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Research Article

Pattern of antibiotic use in neonatal intensive care unit in tertiary care hospital in Southern India

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ABSTRACT

Background: Repeated and prolonged courses of antibiotics exposure have resulted in an increase in the prevalence of hospital acquired infections and antibiotic resistant profile. The objective of this study was to quantify the use of antibiotics in a neonatal intensive care unit (NICU) from rural tertiary health care centre.
Methods: A hospital based cross-sectional study was conducted in the NICU of tertiary care hospital located in western Maharashtra, India during the year 2011-12. A total of 237 neonates admitted to NICU from October 2011 to March 2012 were enrolled in the study according to inclusion criteria of the study. Demographic details, data on antibiotic prescriptions (name, dose, frequency, route of administration) were recorded by utilizing pre-tested structured proforma.
Results: A total of 3822 prescriptions were received by the neonates and commonly prescribed antibiotics were amikacin (75.53%), cefotaxime (43.34%) and ampicillin (31.33%) respectively. It was also noted that 50% of the drugs prescribed were in compliance with the national list of essential medicines 2011. The max, 68.75% of antibiotics prescribed were in generics forms however, 12.5% were prescribed in the form of fixed dose combinations.
Conclusions: The revealed that 3rd generation cephalosporins and amikacin are most commonly used antibiotics in NICU.

Keywords: NICU, Preterm, Drug utilization, Drug prescriptions

INTRODUCTION

Neonates are most prone for infections due to low immunity. Drugs used for treatment of neonates are showing rapid advancements in recent years. Since last half century there is increase in average number of drugs used per neonate in neonatal intensive care unit (NICU).[1-3] Neonates are exposed to high numbers of drugs, putting them at higher risk of adverse drug reactions. Trends in prescription pattern for drugs in NICU are changing drastically but current data on drug utilization patterns in NICU is very limited.[4] Few published studies are available on drug utilization in neonates in India as well as in United States of America and Europe and considering this World Health Organization(WHO) aim to promote research in the pediatric population.[5-7]

Neonates, mainly premature are at high risk of bacterial infections than term neonates as their physiological functions are immature lead to high morbidity and mortality. Therefore clinicians start using antibiotics empirically or most of the times prophylactically. In some cases with the advent of knowledge of culture sensitivity, clinicians either stop or change the antibiotics. But in most of the cases either they do not perform culture and sensitivity or they continue the antibiotics for long period of time though the organisms are not sensitive could be due to lack of knowledge or facilities.

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. Evaluation of antibiotic use is therefore prime important since the prevalence of hospital acquired antibiotic resistance in organisms is increasing in neonates.[8,9] The present study aimed to quantify antibiotic use in a neonatal intensive care unit of tertiary care hospital situated in rural part of western Maharashtra, India and the data generated from this could be used to develop effective drug policy as well as prioritization in future research.

METHODS

A hospital based cross sectional study was conducted in rural tertiary health care centre located in western Maharashtra, India. The study was conducted in the year 1st October 2011 to 31st March 2012 after obtained institutional ethical approval. The study enrolled all neonates admitted and treated in NICU during the period of October 2011 to March 2012. A total of 249 neonates were admitted during study period, of which 237 were enrolled according to exclusion criteria of present study as a time bound sample size.

Exclusion criteria

Neonates who were discharged or transferred to other ward or hospital or died within 2 days of NICU stay are excluded from the study. Neonates suffering from cancer, diagnosed with surgical problem, post-operative neonates admitted in NICU, neonates receiving phototherapy for neonatal jaundice and neonates on oxygen therapy are also not taken in the study.

Data collection

The data were collected by principal investigator utilizing pre-tested structured proforma that include neonates demographic data i.e. date of birth, weight at birth, gestational age in weeks, gender, diagnosis, outcome etc. as well as data pertained to antibiotic prescriptions like name, dose, frequency, route of administration etc. were recorded in NICU from the day of admission till outcome as discharge or death. Neonates were classified into five different groups according to 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. The data so collected were entered into MS Excel, analysed and distributed into frequency percentage in tabular and graphical form.

Ethical consideration

After obtaining permission from the institutional ethics committee (IEC) the study was carried out in the NICU of the tertiary care hospital in Southern India.

RESULTS

The study spanning over six month period enrolled 237 neonates were classified in five different groups according to weeks of gestation.

