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RESEARCH ARTICLE

A prospective study of the pattern of antimicrobial use in neonatal intensive care unit of a tertiary care hospital

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ABSTRACT

Background: Neonatal intensive care management (NICM) involves the use of a multiplicity of medications of different categories. Antimicrobial agents (AMAs) are the most frequently prescribed during NICM, either for prophylaxis or treatment of infections. **Aims and Objectives:** The objective of this study was to study the pattern of antimicrobial AMA use and criteria for their selection. **Materials and Methods:** Case records of 150 neonates admitted to NICU and received AMAs were analyzed prospectively for the pattern of AMA use, criteria for selection, dose, route, frequency, duration of administration, AMA combinations, and any change in AMA therapy. **Results:** A total of 93 male and 57 female neonates with a mean age of 3.44 days were admitted for prematurity and respiratory distress. The mean duration of hospitalization was 10.67 ± 6.29 days, and the total number of AMAs used was 20, with a mean of 2.56 per neonate. The most commonly used AMAs were aminoglycosides and beta-lactams. AMAs were used in combination in most cases (98.7%) and were rational, except ampicillin + cloxacillin. All AMAs were used by IV route, supplemented by oral/topical in 2 cases; the mean duration of administration was 6.02 days. The initial choice of AMAs was mainly empirical. Change of AMAs was required in 60.6% of cases based on clinical response/laboratory data. **Conclusions:** The use of AMAs in NICU was mainly empirical, and definitive therapy was based on laboratory data. AMA combinations were used in most cases, and change in therapy was based on clinical response/laboratory data.

KEY WORDS: Neonatal Intensive Care Management; Neonatal Intensive Care Unit; Antimicrobial Agents; Drug Utilization Research

INTRODUCTION

A neonatal intensive care unit (NICU) provides high-quality skilled care to premature, low birth weight, or critically ill newborns.[1] Neonatal intensive care management (NICM) involves the use of a multiplicity of medications of different categories. Antimicrobial agents (AMAs) are the most frequently prescribed during NICM, either for prophylaxis or treatment of infections.[2] The pattern and extent of AMA use in NICM may differ in different tertiary care hospitals, according to the gestational age, birth weight prevailing perinatal/neonatal problems and complications, the intended purpose of use, and also considering the inherent toxicity of AMA and the special vulnerability of the neonate. There are no universally accepted and standardized guidelines for optimizing AMA use to the given situation. Hence, the present study was taken up to assess the prevailing pattern of AMA use in a tertiary care hospital.

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Objectives

The objectives of this study are as follows:

- To study the pattern of AMA use in NICU.
- To assess the criteria for AMA selection, combination, and any change in AMA therapy.

MATERIALS AND METHODS

Prospective analysis of case records of 150 neonates admitted to NICU of received AMAs were included in the present study. Approval and clearance from the Institutional Ethics Committee were obtained before starting the study. Written informed consent was obtained from parents/legal representatives of all the study subjects after fully explaining the study procedure to their satisfaction, in both English and vernacular language. The pattern of AMA used, the dose, formulation, route, frequency, duration of administration, criteria for AMA selection and combination (fixed dose/separate formulation), number of AMA used per neonate, and also any change in AMA therapy were analyzed and assessed.

Statistical Analysis

The data collected were analyzed using descriptive statistics, namely, mean and standard deviation for quantitative variables. The results were also depicted in the form of tables and graphs. Microsoft Word and Excel were used for the analysis of data and to generate graphs and tables.

RESULTS

A total of 93 male and 57 female neonates with a mean age of 3.44 ± 2.47 days [Table 1] were admitted for prematurity, respiratory distress, neonatal sepsis, birth asphyxia, meconium aspiration syndrome, CHD, and jaundice [Figure 1]. The mean duration of hospitalization 10.67 ± 6.29 days and the total number of AMAs used were 20, with a mean of 2.56 per neonate [Figure 2].[3-6] The most commonly used AMAs were aminoglycosides and beta-lactams, less frequently macrolides, vancomycin, linezolid, metronidazole, fluconazole, and amphotericin B. AMAs were used in combination in most cases (98.7%) [Figure 3] and were rational, except ampicillin + cloxacillin [Table 2].[2,7-10] All AMAs were used by IV route, supplemented by oral/topical in 2 cases; the mean duration of administration was 6.02 days [Figure 4]. The initial choice of AMAs was mainly empirical [Figure 5],[10,11] and the dose and frequency of administration were as per the standard guidelines. Change of AMAs was required in 60.6% of cases based on clinical response/laboratory data [Figure 6].[11]

