%)
Fever	17(20.23%)
Respiratory distress	7(8.33%)
Yellowish discoloration (skin, sclera and urine)	8(9.52%)
Convulsion	4(4.76%)
Vomiting/Abd. distension	4(4.76%)
Not passing stools	2(2.38%)

A total of 18 antibiotics were used to treat neonatal sepsis for 84 patients during the study period. Cefotaxime and amikacin were the most commonly prescribed antibiotics (80%), followed by cefotaxime

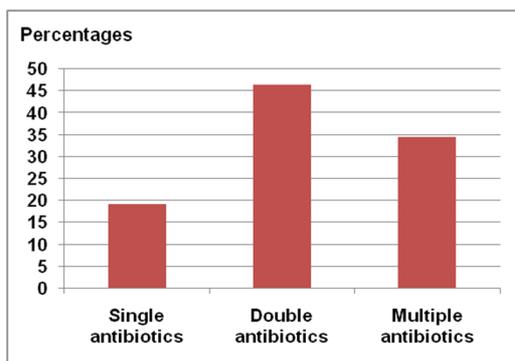
and ampicillin. Other antibiotics used and their frequency of use, the total number of antibiotic days and average no of antibiotic use are mentioned in table 3.

**Table 3: Profile of antibiotics used in neonatal sepsis**

Name of antibiotic	Frequency (%) use of antibiotics	Total days of antibiotics	Average antibiotic days per neonate
Amikacin	66 (78.57%)	929	14.07
Cefotaxime	38(45.23%)	523	13.76
Ampicillin	30(35.71%)	331	11.03
Cefoperazone+sulbactam	7(8.33%)	229	32.71
Vancomycin	16(19.04%)	189	11.81
Metronidazole	20(23.80%)	156	7.8
Ceftriaxone	12(14.28%)	105	8.75
Ceftazidime	10(11.90%)	80	8
Meropenam	5(5.95%)	76	15.2
Ofloxacin	8(9.52%)	57	7.12
Tobramycin eye drops	3(3.57%)	12	4
Crystalline Penicillin	3(3.57%)	9	3
Gentamicin	5(5.95%)	6	1.2
Cotrimoxazole	1(1.90%)	5	5
Mupirocin	1(1.90%)	5	5
Clavulanic acid	2(2.38%)	4	2
Linezolid	1(1.90%)	3	3
Gatifloxacin eye drops	1(1.90%)	1	1

Amikacin is showing highest frequency of use, i.e. 78.57% in neonatal sepsis followed by cefotaxime, 45.23% and ampicillin, 35.71% respectively. Amikacin was used for maximum, 929 d followed by cefotaxime, 523 d and ampicillin 331days respectively. Average days of antibiotic used were higher with cefoperazone and

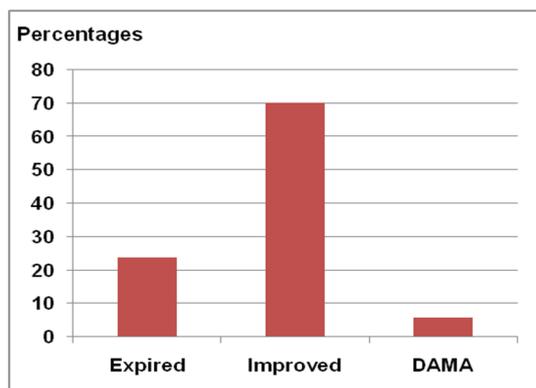
sulbactam combination 32.71 d followed by meropenam 15.2 d and amikacin 14.07 d. Cefotaxim with amikacin is the commonest antibiotic regimen used for the empirical purpose. The 12.5% of antibiotics are prescribed in the form of fixed dose combinations (sulfamethoxazole+trimethoprim, cefoperazone+sulbactam).



**Fig. 1: Antibiotics regimen practiced for treatment of neonatal sepsis**

Fig. 1 depicts, the single antibiotic regimen was received by 16(19.04%) neonates, two antibiotics were received by 39(46.42%) neonates and more than two antibiotics/multiple antibiotics regimen were received by 29(34.52%) neonates respectively.

According to the data available on the condition of patients at the time of discharge, they are divided into improved (70%), expired (25%) and Discharge against Medical Advice (DAMA) (5%) as shown in fig. 2.



**Fig. 2: Treatment outcome of neonatal septicemia**

## DISCUSSION

The present study revealed, among total 84 neonates admitted with sepsis max, proportions of neonates were full term 60.71% and males 71.42% by gender. A hospital-based study done at Rawalpindi enrolled 104 infants out of which 50% were full term infants [9]. The differences in results could be due to the quality of ante-natal health care services provided in India. A study conducted in Malaysia included 121 neonates with 58% males which were less than present study could be due to male preference or gender discrimination in India. Mean birth wt. in our study was 2.003±0.62 Kg. whereas, it was 2.75±0.63 kg in Malaysian study [10]. This difference in mean birth wt. might be because of the prevalence of maternal malnutrition in rural India.

