Original Article

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Paediatrics Section

An Audit of Antibiotic Usage among Neonates in a Neonatal Intensive Care Unit: A Prospective Observational Study

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ABSTRACT

Introduction: Antibiotics are used frequently in the Neonatal Intensive Care Unit (NICU). Evaluating the antibiotic usage pattern at institutional or unit level would help in preventing antibiotic overuse and antibiotic resistance.

Aim: To assess antimicrobial usage among neonates admitted to the NICU.

Materials and Methods: The study was a prospective observational study done in the level III NICU at Hyderabad, India. All the antibiotics used among infants admitted to the NICU from January 2019 to December 2019 were monitored. Data collected were entered in Microsoft Office Excel 2016 and analysed using OpenEpi Version 3. Student t-test for continuous variables and chi-square test for dichotomous variables was used.

Results: A total of 986 infants were admitted to the NICU during the study period. Antimicrobials were prescribed in 322 (32%) infants. Antibiotics were most frequently prescribed in symptomatic infants (48%) for suspected sepsis. Amikacin was prescribed most frequently in 74% of infants. Cephalosporin was prescribed only in 8.9% cases. Blood culture positivity rate was 28%. Antibiotics were stopped only in 40% of the infants after the receipt of a negative blood culture report.

Conclusion: In this study, 68% of the infants were managed without any exposure to antibiotics. Half of the antibiotic usage was in suspected infection cases and antibiotics were continued in majority of cases with negative blood culture report. These clinical scenarios are amenable to antibiotic stewardship strategies in reducing antibiotic usage. Cephalosporin usage can be minimised with proper antibiotic usage guidelines.

Keywords: Antimicrobial resistance, Antimicrobial stewardship, Neonates

INTRODUCTION

Antimicrobials are one of the most frequently used, as well as misused drugs. In the last two decades, no new antibiotics have been discovered and there is a widespread antibiotic resistance reported across the globe [1].

Globally, infection is the most common cause of mortality in neonates [2]. Neonates are physiologically vulnerable to infection and have limited repertoire of clinical signs and symptoms. Dullness, lethargy, and poor feeding represent underlying infection and are also associated with non infectious conditions like hypothermia and hypoglycaemia. Hence, the clinicians start using antibiotics empirically or prophylactically out of the fear of vulnerability of the neonates to sepsis. Neonates are also prone to harmful effects of antimicrobial drugs due to differences in pharmacodynamic and pharmacokinetic characteristics and are at high risk for opportunistic or nosocomial infections due to prolonged hospitalisation and immune suppressed condition.

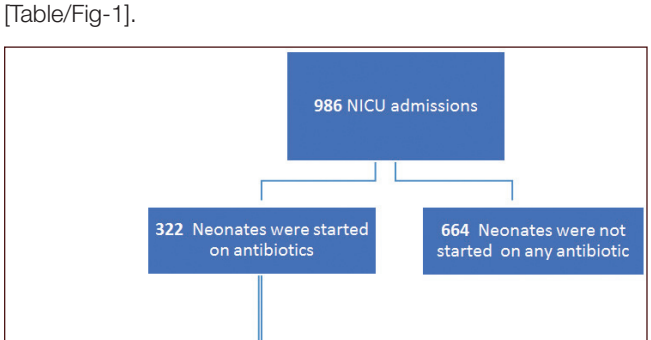
Earlier studies assessing antimicrobial utilisation rate in the NICU settings from India have reported widespread antibiotic usage [3,4]. There is a need for such larger studies over a wider geographic area in different settings to understand the antibiotic consumption. Such studies form an essential initial step in the implementation of antibiotic stewardship guidelines. Therefore, the present study was designed to assess and procure data of the antimicrobial usage pattern in a prospective manner from the NICU.

MATERIALS AND METHODS

This prospective observational study was conducted in a level III NICU at a children's hospital, in Hyderabad, India. The study was done over a period of one year from January 2019 to December 2019. Ethical approval was obtained from Institutional Ethical Committee (24545/19).

All the inborn and outborn neonates admitted to the NICU were eligible for the study and infants started on the antibiotics were enrolled in the study after obtaining the parent's consent. Neonates that died or were discharged within 24 hours of admission were excluded. The unit has an established antimicrobial usage protocol. Amikacin was the first line of

antimicrobial in suspected sepsis cases. Antimicrobials were started in babies after sending appropriate blood cultures and antimicrobial sensitivity. Use of cephalosporins was restricted [Table/Fig-1].



