

Antibiotic Prescribing Pattern in a Tertiary Level Neonatal Intensive Care Unit

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ABSTRACT

Introduction: Neonatal sepsis is a major cause of morbidity and mortality worldwide especially in developing countries, which justifies early diagnosis and prompt treatment with antibiotics. Antibiotics are the most frequently used medicines in Neonatal Intensive care units. Data regarding rational antibiotic use in neonates is very limited. Hence, it is essential that the antibiotic prescribing patterns be evaluated periodically for its rational use. Therefore, the present study been carried out to identify the prescribing patterns of antibiotics in neonatal intensive care unit of a tertiary care hospital, Western Maharashtra, India.

Materials and Methods: A prospective observational study was carried out for 6 months between April to September 2014. The data regarding patient demographics and antibiotic use was collected daily in a structured proforma. Collected data was subjected to statistical analysis.

Results: Out of total 528 neonates with male preponderance (62%), 370 received antibiotics. Mean gestational age and

birth weight were 35±3.2 weeks and 2±0.7 kg respectively. Mean length of hospital stay was 14.26±15.36 days (range 1 to 136 days). A total of 1123 antibiotics were prescribed to 370 neonates. The majority of neonates (55.9%) received between 1-2 antibiotics, 37.3% had 3 to 5 antibiotics prescribed, while 6.7% neonates were prescribed more than 5 antibiotics. Number of antibiotics used had statistically significant inverse relationship with gestational age. Among antibiotics; Amikacin, Cefotaxime and Levofloxacin were the drugs most often prescribed. Amikacin and Cefotaxime were given more to term infants whereas other antibiotics like Levofloxacin, Piperacillin-tazobactam and Meropenem were prescribed more to preterm and outborn neonates.

Conclusion : The use of a high number of antibiotics is a common practice. Although the indications for use of most antibiotics could be justified, the increased frequency of antibiotics use in some neonates was of concern. Guidelines for the use of antibiotics in neonates are required and larger studies are needed on this issue.

Keywords: Antibiotic usage, Neonatal sepsis, Resistance

INTRODUCTION

Antibiotics are the key drugs for treatment of infections and are among the most commonly prescribed drugs in neonatal intensive care unit (NICU) [1]. Worldwide population consists of about 28% children and infants who are most susceptible to infective diseases due to under developed immune system [2]. Several studies have reported that 50%-85% of children receive antibiotics prescribed by physicians [3]. In addition, neonates are among the most vulnerable population groups to contract infections [4] and are also prone to harmful effects of drugs due to differences in pharmacodynamic and pharmacokinetic characteristics [5].

The use of antimicrobial agents, especially antibiotics has become a routine practice for the treatment of neonatal illnesses [6]. Antibiotic guidelines are standard set of guidelines for the treatment of infectious diseases based on local culture sensitivity data. These guidelines help the physician to prescribe the antibiotics rationally to paediatric patients when definitely indicated (WHO model formulary for children, 2010) [7]. In spite of these, neonates are at high risk for opportunistic or nosocomial infections due to prolonged hospitalization and immunosuppressed condition [8]. An overall rise in health care costs, lack of uniformity in drug prescribing and the emergence of antibiotic resistance, are issues of monitoring and control of antibiotic use is of growing concern [9].

Thus, judicious use of antibiotic is an important way to reduce the problem of antimicrobial resistance. Hence, detailed rational knowledge of antibiotic prescribing pattern must be implemented in clinical practice. Neonates require more attention while prescribing antibiotics in order to avoid the drug resistance, adverse drug reactions and drug-drug interactions. Moreover, antibiotics are the class of drugs commonly prescribed in the NICU. Thus, the aim of our study was to observe and analyse the prescribing pattern of

antibiotics in NICU of a tertiary care hospital in Western Maharashtra, India.

MATERIALS AND METHODS

An observational and prospective study of six months duration was carried out in the NICU of a tertiary care hospital in Pune from April to September 2014. All the 528 neonates admitted to the NICU for more than 24 hours during the study period were included after the Institutional Ethics Committee approval. Neonates died or discharged within 24 hours of admission were excluded from the study. Study was carried out by evaluating medication records of admitted neonates. Data pertaining to gestational age, birth weight, gender, diagnosis, and patient outcome as percentages of survival, discharge and death were recorded. Details of antibiotics administered to each patient were recorded.