The study described common presenting complaints were IUGR care (25%), refusal to feed (25%) and fever (20.43%) whereas, according to Malaysian study, respiratory distress was main problem (18.2%) followed by none(12.39%)and jaundice(10.7%) [10]. Another study reported respiratory distress (100%) followed by abdominal distension (71.42%) and signs of pneumonia (28.57%) of neonatal sepsis [11]. Unusual presentation of generalised neonatal seizures was seen in a study [12]. These complaints were different than ours. The proportion of early and late onset of sepsis was, 47.61% and 52.38% respectively. Total 18 antibiotics were used of which, 88.88% were injectables. The Amikacin was used in, 78.57 % neonates followed by cefotaxime, 45.23% and ampicillin, 35.71% respectively. On an average, cefoperazone with sulbactam was used

for 32 d followed by meropenam 15 d and amikacin 14 d respectively. Prolonged duration of antibiotic therapy (≥5days) was associated with necrotising enterocolitis (NEC) or death. Each additional day of antibiotic therapy was associated with 4% increase in odds of NEC or death [13]. Antibiotic use in the form of single, double and more than double regimen was received by 19.04%, 46.42% and 34.52% respectively. Most commonly used an antibiotic in our study was amikacin (78.57%). It is a drug with very narrow therapeutic range and can cause side effects, such as nephrotoxicity and ototoxicity if 'trough blood level' in excess go uncorrected [14]. The toxicity is increased if amikacin is prescribed for more than 10 d and when two or more aminoglycosides are prescribed together [15]. In our study, dose interval for amikacin was 12 h for all neonates, means in a day two doses are needed. In a study, where once vs. multiple daily dosing was studied in Saudi showed that once-daily dosing is preferred over multiple in efficacy, nephrotoxicity and less need of therapeutic drug monitoring [16]. Another study recommended a new dosing regimen, 15 mg/kg at 36 hr intervals, 14 mg/kg at 24 hr intervals for and 15 mg/kg at 24 hr intervals for neonates ≤ 28weeks, 29-36 w and ≥37weeks postmenstrual age [17]. These findings differ from ours as in our study dosing interval was fixed i.e. 12 H but doses where 20, 15 and 10 mg/kg respectively.

In our study vancomycin was used in (19.04%) neonates. Data shows that therapeutic drug monitoring of vancomycin is highly recommended as it is potentially nephrotoxic. It also ensures efficacy and avoids resistance [18, 19]. A study conducted in Karachi recommended vancomycin+amikacin or carbapenem as the drug of choice for empirical antibiotic regimen treatment of neonatal sepsis [20]. Approximately, 14.28% low birth weight neonates (Weight ≤ 1.5 kg) received third generation Cephalosporins with 39% mortality in among them. It is reported in previously published studies that use of third generation cephalosporins increases the risk of invasive candidiasis and death in low birth weight neonates (weight ≤1.5 kg) [21, 22]. Studies also suggest that third-generation cephalosporins are not more effective in treating sepsis than benzylpenicillin and gentamicin [23]. Previous studies recommended cephalosporins to be used as second line drugs [24]. However in our study cephalosporins were first line drugs whereas benzylpenicillin was not used and gentamicin was used in 5.95% neonates. The study reported, 70% neonates with sepsis were improved, and 25% expired. Malaysian study reported higher improvement rate 88.4% and mortality 3.3% [10]. The difference in results could be the use of intrapartum antibiotic prophylaxis, use of antiseptic to disinfect the birth canal, implementation of hand washing, promotion of clean deliveries, well-equipped health care facilities in Malaysian hospitals. Most suspected early onset sepsis neonates with negative blood cultures were given antibiotics, discontinuing empiric antibiotics when blood cultures are negative in neonates can reduce antimicrobial exposure without compromising clinical outcome. Rational prescribing of antibiotics for empirically use should be encouraged so the development of antibiotic resistance can be prevented and cost of treatment will also get minimised [15, 25-27].

## CONCLUSION

Neonatal sepsis would be well managed by Cefotaxim+ Amikacin/ Cefotaxime and Ampicillin antibiotic empirical regimen in neonates with birth weight>1.5 kg. Survival rate would be increased if newborn birth weight increases to normal birth weight. Rational use of antibiotics, avoid development of new drug-resistant strains. Establishment of drug counselling centre to avoid mis-use of any antibiotics. Establishment of hospital infection control committee to avoid hospital acquired infections.

## Limitations

Short duration of study, limited sample size and single study unit

## CONFLICT OF INTERESTS

Declared none

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