[Table/Fig-1]: Study flowchart.

Before the start of the study, clinical conditions when antimicrobial should be started were classified as infants with blood culture positive sepsis, symptomatic infants with positive laboratory markers (septic screen) and symptomatic infants with no supportive laboratory markers [5]. Data pertaining to gestational age, birth weight, gender, diagnosis and details of antibiotics administered to each patient were collected in structured proforma.

STATISTICAL ANALYSIS

A convenient sample size was used for the study. Data collected were entered in Microsoft Office Excel 2016 and analysed using OpenEpi, Version 3. Descriptive statistical analysis was done using proportion, percentages, median (IQR) and mean±standard deviation.

RESULTS

Baseline Data

During the study period, there were a total of 986 neonates admitted to the NICU. Of the 986 cases, 322 (32%) were prescribed at least one antimicrobial agent. Among 322 infants started on antibiotic therapy, 309 were included in the study and 13 were in exclusion criteria as their duration of stay in NICU was less than 24 hours as shown in [Table/Fig-1].

Among the total 309 neonates, 171 (55%) were male babies and 94 (30%) were inborn. A total of 178 (58%) infants were preterm. Mean gestational age of the cohort was 35 (SD ±2.9) weeks. The mean weight of the population was 2.27 (SD±0.68) kg. Out of the 309, 43 (14%) babies were Small for gestation (SGA) [Table/Fig-2]. In the study cohort, most common reasons for admission to the NICU were suspected sepsis 23% (n-71), respiratory distress 17.5% (n-54), prematurity 11.6% (n-36) [Table/Fig-3].

Baseline variables	Values
Median Age at admission (Hol) IQR	12 (4-24)
Mean Birth weight (Kg) SD	2.27±0.68
Mean Gestational age (Weeks) SD	35±2.9
Male (%)	171 (55%)
Median length of hospital stay IQR	5 (3-8)
Very low birth weight (VLBW) (%)	13 (4.2%)
Infants on invasive respiratory support (%)	20 (6.4%)
Infants on parentral blood stream catheter (%)	13 (4.2%)
Discharged	231 (75%)
LAMA	60 (20%)
Death	18 (5%)

[Table/Fig-2]: Baseline variables.
LAMA: Leave against medical advice

Diagnosis	Number n (%),
Suspected Sepsis	71 (23%)
Respiratory distress	54 (17.5%)
Prematurity	36 (11.6%)
Neonatal Jaundice	27 (9.3%)
Meconium aspiration syndrome	22 (7.2%)
Intra uterine growth retardation	19 (6 %)
Seizures	14 (4.5%)
Urinary tract infection	13 (4.2%)
Birth Asphyxia	12 (3.9)
Congenital Anomalies	11 (3.6%)
Inborn errors of metabolism	11 (3.6%)
Genetic syndrome	10 (3.3%)
Hypoglycaemia	9 (3%)

[Table/Fig-3]: Reason for admission to NICU.
N=309

A total of 2210 antimicrobial prescriptions were made during the study period. Gestation age-wise distribution of antimicrobial prescription is shown in [Table/Fig-4]. Antimicrobials were prescribed frequently for symptomatic infants 150 (48%) followed by bacteriologically proven sepsis in 73 (24%), screen positive sepsis in 61 (20%) and was given as prophylaxis in 25 (8%). The median antibiotic days (DOT) per baby in the study population were 4 (IQR 3-9) days. Indication and the median duration of antibiotic days are shown in [Table/Fig-5].

A total of 13 different types of antimicrobials were utilised. (Fixed drug combinations such as Amoxycillin+Clavulunate, Piperacillin+tazobactam prescriptions were considered as a single type of AMA for analysis). Amikacin (74%), Penicillin-Tazobactam (31%), Ampicillin (8%), Cefotaxime (6%) and Meropenem (6%) were the most frequently prescribed [Table/Fig-6]. All the antibiotics were given intravenously. Nearly, 14% (42) infants received more than two antimicrobials. [Table/Fig-7] shows the comparison of cohort of infants who received more than two antimicrobials versus who received two or less.

Gestational age (In weeks)	Number N= 309 n (%)	Antibiotic prescriptions N= 2210 n (%)
≤28 wk	7 (2.5%)	10
29-30 wk	16 (5%)	20
31-33 wk	50 (16%)	24
34-36 wk	107 (34.5%)	20
≥37 wk	129 (42%)	22

[Table/Fig-4]: Gestational age-wise antibiotic prescriptions.