Table 1: Demographic data

Age (Mean±SD)	3.44±2.47 days
Gender	
Male (%)	93 (62)
Female (%)	57 (38)
Duration of stay (Mean±SD)	10.67±6.29 days

SD: Standard deviation

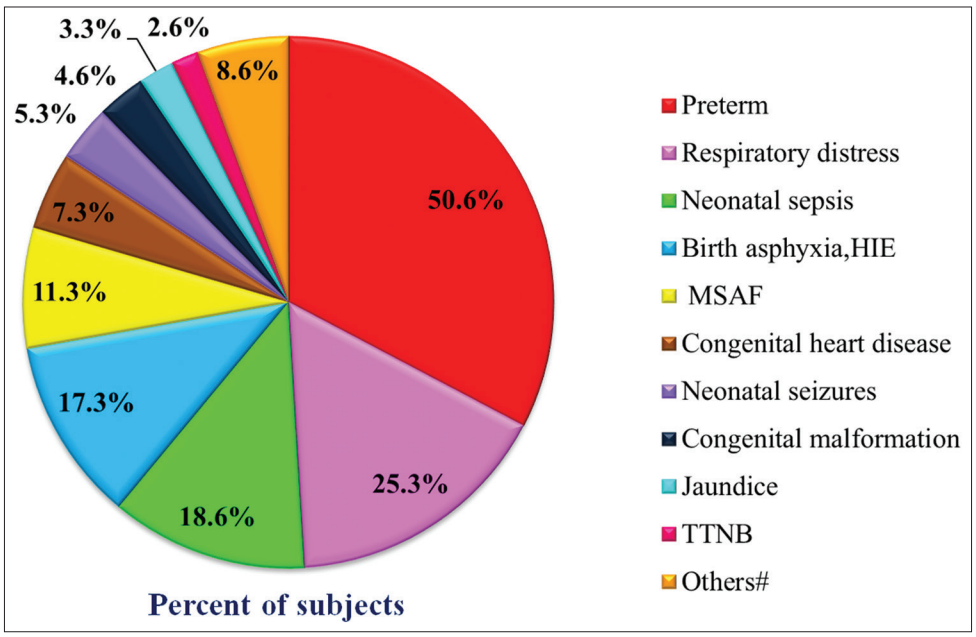

Figure 1: Diagnosis/provisional diagnosis*. *93 (62%) neonates had more than one indication/complication. †Physiological jaundice excluded. HIE: Hypoxic ischemic encephalopathy, MSAF: Meconium stained aspiration fluid, TTNB: Transient tachypnea of the newborn

Table 2: AMAs used

Generic name and dosage		Duration of administration in days (Mean±SD)	Number of subjects[#]
Penicillins			
Co-amoxiclav[*]	20 mg/kg IV BID	5.93±3.63	36
Piperacillin+tazobactam[*]	100 mg/kg IV TID	6.79±4.25	57
Ampicillin+cloxacillin[*]	50 mg/kg IV QID	6.93±4.36	2
Cephalosporins			
Cefotaxime	50 mg/kg IV BID	5.00 days	1
Ceftazidime	50 mg/kg IV BID	9.00 days	1
Ceftriaxone[†]	50 mg/kg IV BID	6.63±4.25	42
Cefepime[†]	50 mg/kg IV BID	10.00 days	1
Carbapenems			
Meropenem[†]	20 mg/kg IV BID	6.89±4.30	15
Aminoglycosides			
Amikacin	7.5 mg/kg IV BID	7.66±4.02	143
Gentamicin	2.5 mg/kg IV BID	7.12±4.08	3
Netilmicin	2.5 mg/kg IV BID	9.00 days	1
Tobramycin	0.3% topical QID	7.04±4.64	4
Glycopeptides			
Vancomycin	15 mg/kg IV BD	7.26±4.38	2
Macrolides			
Erythromycin	10 mg/kg oral TID	9.00 days	1
Azithromycin	10mg/kg IV OD	2.00 days	1
Oxazolidinones			
Linezolid[†]	7.5 mg/kg IV BID	5.97±4.50	3
Nitroimidazoles			
Metronidazole	7.5 mg/kg IV BID	6.41±4.55	6
Antifungal agents			
Amphotericin B	0.5 mg/kg IV OD	7 days	1
Fluconazole[†]		6.42±4.50	10
Loading dose	12 mg/kg IV		
Maintenance dose	6 mg/kg IV OD		
Antiviral agents			
Acyclovir	20 mg/kg IV QID	3 days	1

[*]Fixed-dose combinations considered as single drugs. [†]Off label use, [#]98.5% subjects received more than 1 AMA, SD: Standard deviation, AMA: Antimicrobial agents, QID: Four times a day, OD: Once a day, BID: Twice a day, TID: Three times a day

DISCUSSION

The most widely used drugs in NICU are AMAs, as neonatal sepsis being one of the leading causes for admission and also considering the high susceptibility of the critically ill neonates for infection because of the compromised immune status and the use of various invasive procedures. The AMA combinations were probably chosen to ensure adequate antimicrobial coverage against a wide range of organisms taking into consideration the prevailing pattern of infection, compromised immune status of critically ill neonates, and also the nosocomial or cross infections.