STATISTICAL ANALYSIS

The results were presented as percentage for categorical variables and mean±standard deviation for continuous variables. Chi-square test or Fisher's exact was used to compare categorical data

RESULTS

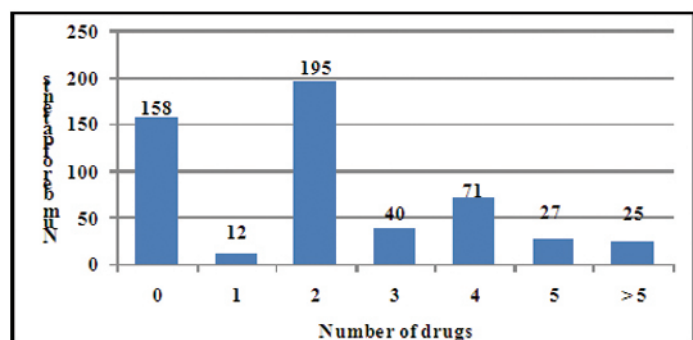
A total of 528 neonates were included in the study with male preponderance (62%) and out born referrals, 64.2%. Among 528 admitted neonates, 246 (46.6%) were term and 282 (53.4%) were preterm. The mean gestational age was 35 weeks (SD ± 3.2, minimum= 23, maximum = 42). The mean birth weight was 2.0 kg. (SD ± 0.7, minimum 0.5 kg, maximum 4.0 kg). Twenty four deaths were recorded during study period. Neonatal jaundice, pneumonia, neonatal sepsis, perinatal asphyxia, prematurity were the common indications for admission in NICU [Table/Fig-1].

Survival rate was highest in perinatal asphyxia, neonatal jaundice and pneumonia. Significantly more number of deaths were observed in the neonates with neonatal RDS and neonatal sepsis ($p < 0.05$).

A total of 1123 antibiotics have been prescribed to 370 neonates. The majority of neonates 207 (55.9%) received between 1- 2 antibiotics, 138 neonates (37.3%) had 3 to 5 antibiotics prescribed, while 25 (6.7%) neonates were prescribed more than 5 antibiotics [Table/Fig-2].

Disease	Survival (%)	Death	DOR	DAMA	Chi ² test value (df) p-value
Neonatal Jaundice	191(88.8)	5(2.3)	4(1.7)	15(7.0)	4.3 (3) p = 0.224
Neonatal Sepsis	55(70.51)	12(15.4)*	1(1.3)	10(12.8)*	30.5 (3) p < 0.001
Respiratory distress syndrome (RDS)	47(73.4)	11(17.2)*	1(1.5)	5(7.8)	27.1 (3) p < 0.001
Perinatal Asphyxia	64(92.8)	1(1.5)	0(0.0)	4(5.8)	3.9 (3) p = 0.372
Pneumonia	91(85.1)	6(5.6)	2(1.9)	8(7.5)	0.40 (3) p = 0.921

[Table/Fig-1]: Disease pattern and patients' outcome
* Higher death rate was observed in these patients as compared to other patients $p < 0.01$ using Chi-square test. Values in parenthesis are in percentages



[Table/Fig-2]: Number of antibiotics received by the neonates

No. Antibiotics received	Gestational age				Total n=528	χ^2 Value (df)	p-value
	T	M	F	P			
0	0 (0)	2 (3.92)	66* (31.73)	84* (34.15)	152	61.33 (9)	<0.001
1 - 2	4 (26.67)	12 (23.53)	85* (40.87)	106* (43.09)	207		
3 - 5	3 (20)	27* (52.94)	57 (27.40)	51 (20.73)	138		
> 5	8 (43.33)	10* (19.61)	8 (3.85)	5 (2.03)	31		

[Table/Fig-3]: Number of antibiotics and gestational age
n= 528; * $p < 0.001$ using chi square test. Values in parenthesis expressed in percentages

Drugs	No. of prescription (%)
Antiinfective for systemic use	1123 (67.7)
Respiratory System	157 (9.5)
Nervous system	149 (9.0)
Cardiovascular System	115 (6.0)
Alimentary tract	52 (3.1)
Sytemic Hormonal preparations	36 (2.1)
Others	26 (1.6)
Total	1658

[Table/Fig-4]: Number of drug prescriptions in NICU according to WHO ATC Classification [10]

[Table/Fig-3] shows that more antibiotics were used in very preterm neonates with stastically significant negative association for number of antibiotics used with gestational age.

According to the WHO ATC classification system 2013 (16th edition accessed on 19th October 2014) anti- infectives for systemic use (67.7%) have been most frequently prescribed, followed by drugs for the respiratory system (n= 157) and nervous system (n= 149) [Table/Fig-4].