Category	Number n (%)	Median antibiotic days (DOT)
Symptomatic	150 (48%)	4 (IQR 3-6)
Blood culture proven sepsis	73 (24%)	12 (IQR 5-17)
Screen positive	61 (20%)	9 (IQR 6-10
Prophylaxis	25 (8%)	4 (IQR 3-6)
Total	309	4 (IQR 3-9)

[Table/Fig-5]: Indications for antimicrobial and median duration.

Antibiotic	Number of neonates n (%) N= 309
Amikacin	230 (74%)
Piperacillin-tazobactam	97 (31%)
Ampicillin	25 (8%)
Vancomycin	21 (6.1%)
Colistin	21(6.1%)
Cefotaxime	20 (6%)
Meropenem	20 (6%)
Amoxicillin- Clavulunate	17 (5.5%)
Metronidazole	12 (3.8%)
Ceftriaxone	9 (2.9%)
Fluconazole	9 (2.9%)
Amphotericin-B	5 (1.6%)
Linezolid	3 (1%)

[Table/Fig-6]: Frequency of antibiotic prescription.
Numbers are not mutually exclusive

Blood Culture Patterns

Among infants started on antibiotics, 260 (84%) had bacteriological culture and sensitivity sent before starting antibiotics. Out of 73 (28%, n=260) infants with positive blood cultures, early onset sepsis (within 72 hours of life) was seen in 46 (63%) infants. A total of 39 (53.4%) blood cultures were Gram-negative organisms, 30 (41%) were Gram-positive organisms and 4 (5.4%) were fungal. Of the 39 gram-negative growth, most common organisms identified were Acinetobacter in 14 (35%), Enterobacter in 12 (31%) and Klebsiella in 13 (34%).

Variables	≤2 AMAs used N=267	>2 AMAs used N=42
Mean weight (Kg)	2.3	1.95
Mean GA (Weeks)	32	30
Culture positive	46 (17.2%)	27(64.2%)
Median DOT	4	17.5
Median duration of stay in days	4 (IQR 3-6)	9.5 (IQR 7-20)
Mortality	13 (4.8%)	5(12%)

[Table/Fig-7]: Comparison between two cohorts based on number of antibiotic exposures.
p= <0.05; AMA: Antimicrobials

In 187 infants with sterile blood cultures, upon receipt of sterile culture report antibiotics were stopped by the clinician in 76 (40%) infants.

DISCUSSION

The present study was done at a tertiary care NICU with established antimicrobial usage protocols in the unit and all the staff trained in antimicrobial guidelines. Nearly, 32% of the admitted infants received at least one antimicrobial during their NICU stay. In similar reported studies from India, the antibiotic exposure rates among infants admitted to the NICU varied from 50-100% [Table/Fig-8] [3,4,6-8]. Such high antimicrobial exposure to the admitted infants can be attributed to the nature of sickness and or absence of protocolised treatments [6,7]. In contrast to the Indian scenario, global data indicates much lower level (30%) of antibiotic exposure to infants admitted to the NICU [9].

In this study epoch, nearly one-third of the admission of the neonates to the NICU was due to suspected sepsis and prematurity. Earlier studies have shown that suspected sepsis and prematurity are the major reasons (50-80%) for hospitalisation to the NICU [4,8]. The reason for admission not only influences outcome of neonates but also has an impact on the usage of the antibiotics.

In this study the median antibiotic days (DOT) per baby in the study population were 4 (IQR 3-9). In a similar study by Patel SJ et al., the median duration of the antibiotic course was 6 days. The median antibiotic days depend on the blood culture positivity or sickness of the baby or it can be due to inappropriate antibiotic usage [10].