The AMAs were mainly used for prophylaxis in all preterm infants and in those maintained on invasive procedures and also to control the preexisting, ongoing, or acquired infections. The initial choice of AMAs was mainly empirical, and definitive therapy was undertaken based on the available laboratory data. All the AMAs employed for systemic therapy were used in combination to ensure a wider antimicrobial coverage. The most widely used AMAs were amikacin, piperacillin + tazobactam, ceftriaxone, and co-amoxiclav, and the most frequently used combinations were piperacillin + tazobactam + amikacin, ceftriaxone + amikacin, and co-amoxiclav + amikacin. The other AMAs

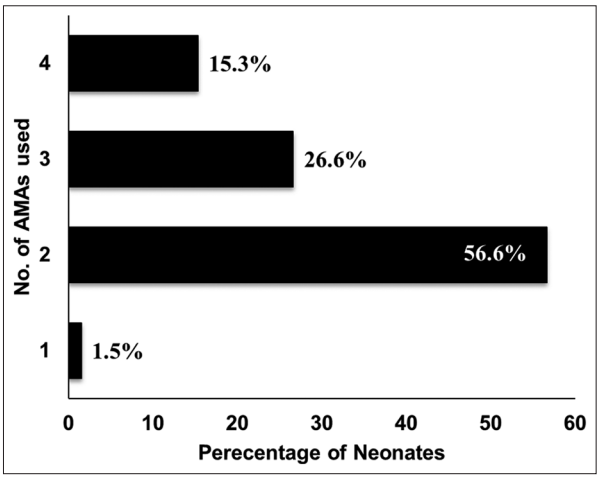

Figure 2: Number of antimicrobial agents used per neonate

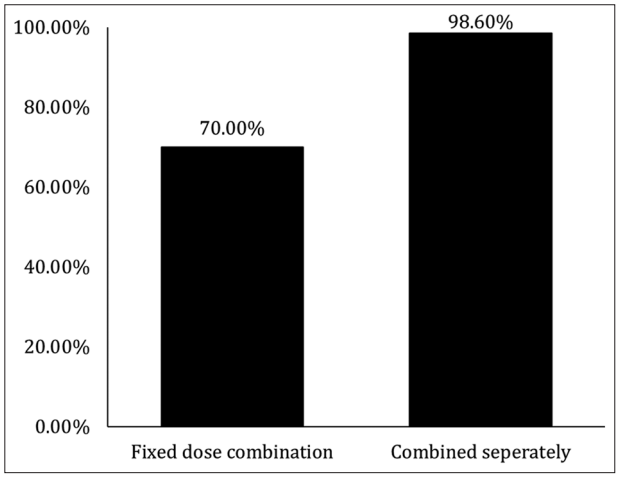

Figure 3: Antimicrobial agent combinations

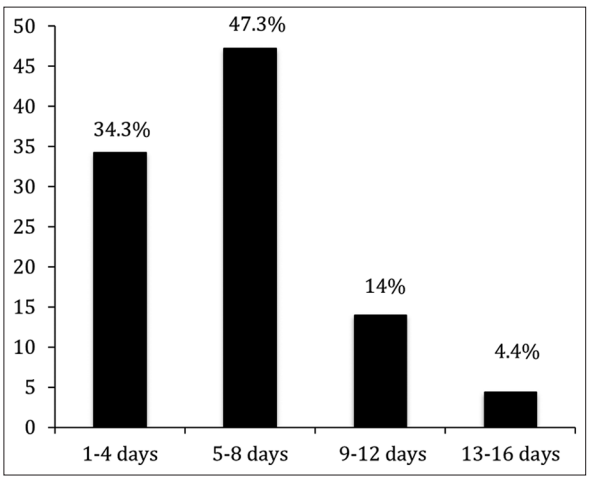

Figure 4: Duration of drug administration

were used as alternatives or reserve options for resistant infections or as definitive therapy based on the laboratory data. AMAs such as vancomycin, linezolid, metronidazole, amphotericin B, fluconazole, and acyclovir were used for specific antimicrobial coverage. The dose of the AMAs was in accordance with the recommended guidelines based on the body weight.