Table 1: Characteristics of the neonates (n= 237).

Weeks of gestation	24-27 (Very early pre-term neonates)	28-30 (Early pre-term neonates)	31-33 (Mid pre-term neonates)	34-36 (Late pre-term neonates)	>37 (Term neonates)
Demographic distribution (M/F)	4/1	16/9	23/21	34/13	85/31
Total birth weight (kg)	6.8	33.86	72.596	84.63	285.01
Mean birth weight (kg)±SD	1.36±0.31	1.35±0.2407	1.649±0.4116	1.800±0.4268	2.457±0.6315
Length of hospital stay (days)	49	270	387	462	667
Length of hospital stay (mean±SD)	9.8±6.30	10±8.54	9.439±5.96	8.864±6.74	6.119±4.53
No. of prescriptions	98	508	906	864	1446

As shown in Table 1, of the 237 neonates studied the proportions of pre-term and term neonates were 51.05% and 48.94% respectively. The proportion of male neonates (68.35%) was higher than females (31.64%). Mean birth wt. for full term neonates was 2.457 (SD±0.6315), and for very early pre-term neonates was 1.36 (SD± 0.3073) and for other groups was in-between. Mean length of hospital stay was higher, 9.8 (SD±8.535) days for the neonates in

group 28-30 weeks of gestation than term neonates, 6.1 (SD±4.53) days. A total of 2376 prescriptions were scrutinized for preterm neonates whereas 1446 were for full term neonates.
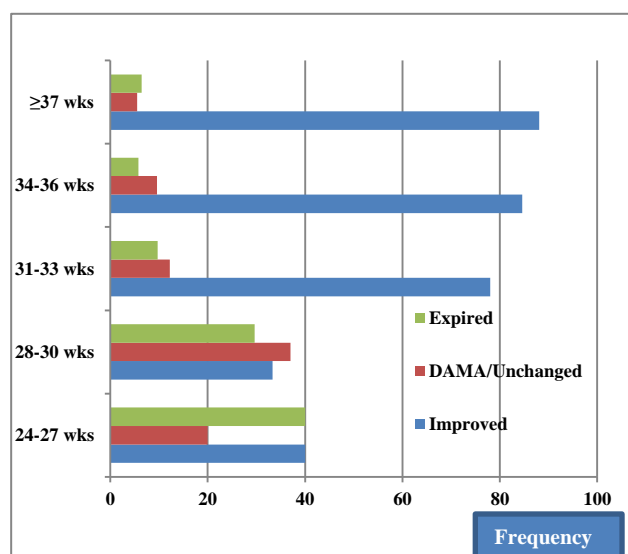

Figure 1: Condition of neonates at the time of discharge.

According to the data available on condition of patients at the time of discharge, we divided them into expired, improved and discharge against medical advice (DAMA) discharge or with unchanged status at discharge. 93.75% improvement was seen in neonates from the group of ≥37 weeks of gestation whereas 36% improvement was seen in neonates from the group of 28-30 weeks of gestation. Mortality was highest in 24-27 weeks group (40%) followed by 28-30 weeks of gestation (32%) group. A total of 24 neonates (10%) of the study population died during their stay in the hospital (Figure 1).

Table 2: Exposure rates (%) of most often prescribed drugs for neonates in 24-27 weeks of gestation.

Drug for week of gestation: 24-27 (n=5)			
	Number	Incidence%	Antibiotic days
Cefotaxime	3	60	24
Amikacin	3	60	24
Cefoperazone +sulbactum	3	60	6
Metronidazole	3	60	4
Vancomycin	3	60	3
Ceftazidime	1	20	3
Ofloxacin	1	20	9
Tobramycin eye drops	1	20	1

Neonates got admission in NICU for preterm care, septicemia, meconium aspiration syndrome, birth asphyxia etc. We observed that 98% of our study patients (neonates) received antibiotics. Pattern of use of single,

double and multiple antibiotics was received by 16%, 55% and 29% neonates respectively. However, four patients did not receive any antibiotic. It was noted that 50% of the antibiotics prescribed were in compliance with the national list of essential medicines 2011. The percentage of prescriptions of generic antibiotics was 68.75% whereas, 12.5% of antibiotics were prescribed in the form of fixed dose combinations (sulfamethoxazole + trimethoprim, cefoperazone + sulbactum).