Among antibiotics Amikacin (n =187), Cefotaxime (n= 168) and Levofloxacin (n= 137) were the drugs most often prescribed [Table/Fig-5]. Antibiotic prescribing trends amongst preterm and term neonates revealed that there was statistically significant difference between the two groups ($p < 0.05$). Amikacin and Cefotaxime were given more to term infants whereas other antibiotics (Levofloxacin, Piperacillin- tazobactam, Meropenem) were prescribed more to preterm neonates. ($p < 0.05$) [Table/Fig-6].

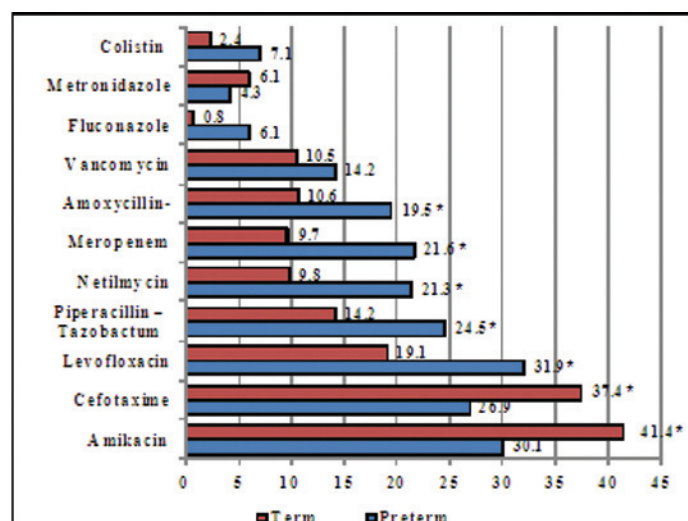
Amikacin and cefotaxime was prescribed to significantly more ($p < 0.05$) number of outborn patients whereas Netilmycin and Amoxycillin-Clavulanic Acid were given more to inborn neonates ($p < 0.05$). Along with these drugs, outborn sick patients also received Piperacillin-tazobactam, Meropenem, Vancomycin ($p < 0.05$) [Table/Fig-7].

DISCUSSION

This study found that antibiotics were the most commonly prescribed drug class in neonates in a tertiary level NICU. The main aim of this study was to evaluate the prescribing pattern of antibiotics. The majority of antibiotics showed highest exposure rates in infants with lower gestational age (<32 weeks) probably because of poor immunity, prolonged hospital stay and high risk of sepsis. [Table/Fig-2] shows 55.94% patients received between 1 to

Antibiotics	No. of Prescriptions
Amikacin	187
Cefotaxime Sulbactam	168
Levofloxacin	137
Piperacillin – Tazobactam	112
Netilmycin	89
Meropenem	84
Amoxycillin-Clavulanic Acid	81
Vancomycin	66
Fluconazole	30
Metronidazole	27
Colistin	26

[Table/Fig-5]: List of the most frequently used systemic antibiotics



[Table/Fig-6]: Antibiotics use with respect to gestational age
* $p < 0.05$ using chi square test

Drug	Inborn(%) n=189	Outborn (%) n=339	Total (%) n=528	χ^2 test values(df)
Amikacin	7.9	50.7 [#]	35.4	97.2 (1) p<0.001
Cefotaxime	6.8	45.7 [#]	31.8	84.4 (1) p<0.001
Levofloxacin	21.7	28.3	25.9	2.8 (1) p = 0.93 NS
Piperacillin-Tazobactam	13.2	23.3 [#]	19.7	7.7 (1) p = 0.005
Netilmycin	39.6 [#]	2.6	15.9	127.6 (1) p < 0.001
Meropenem	11.6	18.5 [#]	16.1	5.1 (1) p = 0.024
Amoxicillin-clavulanic acid	38.1 [#]	2.6	15.3	108.2 (1) p <0.001
Vancomycin	6.9	15.6 [#]	12.5	8.5 (1) p = 0.004
Fluconazole	1.6	4.7	3.4	3.4 (1) p = 0.064 NS
Metronidazole	2.1	6.7 [#]	5.1	5.4 (1) p = 0.020
Colistin	2.6	6.1	4.9	3.2 (1) p = 0.071 NS

[Table/Fig-7]: Antibiotics use in inborn and outborn neonates
*p<0.05 using chi square test