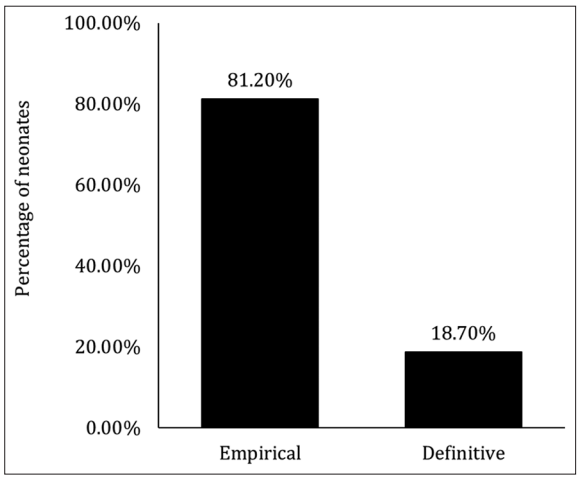

Figure 5: Criteria for selection

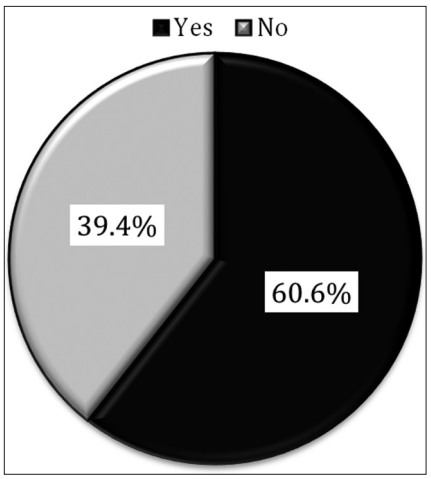

Figure 6: Change in antimicrobial agent therapy

The commonly used AMA combinations reported in other studies were ampicillin + gentamicin and co-amoxiclav + gentamicin.[2,7-10] Thus, the use of AMAs in combinations appears to be justified and rational. Most of the AMAs used in the present study has been approved for use in neonates, and the dose and frequency of administration were in accordance with the standard norms and guidelines. However, cefepime, meropenem, and linezolid, though found to be safe, are not approved for use in neonates, and ceftriaxone is contraindicated in preterm and jaundiced neonates, and the safety of fluconazole is not fully established. Hence, the use of these drugs may not be rational but may be considered as "off-label" use.[12-16] The criteria for initial AMA selection was mainly empirical ($n = 81.2\%$) based on the site and severity of infection, and likely pathogens in most of the neonates and in only 18.7% subjects, it was definitive, based on previous laboratory report. Other studies have also reported a similar pattern of empirical use of AMAs.[10,11] Change in AMA therapy involving addition or substitution with other AMAs was considered in 60.6% of the subjects**.** The reason for the change was an inadequate clinical response and based on laboratory data but not due to any adverse event. The pattern and purpose of the change in AMA therapy were almost similar to other studies.[11]

However, there are no widely accepted, uniform, and standard guidelines for AMA selection in NICM, though some centers have formulated their own norms and guidelines. In the NICU center of the present study, the AMA combinations chosen as initial options were co-amoxiclav + amikacin or ceftriaxone + amikacin, piperacillin + tazobactam + amikacin as the second option, and meropenem + amikacin as the third option. The other AMAs were used for specific indications. Hence, as observed in the present study, the combination of co-amoxiclav + amikacin seems to be most effective as initial therapy both for prophylaxis and treatment, considering the treatment outcome. Ceftriaxone is not approved for use in neonates and also it is contraindicated in the presence of hyperbilirubinemia, may not be suitable as the first option, on the other hand, piperacillin + tazobactam + amikacin combination appears to be most suitable first-line option because of the wider antimicrobial coverage and good safety profile in neonates. The use of AMAs not approved for neonatal use should be avoided as far as possible, unless when it is inevitable, provided the benefits outweigh the risk. The AMAs can be chosen empirically based on the prevailing pattern of infection and cost effectiveness, and definitive therapy (based on laboratory data), may be required only in few subjects, particularly for neonates maintained on invasive procedures.

CONCLUSION

The most commonly used AMAs were aminoglycosides and beta-lactams. IV route was employed in all subjects and supplemented by oral/topical route in two neonates. AMA combinations used in most of the subjects were rational except ampicillin + cloxacillin. The initial choice of AMAs was mainly empirical and definitive therapy based on laboratory data. The dose and frequency of administration were as per the standard guidelines, and the mean duration of administration was 6.02 days. Change in therapy was based on clinical response or laboratory data.

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