Table 3: Exposure rates (%) of most often prescribed drugs for neonates in 28-30 weeks of gestation.

Drugs for weeks of gestation: 28-30 (n=25)			
	Number	Incidence%	Antibiotic days
Amikacin	18	66.66	109
Cefotaxime	12	44.44	84
Ampicillin	6	22.22	23
Vancomycin	5	18.51	24
Cefoperazone +sulbactum	5	18.51	13
Ofloxacillin	4	14.81	27
Meropenam	3	11.11	29
Ceftazidime	3	11.11	18
Metronidazole	3	11.11	10
Clavum	1	3.7	4
Ceftriaxone	1	3.7	4
Linezolid	1	3.7	2
Tobramycin eye drops	1	3.7	2

Table 4: Exposure rates (%) of most often prescribed drugs for neonates in 31-33 weeks of gestation.

Weeks of gestation: 31-33 (n=44)			
	Number	Incidence%	Antibiotic days
Amikacin	27	64.28	146
Ampicillin	16	38.09	71
Cefotaxime	16	38.09	86
Cefoperazone +sulbactum	14	33.33	80
Metronidazole	10	23.80	40
Vancomycin	7	16.66	48
Ceftazidime	4	9.52	20
Meropenam	3	7.14	37
Tobramycin eye drops	3	7.14	4
Ceftriaxone	2	4.76	8
Ofloxacin	2	4.76	10
Syrup cotrimoxazole	1	2.38	5
Mupirocin ointment	1	2.38	5

Table 2, 3, 4, 5 and 6 depicts the exposure rates of antibiotics prescribed according to different gestational age groups. Age group 24-27 weeks of gestation showed higher incidence of prescribing with cefotaxime followed

by amikacin and cefoperazone. Third generation cephalosporins were more commonly prescribed for this group. 20% patients received prescription of ofloxacin, tobramycin eye drops also (Table 2). Age group of 28-30 weeks of gestation showed most commonly prescribed antibiotics was amikacin followed by cefotaxime (Table 3). Similar findings have also been observed in age group 31-33wks of gestation and 34-36 weeks of gestation (Table 4 and 5). The term neonatal age group, ≥37 weeks of gestation showed higher incidence of prescribing of amikacin, cefotaxime followed by ampicillin. Fewer incidences are seen with crystalline penicillin, gatifloxacin, and linezolid (Table 6).

Table 5: Exposure rates (%) of most often prescribed drugs for neonates in 34-36 weeks of gestation.

Weeks of gestation: 34-36 (n=47)			
	Number	Incidence%	Antibiotic days
Amikacin	40	78.43	234
Cefotaxime	20	39.21	108
Ampicillin	19	37.25	98
Vancomycin	9	17.64	59
Metronidazole	9	17.64	42
Cefoperazone +sulbactum	7	13.72	43
Ceftriaxone	4	7.84	49
Ceftazidime	2	3.92	7
Ofloxacin	1	1.96	2
Tobramycin eye drops	1	1.96	4

Table 6: Exposure rates (%) of most often prescribed drugs for patients in ≥37wks of gestation.

Drugs for weeks of gestation: ≥37 weeks (n=116)			
	Number	Incidence%	Antibiotic days
Amikacin	88	80.73	416
Cefotaxime	50	45.87	221
Ampicillin	32	29.35	139
Cefoperazone +sulbactum	22	20.18	93
Metronidazole	14	12.84	60
Vancomycin	10	9.17	55
Ceftriaxone	8	7.33	42
Ceftazidime	8	7.33	32
Tobramycin eye drops	3	2.75	1
Ofloxacin	2	1.83	9
Gentamicin	2	1.83	6
Meropenam	2	1.83	10
Linezolid	1	0.91	1
Gatifloxacin eye drops	1	0.91	1
Crystalline penicillin	1	0.91	9

DISCUSSION

The present study described the prescription profile of antibiotics in neonatal intensive care unit of a tertiary care hospital from rural establishment of western Maharashtra state. The study revealed that cefotaxime and amikacin to be most commonly used antibiotics followed by ampicillin in NICU. The Studies done in UK and Australia, reports that Gentamicin to be the most frequently used antibiotic.[10] A study conducted in Italy, reports amikacin and ampicillin to be most commonly used antibiotic in NICU11 whereas a study conducted by Clark RH from USA reports, cefotaxime as commonly used antibiotics in NICU.[2]