2 antimicrobials, 30% patients had 3 to 5 antimicrobials prescribed, while 14.05% patients received 5 and above antimicrobials. Neubert et al., observed that 90.7% of all study patients were treated with antibiotics & mostly two antibiotics [11]. Within the group of very preterm infants 96.2% patients were treated with antibiotics [11]. These absolute numbers are in line with the data published from another hospital in Germany by Gortner et al., where the exposure to antibiotics in preterm neonates (24–29 weeks' gestation) was 98.8% [12]. Similar high exposure numbers for antibiotics are reported from the USA & Italy [13,14]. The high rate of antibiotic exposure in our study is similar to previous studies carried out in India as well as other countries and is probably due to the standard practice of administering antibiotics pending bacterial culture results in sick neonates and is not a true reflection of the incidence of bacterial infection [15-17]. A study by Fonseca et al., revealed that the highest use was in neonates with birth weight less than 1500 g and 92% of them received antibiotics within the first 48 hours after birth [18]. These findings may be explained by high susceptibility of neonates to bacterial infections, especially for very preterm neonates, who need intubation and mechanical ventilation. Clinical findings are usually variable, laboratory test (i.e. white blood cell count, C-reactive protein) are not highly sensitive and specific during the first hours following birth [19] which also accounts for the high rate of antibiotics treatment of neonates. As deleterious infections often become manifest without obvious clinical and laboratory signs, antibiotic treatment is indicated in sick neonates even if the clinical signs are only minimal. Among antimicrobials, Amikacin, Cefotaxime and Levofloxacin were the drugs most often prescribed. Amikacin and Cefotaxime were given more to term infants whereas higher antibiotics, Levofloxacin, Piperacillin-tazobactam and Meropenem were prescribed more to preterm neonates. Use of higher antibiotics mainly Levofloxacin, Vancomycin, Fluconazole, Metronidazole and Colistin was significantly more in patients with extreme preterm and very preterm babies. Amikacin, cefotaxime were most frequently used antimicrobials in previous Indian studies [16,20]. However, looking at individual drugs a great variation with regard to which drugs are used most frequently is apparent [11,13].

This heterogeneity indicates that empiric antibiotic treatment varies among different countries and in NICUs of the same country. This is because currently no standard guidelines regarding the choice of empiric antibiotics exist. This finding is not surprising as; Cochrane review comparing the antibiotic regimens for suspected late onset

sepsis in newborn infants concluded that there is inadequate evidence from randomized trials in favour of any particular antibiotic regimen for the treatment of suspected late onset neonatal sepsis [21]. The choice of antibiotic regimes depends upon information regarding known flora prevalent in a unit, personal experience of neonatologist and culture reports rather than being guided by comparative clinical studies. Therefore, use of individual antibiotics could not be compared with other studies, as its use in respect to gestational age groups & outborn- inborn groups was not mentioned [13,20,22]. Decisions about how to prevent neonatal sepsis, who and how long to treat, and which antibiotics to use remain important clinical problems [23,24]. So, early sepsis evaluations and empiric antibiotic treatment is required [25]. In the present study, to give wider coverage, according to NICU antimicrobial policy, the out born neonates received Amikacin & cefotaxime as an empirical therapy, while Netilmycin & Amoxicillin- clavulanic acid was common among inborn neonates. This covers both gram positive and gram negative organisms. The microbial culture positive cases showed that the main organisms were Coagulase negative *Staphylococcus*, *Enterococcus fecalis*, *Staphylococcus aureus*. Antibiotics were changed to Levofloxacin, Piperacillin, Meropenem or Colistin according to culture and sensitivity reports. Since in our study, neonatal sepsis was predominantly present in preterm infants. So use of these higher antibiotics was significantly (p<0.001) more in preterm babies than term patients.

LIMITATIONS

Few limitations of our study are, as study comprised most of the outborn population, drug history mainly antibiotics received by these neonates before admission could not be collected. Another limitation of our study is that data pertaining to drugs received by mother just prior or during delivery could not be revealed. This could have impact on antibiotic prescribing pattern, as symptomatic baby can have a false negative blood culture if antibiotics are given prenatally to the mother.

CONCLUSION

In present study, 28% of NICU patients were managed without any drug, 70.7% of neonates had received the antibiotic prescriptions and the maximum numbers of antibiotic prescriptions were found in the preterm and out born patients. The use of higher antibiotics was also more in out born sick infants. In spite of complicated neonates getting admitted to NICU, the number of drugs per prescription was not very high. Problems existed in more number of antibiotics prescribed, less use of generic drugs, the absence of the latest National essential list of medicines and high use of antimicrobial agents, not in line with culture reports. Present study suggests that Antibiotics policy to be framed & periodically reviewed: to reduce unnecessary use of antibiotics and associated problems.

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