In this study epoch, majority of neonates 68% (symptomatic basis 48% and empirical 20%) were started on antibiotics

S. no	Author year	Study design	Centre	Sample size	Antibiotic exposure in cohort %	Cephalosporin usage %
1.	Jinka DR et al., 2017 [4]	Before and after	Single	1176	56	41
2.	Gandra S et al., 2018 [3]	Point prevalence	Multi	403	51.6	14
3.	Amin AJ et al., 2015 [8]	Observational prospective	Single	189	100 Selective case selection	64
4.	Shinde AR et al., 2016 [7]	Observational prospective	Single	237	98	43
5	Suryawanshi S et al., 2015 [6]	Observational prospective	Single	528	55.9	31
6	Present study	Observational prospective	Single	309	32	8.9

[Table/Fig-8]: Studies on Antibiotic usage pattern in Indian NICU [3,4,6,7,8].

without bacteriological proven sepsis. These were the infants where clinicians wanted to rule out infections. This group represents the highest yield target for antimicrobial stewardship since they account for the highest antibiotic use in most NICUs. In similar study by Jinka DR et al., the most common indications for antibiotic initiation were empiric treatment in 70% of the cases [4]. Recent research suggests that some clinical criteria for initiating and/or continuing antimicrobials for suspected infection can be changed and threshold raised without causing harm to the infants [11]. A new objective clinical risk scoring approach to identifying sepsis in infants ≥34 weeks' gestation resulted in empirical antibiotic treatment of a much smaller proportion of this population [12].

In a recent study, at tertiary care NICU, incorporation of the septic risk calculators (based on clinical findings and labs) together with antibiotic time-out strategy i.e., after 36-48 hours of initiation of antimicrobials stopping antibiotics if blood cultures were sterile was well-received by the treating team and did not contribute to any missed sepsis diagnoses, delayed treatment, or clinical deterioration. Furthermore, there was an associated 29.4% decline in antibiotic usage in infants [11-13].

Among the blood culture positive infections, nearly two-third were early onset sepsis. There were nearly equal numbers of gram-negative and gram-positive infections. The present study had very less number of fungal infections (5%) as compared to 22% in other reported studies possibly due to less number of very low birth weight infants and also less cephalosporin usage [14].

Majority of antibiotic prescriptions in this study were Amikacin (74%) followed by Piperacillin+Tazobactam (31%). This was consistent with the unit policy to use amikacin as first line antibiotics which was based on local antibiotic susceptibility profile. Indian National Center for Disease Control (NCDC) recommends ampicillin plus gentamycin as first line antibiotic in neonatal sepsis [15]. A recent review has suggested that there is an increasing resistance to the gentamycin (41%) as compared to amikacin (21%) among the gram-negative bacilli [16]. Unlike other reported studies from our country where cephalosporin usage was high (40-60%) in the NICU, this study had only 8.9% cephalosporin prescriptions [4,7,8]. Since majority of neonatal infections, especially early onset sepsis after birth are gram-negative [14], with the use of amikacin we can avoid other broad spectrum antibiotics like ampicillin and cephalosporins during empirical treatment. Cephalosporin usage in NICU is not only associated with increased antibiotic resistance but also leads to dreaded medical complications like Necrotising Enterocolitis (NEC) and fungal infections [8].

In this study group, 84% of the infants were started on antibiotics after sending blood for culture and sensitivity. The blood culture positivity rate of 24% was comparable with Mhada TV et al., who also observed a culture proven sepsis rate of 24% [17]. Blood culture is the gold standard for the diagnosis of neonatal sepsis. However, in neonates the rate of positivity is low due to intrapartum antimicrobial administration and limitations in blood volume per culture [18].

Among the babies who had sterile blood cultures, only in 40% of the infants on receipt of a negative blood culture report antibiotics were stopped. These infants were continued on antibiotics at the clinical discretion of clinician. Many non infectious conditions can mimic pneumonia (e.g., respiratory distress syndrome, transient tachypnoea of neonates) or suspected sepsis (e.g., hypotension, apnoea). Viral infections can also cause pneumonia and sepsis-like episodes. Finally, in a recent study it was shown that therapy for culture negative sepsis is not always related to physical examination findings or risk factors, but are rather influenced by subjective factors [11]. Quality improvement interventions should be designed to target these areas and then track both subsequent antibiotic use and safety outcomes.

Limitation(s)

This was a single centre study hence limiting the generalisability of results. Complete rationality of antimicrobial prescriptions like dose appropriateness was not established. Antibiotic usage was not analysed separately among the inborn and outborn infants.

CONCLUSION(S)

In this prospective surveillance study of all the antibiotics used in the NICU, we were able to establish that one-third of the infants admitted to the NICU were exposed to antibiotics. Bulk of the antibiotic usage was empirical in symptomatic infants. Amikacin was the single most prescribed antimicrobial. In infants

with negative blood culture report, antibiotics were continued in two-thirds after the receipt of report. Cephalosporins were used sparingly.

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