Third generation cephalosporins like cefotaxime, ceftriaxone, ceftazidime, cefoperazone are prescribed more commonly in all five groups of neonates in our study. Approximately 56% low birth weight neonates (Weight ≤1.5 kg) received third generation cephalosporins with 39% mortality in them. Neonates received these antibiotics in first three days of life. Previous studies report that use of third generation cephalosporins increases the risk of invasive candidiasis and death with risk increased in low birth weight neonates (weight ≤1.5 kg).[2,12,13] In vitro susceptibility data suggest that third-generation cephalosporins are not more effective in treating sepsis than the currently recommended antibiotics viz. benzyl penicillin and gentamicin.[14] Gentamicin-based regimens should be used in preference to cefotaxime-based treatments, because of lower levels of susceptibility to cefotaxime and the need to avoid exerting selective pressure for resistance.[15]

Second most commonly used antibiotic in this study was amikacin and 75% of preterm neonates were receiving amikacin. Dose of amikacin should be once every 36 hours in babies less than 32 weeks of gestation and for all other babies dose is once every 24 hours.[16] 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. Neonates are a high-risk population for hearing loss, and when ototoxicity occurs, it places a burden of disability on the affected individual.[17] Therefore trough serum level should be checked before the fourth dose and dose interval should be increased if level is more than 8 mg/l. The toxicity is increased if amikacin is prescribed for more than 10 days and when two or more aminoglycosides are prescribed together.[16] In our study, dose interval for amikacin was 12 hours for all neonates. 6.25% (11) neonates received amikacin for more than 10 days and 2 neonates received two aminoglycosides antibiotics. We did not get any mention about monitoring of trough levels during the treatment with amikacin in our study.

Vancomycin should be reserved for episodes of staphylococcal infection confirmed to be resistant to flucloxacillin or gentamicin and monitoring of plasma level is necessary if it is to be given in first week of life.[18]

In our study, vancomycin usage was not guided by culture sensitivity testing and we do not get any mention of plasma level monitoring.

There is too little published experience for the manufacturers to have yet recommended the use of meropenam in children less than 3 months old.[19] There is little published information on neonatal use of Linezolid and almost none on uses in preterm babies and manufacturers do not recommend use of Linezolid in children under 18 years of age.[20] In our study, incidence of usage of meropenam was 3.43% and 0.85% for linezolid.

According to summary of product characteristics (SPC) of tobramycin and gatifloxacin eye drops, these drugs should be used in children of one year and above.[21,22] Their usage in neonates is not mentioned in neonatal formulary-6 (NF-6). Ofloxacin is contra-indicated in children or growing adolescents, and in pregnant or breast-feeding women, as there is risk of damage to the cartilage of joints in the growing subjects.[23] In our study ofloxacin was given to only 10 neonates. The use of fixed dose combination, sulfamethoxazole and trimethoprim (SEPTRAN) in neonates is not mentioned in NF-6.[24] In our study we found that 98% neonates received antibiotics with culture sensitivity testing done only in few neonates. Out of which 84% neonates received two or more than two antibiotics increasing the chances of drug interactions and cost of treatment. Therefore average number of antibiotics used per neonate should be kept limited to reduce the risk of drug interactions. Intense monitoring of each neonate for adverse drug reactions should be focused. Use of drugs whose safety has not been established in neonates should be curtailed.

Guidelines should be developed for empiric use of antibiotics in neonates according to microbial profile prevalent in the area which further combat the development of antibiotic resistance and minimize the cost of treatment. Further similar studies should be conducted in periods of time to know the trend of antibiotics usage and change in sensitivity pattern of bacteria in NICU.

Recommendations

- Monitoring of plasma level should be done with amikacin and vancomycin in neonates to minimize the risk of ototoxicity and nephrotoxicity
- Narrow spectrum antibiotics should be used to minimize the risk of bacterial resistance and fungal infections
- Use of antibiotics should be guided by culture sensitivity testing
- Use of drugs whose safety has not been established in neonates should be curtailed
- Empirical and Prophylactic usage of antibiotics for prolonged period of time should be discouraged.

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